Kamal Dua · Srinivas Nammi
Dennis Chang
Dinesh Kumar Chellappan
Gaurav Gupta · Trudi Collet *Editors*

Medicinal Plants for Lung Diseases

A Pharmacological and Immunological Perspective

Springer

Medicinal Plants for Lung Diseases

Kamal Dua • Srinivas Nammi •
Dennis Chang • Dinesh Kumar Chellappan •
Gaurav Gupta • Trudi Collet
Editors

Medicinal Plants for Lung Diseases

A Pharmacological and Immunological Perspective

Springer

Editors
Kamal Dua
Discipline of Pharmacy,
Graduate School of Health
University of Technology Sydney
Sydney, NSW, Australia

Dennis Chang
NICM Health Research Institute
Western Sydney University
Sydney, NSW, Australia

Gaurav Gupta
School of Pharmacy
Suresh Gyan Vihar University
Jaipur, Rajasthan, India

Srinivas Nammi
Discipline of Medical Sciences,
School of Science
Western Sydney University
Sydney, NSW, Australia

Dinesh Kumar Chellappan
Department of Life Sciences,
School of Pharmacy
International Medical University
Kuala Lumpur, Malaysia

Trudi Collet
Faculty of Health
Queensland University of Technology
Brisbane, Queensland, Australia

ISBN 978-981-33-6849-1 ISBN 978-981-33-6850-7 (eBook)
https://doi.org/10.1007/978-981-33-6850-7

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Preface

Much of the burden of respiratory diseases is aggravated by multiple determinants. Among the critical determinants, are, exposure to tobacco smoke, industrial pollutants and household air pollution. The Global Alliance Against Chronic Respiratory Diseases (GARD) which works together with the World Health Oraganization (WHO) has cautioned that chronic respiratory diseases are one of the main leading causes of mortality and morbidity in the world. In its recent news release, the WHO has highlighted that, pneumonia along with other lower respiratory infections rank fourth as the leading cause of death. Tuberculosis (TB) continues to rank one among the top 10 causes of deaths in African and South-East Asian countries. Other chronic respiratory diseases namely, asthma, Chronic Obstructive Pulmonary Disease (COPD) and lung cancer are reported to be collectively responsible for the loss of several million healthy life-years. In addition, for decades, acute lower respiratory tract infections such as bronchitis, bronchiolitis, and influenza have been among the top three causes of death and disability in both children and adults.

Phyto-pharmaceuticals and plant-based therapies have been in practice since time immemorial. There exists a large body of evidence that supports the use of herbals in the therapy and management of several chronic respiratory diseases. There has been a renewed interest in natural products in the last two decades. More than 80% of the world population still relies on traditional plant-based remedies. Multiple, complex regulatory pathways manifest chronic pulmonary disorders, which require chemotherapeutics that produce composite inhibitory effects.

This book, *Medicinal Plants for Lung Diseases: A Pharmacological and Immunological Perspective,* in this direction, is written in a contemporary style to deliberate on the current scientific experimental evidences and inferences gathered on the therapeutic effectiveness of natural product moieties and their related components, that demonstrate medicinal applications on respiratory diseases. It explores state-of-the-art developments and technological advancements in the field of respiratory medicine employing plant products as the source. The book essentially presents a blend of translational, biological, chemical, pharmacy practice and drug delivery aspects of medicinal plants. Furthermore, it provides a critical appraisal on emerging paradigms and insights into the pharmacological and immunological (cellular and molecular) investigations of plant-based moieties and their effectiveness in targeting

lung diseases. Several newer platforms in respiratory research which were developed in this decade have also been elaborated.

The book comprises of several sections which begins with the importance and role of herbal medicines in the treatment and management of respiratory diseases. The introductory section is followed by subsequent chapters that elaborate plants and plant products that have been studied for the treatment of respiratory diseases namely, asthma, COPD, tuberculosis, lung cancer, pulmonary hypertension, lung fibrosis, bronchitis, pulmonary edema, influenza, corona virus disease (SARS-coV2) and medicinal plants-based advanced drug delivery systems. The book concludes with a critical appraisal of the recent advances and applications of nanodrugs that are derived from active metabolites of medicinal plants for the treatment of inflammatory and lung diseases. More than eighteen experts who currently work in this field from around the world have provided critical information on the various facets of herbal medicine strategies along with today's cutting-edge technologies that are experimentally studied in the treatment and management of chronic respiratory diseases.

Moreover, the editorial team comprises of experts from three different countries, namely, Australia, Malaysia and India who hold extensive experience working with plants of medicinal importance in various disease states, which brings an extra edge to the book in its current form.

Sydney, NSW, Australia — Kamal Dua
Sydney, NSW, Australia — Srinivas Nammi
Sydney, NSW, Australia — Dennis Chang
Kuala Lumpur, Malaysia — Dinesh Kumar Chellappan
Jaipur, Rajasthan, India — Gaurav Gupta
Brisbane, Queensland, Australia — Trudi Collet

Acknowledgement

The publication of this book was finalized during the coronavirus (COVID-19) pandemic. We would like to dedicate this book to all those who were affected by the pandemic and, in particular, to our health workforce around the world for their dedication and care during this difficult time.

Contents

About the Editors

Kamal Dua is a Senior Lecturer in the Discipline of Pharmacy at the Graduate School of Health, University of Technology Sydney (UTS), Australia. He has research experience of over 12 years in the field of drug delivery systems targeting inflammatory diseases. Dr. Dua is also a Node Leader of Drug Delivery Research in the Centre for Inflammation at Centenary Institute/UTS, where the targets identified from the research projects are pursued to develop novel formulations as the first step towards translation into clinics. Dr. Dua researches in two complementary areas; drug delivery and immunology, specifically addressing how these disciplines can advance one another, helping the community to live longer and healthier. This is evidenced by his extensive publication record in reputed journals. Dr. Dua's research interests focus on harnessing the pharmaceutical potential of modulating critical regulators such as Interleukins and microRNAs and developing new and effective drug delivery formulations for the management of chronic airway diseases. He has published more than 80 research articles in peer-reviewed international journals and authored or co-authored four books. He is an active member of many national and international professional societies.

Srinivas Nammi is working as Senior Lecturer in Pharmacology and Academic Course (BMedSc) at the School of Science, Western Sydney University (WSU), Australia. He holds a doctorate in Pharmaceutical Sciences, specializing in Pharmacology from Andhra University, India. Before joining the WSU, he worked at the Faculty of Pharmacy, University of Sydney, after gaining postdoctoral experience as DAAD Fellow at the University of Tübingen, Germany and the University of Manitoba, Canada. He has 1 international patent and has published over 80 scientific papers, 10 editorials, and 3 book chapters. He is also serving as Secretary for the Australian DAAD Alumni Association.

Dennis Chang holds a doctorate and MSc degree in Pharmacology from the University of Sydney, Australia. His research interests include clinical and pharmacological studies of complementary medicine (CM). He is a chief investigator of several significant Phase II and III clinical trials to evaluate CM interventions (herbal medicine, yoga and Tai Chi) for the treatment of dementia, mild cognitive impairment, coronary heart disease, metabolic syndrome and type 2 diabetes. He

has led numerous laboratory-based pharmacological studies of herbal medicines to evaluate pharmacokinetics/bioavailability and mechanisms of action underlying the neuro- and cardiac-protective effects of herbal medicines.

Dinesh Kumar Chellappan holds PhD and Master's degree in Pharmaceutical Sciences from Manipal University, India. He has worked on several research projects focused on inflammatory diseases with the core area in diabetes treatment and management. He is actively involved in undertaking research in chronic inflammatory pulmonary diseases, particularly developing and testing novel drug delivery systems. He has published more than 100 research articles in reputed national and international journals.

Gaurav Gupta is currently is working as an Associate Professor with Suresh Gyan Vihar University, Jaipur, Rajasthan, India. He holds a doctoral degree from Pacific University, Udaipur, Rajasthan, India. He has more than nine years of experience in molecular and biochemical pharmacology, including phytochemistry and respiratory diseases, psychopharmacology, and cancer biology by employing experimental animal models to understand the cellular and molecular mechanism. Dr. Gupta has more than 150 research and review articles in the national and international journals of repute.

Trudi Collet is a leader of the Innovative Medicines Group (IMG) at the Kelvin Grove campus of the Queensland University of Technology and is involved in evaluating the biological properties of plant-derived bioactive compounds and extracts, including their bactericidal, viricidal, and wound healing properties. She has done her PhD at the Queensland University of Technology in 2007. Earlier, she has worked as a postdoctoral fellow at the Queensland Institute of Medical Research and investigated novel serological markers for differential diagnosis of inflammatory bowel disease.

Immuno-Pathogenesis of Respiratory Diseases

1

Priya Madhavan, Farzana Rizwan, and Imam Shaik

Abstract

Immuno-pathogenesis, by definition (Nature) is the process of disease development involving an immune response or components thereof. Our immune system comprises innate and adaptive systems. The innate immune system produces receptors that are hard-wired in our genome which encounters all types of pathogens. Innate immunity recognizes pathogen-related patterns known as pattern associated molecular patterns that enables it to distinguish pathogens from commensal organisms, acting as the first line of defense against pathogens. On the other hand, the adaptive immune system has specific receptors that are produced only when specific pathogens are encountered by the human body. Lymphocytes are an important component of the adaptive immunity as it can evolve and differentiate to recognize specific pathogens, protecting the body against subsequent infections. Although they are seen as separate, but both innate and adaptive immune systems work together, in which the former paves way for the latter for effectively providing long lasting immunity. Moreover, since there is a delay in the adaptive immune response (4 to 7 days), the innate immune response has a critical role in taking the lead to protect the body and/or controlling the spread of infection within the body. In this chapter, we will be describing the current findings of immuno-pathogenesis on various respiratory diseases.

P. Madhavan (✉) · F. Rizwan · I. Shaik
School of Medicine, Faculty of Health and Medical Sciences, Taylor's University, Subang Jaya, Selangor, Malaysia
e-mail: priya.madhavan@taylors.edu.my; farzana.rizwan@taylors.edu.my; imam.shaik@taylors.edu.my

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_1

Keywords

Immuno-pathogenesis · Chronic lung diseases · COVID-19 · Tuberculosis · Influenza A · Lung cancer

1.1 Introduction

The body's respiratory system includes the upper and lower respiratory systems. Anatomically, the upper respiratory system includes nose, nasal cavity, mouth, pharynx, and larynx, whereas the lower respiratory tract starts from trachea, bronchi, bronchioles, and alveoli. The lung, being the most vulnerable organ in our body is prone to infections and injury from the external environment. The inhalation of and exposure to chemical, particles from air pollution, and infectious organisms makes the lungs vulnerable to diseases. The global statistics on those who are exposed to tobacco smoke, smoke from biofuel, and polluted outdoor air have been reported by Forum of International Respiratory Societies [1]. Respiratory diseases contribute to a high disease burden regardless of nationality or economy status. However so, people living in poverty, unsanitary conditions, and crowded areas may be at higher risks of infections.

According to a report published by Forum of International Respiratory Societies [1] on the global burden of diseases, there are five most common respiratory diseases which cause severe illness and death. These are moderate to severe chronic obstructive pulmonary disease (estimated at 65 million people), asthma (334 million people, affecting 14% of children globally acute lower respiratory tract infections), tuberculosis (affecting 10.4 million people causing 1.4 million deaths in 2015), and lung cancer, causing 1.6 million deaths annually. Deaths from Influenza A virus worldwide is about 290,000 to 650,000 annually, from 3 to 5 million cases of severe illness [2]. However, at this present time, Covid-19 has become the top respiratory disease with the highest mortality rate.

In this chapter, we will be discussing several important diseases and the immunopathogenesis involved to help in understanding each of the following diseases.

1.2 Immuno-Pathogenesis of Infectious Respiratory Diseases

1.2.1 COVID-19

Coronavirus 2 (SARS-CoV-2) infection leads to COVID-19, causing severe acute respiratory syndrome. It spreads rapidly and is associated with high mortality rate particularly in the elderly patients having co-morbidities. The patients may develop lung damage [3] and exhibit the features of severe acute respiratory distress syndrome (ARDS). In severe cases, it may cause simultaneous failure of various organs [3].

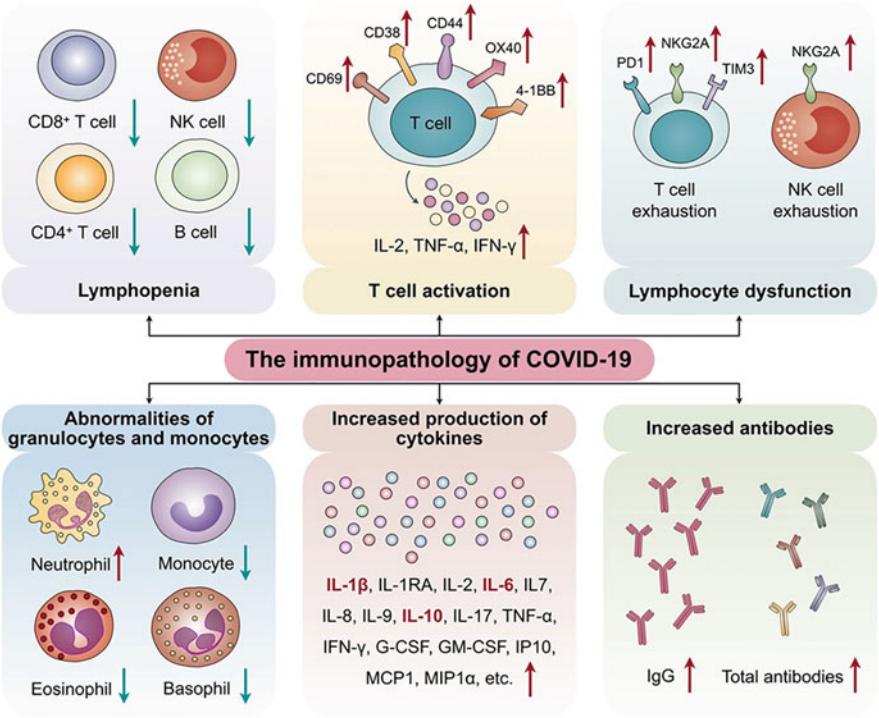


Fig. 1.1 The immune patterns of COVID-19 (Reproduced from [3])

Based on the evidence gathered about SARS and Ebola virus diseases, and the similarity of immune patterns observed in these diseases and Covid-19, it has emerged that there is a close association between the progress of disease and the patterns of immune response in patients who are affected with Covid-19 infection [3]. These immune characteristics may be regarded as significant biomarkers of not only the progression of the disease but also for development of future therapeutic agents in Covid-19.

The clinical evidence has suggested that SARS-CoV-2 infection causes impairment of the normal progression of immune responses, thus triggering an uncontrolled inflammatory response in COVID-19 patients. These patients have shown to develop depletion of lymphocyte number in the blood and exhibit markers of lymphocyte activation and dysfunction. There are abnormalities of other white blood cells such, high levels of cytokines and total antibodies, with a particular hike in immunoglobulin G (IgG). The immune patterns of COVID-19 are summarized in Fig. 1.1.

1.2.2 Abnormalities of Lymphocytes, Granulocytes, and Monocytes

On admission, blood analysis of COVID-19 patients revealed decreased number of lymphocytes, particularly those with severe infection [3], Lymphocyte percentages Tan have been found to be lower than 20% [3], particularly markedly reduced number of CD4+ T, CD8+ T, NK cells. The number of B cells has been within the normal range, indicating that B-lymphocytes are not as affected by the infection as T lymphocytes and NK cells.

There is an increased number of neutrophils, while the percentage of monocytes, eosinophils, and basophils is reduced in Covid-19 [3]. High ratio of neutrophils compared to lymphocytes has been considered an important indicator for severe disease and poor clinical outcome [3].

1.2.3 Lymphocyte Activation and Dysfunction

It has been observed that more frequently it is CD8+ rather than CD4+ T cell response. Virus-specific T cells have high levels of interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and interleukin (IL)-2 and central memory phenotype in severe cases.

Exhaustion phenotypes of T lymphocytes also emerged. CD8+ T cells also exhibited an increase in the programmed cell death protein-1(PD-1), T cell immunoglobulin domain, and mucin domain-3 that peaked in severe conditions [3].

1.2.4 Increased Production of Cytokines and Antibodies

Another characteristic feature observed is an increased cytokine production. There is an upregulation of the inflammatory cytokines and their levels correspond to the severity of the disease. They include IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), interferon-inducible protein-10 (IP10), monocyte chemotactic protein 1 (MCP1), macrophage inflammation protein-1α, IFN-γ, and TNF-α, representing a "cytokine storm" [3]. IL-1β, IL-6, and IL-10 are found to be the most elevated cytokines, particularly when the infection is severe.

Activation and proliferation of B-lymphocytes and the total antibodies in the serum of these patients correlate poorly with the disease outcome [3]. Out of all types of immunoglobulins/antibodies, the level of IgG particularly corresponds to the severity of Covid-19 [3, 4]. Fig. 1.2 Shows the potential mechanisms of SARS-COV-2-induced immunopathology.

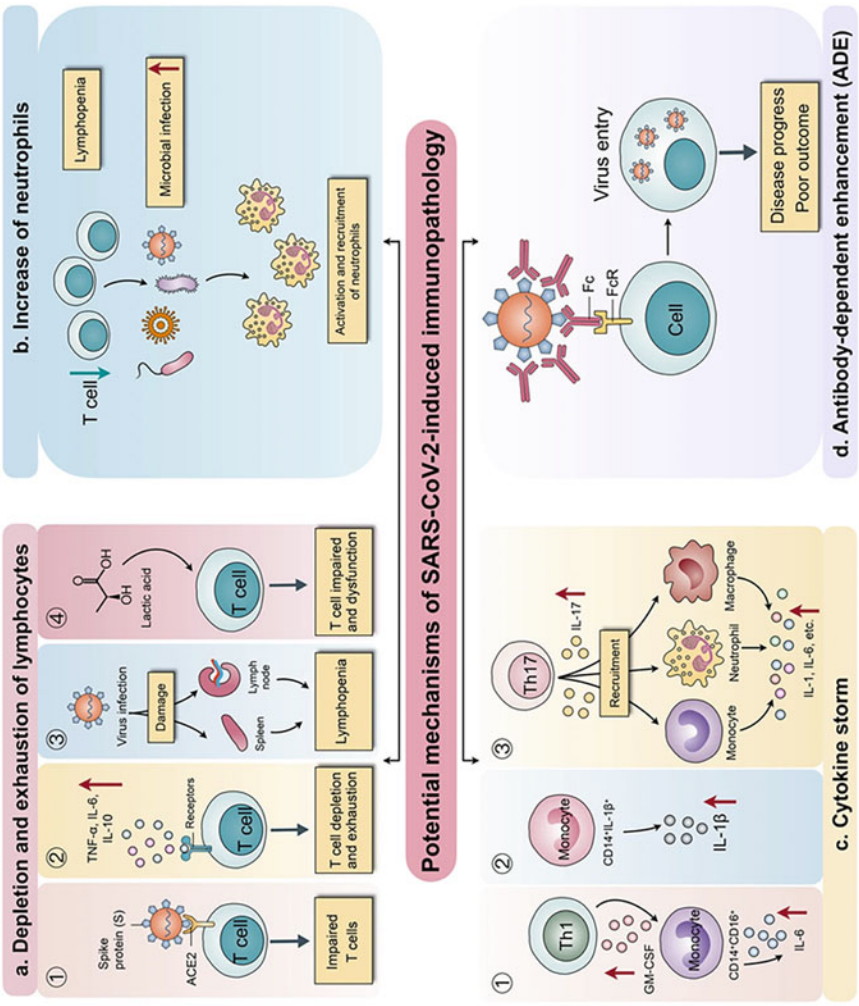


Fig. 1.2 Potential mechanisms of SARS-CoV-2 induced immunopathology (Reproduced from [3])

1.2.5 Depletion and Exhaustion of Lymphocytes and Increase in Neutrophils

The possible mechanisms causing the depletion and dysfunction of lymphocytes and increased neutrophils have been described in a review by Yang et al. [3]

1. S proteins (Spike glycoprotein) on the SARS-CoV-2 bind to angiotensin-converting enzyme 2 (ACE2) receptors and infect human respiratory epithelial cells. This virus can infect T lymphocytes and macrophages directly. Hence, it is hypothesized that ACE2 receptor expression, particularly on T lymphocytes, facilitates the entry of the virus inside these cells.
2. There is a reciprocal relationship between the T cell number and that of the serum levels of TNFα, IL-6, and IL-10. This observation indicates that high level of inflammatory cytokines plays a major role in causing lymphopenia and T cells exhaustion. Both of these factors have a significant influence on disease progression.
3. The infected patients have revealed atrophy of the spleen and necrosis of the lymph nodes indicating that lymphatic organs may be destroyed directly and can cause worsening of the lymphopenia.
4. Elevated lactic acid concentration has been detected in the patients' blood, who suffered with a severe form of disease. This may be another factor that may hamper the proliferation of lymphocytes.
5. Lymphopenia and lymphocyte exhaustion pose a higher risk of microbial infection → neutrophilia, activation and chemotaxis of neutrophils to the infection site.

1.2.6 Cytokine Storm

Infected CD4+ cells are activated into T helper (Th) 1 cells and secrete GM-CSF, which induces CD14+CD16+ monocytes, release of large amounts of IL-6. Th17 cells produce IL-17 that promote recruitment and activation of monocytes/macrophages and neutrophils in the infected tissue, hence triggering production of cytokines IL-1β and IL-6. The recruited eosinophils release large amounts of cytokines including IL-6. All these mechanisms accelerate the inflammatory response and a sharp rise of cytokine levels, thus a "cytokine storm".

1.2.7 Antibody-Dependent Enhancement of Infection

This is a phenomenon where pre-existing antibodies promote viral entry and their propagation/proliferation inside the affected cells. It is shown to exist in conditions like Ebola, Dengue, and MERS [3]. The antibodies facilitate viruses entering cells

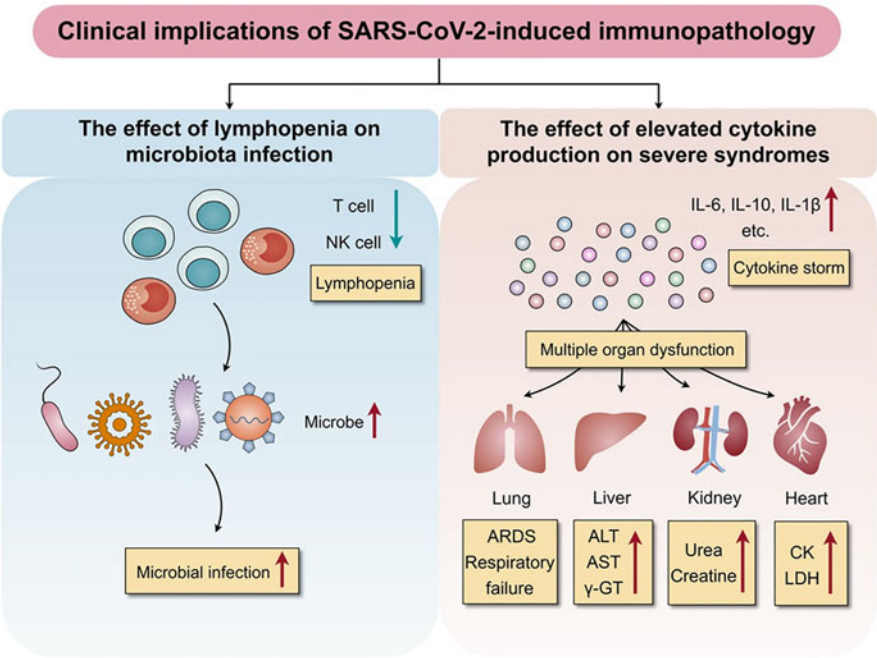


Fig. 1.3 Clinical consequences of SARS-CoV-2-induced immunopathology (Reproduced from [3])

through binding of Fc receptors (FcR) present on the cell surface to Fc portion of the antibody [3]. Antibody upregulation has been observed and has been linked to poor outcome of the infected patients. Clinical consequences of SARS-CoV-2-induced immunopathology are shown in Fig. 1.3.

Patients with COVID-19 who develop lymphopenia are at higher risk of contracting microbial infections hence, increasing the severity of disease. Cytokine storms can trigger dysfunction of multiple organs, including injury to the lung tissue leading to ARDS, respiratory failure, hepatic injury exhibiting a rise in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamine transferase (γ-GT), renal damage causing elevated levels of urea and creatine, and cardiac injury shown by increased creatine kinase (CK) and lactate dehydrogenase (LDH) levels.

The indicators of disease progression in Covid-19 are:

1. Lymphopenia can be detected early and has been observed in both mild and severe forms of disease.
2. High exhaustion levels and impairment of functional capacity of T cells.
3. Increased neutrophils and reduced counts of eosinophils, basophils, and

monocytes.

4. Elevation of inflammatory cytokines, IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), interferon-inducible protein-10 (IP10), monocyte chemotactic protein 1 (MCP1), macrophage inflammation protein-1α, IFN-γ, and TNF-α,2,3,12,15. Particularly IL-1β, IL-6, and IL-10 have shown marked elevation in severe cases.
5. SARS-CoV-2-specific antibodies, IgM and IgG indicate B cell activation and proliferation. They are considered to facilitate virus entry in the cells. Hence, indicators of worse clinical outcome.

1.2.8 Cystic Fibrosis

A major pathogen involved in chronic lung disease is *Pseudomonas aeruginosa*. Symptoms such as overproduction of thick mucus and inflammation of the airway by neutrophils is a characteristic of cystic fibrosis [5]. Therefore, typical features of CF include mucus obstruction and recurrent airway infections. CF arises from mutations in the cystic fibrosis conductance regulator (CFTR) gene [5]. This single gene mutation results in a faulty ion transport. This would eventually lead to airway impairment and host defenses. There are several virulence factors of *P. aeruginosa* which contribute to these pathologies. One of them is producing diffusible pigments such as pyocyanin and pyoverdin. These pigments evade the immune system via their free radical scavenging activities [5]. One of these activities is to synthesize exoenzymes, that are secreted by type III secretion systems (TTSS). These exoenzymes allow the bacteria to modify the host cells by inhibiting phagocytosis and bacterial destruction within the phagocytic cells. In this regard, exoenzyme S (ExoS) enhances the persistence and spread of *P. aeruginosa* in the lungs of patients, which greatly affects patients with acute pneumonia [5]. The implication of these exoenzymes in neutrophil extracellular traps (NET) formation can be proposed. The formation of a few NETs is attributed to free radical formation and phagocytosis [5].

In another study, NET formation induced by *P. aeruginosa* was evaluated from strains isolated from CF patients to correlate between NET formation and the clinical status of the patients [5]. The bacteria use these NETs to scaffold and colonize the lungs which increases their virulence and overproduction, leading to damage of the lungs. Differences in the morphologies were also observed in which "expanded or spread" morphology was observed from isolates obtained from patients with severe disease. On the other hand, the other globular morphology was observed from isolates obtained from patients with mild/moderate disease. This explains the fact that *P. aeruginosa* can induce NET via their nuclear expansion, either in a "spread form" or a more "compact form." Figure 1.4 shows two types of NETs produced in different disease severity.

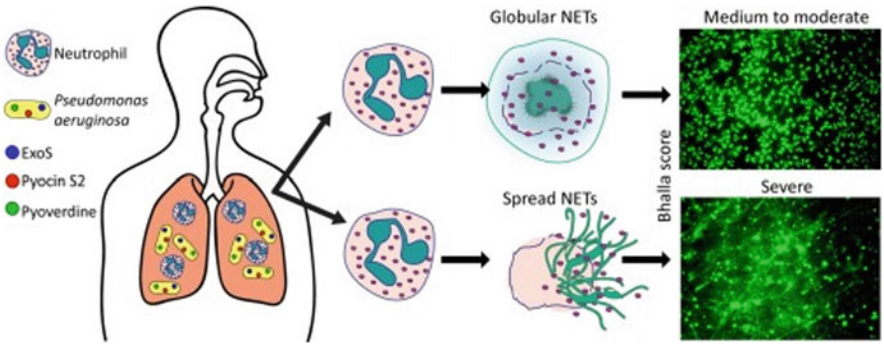


Fig. 1.4 Two types of NETs produced in different disease severity (Reproduced from [5])

Another attribute of CF is the involvement of the nervous system via its neuropeptide signaling. Neural involvement in CF has been proposed by a few research groups as described in the following paragraphs. Neuropeptides, by definition, are peptides that are formed by enzymatic processing of gene-encoded precursor molecules [6]. These peptides are synthesized and secreted via regulated secretory pathways. Some of these neuropeptides have been described in a review by Atanasova and Reznikov [6]. A summary of some of these neuropeptides with their involvement in mucus secretions are stated below.

1. Bombesin—a downstream protein from the activation of the orphan bombesin receptor subtype-3 regulates neutrophil elastase-induced muc5AC hypersecretion in human bronchial epithelial cell line.
2. Calcitonin gene-related peptide (CGRP)—stimulates goblet cell secretion and had induced basal mucus volume, lysozyme, and albumin outputs tested in ferret trachea culture at baseline.
3. Granins—in human HBE16 bronchial epithelial cell line, secretoneurin induced Muc5AC hypersecretion was observed in a dose- and time-dependent study.
4. Neuropeptide Y—modulates mucus output from airway submucosal glands.
5. Substance P (SubP)—stimulates the increase of goblet cell secretion and human airway submucosal gland secretion.

Whereas, in Fig. 1.5 the effects of neuropeptides on mucus secretion from submucosal glands and goblet cells have been described.

An antimicrobial protein stored in neutrophil azurophilic granules known as Bactericidal/permeability-increasing protein (BPI) is an important protein [7]. This antimicrobial protein has high affinity binding to Gram-Negative Bacteria (GNB) lipopolysaccharides (LPS) and is known to perform three main functions, which are i) direct killing of Gram-negative bacteria (GNB), ii) neutralization of bacterial lipopolysaccharide, and iii) opsonization of GNB [7]. In a study conducted in USA with 4 CF patient cohorts, it was demonstrated that serum BPI autoantibodies

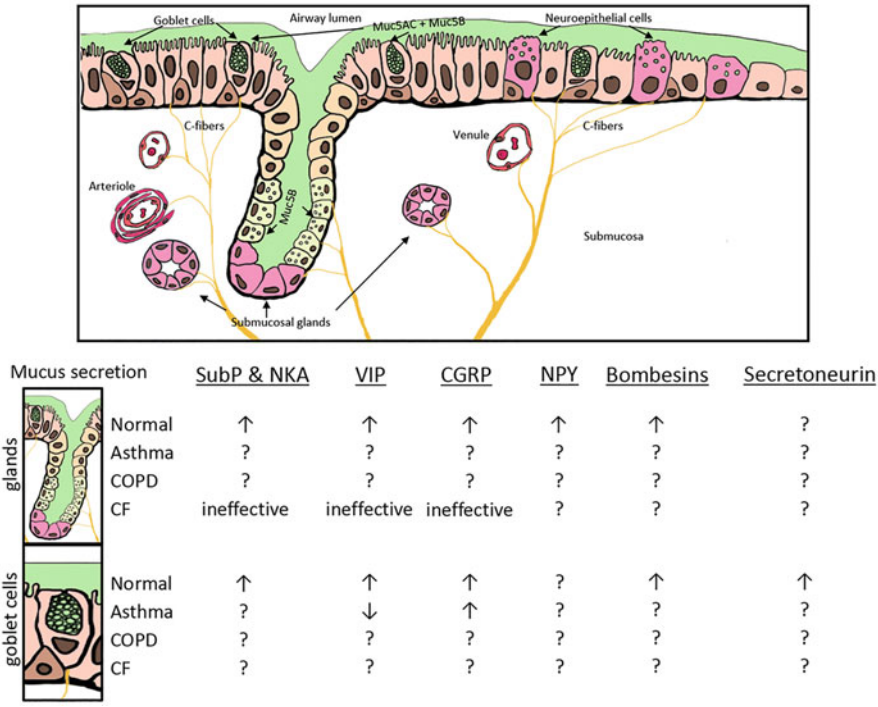


Fig. 1.5 A model of an airway showing the effects of neuropeptides on mucus secretion. (Reproduced from [6]). The arrows indicate increased (up) and decreased (down) secretions. The question mark (?) indicates an unknown effect. Abbreviations used are as follows: SubP for substance P, NKA for neurokinin A, VIP for vasoactive intestinal peptide, CGRP for calcitonin gene-related peptide, NPY for neuropeptide Y, COPD for chronic obstructive pulmonary disease, and CF for cystic fibrosis

were common among (~43%) adult CF patients while rare ($\ll$5%) in pediatric cases ($\leq$18 yrs) [7]. Therefore, in their study, a relationship was established between serum BPI IgG autoantibodies with anti-*P. aeruginosa* IgG responses. The former was of high avidity and strongly correlated with the latter. The same was observed in both adult and pediatric CF patients with IgA responses in their bronchoalveolar lavage (BAL). It was concluded that BAL IgA anti-BPI antibodies correlated with the presence of BPI cleavage in BAL but was not age dependent. Fig. 1.6 shows a model for breaking the immune tolerance to BPI in a chronic *P. aeruginosa* infection via BPI cleavage in the CF airway. Systemic immune response to both *P. aeruginosa* and self-BPI antigens occurs via a different pathway.

BAL fluid analyzed from CF patients infected with nonmucoid variants of *P. aeruginosa* had lower concentrations of IL-6 in BAL fluid samples compared to patients who were not colonized [8]. In another study, BAL fluid obtained from CF patients containing mucoid variants of *P. aeruginosa* and mixed-mucoid/nonmucoid isolates, had higher concentrations of pro-inflammatory cytokines [8]. Based on

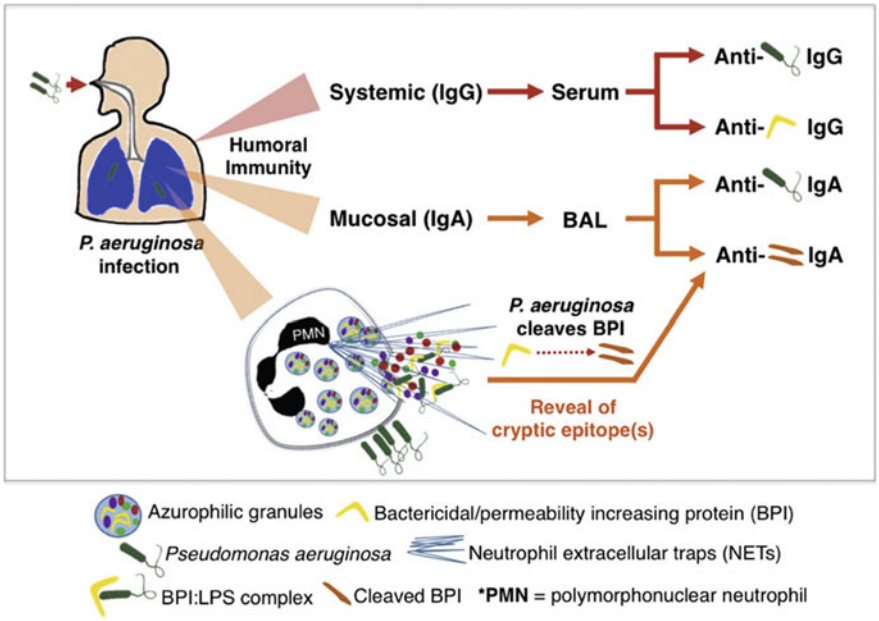


Fig. 1.6 A model describing mucosal immune response exposure to cryptic epitope(s) via BPI cleavage in the CF airway with high anti-*P. aeruginosa* IgA titers. (Reproduced from [7])

these observations, they postulated that nonmucoid *P. aeruginosa* suppresses synthesis or abrogates the stability of IL-6. In a study using a murine model, LasB protease of *P. aeruginosa* had specifically degraded IL-6. This had led to a compromised tissue-protectiveness and antimicrobial defenses in the animal. However, with an overexpression of IL-6 protected these animals from lethal effects of *P. aeruginosa* [8].

B Lymphocyte Differentiation Factor (BAFF) was expressed in the airways of children with CF and the lungs of mice infected with *P. aeruginosa*. Moreover, there was an increasing influx of B cells and T cells [both CD4 and CD8] into the lung of mice within 7 days post-infection. Other studies had also demonstrated the involvement of CD4 cell Th2 and Th17 in *P. aeruginosa*-led infections of CF [9]. CXCL13, which is primarily a B cell chemoattractant was elevated when there was an increase in B cell numbers, suggesting the recruitment of both B1 and B2 B cell types during this infection [9]. Increased BAFF expression implies the increased expression of B cell chemoattractants. This would subsequently increase B cell recruitment, differentiation, and antibody production. On the contrary, chemoattractants of T cell and DC which are CCL19 and CCL21 had increased progressively in a sequencing manner during the 7 days post-infection with *P. aeruginosa*. These studies demonstrate the role of CCL19 and CCL21 in the recruitment of T and B cells, while

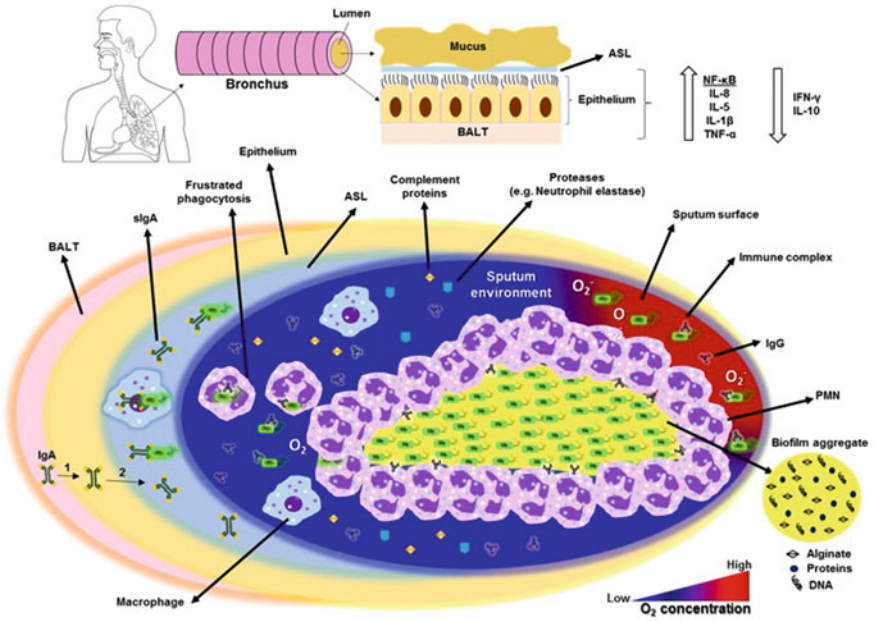


Fig. 1.7 Mucus with a *P. aeruginosa* biofilm surrounded by polymorphonuclear neutrophils (PMN) and IgG antibodies specific to *P. aeruginosa* antigens, such as alginate, lipopolysaccharide, and proteins (Reproduced from [10])

CCL19 could also be responsible for an early recruitment of B cells. Other studies had also reported that CXCL13, CCL19, and CCL21 are components of the local airway immune response to viral infection [9] and are also involved in Inducible Bronchus-Associated Lymphoid Tissues formation, due to a prolonged bacterial exposure of the airways.

Implications of an overproduction of pro-inflammatory cytokines interleukin (IL-) 6 and 8, and Tumor Necrosis Factor Alpha (TNF-α) in infected CF airway epithelial cells (AECs) is due to increased activation of the Nuclear Transcription Factor-Kappa B (NF-κB). An overproduction of NF-κB reduces the synthesis of glutathione, which neutralizes reactive oxygen species (ROS). However, this anti-oxidant peptide was reported to increase production of other inflammatory mediators such as Prostaglandin E2 and Cyclooxygenase-2 (COX-2) [10]. On the same note, it was reported that AEC also produces decreased amount of interferon-gamma (IFN-γ), causing upregulation of IL-33, which are also neutrophil chemoattractants [10].

In Fig. 1.7, activation of PMNs is triggered by immune complexes that are formed between *P. aeruginosa* antigens and IgG. This leads to inflammatory reaction when activated PMNs have heightened oxygen and give rise to reactive oxygen species (ROS). The anaerobic condition caused by this ROS release would disable PMNs

phagocytic activity. High NF-κB production by CF airway epithelial cells (AECs) induced by IgG response will result in hyperproduction of pro-inflammatory cytokines such as IL-5 and IL-8, and low production of anti-inflammatory cytokines such as IL-10 and INF-γ. These responses will eventually lead to tissue damage. On the other hand, in the Bronchi-Associated Lymphoid Tissue (BALT) submucosa, the IgA that are produced here will combine with the secretory component, resulting in sIgA. The sIgA will be transported through the epithelial cells to the airway surface liquid (ASL). This will prevent *P. aeruginosa* attaching to the epithelial cells, thus preventing airway inflammation.

In Fig. 1.8, naïve B cells are first synthesized in the bone marrow, then activated in the secondary lymphoid organs (e.g., CF BALT) when an antigen presenting cell interacts with the antigen. Upon proliferation and differentiation, plasma cells will generate specific antibodies (IgG and IgA). Therefore, antigen specific naïve B cells may differentiate within the secondary lymphoid tissue producing short-lived low-affinity plasma cells. These naïve B cells may also undergo a rapid proliferative phase known as the germinal center (GC) reaction, producing memory B cells or long-lived plasma cells. In the case of CF, the clonal expansion and affinity maturation would be deficient.

A study reported on variations in the inflammatory patterns among male and female patients from end stage CF lung tissues [11]. In female patients, eosinophils, mast cells, and CD4T cells were higher than males but lymphoid follicles had less B cells and more CD8 T cells. This may be the result of the complex immunomodulatory effects of oestrogen on inflammation. Another important component of the innate immune system is the production of antimicrobial peptides (AMP) against bacterial strains, especially that are resistant to antibiotics. More than 3000 AMPs have been isolated from various organisms and are registered in the AMP database (http://aps.unmc.edu/AP/main.php). They are known to serve as natural antimicrobial agents and may replace antibiotics that have gained resistance by many microorganisms [12].

AMPs can either disrupt bacterial membranes or interfere with intracellular processes. There are 3 models illustrated in Fig. 1.9. In the first model, where AMPs such as alamethicin, pardaxin, and protegrins use the "barrel-stave pore model," which is inserting the peptides perpendicularly into the lipid bilayer thus forming transmembrane pores [12]. In the second model known as the "carpet model," AMPs first adsorb parallel to the lipid bilayer, then cover the surface of the target membrane and disintegrate the membrane via the formation of micelles and pores. This is performed by AMPs like cecropins and some magainins. Slightly different mechanisms of action of Magainins and LL-37 are shown in the third model known as the "toroidal-pore model," where peptides are perpendicularly incorporated into the bilayer membranes, thus enabling the lipid monolayers to curve around the pore [12].

AMPs are also involved in other immune modulations, i.e. release of pro-inflammatory cytokines and chemokines, stimulation and differentiation of

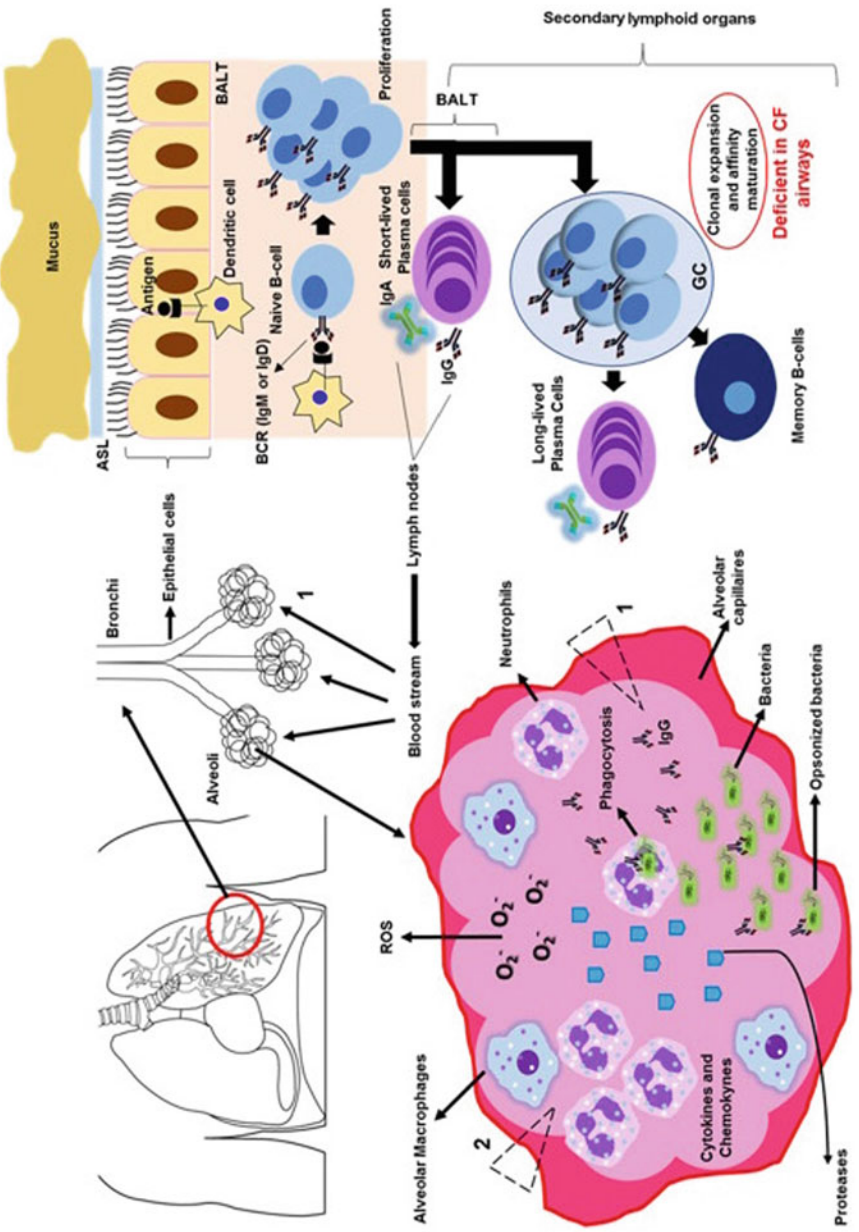


Fig. 1.8 Clonal expansion and affinity maturation of naïve B cells (Reproduced from [10])

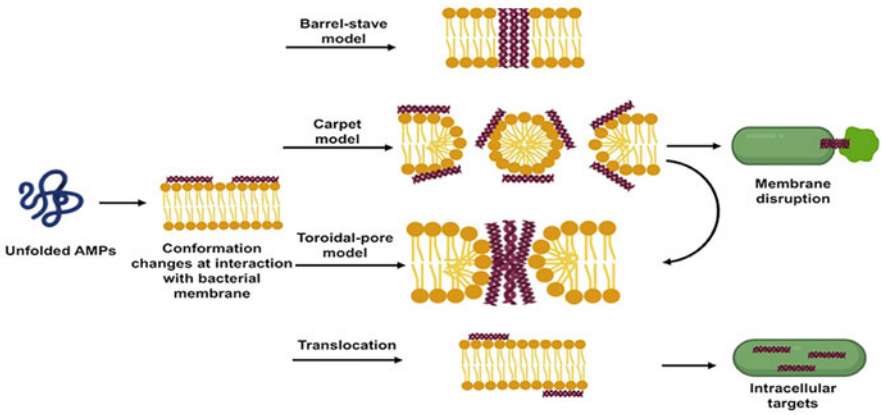


Fig. 1.9 Different models of antibacterial mode of actions of antimicrobial peptides (Reproduced from [12])

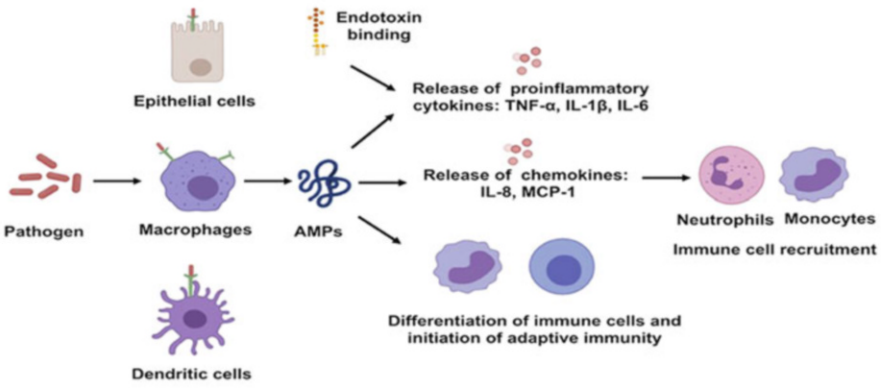


Fig. 1.10 Immune-regulatory functions of antimicrobial peptides (Reproduced from [12]). Abbreviations: AMPs for antimicrobial peptides, IL for interleukin, MCP for monocyte chemoattractant protein, and TNF-a for tumor necrosis factor alfa

immune cells driving the activation of adaptive immune system, as illustrated in Fig. 1.10.

Generally, AMPs are able to kill microbes independently. But many studies have also implicated the use of other AMPs and antimicrobial dugs in combination [12]. There may be concerns in using AMPs as antimicrobial therapy as their half-life may be short and would be subjected to various physio-chemical sensitivity. Thus, *in vivo* studies involving pharmacokinetics, pharmacodynamics, stability of AMPs would provide more data in using them to stimulate immune responses required to target invading pathogens [12].

1.2.9 Influenza A

Influenza A virus (IAV) remains a threat to human and animals with relatively high morbidity and mortality due to their presence of animal reservoirs. High morbidity/mortality in animal hosts may also be due to IAV to undergo point mutations at high frequency [13]. Involvement of the immune system during an IAV infection is a very complex but is a dynamic process. During the first 5 days of IAV infection, the body relies on innate immunity to control viral replication before it damages the respiratory system further. Although, IAV infection can be self-limiting, there has been high morbidity even in otherwise healthy human hosts. The complexity of the innate immune response is summarized in Fig. 1.11 (Reproduced from [13]).

Many AMPs produced at various sites of the body mainly from conjunctiva, nasal, and oral cavities to inhibit IAV at the site of entry. These are like soluble and chemical mediators as well as viral factors which are a part of the innate immunity. For example, β-defensins, surfactant protein D (SP-D) and LL-37, are produced by conjunctival cells and are present in tears [13]. In the saliva, mucin MUC5B, salivary agglutinin, human neutrophil peptides (HNPs), and histatins are produced.

Infection by IAV is initiated when its hemagglutinins attach with sialyl oligosaccharide moieties of cellular glyco-conjugates [13]. Sialic acid-based inhibitors of IAV, such as γ inhibitors have shown inhibitory actions by presenting sialic acid ligands to the viral hemagglutinin (HA), preventing the binding of virus to epithelial cells. Another group of inhibitors, known as β inhibitors such as collectins, SP-D, mannan binding lectin (MBL), H-ficolin, galectin, is calcium-dependent and allows

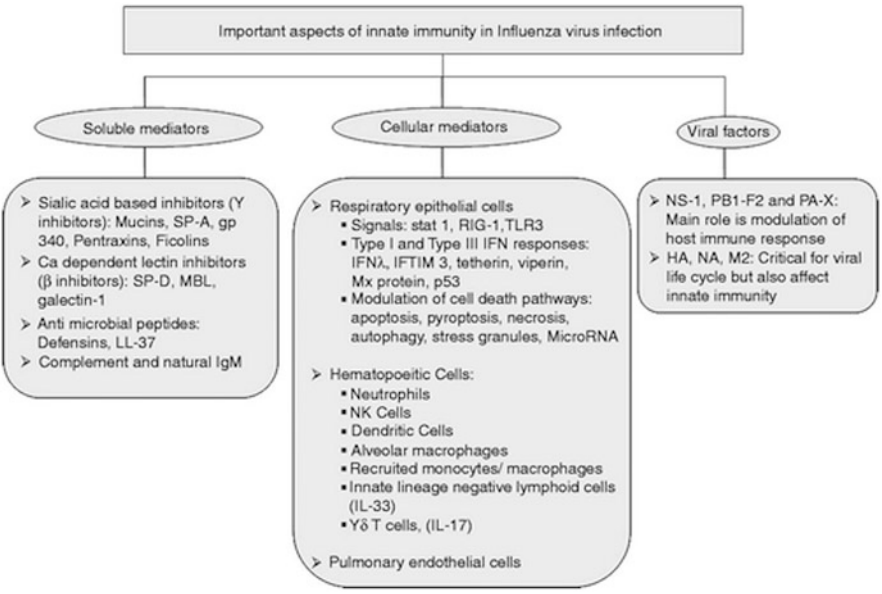


Fig. 1.11 Innate immunity Influenza A virus infection (Reproduced from [13])

binding to carbohydrates on viral proteins [13]. It was also noted that a few of the IAV human strains which have glycans attached to their HA are resistant to inhibition by SP-D or MBL. These strains are like H1N1 of 1918 and 2009, H3N2 of 1968, and H2N2 of 1957 plus H5N1 strains [13]. SP-D expression is a crucial aspect for the host to survive during the IAV infection. Failure to do so was also one of the reasons for fatalities among the IAV-infected patients. Other immunomodulatory functions of SP-D include promotion of viral uptake by phagocytes, down-regulation of chemokine and cytokine, and modulation of lymphocyte activation and dendritic cell (DC) function [13]. H-Ficolin inhibits IAV and fixes the complement during its infectivity. Another group of Gal-binding lectins known as galectins also inhibit infectivity of IAV, the same way as collectins. There is still lack of information on the mechanisms of action of hydrophobic surfactant protein SP-C and surfactant lipids.

Infiltration of neutrophils in the lungs during a viral infection and cytokine storm during a viral infection are caused by Type I interferons (IFN-1). The main IFN-1 during an IAV infection include IFN-α and IFN-β. IFN-1 are produced through TLR7, TLR3, or RIG-I. Moreover, it is known that IAV can be a natural ligand of TLR7 that initiates the TLR7-mediated signal pathway via the recruitment of MyD88 and induce IFN-α/β production by activating IRF3/7 [14]. In the human plasmacytoid dendritic cell (pDC)-like cell line CAL-1 cells, infected with IAV, expression levels of all members in the IRF gene family were altered. The virus was known to regulate IRF expressions through endosomal TLR signals and IFN-I positive-feedback loop [14]. Furthermore, the expression level of IRF6 seems to be related to the severity of influenza virus infection, suggesting that IRF6 may play a negative regulatory role in the IRF family. In this way, it balances the expression profiles of other members in this family.

In a mouse model, transcriptome of more than 16,000 immune cells was sequentially analyzed using a single-cell RNA sequencing (scRNA-seq) assay. They had demonstrated the release of two waves of pro-inflammatory factors in the tissues [4]. On Day 1 and 3, early pro-inflammatory factors were released from C13, C10, and C16 neutrophils. In the C13 neutrophils cluster, high expression of the ligands (IL-1α, IL1-β, and IL-RN) and receptors (IL1R2 and IL1RAP) of IL-1 system were noted. There was a remarkable upregulation of Ccl3 and Ccl4 observed together with high levels of Ccr1, and Cxcl2/Cxcr2 axis. In order to prevent this cytokine storm, regulation of the autocrine loop is a critical point to note. In their study, it was found that high levels of IL-1α and IL-1β were generated by C13/C16-neutrophils, while C13-neutrophils generated only IL-1α on days 1 and 3. On day 7, a second wave of pro-inflammatory factors was generated by C8-Pf4+-macrophages with a high expression of cytokines and chemokines mainly Ccl7, Ccl8, Cxcl2, Ccl2, Ccl6, Ccl9, Ccl12, Cxcl10, TNF-α, Trem2. On the same day, expression of complement C1q was also demonstrated. High expressions of C1qa, C1qb, and C1qc were also detected in C8-Pf4+-macrophages, which could indicate that C8-Pf4+-macrophages assisting T lymphocytes in adaptive immunity [15]. Moderate of monocyte/macro-

phage infiltration and inflammatory factors would favor lung damage repair. However, damage of lungs due to cytokine storm and high C8 Pf4+ monocyte/macrophage infiltration during an uncontrollable cell invasion still remains to be further explored.

Sensing of various viral components using Pattern Recognition Receptors (PRRs) is an important step to stimulate various inflammatory cytokines such as type I interferon (IFN), IL-1β, IL-6, and TNF-α. PRRs such as Toll-Like Receptor (TLR)-3, TLR7/8 are used to detect dsRNA and ssRNA, respectively, whereas cytosolic RIG-I and NLRP3 are used to detect ssRNA. This will then lead to stimulation of three subsets of dendritic cells (DCs) that will activate the adaptive immune system for viral clearing and inducing antibody production [16]. There were a few reported evidences from other studies, i.e. clearance of the viruses from infected cells greatly required the virus-specific adaptive immune responses, which involved antibodies, CD4+T, and CD8+T cells [17]; first viral specific proteins which are bound to MHC complex molecules are recognized using the host's T Cell Receptor (TCR), which is a pre-requisite for the cytotoxicity of Cytotoxic T lymphocytes (CTL) and production of cytokines. The cytotoxicity of CTL is mediated via three mechanisms, mainly via i) perforin/granzyme-mediated cytolysis, ii) apoptosis mediated by FasL/Fas, and iii) TRAIL/TRAIL-DR signaling. Engagement of these ligands, i.e. FasL and TRAIL with their cognate receptors initiates an apoptotic signaling cascade [16]. Fig. 1.12 shows the regulation of CTL magnitude and the effector activity. In the CTL effector mechanism, when viral peptide is presented by MHCI molecules on the surface of infected cells, CTL targets IAV-infected airway in the epithelial cells, leading to the mechanisms stated above. CTLs also can produce cytokines and chemokines such as IFN-γ, TNF-α, IL-2, CCL3, CCL4, etc., to further enhance inflammation and immune activation in the infected lung. Regulatory mechanisms through costimulatory (upper) or coinhibitory (lower) signals provided in the lung draining LNs or the infected lung control the magnitude of the effector activity as well.

Immunity to IAV infections depends on the speed of viral replication. Pre-existing CD8+ and/or CD4+ T cells can still provide protection in mild or asymptomatic seasonal influenza, where innate immunity provides the first line of defense and slows down viral replication, then activates the adaptive immune system to continue with the viral clearance. In a more severe form of infection, the actions of innate immunity may be inhibited and interfere with the adaptive immune response, leading to a cytokine storm [18]. A defective immune system would not be able to provide protection to patients quick enough to prevent detrimental effects of IAV. Therefore, there is a suggestion to recruit naïve $CD8^+$ T cell precursors, instead of only the memory $CD8^+$ T cells into the primary influenza response. This would

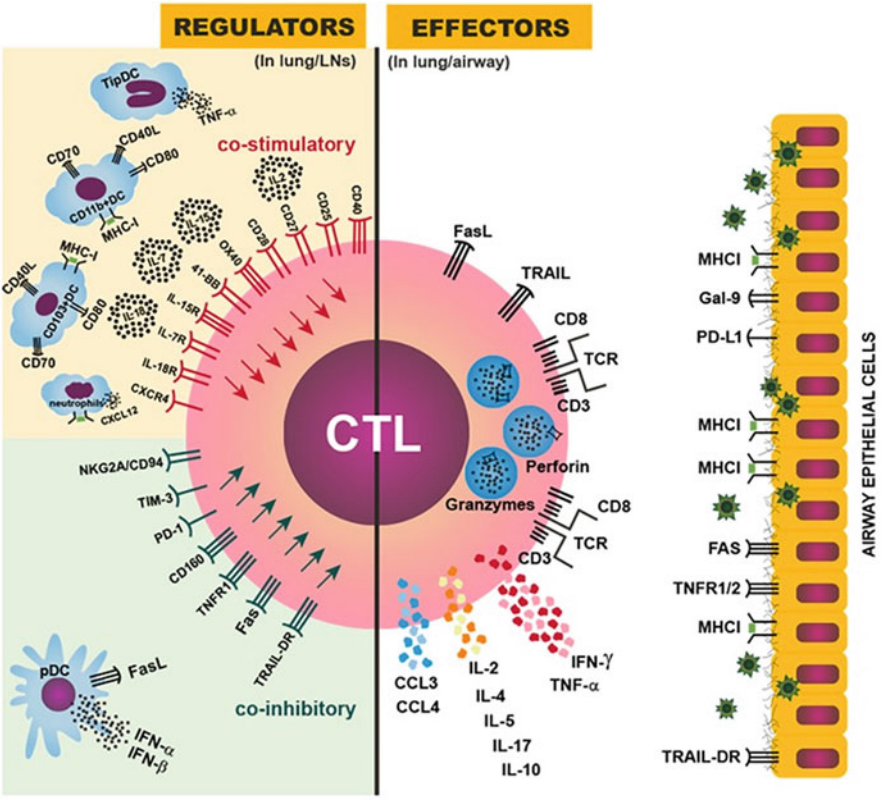


Fig. 1.12 Regulation of CTL magnitude and effector activity (Reproduced from [16])

establish robust memory pools in order to prevent a suppressed innate immune function, with an immediate adaptive immune response [18].

1.2.10 Tuberculosis

It is estimated that 10 million people were infected with tuberculosis (TB) worldwide in 2019, fell ill from the infection, and caused deaths to 1.4 million people (including 208 000 people with HIV). TB is one of the top 10 causes of death worldwide and the leading cause from a single infectious agent (above HIV/AIDS) [19]. TB is caused by *Mycobacterium tuberculosis* (Mtb) that most often affects the lungs. Upon inhalation and reaching the alveoli, the Mtb multiplies in the pulmonary epithelium or macrophages. In macrophage, bacterial sulfolipids will inhibit fusion between phagocyte and lysosomes, making it difficult to digest the bacilli. This will allow

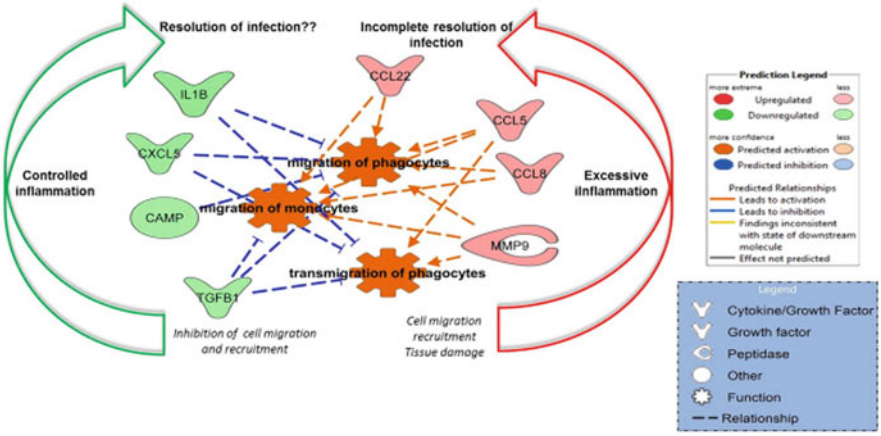


Fig. 1.13 Host inflammatory response in alveolar macrophages from tuberculosis patients. (Reproduced from [22])

bacilli to spread to distant sites and remain viable, even for decades. This is a trait of Mtb which can survive and grow within the host cells [20].

Protective immunity of dendritic cells (DCs) has not been studied extensively even though they have been recognized as an efficient antigen presenting cells to initiate the adaptive immunity [21]. There are two main types of DCs, i.e. plasmacytoid DCs (pDCs) and myeloid DCs (mDCs) which is also known as classical DCs (cDCs). The pDCs produce type I interferons (IFN-α and IFN-β), whereas mDCs prime T cells [21]. The mDCs can also be divided into CD1c and CD 141+. Immune responses to bacterial infections are induced by Th1, Tc1, and Th17 driven via CD1c [21], whereas CD141+ cross presents antigens on MHC I molecules and induces CD8+ T cell responses [21]. Alveolar macrophages (AMs) are important in active TB infections, as Mtb thrives in them. In a study conducted by Lavalett et al. [22], to identify the host inflammatory response in AMs from TB patients (AMsTB), an array of genes was regulated showing the involvement of immune response in resolving the infection. Fig. 1.13 summarizes the immune responses in AMsTB infection in the host. In response to an infection, AMsTB genes, such as MMP9, CCL8, CCL5, and CCL22 were upregulated, which activate the functions of macrophages in cell migration and recruitment. These mechanisms would resolve the infection. On the contrary, effector recruitment would not only clear the pathogens but may lead to tissue damage and cause infection to persist. So, in the situation to control the excessive inflammation, AMsTB down-regulate pro-inflammatory genes (IL1B, CXCL5, CAMP, and TGFB1) to increase anti-inflammatory signaling. As a result of this, effector mechanisms are altered to control the infection.

In another study, monocyte derived DCs were reported to be detected in inflammatory fluids, and the CD14 and CD11b subsets induced Th17 cell differentiation from naive CD4+ T cells [21]. In a study conducted in patients with active TB, their tuberculous pleural effusions detected significant increase of CD11b+ subset of CD1c+ DCs [21]. This subset also expressed higher transcripts of pro-inflammatory cytokines, including IL-1β, IL-6, IL-23, and TGF-β, which were required for the development of Th17 cells.

Tumor necrosis factor (TNF)-α, a pro-inflammatory factor, produced by a variety of immune cells controls intracellular growth of Mtb within phagocytes [23]. TNF-α is key in the immuno-pathological response of TB. TNF-α can promote granuloma formation, envelop tubercle bacillus, inhibit Mtb infection, and accelerate bone destruction [24]. In China, a chronic inflammatory TB known as osteoarticular tuberculosis has become a serious threat. A study by Liu et al. [24] was conducted to assess the involvement of TNF-α in the pathogenesis of osteoarticular tuberculosis. Their study showed that TNF-α promoted the autophagy of mature osteoclasts infected with Mtb and inhibited the apoptosis of the mature osteoclasts. This demonstrated that there is an osteoarticular tuberculosis activated cytokine network through which autophagy may regulate bone metabolism. This finding is an important foundation for drug discovery using mechanisms related to TNF-α-mediated osteoclast autophagy.

A specialized subpopulation of T cells known as Treg act to suppress immune system in terms of inhibiting T cell proliferation and cytokine production. In a study involving multidrug-resistant pulmonary tuberculosis, the role of Foxp3-expressing regulatory T cells (Treg) and T helpers in immuno-pathogenesis was demonstrated [25]. Mononuclear cells of peripheral blood from 115 patients with advanced destructive forms of pulmonary tuberculosis were taken. These patients were categorized into infiltrative pulmonary tuberculosis (ITB), disseminated pulmonary tuberculosis (DTB), and fibrous-cavernous pulmonary tuberculosis (FCTB). Their results showed that there is an increase in the number of CD4+CD25+Foxp3+ Treg in all TB patients, regardless of their clinical form. However, the number of CD25-negative Treg cells, containing the Foxp3 molecule, rose only in fibrous-cavernous pulmonary tuberculosis patients [25]. It was hypothesized that that the decrease in Treg phenotype CD4+CD25+Foxp3- in the blood of FCTB patients is determined by the deficiency of activated T helpers. Later, they had concluded that patients with DTB and FCTB led to a compromised cell mediated protective immunity due to the reduced number of T helper cells.

With a stimulation by mycobacterial antigens, IL-1 and TNF-α, monocytes and alveolar macrophages, prostaglandins E (PG) will be produced, which is mediated by the cyclo-oxygenases (COX) pathway as reported by a few studies previously [26–28]. In a study to analyze the kinetics of COX expression and PGE2 production in BALB/c mice for pulmonary tuberculosis, the production of PGE2 and COX expression was gradually increased during the course of infection [29]. There was a stable concentration of PGE2 and control of infection during the early phase of infection, which contributed to an efficient nitric oxide synthase (iNOS) expression. Whereas, in the late phase of infection, there was a heightened level of PGE2. This

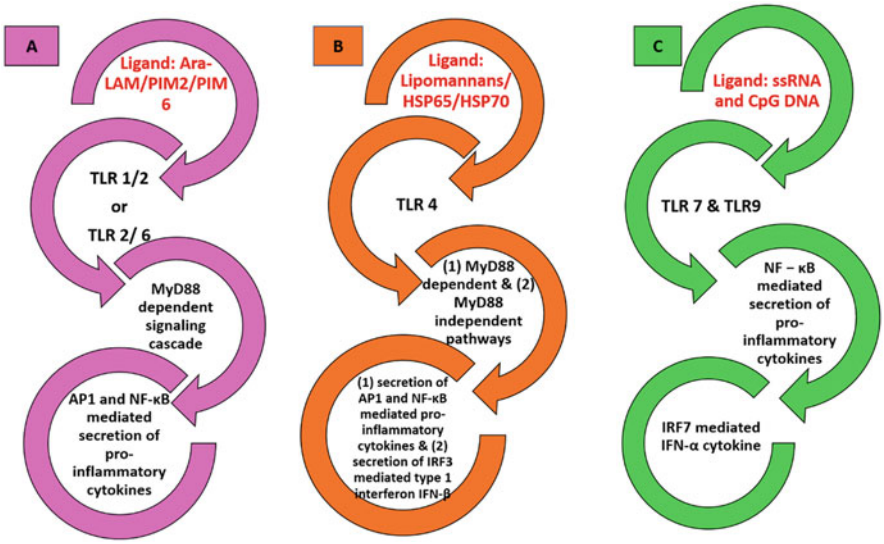


Fig. 1.14 PRR signaling pathways activated during *M. tuberculosis* infection stimulated by different ligands (A) Ara-LAM [Arabinosylated lipoarabinomannan], PIM-2/6 [Phosphatidyl-myo-inositol mannoside]; (B) Lipomannans and HSP-65/70 [Heat shock protein] and (C) ss RNA and CpG DNA

had led to disease progression which was due to down-regulation of the cell-mediated immunity [29]. Therefore, the level of PGE2 most likely affected the severity of TB.

Most soluble and cell mediated immune processes are driven by the stimulation of many pattern recognition receptors (PRRs). These are critical for innate and adaptive immunity and successful protection against TB. Illustration in Fig. 1.14 provides an insight on signaling pathways initiated by the PRRs binding to different ligands of Mycobacteria [30].

Cytosolic receptor was also reported by some groups on its importance in stimulating innate and adaptive immune responses. A homozygous mutation in Nucleotide-binding oligomerization domain-containing protein 2 (NOD2) suggests a defective cytokine response with Mtb [30]. An induction of autophagy was reported to stimulate T cell activation during *M. tuberculosis* and other viral infections [31]. It was also noted from several studies that TLR2 and NOD2 work together to induce cytokine response. In these aspects, the ligand Muramyl dipeptide (MDP) of Mtb targeted by NOD2 receptor triggers the Receptor-interacting *serine/threonine-protein kinase* 2 (RIPK2) and Caspase recruitment domain-containing protein 9 (CARD9) signaling. Whereas DNA-sensing receptor cyclic GMP–AMP synthase (cGAS) and its downstream signaling effector stimulator of interferon genes (STING) target cytosolic DNA and stimulate IRF3 mediated IFN-β secretion [30]. Another pathway activated by cytosolic DNA of Mtb is via inflammasomes

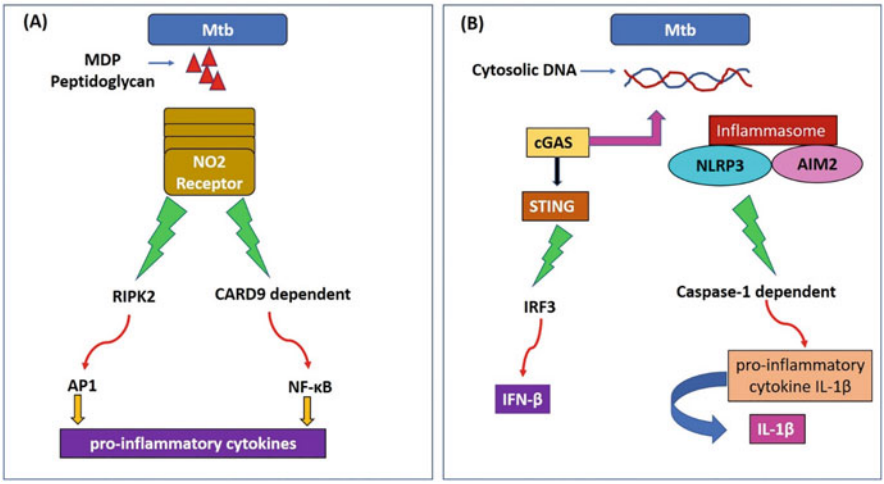


Fig. 1.15 Signaling pathways of NOD2, cGAS/STING, and inflammasome during *M. tuberculosis* infection

with NLRP3 (a subset of NOD) and AIM2 (absent in melanoma 2 or Interferon-inducible protein) triggering caspase-1 dependent signaling [30]. The signaling pathways of NOD2, cGAS/STING, and inflammasome are summarized in Fig. 1.15.

The glycolipid most abundantly found in mycobacterial cell wall, i.e. trehalose-6,6′-dimycolate (TDM) ligates with Mincle, a C-type lectin receptor (CLR) [30]. In a murine model infected with TB, signaling through Mincle resulted in the production of several cytokines such as IL-6, macrophage inflammatory protein-2 (MIP-2), and TNF-α [30]. Another CLR known as dectin-1 activates macrophage's pro-inflammatory response together with TLR2 [32]. However, the exact roles of this receptor require further studies. Other receptors such as Collectin CL-LK recognize mannose-capped lipoarabinomannan of *M. tuberculosis* [33] and Dendritic Cell Immuno Receptor (DCIR) which modulates immunity to TB by sustaining type I IFN signaling [30].

Although there are many PRRs to target mycobacterial pathogen associated molecular patterns (PAMPs), successful evasion of host immune system by mycobacteria to avoid its recognition by PRR was the reason for unresolved infections. This could be done via inhibition of TLR2 signaling via specific lipoproteins of mycobacteria, which then inhibits the antigen presentation cell and T cell activation [30]. Another strategy is to interfere with other PRR signaling pathways and inhibit phagosome maturation as reported by Kang et al. [34], Mishra et al. [30].

1.3 Immuno-pathogenesis of Chronic Respiratory Diseases

1.3.1 Asthma

Asthma is a chronic non-infectious inflammatory disorder of the airways. Understanding immuno-pathological features of asthma is key for the diagnosis, treatment, and prevention of the disease. Traditionally asthma is a disease restricted to the lung, recent data suggest it part of systemic airway disorder involving the entire respiratory system with systemic immune response. Evidence for this is co-occurrence of other atopic disorders (such as allergic rhinitis) in patients of asthma [35]. Worldwide asthma is ranked 16th among the leading causes of morbidity. It is estimated by 2025, it is going to affect around 400 million population worldwide [36].

Asthma is a chronic disease characterized by recurrent episodes of wheezing, dyspnea, chest tightness, and coughing. It varies in severity and frequency from individual to individual [35]. These clinical manifestations of asthma are associated with underlying pathological response in the respiratory system. The responses include inflammation in airway, obstruction of airway, and hyperresponsiveness of airway [37]. Inflammation may result in various pathological changes in the airway, including excess mucus secretion, inflammatory cells infiltrate, subepithelial fibrosis, neo angiogenesis, and excess proliferation of smooth muscle [38]. Hence, airway inflammation plays a key role in immuno-pathogenesis of asthma and clear understanding of this is the key for prevention and management of this condition.

Airway inflammation in asthma involves a sophisticated complex interaction of the respiratory epithelium, innate immunity, and adaptive immunity that induce and progress a chronic inflammation. (Fig. 1.16). Critical to this phenomenon is interplay

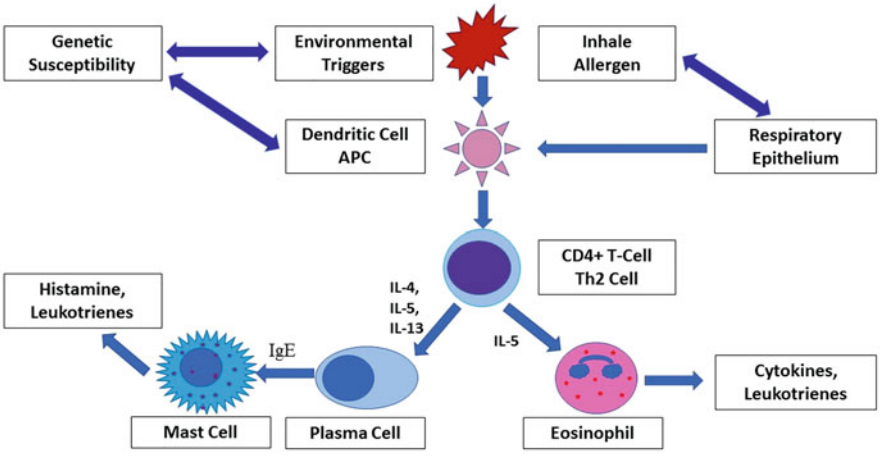


Fig. 1.16 Pathogenesis of a classical atopic asthma with interaction between the respiratory epithelium, leukocytes, and its chemical mediators

of genetic and environment factors. This results in an abnormal immune response to various environmental triggers in a genetically susceptible person [38].

The trigger for these pathological responses in the risk individuals is due to exaggerated response of the airways to a variety of stimuli. These stimuli that trigger asthma in patients would have little or no effect in those with normal airways. Stimuli which triggers asthma can be categories either atopic (with evidence of allergen sensitization) or non-atopic (without evidence of allergen sensitization). The most common stimuli which trigger atopic asthma include pollens, animal dander, house dust mites, cockroach remainders, and mould. Whereas stimuli which trigger non-atopic asthma commonly include viral infections, exposure to tobacco smoke, cold air, and exercise. Exposure to these stimuli leads to series of events that causes chronic airway inflammation and other pathological changes [35].

Formerly it was believed that respiratory epithelium mainly acts as a mechanical barrier along with gas exchange medium. Recent data showed that it plays a critical role in airway inflammation. Respiratory epithelium is a key component of the local innate immunity in the respiratory system and has capacity to produce various chemical mediators which can initiate and drive various component of the immune response. Various triggers can stimulate an inflammatory response from respiratory epithelium (mentioned above in stimuli) leads to secretion of cytokines and chemokines that stimulate leukocytes and enhance the development of an innate and adaptive immune response [38].

In the immuno-pathogenesis of asthma, various cells of immune system are involved. Mainly CD4+ T lymphocytes (T helper cell type-2 (Th2) and type-1 (Th1)) eosinophils, neutrophils, and mast cells [39]. Understanding of the immunologic mechanism of asthma has evolved over the period. Initially it was thought that mast cells and eosinophils play a central role in the process of inflammation in the airway. Recent evidence showed that Th2 helper cells plays the key role in the process of inflammation in the airway [40]. Now asthma is believed to be a Th2 cell response initiated with IgE-mediated sensitization to a variety of stimuli. This will be further progressed by eosinophils predominated inflammation and hyperresponsiveness of airway [40].

In a classical atopic asthma, the initial immunological trigger to the development of airway inflammation is exposure to inhale allergen (e.g., pollens). It may be cleared by respiratory mucociliary transport system avoiding immunologic response completely. In genetically susceptible individuals, the relative overexpression of Th2 cells as compared to Th1 cells is due to the combination of genetic and environmental factors (which are major etiologies in allergic asthma). Dendritic cells process it and present it to T lymphocytes and led to activation of a type of CD4+ T cell, T helper cell type-2 (Th2 cells) [40]. At this point activation of T helper cell type-1 may protect against asthma, since Th1 cells antagonize the functions of Th2 cells. In genetically susceptible individuals, the relative overexpression of Th2 cells as compared to Th1 cells is due to the combination of genetic and environmental factors (which are major etiologies in allergic asthma) [40]. Recent evidence showed that, another class of T helper cell (Th17 cell) has important role in airway inflammation in asthma. It secretes IL17 which enhances Th2 mediated eosinophilic inflammation and promotes neutrophilic infiltration [38].

Specific cytokines are released in the airways by increased number of Th2 cells. This includes various interleukin (such as IL-4, IL-5, IL-9, and IL-13). Release of these cytokines led to several key responses. One of the key responses is increase in activity of eosinophil by IL-5, which then are responsible for release of pro-inflammatory cytokines and leukotrienes [35]. Another key response of activated Th2 cells is stimulation of plasma cell, which is mediated by IL-4, IL-5, and IL-13. These plasma cells then release immunoglobulin E (IgE). Further, IgE activates mast cells to release various chemical mediators, including histamine and cysteinyl leukotrienes. Pathophysiological effect of these chemical mediators ends in classical morphological changes of asthma in airways which includes edema of the wall, mucus hypersecretion, bronchoconstriction, and others [35].

It is observed that, Th2 cells play a precise and critical role in occurrence of acute and less severe form of asthma. But in chronic and severe cases, additionally Th1 cells also has a role in immuno-pathogenesis, which is by releasing chemical mediators like tumor necrosis factor-α and interferon-γ. This complex T lymphocytes profiling can explain the excess tissue damage and other complications in immuno-pathogenesis of severe form of asthma. More detailed studies are needed to understand the exact mechanism by which the complex phenomenon of T-cell immune response in asthma is regulated. This may help in precise management and prevention of complication in asthma. Also, there is need to re-evaluate the precise and critical role of eosinophil in immuno-pathogenesis of asthma, as it is the one of prominent pathological finding in blood and tissue of asthma patients. Precise understanding of these immune-pathological mechanism and its inflammatory mediators' response is critical in planning the specific and individualized treatment and favorable outcome of disease in asthma patient [41].

1.3.2 Chronic Obstructive Pulmonary Disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a chronic progressive disease of the lungs, which may have substantial extrapulmonary effects that will have impact on severity of the disease process in the patient [42]. Immuno-pathological features of COPD have implications for the diagnosis, management, and potential prevention of the disease. COPD is a major non-communicable disease caused by tobacco smoking. COPD is projected to be the 3rd leading cause of death by end of 2020. COPD is characterized by irreversible chronic airflow limitation that is usually progressive and associated with chronic inflammation in the airways and and/or alveoli of lung to noxious particles or gases [43].

In COPD, the distinctive chronic airflow limitation is due to varying combination of small airways disease (Bronchiolitis-chronic bronchitis) and alveolar destruction (emphysema). These pathological changes do not occur always simultaneously but advances at different pace over time. Clinically, COPD can be categorized into 2 overlapping conditions: emphysema and chronic bronchitis [43]. Tobacco and its products smoking are the major risk factor for COPD. Globally, around one in three patients of COPD is considered to be non-smokers. Other key environmental risk

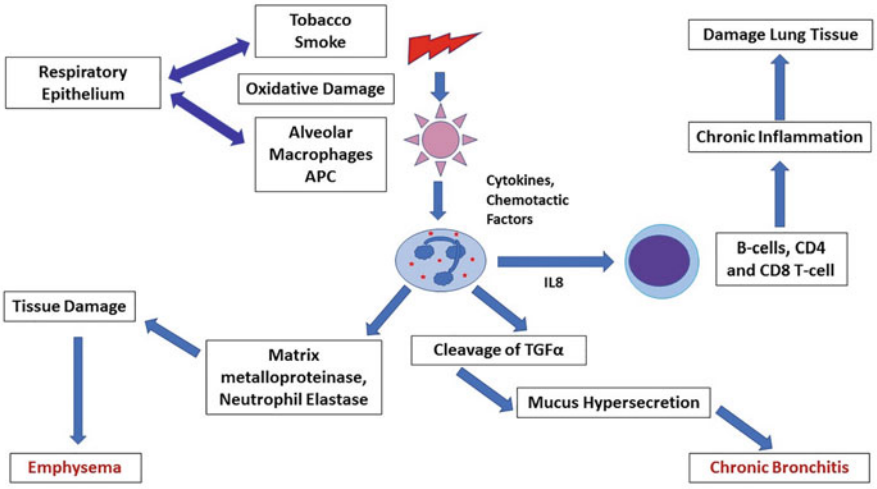


Fig. 1.17 Immuno-pathogenesis of COPD in smokers, with interaction between the respiratory epithelium, leukocytes, and its chemical mediators

factor for COPD includes pollutants from biomass fuel used for cooking and heating, industrial smoke, dust from grain, cotton, and silica. Key genetic risk factor associated with COPD is alpha1-antitrypsin deficiency, but there are possibly other genetic loci associated with this condition [44].

In this condition, exposure to various environmental risk factor (mainly tobacco smoke) results in major immune response leading to chronic inflammation and remodeling in the large and small airways (mainly), and the destruction of lung alveoli. In COPD it is understood to have two immune response phases (Fig. 1.17). Initially innate immune response, in which inhalation of various risk factor initiates inflammation. Followed by acquired immune response, in which enhance inflammation leads to various clinical outcomes [45]. In innate immune response, inhalation of tobacco smoke introduces various active compounds in the lungs. These active compounds stimulate the cells of innate immunity such as alveolar macrophages, dendritic cells, and lung epithelial cells. In response, the stimulated immune cells secrete numerous chemotactic factors (such as IL 8, GRO-α) that recruit inflammatory cells like neutrophils and macrophages to the lung tissue [45].

In acquired immune response, apart from the role of neutrophils and macrophages, there is also recruitment and activation of other immune cells like B-lymphocytes, T lymphocytes (cytotoxic T cells), and natural killer cells. Small airways are the prime area for these events. At this point, the outcome of disease depends upon the intensity of inflammatory response [45]. During this process of acquired immune response, neutrophils and macrophages release various proteolytic enzymes and oxidants which includes matrix metalloproteinase and neutrophil elastase. These active chemical mediators cause lysis of elastin and collagen in lung connective matrix resulting in tissue damage. They also produce various

cytokines and chemokines capable of further intensifying the inflammatory response process. Neutrophil elastase causes enzymatic degradation of transforming growth factor α (TGFα) which in turns excites the mucus secreting glands resulting in excess mucus secretion and mucociliary dysfunction. Granzyme B and Perforin produced by cytotoxic T cells and natural killer cells will also cause damage to lung tissue [45].

Naturally occurring Alpha1-antitrypsin is inhibitor of neutrophil elastase and hence safeguard the lung tissue from damaging effect of neutrophil elastase. Congenital or acquired Alpha1-antitrypsin deficiency (proteinase/anti-proteinase imbalance) leads destruction of lung elastin and connective tissue matrix, results in prominent emphysematous changes in COPD lungs. Similar changes are also seen with inactivation of anti-proteinases such as α-1-proteinase-inhibitor (α-1-PI) and anti-leukoprotease by oxidants from tobacco smoke [45, 46].

It is noticed that in COPD patients, even after cessation of tobacco smoking, chronic inflammation persists. Initial chronic inflammation of smoking related injury may cause a defective immune system. This defective immune response causes persistent low-grade infections, which in turn causes inflammation in the airways causing persistent COPD. It is also explained by cumulative DNA damage. Serious DNA damage such as breaks in the double strands can be caused by reactive oxygen species (ROS) and reactive nitrogen species (RNS) produced by inflammatory cells [45].

To conclude, in COPD associated chronic inflammation caused spectrum of overlapping morphological changes in the lung tissue. These morphological changes are due to various activated immune cells and its released chemical mediators. One side of COPD spectrum is emphysematous changes in lung tissue, in which activated immune cells releases destructive enzymes like neutrophilic elastase and matrix metalloproteinases. These enzymes cause destruction of connective tissue framework in lung mainly in the distal airspaces leading to defective elastic recoiling. Here the predominant morphological changes include permanent abnormal enlargement of airspaces with air trapping and airway collapse. Clinically these patients mainly present with breathlessness, barrel chest, and reduced expiratory flow rates. On other side COPD spectrum is the predominant clinical presentation of chronic bronchitis. Here chronic immune response results in morphological changes mainly in proximal large airways. This includes excess inflammatory cell infiltrate mainly lymphocytes, enlarged mucus secreting glands, increase in number of goblet cell and defective mucociliary function. Also observed chronic inflammatory changes in distal small airways which are considered to be main cause of airflow resistance. Morphological changes that can be observed in small airways include hypertrophy of submucosal smooth muscles with fibrosis and hypersecretion of mucus [45, 47].

1.3.3 Idiopathic Pulmonary Fibrosis (IPF)

The characteristic feature of this chronic lung disease is a slow and progressive deposition of fibrotic tissue in the lung parenchyma, leading to significant morbidity and poor outcome [48]. There is a progressive fibrosis takes a considerable time to develop and produce symptoms. At diagnosis, the lung tissue exhibits alveolar epithelial damage, type 2 epithelial cells (AEC2s) hyperplasia, marked fibrosis, abnormal proliferating mesenchymal cells [48]. There are several factors related to an increased risk of IPF. They include cigarette smoking [48], gastro-esophageal reflux, exposure to metal dust, microbes such as viruses, fungi, and bacteria [48], genetic factors, epigenetic alterations (particularly associated with cigarette smoking and aging), cellular, tissue, and age-related changes that seem to exert a major influence in IPF [48].

Apart from various risk factors and genetic susceptibility playing their role, the pathogenesis of continued development and progression of the fibrotic process in the lung is attributed to recurring minor injury of the alveolar epithelial cells and abnormality in the process of repair → aberrant behaviors of various pulmonary cells →promote the disease process. Due to persistence of injury and impairment of the ability to restore tissue integrity, the process of wound healing goes through a phase of inflammation, laden with high levels of interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α), thus tilting the balance to chronic impairment of regeneration and tissue remodeling [48].

Neutrophils and monocytes accumulate and produce reactive oxygen species (ROS) at the site of persistent injury → worsening the epithelial cell damage → imbalance between oxidants and antioxidants → triggers apoptosis and activation of dysfunctional pathways of tissue repair. The recruited monocytes and macrophages produce a strong pro-fibrotic mediator, platelet derived growth factor (PDGF); in addition, CC chemokine ligand2 (CCL2) and the macrophage-colony stimulating factor (M-CSF) may exert direct pro-fibrotic effects [48]. The working model regarding pathogenesis of interstitial lung diseases stated that inflammation played a major role leading to fibrosis in IPF. This view had been indirectly supported by retrospective case studies. However, based on the poor outcome of IPF patients treated with anti-inflammatory and immunosuppressive therapy has diverted the focus from inflammation playing the central role. Subsequent research has led to a model of injury and inflammatory response followed by aberrant wound repair (Fig. 1.18).

The cells involved in innate and adaptive immune responses influence the (myo) fibroblast biology, synthesis, and accumulation of fibrous tissue (Fig. 1.19).

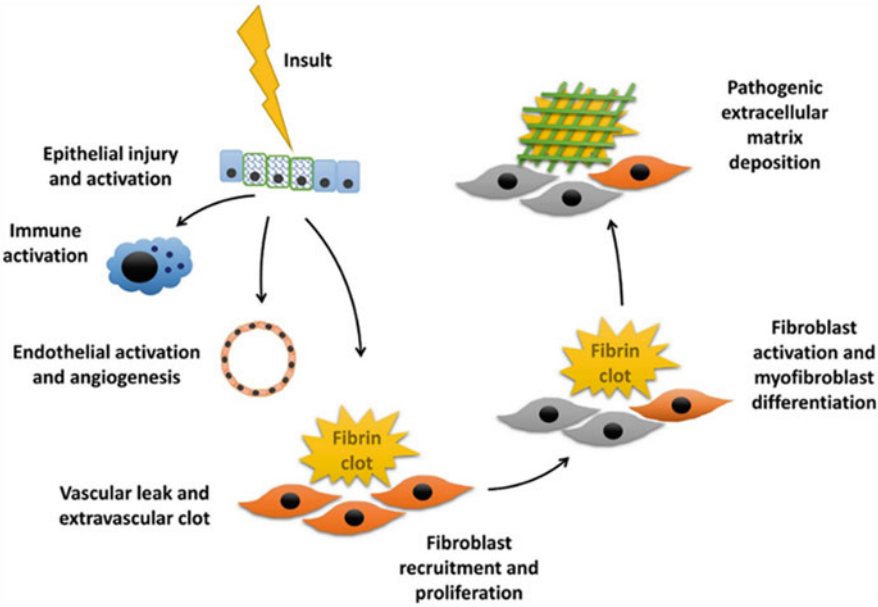


Fig. 1.18 Schematic diagram of sequence of pro-fibrotic processes implicated in IPF pathogenesis (Reproduced from [49])

1.3.4 Role of Immune Cells in Pathogenesis of IPF

1.3.4.1 Th-1, Th-2, Th-17 T Cells, and Tregs

The balance betweenTh1/Th2 is disturbed during the inflammatory phase of pulmonary fibrosis [51]. The Th1 cytokines, IFN-γ and IL-12, reduce/arrest fibrosis [51], while the secretion of IL-1α, TNF-α, PDGF, and TGF-β1 → overall pro-fibrotic effect [48]. The Th2 cytokines, IL-4, IL-5, IL-13, have been associated with accumulation of fibrous tissue [51]. Th2 subset produce IL-4. IL-4 →production of IL-5, IL-13, and TGF-β1, infiltration of macrophages, mast cells, eosinophils, and mesenchymal cells → Have a direct effect on fibroblast activation. Hence, Th1 and Th2 responses promote the process of fibrosis [51].

The Th2 cytokines, IL-4 and IL-13, induce M2 macrophages → Production of IL-10, arginase-1, and CC chemokine ligand (CCL) 17 and CCL18 [51]. On the other hand, M2 macrophages have been linked to antifibrotic activities by employing matrix metalloproteinase-10 (MMP-10) → ECM breakdown [51]. Therefore, the precise roles of M1/M2 macrophage phenotypes in fibrogenesis remain ambiguous and controversial. The Th2 cytokine, IL-13, is elevated in the blood and bronchoalveolar lavage (BAL) fluid of the patients and the levels correlate with the severity of illness. IL-13 differentiates human lung fibroblast to myofibroblast.

Th17 cells → IL-17 release → IL-17-induced pulmonary fibrosis indirectly [51] by increasing TGF-β1 levels, thus creating a positive-feedback loop [48, 51].

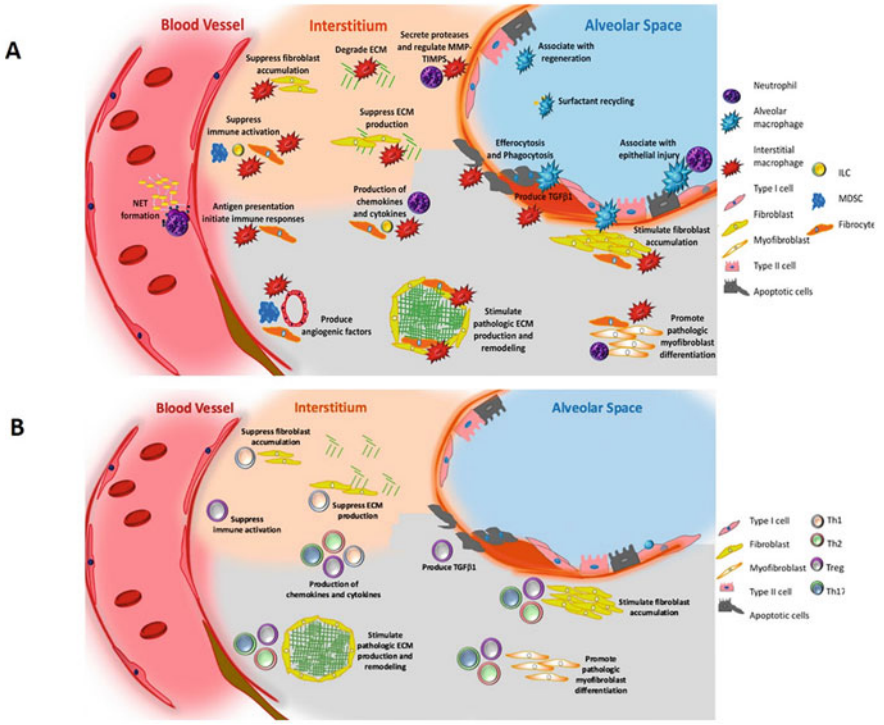


Fig. 1.19 The role of immunity and immune cells in Idiopathic Pulmonary Fibrosis (Reproduced from [50])

It has been found that the number of CD4+ CD25+ FOXP3+ regulatory T cells (Tregs) is reduced in both BAL and peripheral blood of IPF patients, when compared to healthy individuals and patients suffering from other lung diseases.

Quantitative and qualitative defects of Tregs might be responsible during the initial phases and progression of IPF [51].

1.3.4.2 Alveolar Macrophages

They synthesize and secrete the cytokines TGF-β1 and PDGF that favor fibrosis, chemokines, and proteases such as MMPs [51]. However, the studies have shown that alveolar macrophages are capable of having both pro-fibrotic and antifibrotic effects [51]. These opposing effects are acquired through the sub-classes of macrophages designated as M1 and M2 that are classically activated and alternatively activated, respectively.

1.3.4.3 Neutrophils

Bronchoalveolar lavage (BAL) from patients with IPF demonstrated increased number of neutrophils (Kinder et al. 2008; [51]), and this finding is considered an important guideline for marking an injury to the alveolar epithelial cells. It is observed that Cytokeratin 19 estimates correspond well with neutrophilic content in BAL fluid of these patients. These neutrophils are activated → secrete the enzyme neutrophil elastase (NE), found to be elevated in BAL fluid of IPF cases.

NE → extracellular matrix (ECM) proteins breakdown (collagens (types I–IV), laminin, entactin, fibronectin, and elastin) → pulmonary fibrosis. Studies have shown that NE also causes fibroblast proliferation and myofibroblast differentiation.

Neutrophils produce serine proteases, MMP-2, MMP-8 (collagenase 2), and MMP-9 (gelatinase B), implicated in promotion of fibrosis of the lung parenchyma. The degree of an equilibrium between MMPs and their antiproteases (TIMPs) determine the tilt of this equation either in favor of accumulation or degradation of ECM components [51].

1.3.4.4 Fibrocytes

These are circulating myeloid-derived cells that have the potential to enter tissues and transform into fibroblasts and myofibroblasts. Moreover, CCL12 and CXCL12 have been implicated in attracting circulatory fibrocytes to the site of injury. Fibrocytes secrete several chemical mediators that activate native fibroblasts to proliferate and synthesize collagen. An elevated level of circulating fibrocytes could be used as a predictor of prognosis in IPF [51].

1.3.5 Role of Chemical Mediators in Pathogenesis of IPF

TGF-β1 is primarily involved in pulmonary fibrosis [51]. After dissociation from latency-associated protein, it promotes transcription of associated genes. There is increased ECM deposition, particularly of collagen and fibronectin. Fibroblasts transform into myofibroblasts and express (SMAD, SMA/MAD homology) α-SMA. It also exerts mitogenic effect on fibroblasts via enhancement of vascular cell adhesion molecule 1.

Platelet derived growth factor (PDGF) is another potent mitogen and fibrogenic cytokine/growth factor that acts through the PDGF receptor α → chemoattractant and fibroblast activation → pulmonary fibrosis [51]. The expression of PDGF is increased in macrophages and epithelium of the lungs.

IL-1β: It is a product of dendritic cells, epithelial cells, activated macrophages, and neutrophils and has a significant influence in progressive deposition of fibrous tissue in the lung tissue. [51]

CCL2: Also known as monocyte chemoattractant protein-1, is secreted by the alveolar epithelium, fibroblasts, monocytes, macrophages, and acts via interaction with CCR2 [51]. CCL2-enhanced chemotaxis of Fibrocytes, their transformation into fibroblasts → advancement of collagen synthesis and deposition. Likewise, CCL17, CCL18, and CCl12 have been found to promote pulmonary fibrosis.

1.3.6 Suggestions for Further Research

1. Infections with cytomegalovirus, Epstein–Barr-virus, human herpesvirus-8, and hepatitis C virus are considered as risk factors for IPF, however, need to be studied further since the studies have shown conflict in results.
2. Studies have suggested that analyzing the composition of lung microbiome might prove vital to gain deeper knowledge about the progression of ongoing fibrosis and that it could be used as a prognostic tool. However, more data is needed through future research on this aspect.
3. An increasing evidence suggests an elevated count of fibrocytes in the blood during an acute relapse, which declines after the hyper-acute phase is over. Further studies about their role could be beneficial in utilizing the information in predicting the course of disease.
4. New studies aimed to analyze the influence of inflammation in the pathophysiology of IPF should be done, because their results may guide us to understand the events during the early stages and the mechanisms of disease progression.
5. Epithelial–mesenchymal transition (EMT): This phenomenon has been observed in several studies. It involves the epithelial cells losing their cell-to-cell adhesion, acquiring the potential of migration and mesenchymal transformation, enhancement of their potential to convert to fibroblasts and myofibroblasts leading to deposition of ECM components. However, other studies have shown no findings suggestive of this transition in fibrotic settings. Therefore, further research studies are required to resolve such conflicts.
6. Despite several studies done on the role of macrophages and their products in pulmonary fibrosis. It is still difficult to clearly define the impact of M1 and M2 subtypes.

1.3.7 Pulmonary Hypertension

Pulmonary hypertension is a term that encompasses [52] the conditions that could elevate the mean pulmonary arterial pressure (mPAP) to 25 mm Hg or more [52]. WHO classification PH is divided into five groups based on etiology, according to WHO classification.

- Group 1—Pulmonary arterial hypertension (PAH)
- Group 2—PH in left heart disease
- Group 3—PH as a consequence of chronic lung disease and/or hypoxemia
- Group 4—PH secondary to pulmonary artery obstructions
- Group 5—PH in miscellaneous pulmonary disorders (e.g., Sarcoidosis, myeloproliferative disorders, multiple sclerosis, systemic lupus erythematous, HIV, herpesvirus infection, schistosomiasis) (Adapted from [53]).

The underlying mechanisms leading to elevation of pulmonary arterial pressure involve extensive obliteration of small and medium-sized arterioles of the lungs.

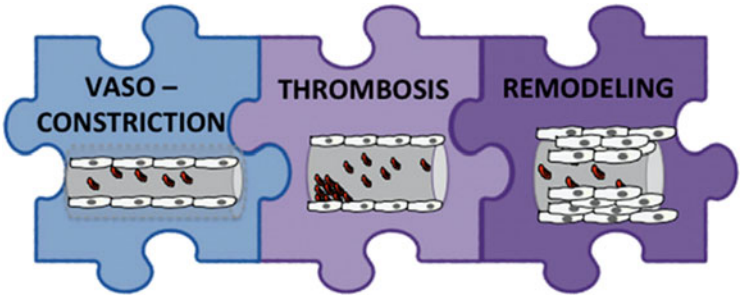


Fig. 1.20 The vascular factors involved in the mechanism of disease (Reproduced from [52]). The three components that play significant role in the pathogenesis of PH include vasoconstrictive influences, formation of micro-thrombi, and remodeling of the pulmonary vasculature.

There are alterations in the endothelial structure and function, along with growth and proliferation of neointimal, medial, and adventitial layers. The net result of these alterations is the development of occlusive arteriopathy resulting in progressive narrowing, obstruction, and hindrance in the pulmonary circulation, culminating in right-sided heart failure and demise of affected individuals.

The three components that play major part in the development of PH include vasoconstrictive influences, formation of micro-thrombi, and remodeling of the pulmonary vasculature (Fig. 1.20).

1. Vasoconstriction:

It has been observed that the vasoactive influences predominate over those causing vasodilation → tilt to vasoconstriction of the pulmonary vasculature. The abnormalities in three major pathways promoting vasoconstriction include the abnormal regulation and actions of prostacyclins, endothelin-1, and nitric monoxide [52]. The important influence of these pathways leading to vasoconstriction has been demonstrated by the therapeutic advantage of treatment modalities targeting this aspect of the disease process [52].

2. Microthrombotic events:

Microthrombotic events are observed in older patients with longstanding disease having important impact on the evolution of PH. The coagulopathies associated with PH include deficiency of protein C and S → impaired anticoagulation, and enhancement of von Willebrand factor activity → favors pro-coagulant activity [52]. However, since inflammation seems to be a significant factor in the pathogenesis of pulmonary hypertension [52] and certain coagulation factors are designated as mediators of the acute phase of inflammatory process, it remains unclear whether

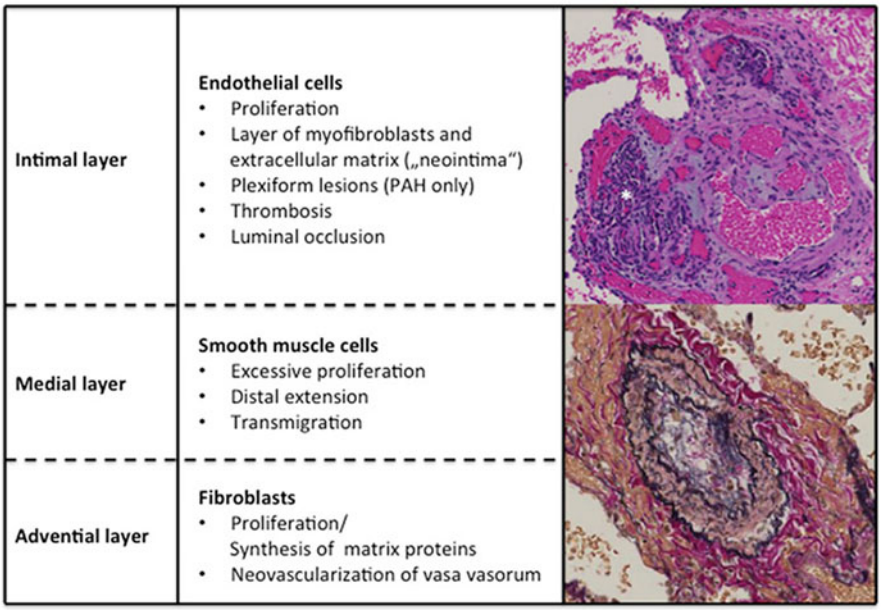


Fig. 1.21 Features of pulmonary artery vascular remodeling—involvement of different cell types (Reproduced from [52])

the altered expression of coagulation factors observed is a true expression of their role in PH.

3. Vascular remodeling:

This process has been termed as a neoplasia-like process that may affect both arteries and veins of the pulmonary circulation. It includes dysregulated cellular proliferation, clonal expansion, somatic instability, altered metabolism, and resistance to apoptosis [52]. The hyperplastic change is evident in all the layers of the vessel wall, and characteristically observed in the vascular smooth muscle cells (Fig. 1.21).

1.3.8 Pathogenesis of Vascular Remodeling

The cells in the vessel wall that undergo excessive proliferation and contribute to the process include those in the endothelial layer, smooth muscle cells, and adventitial fibroblasts. The term "neointima" applies when there is deposition of myofibroblasts and extracellular matrix proteins in the vascular endothelium. Endothelial proliferation leads to development of a network of vessels that consists of dilated vascular channels having thin walls, named as "plexiform lesions." The medial layer (Tunica media) exhibits the most prominent changes, caused by an imbalance of

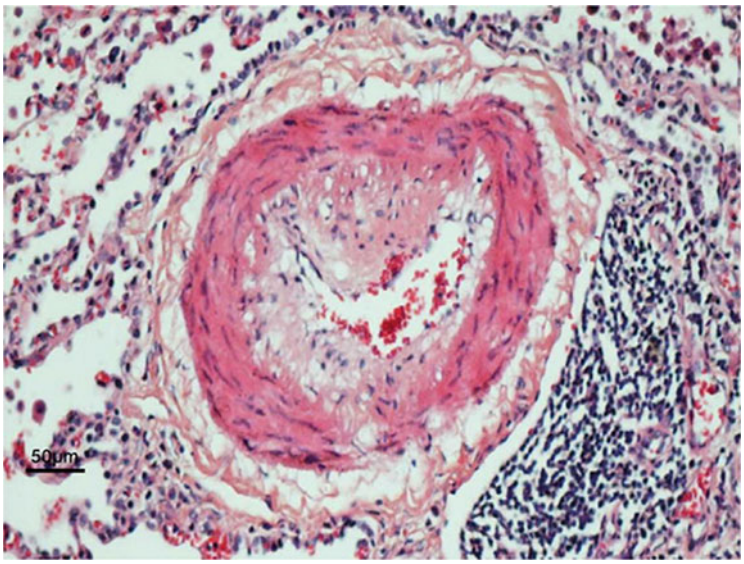


Fig. 1.22 Histopathology: A single layer of endothelium, neointima (in light pink) (Reproduced from [54]). The neointima contains cells that are positive for biological markers of inflammatory cells and those representing smooth muscles. The medial layer containing smooth muscle cells is expanded and the adventitial layer looks abundant

pro-proliferative and anti-apoptotic properties of smooth muscle cells, movement of myofibroblasts to the endothelial space. The adventitia shows development of new vascular channels in vasa vasorum and elevated synthesis of matrix proteins (shown by Elastin-Van Gieson (EVG) staining). All of these structural changes lead to excessive hyperplastic thickening of the vessel wall and hence, occlusion of the vascular lumina (reviewed in [52]. Pulmonary vascular lesions in PH show accumulation of T- and B-lymphocytes, macrophages, dendritic cells (DCs), and mast cells along the vessel walls (Fig. 1.22). Perivascular inflammatory response has a major influence in the remodeling [54]. Hence, altered immune mechanisms exert a vital influence in this condition.

Besides perivascular accumulation and intravascular infiltration of immune cells, there is abnormal elevation of several cytokines and chemokines in the circulation, such as interleukin (IL)-1β,6,8, monocyte chemoattractant protein (MCP)-1, fractalkine, CCL5/RANTES, and tumor necrosis factor (TNF)-α (Fig. 1.23). IL-1β and TNF-α are associated with deposition of fibronectin [54] observed in PH lesions and IL-6 has a mutagenic effect on smooth muscle cells [54]. The existence of dysregulated immune response explains the findings, like perivascular inflammatory infiltrate and the overproduction of the chemical mediators mentioned above. Self-reacting antibodies against nuclear components, endothelium of the alveoli and fibroblasts are detected in patients with PH.

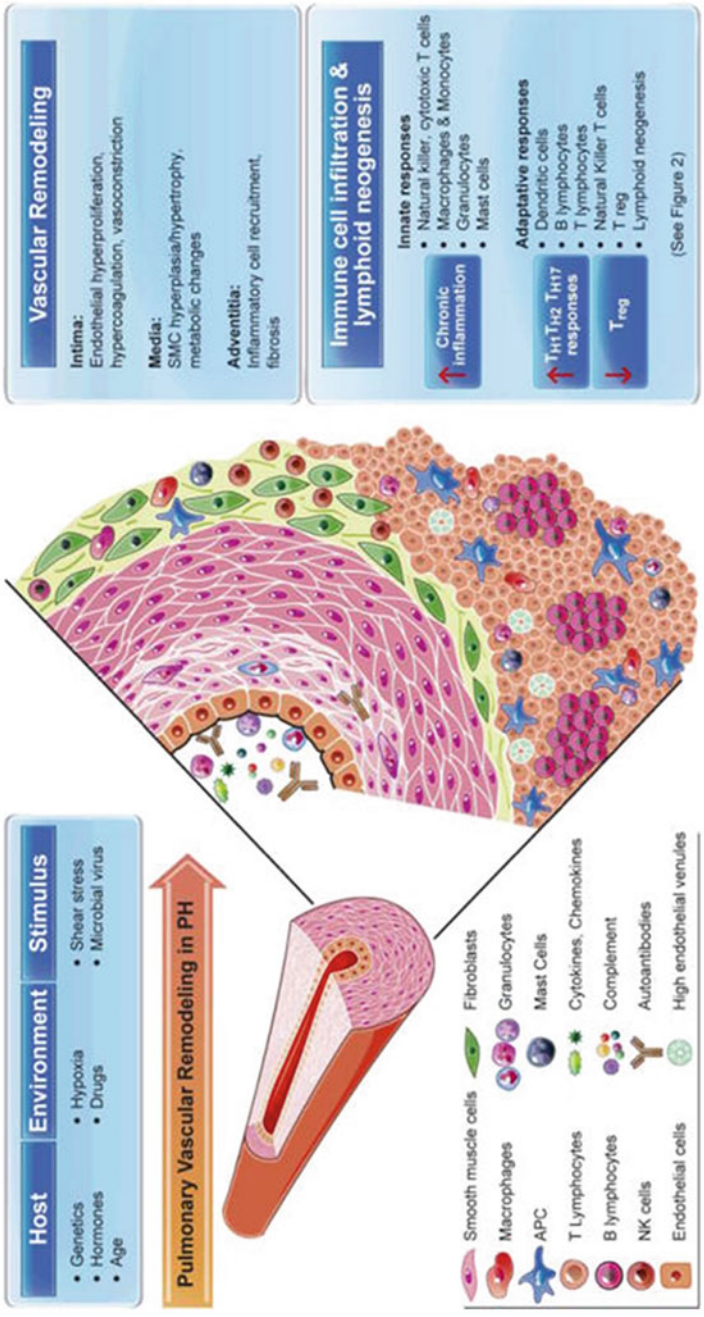


Fig. 1.23 PH-vascular alterations and inflammatory infiltrate (Reproduced from [54])

1.4 Diagrammatic Illustration: A Vessel with Severe Neointimal Formation

The vessel lumen contains complement, autoantibodies, neutrophils, and immune cells bound to the endothelium. The "neointima" is composed of faintly-stained cells, matrix, and infiltrating T- and B-lymphocytes. The adventitial layer has macrophages, dendritic, and mast cells. The space along the adventitia is infiltrated by lymphoid follicles, which contain T- and B-lymphocytes and dendritic cells/ antigen presenting cells (APC).

1.4.1 The Role of Treg cells and T Cells

Tregs are vital in controlling self-tolerance [54]. Tregs exert control on T cells, influence the functions of dendritic cells, natural killer cells, monocytes, macrophages, and B-lymphocytes. Hence, an impairment or deficiency of their function may increase the risk of PH, and is shown to be associated with PH. Deficiency in normal Treg and/or regulatory NK function → Dysregulation of immune response→ Skewing towards TH1/TH17 → predominance of leukotriene B4-secreting-GM-CSFR+ macrophages that cause direct vascular injury by triggering apoptotic mechanisms of EC, hypertrophy, and hyperplasia of smooth muscle cells (Fig. 1.24).

1.4.2 TH1/TH17 and TH2 Immunity in PH

CD4+ T cell responses could be designated as TH1, TH2, and TH17 types and significantly impact the process of autoimmunity in susceptible subjects [54]. There is parallel induction of TH17 effector cells and TH1 cells (producing IFN-γ, TNFs, and IL-2). Both TH1 and 17 cells have the ability to induce inflammatory and autoimmune states. These cells co-localize and may synergize their chemotaxis at the site of tissue injury [54]. Th17 cells synthesize and secrete IL-17, IL-6, TNF-α, GM-CSF, IL-21, and IL-22. Immune dysregulation in the pathogenesis of PH favors TH1/TH17 immune responses → elaboration of TNF-α and IL-6 → other injurious responses that promote structural alterations in the blood lung vessels, as summarized in Fig. 1.25 [54].

1.4.3 Neutrophils and Neutrophil Elastase

Neutrophil elastase influences the pathogenesis by the effect on the biosynthesis and secretion of potent growth factors from extracellular matrix components. Elastase → Release of elastin and fibronectin fragments, that are highly chemoattractant. Elastase also activates complement pathways, enhancing the immunological impact and inflammation [54].

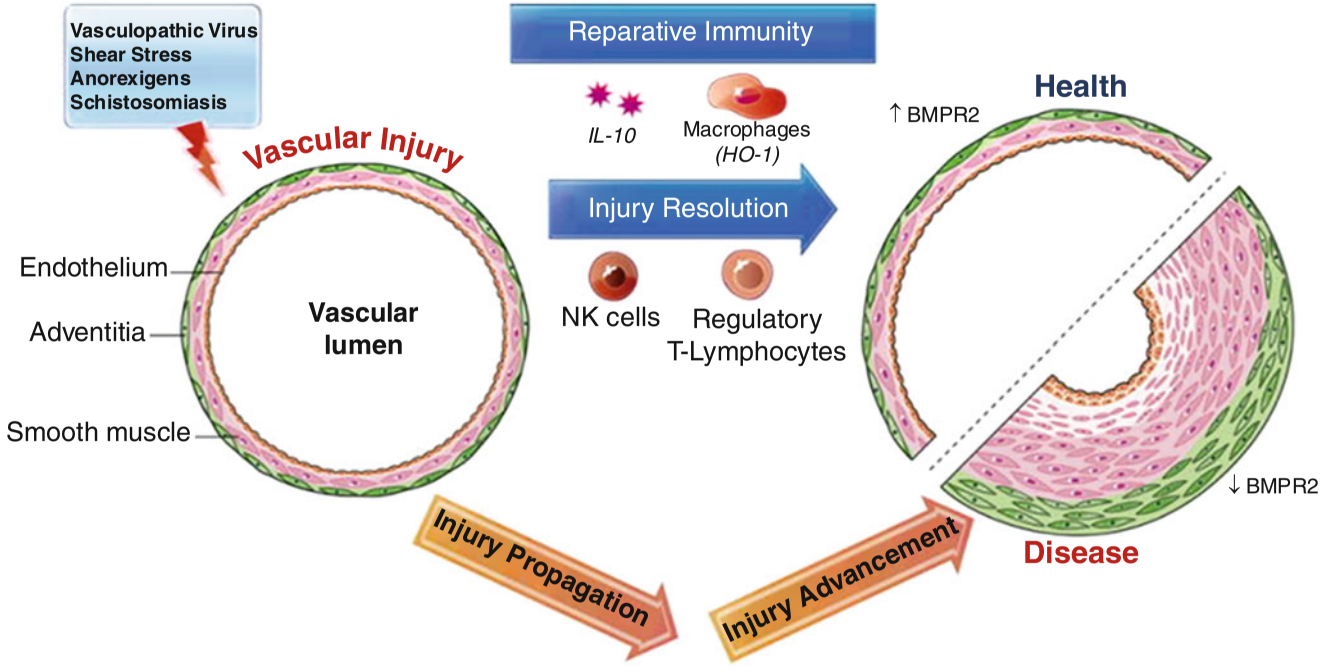


Fig. 1.24 Distinct roles for reparative response following vascular injury (Reproduced from [54]). An inherited or acquired tendency to dysregulated immune response, or if vascular injury stimulates a defective repair mechanism, both may either cause delay of the normal repair or interfere with its progress.

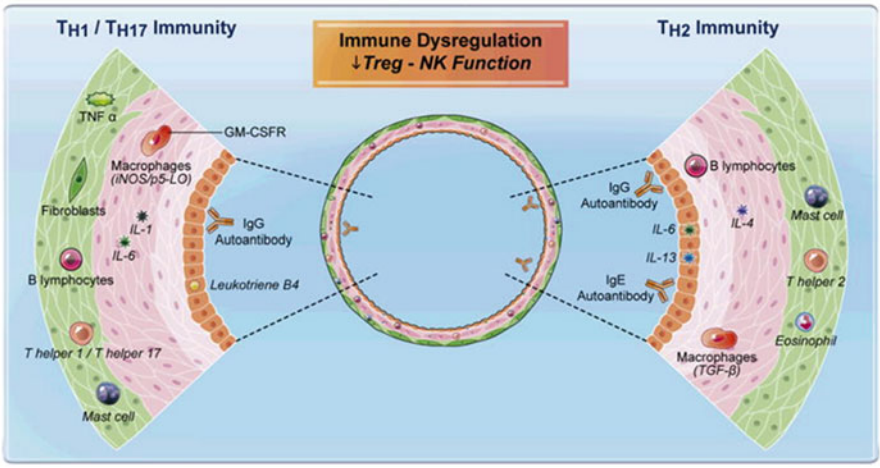


Fig. 1.25 Dysregulated immune mechanisms and their influence in PH**.** (Reproduced from [54])

1.5 Suggestions for Further Research

1. Though studies have explained the pathways involved in vasoconstriction, and effective therapies have been evolved for symptomatic relief, yet more work is recommended that may help in the prevention and to cure PH.
2. Microthrombotic events and their subsequent role in the progression of almost all forms of PH needs attention. There is lack of substantial scientific data about therapeutic usage and benefits of new drugs to treat such events in PH patients.
3. Vascular injury, inflammation, and vascular remodeling go hand in hand in the pathogenesis of PH. Deposition of complement C3 in vascular injury and that of aberrant bone morphogenetic protein receptor type II (BMPR2) in cellular proliferation. Prevention of apoptosis of the vascular elements has been documented in the pathophysiology of PH. However, more research would be beneficial in order to find an effective therapy to combat the process.
4. Studies have described the presence of lymphoid aggregates in the lungs and circulating autoantibodies in the patients with PH, even in the absence of an autoimmune disorder. There are still grey areas to correlate to the events involving vascular injury, inflammation, and obliterative vasculopathy, not only in the idiopathic form of disease but also in autoimmune and infectious forms of PH.

1.6 Immuno-pathogenesis of Lung Cancer

In humans, lung cancer is the leading cause of deaths from cancer worldwide [55]. Lung cancers most likely originate from differentiated or undifferentiated basal cells of bronchial lining in the respiratory tract. These basal cells are

considered to be putative stem cells of the bronchus. It is believed to differentiate into the secretory, ciliated, and goblet cells of the respiratory epithelial lining [56]. This cancer has been described to have various classic morphological patterns based on light microscopy, aided by ancillary techniques. There are two broad types of lung cancers, i.e. the one that accounts for 80% of the cases are non-small cell carcinoma (NSCC) and the other 20% of the cases are made of small cell carcinoma (SCLC). The most distinct types of non-small cell carcinoma include adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (NSCLC) [57].

Vast majority of lung cancers, including NSCC (85%) and SCLC (98%), arise in tobacco smokers, as tobacco smoke contains more than 20 carcinogens which are strongly associated with lung cancer development. The most common ones are polycyclic aromatic hydrocarbons and nicotine-derived nitrosoaminoketone. Globally, around 25% of lung cancer cases are seen in non-smokers. The pathogenesis of lung cancer in non-smokers has several risk factors which include environment, hormones, genetics, and viral infections. Some of the environmental factors include exposure to asbestos, heavy metals, and petrochemical products [58]. Genetic component relates to the host susceptibility to lung cancer, with or without being exposed to carcinogens. Number of polymorphisms at cytochrome P450 associated gene from the Cytochrome P450 (CYP) Gene Superfamily has been identified with increased risk of lung cancer [59].

Genetic mutations in respiratory epithelium occurs due to inhaled carcinogen from tobacco smoke, through DNA adduct formation, in which a segment of the DNA is covalently bound to a cancer-causing carcinogen. Adduct formation is due to metabolic activation of these carcinogens by CYP enzymes. Normally the repair process for these adducts are done by adduct excision, led by nucleotide excision repair, which removes DNA adducts and restores the DNA. Sometimes cells with damaged DNA may undergo apoptosis. Significant mutations may occur at p53 and Ras genes due to the prolonged DNA adduct formation. Similar mutation was also seen in non-smokers. The capacity of DNA repair mechanisms may have an effect on the susceptibility to lung cancer [60, 61].

The other effect of tobacco carcinogen on respiratory epithelium is oxidative lesion, which is usually repaired by specific mechanism (OGG1). Defect in the repair of these oxidative lesion can result in significant DNA damage [61, 62]. Lung cancer associated genetic abnormalities are also found to be linked with altered signaling pathways which includes epidermal growth factor receptor signaling pathway, Thyroid transcription factor 1, MYC family (proto-oncogene family), and others. These information on altered signaling pathways are emerging as considerable importance for the development of targeted therapy. Stimulatory signaling pathways are normally led by oncogenes. The cells upon having a malignant phenotype will lead to proliferation and later escape from apoptosis [61, 63].

Some of the other genetic risk factors associated with lung cancer include abnormalities in tumor suppressor gene pathways such as the p53 and p16INK4/cyclin D1/Rb pathways as well as serine/threonine kinase 11 gene mutation. The protein p53 also known as TP53 or tumor protein is considered as cellular gatekeeper which regulates the cell cycle, hence guards against genetic instability and

abnormality. This protein also senses multiple stress signals such as DNA damage, hypoxia, and oncogene activation. The gene for p53 is the most frequently mutated gene in lung cancer, seen in 90% of SCLC and *large cell neuroendocrine carcinoma* (LCNEC); and 50% of NSCLC [61, 64].

The key pathogenesis in lung cancer is due to the underlying fact that alterations in oncogenes and tumor suppressor genes may lead to inefficient DNA repair mechanisms. Lastly, there is the need for fully unravel and comprehend the complex interrelationship between genetics and other risk factors in the development of lung cancer.

1.7 Tumor Immunology in Lung Cancer

The innate and acquired immune response both have crucial roles in antitumor immunity. Immune response against tumor is mainly mediated by CD8+T cells. Antigen presentation from tumor cells possibly mediated by tumor cells in tumor draining lymph nodes to specific T cells directly or via cross presentation by antigen presenting cells (APCs). This priming of CD8+T cells leads to the formation of tumor specific CD8+T cells, which will then proliferate and increase traffic to the tumor site where they ultimately attack and destroy the tumor cells. Activated CD8 +T cells would then trigger the secretion of interferon-gamma (IFN-ɣ) and TNF-α. The CD4+T cells are also activated by APCs. Cell mediated immunity is coordinated by Th1 subset by producing large amounts of IFN-ɣ and chemokines. The IFN-ɣ exerts anti-tumor actions such as anti-proliferative, pro-apoptotic actions and inhibits angiogenesis. Recruitment inflammatory cells such as macrophages, granulocytes, eosinophils, and NK cells around the tumor are facilitated by Th1 cells [65].

Similarly, other immune cells have prominent roles in tumor suppression [65]. Macrophages are involved in antitumor innate response which is performed by eliminating apoptotic tumor cells in order to obviate autoimmunity. On the other hand, the NK cells induce the tumor cell apoptosis via the secretion of cytoplasmic granules, perforin, and granzymes that will degrade the tumor cells [65].

1.8 Evading the Immune Response

Generally, two mechanisms that allow cancer to avoid the antitumor immune action are categorized as intrinsic and extrinsic mechanisms. The former is mediated by immunosuppressive cytokines, such as vascular endothelial growth factor (VEGF) and Fas ligand, also known as CD95L or CD178 (a type-II transmembrane protein). The latter is mediated by suppressive cells such as activated M2-like tumor-associated macrophages (TAMs), suppressive T cells, immature APCs, and plasmacytoid dendritic cells [65].

There are several mechanisms in which lung cancer evades the immune system. One of which is “immune sculpting,” whereby the lung cancer cells go through a slow process of immunoediting. In this process, a precancerous cell slowly

undergoes selective adaptation to oppose the immune surveillance [65]. The role of APCs in recognizing and processing the tumor antigens could be disrupted through secretions of various proteins such as STAT-3, IDO, TGF-β, and IL-10 by the tumor itself. The dense fibrotic stroma surrounding the tumor can also limit the accession of T cells to this site. Other ways of immune evasion is through downregulating the MHC class I molecule expression, therefore making any endogenous or therapeutic antitumor T cell responses become ineffective [65]. Finally, lung cancer promotes the increase of Treg and MDSC. These immune suppressive cells tend to accumulate in the tumor microenvironment, therefore promoting tumor growth and downregulating antitumor immune responses [65].

1.9 Brief Summary

It is evident that there are many innate and adaptive responses that have been discovered in the immuno-pathogenesis of the respiratory diseases described in this chapter. Although there have been many reported evidences on the components of the innate and adaptive immunity in immuno-pathogenesis, there still lay many undiscovered potentials of these immune system and may continuously surprise us in their functional roles in the disease process. Research in immunology and their roles in pathogenesis could serve as a guide in drug discovery especially for many of the chronic diseases as pathogens have their "intelligent" ways of evading the human immune system.

References

1. Forum of International Respiratory Societies (2017) The global impact of respiratory disease, 2nd edn. European Respiratory Society, Sheffield
2. WHO (2020a) Influenza (Seasonal). https://www.who.int/news-room/fact sheets/detail/influenza-(seasonal)
3. Yang L, Liu S, Liu J, Zhang Z et al (2020) COVID-19: immunopathogenesis and Immunotherapeutics. Nat Signal Transduct Target Ther 5:128
4. Zhang J, Liu J, Yuan Y et al (2020) Two waves of pro-inflammatory factors are released during the influenza A virus (IAV)-driven pulmonary immunopathogenesis. PLoS Pathog 16(2): e1008334. https://doi.org/10.1371/journal.ppat.1008334
5. Martínez-Alemán S, Bustamante AE, Jimenez-Valdes RJ, González GM, Sánchez-González A (2020) Pseudomonas aeruginosa isolates from cystic fibrosis patients induce neutrophil extracellular traps with different morphologies that could correlate with their disease severity. Int J Med Microbiol 310(7):151451. https://doi.org/10.1016/j.ijmm.2020.151451
6. Atanasova KR, Reznikov LR (2018) Neuropeptides in asthma, chronic obstructive pulmonary disease and cystic fibrosis. Respir Res 19(1):149. https://doi.org/10.1186/s12931-018-0846-4
7. Theprungsirikul J, Skopelja-Gardner S, Meagher RE, Clancy JP, Zemanick ET, Ashare A, Rigby WFC (2020) Dissociation of systemic and mucosal autoimmunity in cystic fibrosis. J Cyst Fibros 19(2):196–202. https://doi.org/10.1016/j.jcf.2019.06.006
8. Malhotra S, Hayes D Jr, Wozniak DJ (2019) Mucoid Pseudomonas aeruginosa and regional inflammation in the cystic fibrosis lung. J Cyst Fibros 18(6):796–803. https://doi.org/10.1016/j.jcf.2019.04.009

9. Neill DR, Saint GL, Bricio-Moreno L et al (2014) The B lymphocyte differentiation factor (BAFF) is expressed in the airways of children with CF and in lungs of mice infected with *Pseudomonas aeruginosa*. PLoS One 9(5):e95892. https://doi.org/10.1371/journal.pone.0095892
10. Mauch RM, Jensen PØ, Moser C, Levy CE, Høiby N (2018) Mechanisms of humoral immune response against Pseudomonas aeruginosa biofilm infection in cystic fibrosis. J Cyst Fibros 17 (2):143–152. https://doi.org/10.1016/j.jcf.2017.08.012
11. Lammertyn EJ, Vandermeulen E, Bellon H et al (2017) End-stage cystic fibrosis lung disease is characterised by a diverse inflammatory pattern: an immunohistochemical analysis. Respir Res 18:10. https://doi.org/10.1186/s12931-016-0489-2
12. Geitani R, Moubareck CA, Xu Z, Karam Sarkis D, Touqui L (2020) Expression and roles of antimicrobial peptides in innate defense of airway Mucosa: potential implication in cystic fibrosis. Front Immunol 11:1198. https://doi.org/10.3389/fimmu.2020.01198
13. Tripathi S, White MR, Hartshorn KL (2015) The amazing innate immune response to influenza A virus infection. Innate Immun 21(1):73–98. https://doi.org/10.1177/1753425913508992
14. Tuerxun W, Wang Y, Cui C, Yang L et al (2020) Expression pattern of the interferon regulatory factor family members in influenza virus induced local and systemic inflammatory responses. Clin Immunol. 217:108469. https://doi.org/10.1016/j.clim.2020.108469
15. Ling GS, Crawford G, Buang N, Bartok I, Tian K, Thielens NM, et al. (2018) C1q restrains autoimmunity and viral infection by regulating CD8(+) T cell metabolism. Science 360:558–63. https://doi.org/10.1126/science.aao4555 PMID: 29724957
16. Duan S, Thomas PG (2016) Balancing immune protection and immune pathology by CD8(+) T-cell responses to influenza infection. Front Immunol 7:25. https://doi.org/10.3389/fimmu.2016.00025
17. Chiu C, Openshaw PJ, 2015, Antiviral B cell and T cell immunity in the lungs, NATURE IMMUNOLOGY, Vol: 16, Pages: 18-26, ISSN: 1529-2908
18. Wang Z, Loh L, Kedzierski L, Kedzierska K (2016) Avian influenza viruses, inflammation, and CD8(+) T cell immunity. Front Immunol 7:60. https://doi.org/10.3389/fimmu.2016.00060
19. WHO (2020b) Tuberculosis - key facts. https://www.who.int/news-room/fact-sheets/detail/tuberculosis
20. Harvey RA, Champe PC, Fisher BD (2007) Lippincott's illustrated reviews: microbiology. Wolters Kluwer, Lippincott Williams & Wilkins, p 186
21. Liu Y, Wang R, Jiang J, Cao Z, Zhai F, Sun W, Cheng X (2018) A subset of $CD1c^+$ dendritic cells is increased in patients with tuberculosis and promotes Th17 cell polarization. Tuberculosis (Edinb) 113:189–199. https://doi.org/10.1016/j.tube.2018.10.007
22. Lavalett L, Rodriguez H, Ortega H, Sadee W, Schlesinger LS, Barrera LF (2017) Alveolar macrophages from tuberculosis patients display an altered inflammatory gene expression profile. Tuberculosis (Edinb) 107:156–167. https://doi.org/10.1016/j.tube.2017.08.012
23. Arbués A, Brees D, Chibout SD, Fox T, Kammüller M, Portevin D (2020) TNF-α antagonists differentially induce TGF-β1-dependent resuscitation of dormant-like Mycobacterium tuberculosis. PLoS Pathog 16(2):e1008312. https://doi.org/10.1371/journal.ppat.1008312
24. Liu W, Zhou J, Niu F, Pu F, Wang Z, Huang M, et al (2020) Mycobacterium tuberculosis infection increases the number of osteoclasts and inhibits osteoclast apoptosis by regulating TNF-α-mediated osteoclast autophagy. Exp Ther Med 20:1889–1898. https://doi.org/10.3892/etm.2020.8903
25. Churina EG, Urazova OI, Novitskiy VV (2012) The role of foxp3-expressing regulatory T cells and T helpers in immunopathogenesis of multidrug resistant pulmonary tuberculosis. Tuberc Res Treat. 2012:931291. https://doi.org/10.1155/2012/931291
26. Ristimaki A, Garfinkel S, Wessendorf J, Maciag T, Hla T. Induction of cyclooxygenase by Interleukin 1 alpha. J Biol Chem 1994; 269:1769–75
27. Hempel SL, Monick MM, Hunninghake GW (1994) Lipopolysacharide induces prostaglandin H synthase-2 protein and mRNA in human alveolar macrophages and blood monocytes. J Clin Invest 1994; 93:391–396

28. Rangel Moreno J, Estrada García I, De La Luz García Hernández M, Aguilar Leon D, Marquez R, Hernández Pando R (2002) The role of prostaglandin E2 in the immunopathogenesis of experimental pulmonary tuberculosis. Immunology 106(2):257–66. https://doi.org/10.1046/j.1365-2567.2002.01403.x. PMID: 12047755; PMCID: PMC1782721
29. Rangel Moreno J, Estrada García I, De La Luz García Hernández M, Aguilar Leon D, Marquez R, Hernández Pando R (2002) The role of prostaglandin E2 in the immunopathogenesis of experimental pulmonary tuberculosis. Immunology 106(2):257–266. https://doi.org/10.1046/j.1365-2567.2002.01403.x
30. Mishra A, Akhtar S, Jagannath C, Khan A (2017) Pattern recognition receptors and coordinated cellular pathways involved in tuberculosis immunopathogenesis: emerging concepts and perspectives. Mol Immunol 87:240–248. https://doi.org/10.1016/j.molimm.2017.05.001
31. Shaw MH, Kamada N, Warner N, Kim Y-G, Nuñez G (2011) The ever-expanding function of NOD2: autophagy, viral recognition, and T cell activation. Trends Immunol 32:73–79. https://doi.org/10.1016/j.it.2010.12.007
32. Yadav M, Schorey JS (2006) The beta-glucan receptor dectin-1 functions together with TLR2 to mediate macrophage activation by mycobacteria. Blood 108:3168–3175. https://doi.org/10.1182/blood-2006-05-024406
33. Troegeler A, Mercier I, Cougoule C, Pietretti D, Colom A, Duval C, Vu Manh T-P, Capilla F, Poincloux R, Pingris K, Nigou J, Rademann J, Dalod M, Verreck FAW, Al Saati T, Lugo-Villarino G, Lepenies B, Hudrisier D, Neyrolles O (2017) C-type lectin receptor DCIR modulates immunity to tuberculosis by sustaining type I interferon signaling in dendritic cells. Proc Natl Acad Sci 114:E540–E549. https://doi.org/10.1073/pnas.1613254114
34. Kang PB, Azad AK, Torrelles JB, Kaufman TM, Beharka A, Tibesar E, DesJardin LE, Schlesinger LS (2005) The human macrophage mannose receptor directs Mycobacterium tuberculosis lipoarabinomannan-mediated phagosome biogenesis. J. Exp. Med 202:987–999, https://doi.org/10.1084/jem.20051239
35. Quirt J, Hildebrand KJ, Mazza J et al (2018) Allergy Asthma Clin Immunol 14(Suppl 2):50. https://doi.org/10.1186/s13223-018-0279-0
36. Dharmage SC et al (2019) Epidemiology of asthma in children and adults. Front Pediatrics 7:246. https://doi.org/10.3389/fped.2019.00246
37. Bochner BS, Undem BJ, Lichtenstein LM (1994) Immunological aspects of allergic asthma. Annu Rev Immunol 12:295–335
38. Ishmael FT (2011) The Inflammatory Response in the Pathogenesis of Asthma. J Am Osteopath Assoc 111(11_suppl_7):S11–S17
39. Kay AB (2005) The role of eosinophils in the pathogenesis of asthma. Trends Mol Med 11:148–152
40. Kim YM, Kim YS, Jeon SG, Kim YK (2013) Immunopathogenesis of allergic asthma: more than the th2 hypothesis. Allergy Asthma Immunol Res 5(4):189–196. https://doi.org/10.4168/aair.2013.5.4.189
41. Durrant DM, Metzger DW (2010) Emerging roles of T helper subsets in the pathogenesis of asthma. Immunol Invest 39(4-5):526–549. https://doi.org/10.3109/08820131003615498
42. Decramer M, Janssens W, Miravitlles M (2012) Chronic obstructive pulmonary disease. Lancet 379(9823):1341–1351. https://doi.org/10.1016/S2213-2600(12)70060-7
43. Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report (2020) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. http://www.goldcopd.com/. Accessed 9 Nov 2020
44. Agustí A, Hogg JC (2019) Update on the pathogenesis of chronic obstructive pulmonary disease. N Engl J Med 381(13):1248–1256. https://doi.org/10.1056/NEJMra1900475
45. Joshua JS, Thomas P (2014) COPD: immunopathogenesis and immunological markers. Adv Res 3(2):221–235. https://doi.org/10.9734/AIR/2015/12320
46. Witko-Sarsat V, Rieu P, Descamps-Latscha B et al (2000) Neutrophils: molecules, functions and pathophysiological aspects. Laboratory Invest 80(5):617–653
47. Shapiro SD, Ingenito EP (2005) The pathogenesis of chronic obstructive pulmonary disease: advances in the past 100 years. Am J Respirat Cell Mol Biol 32(5):367–372

48. Sgalla G, Iovene B, Calvello M et al (2018) Idiopathic pulmonary fibrosis: pathogenesis and management. Respir Res 19:32. https://doi.org/10.1186/s12931-018-0730-2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5824456/
49. McLean-Tooke A, Moore I, Lake F (2019) Idiopathic and immune-related pulmonary fibrosis: diagnostic and therapeutic challenges. Clin Trans Immunol:e1086. https://doi.org/10.1002/cti2.1086
50. Desai O, Winkler J, Minasyan M, Herzog EL (2018) The role of immune and inflammatory cells in idiopathic pulmonary fibrosis. Front Med 5:43. https://doi.org/10.3389/fmed.2018.00043
51. Kolahian S, Fernandez IE, Eickelberg O, Hartl D (2016) Immune mechanisms in pulmonary fibrosis. Am J Respirat Cell Mol Biol. https://doi.org/10.1165/rcmb.2016-0121TR
52. Huber LC, Bye H, Brock M (2015) The pathogenesis of pulmonary hypertension – an update. Swiss Medical Weekly 145:w14202. https://doi.org/10.4414/smw.2015.14202
53. Simonneau G, Montani D, Celermajer DS et al (2019) Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir 53
54. Rabinovitch M, Guignabert C, Humbert M, Nicolls MR (2014) Inflammation and immunity in the pathogenesis of pulmonary arterial hypertension. Circ Res 115(1):165–175. https://doi.org/10.1161/CIRCRESAHA.113.301141. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4097142/
55. Ferlay J, Colombet M, Soerjomataram I et al (2018) Global and regional estimates of the incidence and mortality for 38 cancers: GLOBOCAN. CA Cancer J Clin 68(6):394–424. https://doi.org/10.3322/caac.21492
56. National Research Council (US) Panel on Dosimetric Assumptions Affecting the Application of Radon Risk Estimates (1991) Comparative dosimetry of radon in mines and homes. In: Cells of origin for lung cancer. National Academies Press, Washington, DC. Available from: https://www.ncbi.nlm.nih.gov/books/NBK234231/
57. Zheng M (2016) Classification and pathology of lung cancer. Surg Oncol Clin N Am 25 (3):447–468. https://doi.org/10.1016/j.soc.2016.02.003
58. Sun S, Schiller J, Gazdar A (2007) Lung cancer in never smokers - a different disease. Nat Rev Cancer 7:778–790. https://doi.org/10.1038/nrc2190
59. Marshall AL, Christiani DC (2013) Genetic susceptibility to lung cancer--light at the end of the tunnel? Carcinogenesis 34(3):487–502. https://doi.org/10.1093/carcin/bgt016
60. Hecht SS (1999) Tobacco smoke carcinogens and lung cancer. J Natl Cancer Inst 91:1194–1210
61. Brambilla E, Gazdar A (2009) Pathogenesis of lung cancer signaling pathways: roadmap for therapies. Eur Respir J 33(6):1485–1497. https://doi.org/10.1183/09031936.00014009
62. Paz-Elizur T, Sevilya Z, Leitner-Dagan Y, et al (2008) DNA repair of oxidative DNA damage in human carcinogenesis: potential application for cancer risk assessment and prevention. Cancer Lett 266: 60–72
63. Weinstein IB, Joe A (2008) Oncogene addiction. Cancer Res 68:3077–3080
64. Brambilla E, Gazzeri S, Lantuejoul S, et al (1998) p53 mutant immunophenotype and deregulation of p53 transcription pathway (Bcl2, Bax, and Waf1) in precursor bronchial lesions of lung cancer. Clin Cancer Res 4:1609–1618
65. Aldarouish M, Wang C (2016) Trends and advances in tumor immunology and lung cancer immunotherapy. J Exp Clin Cancer Res 35(1):157. https://doi.org/10.1186/s13046-016-0439-3

2 Introduction to Chronic Respiratory Diseases: A Pressing Need for Novel Therapeutic Approaches

Yinghan Chan, Sin Wi Ng, Hui Shan Liew, Lesley Jia Wei Pua, Laura Soon, Jun Sing Lim, Kamal Dua, and Dinesh Kumar Chellappan

Yinghan Chan, Sin Wi Ng, Hui Shan Liew, Lesley Jia Wei Pua, Laura Soon and Jun Sing Lim contributed equally with all other contributors.

Y. Chan (✉)
School of Pharmacy, International Medical University (IMU), Kuala Lumpur, Malaysia

Nanotherapeutics Laboratory, Department of Pharmacology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

S. W. Ng
School of Pharmacy, International Medical University (IMU), Kuala Lumpur, Malaysia

Head and Neck Cancer Research Team, Cancer Research Malaysia, Subang Jaya, Selangor, Malaysia

H. S. Liew · L. J. W. Pua
School of Pharmacy, International Medical University (IMU), Kuala Lumpur, Malaysia

School of Postgraduate Studies, International Medical University (IMU), Kuala Lumpur, Malaysia

Center for Cancer and Stem Cell Research, Institute for Research, Development and Innovation (IRDI), International Medical University (IMU), Kuala Lumpur, Malaysia

L. Soon
School of Pharmacy, International Medical University (IMU), Kuala Lumpur, Malaysia

J. S. Lim
School of Medicine, Faculty of Medicine and Health Sciences, Royal College of Surgeons in Ireland (RCSI), Dublin, Ireland

K. Dua
Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Sydney, NSW, Australia

D. K. Chellappan
Department of Life Sciences, School of Pharmacy, International Medical University, Kuala Lumpur, Malaysia

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_2

Abstract

Chronic respiratory diseases such as asthma, chronic obstructive pulmonary disease, cystic fibrosis, and lung cancer are among the leading causes of global mortality and morbidity, whereby these diseases have brought enormous healthcare, economic, and social burden in many countries. Multiple components of the respiratory system are affected by chronic respiratory diseases, which include the respiratory airways, lung parenchyma, as well as pulmonary vasculature. Recent advances in medical research have led to the development of various pharmacotherapeutic agents for the management of chronic respiratory diseases, such as bronchodilators, corticosteroids, and antibiotics. Despite that, the use of conventional therapeutics has been futile as they are only capable of alleviating the symptoms associated with the diseases but did not effectively cure or prevent the progression of these diseases. This chapter discusses the pathogenesis of various chronic respiratory disorders and the limitations of current therapeutic strategies.

Keywords

Chronic respiratory diseases · Asthma · Chronic obstructive pulmonary disease · Interstitial lung disease · Cystic fibrosis · Tuberculosis · Lung cancer

2.1 Introduction

Chronic respiratory diseases (CRDs) such as asthma, chronic obstructive pulmonary disease (COPD), tuberculosis, and lung cancer can affect individuals from all age groups, and they are the most common and notable causes of worldwide mortality and morbidity [1, 2]. Enormous social and economic burden in terms of treatment costs, hospitalization, as well as reduced workforce productivity have also been brought upon by CRDs [3, 4]. According to the European Respiratory Society, approximately 400 million people globally are suffering from mild to moderate asthma and COPD, whereas lower respiratory tract infection as a result from *Mycobacterium tuberculosis* infection has affected 10.4 million people globally with 14% death rate. Besides, CRDs account for approximately 10% of total disability-related life years (DALYs) in human workforce [2, 5]. In addition, as reported by the World Health Organization (WHO), lung cancer induced by occupational carcinogens and increasing smokers' population has also killed more than 2.09 million individuals in 2018 [2, 6]. Serious concerns have been raised as it is predicted that this figure will grow higher in the near future, shredding a large number of global populations as a result of CRDs.

Currently, conventional management strategies of CRDs rely on the use of therapeutic agents. The developing field of medical research and advancement of

technologies have led to the discovery and development of various chemical drugs for treating these diseases. Nevertheless, most of the conventional therapeutic agents are not capable of curing CRDs, as well as to prevent their progression [7–9]. For example, controlling symptoms is the only management option in asthma and administration of multiple drugs may be needed in patients who are poorly controlled. Likewise, the current therapeutics of COPD are unable to reverse the progression of disease [10, 11]. Besides, the emergence of antimicrobial resistance also brought huge challenge in the management of tuberculosis, a major respiratory communicable disease [12]. These may be attributed to lack of in-depth understanding of the underlying mechanisms and pathogenesis of CRDs, which may assist in the discovery of novel therapeutic targets, both molecular and immunological [13]. In addition, the variable delivery and pharmacokinetic profile of therapeutic drugs provide justification for further research into improving and enhancing the biodistribution, accumulation, and efficacy of both conventional and newly discovered therapeutic agents [2, 13]. In this chapter, we provide an overview to the underlying mechanisms and pathogenesis of various CRDs. We will be highlighting some of the drawbacks of current therapeutic strategies, along with some suggestions to address these drawbacks for achieving better therapeutic outcomes in CRDs.

2.2 The Human Respiratory System

Lungs are the foundational organs of the human respiratory system that play a role in facilitating gaseous exchange from the external environment into the bloodstream (Fig. 2.1). Generally, the human respiratory system can be subdivided into two primary components, namely the conducting portion and the respiratory portion. The conducting portion of the respiratory system functions to direct air to the site of respiration and it consists of the nose, nasopharynx, larynx, trachea, bronchi, and bronchioles, whereas the respiratory portion begins from the respiratory bronchiole

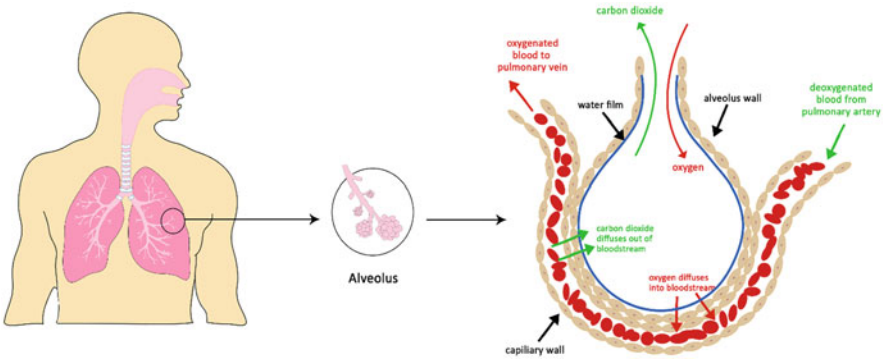


Fig. 2.1 Schematic illustration of gaseous exchange in the human lungs

Table 2.1 Standard lung volumes measured and their definitions

Lung volume	Definition
Expiratory reserved volume (ERV)	Volume of air that can be expired after a normal breath
Forced expiratory volume (FEV_1)	Volume of air that can be expired in 1 s of maximal forced expiration
Functional residual capacity (FRC)	Volume of air that is remained in the lung after a normal expiration
Inspiratory capacity (IC)	Volume of air that can be breathed after normal expiration
Inspiratory reserved volume (IRV)	Volume of air that can be breathed after a normal inspiration
Residual volume (RV)	Volume of air that is remained in the lung after maximal expiration
Tidal volume (TV)	Volume of air that is inspired and expired with each breath
Total lung capacity (TLC)	Volume of air present in the lungs after maximal inspiration
Vital capacity (VC)	The maximal volume of air that can be expired after maximal inspiration

and air is directed into alveolar ducts, alveolar sacs, and ends at the alveoli where the process of gaseous exchange takes place [14, 15]. Alveoli are the structural and functional units of the human respiratory system, whereby approximately 300 million of them are present in adult lungs [16].

Pulmonary gaseous exchange is a continuous process that involves ventilation, diffusion, and perfusion. The lungs are well-suited for this process as their walls are made up of a rich capillary network that covers approximately 85 to 95% of the alveolar surface, accompanied by a thin interstitial matrix. This exceptionally thin membrane allows gases to diffuse rapidly between the alveolar gas and rich blood compartments, and ultimately to perfuse body tissues [17, 18]. In addition, the presence of relatively large blood volume within the alveolar capillaries increases blood transit time, thereby allowing longer time for gaseous exchange [18]. During inspiration, each alveolus expands with fresh gas containing high levels of oxygen which has flown down the bronchial tree from the nose and mouth. During expiration, the volume of alveoli decreases, thereby returning exchanged gas containing high levels of carbon dioxide up to bronchial tree and subsequently released from the nose and mouth [16, 18]. The processes of inspiration and expiration are primarily facilitated by the diaphragm and intercostal muscles [2]. Various measurements have been employed for monitoring the normal functioning of the human lungs. In this context, accurate measurement of lung volume is the key to determine presence of obstructive and restrictive lung diseases, such as those observed in asthma and COPD. Spirometry is a safe and reproducible maximum breathing test that has been widely utilized in the diagnosis and management of CRDs through the measurement of lung functionality and determination of lungs ventilatory capacity [15, 19]. Various standard lung volumes that are routinely measured are summarized in Table 2.1 [15].

The human respiratory system is also comprised of multiple specialized cell types, such as airway epithelial cells, alveolar unit type I and type II cells, goblet cells, ciliated cells, Clara cells, as well as neuroendocrine cells. Besides, several immune cells and adipose cells are also present in human lungs [20]. Various studies have established that the functionality of specific cell types may be linked to the development of CRDs. For instance, interstitial lung disease (ILD) has been widely associated with the secretion of surfactant proteins and lipids by respiratory cells [21]. Lung glandular cells are also associated with the induction of lung adenocarcinomas in the presence of disease-inducing risk factors [22, 23]. In addition, airway epithelial cells play crucial role as the modulator of pulmonary inflammation and activation of immune cells, as they are the first line of defence which act as the barrier separating the host-environment axis in the human respiratory system. Therefore, airway epithelial cells are regarded as the major component involved in airway repair and remodelling in CRDs [24]. Furthermore, basal cells that are present in airway epithelium are also demonstrated to play central role in the aetiology of bronchoconstriction and airway remodelling. Other epithelial abnormalities of the lungs include hypertrophy, hyperplasia, dysplasia, and metaplasia of squamous and goblet cells [24, 25].

Among the major organs in the human body, human lungs are constantly exposed to a wide range of allergens and environmental pollutants, which may include organic, inorganic, and biological agents. The lungs are at a constant threat of developing minor to complex pulmonary disorders that can compromise the quality of life of these patients. Hence, a comprehensive understanding of the underlying mechanisms implicated in the initiation and progression of CRDs with respect to the physiology of lungs is essential to formulate effective treatment and management strategies for these diseases.

2.3 Overview of Chronic Respiratory Diseases

2.3.1 Asthma

Asthma is a common yet poorly understood CRD in which the airways become narrow, swollen, and produce extra inflammation-causing mucus. The disease is highly prevalent whereby it affects an estimated 241 million people worldwide at all stages of life, and resulted in approximately 380 thousand deaths annually [26–28]. Besides, a higher prevalence of asthma is observed in low- to middle-income countries, with more than 80% of asthma-related deaths reported from these countries [28, 29]. Asthma is regarded as an alarming medical condition as it has resulted in huge economic loss associated with high medical expenditure, loss of productivity from work and school, as well as premature death [30].

Asthma is a disease that can present itself as episodic and persistent in different individuals. Episodic asthma is when symptoms appear and resolve upon therapeutic intervention, whereas persistent asthma is when clinical symptoms are continuously present [31]. The primary symptoms of asthma are breathing difficulty, shortness of

breath, as well as signs of coughing and wheezing. The cough may be dry or productive of clear mucoid or pale-yellow sputum. Some patients had reported that they had experienced chest tightness during asthma exacerbation [32]. Asthma is commonly triggered by exposure to indoor pollutants, outdoor allergens, occupational exposure to chemical fumes, air pollution, and tobacco smoke. However, asthma triggers are found to vary from person to person and can be more pronounced due to various factors such as cold air, thunderstorm, use of medications including beta-blockers, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), emotions and stress, physical exercise, food preservatives, beer and wine, as well as medical history such as gastroesophageal reflux disease (GERD) [33, 34].

Based on the pathophysiology of the disease, asthma can be categorized into multiple phenotypes and endotypes. This categorization is crucial in the management of asthma as specific traits can be targeted for effective therapy of the disease [35]. On the other hand, based on the triggers, asthma can also be categorized as allergic asthma or non-allergic asthma. Allergic asthma is generally caused by biological and organic allergens such as dust mite, mold, and pollen, whereas non-allergic asthma is attributed to risk factors such as infections, diet, and tobacco smoke. Typically, the initiation of asthma is modulated by Th2 responses as a result of external and internal triggers, leading to recruitment of type 2 T-helper cells into the airway and produces pro-inflammatory cytokines at elevated levels, which include interleukin (IL)-4, IL-5, IL-9, and IL-13 [36]. Another mechanism underlying asthma exacerbation is by stimulation of mast cells, whereby upon exposure to allergens, airway mast cells along with IL-4 trigger the activation of immunoglobulin E (IgE), which then leads to the release of histamine and tryptase along with prostaglandin D_2, cysteinyl leukotrienes (LTC_4 and LTD_4), and adenosine [37]. Besides, IL-5 is involved in the recruitment of eosinophils, resulting in the development of allergic rhinitis in the upper airways. Synergistically, these mediators act together to narrow the airway and induce bronchospasm via contraction of smooth muscles, promote vascular leakage, increase infiltration of immune cells, as well as mucus hyperproduction. These ultimately lead to airway hyperresponsiveness and reduced lung FEV_1 as observed in asthmatic patients. In this context, airway epithelium produces thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 which act as the master regulators of Th2 cytokines expression and results in early onset of childhood asthma [36, 38]. Furthermore, group 2 innate lymphoid cells (ILC2) also appear to play a crucial role in augmenting type 2 responses in the airway, which suggest that innate immunity is involved in the pathogenesis of asthma. The intricate relationship between adaptive and innate immunity offers synergistic effect whereby Th2 cells and ILC2s act together to express the master transcription factor GATA-3, thus regulating the synthesis of type 2 cytokines [39].

Usually, asthma is diagnosed based on the medical and social history of the patient. Manifestation of symptoms such as shortness of breath, wheezing, coughing, and chest tightness may indicate underlying asthma. Clear identification of the patient's history of medical illnesses also facilitate in the diagnosis of asthma. For example, a history of allergies or eczema, as well as a family history of asthma

Table 2.2 Categorization of asthma severity based on symptoms and lung function

Severity	Symptoms/Lung function
Intermittent	– Daytime asthmatic symptoms of 2 days or less per week – Bothered by night-time symptoms twice a month or less – Uses inhaler twice a month or less – No interference with daily activities – Normal FEV_1 – Peak flow <20% variability from daytime to night-time – ≤1 exacerbation per year that requires oral corticosteroids
Mild persistent	– Daytime asthmatic symptoms of ≥2 days per week, <1 time per day – Bothered by night-time symptoms 3–4 times a month, <1 time per week – Uses short-acting beta agonists as reliever >2 per week – Minor interference with daily activities – $FEV_1 \geq 80\%$ – Peak flow 20 to 30% variability from daytime to night-time – ≥2 exacerbation per year that requires oral corticosteroids
Moderate persistent	– Daytime asthmatic symptoms every day – Bothered by night-time symptoms >1 time per week, but not daily – Major interference with daily activities – Peak flow >30% variability from daytime to night-time – FEV_1 between 60% and 80%
Severe persistent	– Daytime asthmatic symptoms happen throughout the day – Bothered by night-time symptoms every night – Frequent severe attacks – Extreme limitations of daily activities – $FEV_1 < 60\%$

greatly increases the risk of asthma [40]. Apart from that, lung function test is another popular method utilized to diagnose asthma. Lung function test plays a vital role in determining standard lung volumes in patients and it is often performed prior to and after inhaling a bronchodilator. As such, asthma is generally indicated if lung function appears to improve with the use of a bronchodilator [41]. Some of the primary lung function tests used to diagnose asthma include spirometry, peak airflow, FeNO tests (exhaled nitric oxide), and provocation tests [41]. The severity of asthma can then be determined based on the presented symptoms and lung function test results, thereby aiding medical practitioners in selecting a proper treatment plan tailored to the patient (Table 2.2) [42].

The treatment goals of asthma are mainly focused on two domains, which are to achieve good control of asthma-related symptoms as well as to minimize the risk of asthma exacerbations, decline in lung function, and adverse effects of medications [43, 44]. Generally, therapeutic options of asthma include inhaled corticosteroids (ICS), short-acting beta agonist (SABA), long-acting beta agonist (LABA), cromones, leukotriene modifiers, methylxanthine, anti-IgE monoclonal antibodies, and IL-5 antagonists. The recommended step-up therapeutic strategies for adults and children aged between 6 and 11 are summarized in Fig. 2.2 [43].

In most cases, ICS such as budesonide, fluticasone propionate, and mometasone furoate will be given together with SABA as the first line treatment after asthma is

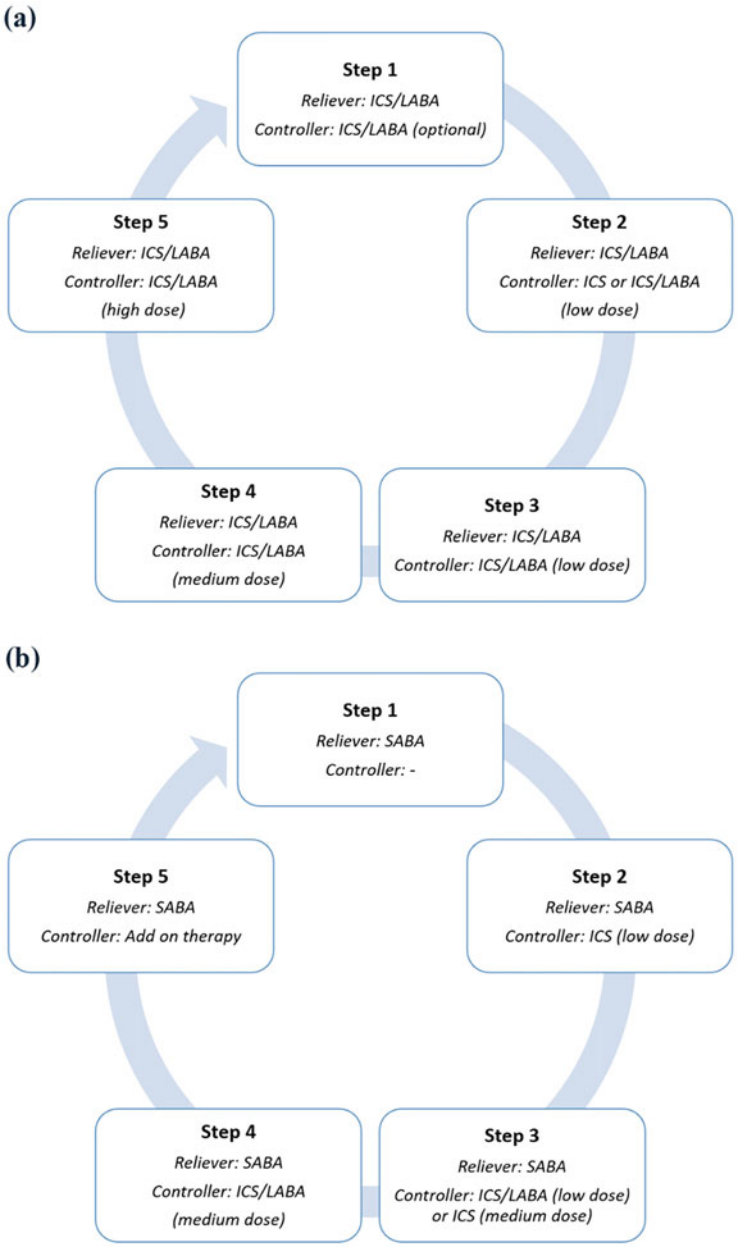


Fig. 2.2 Step-up therapeutic strategy of asthma in (**a**) adults; (**b**) children aged between 6 and 11

diagnosed [43]. Initially, it is recommended that ICS/LABA especially formoterol to be used as the reliever instead of SABA, such as salbutamol, for adults who are suffering from asthma. O'Bryne and co-workers have conducted a large double-blind study and found that in mild asthmatic patients, significant reduction of asthma exacerbation (64%) was seen in patient treated with ICS/LABA (budesonide/formoterol) in comparison with those who were treated with SABA as reliever [43, 45]. Similarly, another recent study conducted by Beasley et al. has also shown a prominent decrease of severe exacerbations (60%) in patients using ICS/LABA as reliever therapy [43, 46]. These are in-line with the Global Initiative for Asthma (GINA) Guidelines 2020, which reported that ICS treatment can reduce the risk of severe asthma exacerbations, improve lung function, prevent symptoms and exercise-induced bronchoconstriction occurrence in patients with mild asthma as compared to the patients who did not use ICS [43]. Nevertheless, prolonged used of ICS was found to induce several local to systemic adverse effects which include osteoporosis, candidiasis, dysphonia, and adrenal suppression [38]. Formoterol is the recommended LABA in the management of asthma as it possesses quick onset of action and it is a long-acting bronchodilator with therapeutic action up to 12 h [47]. The management strategy of having both ICS and LABA to be used daily for symptom relief is known as SMART therapy (Single-Inhaler for Maintenance and Reliever Therapy). As such, this will improve patients' adherence to treatment as it is cost effective and can exert dual therapeutic action at the same time. In the contrary, for patients who have moderate to severe asthma, tiotropium will be added on to tackle the conditions that cannot be controlled by ICS [32, 47]. Other therapeutic agents such as cromones, leukotriene modifiers, methylxanthine, anti-IgE monoclonal antibodies, and IL-5 antagonists will be added in cases where asthma cannot be controlled by existing regimens. Otherwise, the medications can be stepped down with careful monitoring if the patient's condition is well-controlled after treatment [47, 48].

In the recent years, biological inhibitors have gained attention for their use as novel asthma therapeutics. For example, tezepelumab is an anti-TSLP that blocks 'alarmins', which are a group of cytokines that play critical role in the pathogenesis of asthma by inducing several inflammatory cascades in the bronchial epithelium [49]. Phase 2 clinical trials have shown that tezepelumab decreases annual asthma exacerbation rates in patients with low and high inflammatory status. It is also demonstrated that tezepelumab diminished blood eosinophils and total serum IgE levels. However, the disadvantages of tezepelumab include the suppression or dysregulation of host defence immune system. Thus, close monitoring is recommended when patients are given tezepelumab although they are generally reported safe so far [50]. Another example is omalizumab, an anti-IgE biological inhibitor, which exerts its therapeutic effects by forming an irreversible complex with IgE, thereby blocking the production of inflammatory mediators and inflammatory cells that are involved in asthma pathogenesis. This is proven in a study by Busse et al. whereby administration of omalizumab led to a remarkable reduction in exacerbation of severe asthmatic patients in comparison with patients treated with ICS [51]. Furthermore, fevipripant, a prostaglandin D2 receptor inhibitor, also known as Th2 expressed chemoattractant receptor molecule (CRTH2), has also

been recently classified as one of the potential asthma treatment strategies. Fevipripant modulates the receptors of major inflammatory cells involved in the pathogenesis of asthma, thereby improving lung function in moderate or severe asthmatic patients with limited airflow or sputum eosinophilia, as demonstrated in phase II clinical trials [50]. In a nutshell, biological inhibitors may be efficacious and can potentially be utilized in the development of novel asthma therapeutics due to their intriguing key inflammatory pathways-targeting properties.

Although multiple prominent clinical studies have proven that biologics therapy targeting key cytokines in the asthma inflammatory pathways are the future generation medication for the treatment of asthma, there are insufficient biomarkers to-date to carefully assess the presiding inflammatory cascade in an asthmatic patient. Therefore, future research can focus on the identification of accurate biomarkers of the inflammatory pathways in a specific asthmatic patient to create a personalized therapeutic regimen [52]. Besides, combination therapies with current treatment and the new generation of biologics therapy can be further investigated, with medication safety as the topmost priority for such strategy. On-going research is still focused on developing new biological inhibitors as clinical trials have demonstrated decreased exacerbations as well as reduced adverse reactions attributed to reduction in the use of oral glucocorticoids and ICS, thereby providing precision medicine by targeting the key inflammatory cells involved in the pathogenesis of asthma [50, 52–54].

2.3.2 Chronic Obstructive Pulmonary Disease

COPD is a preventable, treatable but irreversible disease that is distinguished by airflow limitation and continuous respiratory symptoms that is normally caused by alveolar and/or airway deformities as a result of significant exposure to noxious gases or particles [55, 56]. COPD comprises a bunch of chronic, progressive conditions which includes chronic asthma, chronic bronchitis, emphysema (parenchymal destruction), and small airways deterioration (obstructive bronchiolitis) [55]. It is predicted that roughly 10% of people aged 40 years and above suffer from COPD even though such statistics may differ between countries and escalates with age [57–59]. According to a report by the WHO, the global burden of disease study presented that a total of 251 million COPD cases were discovered in 2016 globally. Besides, it was estimated that COPD resulted in 3.17 million deaths in the year 2015 alone, which is about 5% of total death [60]. Consequently, COPD poses huge economic burden in addition to its mortality rate, attributed to high medical costs as a result of frequent hospitalizations, necessities for chronic therapies such as medications and supplemental oxygen therapy, as well as productivity loss due to absence from work [61].

COPD can be diagnosed in patients presenting key symptoms which include slow progressive chronic cough, shortness of breath (dyspnoea), chronic sputum production, a history of recurrent lower respiratory tract infections, a history of exposure to risk factors of the disease, and/or family history of COPD (Fig. 2.3). The most common causative agent towards COPD is smoking. COPD can also be developed from several other risk factors and these include occupational exposures to dust and

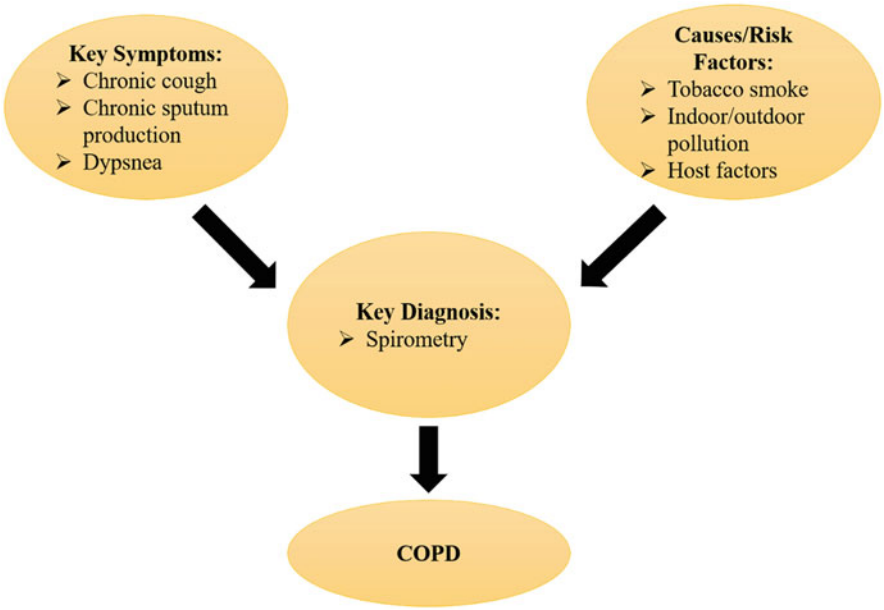


Fig. 2.3 The general diagnostic pathway of COPD

Table 2.3 GOLD classification of COPD severity based on lung FEV_1/FVC ratio

Stage	COPD severity	FEV_1/FVC ratio
Stage 1	Mild COPD	≥80% of normal
Stage 2	Moderate COPD	Between 50% and 80% of normal
Stage 3	Severe emphysema	Between 30% and 50% of normal
Stage 4	Very severe emphysema/ COPD	<30% of normal or stage 3 with low blood oxygen levels

chemical agents, indoor and outdoor air pollution, age, sex, genetic factors, poor lung growth, and/or pre-existing diseases such as respiratory infections, chronic bronchitis, asthma [62–64]. Typically, the severity of disease progression in COPD is estimated using spirometry and a staging system developed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Spirometry, the most objective and reproducible measurement of airflow limitation, has good sensitivity and can be used repetitively as it is non-invasive and readily available. On the other hand, the GOLD staging system of COPD classifies the severity of patients based on their pulmonary function in terms of forced expiratory volume in 1 s to forced vital capacity (FEV_1/FVC) ratio (Table 2.3) [65, 66].

The pathogenesis of COPD is primarily characterized by airflow obstruction and infiltration of inflammatory cells, particularly CD8+ T lymphocytes, macrophages, and neutrophils in both peripheral and alveolar spaces as a result of tobacco smoke

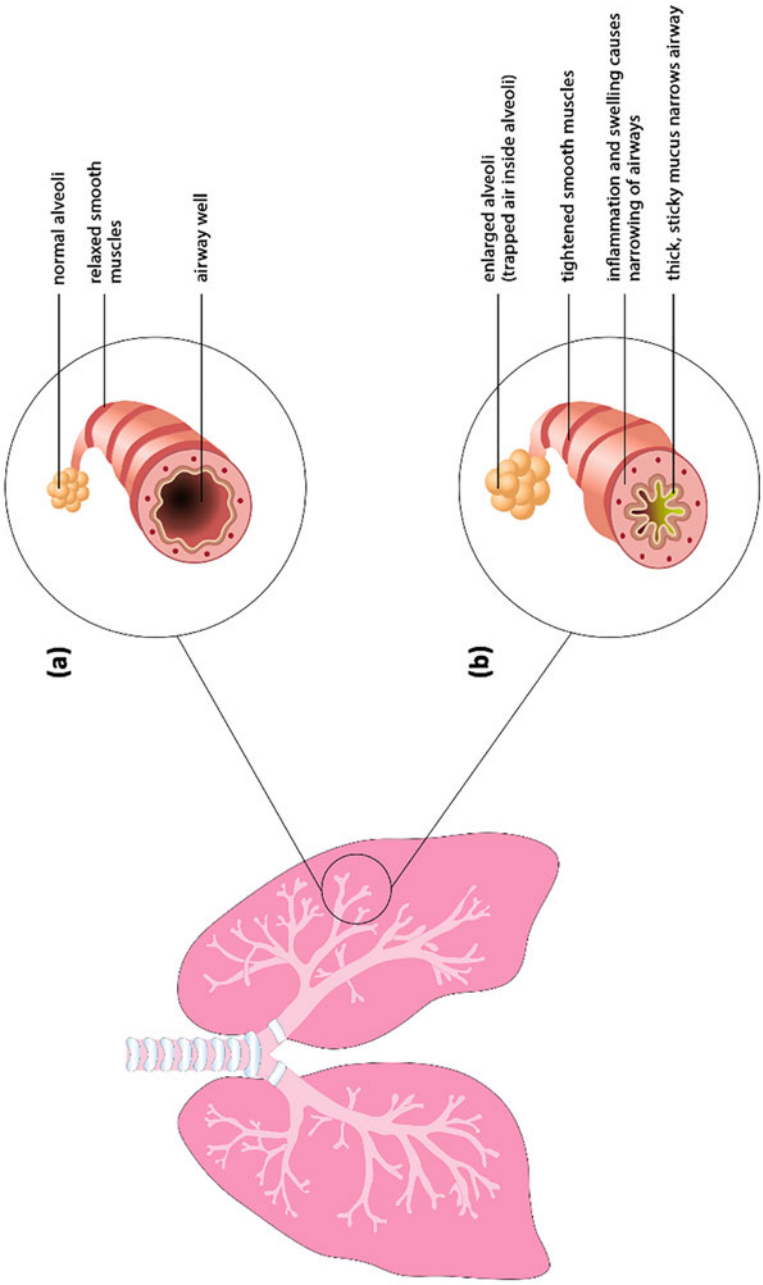


Fig. 2.4 Schematic illustration of the airways and alveoli in (**a**) healthy individuals and (**b**) patients with COPD

and/or environmental pollutants. Chronic inflammation and structural changes due to continuous injury and repair as a result of inhaled cigarette smoke and other toxic particles are the key pathological changes found in the peripheral, proximal airways, pulmonary vasculature, and lung parenchyma in COPD patients (Fig. 2.4). However, the immune responses are found to differ according to various subtypes of COPD [2, 67, 68]. Mucus hypersecretion, elevated inflammatory cells, serine proteases-induced MUC5AC gene overexpression, cigarette smoke-induced reactive oxygen species (ROS) production, as well as activated macrophages are the major driver of chronic bronchitis, whereby restricted airways and damaged adjacent cells lead to airway remodelling and loss of lung elasticity. Mucus hypersecretion can also further result in chronic productive cough and lung hyperinflation, leading to shortness of breath [69, 70]. In the contrary, emphysema is the direct result of cigarette smoke. Activated neutrophils, decreased antiprotease activity, reduced alpha$_1$-antitrypsin (AAT), and imbalance between antiprotease and protease activities are the key drivers that lead to gradual destruction of smaller airway walls and alveolar sacs [71]. Ultimately, alveoli lose their structure and normal functions, for instance, reduced gaseous transfer and airflow limitation, thereby contributing to hypoxemia, reduced ventilation, and dyspnoea [55, 72]. Nonetheless, the role and relationship between innate and adaptive immune responses in the pathogenesis of COPD remained unclear. It is generally believed that the exacerbation of COPD is triggered by overexpression of IL-8, matrix metalloproteinase (MMP), and CXC chemokines, as well as hyperproduction of pro-inflammatory mediators such as IL-1β, transforming growth factor (TGF)-β, tumor necrosis factor (TNF)-α, and leukotriene B4 that induce local fibrosis and dysregulation of oxidant/antioxidant homeostasis [2, 68].

The desired treatment outcomes for COPD are to decrease the severity and frequency of exacerbations, reduce the symptoms, prevent disease progression, decrease mortality, as well as to improve the patients' quality of life and their exercise tolerance. As the single most common risk factor for COPD is smoking, smoking cessation is important to improve one's COPD condition [73]. For this instance, the Lung Health Study has proven a remarkable lower decline in post-bronchodilator FEV_1 for patients' who quit smoking (22 to 30 mL/year) as compared to those who do not quit smoking (54 to 66 mL/year) [74].

In terms of pharmacological management, patients will be first grouped into either A, B, C, or D, based on a report published by GOLD (Fig. 2.5) [55]. According to Ferguson et al., it was suggested that inhaled bronchodilators (muscarinic antagonists and beta agonists) remain as the mainstay of pharmacological therapy in asthma, which are either given alone or in combination with inhaled glucocorticoids [75]. The major drawback of short-acting bronchodilators is that it may not provide effective relieve in patients with more often exacerbations as they have shorter duration of action (between 4 h and 6 h) as compared to the long-acting bronchodilators. Therefore, short-acting bronchodilators are mostly recommended for group A patients with minimum signs and symptoms, as well as low exacerbation risk. The combination of short-acting muscarinic agonist (SAMA) and short-acting beta agonist (SABA) is often preferably prescribed than either agent alone as such combination therapy can provide synergistic bronchodilator response [55]. This is

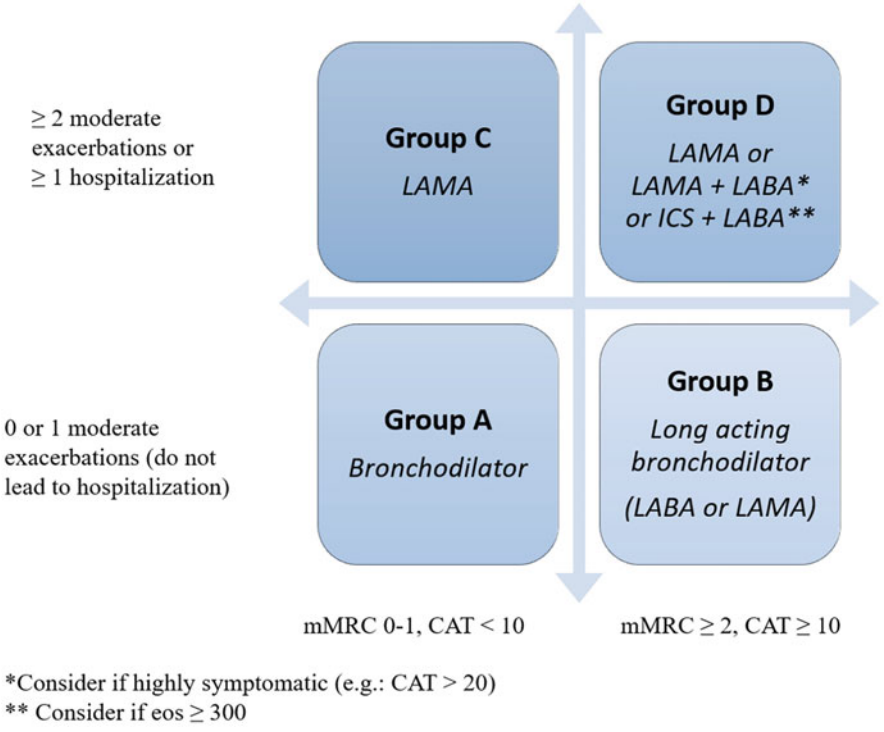


Fig. 2.5 Overview of pharmacological management in COPD patients

proven in a clinical trial whereby 534 patients were assigned randomly to receive either albuterol, a SABA, or ipratropium, a SAMA alone, or in combination of albuterol and ipratropium. The study demonstrated that combination therapy enhanced the mean peak FEV_1 significantly in comparison with either drug alone [76]. As for group B patients, long-acting bronchodilators, namely long-acting beta agonist (LABA) and long-acting muscarinic antagonists (LAMA) are usually given. The therapeutic efficacies of both LABA and LAMA have been evaluated and compared in various randomized trials and meta-analyses. It has been proven that the overall safety and efficacy were similar, except for LAMA which exhibited a greater reduction of exacerbations in COPD patients [55]. However, among the LAMAs, tiotropium has presented the greatest potential in minimizing exacerbations. This is proven through a seven trial-meta analysis which involved 12,223 participants [77]. Thus, tiotropium is generally the drug of choice for patients who fall in the group C category as well. Similarly, in a large randomized controlled clinical trial involving over 3000 individuals, tiotropium has demonstrated its capability of providing better protection against COPD exacerbations in comparison with indacaterol, a LABA [55, 78]. On the other hand, LABA-LAMA combination is undeniable the most reasonable approach for patients with severe shortness of breath (COPD assessment test (CAT) $\geq$ 20). Multiple studies have proven that

combination of LABA-LAMA is better in preventing exacerbations and significantly improved lung function as compared to either drug alone, or with LABA/ICS [55, 79]. Moreover, LABA-LAMA fixed dose combination inhaler is preferred over two separate inhalers because of its potential to improve patient adherence, therapeutic outcomes, as well as reduced medication costs [80].

In certain cases, inclusion of ICS in the therapeutic regimen of COPD patients with a history of severe exacerbations may further improve health status and lung function when used in combination with LABA and LAMA. This is in-line with the recommendations of GOLD guideline which indicated that triple therapy (LABA/LAMA/ICS) presented better therapeutic outcomes in comparison with dual or monotherapy [81]. Besides, addition of mucolytic agent to regular therapeutic regimen, such as bromhexine and erdosteine may help in enhancing health status and reducing the risk of exacerbation in COPD patients who are not receiving any ICS. Other medications such as methylxanthine (e.g. theophylline), antibiotics (e.g. azithromycin), and phosphodiesterase-4 inhibitors (e.g. roflumilast) can also be given on a case-to-case basis [55]. In short, the use of medication varies with individuals depending on their disease condition. The published references may serve as a guide for healthcare professionals to decide and weigh upon the benefits and the risks assessed individually for different patients.

Despite advancements in medical research over the years, current treatments can only help to relieve the symptoms associated with COPD and retard the progression of lung destruction, but there is no cure to the disease and regeneration of damaged lung tissue is not possible. As COPD is a progressive disease that deteriorates with ageing, existing therapies are designed to slow the progression of COPD and to provide temporary relief for patients, but these therapies are not capable of restoring normal functions of the lung in its damaged regions. Complete recovery is currently only possible with a lung transplant, which is normally a less feasible approach in most patients [2, 73]. Although ICS demonstrated benefits in reducing the risks of exacerbation when used concurrently with LAMA and LABA, it has been recently discovered that patients using ICS are often associated with a higher risk of getting pneumonia. Morjaria et al. have performed a randomized controlled trial study to determine whether patients treated with ICS presented a higher risk in developing pneumonia as compared to ICS-free therapy. The results demonstrated that with ICS, the incidence rate of pneumonia is approximately 20 to 30% higher than those with ICS-free treatment [82, 83].

Future studies in the development of novel COPD therapies are focused on the identification of key biomarkers driving the pathogenesis of COPD in specific patients, in an attempt to design individualized COPD therapeutic regimen via specific targeting to cure this disease instead of just relieving the symptoms and preventing exacerbations. A recent study conducted by Broekman et al. has reported that cell therapy utilizing mesenchymal stromal cell might be one of the potential novel COPD therapeutics. In pre-clinical studies, regenerative mesenchymal cells have demonstrated the ability to alter immune response and improve the process of tissue repair. This further enhances target cells proliferation and migration which in turns decreases cell apoptosis. However, its precise mechanism of action is still yet to be known [84].

2.3.3 Interstitial Lung Disease

Interstitial lung disease (ILD) is an umbrella term that refers to a wide range of diseases that cause scarring or fibrosis in the lungs [85]. The term 'interstitial' suggests that the abnormality begins in the interstitium, however, most of the ILDs are also associated with pathological changes in the alveolar and airway architecture [86]. Typically, ILDs are linked to inflammation in the airways, such as bronchiolitis, alveolitis, and vasculitis. However, the manifestations of ILD may differ by individuals and comprised of respiratory symptoms such as shortness of breath and non-productive cough, loss of weight, decreased pulmonary capacities, chest discomfort and abnormalities in chest radiography, as well as pulmonary haemorrhage [87]. ILDs can be classified according to their clinical, radiological, physiological, and histopathological features, for example, sarcoidosis indicates the presence of granulomatous inflammation with no parenchymal fibrosis, whereas idiopathic pulmonary fibrosis (IPF) indicates the presence of broad pulmonary fibrosis with lung distortion [85]. ILDs are highly prevalent globally and affect mostly adults, with IPF being the most common form of ILD, whereby it has been estimated that about three million individuals suffered from IPF [88]. As treatment plan varies according to the causes and types of ILD, ascertaining the correct diagnosis is very important. Diagnosis of ILD usually involves detailed screening of patients' medical and family history, physical examination, laboratory testing, imaging, physiologic testing, and biopsy [89]. When observed through a chest radiograph, the most common feature seen is a reticular pattern, but nodular or mixed patterns are also observed. High-resolution computed tomography (HRCT) can offer a better characterization of the disease and support the diagnosis in case of a negative chest X-ray. Generally, a complete lack of pulmonary parenchymal changes on HRCT imaging virtually excludes a diagnosis of ILD, although in rare cases, ILD may still be present within the lungs having microscopic involvement that does not reach the threshold for the detection of an abnormality which is usually detectable by HRCT [85, 87].

The disease outcome of ILD is heterogenous and it can vary from partially reversible fibrosis to deadlier chronic progressive fibrotic ILDs. Specifically, IPF, the most common type of ILD, has a very poor prognosis whereby the mean survival rate of patients diagnosed with IPF is only approximately 2-5 years [90]. The management of IPF is further complicated by its high intra- and interindividual heterogeneity, as some patients presented slower disease progression whereas some other patients presented rapid decline in lung function. Furthermore, in the same patient, periods of minimal changes in lung function can also alternate with periods of rapid decline of lung function [91]. Therefore, it is important to obtain a complete history during the initial evaluation of a patient with suspected ILD so that the probable cause of disease can be recognized. There are a wide range of causes that may lead to ILD, including environmental and occupational factors, tobacco and medication use, infections, as well as autoimmune disease such as rheumatoid arthritis [92]. Certain cases of ILDs have also been associated with genetic alterations that cause increased fibrosis [93]. Nonetheless, most ILDs are idiopathic diseases which indicate that the causes of lung injury and fibrosis are generally

unknown. Besides, ILDs often present with comorbidities and lack specific symptoms which may complicate diagnosis, thereby resulting in delay of treatment in these patients [85].

Despite advancing technologies in the field of medical research, the exact mechanisms involved in the pathogenesis of ILDs are still relatively vague; however, they appear to be multifactorial. ILDs are primarily characterized by a combination of chronic inflammation in the lungs, where there is an accumulation in inflammatory cells and surge in pro-inflammatory cytokines, as well as lung fibrosis due to abnormal deposition of collagens and other extracellular matrix components [92, 94]. Morphological changes can be observed in the parenchyma due to events of inflammation. Following chronic injury in the alveolar epithelium, proteins, and profibrotic elements present in the parenchyma would undergo repetitive activation, which then results in accumulation of connective tissues and fibrosis. Such proliferation and excessive accumulation of fibroblasts, myofibroblasts, and extracellular matrix eventually lead to chronic respiratory failure in ILD patients [94]. Nevertheless, the key underlying mechanisms of these events remained unclear and poorly understood, with possibility of the involvement of multiple signalling pathways that contributed to the large diversity of clinical manifestations in ILD patients [94, 95].

The treatment of ILD mainly depends on the cause and severity of the disease. Patients who have mild and stable ILD, characterized by mild symptoms and minimal pulmonary impairment, may improve without therapeutic interventions, and may only require close monitoring until there is evidence of disease progression. However, most patients with ILD require pharmacological treatment and supportive care [96]. For ILDs with known causes, such as medication or inhalational exposure, the first step is to avoid the offending agent and other possible risk factors. Current smokers should also be strongly advised to stop smoking [96, 97]. The pharmacological treatment for ILD mainly aims to preserve lung function by reducing exacerbations and to improve patients' quality of life. It involves the use of glucocorticoids and immunosuppressive drugs such as cyclophosphamide, prednisolone, and azathioprine. Systemic glucocorticoids are initiated in patients with moderate symptoms and impairment on pulmonary function testing, and diffuse abnormalities on high-resolution computed tomography. An additional immunosuppressive agent will be added in most patients after 3–6 months of treatment with glucocorticoid therapy. In severe cases, oral glucocorticoids are initiated in combination with an immunosuppressive agent [85, 96–98]. Despite that, administration of these therapies seemed to present little to no effects in providing long-term improvements for patients with most severe cases of progressive fibrosis [97]. In addition, glucocorticoids are commonly associated with various adverse effects, such as loss of bone density, dermal atrophy, cataracts, glaucoma, obesity, and elevated levels of triglyceride and blood glucose [99]. Hence, more detailed studies and reviews are needed to support the use of corticosteroids in the management of ILDs.

Currently, pirfenidone and nintedanib are among the two approved antifibrotic agents that demonstrated therapeutic effects of ILDs by slowing down the progression of disease and preventing decline in lung function [100, 101]. Nintedanib is

believed to exert its therapeutic effect on ILDs by inhibiting intracellular tyrosine kinase inhibitors involved in the pathogenesis of ILDs, such as platelet-derived growth factor receptor, vascular endothelial growth factor receptor, fibroblasts growth factor receptor, and profibrotic mediators [100, 102, 103]. On the other hand, pirfenidone exhibited broad anti-inflammatory, antioxidant, and antifibrotic activities, such as its ability to reduce transforming growth factor (TGF)-β and TNF-α [100, 104, 105]. However, their precise mechanism of action is still not well elucidated, and several adverse reactions have been associated with the use of these medications [102, 106]. Apart from that, azathioprine and mycophenolate mofetil are the common immunosuppressive agents used for the treatment of ILDs [96]. A study by Ayer Fischer noted that mycophenolate mofetil is well tolerated and effective towards connective tissue disease associated ILD. The treatment has low rate of discontinuation and improved pulmonary physiology over a median 2.5 years of follow-up studies [107]. Likewise, another study by Huapaya JA et al. also concluded that ILD patients treated with both azathioprine and mycophenolate mofetil had improved FVC percentage predicted and required lower dosage of prednisone [108]. Oldham JM et al. also noted that azathioprine and mycophenolate mofetil therapies were associated with improved stability in pulmonary function in ILD patients. However, minority of the patients could not tolerate the adverse effects of immunosuppressants. Specifically, 10 out of 64 patients prescribed with azathioprine switched to mycophenolate mofetil due to side effects such as nausea and vomiting, elevated transaminases, and rashes. Notably, no patients prescribed with mycophenolate mofetil switched to azathioprine due to side effects [109].

The prognosis of ILD strongly depends on its aetiology and disease progression. Although several drugs have shown certain effects in managing ILDs, IPF is widely known for its poor prognosis and resistance towards treatment [89]. It has been established that ILD patients with IPF had a significantly shorter survival in acute exacerbation when compared to those with non-IPF ILDs. This remained as a major health concern as the efficacy of current therapeutic agents remains debatable and the use of such agents has resulted in adverse effects to a certain extent [97]. Hence, development of new therapeutic strategies is needed to enhance the treatment efficacy in ILDs and to minimize the incidences of adverse effects. Recently, advanced materials are being studied as novel strategies in the treatment of ILDs. A study by Yhee JY et al. noted that glycol chitosan nanoparticles can be used as a drug-carrier system in the treatment of fibrotic lung fibroblasts due to its remarkable interaction with collagen-rich matrix that leads to enhancement of its intracellular delivery [110]. Similarly, another study by Garbuzenko OG et al. also proposed that inhalation delivery of nanostructured lipid carriers loaded with prostaglandin E and siRNAs can be developed as an efficient therapeutic for IPF [111]. In a nutshell, more researches are needed to further explore on the treatments of ILDs, including the use of novel strategies such as nanomedicine as well as precise identification of the mechanistic and molecular pathways underlying development of ILDs. The novel therapies should ultimately improve patients' survival, slow disease progression, and enhance patients' quality of life with better tolerability towards these therapies.

2.3.4 Cystic Fibrosis

Cystic fibrosis (CF) is a multisystem autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene [112]. It is the most common life-shortening gene disorder whereby approximately 70,000 individuals are affected by this disease, primarily in Caucasian children [113]. CFTR is a protein-encoding gene that translates cAMP-activated anion channels in epithelial cells, which functions to regulate the transport of anion and mucociliary clearance in the respiratory airways. Therefore, dysfunction of the CFTR gene can result in thick, viscous secretions in the lungs, which then hinders the intrinsic clearance and defence system, leading to inflammation and impairment of the lungs [114]. The initiation of CF primarily involves mutation in the ΔPhe508 gene that is found in the gene locus on the long arm of chromosome 7, accounting for approximately 70% of CF cases. Such mutation commonly occurs as a three-base-pair deletion which leads to loss of phenylalanine at the 508th residue within the predicted 1480 amino acid of CFTR protein [115, 116]. The mutations in CFTR gene can be generally classified as: (a) Class I, protein synthesis defect, such as nonsense and splice mutations that affect protein production; (b) Class II, maturation defect, such as abnormal addition and deletion of amino acids; (c) Class III, gating defect, which is a type of mutation that cause the CFTR protein to remain closed; (d) Class IV, conductance defect, which is the malfunction in protein functionality; (e) Class V, insufficient protein mutations that lead to reduced amino acid quantity; and (f) Class VI, reduced stability mutation [117, 118]. Furthermore, Class VII mutation is a new class whereby there is an absence of CFTR protein and it cannot be rescued by any corrective therapies [119]. Classes I, II, and III are more severe mutations of the CFTR gene, hence they result in greater lung dysfunction and damage as compared to other milder mutations, such as classes IV and V [118].

CF is clinically characterized by persistent and recurrent pulmonary infections, pancreatic insufficiency, and elevated levels of chloride found in sweat ($\geq$60 mmol/L) [120]. Mutations in the CFTR gene often result in malfunctioning and misfolded proteins causing dehydrated mucus, ultimately affecting the normal mucociliary clearance processes. As mucus is regularly produced by other components of the respiratory system, namely the goblet cells and submucosal glands, they cannot be adequately cleared from the lungs, thereby forming mucus plugs that further lead to local tissue hypoxia on epithelial cell surface [121, 122]. Mucus plugging has been established as the nutrient-rich nidus that contributes to pulmonary bacterial infection, which is a potent stimulus of neutrophilic airway inflammation that leads to progressive lung damage in CF patients. Thus, bacterial infections of the airways are important determinants of prognosis in CF patients, particularly in the first few years of life [121, 123].

Current treatment for CF mainly aims to relieve the symptoms of CF and to maintain pulmonary health; however, there is still no cure for CF. Conventional treatment strategies are primarily focused on targeting the downstream consequences of the disease, such as infection and mucus plugging. Treatment generally comprised of CFTR modulators, bronchodilators, anti-inflammatory agents, and mucolytics

[124, 125]. Patients with CF may also be started on antibiotic therapy to prevent and eradicate infection in the airway [126]. Multivitamins, including fat-soluble vitamins and pancreatic enzyme supplements are also given to support nutrition in both adults and children [126, 127]. Recently, novel treatments are being explored to improve the lifespan and quality of life in patients with CF. For instance, the use of nanotechnology as drug carriers allows effective delivery of drugs to the target site and minimizing the adverse effects of the drugs. The size of nanoparticles allows it to penetrate through the thick mucus of patients with CF, as well as bacteria biofilm [127, 128]. This is proven in a study by Günday Türeli et al. which tested the antibacterial potential of ciprofloxacin complex-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles in CF-associated *P. aeruginosa* lung infections. It was shown that when treated using the nanoformulation, antibacterial activity was enhanced and there was a decrease in mucus turbidity [129]. Gene therapy is also being studied as a promising approach for CF treatment, such as the addition of a normal functioning CFTR gene into defective airway cells, which could ultimately alter the underlying structural and functional abnormalities of the lungs [130–132]. Nonetheless, more studies and larger clinical trials are needed to support the use of such therapies in the treatment of CF.

2.3.5 Pulmonary Tuberculosis

Tuberculosis (TB) is a multisystemic disease with myriad presentations and manifestations caused by an acid-fast, aerobic bacilli bacterium known as *Mycobacterium tuberculosis* [133]. According to the WHO, TB is presently the leading cause of worldwide mortality resulted from a single infectious agent, whereby it was estimated that there are more than ten million individuals infected and more than 1.5 million deaths from this disease [134]. The symptoms of TB are usually gradual in onset and the duration varies from weeks to months, although more acute onset can occur in young children and immunocompromised individuals, such as in patients co-infected with human immunodeficiency type 1 virus (HIV-1) [135, 136]. The most reported symptom is persistent non-remitting cough, which can be accompanied by malaise, fever, weight loss, night sweats, and anorexia [136]. In some cases, TB patients are also reported to present haemoptysis and shortness of breath [137].

TB is an inhaled infectious disease that primarily affects the lungs but may also affect the central nervous system, lymphatic and circulatory systems, bones, and tissues. *M. tuberculosis* is highly contagious, and it is transmitted in aerosols from the lungs of active TB patients via coughing, sneezing, and spitting. When a susceptible individual is exposed to these droplets containing the active bacterium, the pathogen will be inhaled and deposited in the alveoli [138–140]. The bacterium then stimulates the alveolar macrophages and proliferates within, leading to the production of cytokines and chemokines. This further attracts phagocytic cells such as monocytes and neutrophils to form aggregates that surround the bacteria, resulting in a granuloma. Hence, granuloma is known as a diagnostic

histopathological hallmark of tuberculosis [138, 140]. As *M. tuberculosis* can strongly withstand degradation by ROS and nitrogen intermediates whilst impeding acidification by phagosomes and lysosomal fusion, the pathogen can remain in the host upon phagocytosis by alveolar macrophages. Such characteristics of the pathogen facilitate its rapid replication, leading to tissue dissemination and eventually tissue damage in active TB patients, as well as downstream person-to-person transmission. This may also be attributed to the capability of the pathogen to secrete various effector proteins that modulates the host immune system, which in turn promote its survival to persist in granulomas during the latency phase of infection [133, 141, 142]. Nevertheless, *M. tuberculosis* is an intracellular pathogen that lacks classical virulence factors; therefore, it can persist in the host during long-term latency and does not pose significant damage if the host immunity is not compromised [133, 141]. Typically, the types of structural lung damage that may occur in pulmonary TB patients include traction bronchiectasis, bronchostenosis, pulmonary fibrosis, cavitation, as well as destruction of lung parenchymal [143].

Generally, antituberculosis regimen consists of a two-month period of intensive phase, followed by a maintenance regimen, which may range from 4 to 7 months. As recommended by the WHO, the first line drugs utilized in drug-susceptible TB include isoniazid, rifampicin, pyrazinamide, and ethambutol [144, 145]. These drugs are given at the same time to synchronize peak serum concentrations so that the pathogen killing effect can be further optimized [146]. It has been reported that the 6-month regimen is effective, with relapse rate ranging from only 0% to 7% in a follow-up after 2 years. Likewise, the treatment regimen for extrapulmonary TB is the same as pulmonary TB, however, the duration of treatment may vary [147]. Despite the effectiveness of the antituberculosis regimen in eradicating infection, the success rate may be lowered in cases of TB that are resistant to rifampicin and isoniazid. In cases of resistance or intolerance towards the first line drugs, fluoroquinolones, such as moxifloxacin and levofloxacin, are recommended as the alternative treatment for TB [146, 148]. In addition, adverse effects of drugs are also reported, which has led to discontinuation of these drugs in certain patients. The most common adverse effect is hepatotoxicity, particularly in patients treated with combination of isoniazid, rifampicin, and pyrazinamide [149, 150]. Thrombocytopenia, although uncommon but potentially fatal, is also reported in TB patients treated with isoniazid and rifampicin [149, 151].

WHO has also reported a rising trend in the cases of multi-drug resistant TB (MDR-TB) over the years [152]. It is estimated that there were 480, 000 cases of MDR-TB in 2015, and over 484,000 cases of MDR-TB and rifampicin-resistant (RR)-TB in 2018 [134]. This can be challenging because MDR-TB has high mortality rate, and the treatment is often complicated and involves longer therapeutic duration that stretches up to 20 months [145]. Despite extensive research, the treatment outcomes of MDR-TB are still suboptimal, with only approximately 52% success rate. To make things worse, some patients with MDR-TB may also develop extensively drug-resistant TB (XDR-TB), where the pathogen is resistant to any fluoroquinolone and to at least one of the three injectable agents (kanamycin, amikacin, or capreomycin) [153]. Furthermore, the cost associated with drug

administration in MDR-TB patients is also much higher due to longer therapeutic duration and more drugs being utilized [154]. WHO has recommended a 4–6 months intensive phase of MDR-TB treatment using a regimen of moxifloxacin, kanamycin, clofazimine, prothionamide, isoniazid, ethambutol, and pyrazinamide, followed by 5 months continuation phase using moxifloxacin, pyrazinamide, clofazimine, and ethambutol [155]. Other alternative treatments are also being explored for their potential in managing MDR-TB, including new drugs such as delamanid and bedaquiline, and repurposed drugs, such as linezolid and carbapenems [153].

Novel treatment strategies are currently being actively studied and developed to improve patients' adherence to TB regimens and to improve the efficacy of existing TB regimens. For example, the pulmonary route of drug delivery is being evaluated for its effectiveness in combating TB as it is believed that the drugs can be targeted to the lungs, which is the principal entry route of the pathogen and primary site of the disease [156]. Besides, advanced delivery systems such as liposomes and nanoparticles are now being studied as potential drug carriers for antituberculosis drugs. The use of nanocarriers offers several benefits including reduced side effects, higher drug bioavailability through their controlled-release design, and their feasibility for inhalational delivery, thereby requiring lower dosage frequency and resolves the issue of poor medication compliance [156–158]. This is attributed to their small size which facilitates uptake by macrophages and allows selective accumulation of drugs in the sites of invading pathogens [159]. A study by Estevez H et al. has found that selenium nanoparticles can inhibit the growth of *M. tuberculosis* by damaging their cell envelope integrity [160]. Similarly, Tăbăran AF et al. also presented the benefits on the use of silver nanoparticles in the treatment of TB and MDR-TB, in which silver nanoparticles can be incorporated with multiple antituberculosis drugs to overcome critical therapeutic issues associated with existing therapies [161]. Apart from that, these nanocarriers can also be designed to release their cargo only after their entry into macrophages. A study by Clemens et al. has designed mesoporous silica nanoparticles equipped with cyclodextrin-based pH-operated valves to release isoniazid upon exposure to the acidic pH environment in *M. tuberculosis*-infected lung macrophages. The results showed that such nanoparticles achieve significantly improved killing effect towards *M. tuberculosis* as compared to an equivalent amount of free isoniazid [162].

Although these novel strategies demonstrated great potential in the management of TB, the number of studies is still scarce to provide a solid evidence for its clinical application. Most of these studies are still in the in-vitro stage; hence, more in-vivo studies and clinical trials should be performed to evaluate its therapeutic efficacy and safety profile. It is hoped that these novel strategies can be translated into effective, tolerable, affordable, and successful treatments that can address the current issues of drug resistance and adverse effects faced by patients in the treatment of both TB and MDR-TB.

2.3.6 Lung Cancer

Lung cancer is one of the most common cancer and leading cause of cancer death worldwide, presenting itself as a highly invasive and rapidly metastasizing disease in both men and women. It is defined as the malignancies caused by uncontrolled cell proliferation in tissues of the lung [163]. Lung cancer-related mortality is primarily driven by late diagnoses and inadequate therapeutic interventions, whereby more than 70% of patients only seek treatment when the disease is at its advanced stage. The American Cancer Society has reported that there are about 228,820 new cases of lung cancer and about 135,720 deaths from lung cancer every year [164]. The frequency of lung cancer development and its mortality is highly attributed to an individual's smoking history, whereby the competitive gene–enzyme interactions at the procarcinogen level and subsequent extent of DNA damage strongly influence the tobacco-induced susceptibility of lung cancer. Therefore, lung cancer is widely regarded as a preventable disease through smoking cessation. As such, public awareness and education are crucial in the efforts of combating lung cancer, in order to avoid drastic rise in the prevalence of the disease and to reduce the healthcare burden and enormous costs associated with lung cancer [165, 166]. Other risk factors linked to the development of lung cancer include passive tobacco smoke inhalation, environmental pollution and contamination, radiation, occupational exposures, infection, as well as genetic susceptibility [163].

Depending on its origin in various locations in the lung, lung cancer can be classified into two major types, namely small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) (Table 2.4). Statistically, most cases of lung cancers are NSCLC (84%) as compared to SCLC (13%). NSCLC can further be subdivided into three different subtypes, which are squamous cell carcinoma, adenocarcinoma, and large cell carcinoma [167]. Specific histopathologic characteristics along with reliable immunohistochemical markers facilitate the clear distinction between pre-invasive lesions and invasive adenocarcinomas. There have been increasing evidence which suggests that lung cancer comprises a group of molecularly and histologically heterogenous diseases, even within the identical histological subtype [168]. Generally, patients with lung cancer will present symptoms of haemoptysis,

Table 2.4 Differences between non-small cell lung cancer and small cell lung cancer

	NSCLC	SCLC
Origin	Epithelial cells of the lungs	Nerve producing cells of the lung
Classification	• Adenocarcinoma which originates from peripheral lung tissue • Squamous cell carcinoma which develops nearby the large airways • Large cell carcinoma which presents with large and excess cytoplasm, as well as large and visible nuclei	• Limited stage • Extensive stage
Metastatic potential	Variable	Rapid

weight loss, breathing difficulty, and chest pain. However, these signs and symptoms may differ depending on the type and anatomical location of the cancer [169, 170]. On the other hand, among the various histologies of lung cancer, SCLC presented a relatively high risk to metastasize to the brain as compared to NSCLC. In NSCLC, frequency of patients with large cell carcinoma and adenocarcinoma to develop brain metastasis is much higher than those with squamous cell carcinoma. Patients that developed lung cancer associated brain metastasis commonly present neurological symptoms such as headaches, fainting, convulsion, and weakness of limbs [171].

The cause of lung cancer development is mostly associated with genetic damage to DNA and mutations that affect normal cell regulation processes. Some of the driver mutation genes that have been established to be correlated with NSCLC are epidermal growth factor receptor (EGFR), B-Raf proto-oncogene (BRAF), echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) fusion oncogene, c-ROS oncogene 1 (ROS1) fusions, and p53 gene mutations [172, 173]. Apart from that, CD44 gene mutations have been observed in both NSCLC and SCLC [174–176]. Overexpression of programmed death ligand 1 (PD-L1) is also observed in NSCLC patient without driver mutations [175].

Diagnosis will be initiated if symptoms of primary or metastatic lung cancer are observed. The preferred approach will be imaging and invasive biopsy as they are useful tools to determine histopathological changes and to identify the stage of the disease. For instance, chest radiograph showing enlarging lesion, collapse of lung, pneumonia, or excessive fluid in pleural cavity may be suggestive of lung cancer [177]. Patients will also be evaluated by using computed tomography (CT) scan to identify abnormalities in lung nodules. Whole body positron emission tomography (PET) or integrated PET/CT may be performed, followed by biopsy or surgical excision for histopathology if the nodule is found abnormal and indicative of lung cancer [178–180]. These tests can provide essential information for NSCLC staging, which include tumour size, mediastinal node enlargement, and potential intra- or extra-thoracic metastases [181]. PET scan can also be used for the assessment of recurrent lung cancer. Other tests such as sputum cytology, complete blood count, and blood chemistry profile can be performed for further evaluation and to generate precise diagnosis of lung cancer [178]. An accurate diagnostic is essential as it has a huge impact on treatment planning and the subsequent prognosis of the disease.

Treatment will only be recommended after the staging of the patient, whereby the goals of treatment are to improve patients' quality of life, palliation of the symptoms, and survival prolongation [182, 183]. Initiation and the choice of treatment regimen depend on the type of the lung cancer, its spread, and the underlying health status of the patient. If the patient is confirmed with stage I or II NSCLC, surgical resection, or lobectomy, will be recommended as the first line therapeutic strategy to improve long-term survival rate and as a cure for the disease [175]. For patients who refuse or are not suitable for surgery due to poor pulmonary function and presence of other comorbidities, non-surgical local therapies such as radiation therapy, radiofrequency ablation, cryoablation, and photodynamic therapy (PDT) will be preferred instead [175, 184]. PDT has long been approved to treat lung cancer, especially in NSCLC.

However, the photosensitizer utilized, porfimer sodium, may result in adverse effects such as hypoxia and photosensitivity [185].

For the management of stage III NSCLC, the combination of chemotherapy and radiotherapy is preferred. Combination of cisplatin and etoposide daily, or carboplatin and paclitaxel weekly are the choices of chemotherapy regimen. Nevertheless, Liang and co-workers have demonstrated that concurrent use of cisplatin with etoposide and radiotherapy increases survival rate of patients for additional three to 5 years as compared to carboplatin with paclitaxel [186]. However, this treatment option may not be suitable in patients with unresectable stage III NSCLC. As such, immunotherapy such as PD-L1 antibody, durvalumab, may be useful. A randomized phase III clinical trial has demonstrated improvement of 36-month survival rate in NSCLC patient on durvalumab as compared to those on placebo [187]. Patients with stage IV NSCLC are generally treated with systemic therapy and palliative care. Systemic therapy is usually focused on the mutated genes that result in advanced NSCLC, such as PD-L1, EGFR, and ALK [188]. As such, patients in stage IV NSCLC with identified driver mutation gene will be initiated with the respective gene inhibitor as monotherapy. For instance, NSCLC caused by EGFR driver mutation gene will be treated with EGFR tyrosine kinase inhibitors (TKIs) such as osimertinib, erlotinib, gefitinib, and afatinib. In this case, osimertinib is more preferable as the frontline agent as it demonstrated more improvements in progression-free survival as compared to erlotinib and gefitinib [189]. Likewise, NSCLC caused by ALK fusion oncogene will be treated by ALK inhibitors such as alectinib, ceritinib, crizotinib, and brigatinib. Nonetheless, all these gene inhibitors are not advisable to be combined with chemotherapies as they possess significant toxicity. If other metastatic sites have been detected, radiation therapy or surgical intervention may be employed to improve quality of life of the patient [188].

In terms of SCLC, patients rarely survive more than a couple of months without treatment. As SCLC is more sensitive towards chemotherapy, it is the mainstay of therapy in SCLC patients. Like stage III NSCLC, the initial treatment for limited stage-SCLC will be cisplatin or carboplatin, and etoposide. As compared to platinum-based chemotherapies, cisplatin has lower risk of haematologic toxicity. However, the response rate, progression-free survival, and overall survival rate are similar [190]. Furthermore, the combination of cisplatin and etoposide presented lesser toxicity in comparison with the older regimens like such as cyclophosphamide and vincristine with doxorubicin, or with epirubicin [191]. Two alternative regimens, namely irinotecan with cisplatin, or paclitaxel and etoposide with cisplatin or carboplatin, can also be used to enhance the overall therapeutic outcome in SCLC patients [192]. Apart from that, thoracic radiation therapy is employed concurrently with chemotherapy in certain cases, whereby such therapeutic strategy has shown significant improvement in both local control of the disease and overall survival rate [192, 193]. In extensive stage-SCLC, immunotherapy will be initiated along with chemotherapy. For instance, the humanized monoclonal anti PD-L1 antibodies atezolizumab and durvalumab have shown to improve survival of SCLC patients when combined with platinum-based chemotherapies and etoposide [194, 195]. Another drug of choice will be pembrolizumab, however, it only

shows improvement in progression-free survival with no effect on overall survival [196].

Till date, there is still no exact cure for lung cancer. All treatment options can only prolong survival rates of patients instead of full recovery from the disease. Besides, current cancer therapeutics has resulted in long-term adverse effects that decrease patients' quality of life. Hence, more studies should be done to identify the exact mechanisms of lung cancer, as well as to develop novel therapeutic agents and novel therapeutic strategies that target the pathogenesis of disease in a specific, precise, and non-invasive manner. For instance, angiogenesis inhibitors, histone deacetylase inhibitors, insulin-like growth factor inhibitors, and pro-apoptotic agents are among the novel classes of chemotherapy investigated for their therapeutic effects in lung cancer [197–200].

2.4 Novel Strategies in the Management of Chronic Respiratory Diseases

Although the pathogenesis and epidemiology of CRDs have been established by many researchers, most of the existing therapeutics are unable to effective combat these diseases. For example, bronchodilators, LABAs, and LAMAs that are employed in asthma and COPD have only shown efficacy in controlling exacerbations in patients with mild to moderate symptoms but are not fully effective in patient with chronic diseases. Besides, the emergence of drug resistance has hindered the optimal performance of therapeutic agents in the treatment of communicable respiratory diseases, such as those manifested in MDR-TB. Conventional therapeutics are also widely associated with adverse effects, which may affect patient's compliance to the medications and have a serious impact on patients' quality of life. Moreover, severe forms of CRDs are usually characterized by irreversible damage of lung tissues, which cannot be cured or restored by any of the conventional therapeutics. Hence, there is a pressing need for the scientific community to develop novel agents or treatment strategies that can effectively combat these pulmonary diseases.

2.4.1 Plant-Based Chemical Moieties

Plants and herbal-based bioactive compounds have been used as the backbone of traditional healing systems since the inception of human beings [201]. Unlike traditional use of plant-based therapies that utilizes unmodified whole plant, modern therapeutics are focused on the identification of biologically active compounds from natural plant and herbal sources, and extracting these compounds for specific therapeutic applications [202, 203]. Numerous studies conducted throughout these years have proven that plant-based chemical moieties are effective in targeting cell signalling pathways and mechanisms involved in the pathogenesis of CRDs. As these compounds are naturally occurring, they also exhibited lower incidences of

adverse effects as compared to chemically synthesized compounds, which eventually leads to better compliance and improved therapeutic outcomes. Furthermore, the cost of plant-based therapeutics is also much cheaper as compared to synthesized drugs [4, 204]. Some examples of plant-based chemical moieties that have been studied in CRDs for their potential pharmacological effects include celastrol *(Tripterygium wilfordii)* [205], asperuloside *(Eucommia)* [206], berberine *(Berberis vulgaris, Hydrastis canadensis)* [207, 208], capsaicin (Chili pepper) [209], curcumin *(Curcuma longa)* [210–212], wogonin (*Scutellariae radix*) [213], and silymarin (*Silybum marianum*) [214, 215]. Nonetheless, ethnopharmacological studies are essential to establish the parameters for safety, toxicity, quality, and effectiveness of these plant-based chemical moieties in the management of CRDs before they are used in the clinical setting.

2.4.2 Advanced Drug Delivery Systems

Advancements in the field of nanotechnology have led to the development of various drug delivery systems. These are nanosized structures distinguished by their remarkable stability and high surface area, therefore they are widely utilized as drug carriers in the pharmaceutical field [216, 217]. In addition, nanocarriers possess unique chemical, biological, and physical properties that allow them to interact with the biological system, natural biologic substances on cell surfaces, as well as the intracellular environment to effectively target sites of disease pathology [218]. As such, advanced drug delivery systems can improve the bioavailability and pharmacokinetic profile of therapeutics with selectivity and specificity towards target site, thereby resulting in improved therapeutic outcomes [219]. In terms of CRDs, the advantages of utilizing advanced drug delivery systems include sustained release for enhanced drug accumulation at the diseased site, minimal drug loss and degradation, reduced toxicity, as well as feasibility of designing inhalable nanoformulations. Another major advantage of advanced drug delivery systems is their ability for cell and tissue specific targeting through the use of targeting ligands, which is particularly useful in lung cancer. Moreover, nanocarriers can also be utilized to improve the biodistribution and bioavailability of existing and newly discovered therapeutic agents [217, 220]. Overall, these advantageous characteristics of advanced drug delivery systems can ultimately lead to eradication of CRDs, benefiting millions of patients suffering from CRDs. As biological toxicity is often the main concern in respiratory medicine, further understanding of the interactions between the nanocarriers and the biological environment must be further elucidated. Some examples of advanced drug delivery systems that have been studied in CRDs include liquid crystalline nanoparticles [221], liposomes [222, 223], polymeric nanoparticles [224–226], as well as inorganic nanoparticles such as mesoporous silica nanoparticles and silver nanoparticles [224].

2.5 Conclusion

Chronic respiratory diseases are widely considered as major healthcare crisis as they have resulted in huge social and economic burden across the world. Besides, the prevalence of chronic respiratory diseases is increasing at an alarming rate due to lack of effective management strategies and insufficient measures to reduce the risk factors linked to the initiation, development, and progression of these diseases. Hence, there is an incipient need for medical researchers to identify novel approaches that can be utilized for tackling and preventing these pulmonary diseases. The development of novel therapeutic agents should be focused on identification of the mechanisms and pathways involved in the pathogenesis of respiratory diseases, as the targeting of specific cell types and signalling pathways may play a crucial role in delaying disease progression and eventual eradication of these diseases. As such, plant-based chemical moieties can be explored due to their potent pharmacological profiles and improved toxicity profiles. In addition, advanced delivery systems can also be utilized as they can achieve specific drug delivery to the site of pathology in the lungs. Nevertheless, extensive research and trials must be conducted to ascertain the efficacy and safety of those novel therapeutics in chronic respiratory diseases before translating them into clinical use.

References

1. Chan Y, Ng SW, Mehta M et al (2020a) Sugar-based nanoparticles for respiratory diseases: a new paradigm in the nanoworld. Future Med Chem. https://doi.org/10.4155/fmc-2020-0206
2. Shukla SD, Swaroop Vanka K, Chavelier A et al (2020a) Chronic respiratory diseases: an introduction and need for novel drug delivery approaches. In: Targeting chronic inflammatory lung diseases using advanced drug delivery systems. Elsevier, Amsterdam, pp 1–31
3. Ambrosino N, Bertella E (2018) Lifestyle interventions in prevention and comprehensive management of COPD. Breathe 14:186–194
4. Prasher P, Sharma M, Mehta M et al (2020) Plants derived therapeutic strategies targeting chronic respiratory diseases: chemical and immunological perspective. Chem Biol Interact 325:109125
5. Forum of International Respiratory Societies (2017) The global impact of respiratory disease-2[a] ed, 2nd edn. European Respiratory Society
6. World Health Organization (2018) Cancer. https://www.who.int/news-room/fact-sheets/detail/cancer. Accessed 26 Oct 2020
7. Lin BF, Chiang BL, Ma Y, et al (2015) Traditional herbal medicine and allergic asthma. Evidence-based complement. Altern Med 2015
8. Liu F, Xuan NX, Ying SM et al (2016) Herbal medicines for asthmatic inflammation: from basic researches to clinical applications. Mediat Inflamm 2016
9. Santana FPR, Pinheiro NM, Mernak MIB et al (2016) Evidences of herbal medicine-derived natural products effects in inflammatory lung diseases. Mediators Inflamm:2016
10. Durham AL, Caramori G, Chung KF, Adcock IM (2016) Targeted anti-inflammatory therapeutics in asthma and chronic obstructive lung disease. Transl Res 167:192–203
11. Kim HP, Lim H, Kwon YS (2017) Therapeutic potential of medicinal plants and their constituents on lung inflammatory disorders. Biomol Ther 25:91–104

12. Khaltaev N, Axelrod S (2019) Chronic respiratory diseases global mortality trends, treatment guidelines, life style modifications, and air pollution: preliminary analysis. J Thorac Dis 11:2643–2655
13. Gross NJ, Barnes PJ (2017) New therapies for asthma and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 195:159–166
14. Brown K, Lynch DT (2018) Histology, Lung. StatPearls Publishing
15. Haddad M, Sharma S (2019) Physiology, Lung. StatPearls Publishing
16. Wagner PD (2015) The physiological basis of pulmonary gas exchange: implications for clinical interpretation of arterial blood gases. Eur Respir J 45:227–243. https://doi.org/10.1183/09031936.00039214
17. Butler JP, Tsuda A (2011) Transport of gases between the environment and alveoli-theoretical foundations. Compr Physiol 1:1301–1316. https://doi.org/10.1002/cphy.c090016
18. Petersson J, Glenny RW (2014) Gas exchange and ventilation-perfusion relationships in the lung. Eur Respir J 44:1023–1041
19. Haynes JM (2018) Basic spirometry testing and interpretation for the primary care provider. Can J Respir Ther 54:92–98. https://doi.org/10.29390/cjrt-2018-017
20. Franks TJ, Colby T V., Travis WD, et al (2008) Resident cellular components of the human lung current knowledge and goals for research on cell phenotyping and function. In: Proceedings of the American Thoracic Society. pp. 763–766
21. Whitsett JA, Wert SE, Weaver TE (2010) Alveolar surfactant homeostasis and the pathogenesis of pulmonary disease. Annu Rev Med 61:105–119
22. Abe J, Ito S, Takahashi S et al (2016) Mixed squamous cell and glandular papilloma of the lung resembling early adenocarcinoma: a case report. Ann Med Surg 7:61–64. https://doi.org/10.1016/j.amsu.2016.03.025
23. Travis WD, Garg K, Franklin WA et al (2006) Bronchioloalveolar carcinoma and lung adenocarcinoma: the clinical importance and research relevance of the 2004 world health organization pathologic criteria. J Thoracic Oncol, In, pp S13–S19
24. Harkness LM, Kanabar V, Sharma HS et al (2014) Pulmonary vascular changes in asthma and COPD. Pulm Pharmacol Ther 29:144–155. https://doi.org/10.1016/j.pupt.2014.09.003
25. Rock JR, Randell SH, Hogan BLM (2010) Airway basal stem cells: a perspective on their roles in epithelial homeostasis and remodeling. DMM Dis Model Mech 3:545–556
26. Busse PJ, McDonald VM, Wisnivesky JP, Gibson PG (2020) Asthma across the ages: adults. J Allergy Clin Immunol Pract 8:1828–1838. https://doi.org/10.1016/j.jaip.2020.03.044
27. Ebmeier S, Thayabaran D, Braithwaite I et al (2017) Trends in international asthma mortality: analysis of data from the WHO mortality database from 46 countries (1993–2012). Lancet 390:935–945. https://doi.org/10.1016/S0140-6736(17)31448-4
28. Stern J, Pier J, Litonjua AA (2020) Asthma epidemiology and risk factors. Semin Immunopathol 42:5–15
29. Papi A, Brightling C, Pedersen SE, Reddel HK (2018a) Asthma. Lancet 391:783–800
30. Nunes C, Pereira AM, Morais-Almeida M (2017) Asthma costs and social impact. Asthma Res Pract 3. https://doi.org/10.1186/s40733-016-0029-3
31. Ray A, Oriss TB, Wenzel SE (2015) Emerging molecular phenotypes of asthma. Am J Physiol - Lung Cell Mol Physiol 308:L130–L140
32. Fanta CH Asthma in adolescents and adults: evaluation and diagnosis. In: UpToDate.. https://www.uptodate.com/contents/asthma-in-adolescents-and-adults-evaluation-and-diagnosis
33. Subbarao P, Mandhane PJ, Sears MR (2009) Asthma: epidemiology, etiology and risk factors. CMAJ 181:E181
34. Win PH, Hussain I (2008) Asthma triggers: what really matters? Clinical Asthma. Elsevier Inc., In, pp 149–156
35. Pavord ID, Beasley R, Agusti A et al (2018) After asthma: redefining airways diseases. Lancet 391:350–400
36. Quirt J, Hildebrand KJ, Mazza J et al (2018) Asthma. Allergy, asthma. Clin Immunol 14:50
37. Barnes PJ (2016) Asthma mechanisms. Medicine 44:265–270

38. Fahy JV (2015) Type 2 inflammation in asthma-present in most, absent in many. Nat Rev Immunol 15:57–65
39. Kuruvilla ME, Lee FEH, Lee GB (2019) Understanding asthma phenotypes, endotypes, and mechanisms of disease. Clin Rev Allergy Immunol 56:219–233
40. Kaplan AG, Balter MS, Bell AD et al (2009) Diagnosis of asthma in adults. CMAJ 181:E210
41. Gallucci M, Carbonara P, Pacilli AMG et al (2019) Use of symptoms scores, spirometry, and other pulmonary function testing for asthma monitoring. Front Pediatr 7:54
42. Colice GL (2004) Categorizing asthma severity: an overview of national guidelines. Clin Med Res 2:155–163
43. Global Initiative for Asthma (2020) Pocket guide for asthma management and prevention (for adults and children older than 5 years)
44. National Heart Lung and Blood Institute (2007) Expert panel report 3: guidelines for the diagnosis and management of asthma. https://www.nhlbi.nih.gov/sites/default/files/media/docs/EPR-3_Asthma_Full_Report_2007.pdf
45. O'Byrne PM, FitzGerald JM, Bateman ED et al (2018) Inhaled combined Budesonide–Formoterol as needed in mild asthma. N Engl J Med 378:1865–1876. https://doi.org/10.1056/nejmoa1715274
46. Beasley R, Holliday M, Reddel HK et al (2019) Controlled trial of Budesonide–Formoterol as needed for mild asthma. N Engl J Med 380:2020–2030. https://doi.org/10.1056/nejmoa1901963
47. Fanta CH (n.d.-b) An overview of asthma management. In: UpToDate. https://www.uptodate.com/contents/an-overview-of-asthma-management
48. Rank MA, Hagan JB, Park MA et al (2013) The risk of asthma exacerbation after stopping low-dose inhaled corticosteroids: A systematic review and meta-analysis of randomized controlled trials. J Allergy Clin Immunol 131. https://doi.org/10.1016/j.jaci.2012.11.038
49. Wang W, Li Y, Lv Z et al (2018) Bronchial allergen challenge of patients with atopic asthma triggers an Alarmin (IL-33, TSLP, and IL-25) response in the airways epithelium and submucosa. J Immunol 201:2221–2231. https://doi.org/10.4049/jimmunol.1800709
50. Eger KA, Bel EH (2019) The emergence of new biologics for severe asthma. Curr Opin Pharmacol 46:108–115
51. Busse W, Corren J, Lanier BQ et al (2001) Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol 108:184–190. https://doi.org/10.1067/mai.2001.117880
52. Hynes G, Pavord ID (2020) Targeted biologic therapy for asthma. Br Med Bull 133:16–35. https://doi.org/10.1093/bmb/ldaa004
53. Doroudchi A, Pathria M, Modena BD (2020) Asthma biologics: comparing trial designs, patient cohorts and study results. Ann Allergy Asthma Immunol 124:44–56
54. McCracken JL, Tripple JW, Calhoun WJ (2016) Biologic therapy in the management of asthma. Curr Opin Allergy Clin Immunol 16:375–382
55. Global Initiative for Chronic Obstructive Pulmonary Disease (2018) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2018 report)
56. Han MK, Dransfield MT, Martinez FJ (n.d.) Chronic obstructive pulmonary disease: definition, clinical manifestations, diagnosis, and staging - UpToDate. In: UpToDate. https://www.uptodate.com/contents/chronic-obstructive-pulmonary-disease-definition-clinical-manifestations-diagnosis-and-staging
57. Burney P, Jithoo A, Kato B et al (2014) Chronic obstructive pulmonary disease mortality and prevalence: the associations with smoking and poverty-A bold analysis. Thorax 69:465–473. https://doi.org/10.1136/thoraxjnl-2013-204460
58. Ford ES, Croft JB, Mannino DM et al (2013a) COPD surveillance - United States, 1999-2011. Chest 144:284–305. https://doi.org/10.1378/chest.13-0809
59. Ford ES, Mannino DM, Wheaton AG et al (2013b) Trends in the prevalence of obstructive and restrictive lung function among adults in the United States: findings from the National Health

and nutrition examination surveys from 1988-1994 to 2007-2010. Chest 143:1395–1406. https://doi.org/10.1378/chest.12-1135
60. World Health Organization (2017) Chronic obstructive pulmonary disease (COPD). https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd). Accessed 31 Oct 2020
61. Buist AS, McBurnie MA, Vollmer WM et al (2007) International variation in the prevalence of COPD (the BOLD study): a population-based prevalence study. Lancet 370:741–750. https://doi.org/10.1016/S0140-6736(07)61377-4
62. Rajendra KC, Shukla SD, Gautam SS et al (2018) The role of environmental exposure to non-cigarette smoke in lung disease. Clin Transl Med 7:39. https://doi.org/10.1186/s40169-018-0217-2
63. Shah PL, Herth FJ, van Geffen WH et al (2017) Lung volume reduction for emphysema. Lancet Respir Med 5:147–156
64. Terzikhan N, Verhamme KMC, Hofman A et al (2016) Prevalence and incidence of COPD in smokers and non-smokers: the Rotterdam study. Eur J Epidemiol 31:785–792. https://doi.org/10.1007/s10654-016-0132-z
65. Global Initiative for Chronic Obstructive Lung Disease (GOLD). https://goldcopd.org/. Accessed 31 Oct 2020
66. Rabe KF, Hurd S, Anzueto A et al (2007) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 176:532–555
67. Berg K, Wright JL (2016) The pathology of chronic obstructive pulmonary disease: progress in the 20th and 21st centuries. Arch Pathol Lab Med 140:1423–1428
68. MacNee W (2005) Pathogenesis of chronic obstructive pulmonary disease. In: Proceedings of the American Thoracic Society. American Thoracic Society, pp 258–266
69. Kim V, Criner GJ (2013) Chronic bronchitis and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 187:228–237
70. Kim V, Criner GJ (2015) The chronic bronchitis phenotype in chronic obstructive pulmonary disease: features and implications. Curr Opin Pulm Med 21:133–141
71. Agustí A, Hogg JC (2019) Update on the pathogenesis of chronic obstructive pulmonary disease. N Engl J Med 381:1248–1256
72. Kent BD, Mitchell PD, Mcnicholas WT (2011) Hypoxemia in patients with COPD: cause, effects, and disease progression. Int J COPD 6:199–208
73. Barnes PJ (2019) Chronic obstructive pulmonary disease. In: Genomic and precision medicine: infectious and inflammatory disease. N Engl J Med, pp 383–399
74. Broekman W, Khedoe PPSJ, Schepers K et al (2018) Mesenchymal stromal cells: a novel therapy for the treatment of chronic obstructive pulmonary disease? Thorax 73:565–574
75. Ferguson GT, Make B (2019) Stable COPD: initial pharmacologic management. In: UpToDate. https://www.uptodate.com/contents/stable-copd-initial-pharmacologic-management
76. Gordon J, Panos RJ (2010) Inhaled albuterol/salbutamol and ipratropium bromide and their combination in the treatment of chronic obstructive pulmonary disease. Expert Opin Drug Metab Toxicol 6:381–392
77. Chong J, Karner C, Poole P (2012, 2012) Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev
78. Rossi A, Polese G (2013) Indacaterol: a comprehensive review. Int J COPD 8:353–363
79. Rogliani P, Calzetta L, Braido F et al (2018) LABA/LAMA fixed-dose combinations in patients with COPD: a systematic review. Int J COPD 13:3115–3130
80. Malerba M, Foci V, Patrucco F et al (2019) Single inhaler LABA/LAMA for COPD. Front Pharmacol 10:390. https://doi.org/10.3389/fphar.2019.00390
81. Tashkin DP, Strange C (2018) Inhaled corticosteroids for chronic obstructive pulmonary disease: what is their role in therapy? Int J COPD 13:2587–2601

82. Caruso M, Morjaria J, Emma R et al (2018) Biologic agents for severe asthma patients: clinical perspectives and implications. Intern Emerg Med 13:155–176
83. Morjaria JB, Rigby AS, Morice AH (2017) Asthma phenotypes: do cough and wheeze predict exacerbations in persistent asthma? Eur Respir J 50:1701366. https://doi.org/10.1183/13993003.01366-2017
84. Papi A, Vestbo J, Fabbri L et al (2018b) Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. Lancet 391:1076–1084. https://doi.org/10.1016/S0140-6736(18)30206-X
85. Meyer KC (2014) Diagnosis and management of interstitial lung disease. Transl Respir Med 2. https://doi.org/10.1186/2213-0802-2-4
86. King TE (n.d.) Approach to the adult with interstitial lung disease: clinical evaluation. UpToDate
87. Ryu JH, Daniels CE, Hartman TE, Yi ES (2007) Diagnosis of interstitial lung diseases. Mayo Clin Proc 82:976–986
88. Hutchinson J, Fogarty A, Hubbard R, McKeever T (2015) Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. Eur Respir J 46:795–806. https://doi.org/10.1183/09031936.00185114
89. Antoine M, Mlika M (2020) Interstitial lung disease. StatPearls Publishing
90. Torrisi SE, Palmucci S, Stefano A et al (2018) Assessment of survival in patients with idiopathic pulmonary fibrosis using quantitative HRCT indexes. Multidiscip Respir Med 13. https://doi.org/10.1186/s40248-018-0155-2
91. Sauleda J, Núñez B, Sala E, Soriano J (2018) Idiopathic pulmonary fibrosis: epidemiology, natural history, phenotypes. Med Sci 6:110. https://doi.org/10.3390/medsci6040110
92. Kalchiem-Dekel O, Galvin J, Burke A et al (2018) Interstitial lung disease and pulmonary fibrosis: a practical approach for general medicine physicians with focus on the medical history. J Clin Med 7:476. https://doi.org/10.3390/jcm7120476
93. Devine MS, Garcia CK (2012) Genetic interstitial lung disease. Clin Chest Med 33:95–110
94. Bagnato G, Harari S (2015) Cellular interactions in the pathogenesis of interstitial lung diseases. Eur Respir Rev 24:102–114
95. Maher TM, Wells AU, Laurent GJ (2007) Idiopathic pulmonary fibrosis: multiple causes and multiple mechanisms? Eur Respir J 30:835–839
96. Flaherty KR (n.d.) Treatment and prognosis of nonspecific interstitial pneumonia. UpToDate
97. Kim R, Meyer KC (2008) Review: therapies for interstitial lung disease: past, present and future. Ther Adv Respir Dis 2:319–338
98. Baughman RP, Grutters JC (2015) New treatment strategies for pulmonary sarcoidosis: antimetabolites, biological drugs, and other treatment approaches. Lancet Respir Med 3:813–822
99. Janahi IA, Rehman A, Baloch NU-A (2018) Corticosteroids and their use in respiratory disorders. In: Corticosteroids. InTech
100. Knuppel L, Ishikawa Y, Aichler M et al (2017) A novel antifibrotic mechanism of nintedanib and pirfenidone inhibition of collagen fibril assembly. Am J Respir Cell Mol Biol 57:77–90. https://doi.org/10.1165/rcmb.2016-0217OC
101. Richeldi L, Varone F, Bergna M et al (2018) Pharmacological management of progressive-fibrosing interstitial lung diseases: a review of the current evidence. Eur Respir Rev 27
102. Rivera-Ortega P, Hayton C, Blaikley J et al (2018) Nintedanib in the management of idiopathic pulmonary fibrosis: clinical trial evidence and real-world experience. Ther Adv Respir Dis 12
103. Wollin L, Wex E, Pautsch A et al (2015) Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. Eur Respir J 45:1434–1445
104. Lopez-de la Mora DA, Sanchez-Roque C, Montoya-Buelna M et al (2015) Role and new insights of Pirfenidone in fibrotic diseases. Int J Med Sci 12:840–847

105. Margaritopoulos GA, Trachalaki A, Wells AU et al (2018) Pirfenidone improves survival in IPF: results from a real-life study. BMC Pulm Med 18. https://doi.org/10.1186/s12890-018-0736-z
106. Lancaster LH, de Andrade JA, Zibrak JD et al (2017) Pirfenidone safety and adverse event management in idiopathic pulmonary fibrosis. Eur Respir Rev 26
107. Fischer A, Brown KK, Du Bois RM et al (2013) Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease. J Rheumatol 40:640–646. https://doi.org/10.3899/jrheum.121043
108. Huapaya JA, Silhan L, Pinal-Fernandez I, et al (2019) Long-term treatment with azathioprine and Mycophenolate Mofetil for myositis-related interstitial lung disease. In: Chest. Elsevier, pp 896–906
109. Oldham JM, Lee C, Valenzi E et al (2016) Azathioprine response in patients with fibrotic connective tissue disease-associated interstitial lung disease. Respir Med 121:117–122. https://doi.org/10.1016/j.rmed.2016.11.007
110. Yhee JY, Yoon HY, Kim H et al (2017) The effects of collagen-rich extracellular matrix on the intracellular delivery of glycol chitosan nanoparticles in human lung fibroblasts. Int J Nanomedicine 12:6089–6105. https://doi.org/10.2147/IJN.S138129
111. Garbuzenko OB, Ivanova V, Kholodovych V et al (2017) Combinatorial treatment of idiopathic pulmonary fibrosis using nanoparticles with prostaglandin E and siRNA(s). Nanomed Nanotechnol Biol Med 13:1983–1992. https://doi.org/10.1016/j.nano.2017.04.005
112. Dowsett J, Tully O (2012) Cystic fibrosis. In: Encyclopedia of human nutrition. Elsevier, Amsterdam, pp 416–422
113. Massie J (2013) Cystic fibrosis. In: Brenner's encyclopedia of genetics, 2nd edn. Elsevier, Amsterdam, pp 268–270
114. Cutting GR (2016) Cystic fibrosis. In: International Encyclopedia of public health. Elsevier, Amsterdam, pp 208–210
115. Lukacs GL, Verkman AS (2012) CFTR: folding, misfolding and correcting the ΔF508 conformational defect. Trends Mol Med 18:81–91
116. Robert R, Carlile GW, Liao J et al (2010) Correction of the ΔPhe508 cystic fibrosis transmembrane conductance regulator trafficking defect by the bioavailable compound glafenine. Mol Pharmacol 77:922–930. https://doi.org/10.1124/mol.109.062679
117. Cutting GR (2015) Cystic fibrosis genetics: from molecular understanding to clinical application. Nat Rev Genet 16:45–56
118. Veit G, Avramescu RG, Chiang AN et al (2016) From CFTR biology toward combinatorial pharmacotherapy: expanded classification of cystic fibrosis mutations. Mol Biol Cell 27:424–433. https://doi.org/10.1091/mbc.E14-04-0935
119. Marson FAL, Bertuzzo CS, Ribeiro JD (2016) Classification of CFTR mutation classes. Lancet Respir Med 4:e37–e38
120. Katkin JP (n.d.) Cystic fibrosis: clinical manifestations and diagnosis. UpToDate
121. Balázs A, Mall MA (2019) Mucus obstruction and inflammation in early cystic fibrosis lung disease: emerging role of the IL-1 signaling pathway. Pediatr Pulmonol 54:S5–S12
122. Kurbatova P, Bessonov N, Volpert V et al (2015) Model of mucociliary clearance in cystic fibrosis lungs. J Theor Biol 372:81–88. https://doi.org/10.1016/j.jtbi.2015.02.023
123. Shukla SD, Walters EH, Simpson JL et al (2020b) Hypoxia-inducible factor and bacterial infections in chronic obstructive pulmonary disease. Respirology 25:53–63
124. Edmondson C, Davies JC (2016) Current and future treatment options for cystic fibrosis lung disease: latest evidence and clinical implications. Ther Adv Chronic Dis 7:170–183
125. Simon RH (n.d.-a) Cystic fibrosis: overview of the treatment of lung disease. UpToDate
126. Simon RH (n.d.-b) Cystic fibrosis: antibiotic therapy for chronic pulmonary infection. UpToDate
127. Ong V, Mei V, Cao L et al (2019) Nanomedicine for cystic fibrosis. SLAS Technol 24:169–180

128. Velino C, Carella F, Adamiano A et al (2019) Nanomedicine approaches for the pulmonary treatment of cystic fibrosis. Front Bioeng Biotechnol 7:406
129. Günday Türeli N, Torge A, Juntke J et al (2017) Ciprofloxacin-loaded PLGA nanoparticles against cystic fibrosis P. aeruginosa lung infections. Eur J Pharm Biopharm 117:363–371. https://doi.org/10.1016/j.ejpb.2017.04.032
130. Donnelley M, Parsons DW (2018) Gene therapy for cystic fibrosis lung disease: overcoming the barriers to translation to the clinic. Front Pharmacol 9
131. Rafeeq MM, Murad HAS (2017) Cystic fibrosis: current therapeutic targets and future approaches. J Transl Med 15:84
132. Yan Z, McCray PB, Engelhardt JF (2019) Advances in gene therapy for cystic fibrosis lung disease. Hum Mol Genet 28:R88–R94
133. Chai Q, Zhang Y, Liu CH (2018) Mycobacterium tuberculosis: an adaptable pathogen associated with multiple human diseases. Front Cell Infect Microbiol 8:158
134. World Health Organization (2020) Global tuberculosis report 2020. World Health Organization
135. Bell LCK, Noursadeghi M (2018) Pathogenesis of HIV-1 and mycobacterium tuberculosis co-infection. Nat Rev Microbiol 16:80–90
136. Heemskerk D, Caws M, Marais B, Farrar J (2015) Clinical manifestations. In: Tuberculosis in adults and children. Springer, Berlin
137. Desalu OO, Adeoti AO, Fadeyi A et al (2013) Awareness of the warning signs, risk factors, and treatment for tuberculosis among urban Nigerians. Tuberc Res Treat 2013:1–5. https://doi.org/10.1155/2013/369717
138. Adigun R, Singh R (2020) Tuberculosis. StatPearls Publishing
139. Pieters J (2008) Mycobacterium tuberculosis and the macrophage: maintaining a balance. Cell Host Microbe 3:399–407
140. Smith I (2003) Mycobacterium tuberculosis pathogenesis and molecular determinants of virulence. Clin Microbiol Rev 16:463–496
141. Forrellad MA, Klepp LI, Gioffré A et al (2013) Virulence factors of the mycobacterium tuberculosis complex. Virulence 4:3–66
142. Zhai W, Wu F, Zhang Y et al (2019) The immune escape mechanisms of Mycobacterium Tuberculosis. Int J Mol Sci 20
143. Dheda K, Booth H, Huggett JF et al (2005) Lung remodeling in pulmonary tuberculosis. J Infect Dis 192:1201–1210. https://doi.org/10.1086/444545
144. WHO (n.d.-a) World Health Organization treatment of tuberculosis guidelines, 4th edn
145. WHO (n.d.-b) World Health Organization Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis
146. Sterling TR (n.d.) Treatment of drug-susceptible pulmonary tuberculosis in HIV-uninfected adults. UpToDate
147. Sotgiu G, Centis R, D'Ambrosio L, Battista Migliori G (2015) Tuberculosis treatment and drug regimens. Cold Spring Harb Perspect Med 5. https://doi.org/10.1101/cshperspect.a017822
148. Ramappa V, Aithal GP (2013) Hepatotoxicity related to anti-tuberculosis drugs: mechanisms and management. J Clin Exp Hepatol 3:37–49
149. Dixit R, George J, Sharma AK (2012) Thrombocytopenia due to rifampicin. Lung India 29:90–92
150. Schaberg T, Rebhan K, Lode H (1996) Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. Eur Respir J 9:2026–2030. https://doi.org/10.1183/09031936.96.09102026
151. Yakar F, Yildiz N, Yakar A, Kiliçaslan Z (2013) Isoniazid- and rifampicin-induced thrombocytopenia. Multidiscip Respir Med 8:13. https://doi.org/10.1186/2049-6958-8-13
152. Pontali E, D'Ambrosio L, Centis R et al (2017) Multidrug-resistant tuberculosis and beyond: an updated analysis of the current evidence on bedaquiline. Eur Respir J 49

153. Schluger NW, Heysell SK, Friedland G (n.d.) Treatment of drug-resistant pulmonary tuberculosis in adults. UpToDate
154. Diel R, Vandeputte J, De Vries G et al (2014) Costs of tuberculosis disease in the European Union: a systematic analysis and cost calculation. Eur Respir J 43:554–565. https://doi.org/10.1183/09031936.00079413
155. World Health Organization (2016) The shorter MDR-TB regimen
156. Goyal AK, Garg T, Bhandari S, Rath G (2017) Advancement in pulmonary drug delivery systems for treatment of tuberculosis. In: Nanostructures for drug delivery. Elsevier, Amsterdam, pp 669–695
157. Nasiruddin M, Neyaz MK, Das S (2017) Nanotechnology-based approach in tuberculosis treatment. Tuberc Res Treat 2017:1–12. https://doi.org/10.1155/2017/4920209
158. Pham DD, Fattal E, Tsapis N (2015) Pulmonary drug delivery systems for tuberculosis treatment. Int J Pharm 478:517–529
159. Saifullah B, Hussein MZB, Al Ali SHH (2012) Controlled-release approaches towards the chemotherapy of tuberculosis. Int J Nanomedicine 7:5451–5463
160. Estevez H, Palacios A, Gil D et al (2020) Antimycobacterial effect of selenium nanoparticles on Mycobacterium tuberculosis. Front Microbiol 11:800. https://doi.org/10.3389/fmicb.2020.00800
161. Tăbăran AF, Matea CT, Mocan T et al (2020) Silver nanoparticles for the therapy of tuberculosis. Int J Nanomedicine 15:2231–2258
162. Clemens DL, Lee BY, Xue M et al (2012) Targeted intracellular delivery of antituberculosis drugs to Mycobacterium tuberculosis-infected macrophages via functionalized mesoporous silica nanoparticles. Antimicrob Agents Chemother 56:2535–2545. https://doi.org/10.1128/AAC.06049-11
163. de Groot PM, Wu CC, Carter BW, Munden RF (2018) The epidemiology of lung cancer. Transl Lung Cancer Res 7:220–233
164. Lung Cancer (n.d.) In: Am Cancer Soc. https://www.cancer.org/cancer/lung-cancer.html. Accessed 2 Nov 2020
165. Furrukh M (2013) Tobacco smoking and lung cancer: perception-changing facts. Sultan Qaboos Univ Med J 13:345–358
166. O'Keeffe LM, Taylor G, Huxley RR et al (2018) Smoking as a risk factor for lung cancer in women and men: a systematic review and meta-analysis. BMJ Open 8
167. Travis WD, Brambilla E, Burke AP et al (2015) Introduction to the 2015 World Health Organization classification of tumors of the lung, pleura, thymus, and heart. J Thorac Oncol 10:1240–1242
168. Inamura K (2017) Lung cancer: understanding its molecular pathology and the 2015 WHO classification. Front Oncol 7:193. https://doi.org/10.3389/fonc.2017.00193
169. Bradley SH, Kennedy MPT, Neal RD (2019) Recognising lung Cancer in primary care. Adv Ther 36:19–30
170. Travis WD, Brambilla E, Noguchi M et al (2011) International association for the study of lung cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 6:244–285. https://doi.org/10.1097/JTO.0b013e318206a221
171. Chi A, Komaki R (2010) Treatment of brain metastasis from lung cancer. Cancers (Basel) 2:2100–2137
172. Gariani J, Martin SP, Hachulla AL et al (2018) Noninvasive pulmonary nodule characterization using transcutaneous bioconductance: Preliminary results of an observational study. Medicine 97. https://doi.org/10.1097/MD.0000000000011924
173. Herbst RS, Heymach JV, Lippman SM (2008) Molecular origins of cancer: lung cancer. N Engl J Med 359:1367–1380. https://doi.org/10.1056/NEJMra0802714
174. Li G, Gao Y, Cui Y et al (2016) Overexpression of CD44 is associated with the occurrence and migration of non-small cell lung cancer. Mol Med Rep 14:3159–3167. https://doi.org/10.3892/mmr.2016.5636

175. Midthun DE (n.d.) Overview of the initial treatment and prognosis of lung cancer. In: UpToDate. https://www.uptodate.com/contents/overview-of-the-initial-treatment-and-prognosis-of-lung-cancer
176. Mulvihill MS, Kratz JR, Pham P et al (2013) The role of stem cells in airway repair: implications for the origins of lung cancer. Chin J Cancer 32:71–74
177. Latimer KM, Mott TF (2015) Lung cancer: diagnosis, treatment principles, and screening
178. Bhimji SS, Wallen JM (2018) Cancer, lung, adenocarcinoma. StatPearls Publishing
179. Purandare NC, Rangarajan V (2015) Imaging of lung cancer: implications on staging and management. Indian J Radiol Imaging 25:109–120. https://doi.org/10.4103/0971-3026.155831
180. Thomas KW, Gould MK (n.d.) Overview of the initial evaluation, diagnosis, and staging of patients with suspected lung cancer. In: UpToDate. https://www.uptodate.com/contents/overview-of-the-initial-evaluation-diagnosis-and-staging-of-patients-with-suspected-lung-cancer
181. Silvestri GA, Gonzalez A V., Jantz MA, et al (2013) Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. Chest 143. https://doi.org/10.1378/chest.12-2355
182. Li H, Li J (2016) Effectiveness of palliative care for non-small cell lung cancer. Exp Ther Med 12:2387–2389
183. Plunkett TA, Chrystal KF, Harper PG (2003) Quality of life and the treatment of advanced lung cancer. Clin Lung Cancer 5:28–32
184. West H, Vallières E, Schild SE (n.d.) Management of stage I and stage II non-small cell lung cancer. In: UpToDate. https://www.uptodate.com/contents/management-of-stage-i-and-stage-ii-non-small-cell-lung-cancer
185. Shafirstein G, Battoo A, Harris K et al (2016) Photodynamic therapy of non-small cell lung cancer narrative review and future directions. Ann Am Thorac Soc 13:265–275
186. Liang J, Bi N, Wu S et al (2017) Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: a multicenter randomized phase III trial. Ann Oncol 28:777–783. https://doi.org/10.1093/annonc/mdx009
187. Gray JE, Villegas A, Daniel D et al (2020) Three-year overall survival with durvalumab after chemoradiotherapy in stage III NSCLC—update from PACIFIC. J Thorac Oncol 15:288–293. https://doi.org/10.1016/j.jtho.2019.10.002
188. Lilenbaum RC (n.d.) Overview of the initial treatment of advanced non-small cell lung cancer. In: UpToDate. https://www.uptodate.com/contents/overview-of-the-initial-treatment-of-advanced-non-small-cell-lung-cancer
189. Soria J-C, Ohe Y, Vansteenkiste J et al (2018) Osimertinib in untreated EGFR -mutated advanced non–small-cell lung Cancer. N Engl J Med 378:113–125. https://doi.org/10.1056/nejmoa1713137
190. Rossi A, Di Maio M, Chiodini P et al (2012) Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. J Clin Oncol 30:1692–1698. https://doi.org/10.1200/JCO.2011.40.4905
191. Sundstrøm S, Bremnes RM, Kaasa S et al (2002) Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. J Clin Oncol 20:4665–4672. https://doi.org/10.1200/JCO.2002.12.111
192. Baldini EH, Kalemkerian GP (n.d.) Limited-stage small cell lung cancer: initial management. In: UpToDate. https://www.uptodate.com/contents/limited-stage-small-cell-lung-cancer-initial-management
193. Corso CD, Rutter CE, Park HS et al (2015) Role of chemoradiotherapy in elderly patients with limited-stage small-cell lung cancer. J Clin Oncol 33:4240–4246. https://doi.org/10.1200/JCO.2015.62.4270

194. Horn L, Mansfield AS, Szczęsna A et al (2018) First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 379:2220–2229. https://doi.org/10.1056/NEJMoa1809064
195. Paz-Ares L, Dvorkin M, Chen Y et al (2019) Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 394:1929–1939. https://doi.org/10.1016/S0140-6736(19)32222-6
196. Rudin CM, Awad MM, Navarro A et al (2020) Pembrolizumab or placebo plus Etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: randomized, double-blind, phase III KEYNOTE-604 study. J Clin Oncol 38:2369–2379. https://doi.org/10.1200/JCO.20.00793
197. Capelletto E, Novello S (2012) Emerging new agents for the management of patients with non-small cell lung cancer. Drugs 72:37–52
198. Ellis PM, Al-Saleh K (2012) Multitargeted anti-angiogenic agents and NSCLC: clinical update and future directions. Crit Rev Oncol Hematol 84:47–58
199. Haura EB, Cress WD, Chellappan S et al (2004) Antiapoptotic signaling pathways in non-small-cell lung cancer: biology and therapeutic strategies. Clin Lung Cancer 6:113–122. https://doi.org/10.3816/CLC.2004.n.025
200. Neal JW, Sequist LV (2010) Exciting new targets in lung cancer therapy: ALK, IGF-1R, HDAC, and Hh. Curr Treat Options in Oncol 11:36–44
201. Veeresham C (2012) Natural products derived from plants as a source of drugs. J Adv Pharm Technol Res 3:200–201
202. Falzon CC, Balabanova A (2017) Phytotherapy: an introduction to herbal medicine. Prim Care Clin Off Pract 44:217–227
203. Wright GD (2019) Unlocking the potential of natural products in drug discovery. Microb Biotechnol 12:55–57. https://doi.org/10.1111/1751-7915.13351
204. Atanasov AG, Waltenberger B, Pferschy-Wenzig EM et al (2015) Discovery and resupply of pharmacologically active plant-derived natural products: a review. Biotechnol Adv 33:1582–1614
205. Ng SW, Chan Y, Chellappan DK et al (2019) Molecular modulators of celastrol as the keystones for its diverse pharmacological activities. Biomed Pharmacother 109:1785–1792
206. Chan Y, Ng SW, Xin Tan JZ et al (2020b) Emerging therapeutic potential of the iridoid molecule, asperuloside: a snapshot of its underlying molecular mechanisms. Chem Biol Interact 315:108911
207. Fu L, Chen W, Guo W et al (2013) Berberine targets AP-2/hTERT, NF-κB/COX-2, HIF-1α/VEGF and cytochrome-c/Caspase signaling to suppress human Cancer cell growth. PLoS One 8:e69240. https://doi.org/10.1371/journal.pone.0069240
208. Xu D, Wan C, Wang T et al (2015) Berberine attenuates cigarette smoke-induced airway inflammation and mucus hypersecretion in mice. Int J Clin Exp Med 8:8641–8647
209. Chakraborty S, Adhikary A, Mazumdar M et al (2014) Capsaicin-induced activation of p53-SMAR1 auto-regulatory loop down-regulates VEGF in non-small cell lung cancer to restrain angiogenesis. PLoS One 9:e99743. https://doi.org/10.1371/journal.pone.0099743
210. Chauhan PS, Singh DK, Dash D, Singh R (2018) Intranasal curcumin regulates chronic asthma in mice by modulating NF-κB activation and MAPK signaling. Phytomedicine 51:29–38. https://doi.org/10.1016/j.phymed.2018.06.022
211. Wang A, Wang J, Zhang S et al (2017) Curcumin inhibits the development of non-small cell lung cancer by inhibiting autophagy and apoptosis. Exp Ther Med 14:5075–5080. https://doi.org/10.3892/etm.2017.5172
212. Zhang M, Tang J, Li Y et al (2017) Curcumin attenuates skeletal muscle mitochondrial impairment in COPD rats: PGC-1α/SIRT3 pathway involved. Chem Biol Interact 277:168–175. https://doi.org/10.1016/j.cbi.2017.09.018
213. Ryu EK, Kim TH, Jang EJ et al (2015) Wogonin, a plant flavone from Scutellariae radix, attenuated ovalbumin-induced airway inflammation in mouse model of asthma via the

suppression of IL-4/STAT6 signaling. J Clin Biochem Nutr 57:105–112. https://doi.org/10.3164/JCBN.15-45
214. Li D, Xu D, Wang T et al (2015) Silymarin attenuates airway inflammation induced by cigarette smoke in mice. Inflammation 38:871–878. https://doi.org/10.1007/s10753-014-9996-9
215. Singh T, Prasad R, Katiyar SK (2016) Therapeutic intervention of silymarin on the migration of non-small cell lung cancer cells is associated with the axis of multiple molecular targets including class 1 HDACs, ZEB1 expression, and restoration of miR-203 and E-cadherin expression. Am J Cancer Res 6:1287–1301
216. Khan WS, Asmatulu R (2013) Nanotechnology emerging trends, markets, and concerns. In: Nanotechnology safety. Elsevier, Amsterdam, pp 1–16
217. Omlor JA, Nguyen J, Bals R, Dinh QT (2015) Nanotechnology in respiratory medicine. Respir Res 16:64. https://doi.org/10.1186/s12931-015-0223-5
218. Bahadori M, Mohammadi F (2012) Nanomedicine for respiratory diseases. Tanaffos 11:18–22
219. da Silva AL, Cruz FF, Rocco PRM, Morales MM (2017) New perspectives in nanotherapeutics for chronic respiratory diseases. Biophys Rev 9:793–803
220. Yhee J, Im J, Nho R (2016) Advanced therapeutic strategies for chronic lung disease using nanoparticle-based drug delivery. J Clin Med 5:82. https://doi.org/10.3390/jcm5090082
221. Chan Y, Ng SW, Chellappan DK et al (2020c) Celastrol-loaded liquid crystalline nanoparticles as an anti-inflammatory intervention for the treatment of asthma. Int J Polym Mater Polym Biomater. https://doi.org/10.1080/00914037.2020.1765350
222. Mehta PP, Ghoshal D, Pawar AP et al (2020) Recent advances in inhalable liposomes for treatment of pulmonary diseases: concept to clinical stance. J Drug Deliv Sci Technol 56:101509
223. Rudokas M, Najlah M, Alhnan MA, Elhissi A (2016) Liposome delivery systems for inhalation: a critical review highlighting formulation issues and anticancer applications. In: Medical principles and practice. S. Karger AG, pp 60–72
224. Chakraborty A, Selomulya C (2020) Formulation and role of polymeric and inorganic nanoparticles in respiratory diseases. In: Targeting chronic inflammatory lung diseases using advanced drug delivery systems. Elsevier, Amsterdam, pp 261–280
225. Chan Y, Ng SW, Mehta M et al (2020d) Advanced drug delivery systems can assist in managing influenza virus infection: a hypothesis. Med Hypotheses 144:110298. https://doi.org/10.1016/j.mehy.2020.110298
226. Lim YH, Tiemann KM, Hunstad DA et al (2016) Polymeric nanoparticles in development for treatment of pulmonary infectious diseases. Wiley Interdiscip. Rev Nanomed Nanobiotechnol 8:842–871

Role of Indian Herbal Medicine in the Treatment of Pulmonary Diseases

3

M. Ovia, M. Yasasve, and L. Ansel Vishal

Abstract

Pulmonary diseases such as asthma, chronic obstructive pulmonary disease, lung cancer, cystic fibrosis, pulmonary hypertension, pneumonia, pleurisy, sarcoidosis, and pulmonary embolism cause severe respiratory difficulties and can even be fatal without proper treatment. Although several chemical drugs are available for the treatment of pulmonary diseases, these drugs cause severe side effects and are not completely efficient. Herbal medicine is a suitable alternative with lesser side effects and can be used for the treatment of pulmonary diseases. Several herbal plants such as *Allium sativum, Crataegus rhipidophylla, Moringa oleifera, Salvia miltiorrhiza, Terminalia arjuna, Withania somnifera* can be used for the treatment of pulmonary diseases. Apple polyphenol, ligustrazine, salidroside, Resveratrol, quercetin are some examples of phytochemicals which exhibit characteristics with the potential to modulate the symptoms of pulmonary diseases. These herbal plants and phytochemicals undergo various mechanisms such as decreasing proliferation of epithelial cells, reducing oxidative stress, anti-inflammation, inhibiting proliferation of tumor cells, vasodilation, reducing bronchial constrictions, etc., to reduce the progression of pulmonary diseases. The different types of medicinal plants and phytochemicals which can be used to treat

M. Ovia
Department of Biotechnology, Anna University, Chennai, Tamil Nadu, India

M. Yasasve
Department of Biotechnology, Sri Venkateswara College of Engineering (Autonomous – Affiliated to Anna University), Sriperumbudur, Tamil Nadu, India

L. Ansel Vishal (✉)
Department of Biotechnology, Sree Sastha Institute of Engineering and Technology (Affiliated to Anna University), Chennai, Tamil Nadu, India
e-mail: vicchuansel@gmail.com

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_3

pulmonary diseases along with their mechanisms will be discussed in detail in this chapter.

Keywords

Pulmonary diseases · Herbal medicine · Phytochemicals · Respiratory difficulties

3.1 Introduction

Respiratory medicine is a fast-growing field with a vital emphasis and desire for continuous technological developments. The key explanation for this may be pulmonary diseases which are the primary causes of morbidity and death worldwide [1]. World Health Organization (WHO) estimates that some 235 million people are afflicted by asthma found generally in children and about three million people die from Chronic Obstructive Pulmonary Disease (COPD) adding 6% of the world's total death rate. It is also predicted that COPD will become the third major contributor to death by 2020 [2]. Pollution and low quality of life are the main reasons for the widespread growth of pulmonary diseases. Similarly, lung cancer is now an emerging high-mortality condition. The disease has been identified with approximate mortality of 2.09 million [3]. With the latest COVID-19 pandemic, a respiratory-based disease caused more than 12,00,000 deaths and continuing to increase [4]. This type of current scenario seeks the need to obtain a higher rate of prevention and treatment for pulmonary diseases.

As a compendium of medicinal substances, traditional plants have grown to play a leading role in maintaining human health since ancient times [5, 6]. Good immunomodulatory, anti-oxidant, antibacterial, antidiabetic and anti-cancer functions are known to have been exhibited by several Indian herbal plants [7, 8]. In medicinal drugs, the method of using green extracts and phytoconstituents, each with their known properties, can be of utmost significance. In recent times, several treatment interventions have been adopted for many years in different countries to explain the efficacy and relevance of these medicinal compounds synthesized in the secondary metabolism of the medicinal herb [9]. As per the latest WHO reports, eighty percent of the world's population relies predominantly on traditional medicines [10]. In Ayurveda, a mixture of different medicinal plants is offered to a person for the treatment of the disease in a specific ratio (a polyherbal formulation). Recently, herbal formulations have gained a lot of significance and increased global interest [11]. In the treatment of asthma, malignant tumors, diabetes mellitus, obesity, etc., different formulations such as *Kanchnar guggulu*, *Chandraprabha vati,* and *Trayodashang guggulu* have been successfully used [12–14]. This chapter thus aims to review the broad classification of pulmonary diseases and the advancements in the field of traditional medicine in treating them. Furthermore, the various types of herbal plants, formulations, and phytoconstituents currently being used in the treatment of respiratory ailments would be discussed in detail.

3.2 Classification of Pulmonary Diseases

Pulmonary disease is a type of illness affecting the lungs and other areas of the respiratory system. Lung infections may be caused by microbes, chewing cigarettes, inhaling tobacco smoke, asbestos, or other air pollutants. Chronic obstructive pulmonary disease (COPD), lung cancer, pulmonary embolism, hypertension are some examples of pulmonary diseases [15]. Pulmonary diseases are broadly classified into three categories mainly: (1) lung airway diseases, (2) lung circulatory diseases, and (3) lung tissue diseases.

3.2.1 Lung Airway Diseases

These diseases affect the airway channels that hold oxygen (O_2) as well as other gases in and out of the lungs. They typically lead to the airway passage shortening and obstruction. Chronic obstructive pulmonary disease (COPD) is considered a widespread airway disease related to exhalation problems and breathing restriction due to alveoli defects typically caused by greater exposure to harmful particles (e.g. cigarette smoke) [16]. Important variability in symptoms, disease development, pathogenesis, lung pathology, and treatment response are mostly observed in COPD patients (Table 3.1). There are mainly three types of COPD issues which include: (1) asthma, (2) emphysema, and (3) chronic bronchitis.

3.2.1.1 Asthma

Asthma is an illness in which the air sacs close and enlarge and can induce mucus in the lungs (Fig. 3.1a). This will make it extremely difficult to breathe, cause cough, wheezing (a howling noise as you exhale), and breathlessness [18]. Asthma is the mainly prevalent debilitating condition in children. It can occur at any age but is probably more frequent in children than in adults. It is important to obtain immediate treatment if the infant begins to develop asthma since it can be potentially fatal [19]. Your physician can advise you on several of the appropriate ways of treating your condition. However, it is a chronic condition lifelong for many individuals. Exposure to numerous allergens and pollutants (e.g. pollen grains, fine dust particles, smoke) that cause allergic reactions can elicit early symptoms of asthma [20].

Table 3.1 Factors responsible for causing variations in chronic obstructive pulmonary disease [17]

S. No.	Factors contributing	Example
1.	Risk factors	Smoking, pollution, genetic susceptibility
2.	Inflammation patterns	Lung irritation, systematic inflammation
3.	Lung pathology	Airway abnormalities, parenchymal destruction
4.	Clinical manifestation	Dyspnea, exacerbation, comorbidities
5.	Airflow limitation	Difficulty in breathing, exercise restriction

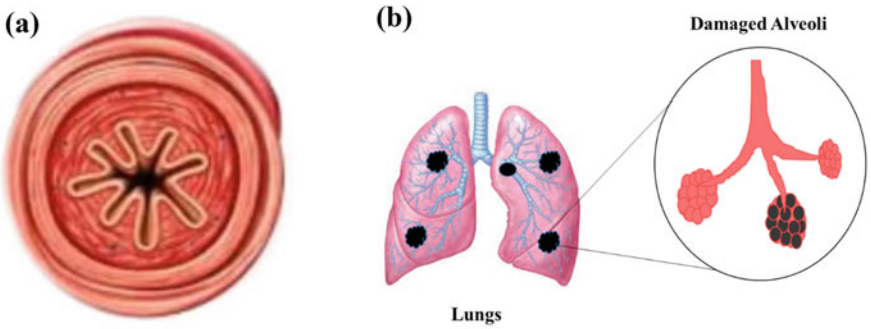


Fig. 3.1 (**a**) Airway of asthma individual (**b**) Lungs condition during emphysema

3.2.1.2 Emphysema

Emphysema is a respiratory illness that makes breathing difficult. Airbags in the lungs, i.e., alveoli sacs are impaired in people with emphysema (Fig. 3.1b). The interior walls of the airbags will deteriorate and break (creating wider air gaps instead of many smaller ones) over some time [21]. This decreases the surface area of your lungs in-turn reducing the amount of oxygen that enters your blood-stream. As you exhale, the weakened alveoli will not function properly and old air will become blocked, leaving no space for fresh, oxygen-rich air to inhale inside. Prolonged exposure to airborne allergens is the primary cause of emphysema, which includes dust, chemical smoke, tobacco smoke, and other airborne pollutants [22].

3.2.1.3 Chronic Bronchitis

Chronic bronchitis is an inflammatory disease and discomfort of the bronchial channels. These channels are the airways that take air in and out of the airbags in your lungs. The inflammation of the pathways triggers the secretion of mucus. This mucus and the inflammation of the tubes make it difficult for the lungs to pump in O_2 and CO_2 out of the body (Fig. 3.2). Chronic bronchitis seems to be a more serious illness that progresses across time rather than occurs unexpectedly [23]. Cigarette smoke is a significant cause of chronic bronchitis. When tobacco smoke is inhaled into the lungs, it irritates the air passages and produces mucus. Individuals who are exposed for a long period to other factors that irritate their lungs, such as toxic fumes, pollen, and other pollutants, can also experience persistent bronchitis [24].

3.2.2 Lung Circulatory Diseases

Lung circulatory disease is an illness that damages the blood vessels (e.g. clotting, inflammation) in the path between the heart and the lungs. Blood flows from the heart towards the lungs and back to the heart. This mechanism constantly floods the blood with oxygen, allowing carbon dioxide to be exhaled. Any portion of the blood

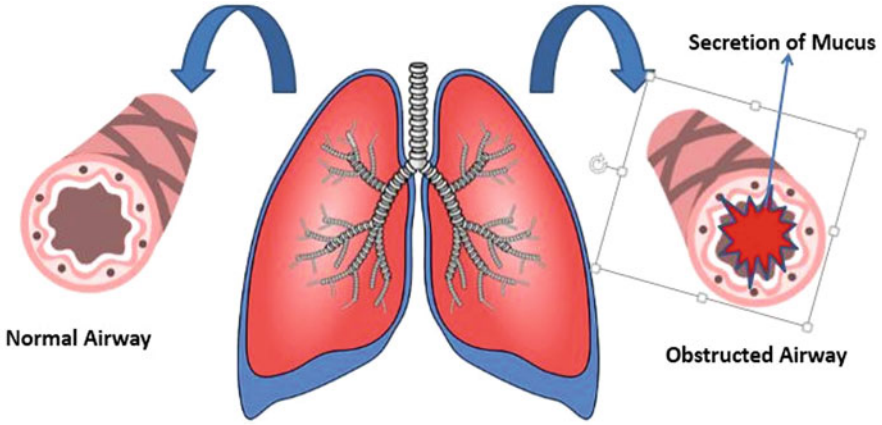


Fig. 3.2 Diagrammatic representation of mucus secretion in bronchial channels

circulation between the lung and heart may be compromised or blocked, leading to lung circulation diseases [25].

3.2.2.1 Pulmonary Hypertension

Individual sufferings from pulmonary arterial hypertension (PAH) have elevated blood pressure in the arteries that pass from your heart towards the lungs. The small arteries in your lungs are shortened or obstructed in this condition. It is difficult for the blood to flow thereby increasing the blood pressure in the lungs [26]. The heart needs to work harder to pump blood into these vessels and the heart muscle will get sluggish for a while. Eventually, this prolonged condition will lead to a heart attack in severe cases. Chest pain and tiredness are the early symptoms of PAH. Elevated levels of blood pressure in the pulmonary veins (channels carrying blood away from the lungs, to the heart) cause pulmonary venous hypertension (PVH). It is one of the most often caused due to congestive heart failure that damages heart mitral valves [27].

3.2.2.2 Pulmonary Embolism (PE)

A disease in which the arteries in the lungs are impaired by a blood clot. Most of the time, pulmonary embolism is caused by blood clots that migrate from the legs or occasionally other areas of the body also known as deep vein thrombosis. PE develops as deep venous thrombi break and embolize into the circulatory system [28]. Pulmonary vascular occlusion occurs which impairs the exchange and distribution of oxygen. In the lungs, the lower lungs are more commonly affected than the upper lungs, although bilateral lung involvement is normal. Symptoms include shortness of breath, chest pain, and coughing. Prompt surgery to break up the clot dramatically or administration of blood thinners (anti-coagulants) decreases the risk of death [29].

3.2.3 Lung Tissue Diseases

This disease type mainly impacts the composition of the lung tissue. Bruising or inflammation of the tissue renders the lungs unable to completely expand to its full extend. This makes it impossible for the lungs to take oxygen and release carbon dioxide [30]. Examples of certain lung tissue diseases include sarcoidosis and cystic fibrosis.

3.2.3.1 Cystic Fibrosis

An autosomal recessive disorder is cystic fibrosis. It is associated with mutations of the cystic fibrosis transmembrane conductance regulator gene. The most common mutation is the removal of phenylalanine at codon 508, termed as ΔF508. The cells which produce mucus, sweat, and digestive juices are affected by cystic fibrosis [31]. These fluids are induced to become thick and sticky, which blocks the various ducts passages. Symptoms vary, from cough, frequent respiratory infections, weight failure, and heavy stools. You have problems clearing mucus out of your bronchi in the particular individual suffering from this disease which leads to recurrent infection of lungs [32].

3.2.3.2 Sarcoidosis

Sarcoidosis is a condition characterized by the proliferation of any portion of your body with tiny colonies of inflammatory cells (granulomas), most frequently the lungs and lymph nodes. The cause of sarcoidosis is unclear, but doctors agree that it arises from reacting to an unknown material from the body's immune system [33].

Literature sources indicate that in genetically predisposed persons, infectious agents, contaminants, dust, and a possible pathological response to the body's proteins (self-proteins) may be responsible for the development of granulomas [34]. The early symptoms of sarcoidosis include fatigue, swollen lymph nodes, and weight loss [35]. The four stages of pulmonary involvement are based on the disease's radiological detection, which is beneficial for prognosis (Fig. 3.3).

3.2.4 Other Pulmonary Diseases

COVID-19 is a lung disease caused by a novel coronavirus (SARS CoV-2) first identified at the end of 2019. COVID-19 is mainly a lung respiratory disease leading to secretion of fluid in the air sacs restricting their ability to consume oxygen, eventually contributing to symptoms such as breathlessness, cough, etc. [36]. In pneumonia, the lungs are filled with fluid and inflamed, leading to breathing difficulty. For certain patients, respiratory issues can become bad enough to require treatment with oxygen or even a ventilator in the hospital. Although most people recover from pneumonia without significant lung injury, pneumonia associated with COVID-19 can be serious. Also after the illness has passed, lung damage may lead to respiratory problems that can take months to recover [37]. Pneumonia caused by COVID-19 continues to hold in both lungs. Airbags in the lungs are filled with fluid

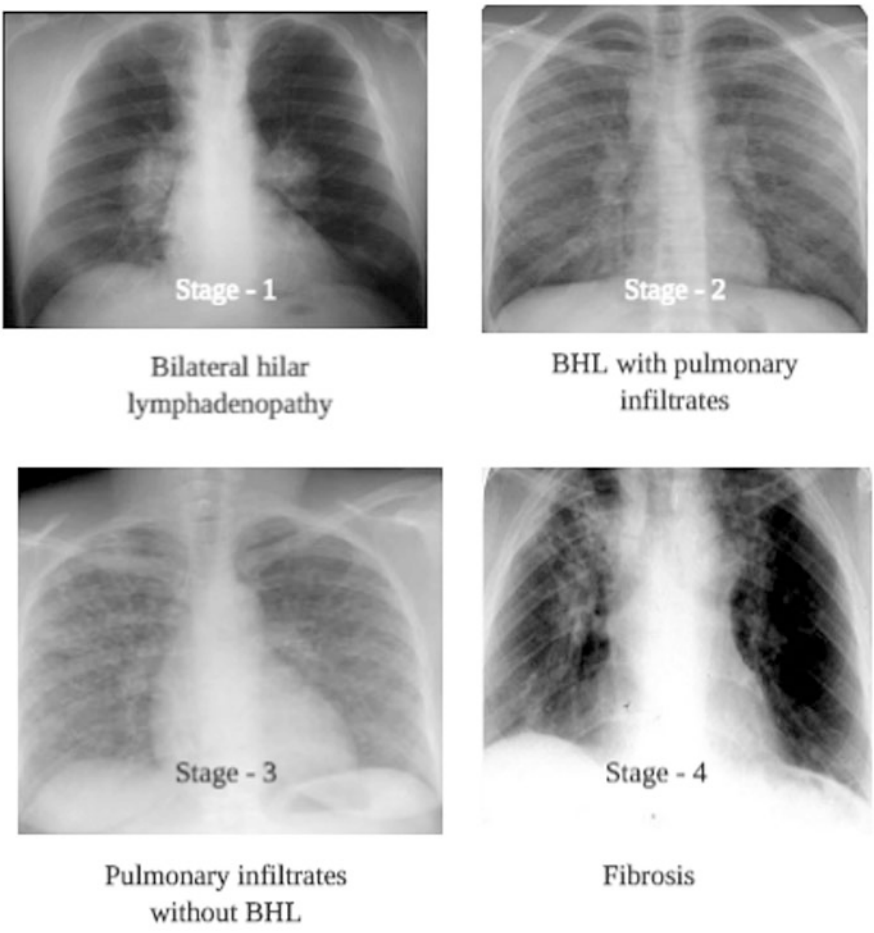


Fig. 3.3 Different stages of sarcoidosis in radiological detection

(Fig. 3.4), restricting their capacity to take oxygen completely leading to acute respiratory distress syndrome (ARDS), a form of lung failure [38].

3.3 Indian Herbal Medicine Involved in Treatment of Pulmonary Diseases

3.3.1 Asthma

Aleurites moluccana also known as candlenut tree dispersed in various parts of the country has been traditionally used for the treatment of asthma, pain, fever, and headaches. This can be attributed to its various properties such as anti-nociceptive,

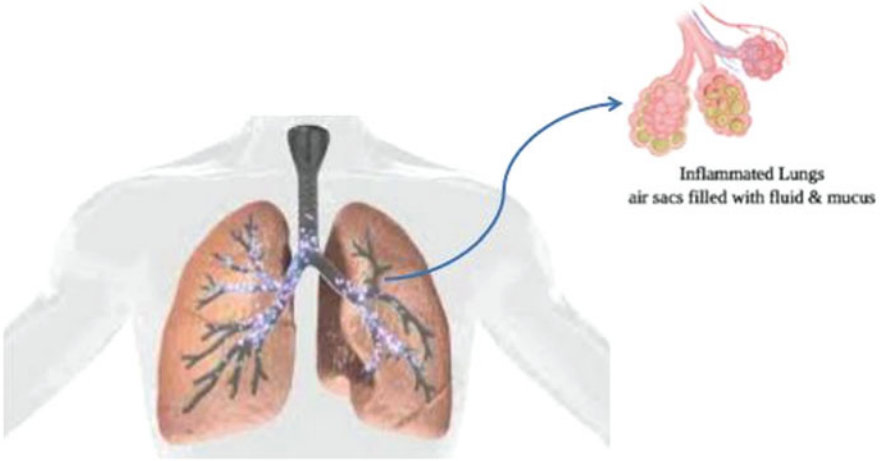


Fig. 3.4 Pneumonia associated with COVID-19

anti-viral, anti-microbial, and anti-hypersensitivity [39]. A dried leaf extract prepared from *A.moluccana* into a semisolid herbal medicine exhibited analgesic, anti-inflammatory, and wound healing effects in the pre-clinical studies shows promise as a phytomedicine which can be used for the treatment of asthma [40]. *Nigella sativa* (Black cumin) extracts display a wide range of therapeutic properties such as anti-oxidant, anti-inflammatory, antihistaminic, anti-allergic, anti-tussive, immunomodulatory, and bronchodilatory properties. Clinical studies indicate that administration of *N. sativa* seed, boiled extract, or oil alleviated asthma symptoms in patients [41]. *Aerva lanata* (mountain knotgrass) is a common weed abundantly found in the warmer plain terrain in the country. Its ethanol extract shows anti-asthmatic potential through catalepsy and mast cell degranulation [42]. *Bacopa monnieri* (Brahmi) is another medicinal plant capable of stabilizing mast cells [43]. The extracts obtained from different parts of medicinal plants such as leaves, stem bark, and roots of *Cassia sophera* (Kasaunda), *Casuarina equisetifolia* (Whistling Pine), *Clerodendrum Serratum* (Bharangi), *Bauhinia variegate* (Rakta Kanchnar) exhibit anti-asthmatic potential against the immune responses such as histamine induced bronchial and trachea constriction, clonidine induced catalepsy, milk induced leukocytosis, and eosinophilia which plays a vital role in aggravating asthma symptoms as tested in animal models [44, 45].

3.3.2 Chronic Obstructive Pulmonary Disease

Solanum nigrum (Manathakkali) has been traditionally used as a Siddha medicine and its leaves and fruits have also been widely consumed as a food ingredient in India. Its leaf extracts can inhibit swelling caused by an inflammatory response. A

glycoprotein isolated from *S. nigrum* was found to inhibit the synthesis of pro-inflammatory compounds by interfering with the DNA binding of NF-kB and AP-1. The ethanolic extract of *Boerhavia diffusa* (Punarnava) was found to reduce the levels of nitric oxide and superoxide which have a major role in the pathogenesis of COPD. It also exhibits spasmolytic, anti-microbial, and cytoprotective activities [46]. Clinical trials involving the administration of two Indian herbal medicine Vasadi syrup and Shwasaghna dhuma to patients diagnosed with COPD as two trial groups showed vast improvements in their COPD symptoms as well as FEV_1%. The constituents of Vasadi syrup are *Justicia adhatoda* (Vasa), *Curcuma longa* (Haridra), *Coriandrum Sativum* (Dhanyaka), *Clerodendrum Serratum* (Bharangi), *Tinospora cordifolia* (Guduchi), *Zingiber officinale* (Shunthi), *Solanum virginianum* (Kantakari), *Piper longum* (Pippali) in equal parts. Contents of Shwasaghna dhuma are powder of seeds of *Solanum virginianum* (Kantakari), dry leaves of *Datura stramonium* (Dhatura), *Trachyspermum ammi* (Ajwain), seeds of *Hyoscyamus niger* (Khurasani ajwain), Potassium Nitrate (Kalmi shora), *Curcuma longa* (Haridra), *and Cannabis sativa* (Bhanga) in equal parts [47].

3.3.2.1 Chronic Bronchitis

Ocimum sanctum (Tulsi) traditionally used as a medicine can be used for the treatment of bronchitis as well as bronchial asthma. It displays several therapeutic properties such as anti-microbial, analgesic, antispasmodic, adaptogenic which can be attributed to Eugenol, the active compound present in Tulsi [48]. Clinical studies carried out in bronchitis patients in a double-blind, randomized, placebo-controlled manner by the administration of a mix of thyme fluid extract and primrose root tincture resulted in a decrease in bronchitis symptoms as well as the duration of bronchitis [49]. *Hedera helix* (Ivy) leaf extract was also found to alleviate the symptoms of chronic bronchitis in some studies [50]. Nigellone, a phytochemical isolated from *Nigella sativa* (Black cumin) was found to exhibit antispasmodic and facilitating respiratory clearance while thymoquinone another phytochemical did not show the same effect [51].

3.3.2.2 Emphysema

Curcumin isolated from *Curcuma longa* (Turmeric) was found to alleviate the symptoms of pulmonary inflammation and emphysema induced by cigarette smoking and porcine pancreatic elastase activity in a mice model [52]. Epigallocatechin-3-gallate, a phytochemical which is abundantly found in *Camellia sinensis* (Green tea) was found to reduce the progression of emphysema by inhibiting the leukocyte elastase activity in a dose-dependent manner [53]. Quercetin, a flavonoid compound was found to attenuate the progression of emphysema by decreasing the level of oxidative stress, pulmonary inflammation and reducing the expression of MMP9 and MMP12 in mice model [54].

3.3.3 Lung Cancer

Curcuma longa (Turmeric) is a commonly used food ingredient throughout India. *C. longa* extract was found to exhibit cytotoxic property and inhibition of telomerase activity in a dose-dependent manner in an in vitro study carried out in the A549 lung cancer cell line [55]. Conferone, a phytochemical isolated from *Ferula* species exhibited mild cytotoxic effects against A549 lung cancer cell line [56, 57]. *Annona muricata (Mamaphal)* also shows the cytotoxicity effect in the A549 lung carcinoma cell line which can be attributed to its constituent compounds annomuricin A and B [58]. *Andrographis paniculata (*Kiryat) alcoholic extracts were found to show chemopreventive effects by enhancing the levels of DT-diaphorase (DTD), superoxide dismutase (SOD), and catalase in the lungs in a mouse model [59]. *Phyllanthus urinaria (*Jaramla) extract showed anti-angiogenic potential by inhibiting neovascularization in the tumor cells and also inhibiting the migration of HUVEC in a mice model implanted with Lewis lung carcinoma cells [60]. Other medicinal plants that can be used to alleviate the symptoms of lung cancer include *Zingiber officinale* (Ginger), *Glycyrrhiza glabra* (Liquorice), *Terminalia chebula* (Myrobalan), *Ocimum sanctum* (Tulsi), and *Adhatoda vasica* (Malabar nut) [61].

3.3.4 Cystic Fibrosis

Herbal extracts from *Phyllanthus acidus* (Star gooseberry) play a vital role in epithelial transport by enhancing the levels of cAMP, activating Ca^{2+}, K^{+} channels, and subsequent cellular signaling pathways as well as activating CFTR thus preventing the progression of cystic fibrosis [62]. Genistein is a phytochemical compound found in several medicinal plants that are capable of regulating various ions channels in CFTR, activates ΔF508 CFTR mutant and enhances the expression of mutant CFTR proteins [63, 64]. Curcumin, a phytochemical isolated from *Curcuma longa* (Turmeric) responsible for its characteristic yellow color can inhibit the calcium pump in the endoplasmic or sarcoplasmic membrane facilitating the removal of ΔF508 CFTR from the endoplasmic reticulum [65]. Resveratrol, a polyphenolic phytochemical commonly found in grapes and peanuts is capable of significantly elevating the cellular cAMP concentrations by activating adenylate cyclase and inhibition of cAMP phosphodiesterases which in turn leads to an increase in CFTR activity [66].

3.3.5 Pulmonary Hypertension

Allium ursinum (Wild garlic) and its compounds were found to alleviate the symptoms of pulmonary hypertension by decreasing the blood pressure, inhibiting of ACE activity and enhancing right ventricle function in animal models [67]. Administration of *Crataegus rhipidophylla* (Hawthorn) extract in broiler chickens with pulmonary hypertension induced by high altitude showed an increase

in expression of proteins such as albumin and globulin with a simultaneous decrease in the level of enzymes responsible for liver damage such as ALT and AST which occurs as a consequence of pulmonary hypertension progression [68]. *Moringa oleifera* (Drumstick tree) is abundantly found in the country and its various plant parts are commonly consumed as food ingredients. The alcoholic leaf extract of *Moringa oleifera* was administered to Wistar rats after inducing induced pulmonary hypertension by treatment with monocrotaline. It was found that the extract inhibited pulmonary hypertension by enhancing vasodilation and through its anti-oxidant properties [69].

3.3.6 Pneumonia

Various medicinal plants from the *Verbascum* species also known as Mullein have been used for the treatment of pneumonia as part of traditional herbal medicine due to its antibacterial activity. The extract isolated from *Verbascum fruticulosum* exhibited a high level of antibacterial activity against the multidrug-resistant strain of *Streptococcus pneumoniae* and can be used for the treatment of pneumonia. Similarly in the same study the extract obtained from *Urtica urens* (Dwarf nettle) also showed anti-microbial activity against *S. pneumoniae* although lesser than that of *V. fruticulosum* [70]. *Beta vulgaris* (Beetroot) is a commonly consumed vegetable. The alcoholic leaf extracts of *B. vulgaris* fractionated by n-hexane and chloroform displayed antibacterial activity by an increase in zone of inhibition in a concentration-dependent manner against *Klebsiella pneumonia* [71]. Other medicinal plants that have been used for the treatment of pneumonia include *Ficus racemosa* (Gular fig), *Nepeta glutinosa (Benth)*, *Ricinus communis* (Castor bean), *Terminalia chebula* (Myrobalan), and *Vitex negundo* (Chaste tree) [72].

3.3.7 Pleurisy

Ayurvedic medicines such as Praanrakshak can be used for the treatment of pleurisy. It consists of various medicinal plants such as *Cinnamomum zeylanicum* (Cinnamon), *Albizia lebbeck* (Shirish), *Adhatoda vasica* (Malabar nut), *Tylophora asthmatica* (Anantmool), and *Clerodendrum serratum* (Bharangi). *Cinnamomum zeylanicum* was found to exhibit anti-microbial, anti-oxidant, anti-inflammatory, and anti-nociceptive properties [73]. The stem bark extract of *Albizia lebbeck* exhibits various therapeutic properties such as anti-inflammatory, anti-anaphylactic, and analgesic which can alleviate the symptoms of pleurisy [74]. Vasicine, a phytochemical isolated from *Adhatoda vasica* showed antibacterial, anti-fungal, and anti-inflammatory activities in an in vitro study [75]. The plant extracts of *Tylophora asthmatica* exhibited immunosuppressive, anti-inflammatory, inhibition of delayed hypersensitivity response, and expectorant abilities in various clinical studies [76]. *Clerodendrum serratum* (Bharangi) extracts obtained from its roots and leaves display anti-asthmatic, anti-allergic, anti-inflammatory, anti-cancer, mast cell

stabilization effects according to various scientific investigations [77]. All these studies indicate that ayurvedic medicine such as Praanrakshak can be used for the treatment of pleurisy.

3.3.8 COVID-19

The extract of medicinal plants such as *Agastache rugosa* (Indian mint), *Astragalus membranaceus* (Katira), *Cassia alata* (Candlebush), *Cullen corylifolium* (Scurfy Pea), *Gymnema sylvestre* (Gurmar), *Mollugo cerviana* (Carpetweed), *Quercus infectoria* (Manjakani), *Tinospora cordifolia* (Gurjo) is capable of inhibiting the action of coronavirus [78]. Various phytochemicals isolated from medicinal plants such as quercetin, curcumin, withaferin A, luteolin, amaranthin, apigenin, gallic acid can also be used as potential drug candidates due to their ability to inhibit the mechanism of action of SARS-CoV-2 by targeting spike protein, the main protease, ACE-2 and its receptor [79]. In a case study, a 43-year-old male with COVID-19 symptoms was treated solely with Ayurvedic medicine and recovered completely. The treatment regimen involved the administration of Sudarsana Churna (for alleviating fever), Talisadi Churna (for loss of taste), and Dhanwantara Gutika (aids in overcoming breathing problems) [80, 81].

3.3.9 Sarcoidosis

Medicinal plants such as *Ocimum tenuiflorum* (Tulsi), *Curcuma longa* (Haridra), *Phyllanthus emblica* (Amalaki), *Tribulus terrestris* (Gokshura), *Asparagus racemosus* (Shatavari), *Withania somnifera* (Ashwagandha), and *Commiphora wightii* (Guggul) can be used for the treatment of sarcoidosis since they exhibit a wide range of therapeutic potential such as anti-oxidant, anti-inflammatory, anti-angiogenic, anti-microbial, immunomodulatory properties. Ayurvedic medicines that can be used for sarcoidosis treatment include Punarnava mandur and Kanchnar guggul which are capable of boosting the immune system as well as reducing the pain, inflammation, and other symptoms of the disease [82]. A clinical study involving the administration of herbal medicine called Reumaherb made up of three medicinal plants, namely *Echinacea purpurea, Harpagophytum procumbens,* and *Filipendula ulmaria* was found to exhibit anti-angiogenic and anti-inflammatory activity in a mice model transplanted with bronchoalveolar lavage (BAL) cells obtained from sarcoidosis patients. This anti-angiogenic potential could play a vital role in preventing the progression of sarcoidosis [83].

3.3.10 Pulmonary Embolism

Selaginella bryopteris (Sanjeevini) plant extract possesses anti-microbial, anti-coagulant, and anti-platelet properties which shows promise as a medicinal plant that can

Table 3.2 Medicinal plants used in the treatment of pulmonary diseases

Medicinal plant	Disease condition	Reference
Acalypha indica	Bronchitis and asthma	Ram et al. [90]
Brassica nigra	Chronic bronchitis	
Glycyrrhiza glabra	COPD and asthma	
Pimpinella anisum	Emphysema, bronchitis, asthma	
Trachyspermum ammi	Emphysema, asthma, bronchitis	
Semecarpus anacardium	Lung cancer	de Monteiro et al. [91]
Ervatamia heyneana		
Calamus rotang		
Sida rhombifolia	Pneumonia	Adnan et al. [92]
Cajanus cajan		
Vitex negundo		
Allium sativum	Pulmonary hypertension	Jasemi et al. [93]
Crataegus rhipidophylla		
Moringa oleifera		
Salvia miltiorrhiza		
Terminalia arjuna		
Withania somnifera		

be used for the treatment of pulmonary embolism [84]. The aqueous and ethanolic extracts of the fruit of *Terminalia bellirica* (Behada) one of the constituent medicinal plants of Triphala churna displayed anti-thrombotic and thrombolytic activity in an in vitro study [85]. The aqueous leaf extract of *Leucas indica* (Guma) was found to exhibit fibrinolytic, anti-platelet, and anti-coagulant activity by inhibition of thrombin and factor Xa [86]. The polyphenolic extract of *Vitis vinifera* (Grapeseed) commonly consumed as fruit also showed anti-coagulant and anti-platelet activities in an in vitro model [87]. *Fagonia arabica* (Dhamasa) is widely distributed throughout the Indian subcontinent and its aqueous extract and fractions displayed thrombolytic, anti-coagulant, and anti-oxidative properties in an in vitro study [88, 89]. The various medicinal plants used currently in the treatment of pulmonary disease ailments have been summarized in Table 3.2.

3.4 Phytoconstituents Involved in Treatment of Pulmonary Diseases

Phytochemicals are biologically active compounds present in plants with defensive and disease-preventive properties. Important clinical effects against cardiovascular and respiratory disorders have been shown by various phytochemical components like quercetin, resveratrol, triterpenoids, etc., [93]. A few examples of plant-derived compounds that have medicinal value in treating pulmonary diseases are been listed in Table 3.3.

Table 3.3 Phytochemicals used for the treatment of pulmonary diseases

Phytochemicals	Disease condition	References
Androsin	Bronchial asthma	Sharafkhaneh et al. [76]
Apple polyphenol	Pulmonary hypertension	Jasemi et al. [93]
Curcumin	Bronchitis, emphysema, cystic fibrosis	Sharafkhaneh et al. [76]
Ligustrazine	Pulmonary hypertension	Jasemi et al. [93]
Quercetin	Asthma, COPD, pulmonary hypertension	Jasemi et al. [93]
Resveratrol	Asthma, COPD, pneumonia, Sarcoidosis, pulmonary hypertension	Sharafkhaneh et al. [76]
Salidroside	Pulmonary hypertension	Jasemi et al. [93]
Triterpenoids	Chronic bronchitis, pulmonary hypertension	Ram et al. [90]

3.5 Conclusion

This chapter provides a comprehensive review about various Indian herbal medicinal plants and their therapeutic potential in the treatment of several pulmonary diseases. These medicinal plants and their phytochemical constituents exhibit a diverse range of therapeutic properties such as anti-oxidant, anti-inflammatory, anti-angiogenic, anti-coagulant, anti-microbial and immunomodulatory properties. So herbal medicine can be used as a viable alternative for treatment of respiratory ailments due to their efficacy as well as to avoid the side effects caused by various chemical drugs. Although various herbal formulations have been traditionally used in Ayurveda and Siddha for treatment of pulmonary diseases more clinical studies are required to elucidate the mechanisms behind the pharmacological effects of these herbal medicine.

References

1. Donnelly JP, Baddley JW, Wang HE (2014) Antibiotic utilization for acute respiratory tract infections in U.S. emergency departments. Antimicrob Agents Chemother 58:1451–1457
2. WHO (2007) Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach. https://www.who.int/gard/publications/GARD_Manual/en/. Accessed 30 Oct 2020
3. WHO (2018) Cancer fact sheet. https://www.who.int/news-room/fact-sheets/detail/cancer. Accessed 30 Oct 2020
4. Hu Y, Sun J, Dai Z et al (2020) Prevalence and severity of corona virus disease 2019 (COVID-19): a systematic review and meta-analysis. J Clin Virol 127:104371
5. Petrovska BB (2012) Historical review of medicinal plants usage. Pharmacogn Rev 6:1–5
6. Sofowora A, Ogunbodede E, Onayade A (2013) The role and place of medicinal plants in the strategies for disease prevention. Afr J Tradit Complement Altern Med 10:210–229

7. Farzaei F, Morovati MR, Farjadmand F et al (2017) A mechanistic review on medicinal plants used for diabetes mellitus in traditional persian medicine. J Evid Based Complement Altern Med 22:944–955
8. Yuan H, Ma Q, Ye L et al (2016) The traditional medicine and modern medicine from natural products. Molecules 21:559
9. Ekor M (2014) The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol 4:177
10. WHO (2019) WHO global report on traditional and complementary medicine 2019. https://www.who.int/traditional-complementary-integrative-medicine/. Accessed 30 Oct 2020
11. Mathew L, Babu S (2011) Phytotherapy in India: transition of tradition to technology. Curr Bot 2:17–22
12. Dadoriya P, Dey YN, Sharma D et al (2020) In-vitro anti-inflammatory and antioxidant activities of an Ayurvedic formulation – Trayodashang guggulu. J Herb Med. https://doi.org/10.1016/j.hermed.2020.100366
13. Tomar P, Dey YN, Sharma D et al (2018) Cytotoxic and antiproliferative activity of kanchnar guggulu, an Ayurvedic formulation. J Integr Med 16:411–417
14. Wanjari MM, Mishra S, Dey YN et al (2016) Antidiabetic activity of Chandraprabha vati - a classical Ayurvedic formulation. J Ayurveda Integr Med 7:144–150
15. Liao SX, Sun PP, Gu YH et al (2019) Autophagy and pulmonary disease. Ther Adv Respir Dis 13:1753466619890538
16. Rabe KF, Watz H (2017) Chronic obstructive pulmonary disease. Lancet 389:1931–1940
17. Manian P (2019) Chronic obstructive pulmonary disease classification, phenotypes and risk assessment. J Thorac Dis 11:S1761–S1766
18. Mims JW (2015) Asthma: definitions and pathophysiology. Int Forum Allergy Rhinol 1:S2–S6
19. Chung KF (2017) Clinical management of severe therapy-resistant asthma. Expert Rev Respir Med 11:395–402
20. Wu TD, Brigham EP, McCormack MC (2019) Asthma in the primary care setting. Med Clin North Am 103:435–452
21. Janssen R, Piscaer I, Franssen FME et al (2019) Emphysema: looking beyond alpha-1 antitrypsin deficiency. Expert Rev Respir Med 13:381–397
22. Kurashima K, Takaku Y, Ohta C et al (2017) Smoking history and emphysema in asthma-COPD overlap. Int J Chron Obstruct Pulmon Dis 12:3523–3532
23. Kim V, Criner GJ (2013) Chronic bronchitis and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 187:228–237
24. Guillien A, Soumagne T, Dalphin JC et al (2019) COPD, airflow limitation and chronic bronchitis in farmers: a systematic review and meta-analysis. Occup Environ Med 76:58–68
25. Naeije R (2013) Physiology of the pulmonary circulation and the right heart. Curr Hypertens Rep 15:623–631
26. Vonk Noordegraaf A, Groeneveldt JA, Bogaard HJ (2016) Pulmonary hypertension. Eur Respir Rev 25:4–11
27. Humbert M, Montani D, Evgenov OV et al (2013) Definition and classification of pulmonary hypertension. Handb Exp Pharmacol 218:3–29
28. Essien EO, Rali P, Mathai SC (2019) Pulmonary embolism. Med Clin North Am 103:549–564
29. Ramiz S, Rajpurkar M (2018) Pulmonary embolism in children. Pediatr Clin N Am 65:495–507
30. Fischer A, du Bois R (2012) Interstitial lung disease in connective tissue disorders. Lancet 380:689–698
31. Rafeeq MM, Murad HAS (2017) Cystic fibrosis: current therapeutic targets and future approaches. J Transl Med 15:84
32. Paranjape SM, Mogayzel PJ Jr (2014) Cystic fibrosis. Pediatr Rev 35:194–205
33. Llanos O, Hamzeh N (2019) Sarcoidosis. Med Clin North Am 103:527–534
34. Soto-Gomez N, Peters JI, Nambiar AM (2016) Diagnosis and management of sarcoidosis. Am Fam Phys 93:840–848

35. Bargagli E, Prasse A (2018) Sarcoidosis: a review for the internist. Intern Emerg Med 13:325–331
36. Ahn DG, Shin HJ, Kim MH et al (2020) Current status of epidemiology, diagnosis, therapeutics, and vaccines for novel coronavirus disease 2019 (COVID-19). J Microbiol Biotechnol 30:313–324
37. Hani C, Trieu NH, Saab I et al (2020) COVID-19 pneumonia: a review of typical CT findings and differential diagnosis. Diagn Interv Imaging 101:263–268
38. Wang F, Nie J, Wang H et al (2020) Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. J Infect Dis 221:1762–1769
39. Clarke R, Lundy FT, McGarvey L (2015) Herbal treatment in asthma and COPD – current evidence. Clin Phytosci 1:4
40. Cesca TG, Faqueti LG, Rocha LW et al (2012) Antinociceptive, anti-inflammatory and wound healing features in animal models treated with a semisolid herbal medicine based on Aleurites moluccana L. Willd. Euforbiaceae standardized leaf extract: semisolid herbal. J Ethnopharmacol 143:355–362
41. Gholamnezhad Z, Shakeri F, Saadat S et al (2019) Clinical and experimental effects of Nigella sativa and its constituents on respiratory and allergic disorders. Avicenna J Phytomed 9:195–212
42. Kumar D, Prasad D, Parkash J et al (2009) Antiasthmatic activity of ethanolic extract of Aerva lanata Linn. Pharmacologyonline 2:1075–1081
43. Samiulla DS, Prashanth D, Amit A (2001) Mast cell stabilising activity of Bacopa monnieri. Fitoterapia 72:284–285
44. Mali RG, Dhake AS (2011) Evaluation of effects of Bauhinia variegata stem bark extracts against milk-induced eosinophilia in mice. J Adv Pharm Technol Res 2:132–134
45. Taur DJ, Patil RY (2011) Some medicinal plants with antiasthmatic potential: a current status. Asian Pac J Trop Biomed 1:413–418
46. Ram A, Duraisamy A, Selvakumar B et al (2009) Medicinal plants from siddha system of medicine useful for treating respiratory diseases. Int J Pharm Anal 1:975–3079
47. Sharma PK, Johri S, Mehra BL (2010) Efficacy of Vasadi syrup and Shwasaghna Dhuma in the patients of COPD (Shwasa Roga). Ayu 31:48–52
48. Prakash P, Gupta N (2005) Therapeutic uses of Ocimum sanctum Linn (Tulsi) with a note on eugenol and its pharmacological actions: a short review. Indian J Physiol Pharmacol 49:125–131
49. Gruenwald J, Graubaum H-J, Busch R (2005) Efficacy and tolerability of a fixed combination of thyme and primrose root in patients with acute bronchitis. A double-blind, randomized, placebo-controlled clinical trial. Arzneimittelforschung 55:669–676
50. Guo R, Pittler MH, Ernst E (2006) Herbal medicines for the treatment of COPD: a systematic review. Eur Respir J 28:330–338
51. Wienkötter N, Höpner D, Schütte U et al (2008) The effect of nigellone and thymoquinone on inhibiting trachea contraction and mucociliary clearance. Planta Med 74:105–108
52. Suzuki M, Betsuyaku T, Ito Y et al (2009) Curcumin attenuates elastase- and cigarette smoke-induced pulmonary emphysema in mice. Am J Physiol Lung Cell Mol Physiol 296:L614–L623
53. Sartor L, Pezzato E, Garbisa S (2002) (−)Epigallocatechin-3-gallate inhibits leukocyte elastase: potential of the phyto-factor in hindering inflammation, emphysema, and invasion. J Leukoc Biol 71:73–79
54. Ganesan S, Faris AN, Comstock AT et al (2010) Quercetin prevents progression of disease in elastase/LPS-exposed mice by negatively regulating MMP expression. Respir Res 11:131
55. Mohammad P, Nosratollah Z, Mohammad R et al (2010) The inhibitory effect of Curcuma longa extract on telomerase activity in A549 lung cancer cell line. Afr J Biotechnol 9:912–919
56. Kooti W, Servatyari K, Behzadifar M et al (2017) Effective medicinal plant in cancer treatment, part 2: review study. J Evid Based Complement Altern Med 22:982–995
57. Valiahdi SM, Iranshahi M, Sahebkar A (2013) Cytotoxic activities of phytochemicals from Ferula species. Daru 21:39

58. Desai AG, Qazi GN, Ganju RK et al (2008) Medicinal plants and cancer chemoprevention. Curr Drug Metab 9:581–591
59. Singh RP, Banerjee S, Rao AR (2001) Modulatory influence of Andrographis paniculata on mouse hepatic and extrahepatic carcinogen metabolizing enzymes and antioxidant status. Phytother Res 15:382–390
60. Huang S-T, Yang R-C, Lee P-N et al (2006) Anti-tumor and anti-angiogenic effects of Phyllanthus urinaria in mice bearing Lewis lung carcinoma. Int Immunopharmacol 6:870–879
61. Garodia P, Ichikawa H, Malani N et al (2007) From ancient medicine to modern medicine: ayurvedic concepts of health and their role in inflammation and cancer. J Soc Integr Oncol 5:25–37
62. Sousa M, Ousingsawat J, Seitz R et al (2007) An extract from the medicinal plant Phyllanthus acidus and its isolated compounds induce airway chloride secretion: a potential treatment for cystic fibrosis. Mol Pharmacol 71:366–376
63. Dey I, Shah K, Bradbury NA (2016) Natural compounds as therapeutic agents in the treatment cystic fibrosis. J Genet Syndr Gene Ther 7:284
64. Hwang TC, Wang F, Yang IC et al (1997) Genistein potentiates wild-type and delta F508-CFTR channel activity. Am J Phys 273:C988–C998
65. Sumbilla C, Lewis D, Hammerschmidt T et al (2002) The slippage of the Ca2+ pump and its control by anions and curcumin in skeletal and cardiac sarcoplasmic reticulum. J Biol Chem 277:13900–13906. https://doi.org/10.1074/jbc.M111155200
66. El-Mowafy AM, Alkhalaf M (2003) Resveratrol activates adenylyl-cyclase in human breast cancer cells: a novel, estrogen receptor-independent cytostatic mechanism. Carcinogenesis 24:869–873
67. Bombicz M, Priksz D, Varga B et al (2017) A novel therapeutic approach in the treatment of pulmonary arterial hypertension: allium ursinum liophylisate alleviates symptoms comparably to sildenafil. Int J Mol Sci 18:1436
68. Ahmadipour B, Kalantar M, Hosseini SM et al (2017) Hawthorn (Crataegus Oxyacantha) extract in the drinking water of broilers on growth and incidence of pulmonary hypertension syndrome (PHS). Rev Bras Cienc Avic 19:639–644
69. Chen K-H, Chen Y-J, Yang C-H et al (2012) Attenuation of the extract from Moringa oleifera on monocrotaline-induced pulmonary hypertension in rats. Chin J Physiol 55:22–30
70. Gupta VK, Kaushik A, Chauhan DS et al (2018) Anti-mycobacterial activity of some medicinal plants used traditionally by tribes from Madhya Pradesh, India for treating tuberculosis related symptoms. J Ethnopharmacol 227:113–120
71. Hussain Z, Muhammad P, Sadozai S et al (2011) Extraction of anti-pneumonia fractions from the leaves of sugar beets Beta vulgaris. J Pharm Res 4:4783–4785
72. Asadbeigi M, Mohammadi T, Rafieian-Kopaei M et al (2014) Traditional effects of medicinal plants in the treatment of respiratory diseases and disorders: an ethnobotanical study in the Urmia. Asian Pac J Trop Med 7S1:S364–S368
73. Ranasinghe P, Pigera S, Premakumara GS et al (2013) Medicinal properties of 'true' cinnamon (Cinnamomum zeylanicum): a systematic review. BMC Complement Altern Med 13:275
74. Desai TH, Joshi SV (2019) Anticancer activity of saponin isolated from Albizia lebbeck using various in vitro models. J Ethnopharmacol 231:494–502
75. Singh B, Sharma RA (2013) Anti-inflammatory and antimicrobial properties of pyrroloquinazoline alkaloids from Adhatoda vasica Nees. Phytomedicine 20:441–445. https://doi.org/10.1016/j.phymed.2012.12.015
76. Sharafkhaneh A, Velamuri S, Badmaev V et al (2007) The potential role of natural agents in treatment of airway inflammation. Ther Adv Respir Dis 1:105–120
77. Patel JJ, Acharya SR, Acharya NS (2014) Clerodendrum serratum (L.) moon. - a review on traditional uses, phytochemistry and pharmacological activities. J Ethnopharmacol 154:268–285
78. Benarba B, Pandiella A (2020) Medicinal plants as sources of active molecules against COVID-19. Front Pharmacol 11:1189

79. Bhuiyan FR, Howlader S, Raihan T et al (2020) Plants metabolites: possibility of natural therapeutics against the COVID-19 pandemic. Front Med 7:444
80. Adhikari B, Marasini BP, Rayamajhee B et al (2020) Potential roles of medicinal plants for the treatment of viral diseases focusing on COVID-19: a review. Phytother Res. https://doi.org/10.1002/ptr.6893
81. Girija PLT, Sivan N (2020) Ayurvedic treatment of COVID-19/SARS-CoV-2: a case report. J Ayurveda Integr Med. https://doi.org/10.1016/j.jaim.2020.06.001
82. Parasuraman S, Thing GS, Dhanaraj SA (2014) Polyherbal formulation: concept of ayurveda. Pharmacogn Rev 8:73–80
83. Radomska-Leśniewska DM, Skopińska-Różewska E, Demkow U et al (2016) A natural herbal remedy modulates angiogenic activity of bronchoalveolar lavage cells from sarcoidosis patients. Cent Eur J Immunol 41:25–34
84. Mahmud S, Akhter S, Rahman MA et al (2015) Antithrombotic effects of five organic extracts of bangladeshi plants in vitro and mechanisms in in silico models. Evid Based Complement Alternat Med:782742
85. Ansari V, Siddiqui H, Singh SP (2012) Antithrombotic and thrombolytic activity of terminalia belerica fruit extracts. Res J Pharm Biol Chem Sci 3:471–478
86. Gogoi D, Arora N, Kalita B et al (2018) Anticoagulant mechanism, pharmacological activity, and assessment of preclinical safety of a novel fibrin(ogen)olytic serine protease from leaves of Leucas indica. Sci Rep 8:6210
87. Bijak M, Sut A, Kosiorek A et al (2019) Dual anticoagulant/antiplatelet activity of polyphenolic grape seeds extract. Nutrients 11:93
88. Chourasia SR, Kashyap RS, Deopujari JY et al (2014) Effect of aqueous extract and fractions of Fagonia arabica on in vitro anticoagulant activity. Clin Appl Thromb Hemost 20:844–850
89. Gholkar AA, Nikam YP, Zambare KK et al (2020) Potential anticoagulant herbal plants: a review. Asian J Res Pharm Sci 10:51–55
90. Ram A, Balachandar S, Vijayananth P et al (2011) Medicinal plants useful for treating chronic obstructive pulmonary disease (COPD): current status and future perspectives. Fitoterapia 82:141–151
91. de Monteiro LS, Bastos KX, Barbosa-Filho JM et al (2014) Medicinal plants and other living organisms with antitumor potential against lung cancer. Evid Based Complement Alternat Med:604152
92. Adnan M, Ali S, Sheikh K et al (2019) Review on antibacterial activity of Himalayan medicinal plants traditionally used to treat pneumonia and tuberculosis. J Pharm Pharmacol 71:1599–1625
93. Jasemi SV, Khazaei H, Aneva IY et al (2020) Medicinal plants and phytochemicals for the treatment of pulmonary hypertension. Front Pharmacol 11:145

Asthma-Induced Inflammatory Responses and Reversal by Botanicals

4

Tuyelee Das, Samapika Nandy, and Abhijit Dey

Abstract

Asthma is the most prevailing chronic inflammatory medical condition which is the outcome of extensive air pollution and which is associated with hyper-responsiveness of the respiratory system. Asthma causes excessive mucus production, blockage of air-passage, triggers inflammatory allergic responses, chronic lung infection, lifelong breathing troubles, and prolonged hospitalization in worst cases. Plant derived pollens may trigger asthmatic responses but on the other hand a number of medicinal plants and phytochemicals have been reported to ameliorate the symptoms associated with asthma. According to ethnomedicinal reports inhalation of certain kinds of herbs and administration of certain plant products could alleviate breathing and respiratory complexities. A number of animal model based studies have highlighted the role of plant extracts (PEs) and plant derived phytochemicals could alter the inflammatory responses by modulating the production of immunoglobulin E (IgE) and pro-inflammatory cytokine based immune signals. They could also suppress the accumulation of inflammatory cells which may lead to "hyper-drive" stage in respiratory system. Detailed analysis have highlighted the effective role of plant extracts and secondary metabolites modulating the release of TNF-α, IL-1β, IL-2, 4, 5, 6, 8, 13, IFN-γ, and other messenger molecules. Along with the experimental details and possible molecular mechanisms of the anti-asthmatic botanicals, this review also highlights constraints in medicinal plant oriented anti-asthmatic research, protocol based lacunae, details of toxicity and quality control studies and tries to link the traditional knowledge with laboratory-based findings.

T. Das · S. Nandy · A. Dey (✉)
Department of Life Sciences, Presidency University, Kolkata, West Bengal, India
e-mail: abhijit.dbs@presiuniv.ac.in

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_4

Keywords

Asthma · Medicinal plants · Natural products · Polyherbal · Inflammatory responses

4.1 Introduction

Asthma is a chronic inflammatory disorder associated with hyper-responsiveness that causes airway narrowing. Asthma also changes levels of eosinophils, lymphocytes, neutrophilia, cytokines, chemokines, mast cells, and other inflammatory cell products. Hyper-responsiveness of the immune system causes wheezing, breathlessness, chest tightness, and coughing, mainly at night or in the early morning. Factors that have been found to trigger asthma include viral respiratory infections, vitamin D, dietary changes, stress, acute anxiety, air-borne allergens, air pollution, and chemical exposure [1–5]. Worldwide, the occurrence of asthma increased by 13% from 1990 to 2015 [6]. WHO estimates, in 2005, 2, 55, 000 people died and 300 million people endured asthma. According to the global asthma report 2018, around 1000 people are killed every day because of asthma. In India, about 6% of children and 2% of adults have asthma (http://www.globalasthmareport.org/). In this present year 2020, 339 million people are reportedly suffering from asthma and mostly low-and lower-middle-income countries recorded almost 80% deaths from asthma [7]. According to the Centers for Disease Control and Prevention (CDC), 1in 13 people in America have asthma (https://www.aafa.org/asthma-facts/). It is estimated that by 2025, 340 million people will be affected by asthma. The worldwide event of asthma is foreseen to be added in excess of 100 million by 2025 [8]. One study revealed that obesity in women is highly related to initiating asthma but the same is not observed in men [9]. Women with polycystic ovary syndrome have a higher chance of developing asthma [10]. Another study has also revealed that women are more prone to develop severe asthma as compared to men. Moreover, among rural patients severioty of asthma is more rigorous than urban patients [11]. A population-based study by [12] demonstrated that several factors are causing asthma that includes obesity, low socioeconomic status, gender, occurrence of hay fever, and smoking. They have also observed in their study that most of the people's quality of life is compromised because of asthma [12]. More than a few million people who have suffered due to the absence of proper medication were out of job as well as other facilities and their ailment has triggered huge economic loss induced by inadequate work force in several industries.

4.2 Symptoms and Types of Asthma

The National Asthma Education and Prevention Program has categorized asthma based on the symptoms and severity. Types of asthma include intermittent, mild persistent, moderate persistent, and severe persistent. In intermittent asthma patients

develop airways inflammation along with the symptoms come out more than two times in a week [13]. While in moderate type, symptoms appear daily as well as they require β2-adrenergic drugs. In severe asthma, symptoms are persistent. The Ayurvedic medicinal system divided *swasa* (asthma) into five different types such as *Kshudra swasa* (Dyspnoea minor), *Mahaswasa* (Dyspnoea major), *Urdhawaswasa* (Expiratory Dyspnoea), *Chinna swasa* (Chyne-stroke respiration), *Tamaka swasa* (Bronchial Asthma) [14]. Plant-based anti-asthmatics were classified into bronchodilator, mast cell stabilizers, anti-allergic agents, anti-inflammatory agents, antispasmodics, and lipoxygenase inhibitors [14] Studies have showed different cell types are involved in asthma such as eosinophils [15, 16], lymphocytes [15], mast cells [17, 18], macrophages [15], and epithelial cells [19]. Asthma can be amassed by intrinsic and extrinsic types. Intrinsic asthma is brought about by inherited genetics and structural crisis, stress, and contaminations. While, extrinsic asthma is caused by air-borne pollutants, dust, and various foods [20]. Almost 10%–13% cases of asthma occur globally [11]. The main symptom of this disease is the shortness of breath, wheezing, coughing, sleeplessness, daytime fatigue, adequate air exchange, and mild dyspnoea. Asthma is caused by gene–environment interactions. The asthmatic symptoms may develop due to the release of intrinsic cytokines, histamine, leukotrienes, nitric oxide, and chemokines. Mast cell endothelin liberation and airway inflammation in the lungs are different indication of the symptoms of asthma [2].

4.3 Current Treatment

Asthma is incurable; the current treatment offers temporary symptomatic relief only. According to the Education and Prevention Program (NAEPP) for the diagnosis and management of asthma, the asthma treatment ought to be founded upon the maintenance of pulmonary function, respiratory rate, and normal activity levels of patients. Asthmatic drug categories include bronchodilators, mast cell stabilizers, and corticosteroids; bronchodilators drugs further categorized into β-adrenergic agonists (albuterol, adrenaline, ephedrine), methylxanthines (proxyphylline, theophylline, aminophylline), and anticholinergics (atropine methonitrate, ipratropium bromide, tiotropium bromide) [21]. This highly assorted anti-asthmatic drugs have already proven their efficiency but several side effects like adrenal suppression, convulsions, cardiovascular effects, headaches, osteoporosis, myopathies, nausea, and vomiting are results of conventional medication [22–27]. Therefore, considering all side effects of conventional drugs and their cost, there is an urgent need for the development of alternative sustainable therapeutic approaches to prevent asthma.

4.4 Preclinical and Clinical Study of Potent Medicinal Plants as Anti-Asthmatic Resource

Medicinal plants, natural products as therapeutics and herbal therapy have become a topic of huge pharmacological importance due to their efficacy, economic impact, and safety implications against asthma. Indeed, Asthma mostly results in inflammatory cell activation and the production of various pro-inflammatory mediators. The dose-dependent anti-asthmatic activity of plants has shown significant results in bronchodilation, mast cell stabilization, anti-inflammatory, anti-spasmodic, anti-allergic, immunomodulatory via inhibition of mediators. β2-adrenergic receptor agonists present in medicinal plants can relieve airway bronchoconstriction via activating β2-adrenergic receptors on airway smooth muscle cells. These medicinal plant-based approaches have regained their popularity, with their efficacy and safety aspects being supported by controlled preclinical and clinical studies. Medicinal plant crude extracts/fraction application or administration on in vitro and in vivo animal models resulting decreasing level of leukocytes count, eosinophil, neutrophils migration, histamine release, lipoxygenase enzyme production, IgE (immunoglobulin E), IL-4 (Interleukin-4), IL-5, IL-6, IL-13, TNF-α (Tumor necrosis factor (TNF)-alpha), p53 (Tumor suppressor protein), NGF (nerve growth factor), bax, COX-2 (cyclooxygenase-2), caspase-3, and nitric oxide synthase and increasing level of antioxidant enzymes, IFN-γ, and Bcl-2; associated with improvement in inflammation site and curing asthma. The summarized result compiles a total number of 21 plant species belonging to 18 numbers of genera and a total number of ten traditional polyherbal formulations with asthmatic activities. Table 4.1 represents a list of anti-asthmatic medicinal plants with their scientific names, plant families, parts used, extraction solvent, anti-asthmatic efficacy exhibited on in vitro and/or in vivo animal models/human trials, and mechanism(s) of action. Figure 4.1 represents the chemical structure of phytoconstituents isolated from medicinal plants having anti-asthmatic activity. Figure 4.2 represents the mode of action of medicinal plants and polyherbal formulation as anti-asthmatic agents.

4.4.1 *Abrus precatorius* L. (Fabaceae)

A. precatorius (Jequirity bean) possesses immunopotentiating, anti-implantation, and anti-tumor activity. Triterpenoid saponins and lectins from this plant have anti-inflammatory activity. The anti-asthmatic activity of the ethanolic extract of fresh leaves of *A. precatorius* was evaluated against clonidine-induced catalepsy and haloperidol induced catalepsy in mice. The extract significantly active against clonidine-induced catalepsy in but no change observed in haloperidol induced catalepsy [28].

Table 4.1 Anti-asthmatic activity of medicinal plants

Scientific name of source plant	Family	Part use	Extraction solvent	Dose(s)	Active compound isolated	In vitro/in vivo model	Mechanism of action	Reference
Abrus precatorius	Fabaceae	Leaves	Ethanol	100, 125, 150 mg/kg	–	Clonidine-induced catalepsy mice	Clonidine-induced catalepsy ↓	Taur and Patil [28]
Achyranthes aspera	Amaranthaceae	Whole plant	Ethanol	500 mg/kg	–	Toluene diisocyanate induced Wistar rats	Leukocyte ↓, infiltration ↓, Antioxidant enzymes ↑	Goyal et al. [29]
		Aerial parts	Ethanol	375 mg/kg	Flavonoids, phenolic compound, glycosides, tannins, saponins, alkaloids, carbohydrates	Goat tracheal chain and Guinea pig ileum preparation isolated/ histamine-induced bronchoconstriction Guinea pig	Leukocytes count ↓	Shukla et al. [30]
Aerva lanata	Amaranthaceae	Aerial part	Ethanol	100μg/mL	–	Goat tracheal chain 30 & 60 mg/kg doses mice	Mast cell degranulation↓, Clonidine produced catalepsy ↓	Kumar et al. [31]
Asystasia gangetica	Amaranthaceae	Leaf	Methanol, hexane, ethyl acetate	2150 mg/kg	Flavonoids, alkaloids, steroidal aglycones, saponins, reducing sugars, tannins, triterpenoids	A/5-hydroxytriptamine (5-HT; serotonin)-induced Guinea pig tracheal chain	Histamine release ↓	Akah et al. [32]
Bacopa monniera	Scrophulariaceae	Leaves	Methanol	–	–	–	–	Samiulla et al. [33]
Cassia alata	Fabaceae	Leaves	Hydroalcoholic	200 mg/kg	Rhein, kaempferol	Triple antigen/sheep serum-induced mast cell degranulation rats	Mast cell degranulation ↓, LOX↓	Singh et al. [34]
Cassia obtusifolia	Fabaceae	–	Cassia semen	–	–	Histamine Ova-albumin-induced asthmatic mice	IgE ↓, IL-4 ↓	Kang and Park [35]

(continued)

Table 4.1 (continued)

Scientific name of source plant	Family	Part use	Extraction solvent	Dose(s)	Active compound isolated	In vitro/in vivo model	Mechanism of action	Reference
Cassia occidentalis	Fabaceae	Aerial part	Ethanol	1600 mg/kg	Anthraquinones	Ova-albumin-induced asthmatic mice	IL-4↓, IL-5 ↓, IL-13 ↓, inflammatory cell counts ↓, IgE↓, IFN-γ ↑	Xu et al. [36]
Clerodendrum Serratum	Verbenaceae	Root	Ethanol	50,100 and 200 mg/kg	Pentacyclic triterpenoid saponin	Goat tracheal chain preparation Mice	Mast cells degranulation ↓, Histamine release↓	Bhujbal et al. [37]
		Leaves	Hydro alcoholic	5 mg/kg	–	Wistar rats	Total and differential WBC cell count↓, migration of neutrophils ↓, intact mast cells↑	Nageswari et al. [38]
Picrorhiza kurroa	Plantaginaceae	Roots, rhizomes	Ethanol	100 mg/mL	Saponins, flavonoid	Guinea pig ileum/ histamine and ach-induced bronchoconstriction Guinea pig ileum	Histamine release ↓	Sehgal et al. [39]
Inula racemosa	Asteraceae	Dried root	Ethanol	5,10,20, 40 mg/mL	Dihydroisoalantolactone, isoalantolactone, alantolactone	48/80 and egg albumin-induced Wister rats	Mast cells degranulations↓	Choudhary [40]
		Dried root	Petroleum ether	4 mg/mL	–	Goat tracheal chain preparation	Mast cell degranulation ↓	Vadnere et al. [41]
Gleditsia sinensis	Fabaceae	Thorn	Ethanol	50 mg/ kg,100 mg/ kg	(−)-epicatechin, caffeic acid, ethyl gallate, eriodictyol, quercetin	Ovalbumin-induced BALB/c mice	Oxidative stress ↓, IL-4 ↓, IL-5 ↓, IgE ↓	Lee et al. [42]
		Anomalous fruits	Ethanol	20 mg/mL, 50 mg/mL	Oleanane-type triterpenoidal saponins	Passive cutaneous anaphylaxis rat	Histamine release ↓	Dai et al. [43]

Eclipta prostrata	Asteraceae	–	Methanol	100 mg/kg, 250 mg/kg, 500 mg/kg	Oroboside, demethylwedelolactone, wedelolactone	Ovalbumin-induced Balb/c mice	Inflammatory cells ↓, eosinophils ↓, IL-4 ↓, IL-5↓, IL-13↓	de Freitas Morel et al. [44]
Euphorbia hirta	Euphorbiaceae	Leaves	Ethanol	100µg/ 100µL, 200µg/ 100µL	9,12,15-octadecatrien-1-ol, pentadecylic acid, ethyl linoleate, 1,2,3-trihydroxy benzene, gamma-tocopherol, 5-hydroxymethyl-2-furancar-boxaldehyde, myristic acid, 7,10-octadecadienoic acid methyl ester, phytol, ethyl palmitate, squalene	Asthma-induced neonatal rats	Total leukocytes ↓, eosinophils ↓, IL-6 ↓, lipid peroxidation ↓, TNF-α↓, nitric oxide synthase↓, COX-2↓, caspase-3↓, p53↓, NGF ↓, Bax ↓, Bcl-2 ↑, antioxidant levels↑	Xia et al. [45]
Ficus benghalensis	Moraceae	Bark	Aqueous, ethanol, ethyl acetate	–	–	Asthma by milk-induced leukocytosis and milk-induced eosinophilia swiss albino mice weighing	Leucocytes↓, eosinophils↓	Taur et al. [46]
Lepidium sativum	Brassicaceae	Seeds	Methanol	0.03 mg/mL, 0.1–0.3 mg/ mL	Glycerin, monoethanolamine, 1-deoxy-d-mannitol, 1-nitro-2-propanol, 2-butanamine, (S)-, furfural, Allyl isothiocyanate, paromomycin, 2-Hydroxy-2-(5-methylfuran-2-yl)1-phenylethanone, 3,6-Diazahomoadamantan-9-one Hydrazone, 2,3,4-Trimethoxycinnamic acid,	Guinea pig trachea	–	Rehman et al. [47]

(continued)

Table 4.1 (continued)

Scientific name of source plant	Family	Part use	Extraction solvent	Dose(s)	Active compound isolated	In vitro/in vivo model	Mechanism of action	Reference
					2-Naphthalenol, cis-Vaccenic acid, 9-Octadecenamide, γ-Tocopherol, Phthalic acid, decyl oct-3-yl ester, campesterol, cholest-5-en-3-ol			
Tamarindus indica	Fabaceae	Leaves	Methanol	250 mg/kg, 500 mg/kg, 1000 mg/kg,	Ascorbic acid, â-carotene	Clonidine-induced catalepsy mice, Milk-induced leukocytosis and eosinophilia mice	Mast cell degranulation ↓	Tayade et al. [48]
Piper longum	Piperaceae	Fruit	–	1000 mg/mL	–	Guinea pig ileum preparation/ histamine-induced bronchospasm in Guinea pig, haloperidol induced catalepsy mice	Histamine release↓	Kaushik et al. [49]
Urtica dioica	Urticaceae	Leaves	Aqueous	–	Gallic acid	Ovalbumin sensitized/challenged rats	Eosinophilia ↓, leucocytes ↓, lymphocytes↓	Zemmouri et al. [50]

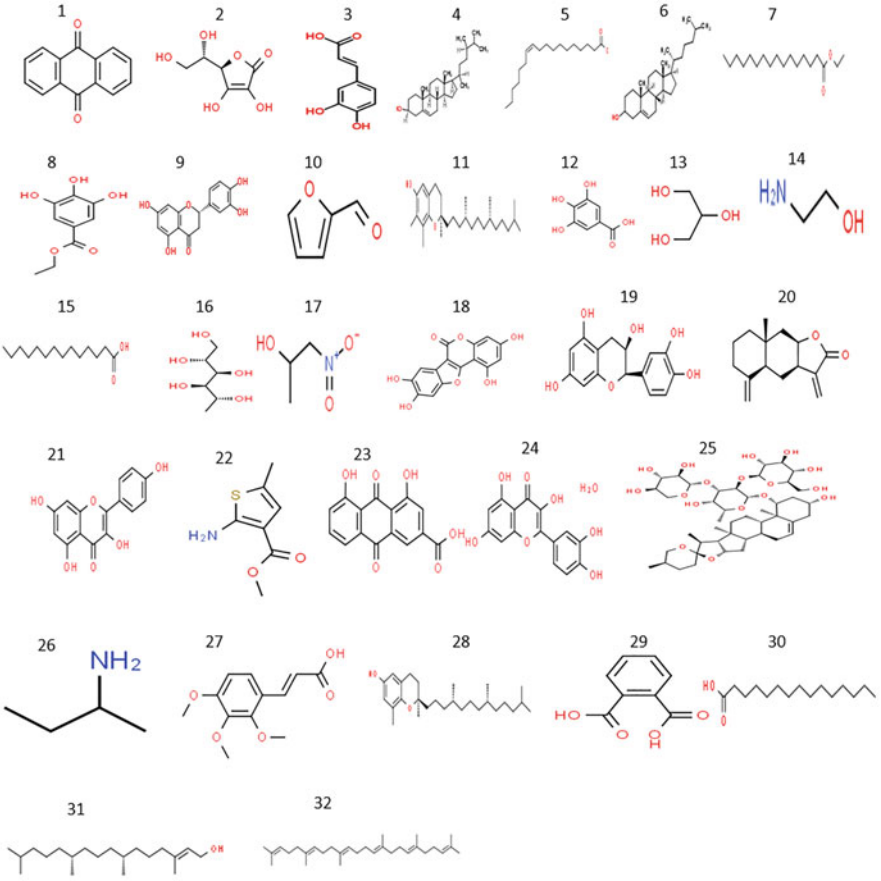


Fig. 4.1 Anti-asthmatic chemical compounds from medicinal plants. 1. Anthraquinone, 2. Ascorbic acid, 3. Caffeic acid, 4. Campesterol 5. cis-Vaccenic acid, 6.Cholest-5-en-3-ol 7. Ethyl palmitate, 8. Ethyl gallate, 9. Eriodictyol, 10. Furfural, 11. Gamma-tocopherol, 12. Gallic acid, 13. Glycerin, 14. Monoethanolamine, 15. Myristic acid, 16. 1-deoxy-d-mannitol, 17. 1-nitro-2-propanol, 18. demethylwedelolactone, 19. (−)-epicatechin, 20. Isoalantolactone, 21.kaempferol, 22. Methyl ester, 23. Rhein, 24. Quercetin, 25. Saponins, 26. 2-butanamine, 27. 2,3,4-Trimethoxycinnamic acid, 28. γ-Tocopherol, 29. Phthalic acid, 30. Pentadecylic acid, 31. Phytol, 32. Squalene

4.4.2 *Achyranthes aspera* L. (Amaranthaceae)

A. aspera (chaff-flower) is a tropical herbaceous plant already proven its effectiveness against bronchial asthma [51]. Saponin C and D are the main anti-asthmatic component present in the fruit of *A. aspera* [52]. [29] also demonstrate the beneficial role of *A. aspera* against toluene diisocyanate-induced asthma in Wistar rats. Ethanol extracts of *A. aspera* reduced neutrophils and eosinophils count in blood. Moreover, *A. aspera* did not showed any airway abnormality [29]. Steroidal drugs are generally

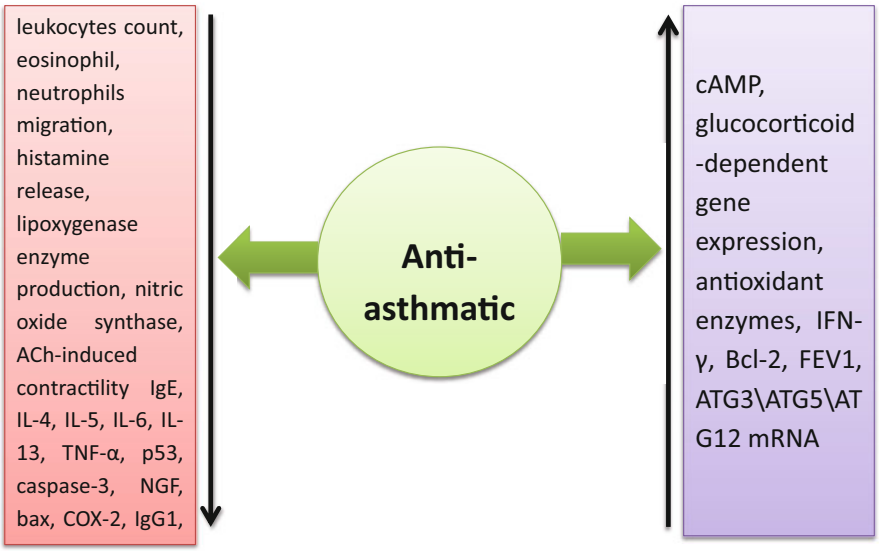


Fig. 4.2 Mode of action of medicinal plants and polyherbal formulations against asthma

effective in asthma. Ethanol extract of aerial parts of *A. aspera* contains triterpenoids, sapogenins, and saponin glycosides, which are different forms of the steroidal nucleus, showed anti-asthmatic activity at a dose of 375 mg/kg [30].

4.4.3 *Aerva lanta* (Linn) Juss. ex. Schult (Amaranthaceae)

A. lanta (Gorakshaganja) a herbaceous plant found in tropical Asia and Africa, Madagascar, and Saudi Arabia is the source of the β-sitosteryl palmitate, α-amyrin, and β-sitosterol and tannin with potential urolithiasis effects [53], antimicrobial [54], cytotoxicity [55], antidiabetic [56], nephroprotective [57], immunomodulatory [58] activities. *A. lanata* is a potent member of anti-asthmatic activity. The ethanol extract (100μg/mL) of areal parts of *A. lanata* decreased contraction produced by histamine in in vitro study of goat tracheal chain preparation. An in vivo study of mice 30 & 60 mg/kg doses of ethanolic extract induced catalepsy and mast cell degranulation. However, they did not isolate and characterize active compounds from the ethanolic extract [31].

4.4.4 *Argemone mexicana* L. (Papaveraceae)

A. mexicana (Brahmadandi) is a common roadside plant from India. Berberine and protopine are the main active compound isolated from *A. mexicana* for asthma treatment [59]. For curing asthma indigenous people of Andhra Pradesh taken,

100–200 mg seed powder twice a day for 2 weeks [60]. Aqueous extracts of *A. Mexicana* stem possesses anti-allergic and anti-stress activity at a dose of 50 mg/kg by milk-induced leukocytosis and milk-induced eosinophilia [61].

4.4.5 *Asystasia gangetica* (L.) T. Anderson (Acanthaceae)

A. gangetica (Chinese violet) is a trail herb and a popular constituent of traditional medicine of East Africa (Kenya). Leaves of *A. gangetica* are effective against asthma. Standardized *A. gangetica* methanol extract containing alkaloids, carbohydrates, flavonoids, proteins, steroidal aglycones, saponins, tannins, reducing sugars, and triterpenoids showed anti-asthmatic like properties. Result of study conducted by [32] revealed that the extracts from *A. gangetica* did not showed any contraction or relaxation activity in isolated tissue preparations. Additionally, they noticed that extract prevented the contraction evoked by spasmogens [32]. A study showed terpenoid (bronchospasmolytic) compounds of leaves of *A. gangetica* that induced histamine contraction of the guinea pig trachea [62].

4.4.6 *Bacopa monnieri* L. (Scrophulariaceae)

Methanolic extract of leaves of *B. monnieri* is a potent mast cell stabilizing effect at doses 10μg/mL for mast cell stabilizing activity in rats [33].

4.4.7 *Cassia alata* L. (Fabaceae)

Cassia alata (Candle-tree) is a tropical medicinal tree that grows in the Philippines and has been used as an expectorant, asthma attacks, tinea infections, eczema, and mycosis [63]. Hydro-alcoholic extract OF *C. alata* leaves inhibits mast cell stabilization and lipoxygenase at 200 mg/kg dose. In this study, the suggested antiallergic activity of *C. alata* is attributed to the presence of anthraquinones and flavonoids [34].

4.4.8 *Cassia obtusifolia* L. (Fabaceae)

Cassiae semen extract stops damage causing by asthma by balancing the allergic immune response. Seo and Park [64] investigated *the Cassia obtusifolia* effect on mice asthma-induced by ovalbumin. Dose-dependent administration of cassiae semen extract in ovalbumin-induced asthmatic mice lowered Ovalbumin-specific IgE and IL-4. Additionally, this extract prevented bronchiolar damage in lung tissues of ovalbumin-induced asthmatic mice., human mast cells (HMC-1) were treated with Cassiae semen extract for in vitro study and resulted in lowered expression of IL-4 and IL-4 mRNA and histamine release [35].

4.4.9 *Cassia occidentalis* L. (Fabaceae)

Another study in an in vivo mice model by [36] showed *C. occidentalis* aerial part of anthraquinones extract (AQE) results in significant effects on allergic asthma. AQE lowered inflammatory cell counts and IL-4, IL-5, and IL-13 production, but increased Th1 cytokine IFN-γ production in bronchoalveolar lavage fluid. AQE also suppressed OVA-specific IgE in serum [36].

4.4.10 *Casuarina equisetifolia* L. (Fabaceae)

C. equisetifolia (Australian pine) is generally cultivated in Coastal regions from Gujarat to Orissa, some parts of West Bengal and Andaman. The methanol extract of *C. equisetifolia* wood and bark showed antihistaminic activity at doses 100 mg/kg by suppressing the histamine-induced tracheal contraction, clonidine-induced catalepsy, and mast cell degranulation [65].

4.4.11 *Clerodendrum serratum* (L) Moon (Verbenaceae)

C. Serratum (Bharangi) is traditionally useful for asthma, cholera, and rheumatism. Saponin from the root ethanol extract of *C. serratum* showed anti-asthmatic activity by isolated goat tracheal chain preparation and clonidine-induced catalepsy at doses 50,100, and 200 mg/kg in mice. This study also indicated that pentacyclic triterpenoid saponins have a role in Type-1 allergic conditions [37].

4.4.12 *Eclipta prostrata* (L.) L. (Asteraceae)

E. prostrata (Bhringraj) widely used medicinal plant was selected to test against pulmonary disorders activity. Methanol extracts of the whole plants were prepared along with NMR screening detected the presence of oroboside, demethylwedelolactone, and wedelolactone. These active components have been shown to inhibit IL-4, IL-5, IL-13, and eosinophils at the dose of doses 100, 250, 500 mg/kg [44].

4.4.13 *Euphorbia hirta* L. (Euphorbiaceae)

Essential oil from *E. hirta (*Bara dudhi) is common to East and West Africa and used traditionally for the treatment of asthma [66]. The isolated compounds (phytol and its isomer 3,7,11,15-tetramethyl-2-hexadecen-1-ol) possesses significant anti-asthmatic activity [66]. The ethanol extract of leaves was prepared and tested for their anti-asthmatic activity by inhibiting IL-6, lipid peroxidation, total leukocytes,

eosinophils, IL-6, cyclooxygenase-2, caspase-3, p53, NGF, TNF-α, and inducing antioxidant content neonatal asthmatic rats with inflammation [44].

4.4.14 *Ficus bengalensis* Merr. (Moraceae)

*F. bengalensis (*Indian banyan) is used traditionally for the treatment of asthma. Various solvent extracts of the leaves such as aqueous, ethanol, petroleum ether, chloroform, and ethyl acetate were prepared and are tested decrease in leucocytes and eosinophils on Swiss albino mice. The result of the investigation observed that aqueous, ethanol, and ethyl acetate extracts significantly decrease leucocytes, and eosinophils, whereas petroleum ether and chloroform were inactive [46].

4.4.15 *Gleditsia sinensis* Lam. (Fabaceae)

G. sinensis (Chinese honey locust) is an important perennial shrub common to China and popularly used in the management of asthma. (−)-epicatechin, caffeic acid, ethyl gallate, eriodictyol, quercetin extracts of the thorn of *G. sinensis* were prepared by Lee et al. [42]. The extracts were subjected to anti-allergic asthma using ovalbumin-Induced BALB/c mice. The results indicated that the extracts reduce IL-4, IL-5, IgE, oxidative stress, and airway inflammation IL-4, IL-5, IgE in a dose-dependent manner (50 and 100 mg/kg) [42]. Another study of ethanolic anomalous fruits extract of *G. sinensis* revealed its anti-allergic activity via histamine reduction in peritoneal mast cells triggered 48/80 in the rat [43].

4.4.16 *Hemidesmus indicus* (L.) R. Br. ex Schult. (Apocynaceae)

Hemidesmus indicus (Anantamul) is a twining shrub commonly distributed in India. Alcoholic extract of *Hemidesmus indicus* roots at doses 25, 50, 100 mg/kg showed antihistaminic activity in the isolated goat tracheal chain preparation and in vivo model using clonidine-induced catalepsy in mice [67].

4.4.17 *Inula racemosa* Hook.f. (Asteraceae)

I. racemosa (Pushkarmool) is a herbaceous perennial medicinal plant known as Pushkarmool popularly root used in Ayurveda as bronchodilator and expectorant for bronchial asthma [68]. Sesquiterpene lactones (dihydroisoalantolactone, isoalantolactone, and alantolactone) isolated the roots of *I. racemosa* showed significant in immunologically induced degranulation of mast cells in Wister rats [40].

4.4.18 *Lepidium sativum* L. (Brassicaceae)

L. sativum (Garden cress) is a cultivated species in India, Europe, and the USA [69]. In Sikkim and West Bengal, the indigenous people use Garden cress for the treatment of asthma, bronchitis, dysentery, pain, and stomachache [69]. L. sativum bronchodilatory effects are enhanced via anticholinergic, Ca++ antagonist, and PDE inhibitory pathways and prevent hyperactive airways disorders [47].

4.4.19 *Picrorhiza kurroa* Royle ex Benth. (Plantaginaceae)

P. kurroa (karu) grows in the Himalayas. In the traditional Indian medicinal system, roots of *P. kurroa* are used in bronchial and liver-related problems. Glycosides are the main active component in roots. Androsin a type of glycosides has been assigned for anti-asthmatic activities mainly in bronchial asthma, which prevents PAF activity [70]. [39] evaluated *P. kurroa* in vitro and in vivo activities and resulted in ethanolic root extract at a concentration of 100 mg/mL prevented histamine and acetylcholine-induced contraction. Saponins and flavonoids are the main anti-asthmatic activity compounds [39].

4.4.20 *Piper longum* L. (*Piperaceae)*

P. longum (*long pepper*) indigenous to India possess fruits used in Ayurvedic and Unani system of medicine piperine isolated from *P. longum* fruit reported anti-asthmatic and antibronchitis activity [71]. The fruits of Piper longum contain Alkaloid, steroid, glycosides, flavonoids. The fruit successfully reduces Histamine-induced bronchospasm in the guinea pig [49].

4.4.21 *Tamarindus indica* L. (Fabaceae)

*T. indica (*Tamarind), a tropical traditional medicine is known for its use in folk medicine for treating asthma, vaginal and uterine complaints, and inflammation. *T. indica* leaves extract present investigation that possesses significant anti-asthmatic activity by attributed to bronchodilating, antihistaminic (H1-antagonist), and anti-inflammatory [48].

4.5 Traditional Formulations

Preclinical and clinical trials of several traditional herbal formulations have also been reported as anti-asthmatic agents such as ASHMI, Ding Chuan Tang, Pentapala-04, Gakani, Bharangyadi, Xiao-Qing-Long-Tang (XQLT), Shirishadi STA-1, San'ao Decoction, and Bakumondo-to have been evaluated; the outcomes

are safe and improve lung function [72]. Table 4.2 represents a compilation of traditional herbal formulations commonly prescribed in the treatment of asthma and their efficacy in preclinical and clinical studies. For, centuries, Traditional Chinese medicine (TCM) has been using in Asia, and nowadays gradually accepting by western countries as well.

4.5.1 The Antiasthma Simplified Herbal Medicine Intervention (ASHMI)

ASHMI is a type of Chinese herbal medicine, which was the first herbal medicine that got approval from the Food and Drug Administration (FDA) for clinical trials for treating asthma [86]. ASHMI is composed of three herbs, i.e. *Glycyrrhiza uralensis (rhizome)*, *Sophorae flavescentis* (root), and *Ganoderma lucidum (fruiting body).* ASHMI prevent asthma symptoms by modulating group 1 and group 2 cytokine [87, 88]. Active components of ASHMI reduced Th2 cytokines (IL-4, IL-5, and IL-13) in BALB/c mice [73]. ASHMI also lower IL-5 secretion by peripheral blood mononuclear cells from asthma patients [74].

4.5.2 Bakumondo-to

Bakumondo-to is a Chinese formula (composed of Chinese Ophiopogonis (tuber), Pinelliae (tuber), Zizyphi (fruit), Glycyrrhiza (root), Ginseng (root), and Oryzae (fruit)). Bakumondo-to has some similarities to glucocorticoids that are implicated in the treatment of asthma. Bakumondo-to directly increased cAMP level and mRNA expression for β-adrenergic receptors and decreased cAMP dependent gene expression, which leads to bronchodilation [75]. However, [76] investigated Bakumondo-to did not decrease cyclic AMPin smooth muscle cells. Additionally, they revealed that Bakumondo-to enhanced isoproterenol-induced cyclic AMP accumulation in airways smooth muscle cells [76].

4.5.3 Bharangyadi

Bharangyadi is a polyherbal formulation composed of *Bharangi (Clerodendrum serratum), Sati (Hedychium spicatum)*, and *Pushkarmoola (Inula racemosa) active against* bronchial asthma. *Bharangyadi* extract treatment showed inhibition of smooth muscle contraction and mast cell stabilizing activity in guinea pigs by the histamine-induced model [77].

Table 4.2 Polyherbal formulations for asthma

formulations	In vitro/in vivo models/clinical trials	mode of action	reference
ASHMI	BALB/c mice	IL-4↓, IL-5↓, IL-13↓ ACh-induced contractility ↓	Jang et al. [73]
	Peripheral blood mononuclear cells	IL-5 ↓	Patil et al. [74]
Bakumondo-to	A549 lung epithelial cells	cAMP ↑, glucocorticoid-dependent gene expression↑	Isohama et al. [75]
	Canine bronchial segments	Isoproterenol-induced cAMP ↑	Tamaoki et al. [76]
Bharangyadi	Histamine-induced Guinea pig ileum	Smooth muscle contraction ↓	Kajaria et al. [77]
Ding Chuan Tang	Lipopolysaccharidestimulated RAW264.7 cells	IRAK/NF-κB ↓, IRAK/AP-1 ↓, MCP-1↓, MIP-1α↓, IκB-α↓, ERK↓, JNK↓, TBK1/IRF3 LPS-triggered production of NO ↓	Zhang et al. [78]
Pentapala-04	Ova-albumin-induced Wistar albino rats	Lipid peroxidation ↑	Rao et al. [79]
	Ova-albumin and aluminum hydroxide induced Wistar albino rats	Lung body weight index (LBI) ↑, lung lipid content ↓	Srinivasarao and Jayraaj [80]
San'ao decoction	Ova-albumin sensitization asthmatic BALB/c mice	CD4+CD25+Foxp3+ Treg cells ↑, Foxp3 ↑, Lymphocyte ↓	Yun et al. [81]
	Ova-albumin plus PM2.5 aggravated asthma model	TRPA1 ↓, TRPV1 ↓, IL-13↓, PGD2↓, NGF ↓	Wang et al. [82]
STA-1	Patients 5–20 years with dyspnea, cough, wheezing	FEV1 ↑, Total IgE ↓, specific IgE↓	Chang et al. [83]
Xiao-Qing-long-Tang	LA4 (murine lung adenoma) BALB/c mice	NGF ↓, IgE ↓, IgG1↓, IgG2a ↓, TARC ↓, eosinophil ↓	Chang et al. [84]
Winyanghuayin + Xiaoqinglong	Wistar rats	ATG3\ATG5\ATG12 mRNA↑, PI3K-p110α ↓	Chang et al. [85]

4.5.4 Ding Chuan Tang (DCT)

DCT is a type of Chinese herbal medicine with 400 years of its use in china for asthma. This herbal decoction is composed of nine herbs including *Ginkgo biloba, Ephedra sinica, Tussilago farfara, Morus alba, Pinellia ternata, Perilla frutescens, Prunus armeniaca, Scutellaria baicalensis, Glycyrrhiza uralensis*) used in the treatment of children with coughing, wheezing, and chest tightness. [89] investigated the effect of DCT in airway hyper-responsiveness on children with asthma. DCT can lower symptoms of persistent asthma in children after 12 weeks of treatment [89]. DCT essential oil inhibited IRAK/NF-κB (c-Jun N-terminal kinase/nuclear factor-kappa B), IRAK/AP-1(c-Jun N-terminal kinase/activator protein-1), and TBK1/IRF3 (TANK-binding kinase 1/interferon regulatory factor 3) in RAW264.7 cells [78].

4.5.5 Pentapala-04

Pentapala-04 is the aqueous extract that composed of five medicinal plant formulation (*Adhatoda vasica* Nees, *Ocimum sanctum* Linn, *Coleus aromaticus* Benth, *Glycyrrhiza glabra* Linn, and Alpiania galangal Sw.). Pentapala-04 prevented ova-albumin and aluminum hydroxide induced lung damage in albino Wistar rats [79]. Aqueous extract of Pentapala-04 prevent asthma via enhanced Lung Body Weight Index (LBI) and suppressed lung lipid content [80].

4.5.6 San'ao Decoction (SAD)

SAD (composed of Herba Ephedrae, Radix Glycyrrhizae, and Amygdalus Communis V) is a classical Chinese medicine, which protected patients from asthma, and cough for 1000 years via suppression of IL-4 induced apoptosis [90]. In ovum albumin sensitization asthmatic BALB/c mice, SAD regulating asthma via enhanced CD4+CD25+Foxp3+ [81]. SAD improved pulmonary functions in asthmatic mice model via inhibiting IL-13 (interleukin-13), PGD_2 (prostaglandin D2), and NGF (nerve growth factor) levels, and TRPA1 and TRPV1 channels [82].

4.5.7 Shirishadi

Shirishadi is an ayurvedic formulation composed of *Albizia lebbeck* (L.) Benth., *Cyperus rotundus* Linn., and *Solanum xanthocarpum* Schrad and Wendl herbs used in the treatment of an acute attack of asthma administrated through nasal route. Human clinical trial stages I, II, III revealed little side effects like leg cramps, dizziness, palpitation, acidity, and nervousness. Additionally, no recurrent cases

were found after several days *Shirishadi* has a powerful anti-asthmatic activity that can be utilized in an alternative remedy for asthma [91].

4.5.8 STA-1

STA-1 TLJN is a Chinese formula composed of a combination of the decoction of Mai-Men-Dong-Tang (MMDT) and Lui-Wei-Di-Huang-Wan (LWDHW), suppressed clinical asthma symptoms, specific IgE synthesis, improved pulmonary function [83].

4.5.9 Winyanghuayin (WYHY) and Xiaoqinglong (XQL)

Xiaoqinglong decoction is a type of Chinese herbal medicine with over 1000 years to treat cold asthma. WYHY decoction added Ginseng and Astragali based on Xiaoqinglong. WYHY and XQL prevented infiltration of airway inflammation cells in Wistar rats via inhibiting the expression of IL-13\TNF-α\TGFβ1 and increasing the expression of IL-10 [85].

4.5.10 Xiao-Qing-Long-Tang (XQLT)

XQLT is a Chinese formula used in the clinical treatment of bronchial asthma [92]. XQLT exerted antiasthmatic effects in a female BALB/c mice via inhibited of NGF (nerve growth factor) in broncho-alveolar lavage fluids. XQLT also reduced thymus- and activation-regulated cytokine (TARC) and serum brain-derived neurotrophic factor (BDNF) levels that further lowered eosinophil infiltration [84].

4.6 Conclusion

This book chapter is based on a comprehensive account of the medicinal plant and polyherbal formulation of the current research trends based on the anti-asthmatic properties. Asthma is a type of lifestyle disease and can cure by natural herbs. One of the main treatments for asthma is based on Cromolyn sodium. Cromolyn derived from the plant Ammi Visnaga and used in the relaxation of the muscle. Ayurvedic medicinal system and Chinese herbal medicines display broad activities on various asthma pathologic systems. The scientific improvements convey with perfection in Polyherbal formulation by the investigation of active chemical constituents. Combinations of plants, which work synergistically, give wanted impact as anti-asthmatic formulation. From the literature, research articles, various medicinal plants extract in different solutions, plant parts, phytochemicals, and formulation details are accounted for to have against asthmatic properties. In this book chapter, we featured the current survey of therapeutic plants preclinical and clinical studies against

asthma. More controlled clinical investigations are warranted, and a portion of the medicinal plants research might end up being successful for asthma treatment when utilized as corresponding treatment.

Acknowledgments Authors acknowledge UGC for providing the funding and authors are thankful to the Presidency University-FRPDF fund.

References

1. Bunyavanich S, Schadt EE (2015) Systems biology of asthma and allergic diseases: a multiscale approach. J Allergy Clin Immunol 135:31–42. https://doi.org/10.1089/ped.2014.0444
2. Chaudhari SP, Talele P (2014) Asthma management: a review. World J Pharm Res 3:275–326
3. DeChristopher LR, Uribarri J, Tucker KL (2016) Intakes of apple juice, fruit drinks and soda are associated with prevalent asthma in US children aged 2-9 years. Public Health Nutr 19:123–130. https://doi.org/10.1017/S1368980015000865
4. Raissy H, Blake K (2015) Vitamin D and asthma: association, causality, or intervention? Pediatr Allergy Immunol Pulmonol 28:60–62
5. Wong KO, Hunter Rowe B, Douwes J, Senthilselvan A (2013) Asthma and wheezing are associated with depression and anxiety in adults: an analysis from 54 countries. Pulm Med 2013:929028
6. Chronic Respiratory Disease Collaborators (2017) Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med 5:691–706
7. Yu L, Wang B, Cheng M et al (2020) Association between indoor formaldehyde exposure and asthma: a systematic review and meta-analysis of observational studies. Indoor Air 30 (4):682–690. https://doi.org/10.1111/ina.12657
8. Akmatov MK, Holstiege J, Steffen A et al (2020) Trends and regional distribution of outpatient claims for asthma, 2009–2016, Germany. Bull World Health Organ 98:40. https://doi.org/10.2471/BLT.19.229773
9. Chen Y, Dales R, Tang M et al (2002) Obesity may increase the incidence of asthma in women but not in men: longitudinal observations from the Canadian National Population Health Surveys. Am J Epidemiol 155:191–197. https://doi.org/10.1093/aje/155.3.191
10. Htet TD, Teede HJ, De Courten B et al (2017) Asthma in reproductive-aged women with polycystic ovary syndrome and association with obesity. Eur Respir J 49:1601334. https://doi.org/10.1183/13993003.01334-2016
11. Alem K, Gebeyehu S, Arega Y (2020) Risk factors and treatment types for asthma severity among adult patients. J Asthma Allergy 13:167. https://doi.org/10.2147/JAA.S246464
12. Arif AA, Rohrer JE, Delclos GL (2005) A population-based study of asthma, quality of life, and occupation among elderly Hispanic and non-Hispanic whites: a cross-sectional investigation. BMC Public Health 5:97. https://doi.org/10.1186/1471-2458-5-97
13. Vignola AM, Chanez P, Campbell AM et al (1998) Airway inflammation in mild intermittent and in persistent asthma. Am J Respir Crit Care Med 157:403–409. https://doi.org/10.1164/ajrccm.157.2.96-08040
14. Goyal BR, Agrawal BB, Goyal RK et al (2007) Pharmacological classification of herbal antiasthmatics. Orient Pharm Exp Med 7:11–25
15. Bentley AM, Menz G, Storz CHR et al (1992) Identification of T lymphocytes, macrophages, and activated eosinophils in the bronchial mucosa in intrinsic asthma. Am Rev Respir Dis 146:500–506. https://doi.org/10.1164/ajrccm/146.2.500
16. Bousquet J, Chanez P, Lacoste JY, Barnéon G et al (1990) Eosinophilic inflammation in asthma. N Engl J Med 323:1033–1039. https://doi.org/10.1056/NEJM199010113231505

17. Djukanovic R, Wilson JW, Britten KM et al (1990) Quantitation of mast cells and eosinophils in the bronchial mucosa of symptomatic atopic asthmatics and healthy control subjects using immunohistochemistry. Am Rev Respir Dis 142:863–871. https://doi.org/10.1164/ajrccm/142.4.863
18. Pesci A, Foresi A, Bertorelli G et al (1993) Histochemical characteristics and degranulation of mast cells in epithelium and lamina propria of bronchial biopsies from asthmatic and normal subjects. Am Rev Respir Dis 147:684–689. https://doi.org/10.1164/ajrccm/147.3.684
19. Jeffery PK, Wardlaw AJ, Nelson FC et al (1989) Bronchial biopsies in asthma. Am Rev Respir Dis 140:1745–1753. https://doi.org/10.1164/ajrccm/140.6.1745
20. Singh SK, Patel JR, Dubey PK, Thakur S (2014) A review on antiasthmatic activity of traditional medicinal plants. Int J Pharm Sci Res 5:2095–2112. https://doi.org/10.13040/IJPSR.0975-8232.5(10).1000-07
21. Vikas S, Dhar KL, Pooja S, Parul S (2014) Indian herbal medicine - a natural cure to asthma. Int J Pharmacogn Phytochem Res 5:302–310
22. Adams BK, Cydulka RK (2003) Asthma evaluation and management. Emerg Med Clin N Am 21:315–330. https://doi.org/10.1016/s0733-8627(03)00015-4
23. Banner KH, Trevethick MA (2004) PDE4 inhibition: a novel approach for the treatment of inflammatory bowel disease. Trends Pharmacol Sci 25:430–436. https://doi.org/10.1016/j.tips.2004.06.008
24. Barnes PJ (2006) Drugs for asthma. Br J Pharmacol 147:297–303. https://doi.org/10.1038/sj.bjp.0706437
25. DiMartino SJ (2008) Idiopathic inflammatory myopathy: treatment options. Curr Rheumatol Rep 10:321–327. https://doi.org/10.1007/s11926-008-0051-4
26. Kesler SM, Sprenkle MD, David WS et al (2009) Severe weakness complicating status asthmaticus despite minimal duration of neuromuscular paralysis. Intensive Care Med 35:157–160. https://doi.org/10.1007/s00134-008-1267-5
27. Lugnier C (2006) Cyclic nucleotide phosphodiesterase (PDE) superfamily: a new target for the development of specific therapeutic agents. Pharmacol Ther 109:366–398. https://doi.org/10.1111/j.1476-5381.2011.01729.x
28. Taur DJ, Patil RY (2012) Antihistaminic activity of *Abrus precatorius* using clonidine induced catalepsy in mice. Orient Pharm Exp Med 12(1):1–14
29. Goyal BR, Goyal RK, Mehta AA (2008) Beneficial effect of *Achyranthes apsera* Linn. In toluene-di-isocyanate induced occupational asthma in rats. Open Nat Prod J 1:44–49. https://doi.org/10.2174/1874848100801010044
30. Shukla A, Garg S, Garg A et al (2016) *In vitro* Achyranthes aspera evaluation of antiasthmatic activity of aerial parts. Asian J Pharm Pharmacol 2:128–131
31. Kumar D, Prasad DN, Parkash J et al (2009) Antiasthmatic activity of ethanolic extract of *Aerva lanata* Linn. Pharmacologyonline 2:1075–1081
32. Akah PA, Ezike AC, Nwafor SV et al (2003) Evaluation of the anti-asthmatic property of Asystasia gangetica leaf extracts. J Ethnopharmacol 89:25–36. https://doi.org/10.1016/S0378-8741(03)00227-7
33. Samiulla DS, Prashanth D, Amit A (2001) Mast cell stabilising activity of Bacopa monnieri. Fitoterapia 72:284–285. https://doi.org/10.1016/S0367-326X(00)00309-9
34. Singh B, Nadkarni JR, Vishwakarma RA et al (2012) The hydroalcoholic extract of *Cassia alata* (Linn.) leaves and its major compound rhein exhibits antiallergic activity via mast cell stabilization and lipoxygenase inhibition. J Ethnopharmacol 141:469–473. https://doi.org/10.1016/j.jep.2012.03.012
35. Kang SY, Park Y-K (2015) Effects of *Agastachis herba* extract on OVA-induced allergic asthma in mice. Korea J Herbol 30:1–12. https://doi.org/10.6116/kjh.2015.30.3.1
36. Xu W, Hu M, Zhang Q et al (2018) Effects of anthraquinones from *Cassia occidentalis* L. on ovalbumin-induced airways inflammation in a mouse model of allergic asthma. Elsevier Ireland Ltd, Shannon

37. Bhujbal SS, Nanda R, Ganu GP et al (2010) Protective effects of icosahydropicenic acid isolated from the roots of *Clerodendrum serratum* (L) moon on experimental allergic asthma. J Complement Integr Med 7:32. https://doi.org/10.2202/1553-3840.1401
38. Nageswari T, Ayesha K, Kumar B et al (2017) Evaluation of hydro alcoholic extract of *Clerodendrum serratum* leaf for anti-asthmatic activity. Int J Pharmacomet Integr Biosci 2:92–96
39. Sehgal R, Chauhan A, Gilhotra UK, Gilhotra A (2013) *In vitro* and *in vivo* evaluation of antiasthmatic activity of picrorhiza kurroa plant. Int J Pharm Sci Res 4:3440–3443. https://doi.org/10.13040/IJPSR.0975-8232.4(9).3440-43
40. Choudhary GP (2006) Mast cell stabilizing activity of Piper longum Linn. Indian J Allergy Asthma Immunol 20:112–116
41. Vadnere GP, Gaud RS, Singhai AK, Somani RS, (2009) Effect of Inula racemosa root extract on various aspects of asthma. Pharmacologyonline 2:84–94
42. Lee MY, Shin IS, Seo CS et al (2011) Antiasthmatic effects of *Gleditsia sinensis* in an ovalbumin-induced murine model of asthma. Int J Toxicol 30:528–537. https://doi.org/10.1177/1091581811412398
43. Dai Y, Chan YP, Chu LM, But PPH (2002) Antiallergic and anti-inflammatory properties of the ethanolic extract from *Gleditsia sinensis*. Biol Pharm Bull 25:1179–1182. https://doi.org/10.1248/bpb.25.1179
44. de Freitas Morel LJ, de Azevedo BC, Carmona F et al (2017) A standardized methanol extract of *Eclipta prostrata* (L.) L. (Asteraceae) reduces bronchial hyperresponsiveness and production of Th2 cytokines in a murine model of asthma. J Ethnopharmacol 198:226–234. https://doi.org/10.1016/j.jep.2016.12.008
45. Xia M, Liu L, Qiu R et al (2018) Anti-inflammatory and anxiolytic activities of *Euphorbia hirta* extract in neonatal asthmatic rats. AMB Express 8:179. https://doi.org/10.1186/s13568-018-0707-z
46. Taur DJ, Nirmal SA, Patil RY, Kharya MD (2007) Antistress and antiallergic effects of *Ficus bengalensis* bark in asthma. Nat Prod Res 21:1266–1270. https://doi.org/10.1080/14786410701757330
47. Rehman NU, Khan AU, Alkharfy KM, Gilani AH (2012) Pharmacological basis for the medicinal use of *Lepidium sativum* in airways disorders. Evidence-based Complement Altern Med 2012:596524. https://doi.org/10.1155/2012/596524
48. Tayade PM, Ghaisas MM, Jagtap SA, Dongre SH (2009) Anti-asthmatic activity of methanolic extract of leaves of *Tamarindus Indica* Linn. J Pharm Res 2:944–947
49. Kaushik D, Rani R, Kaushik P et al (2012) *In vivo* and *in vitro* antiasthmatic studies of plant Piper longum Linn. Int J Pharmacol 8:192–197. https://doi.org/10.3923/ijp.2012.192.197
50. Zemmouri H, Sekiou O, Ammar S et al (2017) *Urtica dioica* attenuates ovalbumin-induced inflammation and lipid peroxidation of lung tissues in rat asthma model. Pharm Biol 55:1561–1568. https://doi.org/10.1080/13880209.2017.1310905
51. Saad A, Siddiqui MMH, Aleem S et al (2002) Effect of Namak Chirchita (*Achyranthes aspera* Linn.) in Zeeq-un-Nafs Sho'bi (bronchial asthma). Hamdard Med 45:37–40
52. Saxena RC (2003) Antihistaminic activity of the Saponin isolated from Achyranthes aspera Linn. Presented paper published in the proceeding of 3rd World Congress on Medicinal & Aromatic Plant (WOCMAP), 3–7 Feb., Chiang Mai University, Thailand. pp 137
53. Soundararajan P, Mahesh R, Ramesh T et al (2006) Effect of *Aerva lanata* on calcium oxalate urolithiasis in rats. Indian J Exp Biol 44:981–986
54. Sabahi M, Mansouri SH, Ramezanian M (1987) Antimicrobial activity of amaranthaceous plants. Int J Crude Drugs Res 25:72
55. Nevin KG, Vijayammal PL (2003) Effect of *Aerva lanata* on solid tumor induced by DLA cells in mice. Fitoterapia 74:578. https://doi.org/10.1016/S0367-326X(03)00148-5
56. Vetrichelvan T, Jegadeesan M (2002) Anti-diabetic activity of alcoholic extract of *Aerva lanata* (L) Juss.Ex.Schultes in rats. J Ethnopharmacol 80:103. https://doi.org/10.1016/s0378-8741(01)00412-3

57. Shirwaikar A, Issac D, Malini S (2004) Effect of *Aerva lanata* on Cisplatin and gentamicin models of acute renal failure. J Ethnopharmacol 90:81–86. https://doi.org/10.1016/j.jep.2003.09.033
58. Nevin KG, Vijayammal PL (2006) Pharmacological and immunomodulatory effects of *Aerva lanata* in Daltons lymphoma ascites bearing mice. Pharm Biol 43:640–646. https://doi.org/10.1080/13880200500303858
59. Agharkar SP (ed) (1991) Medicinal plants of Bombay presidency. Scientific Publishers, Jodhpur, pp 41–213
60. Savithramma N, Sulochana C, Rao KN (2007) Ethnobotanical survey of plants used to treat asthma in Andhra Pradesh, India. J Ethnopharmacol 113:54–61. https://doi.org/10.1016/j.jep.2007.04.004
61. Bhalke RD, Gosavi SA (2009) Anti-stress and antiallergic effect of *Argemone mexicana* stems in asthma. Arch Pharm Sci Res 1:127–129
62. Ezike AC, Akah PA, Okoli CO (2008) Bronchospasmolytic activity of the extract and fractions of *Asystasia gangetica* leaves. Int J Appl Res Nat Prod 1:8–12
63. Khare C (2007) Indian medicinal plants: an illustrated dictionary. Springer-Verlag, Berlin, pp 699–700
64. Seo BS, Park YK (2015) Effect of Cassiae semen extract on ovalbumin-induced allergic asthma in mice. Korea J Herbol 30(1):25–32
65. Aher AN, Pal SC, Patil UK et al (2009) Evaluation of anthistaminic activity of *Casuarina equisetifolia* frost (Casuarinaceae). Pharmacologyonline 1:1144–1149
66. Ogunlesi M, Okiei W, Ofor E, Osibote AE (2009) Analysis of the essential oil from the dried leaves of *Euphorbia hirta* Linn (Euphorbiaceae), a potential medication for asthma. Afr J Biotechnol 8:7042–7050. https://doi.org/10.5897/AJB09.1324
67. Bhujbal SS, Kumar D, Deoda RS et al (2009) Antiasthmatic activity of roots of *Hemidesmus indicus* R. Br Pharmacologyonline 1:209–216
68. Gobindgarh M (2016) Role of Pushkarmool in the asthma management: a conceptual study. J Trad Nat Med 1:10–12
69. Mali RG, Mahajan SG, Mehta AA (2007) Lepidium sativum (garden cress): a review of contemporary literature and medicinal properties. Orient Pharm Exp Med 7:331–335. https://doi.org/10.3742/opem.2007.7.4.331
70. Dorsch W, Stuppner H, Wagner H et al (1991) Antiasthmatic effects of *Picrorhiza kurroa*: androsin prevents allergen-and PAF-induced bronchial obstruction in Guinea pigs. Int Arch Allergy Immunol 95:128–133. https://doi.org/10.1159/000235416
71. Gani HMO, Hoq MO, Tamanna T (2019) Ethnomedicinal, phytochemical and pharmacological properties of Piper longum (Linn). Asian J Med Biol Res 5:1–7. https://doi.org/10.3329/ajmbr.v5i1.41038
72. Li J, Zhang F, Li J (2015) The immunoregulatory effects of traditional chinese medicine on treatment of asthma or asthmatic inflammation. Am J Chin Med 43:1059–1081. https://doi.org/10.1142/S0192415X15500615
73. Jang MH, Piao XL, Kim JM et al (2008) Inhibition of cholinesterase and amyloid-beta aggregation by resveratrol oligomers from *Vitis amurensis*. Phytother Res 22:544–549. https://doi.org/10.1002/ptr.2406
74. Patil SP, Ji WJ, Singha A et al (2010) *In vitro* immunomodulatory effect of ASHMI (anti-asthma herbal medicine intervention) on PBMCs from asthmatics. J Allergy Clin Immunol 125:AB198. https://doi.org/10.1016/j.jaci.2009.12.772
75. Isohama Y, Moriuchi H, Kai H, Miyata T (2002) Glucocorticoid-like and glucocorticoid-unlike regulation of gene expression by Bakumondo-to (Mai-Men-Dong-Tang) in airway epithelial cells. Kampo Med 53:1–9
76. Tamaoki J, Chiyotani A, Takeyama K et al (1993) Potentiation of beta-adrenergic function by saiboku-to and bakumondo-to in canine bronchial smooth muscle. Jpn J Pharmacol 62:155–159. https://doi.org/10.1254/jjp.62.155

77. Kajaria D, Tripathi JS, Tiwari SK et al (2012) Anti-histaminic, mast cell stabilizing and bronchodilator effect of hydroalcoholic extract of polyherbal compound–Bharangyadi. Anc Sci Life 31:95. https://doi.org/10.4103/0257-7941.103182
78. Zhang Y, Guo H, Cheng BCY et al (2018) Dingchuan tang essential oil inhibits the production of inflammatory mediators via suppressing the IRAK/NF-κB, IRAK/AP-1, and TBK1/IRF3 pathways in lipopolysaccharide-stimulated RAW264.7 cells. Drug Des Devel Ther 12:2731–2748. https://doi.org/10.2147/DDDT.S160645
79. Rao DS, Jayaraaj IA, Jayaraaj R (2005) Antiasthmatic role of "Pentapala-04" a herbal formulation against ova albumin and aluminium hydroxideinduced lung damage in rats. Anc Sci Life 24:134
80. Srinivasarao D, Jayraaj IA (2004) Evaluation of activity of a herbal formulation "Pentapala 04" on the lung lipids against ova albumin and aluminium hydroxide induced lung damage in rats. Anc Sci Life 26:68–72
81. Yun L, Xin-Sheng F, Jing-Hua Y et al (2014) CD4+CD25+FOXP3+ T cells, Foxp3 gene and protein expression contribute to antiasthmatic effects of San'ao decoction in mice model of asthma. Phytomedicine 21:656–662. https://doi.org/10.1016/j.phymed.2013.11.009
82. Wang P, Liu H, Fan X et al (2019) Effect of San'ao decoction on aggravated asthma mice model induced by PM2.5 and TRPA1/TRPV1 expressions. J Ethnopharmacol 236:82–90. https://doi.org/10.1016/j.jep.2019.02.043
83. Chang TT, Huang CC, Hsu CH (2006) Clinical evaluation of the Chinese herbal medicine formula STA-1 in the treatment of allergic asthma. Phytother Res 20:342–347. https://doi.org/10.1002/ptr.1843
84. Chang RS, Wang SD, Wang YC et al (2013) Xiao-Qing-long-Tang shows preventive effect of asthma in an allergic asthma mouse model through neurotrophin regulation. BMC Complement Altern Med 13:1–13. https://doi.org/10.1186/1472-6882-13-220
85. Chang X, Lu Z, Qingxiang Z et al (2020) Winyanghuayin decoction and Xiaoqinglong decoction treatment airway inflammation of Cold Asthma Through PI3K-mTOR signal pathway. https://doi.org/10.21203/rs.3.rs-38579/v1
86. Kelly-Pieper K, Patil SP, Busse P et al (2009) Safety and tolerability of an antiasthma herbal formula (ASHMI) in adult subjects with asthma: a randomized, double-blinded, placebo-controlled, dose-escalation phase I study. J Altern Complement Med 15:735–743. https://doi.org/10.1089/acm.2008.0543
87. Busse PJ, Schofield B, Birmingham N et al (2010) The traditional Chinese herbal formula ASHMI inhibits allergic lung inflammation in antigen-sensitized and antigen-challenged aged mice. Ann Allergy Asthma Immunol 104:236–246. https://doi.org/10.1016/j.anai.2009.12.006
88. Srivastava KD, Dunkin D, Liu C et al (2014) Effect of antiasthma simplified herbal medicine INTERVEntion on neutrophil predominant airway inflammation in a ragweed sensitized murine asthma model. Ann Allergy Asthma Immunol 112:339–347. https://doi.org/10.1016/j.anai.2014.01.021
89. Chan CK, Kuo ML, Shen JJ et al (2006) Ding Chuan Tang, a Chinese herb decoction, could improve airway hyper-responsiveness in stabilized asthmatic children: a randomized, double-blind clinical trial. Pediatr Allergy Immunol 17:316–322. https://doi.org/10.1111/j.1399-3038.2006.00406.x
90. Li Y, Wang MY, Fan XS et al (2010) Effect of san-ao decoction, a traditional Chinese prescription, on IL-4 treated normal human bronchial epithelium. J Ethnopharmacol 131:104–109. https://doi.org/10.1016/j.jep.2010.06.006
91. Kajaria D, Tripathi J, Tiwari S (2014) Anti-asthmatic effect of Shirishadi compound through nasal spray actuation. Ayu 35:261. https://doi.org/10.4103/0974-8520.153738
92. Kung YY, Chen YC, Hwang SJ, et al (2016) The prescriptions frequencies and patterns of Chinese herbal medicine for allergic rhinitis in Taiwan. Allergy 61:1316–1318

Medicinal Plants in Targeting Asthma

5

Shabnum Shaheen and Mehwish Jaffer

Abstract

Asthma is the inflammation of the respiratory tract, and is becoming increasingly prevalent around the globe, more so in industrialized areas than non-industrialized regions. The disease has been estimated to affect around 300 million people all over the world, as of yet, but this number has been predicted to swell by a further 100 million by 2025. The prevalence of the disease has been rising, throughout the world, especially in children, since the 1970s.

The disease causes a narrowing of the air passageway, which happens parallel to dramatic fluctuations in the levels of mast cells, lymphocytes, eosinophils, and several inflammatory cellular products like the cytokines. Asthma patients also show elevated levels of the IgE antibody that is known to bind with receptors of mast cells and assorted inflammatory cells to trigger an inflammatory response of the body. These responses include the release of biochemical such as histamines, prostaglandins, and leukotrienes, which trigger bronchoconstriction or the narrowing of the bronchi.

In the present, conventional medicinal procedures and products have proven inadequate in combatting the disease, forcing people to seek other alternatives. This pursuit has presented plants, the reservoirs of several biologically active compounds, many of which are used in plant-based medicine, as the possible counter for the spread of this disease. The Indian subcontinent, including modern-day Pakistan, India, and Bangladesh, houses 45,000 plant species that have potential medicinal properties, as perfectly reflected in the ancient Ayurveda philosophy.

Plant species commonly employed in combatting asthma have proven to have antihistaminic, antiasthmatic, and antiallergic properties. Ayurvedic

S. Shaheen (✉) · M. Jaffer
Department of Botany, LCWU, Lahore, Pakistan

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_5

antiasthmatic medicines must be able to counter the effects of the cellular inflammatory biochemical, one such inhibitory chemical is quercetin, a common flavonoid that inhibits the release of histamine.

Keywords

Asthma · Inflammatory cellular products · Inflammatory response · Bronchoconstriction · Plant-based medicine · Medicinal properties · Ayurveda · Quercetin

5.1 Introduction

The foremost symptoms of Asthma include the inflammation of the trachea and bronchi, dramatic changes in the levels of inflammation-related blood cells like lymphocytes, eosinophils, mast cells, cytokines, and assorted cells and cell-products. There appears to be a correlation between the elevations in the levels of IgE type antibodies which are sensitive to certain receptor sites present on the membranes of inflammatory cells including mast cells. The interaction between this antibody and the surface receptors is the key to the activation of several inflammatory reactions. These reactions include the release of biochemicals such as leukotrienes, histamines, and prostaglandins. When these chemicals are released, they contract the smooth muscles lining the wall of the respiratory tract of the patient, which is termed as bronchoconstriction [1, 2].

Asthma is becoming more and more prevalent all over the world, the density is especially high in industrialized countries that lack a decent vegetation ratio. As of writing this text, 300 million people are estimated to be infected with the said disease worldwide, which will be added upon by a further 100 million by the year 2025 [3, 4]. Asthma has increasingly caused economic and mortal losses to the global human populations, mostly in children [5].

Plants, exploited for their medicinal properties, that are used to target the symptoms of asthma, must have certain traits that counter the disease's effects. These traits include antihistaminic properties, anti-inflammatory properties, muscle-relaxing properties, immunomodulatory properties, and allergic response activities [6]. Ayurvedic medicinal plant products are loaded with anti-Kapha and anti-Vata properties which allow them to target the infected tissues and alleviate the symptoms [7]. Similarly, bronchoconstriction can be targeted by anti-oxidants which can target and inhibit the inflammatory responses that caused the problem in the first place. This is achieved by countering the effects of radical oxygen entities and nitrogen radicals, both of which are strong oxidizing agents [8].

However, at present, remedies for asthma are subpar, owing mostly to the flaws in the drugs, most notably, their adverse effects on the infected individual. This has forced people to seek alternative treatment methods, which are less adverse to the patient. In this pursuit, Quercetin has emerged as a favorable solution as it is a common flavonoid compound, found in many food-stuffs, and which can inhibit the

effects of the inflammatory response cellular machinery. Several other solutions are also being sought after [9].

Asthma makes its first impression on the patient through recurrent difficulties in breathing, episodes of chest tightening, coughing, sneezing, breathlessness, disturbances in the sleep/wake cycles, and overall discomfort [10]. These effects are the direct result of the bronchoconstriction, which have been listed beforehand. According to WHO estimates, the disease is showing increasing prevalence, and the aforementioned 300 million figure is accredited to them [11]. Among the 70 countries studied by WHO, it was concluded that Brazil was afflicted the most, whereby 12.6% of women and 11.5% of men were confirmed to be infected [12].

In Brazil, the infection rate is much higher in children and adolescents, around 24 and 20%, respectively, making them the most vulnerable of all. Just like Brazil, other countries, worldwide, have also shown an increasing prevalence of the said disease, over the past few decades [13–15]. Conventionally, anti-inflammatory drugs, mostly inhaled versions, and relief medications are used to alleviate the symptoms [10, 16].

Preventing asthma is the most cost-effective solution to the growing spread of this disease [17]. Since the conventional options are often very expensive, in India, 79% of the patients use home remedies, instead of certified medicines, such as teas, home-made concoctions, yoga, homeopathy, herbal medicine, and so on [18]. These alternate remedies ranged between 4 and 79% in the adult populations, while this prevalence is 33–89% in children. However, it is not possible to determine the effectiveness of the said home remedies [19].

Since such remedies are used with an ever-increasing frequency, it makes sense to study them in detail, and assess their effects. There are several reasons as to why people opt for such options instead of certified medicines, the most important reason in this context is the widespread belief that conventional medicine is harmful in one way or the other, however, another factor may be affordability and accessibility. Medicinal plants, since they are natural, are seen as a better alternative, and hence endorsed by herbalists.

Since asthma is a chronic infection, requiring a prolonged, and at times, tedious treatment process. This is also one of the reasons why people seek alternative therapies and home remedies, mostly based on medicinal herbs [9]. The use of such medicinal herbs is also endorsed by the cultural values or the social makeup of communities in countries like India and Brazil.

5.2 Adverse Effects of Current Treatments Used in Asthma

Here are some adverse effects of traditional chemical-based treatments used for treating asthma [20]:

5.2.1 Isoprenaline

It can cause tachycardia.

5.2.2 Salbutamol

There can be events of dose-related muscle tremors (the more the doses, the greater the tremors), restlessness, heart palpitations, nervousness, irritation in the throat, and even edema in the ankle region.

5.2.3 Theophylline

This medication can cause dose-dependent tachypnoea, in addition to other conditions like arrhythmia, convulsions, muscle bulkiness, shock, hypotension, flushing, vomiting, heart palpitation, restlessness, dyspepsia, insomnia, tremors, and so on.

5.2.4 Anticholinergics

This medication can dry up the subject's mouth and make it difficult for you to swallow or talk. The patient may also develop a scarlet rash, may be subjected to photophobia, your near vision may become blurred, you may experience heart palpitations, hallucinations, delirium, face problems with your pulse, severe heart issues, and in case of extreme poisoning, the patient may enter a state of coma.

5.2.5 Ketotifen

It can make the patient dizzy, even sedate them. Other side effects include weight gain, feeling nauseated, and having a dry mouth.

5.2.6 Corticosteroids

These are by far the most destructive and can cause serious damage if things go wrong. The side effects include Cushing's habitus, hyperglycemia, delaying of the wound healing process, osteoporosis, vulnerability to infections, weakness in the muscles, hyperglycemia, restriction of the hypothalamo–pituitary–adrenal (HPA) axis, and so on.

The aforementioned side effects have forced researchers to come up with innovative natural solutions to combat the disease. The target solutions should be practical, applicable, available to the people, and most of all, clinically acceptable.

Alternative medicine has been under consideration for a while now, and its usage in the treatment of asthma has only increased over the years [9].

5.3 Some Traditional Plants with Antiasthmatic Potential

5.3.1 *Aerva lanata* (L.) Juss. Ex Schult

Aerva lanata, shortened as *A. lanata* is a common herbaceous weed, distinguished by its white wooly flowers which form auxiliary bunches. It is a common sight in the plains of the warmer regions in the Indian subcontinent. The plant was successfully tested for medicinal properties by a team of researchers who used its extract (mostly ethanol-soluble) at a minute concentration of 100 μg/mL mixed in preparations from the trachea of a goat, and in another experiment, prepared into oral doses of 30 and 60 mg/kg to be tested on mice, in both cases, it proved to possess effective antihistamine properties [21] (Fig. 5.1).

Fig. 5.1 *Aerva lanata* inflorescence (Source: By J.M.Garg—Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=6608619)

5.3.2 *Ageratum conyzoides* L.

Ageratum conyzoides, shortened as *A. conyzoides*, is an annual herb belonging to the family Asteraceae, formerly known as Compositae, and is indigenous to the tropical regions of the New World. However, its distribution also spreads across the tropical and sub-tropical regions of the rest of the world. The extract of its leaves is hydroalcoholic, and when prepared in oral doses of 250, 500, and 1000 mg/kg exhibit impressive antihistaminic potential and have experimentally inhibited catalepsy induced by clonidine in lab mice [22] (Fig. 5.2).

5.3.3 *Argemone mexicana* L.

It is quite common to encounter *Argemone mexicana*, shortened as *A. mexicana*, in the fields and even the roadsides of India. This plant is known to possess antiallergic properties. Its aqueous extracts, when prepared as an oral dose of 50 mg/kg can be effective in combatting leukocytosis and eosinophilia [23] (Fig. 5.3).

Fig. 5.2 *Ageratum conyzoides* (Source: By Minghong—Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=4030608)

Fig. 5.3 *Argemone mexicana* (Source: By B. Navez—Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=4732240)

5.3.4 *Asystasia gangetica* (L.) T. Anderson

Asystasia gangetica, shortened as *A. gangetica*, is a common remedy option for asthma throughout various parts of Nigeria. The extract of its leaves, concurrent with hexane, ethyl acetate, and methanol, was proven to be quite effective in their antihistaminic activity (countering allergic reactions and inflammations). It did not inhibit the contractions and relaxations in the target tissues, however, it did stop spasmodic contractions [24] (Fig. 5.4).

5.3.5 *Bacopa monnieri* (L.) Pennell

The extracts of *Bacopa monnieri*, shortened as *B. monnieri*, contain compounds soluble in petroleum ether, methanol, chloroform, and water, which at doses of 10 μg/mL can effectively stabilize mast cells in lab rats. The extract proved to be quite effective at stopping mast cell degranulation [25] (Fig. 5.5).

5.3.6 *Senna sophera* (L.) Roxb

Senna sophera, formerly known as, *Cassia sophera*, is a part of traditional asthma treatments, and that of assorted diseases too. The leaf extracts of this plant contain

Fig. 5.4 *Asystasia gangetica* (Source: CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=70915)

fractions soluble in ethyl acetate, ethanol, and chloroform, which have a proven antihistaminic potential at concentrations of 250, 500, and 750 mg/kg, researchers believe that the underlying cause of this potential may be the presence of flavonoids [26] (Fig. 5.6).

5.3.7 *Casuarina equisetifolia* L.

Casuarina equisetifolia, shortened as *C. equisetifolia*, is an evergreen tree, measuring as high as a whopping 50 meters in some cases. It is cultivated in the coastal areas of stretch of land in India between Gujrat and Orissa, in some regions of West Bengal (also part of India), and the Andamans. The wood and bark extracts of this tree possess methanol-soluble fractions which have appreciable antihistaminic potential, which has been experimentally proven by Ahel et al., [27] (Fig. 5.7).

5.3.8 *Rotheca serrata* (L.) Steane & Mabb

Rotheca serrata, formerly known as *Clerodendrum serratum*, is known by its common name "bharangi" by the practitioners of Ayurveda. Traditionally, this

Fig. 5.5 *Bacopa monnieri* (Source: By Forest and Kim Starr, CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=6109556)

plant has been used to cure several diseases and conditions like inflammation, pain, rheumatism, malaria, and respiratory diseases. The root extract of this plant contains a major fraction of ethanol-soluble compounds which exhibit antihistaminic potential, as was noted by researchers who tested it on goat tracheal tissues, and via doses to mice at 50, 100, and 200 mg/kg [28, 29].

5.3.9 *Cnidium monnieri* (L.) Cusson

Cnidium monnieri, shortened as *C. monnieri*, is a common part of traditional Chinese medical treatments, such as for alleviating pain in the vagina, treating impotence, curing suppurative dermatitis, and so on. However, researchers also discovered that its antiallergic properties, owing to its ethanol and osthol (a chromame) soluble extracts can tackle cutaneous anaphylaxis in lab rats [30].

5.3.10 *Crinum glaucum* A. Chev

Crinum glaucum, shortened as *C. glaucum*, is popularly used in traditional remedies in South-Western Nigeria. It is believed to be effective in countering cough,

Fig. 5.6 *Senna sophera* seeds (Source: By Tracey Slotta—http://plants.usda.gov/java/largeImage?imageID=seso2_001_ahp.tif, Public Domain, https://commons.wikimedia.org/w/index.php?curid=12236440)

convulsions, and asthma. Researchers isolated aqueous extracts of this plant, prepared doses of 100–400 mg/kg, and tested it on guinea pigs, where it showed great effectiveness in antihistaminic activities [31].

5.3.11 *Curculigo orchioides* Gaertn

Curculigo orchioides, shortened as *C. orchioides*, is a small herb spread widely across regions in India, China, and the islands to the east and south-east: Japan and the Malayan archipelago. *C. orchioides* rhizome extract contains fractions of alcohol-soluble compounds, which at doses of 100–400 mg/kg were proven to be effective in stabilizing mast cells. The extract's antihistaminic properties are worth praising [32].

It was also proven effective in tackling and even reversing histamine-induced contractions of the respiratory tract, bronchoconstriction, leukocytosis, eosinophilia, and assorted conditions. These experiments proved effective on goat, pig, and mice tissues [33] (Fig. 5.8).

Fig. 5.7 *Casuarina equisetifolia* (Source: By Ethel Aardvark—Own work, CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=4989854)

5.3.12 *Eclipta alba* L.

The extract of *Eclipta alba*, shortened as *E. alba*, contains a 50% fraction of ethanol which has proven antihistaminic and anti-anaphylactic potentials which become significant at doses of 250 and 500 mg/kg. These doses proved to be effective in countering mast cell degranulation, anaphylaxis, tracheal issues, and assorted respiratory problems [34] (Fig. 5.9).

5.3.13 *Euphorbia hirta* L.

Euphorbia hirta, shortened as *E. hirta*, is a wild herb that is found in the warmer regions of India. The extracts of this plant are ethanol-soluble, which, at doses of 100–1000 mg/kg exhibit effective antihistaminic and antiallergic potentials. These extracts have been proven to inhibit degranulation of mast cells, and assorted medical issues [35] (Fig. 5.10).

Fig. 5.8 *Curculigo orchioides* (Source: By Viren Vaz (self)—at CEC, Mumbai, CC BY-SA 2.5, https://commons.wikimedia.org/w/index.php?curid=863216)

5.3.14 *Ficus benghalensis* L.

Ficus benghalensis, shortened as *F. benghalensis*, is a huge tree, growing as high as 30 meters, forming an expansive canopy which has inspired its local name: banynan tree (banyan meaning small residence). The aqueous extracts of this plant contain ethanol and ethyl acetate soluble compounds, the tree's bark has proven antihistaminic potential which becomes noticeable at a dose of 50 mg/kg. This potential is accredited to the presence of flavonoid compounds [36, 37] (Fig. 5.11).

5.3.15 Gakani

The said herbal mixture is a polyherbal traditional drug that contains extracts of *Cenchrus biflorus*, *Olax subscorpioidea*, *Piper guineense*, *Psorospermum guineense*, *Securidaca longipedunculata*, and *Syzygium aromaticum*. Gakani has been honed, traditionally, for its antiasthmatic power, this potential has been tried and tested by researchers. It was tested on the tracheal tissues of guinea pigs, their ileum tissues, rat stomach tissues, and on a hind paw edema caused by albumin. In all cases, the extract proved to be effective at inhibiting the histamine-induced contraction of affected tissues. The extract was proven to be effective [38].

Fig. 5.9 *Eclipta alba* (Source: By J.M.Garg—Own work, CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=7606450)

5.3.16 *Hemidesmus indicus* (L.) R.Br

Hemidesmus indicus, shortened as *H. indicus*, is a shrub widely distributed in regions of Indian. The extracts of this plant, which are ethanol-soluble, have proven to possess antihistaminic activity which becomes prominent at doses of 25, 50, and 100 mg/kg which was tested on tracheal extracts of goat, anaphylaxis-infested paw, and catalepsy, and proven effective [28, 29] (Fig. 5.12).

5.3.17 *Amburana cearensis* (Allemão) A.C.Sm

Amburana cearensis, shortened as *A. cearensis*, is a plant endowed with medicinal properties, used in traditional herbal medicine, commonly found in Northeast Brazil savannah. It is used to treat respiratory distresses, mostly asthma. The trunk extracts are endowed with flavonoids which may be the causative factor behind its effectiveness [39] (Fig. 5.13).

Fig. 5.10 *Euphorbia hirta* (Source: By Forest and Kim Starr, CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=6160393)

5.3.18 Members of Family Zingiberaceae

Some members of the Zingiberaceae family have been proven to possess antiallergic potentials, as noted by [40].

5.3.19 *Lepidium sativum* L.

Lepidium sativum, shortened as *L. sativum*, is commonly termed as Asaliyo, is an annual herb with a glabrous appearance, commonly used in salads in several regions of India. The extracts of this plant are soluble in ethyl acetate, ethanol, n-butanol, and methanol which inhibit the activity of histamine and other allergens [41] (Fig. 5.14).

5.3.20 *Mentha spicata* L.

Mentha spicata, shortened as *M. spicata*, is endowed with unique flavonoids and glycosides, soluble in ethyl acetate, which shows antihistaminic properties [42] (Fig. 5.15).

Fig. 5.11 *Ficus benghalensis* (Source: By McKay Savage—originally posted to Flickr as India—Kolkata—10—Great Banyan Tree, CC BY 2.0, https://commons.wikimedia.org/w/index.php?curid=6028234)

Fig. 5.12 *Hemidesmus indicus* (Source: By No machine-readable author provided. Shyamal assumed (based on copyright claims)—No machine-readable source provided. Own work assumed (based on copyright claims), CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=801456)

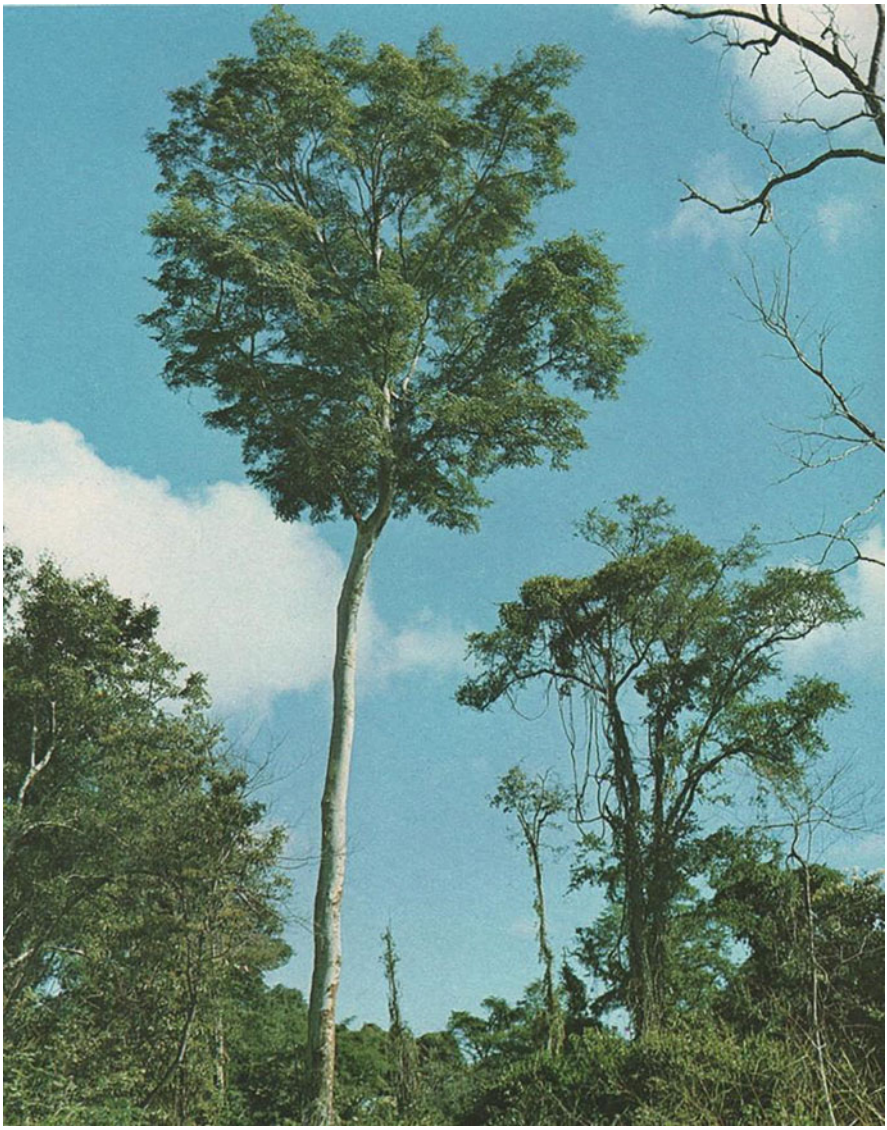


Fig. 5.13 *Amburana cearensis* (Source: By Jorge Vallmitjana - Libro del Árbol, Tome II, edited by Celulosa Argentina S. A., Buenos Aires, Argentina, October 1975. The visual material is not explicitly copyrighted, but the editors thank Mr. Jorge Vallmitjana for his photographic contribution; Public Domain, https://commons.wikimedia.org/w/index.php?curid=4473843)

5.3.21 *Momordica dioica* Roxb. Ex Willd

Momordica dioica, shortened as *M. dioica*, is a creeper with medicinal properties. The leaves and fruits are used for medicinal purposes, to cure several diseases such

Fig. 5.14 *Lepidium sativum* (Source: CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=116773)

as fever, bronchitis, asthma, and even severe conditions like leprosy. Extracts dissolved in water and methanol from its pulp are endowed with antihistaminic properties which have been experimentally verified with lab mice, using doses of 50 mg/kg [43] (Fig. 5.16).

5.3.22 *Mucuna pruriens* (L.) DC

The methanol-soluble fractions, extracted from seeds, are rich with L-DOPA which has endowed with impressive antihistaminic properties that were tried, tested, and proven at doses of 50, 100, and 200 mg/kg with lab mice [44] (Fig. 5.17).

5.3.23 *Myrica esculenta* Buch.-Ham. Ex D.Don

Myrica esculenta, shortened as *M. esculenta*, is famous by its vernacular name Kaiphal. It is traditionally used in herbal medicines for treating diseases like asthma and bronchitis in the Ayurvedic medical philosophy—which has been thoroughly scrutinized scientifically and has been most proven to be effective. Researchers tested the antiallergic and anti-inflammatory potentials of ethanol-soluble compounds extracted from the plant. Using doses of 75 and 150 mg/kg of its extract, researchers verified its potential [45]. The bark of the plant also contains extracts

Fig. 5.15 *Mentha spicata* (Source: By Simon Eugster—Simon 13:07, 2 July 2006 (UTC)—Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=913901)

with proven medical properties, which the researchers put to test using doses of 75 mg/kg which tackled the effects of histamine and acetylcholine in guinea pigs [46].

5.3.24 *Nyctanthes arbortristis* L.

Nyctanthes arbortristis, shortened as *N. arbortristis*, is a traditional herbal option for treating asthma. The extract of this plant, soluble in petroleum ether, is effective against histamine-induced distress, which it can alleviate at doses of 50 mg/kg [47].

5.3.25 *Olea europaea* L.

Olea europaea, shortened as *O. europaea*, needs no introduction. It has been revered and honed throughout history not only for its medicinal properties but even due to spiritual involvement. This small tree, which remains evergreen, can grow anywhere between 12 and 20 ft, with rigid branches and a grey-colored bark. The aqueous extract of this plant has impressive antihistaminic potential which inhibited mast cell

Fig. 5.16 *Momordica dioica* (Source: By Sivahari—Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=16283137)

degranulation at doses of 4 and 8 mg/kg in mice, and at a dose of 100 μg/mL for goat and guinea pig [48] (Fig. 5.18).

5.3.26 *Microsorum scolopendria* (Burm.F.) Copel

The ethanol extracts of *Microsorum scolopendria*, formerly known as *Phymatosorus scolopendria*, have been proven to show histamine inhibiting potential [49].

5.3.27 *Piper betle* L.

Its aqueous and ethanol-soluble extracts were tested and proven to be effective against asthma for guinea pigs at doses of 100 and 200 mg/kg [50].

5.3.28 Striga Orobanchioides

The ethanol-soluble and aqueous extracts of this plant proved effective in countering the effects of histamine in guinea pigs [51].

Fig. 5.17 *Mucuna pruriens* (Source: By Agong1—Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=13865651)

5.3.29 *Sphaeranthus indicus* L.

Its ethanol based and ethyl acetate-based extracts showed great effectiveness in countering the degranulation of mast cells [52].

5.3.30 *Cynodon dactylon* (L.) Pers.

This is among the most predominant grasses of the Indian subcontinent, its extracts in petroleum ether, methanol, and chloroform show great medicinal potential in counter mast cell degeneration and so on [53].

Fig. 5.18 *Olea europaea* (Source: By en:User:Nickfraser—en:Image:Olivesfromjordan.jpg, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=2208405)

5.4 Conclusion

Many non-prescription drugs are plant-based or based on compounds derived from plants. The use of such medications for the treatment of asthma not only opens up a new avenue in the approach towards this disease but also promises to safeguard patients from the side effects of conventional options. While herbal medicine cannot be endorsed as a solution because of its non-standardization, standardized plant-based medicines appear to be the way forward as their effectiveness is proven by a heap of studies. The only thing that remains to be ascertained is their effect on human beings for which further experimentation is required.

References

1. Holgate ST, Polosa R (2008) Treatment strategies for allergy and asthma. Nat Rev Immunol 8:218–230
2. Tattersfield AE, Knox AJ, Britton JR, Hall IPA (2002) Lancet 360:1313–1322
3. Bousquet J, Bousquet PJ, Godard P, Daures JP (2005) The public health implications of asthma. Bull World Health Organ 83:548–554
4. Masoli M, Fabian D, Holt S, Beasley R (2004) The global burden of asthma: executive summary of the GINA dissemination committee report. Allergy 59:469–478
5. Braman SS (2006) The global burden of asthma. Chest 130:4S–12S
6. Greenberger PA (2003) Therapy in management of rhinitis asthma complex. Allergy Asthma Proc 24:403–407
7. Lyengar MA, Jambaiah KM, Rao GM (1994) Studies on an anti-asthma kada: a proprietary herbal combination. part-I clinical study. Indian Drug 31(5):183–186
8. Henricks PA, Nijkamp FP (2001) Reactive oxygen species as mediators in asthma. Pulm Pharmacol Ther 14:409–420
9. Slader CA, Reddel HK, Jenkins CR, Armour CL, Bosnic ASZ (2006) Complementary and alternative medicine use in asthma: who is using what? Respir Ther 11:373–387
10. SBPT (Sociedade Brasileira de Pneumologia e Tisiologica) (2006) IV Diretrizes Brasileiras para o manejo da Asma. J Bras Pneumol 32(7):S447–S474
11. WHO (World Health Organization) (2007) Global surveillance, prevention, and control of chronic respiratory diseases: a comprehensive approach. http://www.who.int/entity/gard/publications/GARD_Portuguese.pdf
12. WHO (World Health Organization) (2009) World health survey. http://www.who.int/healthinfo/survey/en
13. Caravajal UI, Marcos GL, Monge BR, Varelas SMM, Andoin NG, Garrido BJ, Blancoquiros A, Silvarrey LA, Garciahernandez G, Grimaj GF, Gonzalezdiaz C, Blasco BJ (2005) Geographic variation in the prevalence of asthma symptoms in Spanish children and adolescents: international study of asthma and allergies in childhood (ISAAC) phase 3. Spain Arch Bronconeumol 41(12):659–666
14. Sole D, Wandalsen GF, Nunes CIC, Naspitz CK (2006) Prevalence of symptoms of asthma, rhinitis, and atopic eczema among Brazilian children and adolescents identified by the international study of asthma and allergies in childhood (ISAAC)-phase 3. J Pediatr 82(5):341–346
15. Yan DC, Ou LS, Tsai TL, Wu W (2005) F & Huang, J. L. prevalence and severity of symptoms of asthma, rhinitis, and eczema in 13- to 14-year-old children in Taipei, Taiwan. Ann Allergy Asthma Immunol 95(6):579–585
16. GINA (Global Initiative for Asthma) Global strategy for asthma management and prevention (2006). https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwj2lcihnInsAhUxx4UKHS2sCzAQFjABegQIAxAB&url=https%3A%2F%2Fginasthma.org%2Fwp-content%2Fuploads%2F2019%2F01%2F2006-GINA.pdf&usg=AOvVaw1UCwetk3y9OuSTPP4OCqYc
17. Franco R, Santos A, Nascimento HF, Ponte E, Machado SA, Machado SC, Loureiro S, Barreto ML, Rodrigues LC, Cruz AA (2007) Cost-effectiveness analysis of a state funded program for control of severe asthma. BMC Public Health 7:82. https://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-7-82
18. Singh V, Sinha HV, Gupta R (2002) Barriers in the management of asthma and attitudes towards complementary medicine. Respir Med 96(10):835–840
19. Szelenyi I, Brune K (2002) Herbal remedies for asthma treatment: between myth and reality. Drugs Today 38(4):265–303
20. Taur DJ, Patil RY (2011) Some medicinal plants with antiasthmatic potential: a current status. Asian Pac J Trop Biomed 1(5):413–418
21. Kumar D, Prasad DN, Parkash J, Bhatnagar SP, Kumar D (2009) Antiasthmatic activity of ethanolic extract of Aerva lanata Linn. Pharmacology 2:1075–1081

22. Tote MV, Mahire NB, Jain AP, Bose S, Undale VR, Bhosale AV (2009) Effect of Ageratum conyzoides Linn on clonidine and haloperidol induced catalepsy in mice. Pharmacology 2:186–194
23. Bhalke RD, Gosavi SA (2009) Antistress and antiallergic effect of Argemone mexicana stem in asthma. Arch Pharm Sci Res 1(1):127–129
24. Akah PA, Ezike AC, Nwafor SV, Okoli CO, Enwerem NM (2003) Evaluation of the anti-asthmatic property of Asystasia gangetica leaf extracts. J Ethnopharmacol 89:25–36
25. Samiulla DS, Prashanth D, Amit A (2001) Mast cell stabilising activity of Bacopa monnieri. Fitoterapia 72:284–285
26. Nagore DH, Ghosh VK, Patil MJ (2009) Evaluation of antiasthmatic activity of Cassia sophera Linn. Phcog Mag 5(19):109–118
27. Aher AN, Pal SC, Patil UK, Yadav SK, Bhattacharya S (2009) Evaluation of antihistaminic activity of Casuarina equisetifolia frost (Casuarinaceae). Pharmacology 1:1144–1149
28. Bhujbal SS, Kumar D, Deoda RS, Deore TK, Patil MJ (2009a) Antiasthmatic activity of roots of Hemidesmus indicus R. Br Pharmacology 1:209–216
29. Bhujbal SS, Kewatkar SM, Kumar D, Mudgade SC, Patil MJ (2009b) In vivo and in vitro antiasthmatic studies of Clerodendrum serratum Linn. Pharmacology 2:745–752
30. Matsuda H, Tomohiro N, Yasuko KM (2002) Anti-allergic effects of cnidii monnieri fructus (dried fruits of Cnidium monnier) and its major component, osthol. Biol Pharm Bull 25 (6):809–812
31. Okpo SO, Adeyemi OO (2002) The anti-allergic effects of Crinum glaucum aqueous extract. Phytomedicine 9:438–441
32. Venkatesh P, Mukherjee PK, Satheesh KN, Neelesh KN, Bandyopadhyay A, Hiroyuki F (2009) Mast cell stabilization and antihistaminic potentials of Curculigo orchioides rhizomes. J Ethnopharmacol 126:434–436
33. Pandit P, Singh A, Bafna AR, Kadam PV, Patil MJ (2008) Evaluation of antiasthmatic activity of Curculigo orchioides Gaertn. Rhizomes Indian J Pharm Sci 70(4):440–444
34. Patel MB, Panchal SJ, Patel JA (2009) Antianaphylactic activity of alcoholic extract of Eclipta alba. J Young Pharm 1(3):244–250
35. Youssouf MS, Kaiser P, Tahir M, Singh GD, Singh S, Sharma VK (2007) Anti-anaphylactic effect of Euphorbia hirta. Fitoterapia 78:535–539
36. Taur DJ, Nirmal SA, Patil RY (2007) Effect of various extracts of Ficus bengalensis bark on clonidine and haloperidol-induced catalepsy in mice. Pharmacology 3:470–477
37. Taur DJ, Patil RY (2009) Effect of bio-fractions isolated from Ficus bengalensis bark on clonidine induced catalepsy. J Pharm Res 2(11):1676–1677
38. Akah PA, Gamaniel KS, Samson A, Wambebe CO (1997) Evaluation of Nigerian traditional medicine: effects of Gakani, a herbal anti-asthmatic drug. J Ethnopharmacol 55:87–92
39. Luzia KAML, Melina FC, Márcia P, Viviane MB, Edilberto RS, Kirley MC (2006) Mechanisms underlying the relaxation induced by isokaempferide from Amburana cearensis in the Guinea-pig isolated trachea. Life Sci 79:98–104
40. Tewtrakul S, Subhadhirasakul S, Kummee S (2008) Anti-allergic activity of compounds from Kaempferia parviflora. J Ethnopharmacol 116:191–193
41. Mali RG, Mahajan SG, Mehta AA (2008) Studies on bronchodilatory effect of Lepidium sativum against allergen induced bronchospasm in Guinea pigs. Phcog Mag 4(15):189–192
42. Satoshi Y, Koichiro O, Kazuhiro O, Ryoji K, Kazuo Y (1998) Antihistaminic flavones and aliphatic glycosides from Mentha spicata. Phytochemistry 48(1):131–136
43. Rakh MS, Raut DN, Chavan MJ, Chaudhari SR (2010) Effect of various extracts of Momordica dioica pulp on clonidine and haloperidol-induced catalepsy in mice. Pharmacol Ther 1:1–11
44. Pathan AA, Kasture SB, Mahalaxmi M (2009) Residue of Mucuna pruriens potentiates haloperidol and clonidine-induced catalepsy in mice. Pharmacology 3:652–658
45. Patel KG, Rao NJ, Gajera VG, Bhatt PA, Patel KV, Gandhi TR (2010) Antiallergic activity of stem bark of Myrica esculenta Buch. Ham. (Myricaceae). J Young Pharm 2(1):74–78

46. Patel KG, Bhalodia PN, Patel AD, Patel KV, Gandhi TR (2008) Evaluation of bronchodilator and anti-anaphylactic activity of Myrica sapida. Iran Biomed J 12(3):191–196
47. Nirmal SA, Pal SC, Mandal SC (2009) Antihistaminic activity of Nyctanthes arbortristis bark. Pharmacology 3:924–928
48. Chandak R, Devdhe S, Changediya V (2009) Evaluation of anti-histaminic activity of aqueous extract of ripe olives of Olea europea. J Pharm Res 2(3):416–420
49. Ramanitrahasimbola D, Rakotondramanana DA, Rasoanaivo P, Randriantsoa A, Ratsimamanga S, Palazzino G (2005) Bronchodilator activity of Phymatodes scolopendria (Burm.) Ching and its bioactive constituent. J Ethnopharmacol 102:400–407
50. Jawale NM, Shewale AB, Nerkar GS, Patil VR (2009) Evalution of antihistaminic activity of leaves of Piper betel Linn. Pharmacology 3:966–977
51. Li PB, Ma Y, Wang YG (2006) Su, W. W. experimental studies on antitussive, expectorant and antiasthmatic effects of extract from Citrus grandis var. tomentosa. Zhongguo Zhong Yao Za Zhi 31(16):1350–1352
52. Mathew JE, Srinivasan KK, Dinakaran V, Joseph A (2009) Mast cell stabilizing effects of Sphaeranthus indicus. J Ethnopharmacol 122:394–396
53. Savali AS, Biradar PR, Jirankali MC (2010) Antianaphylactic and mast cell stabilization activity of Cynodon dactylon. Int J Pharm Pharm Sci 2(2):69–73

Incipient Need of Medicinal Plants in Targeting Chronic Obstructive Pulmonary Disease

6

Ganesh Bhaskar Sonawane, Anurag Mishra, Sarita Rawat, Sushma Rawat, Sachchidanand Pathak, Santosh Kumar Singh, Gaurav Gupta, and Ritu Gilhotra

Abstract

Nowadays, chronic obstructive pulmonary disease (COPD) is a crucial global health issue. There are many therapies available in the management of COPD. But, due to developing resistance and several adverse effects in conventional therapies, it is an immense need to develop new alternative therapies that should be novel, potent, and effective with lesser side effects. Medicinal plants are easily available medication for targeting several human disorders. Plants as well as herbs have many active constituents in it; hence, these can be considered as the best alternative treatment for COPD. In the current chapter, we focused on the adverse effects of existing drugs and the need of various medicinal plants and phytochemicals used in targeting COPD. Some important medicinal plants and phytochemicals with their active constituents are also described.

Keywords

COPD · Medicinal plants · Epidemiology · Bronchitis · Emphysema

G. B. Sonawane
School of Pharmacy, Suresh Gyan Vihar University, Jaipur, India

Shrishakti Shaikshanik Sanstha's, Divine College of Pharmacy, Satana, Nashik, India

A. Mishra · S. Rawat · S. Rawat · S. Pathak · S. K. Singh · G. Gupta (✉) · R. Gilhotra
School of Pharmacy, Suresh Gyan Vihar University, Jaipur, India

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_6

6.1 Introduction

Chronic obstructive pulmonary disease is a crucial global respiratory health issue characterized by partial or complete airway obstruction at any level from the trachea to the smallest airways with the functional disability of the lungs [1]. In short, these are diffuse lung diseases. The airflow obstruction is the complete non-reversible process [2] and which can be due to an insufficient inflammatory response of the lungs to injurious gases and particles [3]. Globally, the cases of COPD are increasing day by day [4], but it is a treatable lung disease. Patients with COPD experience the difficulty in breathing, which cause breath shortness, and may feel tired. Sometimes, the patient feels shortness in breath during exercise also.

The burden of COPD is expected to rise in upcoming years. The main reason behind this is, risk factors like smoke, dust, chemicals, biomass fuel, and other air pollutants [5] because the development of COPD is mainly due to inhalation of toxic gases and particles. During the progression of the disease, it creates more difficulty to inhale and exhale process [6]. Pulmonary diseases like cystic fibrosis and interstitial lung diseases may also create airflow obstruction, but in the case of COPD, it is different clinically and radiologically from such diseases [7]. However, COPD can be preventable and treatable if we reduce exposure to the risk factors [5].

6.2 Epidemiology

COPD is one of the key causes of morbidity and mortality. Incidence and burden is increasing day by day and it is only because of the risk factor exposure. According to the country, population, gender, and diagnostic criteria, the estimate of incidence is different [8].

6.2.1 Prevalence

COPD is one of the responsible diseases for early mortality. It creates an excess burden on health systems. The main risk factor behind this is active smoking. Besides this, some other factors are also responsible for its prevalence. The prevalence of COPD is varied with country, age, sex, survey method, etc. [9]. The prevalence of COPD from a meta-analysis of 62 studies of 28 different countries between 1990 and 2004 reported to 7.6% [10]. From the data of the national health and nutrition examination survey between 2007 and 2010, the prevalence of airway obstruction was found 13.5% for adults age 20–79 [11].

According to examination of persons of the post-bronchodilator airflow obstruction of the above 40 year age in five different cities, the prevalence of COPD was found between 7.8 and 20%. The prevalence found more in older people [12]. From the population-based survey of seven different cities of China, the prevalence of COPD over age 40 was 8.2%, and it is due to over smoking and lower education [13].

6.2.2 Incidence

According to the large population-based cohort study of people over age 40, the overall physician-diagnosed COPD incidence rate was 2.92 per 1000 person-year. And based on these data, the risk to be diagnosed through COPD in the coming 40 years will be 12.7. The incidence was more in men than in women and increasing it by the known risk factors like smoking and increasing age [14].

6.2.3 Mortality

The mortality statics must be closely viewed due to uneven COPD coding in the death record and various diagnosis criteria. Due to the underdiagnosis problem mortality may be underestimated. It is evident, though, COPD is the main cause of death in many nations [15]. As per World health education, COPD is the fourth principal reason of death. About death cases in the year 2002 were around 2.7 million, and half of them were in the China [16].

COPD is the third leading cause of death in the world, according to the global burden of disease study, including deaths between 1990 and 2020 [15]. COPD was fifth leading cause of death in Hong Kong and around 4% of all public hospitals accounted for serious admissions in 2003 [17]. COPD has been classified as the third and fourth leading cause of death in China's rural and urban area [18]. By 2030, COPD will become the world's third most common cause of death, according to WHO forecast [10].

6.3 Classification and Etiology

Chronic bronchitis as well as emphysema are the two most common conditions of COPD. Besides that, some physicians also agree that asthma is also one of the classes of COPD. Bronchiectasis and small airways disease (bronchiolitis) are also found as the classes of COPD. The contrasting features like location, age at diagnosis, etiology, pathogenesis, major gross feature, main histology, and major clinical features of the major form of COPD are clear in Table 6.1 [19].

Smoking is one of the most common etiologic factors in all types of COPD. Exposure to environmental stimuli and genetic susceptibility are the second most common source of COPD after smoking. Besides this, there are few more causative measures (Fig. 6.1) which can increase the risk of COPD [20].

6.3.1 Smoking

Smoking is the main risk factor of COPD. Smoking is the main reason for near about nine of every ten cases. There are two types of smoking, active smoking and passive smoking. Some research suggests that exposure to smoker's smoke can also increase

Table 6.1 Contrasting features of major forms of COPD

Feature	Chronic bronchitis	Emphysema	Asthma	Bronchiectasis	Bronchiolitis
Location	Bronchus	Acinus	Bronchus	Bronchus	Bronchiole
Age at diagnosis	Adults	Adults	Extrinsic: children Intrinsic: adults	Adults	Children
Etiology	Smoking, air pollution	Smoking, air pollution	Extrinsic: allergy Intrinsic: viral infection	Infection, Obstruction	Viral infection, Smoke
Pathogenesis	Impaired ciliary movement	Deficiency of alpha-1 antitrypsin	IgE-sensitized mast cells	Damaged airways	Damage to surfactant
Major gross feature	Thickened bronchial wall	Distended air sacs	Overdistended lungs	Dilated bronchi and bronchioles	Occluded bronchioles
Main histology	Hyperplasia of mucous glands	Broken alveolar septa	Mucus plugs in bronchioles	Inflamed bronchi	Fibrous plugs in bronchioles
Major clinical feature	Persistent cough with expectoration	Exertional dyspnoea	Bronchospasm	Copious foul-smelling Expectoration	Cough, dyspnoea

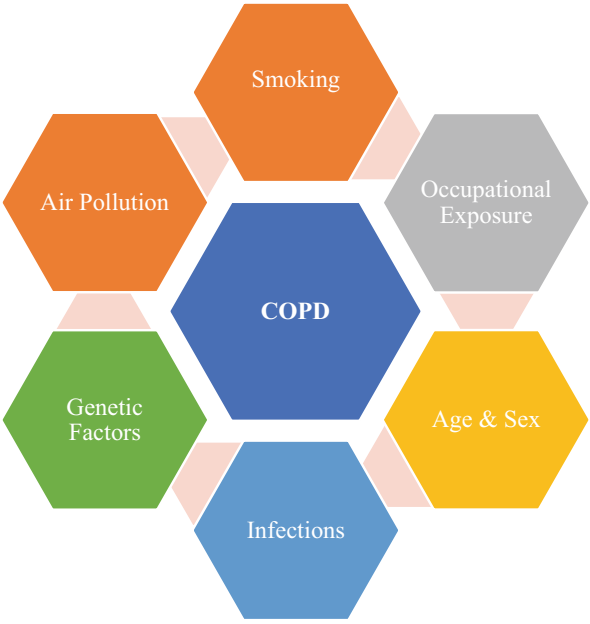


Fig. 6.1 Causative measures of COPD

the risk of COPD [21]. The risk of active smoking is different according to the country and it is 40–70% [22]. Active smoking by females during pregnancy can lead to alteration and/or delay in fetal lung development [23].

There are different harmful chemicals in smoke and that can damage the lining of the lungs and airways. Components of cigarette smoke are also harmful and can affect the lung tissue by several mechanisms. The concentration of neutrophils in the COPD patient is high in sputum [24]. Cigarette smoke can stimulate different types of cells [25], which takes part and helps to increase the production of cytokines, and ultimately it contributes to maintaining inflammatory reaction [26, 27].

6.3.2 Air Pollution

The air pollution has a close relation with the incidence of COPD and air pollution. Exposure to air pollution over a long time can increase the risk of COPD. There are several types of air pollution like indoor, traffic, and industrial air pollution. Exposure to air pollutants like dust, pollens, and other gases can increase the risk of COPD [28]. In low-income countries, indoor air pollution is the main risk factor. In such a country, cooking and heating in poorly ventilated housing, there may be chances of an increase in smoke inside the home, and hence increase in chances of risk and COPD is more, especially in females. In China, the prevalence of COPD is three times more in rural women than in urban [29]. The role of air pollution is unknown to risk factors and its impact has been shown in normal patients of COPD

during the peak in air pollution [30]. In one of the researches, it is also found that the risk of death of COPD is more because of airborne particles [31].

6.3.3 Genetic Factors

Smoking is the most important risk factor, but not every smoker suffers from COPD. It means that the genetic factor is involved somewhere in the etiology of COPD. The respiratory function of a child is depending on the functions of its parents. So, the child of the parents with low respiratory function has more risk of COPD [32]. Alpha 1-antitrypsin (AAT) is the lung protector protein. A severe deficit in AAT is responsible for the PiZZ phenotype and is the only proven causative genetic factor. It is observed that due to this deficit, 1–3% of the total patients are infected with COPD [32] and is also one of the clinical features of panlobular emphysema. SERPINA 1 (Serpin family A member 1) is the gene which controls the synthesis of AAT. Decrease in the level of AAT can cause several lung complications and hence this gene is considered as the main causative factor in COPD [33].

6.3.4 Occupational Exposure

There is about 19–31% risk of COPD due to occupational exposure. So, this one is also one of the main major risk factors in COPD. Non-smokers can expose due to the high level of organic particles in a rural area [34]. Cigarette smoking and occupational exposure both jointly play a major role in the etiology of COPD [35].

6.3.5 Infections

Infection is the age-dependent cause of COPD. Due to the exposure of infection, the respiratory function can be altered [36]. The repeated exacerbation of bacterial or viral origin can cause lung function failure in adults [37]. COPD risk is significantly increased in people with early-life disadvantages [38]. Adenoviruses are a group of viruses that causes respiratory and intestinal infections. A gastroduodenal ulcer can cause due to the Helicobacter pylori and this adenoviral infection can increase the risk of COPD. The activation of pro-inflammatory genes takes place due to the interaction of adenoviral protein E1A with DNA [39]. The concentration of the E1A is more in the lung tissue of the COPD patients having smoking habits [40].

6.3.6 Age and Sex

The prevalence of COPD is dependent on age and increases with age. Also, due to an increase in life expectancy with age, there may be a physiological failure in respiratory function and generally, it starts at the age of 30–40 years. Besides this,

comparing males with females, the incidence and risk of COPD are more in males than in females due to their smoking habits. But, in developed countries, the risk of COPD is the same due to equivalent smoking by females as compared to males [41].

6.4 Factors Influencing Disease Development and Progression

Cigarette smoking is the main etiologic factor of COPD, but there is a consistent piece of epidemiological evidence that those who never smoke have also the chance to suffer from airflow obstruction [42]. The reason is still unclear that the peoples with the same smoking history still do not progress to COPD, there are different etiologic factors found in their progression of COPD. Globally, cigarette smoking is the primary and common risk factor of COPD. Those who smoke regularly have the highest chances of occurrence of respiratory and lung dysfunctions. Thus, the mortality rate is also high in such cases [43]. There are other types of tobacco and marijuana which can also increase the risk of COPD. Smoking by females throughout pregnancy can also have the risk of COPD to the fetus. Smoking by pregnant women affects the development of utero and lung growth. Occupational exposure with chemical agents, fumes, organic and inorganic dust is also the main risk factor of COPD. Coal, wood, crop residue, animal dung, stoves, etc. are the main causative factors of indoor air pollution. It is proved that indoor pollution due to biomass and coal can increase the risk of COPD. Around the world, most families are using biomass and coal as a source of energy for cooking purposes. This is the reason for the increased risk of COPD in indoor pollution [4].

6.5 Conventional Therapy and their Adverse Effects

Conventional therapy in the management of COPD is not appropriate. There are several different adverse effects with the current therapy of COPD. Currently, there is symptomatic pharmacological treatment of COPD which is based on bronchodilators, such as selective β2-adrenoreceptor agonists, glucocorticoid, anticholinergics, theophylline, and/or a combination of these drugs [44]. The long-acting β2-adrenoreceptor agonists have different adverse effects like tachycardia, myocardial ischemia, hypertension, electrolyte imbalance, osteoporosis, etc., and due to these adverse effects, this class of drugs is not the best choice for COPD management. Due to the risk of efficacy, side effects, and costs factor, glucocorticoids are not recommended for COPD patients. Anticholinergic drugs are not a much effective treatment over COPD due to certain adverse effects like constipation, dryness of mouth, blurred vision, cognitive disorders, and urinary complications. Theophylline has also notable adverse effects like nausea, vomiting, diarrhea, restlessness, headache, myocardial infarction, and arrhythmias [45]. There are many side effects of steroids like glaucoma, hypertension, blurred vision, increased appetite, and weight gain [46]. COPD patients respond to the high dose of steroids [47]. However, steroids are in practice in the management of COPD, but it

can affect the innate immunity and cause susceptibility to other diseases. Hence, there is a massive need to develop novel, potent, and safer pharmacological strategies for the management of COPD [48].

6.6 Need of an Alternative Therapy

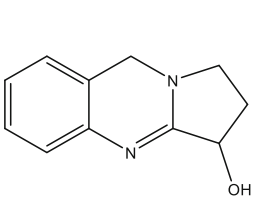
There is number of therapy for COPD management. To treat COPD most of the physician prescribes medication and oxygen therapies, which is not always affordable to all. Synthetic drugs have their drawbacks like the development of resistance and many other side effects. Hence, it is an immense need for alternative therapy. If there is an alternative treatment that can enhance lung function with minimum side effects, breathing capacity, and quality of life can help to resolve COPD. Medicinal plants are easily available medication for the treatment of several human disorders. For COPD treatment there are several plants is practiced globally.

6.6.1 Plants Used in the Management of COPD

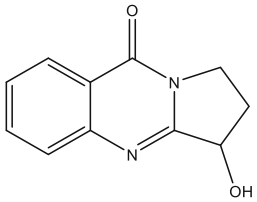
Worldwide numerous plants are available which are used on the treatment of COPD. For the last few years, most of the plants are investigated and reported as an alternative to the synthetic treatment of various ailments. The plants of the Indian origin, which are used in the several comorbidities of the COPD are listed below.

(a) *Acacia farnesiana L.* [49]: It is also known as *Vachellia farnesiana* belonging to the family *Mimosaceae*. It is indigenous to the West Indies, but it is now present all over India. The leaves, bark, roots, and flowers of this plant are generally used in treating various ailments. Ethanolic extract of the leaves has anti-oxidant activity. The MIC value was reported as 0.8 mg/dL against *Bacillus subtilis* and 2.5 mg/dL against *Saccharomyces cerevisiae* [50].

(b) *Adhatoda vasica Nees* [51]: Adhatoda vasica, commonly known as *Malabar nut,* which belongs to the *Acanthaceae* family, native to India. For bronchitis and asthma treatment, the aerial portion of the plant is used. The most important alkaloids that can be isolated from the leaf of the plant with bronchodilator activity are Vasicine, Vasicinone, and Deoxyvasicine. Using histamine-induced anesthetic models, Vasicine and Vasicinone at a dose of 2.5–10 mg/kg showed vasoconstriction activity [52].

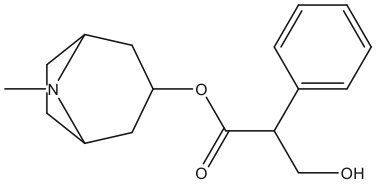


Vasicine



Vasicine

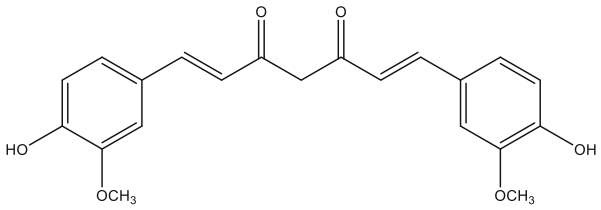
(c) *Atropa acuminata L.* [49]: Atropa acuminata is the native plant of India found in the states of Himachal Pradesh and Kashmir. It is also known as *Indian Belladona,* belonging to the family *Solaneceae.* The root of the plant is generally used in treating bronchial asthma and whooping cough. Atropine is the chemical constituents obtained from the extraction of roots. Due to its anti-mucous secretion property, it can be used for preventing the symptoms of asthma [53].



atropine

(d) *Boswellia serrata Roxb.* [49]: This plant is well known as *Indian olibanum,* belongs to the family *Buceaceae.* The oil is derived from plants and used for the treatment of bronchitis, asthma, and cough. This plant is also native to India. This plant contains boswellic acid as anti-inflammatory triterpenoids. The dried extracts of the tree resin inhibit the pro-inflammatory 5-hydroxylase chemicals and obstruct the production of leukotriene and thus, helpful in treating medical conditions like inflammation and asthma. In the study, it is proved that the gum resins of the tree are helpful in the management of asthma [54].

(e) *Curcuma Longa L.* [49]: This plant is cultivated in the Indian states, mostly in West Bengal, Tamil Nadu, and Maharashtra. It is commonly known as *Turmeric*, belongs to the family *Zingiberaceae.* Roots of the plant used as anti-oxidants and in asthma. The rhizomes of the plant are curcuminoids reach. Curcumin is the important active constituents of the plant. Several animal models have tested curcumin for its protective role in lung fibrosis. Most of the pharmacological data have reported curcumin in treating COPD, acute respiratory syndrome, and asthma [55].



Curcumin

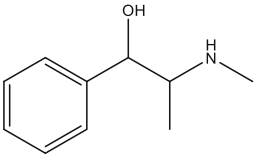
(f) *Datura stramonium L.* [56]: Datura stramonium is a plant native plant of India and found in the hilly part of the Himalaya, belonging to the family *Solanaceae.* This plant is commonly known as *Thorn apple*. The whole plant is useful in treating asthma and bronchitis. The aqueous extract of the leaf, fruit, and seed exhibit good anti-oxidant property [57]. In some countries, the dried flowers, as well as leaves, are cut into minor pieces and used in anti-asthmatic cigarettes. The roots, leaves, and seeds of the plant contain hyoscyamine and atropine alkaloids which are used in treating various respiratory ailments [54].

(g) *Elittaria cardamomum L.* [58]: It is the herbaceous plant found in the hilly forests area of Karnataka and Kerala. This plant belongs to the family *Zingiberaceae* and is commonly known as *Green cardamom.* Seeds of the plant are used in the management of asthma and bronchitis. The oil extracted from the seeds has terpene, esters, flavonoids, and other compounds that have been useful in treating several respiratory disorders [49].

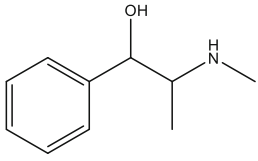
(h) *Emblica officinalis L.* [49]: This plant is native to India belonging to the family *Euphorbiaceae,* and commonly known as Indian gooseberry. Fruits and seeds are generally evaluated for asthma, bronchitis treatment, and anti-oxidant. Fruits of the plant contain not <60% w/w hydrolyzable tannins.

(i) *Echinacea purpurea L.* [59, 60]: It is a medicinal herb, which belongs to the family *Asteraceae.* It is also known as the Purple coneflower. The roots and upper part of the herb are used in the management of bronchitis and respiratory infections. One of the studies revealed that the combination of micronutrients with *Echinacea purpurea* alleviate COPD exacerbation caused by upper respiratory tract infection in COPD [61].

(j) *Ephedra sinica Staf.* [62]: Ephedra sinica belongs to the family *Asteraceae*. An aerial part of the herb is used in the management of bronchitis and respiratory infections. The study has been reported the protective effects of polysaccharide from the plant against pulmonary inflammation [63]. This plant contains 2–3% ephedra alkaloids (ephedrine, pseudoephedrine) which stimulates the alpha and beta-adrenergic receptors and this helps to dilate the bronchial tubes in the asthmatic patient [54].

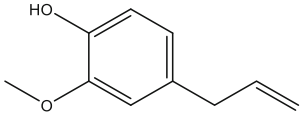


ephedrine

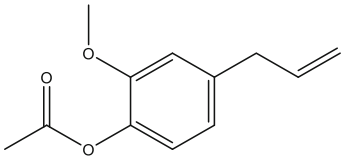


pseudoephedrine

(k) *Eugenia caryophyllata Thumb* [64]: It is the plant found in Tamil Nadu and Kerala states of India. It is well known as *Clove*, belonging to the family *Myrtaceae*. Seeds and flower buds are generally used in the management of bronchitis and bronchial asthma. Eugenol and eugenyl acetate are the constituents of clove which helps in reducing oxidative stress and acts as anti-oxidant [65].



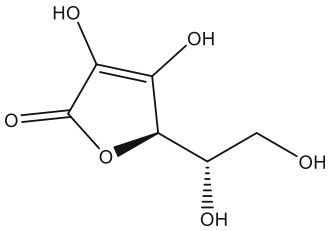
eugenol



eugenyl acetate

(l) Euphorbia hirta L. [66]: It is herbaceous plant, sometimes also called an asthma plant, and belongs to the family *Euphorbiaceae*. In the treatment of asthma, aerial part of the plant is used. It is the native plant of India. Eosinophil aggregation and eosinophil peroxidase activity are prevented by a 90% ethanolic extract from the aerial portion of the plant, which may decrease the protein in bronchoalveolar lavage fluid in asthma [66].

(m) *Foeniculum vulgare Mill* [67]: It is a perennial umbelliferous herb, commonly known as Clove and widely used for medicinal purpose and human consumption, available at Punjab, Maharashtra, Assam, and Gujarat states of India belongs to the family *Apiaceae*. Shoots and leaves are highly recommended for bronchitis and persistent cough coughs. Due to the highest phenolic content and ascorbic acid in the shoots of the herb, it has anti-oxidant property [67].



ascorbic acid

(n) *Glycyrrhiza glabra L.* [68]: It is the plant belongs to the family *Fabaceae* and also known as *Licorice*. The root of the plant is used in the management of COPD and asthma. This plant is grown in Punjab, Jammu-Kashmir, and South India. The main active constituent of the plant is Glycyrrhizic acid and Tilianin, which may have many pharmacological and biological functions including anti-inflammatory and anti-COPD agents [69].

(o) *Mentha aquatica L.* [58]: It is a perennial flowering plant belongs to the family *Lamiaceae*. It is also a native plant of India well known as mint or water mint. Leaves of the plant are used in the management of Bronchitis. The anti-oxidant

activity is shown by aqueous, ethanolic extract and essential oil of the plant [49].

(p) *Ocimum sanctum L.* [70]: It is the most widespread plant grown in houses, temples, and gardens in India. *Holy Basil* or *Tulsi* is the most common name of this plant. This plant belongs to the family *Lamiaceae.* In the treatment of bronchitis and bronchial asthma, the leaves of the plant are used. The plant leaves contain bright yellow volatile constituents called sequiterpenes, and monoterpenes, which have been found to be potential in the treatment of different respiratory disorders. The juice of the leaves of the plant when taken with honey is most helpful in treating asthma and bronchitis [52]. In vivo studies on acetylcholine and histamine-induced model have shown anti-asthmatic activity of 50% aqueous ethanolic extract of the ocimum sanctum [54].

(q) *Prunus armenica L.* [58]: This plant can be recognized as the Apricot, belongs to the family Rosaceae. This plant is found in the North-western Himalayas particularly in the Kashmir. The seeds of the plant are used in managing cough, bronchitis, and asthma. The dries apricot contains quercetin, quercitrin, dihydroxybenzoic, chlorogenic, vanillic acids, and p-coumaric acid which are beneficial as antitussive and anti-asthmatic [49].

(r) *Pimpinella anisum* [71]: This plant is native to the Mediterranean region and belongs to *Umbelliferae* family, and is grown and cultivated in Uttar Pradesh, Punjab, Assam, and Orissa. Oil and seeds of the plant are effective in emphysema, bronchitis, asthma, and whooping cough. The bronchodilator effect is present in the plants essential oil, aqueous, and ethanolic extract. The volatile oil of the plant and wine spirit mixture has the effect on bronchitis and spasmodic asthma [54].

(s) *Piper longum L.* [49]: Piper longum, from the Central Himalayas to Assam, the lower hills of West Bengal, Uttar Pradesh, and Andhra Pradesh, is native to warmer part of India. It is belonging to the family *Piperaceae,* commonly known as Pepper. The fruit of the plant is used for treating cough and bronchitis. The new therapeutic molecules from the piper longum have been identified and characterized by several researchers and their effectiveness has been investigated through in vitro studies in the prevention of asthma and COPD [72]. Some researchers carried open clinical study for 20 pediatric asthmatic patients, in which fruit powder of the plant was given to the patient with milk in a gradually increasing the dose for 5 weeks. This medication minimized 85% severity and asthmatic attacks [54].

(t) *Trachyspermum ammi L.* [49]: This plant is grown and cultivated in Madhya Pradesh, Andhra Pradesh, Gujarat, Maharashtra, Rajasthan, Uttar Pradesh, and the Bihar state of India. It is belonging to the family *Umbelliferae* and is commonly known as *Ammi*. In the treatment of emphysema, asthma, and bronchitis, the plant oil is used.

6.6.2 Phytochemicals Used in Targeting COPD

Phytochemicals are the chemicals which are obtained by primary and secondary metabolism of various naturally occurring plants. Phytochemicals generally have biological activity which helps in the management of various ailments. Herbs and plants have many active constituents and due to this, phytochemicals can be considered as the best alternative for the management of COPD [73]. Phytochemicals from the plant source, like coumarins, flavonoids, phenolics, iridoids, and terpenes (Fig. 6.2) are effective in the management of COPD.

1. *Coumarins*: Coumarins are the secondary metabolites obtained from various plant sources. Coumarin derivatives are the most important class of phytochemicals having anti-oxidant property [74] which is helpful in the management of lung inflammation. Coumarins like esculetin, quercetin, and umbelliferone show the anti-oxidant properties and protect the cellular DNA from damage [75]. The imbalance between oxidants and anti-oxidants may play an important role in the pathogenesis of COPD. These include, increased proteolytic activity and mucus hypersecretion which is characteristic of COPD. Coumarins are well known for their anti-oxidant property [76].
2. *Flavonoids*: The most significant group of polyphenols that have low molecular weights are flavonoids. In roots, fruits, seeds, nuts, vegetables, stems, flowers, and in popular daily dietary substances, flavonoids are located. Flavonoids have anti-oxidant property and due to this property flavonoids are used in treating oxidative stress related airway diseases. Several epidemiologic data have been published that indicate the advantageous effects of flavonoids in treating asthma. Eating fruits decreases the risk of respiratory complications due to increasing the

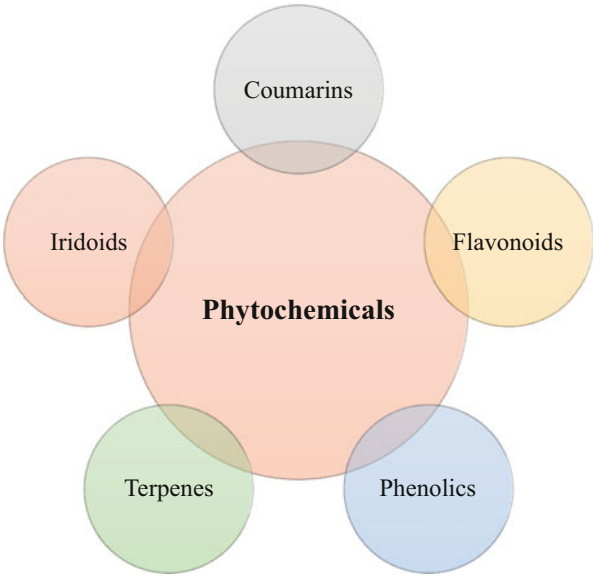


Fig. 6.2 Phytochemicals used in targeting COPD

level and protective effects of flavonoids. In short, an increase in the intake of flavonoids decreases the incidence of asthma [77].

3. *Phenolics*: Phenolics contains one or more aromatic rings and a hydroxyl groups. Phenolics also have anti-oxidant properties and can play significant role in the prevention of COPD [78]. The phenolics are the secondary metabolites mostly found in fruits and plant extract and acts. Elastase and anti-elastase imbalance are responsible for pathogenies of COPD [79]. The extract has anti-elastase activity. Nigella sativa L. seeds and its constituents have beneficial in the management of COPD and emphysema. Plant extracts of Cinnamon, turmeric, rosemary, and nutmeg can inhibit elastase. Polyphenols such as catechin and epigallocatechin gallate has also anti-elastase activity. Polyphenols isolated from persimmon leaf has also shown promising anti-elastase activity [80]. The bioactive phenolics for the prospective COPD treatment are edible *Myrciaria vexator* fruits [81].
4. *Terpenes*: Terpenes are the largest class of secondary metabolites, which has the potential ability in treating respiratory ailments. For the management of lung diseases, inhibition of human neutrophil elastase is the most promising strategy [82]. *Nigella sativa L.* seed extract and its main constituents mainly monoterpenes inhibit human neutrophil elastase [83]. The monoterpene alcohol present in geranium and few other medicinal plants is geraniol. Geraniol has anti-oxidant property. The study has been reported its protective role in ovalbumin-induced asthma. Andrographolide has promising anti-oxidant activity and is one of the diterpenoids purified from the aerial parts of the plants of genus Andrographis. Ursolic acid, a pentacyclic triterpenoid compound present in most of the medicinal plants which also has a protective role against lung disorders [84].

6.7 Summary and Future Prospects

Current conventional therapies are inappropriate for the management of COPD, due to the developing resistance and adverse several effects. Hence, it is an immense need for alternative therapy. Medicinal plants are easily available medication for the treatment of several human disorders. Plant extracts have potential therapeutic efficacy against lung disorders including COPD. Besides, phytochemicals of several classes have the potential ability treating in COPD. There are still many medicinal plants and phytochemicals which are being investigated for its potential and systematic use. However, much work is needed to bring them forward. And this will be a major challenge in the coming years. But the big challenge is to prevent the onset of smoking by spreading COPD awareness.

References

1. Kim YS (2017) Definition and epidemiology of COPD. Springer, Berlin, pp 4–8
2. Smith MC, Wrobel JP (2014) Epidemiology and clinical impact of major comorbidities in patients with COPD. Int J COPD 9:871–888

3. Vestbo J, Rennard S (2010) Chronic obstructive pulmonary disease biomarker(s) for disease activity needed - urgently. Am J Respir Crit Care Med 182(7):863–864
4. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A et al (2013) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease GOLD executive summary. Am J Respir Crit Care Med 187(4):347–365
5. Vogelmeier CF, Román-Rodríguez M, Singh D, Han MLK, Rodríguez-Roisin R, Ferguson GT (2020) Goals of COPD treatment: focus on symptoms and exacerbations. Respir Med 166 (March):105938
6. Vestbo J, Hogg JC (2006) Convergence of the epidemiology and pathology of COPD. Thorax 61(1):86–88
7. Pauwels PRA, Rabe KF (2004) Burden and clinical features of chronic obstructive pulmonary disease (COPD). Lancet 364(9434):613–620
8. Rosenberg SR, Kalhan R, Mannino DM (2015) Epidemiology of chronic obstructive pulmonary disease: prevalence, morbidity, mortality, and risk factors. Semin Respir Crit Care Med 36 (04):457–469
9. Raherison C (2009) Epidemiology of COPD. Eur Respir Rev 18(114):213–221
10. Diaz-guzman E, Mannino DM (2014) Epidemiology and prevalence of COPD. Clin Chest Med 35(1):7–16. https://doi.org/10.1016/j.ccm.2013.10.002
11. Ford ES, Mannino DM, Wheaton AG, Giles WH, Presley-Cantrell L, Croft JB (2013) Trends in the prevalence of obstructive and restrictive lung function among adults in the United States: findings from the national health and nutrition examination surveys from 1988-1994 to 2007-2010. Chest 143(5):1395–1406. https://doi.org/10.1378/chest.12-1135
12. Menezes AMB, Perez-Padilla R, Jardim JRB, Muiño A, Lopez MV, Valdivia G et al (2005) Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. Lancet 366(9500):1875–1881
13. Zhong N, Wang C, Yao W, Chen P, Kang J, Huang S et al (2007) Prevalence of chronic obstructive pulmonary disease in China: a large, population-based survey. Am J Respir Crit Care Med 176(8):753–760
14. Afonso ASM, Verhamme KMC, Sturkenboom MCJM, Brusselle GGO (2011) COPD in the general population: prevalence, incidence and survival. Respir Med 105(12):1872–1884. https://doi.org/10.1016/j.rmed.2011.06.012
15. Chapman KR, Mannino DM, Soriano JB, Vermeire PA, Buist AS (2006) Epidemiology and costs of chronic obstructive pulmonary disease. Eur Respir J 27(1):188–207
16. Soriano JB (2006) Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 27(2):397–412
17. Ko FWS, Ip M, Chan PKS, Chan MCH, To KW, Ng SSS et al (2007) Viral etiology of acute exacerbations of COPD in Hong Kong. Chest 132(3):900–908. https://doi.org/10.1378/chest.07-0530
18. Fang X, Wang X, Bai C (2011) COPD in China. Chest 139(4):920–929. https://doi.org/10.1378/chest.10-1393
19. Mohan H (2015) Textbook of pathology, 7th edn. Jaypee Brothers Medical Publishers, New Delhi, pp 474–482
20. Decramer M, Janssens W, Miravitlles M (2012) Chronic obstructive pulmonary disease. Lancet 379(9823):1341–1351. https://doi.org/10.1016/S0140-6736(11)60968-9
21. Boggia B, Farinaro E, Grieco L, Lucariello A, Carbone U (2008) Burden of smoking and occupational exposure on etiology of chronic obstructive pulmonary disease in workers of southern Italy. J Occup Environ Med 50(3):366–370
22. Heyes A, Lanza L, Becker K (2012) Epidemiology of chronic obstructive pulmonary disease: a literature review. Int J Chron Obstruct Pulmon Dis 7:457–494
23. Gilliland FD, Li Y, Dubeau L, Berhane K, Avol E, Mcconnell R et al (2002) Effects of glutathione S -transferase M1, maternal smoking during pregnancy, and environmental tobacco smoke on asthma and wheezing in children. Am J Respir Crit Care Med 166:457–463

24. Keatings VM, Collins PD, Scott DM, Barnes PJ (1996) Differences in interleukin-8 and tumor necrosis fador-a in induced sputum from patients with chronic obstrudive pulmonary disease or asthma. Am J Respir Crit Care Med 153(2):530–534
25. Stick SM, Burton PR, Gurrin L, Sly PD, Lesouëf PN (1996) Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. Lancet 348:1060–1064
26. Cook DG, Strachan DP (1998) Parental smoking, bronchial reactivity and peak flow variability in children. Thorax 53:295–301
27. Chung KF (2005) The role of airway smooth muscle in the pathogenesis of airway wall remodeling in chronic obstructive pulmonary disease. Thorax 2:347–354
28. Wang F, Ni SS, Liu H (2016) Pollutional haze and COPD: etiology, epidemiology, pathogenesis, pathology, biological markers and therapy. J Thorac Dis 8(1):E20–E30
29. Liu S, Zhou Y, Wang X, Wang D, Lu J, Zheng J, Zhong N, Ran P (2007) Biomass fuels are the probable risk factor for chronic obstructive pulmonary disease in rural South China. Thorax 62:889–897
30. Wordley J, Walters S, Ayres JG (1997) Short term variations in hospital admissions and mortality and particulate air pollution. Environ Health 54:108–116
31. Zanobetti A, Bind MC, Schwartz J (2008) Particulate air pollution and survival in a COPD cohort. Environ Health 9:1–9
32. Mannino DM, Watt G, Hole D, Gillis C, Hart C, Mcconnachie A (2006) The natural history of chronic obstructive pulmonary disease. Eur Respir J 27(2):627–643
33. Chappell S, Daly L, Morgan K, Baranes TG, Roca J, Rabinovich R et al (2006) Cryptic haplotypes of SERPINA1 confer susceptibility to chronic obstructive pulmonary disease. Hum Mutat 27(November 2005):103–109
34. Hnizdo E, Sullivan PA, Bang KM, Wagner G (2002) Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the third national health and nutrition examination survey. Am J Epidemiol 156 (8):738–746
35. Blanc PD, Iribarren C, Trupin L, Earnest G, Katz PP, Balmes J et al (2008) Occupational exposures and the risk of COPD: dusty trades revisited. Thorax 64:6–12
36. Barker P (1991) Relation of birth weight and childhood respiratory infection to adult. BMJ 303:671–675
37. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA (2002) Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 57:847–852
38. Svanes C, Sunyer J, Plana E, Dharmage S, Heinrich J, Jarvis D et al (2009) Early life origins of chronic obstructive pulmonary disease. Thorax 65:14–20
39. Keicho N, Elliott WM, Hogg JC, Hayashi S (1997) Adenovirus EtA gene Dysregulates ICAM-l expression in transformed pulmonary epithelial cells. Am J Respir Cell Mol Biol 16:23–30
40. Higashimoto Y, Elliott WM, Behzad AR, Sedgwick EG, Takei T, Hogg JC et al (2002) Inflammatory mediator mRNA expression by adenovirus E1A-transfected bronchial epithelial cells. Am Thorac Soc 166(8):202–207
41. Chinwong D, Mookmanee N, Chongpornchai J, Chinwong SA (2018) Comparison of gender differences in smoking behaviors, intention to quit, and nicotine dependence among Thai university students. J Addict 2018:1–8
42. Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D et al (2010) An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 182(5):693–718
43. Kohansal R, Martinez-Camblor P, Agustí A, Sonia Buist A, Mannino DM, Soriano JB (2009) The natural history of chronic airflow obstruction revisited: An analysis of the Framingham offspring cohort. Am J Respir Crit Care Med 180(1):3–10
44. Montuschi P (2006) Pharmacological treatment of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 1(4):409–423

45. Gupta P, Mahony MSO (2008) Potential adverse effects of bronchodilators in the treatment of airways obstruction in older people. Drugs Aging 25(5):415–443
46. Hubbard R, Tattersfield A (2004) Inhaled corticosteroids, bone mineral density and fracture in older people. Drugs Aging 21(10):631–638
47. Ia Y, Ms C, Eha S, Km F (2012) Inhaled corticosteroids for stable chronic obstructive pulmonary disease (review). Cochrane Database Syst Rev 7:1–185
48. Singh S, Loke YK (2010) Risk of pneumonia associated with long-term use of inhaled corticosteroids in chronic obstructive pulmonary disease: a critical review and update. Curr Opin Pulm Med 16:118–122
49. Khare CP (2007) Indian medicinal plants. Springer, New York, p 40
50. Ramli S, Harada KI, Ruangrungsi N (2011) Antioxidant, antimicrobial and cytotoxicity activities of Acacia farnesiana (L.) Willd. Leaves ethanolic extract. Pharm J 3(23):50–58
51. Dhuley JN (1999) Antitussive effect of Adhatoda 6 asica extract on mechanical or chemical stimulation-induced coughing in animals. J Ethnopharmacol 67:361–365
52. Rachana, Pant M, Basu S, Jain A, Goel N, Wadi I (2016) A review on herbal therapy for respiratory ailments. Int J Life Sci Pharm Res 6(2):P10–P14. https://www.ijlpr.com/admin/php/uploads/266_pdf.pdf
53. Diaz JE (1997) Efficacy of atropine sulfate in combination with albuterol in the treatment for acute asthma. Respir Care 4(12):107–113
54. Prasad R, Lawania RD, Manvi, Gupta R (2009) Role of herbs in the management of asthma. Pharmacogn Rev 3(6):247–258
55. Venkatesan N, Punithavathi D, Babu M (2007) Protection from acute and chronic lung disease by curcumin. Adv Exp Med Biol 595:379–405
56. Gaire BP, Subedi L (2013) Review a review on the pharmacological and toxicological aspects of Datura stramonium L. J Integr Med 11(March):73–79
57. Srivastava N, Chauhan AS, Sharma B (2012) Isolation and characterization of some phytochemicals from Indian traditional plants. Biotechnol Res Int 2012:1–8
58. Ram A, Arul Joseph D, Balachandar S, Pal SV (2009) Medicinal plants from siddha system of medicine useful for treating respiratory diseases. Int J Pharm Anal 1(2):975–3079. https://bioinfopublication.org/files/articles/1_2_4_IJPA.pdf
59. Kumar KM, Ramaiah S (2011) Pharmacological importance of Echinacea purpurea. Int J Pharm Bio Sci 2(4):304–314
60. Hudson JB (2012) Applications of the phytomedicine Echinacea purpurea (purple coneflower) in infectious diseases. J Biomed Biotechnol 2012:1–16
61. Tharakan S, Lakshmi T (2013) Role of Echinacea purpurea for COPD management - a mini review. Int J PharmTech Res 5(4):1808–1810
62. Tellez MR, Khan IA, Schaneberg BT, Crockett SL, Rimando AM, Kobaisy M (2004) Steam distillation – solid-phase microextraction for the detection of Ephedra sinica in herbal preparations. J Chromatogr A 1025:51–56
63. Liang S, Meng X, Wang Z, Liu J, Kuang H, Wang Q (2018) Polysaccharide from Ephedra sinica Stapf inhibits inflammation expression by regulating factor-β1/Smad2 signaling. Int J Biol Macromol 106:947–954. http://www.sciencedirect.com/science/article/pii/S0141813017321335
64. Parle M (2011) Available online through CLOVE: a champion spice. IJRAP 2(1):47–54
65. Kuete V (2017) Medicinal spices and vegetables from Africa. Academic Press, Cameroon, pp 611–623
66. Singh GD, Kaiser P, Youssouf MS, Singh S, Khajuria A, Koul A et al (2006) Inhibition of early and late phase allergic reactions by Euphorbia hirta L. Phytother Res 20:316–321
67. Barros L, Heleno SA, Carvalho AM, Ferreira ICFR (2009) Systematic evaluation of the antioxidant potential of different parts of Foeniculum vulgare Mill. from Portugal. Food Chem Toxicol 47(10):2458–2464. https://doi.org/10.1016/j.fct.2009.07.003
68. Khoshnam SE, Farzaneh M, Bahaoddini A (2015) Review of the phytochemical, pharmacological and physiological properties of licorice (Glycyrrhizaglabra). Clin Excell 4(1):71–56

69. Kim SH, Hong JH, Yang WK, Geum JH, Kim HR, Choi SY, Kang YM, An HJ, Lee YC (2020) Herbal combinational medication of Glycyrrhiza glabra, Agastache rugosa containing glycyrrhizic acid, tilianin inhibits neutrophilic lung inflammation by affecting CXCL2, interleukin-17/STAT3 signal pathways in a murine model of COPD. Nutrients 12(4):926
70. Banu GS, Kumar G, Murugesan AG (2009) Effects of leaves extract of Ocimum sanctum L. on arsenic-induced toxicity in Wistar albino rats. Food Chem Toxicol 47(2):490–495. https://doi.org/10.1016/j.fct.2008.12.004
71. Prasad R, Lawania R, Gupta R (2009) Role of herbs in the management of asthma. Pharmacogn Rev 3(6):247
72. Kumar S, Malhotra S, Prasad AK, Van der Eycken EV, Bracke ME, Stetler-Stevenson WG, Parmar VS, Ghosh B (2015) Anti-inflammatory and antioxidant properties of Piper species: a perspective from screening to molecular mechanisms. Curr Top Med Chem 15(9):886–893
73. Clarke R, Lundy FT, McGarvey L (2015) Herbal treatment in asthma and COPD – current evidence. Clin Phytosci 1(1):1–7. https://doi.org/10.1186/s40816-015-0005-0
74. Wu L, Wang X, Xu W, Farzaneh F, Xu R (2009) The structure and pharmacological functions of coumarins and their derivatives. Curr Med Chem 16(32):4236–4260
75. Garg SS, Gupta J, Sharma S, Sahu D (2020) An insight into the therapeutic applications of coumarin compounds and their mechanisms of action. Eur J Pharm Sci 152(July):105424. https://doi.org/10.1016/j.ejps.2020.105424
76. MacNee W (2005) Treatment of stable COPD: antioxidants. Eur Respir Rev 14(94):12–22
77. Park HS, Kim SR, Kim JO, Lee YC (2010) The roles of phytochemicals in bronchial asthma. Molecules 15(10):6810–6834
78. Meybodi NM, Mortazavian AM, Monfared AB, Sohrabvandi S, Meybodi FA (2017) Phytochemicals in cancer prevention: a review of the evidence. Int J Cancer Manag 10(1):1–8
79. Maruoka S, Hashimoto S (1999) Elastase anti-elastase imbalance in the pathogenesis of COPD. Nihon Rinsho 57(9):1982–1987. http://europepmc.org/abstract/MED/10497394
80. Kacem R (2013) Phenolic compounds from medicinal plants as natural anti-elastase products for the therapy of pulmonary emphysema. J Med Plants Res 7(48):3499–3507
81. Dastmalchi K, Flores G, Wu SB, Ma C, Dabo AJ, Whalen K, Reynertson KA, Foronjy RF, Kennelly EJ (2016) Edible Myrciaria vexator fruits: bioactive phenolics for potential COPD therapy. Bioorg Med Chem 176(12):139–148
82. Feng L, Liu X, Zhu W, Guo F, Wu Y, Wang R et al (2013) Inhibition of human neutrophil elastase by pentacyclic triterpenes. PLoS One 8(12):1–11
83. Groutas WC, Dou D, Alliston KR (2012) Neutrophil elastase inhibitors. NIH Public Access 21 (3):339–354. http://www.polyurethanes.org/en/faqs
84. Nalban N, Alavala S, Sangaraju R, Mir SM, Sistla R (2019) Therapeutic targeting of oxidative stress and inflammation in asthma and COPD and pharmacological interventions with phytochemicals. In: Oxidative stress in lung diseases. Springer, Singapore, pp 429–449

Utilization of Natural Compounds for Treatment of Tuberculosis-I

7

Madhumanti Mondal, Atmaram Pawar, Kaustuv Sahoo, and Dileep Kumar

Abstract

Tuberculosis (TB) is a contagious infection caused by *Mycobacterium tuberculosis*. It is a highly communicable disease which affects the lungs but if left untreated can also spread to brain or spine. According to the World Health Organization, TB is considered as one of the top ten causes of death throughout the world with ten million cases reported annually. Although TB occurs in most parts of the world yet two thirds of the new cases reported, happened in India, China, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. TB is treated with a combination of *antibiotics* which has to be consumed by patients over a year or more. At present the drugs and vaccines available for treatment of TB has no significant effect on controlling the disease due to the occurrence of *multiple drug-resistant* (Mdr) strains. Hence, this created an urgent need to develop drugs of natural origin. Drugs from *natural sources* have exceptionally rich chemical diversity and a wide spectrum antimicrobial activity. The current chapter states the recent developments that had occurred in the

M. Mondal
Chemical Engineering Department, National Institute of Technology Durgapur, Durgapur, West Bengal, India

A. Pawar · K. Sahoo
Development and Commercial, North America Thermo Fisher Scientific Pharma Services, Cincinnati, OH, USA

Department of Pharmaceutical Chemistry, Poona college of Pharmacy, Bharti VidyaPeeth University, Pune, India

D. Kumar (✉)
Department of Pharmaceutical Chemistry, Poona college of Pharmacy, Bharti VidyaPeeth University, Pune, India

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_7

treatment of TB using natural compounds and also discusses the various natural *anti-mycobacterial compounds*.

Keywords

Tuberculosis · Antibiotics · Multiple drug resistant · Natural sources · Anti-mycobacterial compounds

7.1 Introduction

Tuberculosis (TB) is a contagious infection caused by *Mycobacterium tuberculosis*. It is a highly communicable disease and is transmitted from person to person by inhaling air droplets laden with bacteria. TB is considered one of the top ten infectious diseases in the world and is responsible for over 1.5 million deaths annually [1]. It can affect any individual irrespective of age or sex, however, people with weakened immune systems possess the highest risk of infection. TB is the leading cause of death in HIV (Human immunodeficiency virus) positive individuals [2]. According to World Health Organization (WHO), approximately 4000 people die each day due to TB and 30,000 people fall ill with this disease [2]. March 24 of every year is observed as the "World Tuberculosis Day" by WHO with a view to elevate public awareness about the disease. TB is reported to be one of the most ancient diseases caused to humans with respect to the molecular evidences found in the 9000 year old human remains recovered from Neolithic settlements in Eastern Mediterranean region [3].

Although TB occurs in most parts of the world yet two thirds of the new cases reported, happened in India, China, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. The occurrence of this disease is associated with dense population, poor sanitation, and improper nutrition [4]. The first antibiotic used for TB was streptomycin in the 1940s but, monotherapy of streptomycin did not exist for long due to drug resistance. After which many drugs have been discovered like isoniazid (INH), rifampicin (RMP), ethambutol, and pyrazinamide (PZA). These drugs are called the first line anti-TB drugs and form the core of TB treatment. The second line drugs are aminoglycosides (kanamycin, capreomycin, and amikacin), fluoroquinolones (ofloxacin and ciprofloxacin), thioamides (ethionamide and prothionamide), cycloserine/terizidone and para-aminosalicylic acid (PAS) [3]. Patients are treated with a combination of antibiotics which has to be consumed over a year or more. For most patients it becomes inconvenient due to the expensive nature of such long treatment hence, they quit taking antibiotics prematurely thereby increasing the risk of development of drug-resistant strains. Apart from this, inferior quality drugs; insufficient drug supply; ignorance and poor case handling of heath care workers; illiteracy; availability of drugs without proper prescriptions are also some of the causes of development of multiple drug-resistant (Mdr) strains. While, Mdr strains of *M. tuberculosis* are resistant to the first line anti-TB drugs (INH and

RMP), the extensively drug-resistant (Xdr) strains are resistant to both first line anti-TB drugs and any of the second line anti-TB drugs [5].

The issue of drug-resistance adversity has attracted various researchers and scientists across the globe to put accelerated efforts to understand the mycobacterial biology and search for new and alternative anti-TB drugs source to end the global TB problem. An ideal anti-TB drug must not only have high potency against Mdr strains but also be free from side effects. The drug should also have negligible interference with anti-retro viral drugs. Hence, this created an urgent need to develop anti-TB drugs of natural origin. Anti-TB drugs from natural sources is a beacon of hope and has attracted scientists due to their exceptionally rich chemical diversity and a wide spectrum of antimicrobial activity. Moreover, bioactive molecules from natural sources display higher degree of bioavailability thereby, increasing their capacity to reach target cells [6]. The current chapter addresses the developments that had occurred in the treatment of TB using natural compounds and also discusses various natural anti-mycobacterial compounds.

7.2 Pathogenesis

The TB is spread by viable tubercular bacilli, carried in airborne particles, generated by persons with active TB while sneezing, coughing, laughing loudly or singing. *M. tuberculosis* is transmitted via air and not by surface contact. Transmission of the disease occurs when a healthy person inhales air particles laden with the bacilli, which then passes through the nasal passages, upper respiratory tract and reaches alveoli of lungs. When the bacilli multiplies enough, an antigen-antibody reaction is induced by the T-cells and tubercle formation occurs at the site of infection. The formation of tubercles may suppress the infection or a small amount of bacilli may survive and get released when the macrophages die. *M. tuberculosis* has established various strategies to survive in host macrophages and become a successful intracellular pathogen. It is known to interfere with the intracellular membrane trafficking and restricting phagosome maturation in infected host cells [7].

In people with weak immune system, these alive bacilli spread through lymph and blood vessels and infects distant organs like kidneys and brain. This kind of wide-spread infection is called miliary TB [4]. However, there is also another form of TB called the Latent TB infection. The TB bacteria can live in the body for long periods without making the host sick. The host with latent TB infection will not show any symptoms and cannot spread the disease but will have a positive TB skin test or blood test. In such host, the immune systems fights back strongly thereby, preventing the mycobacterial growth.

7.3 Current Drug Therapy for TB Treatment

The discovery of streptomycin in the 1940s gave a light of hope to patients suffering from TB. The drug worked wonders and reduced morbidity and mortality rates. Efforts of scientists further led to the development of effective combination chemotherapy of TB. The first line and second line drugs for TB was used for treating TB patients. However, the euphoria existed for short period of time and soon the emergence of Mdr and Xdr strains of *M. tuberculosis* killed thousands of humans and WHO declared TB as an emergency in 1993. Apart from the drugs, WHO devised the Directly Observed Treatment Short course (DOTS) program in 1993 and recommended all countries to adopt it [8]. This program was found to be very effective initially in tackling the world wide TB emergency.

The current drug therapy comprises of combination of drugs designed in such a way, so that it can boost the patient body to respond better to the drug and reduce the period of treatment. Patients are given a 9 month course of INH, RMP along with streptomycin and ethambutol. The RMP basically reduces the length of treatment and also shows good results. After many years of research recently, Bedaquiline and Delenamid were approved by Food and Drug Administration (FDA) for use against Mdr and Xdr TB.

7.3.1 Problems with the Current Drug Therapy for TB Treatment

The major disadvantage of the anti-TB drugs used till date for treatment is the extensive period over which the medicine has to be consumed and also the large amount of medicines that has to be taken by patients. Poor patients stop using the medicine and do not complete the dosage when they face financial problems. Sometimes, they use a single drug and leave the multiple drug treatment. The second line drugs are more expensive than the first line drugs and have to be used for longer duration of time than the first line drugs, which makes it even harder for most people to afford. Such problems with the current drug therapy increase the chance of spreading of disease as well as development of resistant *M. tuberculosis* strains. The current drug therapy is also not very effective against latent TB [6, 8]. The internationally acclaimed DOTS program also faced major shortfalls. Even though the program claimed to be a short course yet, the regime involved a treatment for 6–9 months for regular TB and 12–24 months for TB from Mdr and Xdr strains. The mixture of various antibiotics produced serious side effects in patients which discouraged them to continue the use of antibiotics further. Finally, people treated under DOTS program exhibited reinfection and disease reactivation [9].

Therefore, the immense burden of the TB worldwide, lengthy treatment schedules, increasing number of Mdr and Xdr strains and the complications associated with HIV co-infections has created an urgent need for efficient and affordable treatments. In such an hour of need, natural compounds from plants, microbes, and invertebrates might be a silver lining to the treatment of such a notorious pathogen. Natural products have proven to be an essential component of

therapeutic development in almost all areas of human health. Scientists around the world are working on the utilization of natural compounds against *M. tuberculosis* and developing sustainable treatments from them.

7.4 Utilization of Natural Compounds for TB Treatment

Natural sources are considered a safe and attractive alternative for exploration of new and better anti-TB drugs since they possess a rich chemical diversity and remarkable antimicrobial activity. Natural compounds are observed to have higher hit rates during large high-throughput screening (HTS) and reaches target cells efficiently [6]. Natural compounds derived from medicinal plants have been used for treating diseases like tuberculosis, respiratory tract infections, dysentery, etc. for centuries. Extracts of leaves, stem bark, roots, fruits, and flowers of medicinal plants in the form of tinctures, decoctions, macerations, and infusions have been used by communities throughout the world for treating TB. Medicinal plants and their use have been recognized as one of the oldest sciences in countries like China, Greece, India, and Egypt. Over 60% of the people in today's world still depends on medicinal plants for primary healthcare [10].

Africa is one of the major hubs of TB disease and many communities rely on the traditional healers for treatment. Traditional healers use extracts of medicinal plants as primary source of medicine. Rinne reported that family of TB infected patients regularly visit their traditional healer and consult them since, they are familiar with the local culture and provide a cheap treatment when compared to standard anti-TB drugs. The healers are also found within shorter distance and remain available always for the community [11]. Many researchers like Tabuti et al. [12]; Semeny aand Maroyi [13]; Nguta et al. [14] have tried to document this indigenous knowledge on traditional remedies of Africa so that they can help in development of effective medicine in future (Table 7.1).

Secondary metabolites of plants, also known as phytochemicals, are responsible for rendering the anti-mycobacterial properties to plants. Phytochemicals are not directly involved in growth, reproduction, and development in plants, however, their presence is very much important for the long time survival and well-being of the plant. The specific odor, color or taste of plant parts are due to the presence of these phytochemicals, like, the strong smell and taste of freshly crushed garlic occurs due to the presence of allicin. These chemicals protect the plants from biotic and abiotic stresses. The distribution of phytochemicals is limited in plant kingdom and varies from species to species [15]. The utilization of natural compounds for treatment of TB is not only restricted to plant phytochemicals. Scientist have reported the use of bee propolis [16], fungal metabolites [17], microalgal bioactive compounds [18], as well as compounds isolated from marine microorganisms against active and dormant *M. tuberculosis.* Some of the potential natural anti-mycobacterial compounds are discussed below:-.

Table 7.1 Plant species used for the treatment of TB in Africa [12–14]

Serial no:	Plant name	Family	Main part used
1.	*Eucalyptus camaldulensis*	Myrtaceae	Leaves and roots
2.	*Artemisia afra*	Asteraceae	Leaves
3.	*Cannabis sativa*	Cannabaceae	Leaves
4.	*Salix mucronata*	Salicaceae	Seeds
5.	*Kalanchoe* sp.	Crassulaceae	Leaves
6.	*Lippia javanica*	Verbenaceae	Leaves
7.	*Zanthoxylum chalybeum* Engl.	Rutaceae	Roots
8.	*Acacia polyacantha* Willd.	Mimosaceae	Stem (bark)
9.	*Warburgia salutaris*	Canellaceae	Stem (bark)
10.	*Aloe vera* var. *barbadensis*	Xanthorrhoeaceae	Leaves
11.	*Brillantaisia owariensis*	Acanthaceae	Leaves
12.	*Bidens pilosa* L.	Asteraceae	Whole plant
13.	*Leonotis nepetifolia*	Lamiaceae	Leaves
14.	*Solanum torvum* Sw.	Solanaceae	Leaves and fruits
15.	*Zingiber officinale* roscoe	Zingiberaceae	Rhizomes

7.4.1 Resveratrol

Resveratrol (3, 5, 4′-trihydroxystilbene) is a type of natural phenol and a phytoalexin, produced by plants when they are attacked by bacterial or fungal pathogens (Fig. 7.1). It is found in the skin of grapes, mulberries, cranberries, blueberries, raspberries, and in peanuts. Apart from its anti-TB properties, resveratrol has also been recognized to be an active anti-cancer compound.

In the search for natural anti-mycobacterial drugs Smolarz et al. reported the presence of components like resveratrol, barbaloin, aloe-emodin, deoxy-raphonticin, and raphonticin in root extracts of *Rheum rhaponticum* plant. The plant has light greenish yellow flowers and is found in the Rila mountain range of Bulgaria. It grows from a woody rhizome and bears large heart shaped leaves with succulent petioles. The compounds were found to possess anti-mycobacterial properties against *M. tuberculosis* H37Ra and *M. bovis*. The methanolic extract, at a concentration of 50 μg mL^{-1} obtained from the roots of this plant inhibited the growth of *M. tuberculosis* by 67%. The MIC value of resveratrol was 128 μg mL^{-1}. However, authors suggested that the crude extract of the plant had more significant anti-mycobacterial effect than the compounds isolated from it [19]. Resveratrol is also documented as the Sirt1 activator in *M. tuberculosis* infected macrophages, which in

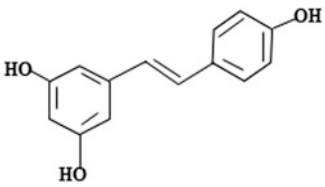


Fig. 7.1 Structure of resveratrol

turn inhibits the activation of TAK1, mitogen-activated protein kinase (MAPK), and nuclear factor (NF)–κB pathways. It was observed that mice treated with resveratrol were found to be more resistant to *M. tuberculosis* infection. The study also indicates Sirt1 to be a novel therapeutic target for TB treatment [20].

7.4.2 Quercetin

Quercetin (3, 3′, 4′5, 7-pentahydroxyflavone) is a flavonoid, found in apples, onions, berries, broccoli, and in herbs such as ginkgo and St. John's wort (Fig. 7.2). It is a common chemical pigment found in the rinds and barks of a wide variety of plants. It is known to scavenge reactive oxygen species (ROS) and neutralizes these free radicals by converting them to water molecules. Free radicals interfere with the cellular functions through lipid peroxidation leading to cell membrane damage and eventually to cell death [21]. In addition to its anti-oxidant properties, quercetin can also act as an anti-inflammatory agent. The presence of five hydroxyl groups in a quercetin molecule determines its biological activity.

Inhibition of a key enzyme of the glyoxylate shunt—isocitrate lyase by quercetin was reported by Shukla et al. [22]. The enzyme isocitrate lyase catalyzes the conversion of isocitrate to succinate and glyoxylate. The glyoxylate shunt is very important for the persistence of *M. tuberculosis* inside the phagosomes of macrophages, which are rich in fatty acid but deficient in glucose. Authors suggested that isocitrate lyase of *M. tuberculosis* to be a potential target for drug development by observing the strong binding affinity of quercetin (K_d of 6.68 μM) and low IC_{50} (3.57 μM). The pocket detection algorithm and blind docking methodology identified a small cavity at the N-terminus of isocitrate lyase of *M. tuberculosis* as the binding spot of quercetin [22]. Methanolic extract of the plant *Euphorbia paralis* was found to possess anti-mycobacterial properties. The active component in the fraction was identified to be quercetin-3-O-β-D-glucoside by ultraviolet spectroscopy. Docking analysis suggested that the inhibition of glutamine synthetase enzyme by quercetin-3-O-β-D-glucoside. Glutamine synthetase enzyme plays essential role in the nitrogen metabolism and its inhibition affects the survival of *M. tuberculosis*. In vitro studies performed in the presence and absence of quercetin-3-O-β-D-glucoside revealed that enzymatic activity of glutamine synthetase of *M. tuberculosis* depends upon the concentration of the inhibitor [23]. Butov et al. suggested that the hepatoprotective effect of quercetin and polyvinylpyrrolidone in

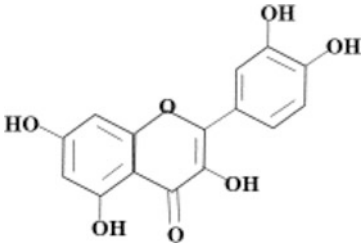


Fig. 7.2 Structure of quercetin

mice infected with *M. tuberculosis* H37Rv strain. The administration of quercetin and polyvinylpyrrolidone along with INH and streptomycin to infected mice showed pronounced effects [24]. Anti-mycobacterial activity of quercetin was also studied by Sasikumar et al., using *M. tuberculosis* H37Rv strain. Quercetin exhibited 99.30% at 200 μg mL^{-1} and 56.21% at 50 μg mL^{-1} inhibition in Luciferase reported phage assay and broth micro-dilution method respectively [25]. In search of good microbial cellular targets for drug designing, Glutamate racemase encoded by gene Mur1 was considered. The enzyme glutamate racemase catalyzes the inter-conversion of L- to D-glutamate, required for peptidoglycan layer formation in mycobacterial cell wall. By the use of docking and molecular dynamics simulation quercetin was found to have a good binding affinity with mycobacterium Mur1. Electron microscopy also confirmed the cell wall damages on exposure to quercetin [26].

7.4.3 Curcumin

Curcumin [(1E, 6E)-1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione] obtained from *Curcurma longa*, is a bright yellow color compound commonly known as turmeric (Fig. 7.3). Curcumin is a major constituent of the Indian Ayurvedic medicine and has been used to treat skin problems, digestion issues, arthritis, cancer, and cardiovascular disorders [27]. It is a potent oxidized free radical scavenger. The noteworthy anti-inflammatory, anti-oxidant and anti-carcinogenic properties makes curcumin an important herbal complement, cosmetic ingredient as well as food supplement [28].

The effect of curcumin on intracellular growth of *M. tuberculosis* H37Rv and two other clinical isolates were observed in Raw 264.7 cell lines. The results obtained from the study revealed that curcumin inhibited the survival of *M. tuberculosis* inside the macrophages but did not show any direct inhibitory actions on the pathogen. Authors suggested that curcumin could be used as an adjuvant along with TB drugs [29]. Baldwin et al. worked on the development of structural variations of curcumin to curtail its poor bioavailability. They synthesized mono-carbonyl analogs of curcumin and observed the effect of them on *M. tuberculosis* and *M. marinum.* With respect to the IC_{50} value USB-109 analog displayed the best inhibitory effect on the two mycobacterial species [30]. Another group of researchers has also worked on the enhancement of bioavailability of curcumin. Tousif et al. has developed curcumin nanoparticles (~200 nm) using a simple one step process which increased the bioavailability of curcumin by five times when compared to regular

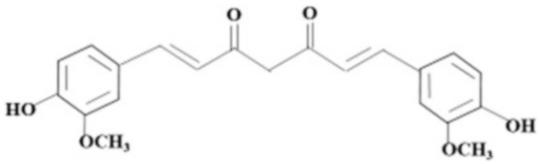


Fig. 7.3 Structure of curcumin

curcumin. The effect of curcumin nanoparticles were tested in murine TB model. The controlled and extended release of curcumin reduced the hepatotoxicity induced by INH and amplified the T cell immunity thereby preventing reinfection and return of the disease [9]. Curcumin was observed to offer host-protective role against the *M. tuberculosis* H37Rv infection in differentiated THP-1 human monocytes and primary human alveolar macrophages. Authors proposed that such anti-tubercular cell mediated functions was possible for curcumin via inhibition of the nuclear factor–kappa B (NF-κB) activation and induction of caspase-3-dependent apoptosis and autophagy in macrophages [31]. Researchers summarized that curcumin could be used as an adjuvant with standard TB drug regime and might also help in reducing the risk of Mdr-TB and Xdr-TB.

7.4.4 Tannins

Tannins are water soluble polyphenols found abundantly in nature (Fig. 7.4). They are present in wood, bark, leaves, and fruits of most plants and trees like, barley, plum, strawberries, cranberries, oak, rhubarb, tea, walnut, cocoa, and grapes. The presence of tannins in plants helps them to deter animals from eating fruits and seeds before ripening. The tannins in raw fruits render an astringent like feeling in mouth which prevents animals from consuming them. Tannins have been used by humans since ages to tan animal hides and make leather [32].

To response to the urgent need for development of plant based anti-TB drugs Lawal et al. and his co-workers investigated the anti-mycobacterial activity of crude extracts of root and leaves of *Uvaria afzelii* Scot Elliot and root of *Tetracera alnifolia,* respectively, against *M. tuberculosis*. The selection of the plants were based on the fact that these plants were being used by local people for cough associated with TB and other respiratory tract infections. Microplate Alamar Blue Assay (MABA) was used to observe the susceptibility of *M. tuberculosis* H37Rv. The MIC <100 μg mL^{-1} was observed against *M. tuberculosis* H37Rv for hexane and chloroform extracts of root of *Tetracera alnifolia* and chloroform extract of

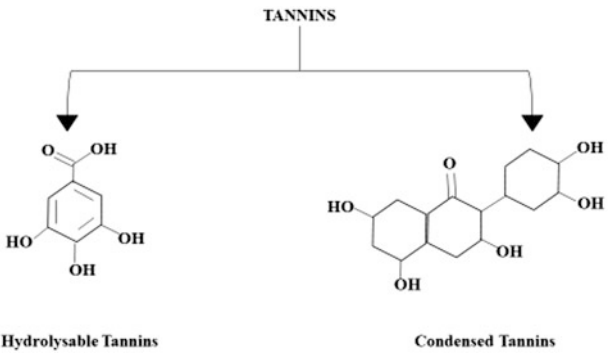


Fig. 7.4 Structure of tannins

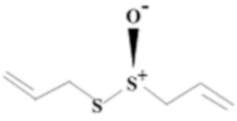
Uvaria afzelii, respectively. The strong anti-mycobacterial activity was attributed to the presence of tannins, saponins, and alkaloids in the plant extracts. Therefore, the results obtained from the study supported the local use of these plants against TB [33]. Tannins obtained from *Globularia alypum* L. were also investigated for their anti-mycobacterial activity [34]. *Globularia alypum* L. is a low, dense, perennial plant which bears small, purple or pinkish tightly packed flowers in February or March. Methanol, petroleum, and dichloromethane; Methanol, acetone, and water were the two mixtures used to prepare extracts of the plant. Both the extracts were screened for active anti-mycobacterial compounds using α-diphenyl-β-picrylhydrazyl (DPPH) and 2, 29-azinobis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS) assays. The extract contained polyphenols—Tannins, flavonoids, and anthocyanins in good proportions. Evaluation of anti-mycobacterial activity of the extracts performed carried out using colorimetric microassays. Results revealed that extract obtained using methanol, petroleum, and dichloromethane mixture displayed improved anti-TB activity [34]. Hot water decoctions of root and stem bark extracts of plants of Terminalia genus are used by local people of Africa for treating various infectious diseases and is a part of their traditional medicine. Hence, it has attracted researchers to detect the active compounds present in this plant. Fyhrquist et al. reported the presence of good amounts of ellagitannins and ellagic acid glycosides in the methanol and aqueous extracts of *T. sambesiaca* roots by using high performance liquid chromatography-diode array detector (HPLC-DAD) method. Ellagitannins are a very diverse group of hydrolysable tannins and might be the reason of the good anti-mycobacterial effects of the plant extracts [35].

7.4.5 Allicin

Allicin is a sulfur containing organic compound obtained from *Allium sativum*, commonly known as garlic (Fig. 7.5). Allicin is responsible for the unique odor of garlic. It is formed by the enzymatic conversion of alliin to allicin by alliinase when a fresh garlic is chopped. Allicin is known to target the thiol-containing proteins and enzymes of pathogenic microorganisms [36]. Apart from being antimicrobial, it is also considered an anti-oxidant, anti-inflammatory, anti-fungal, anti-viral as well as an anti-cancer agent. Hence, it is sometimes called the wonder compound with astonishing abilities [37].

The anti-mycobacterial property of ethanol extract of garlic was studied by Ratnakar and Murthy [38]. They used the extract against *M. tuberculosis* H37Rv and *M. tuberculosis* TRC-C 1193 strains resistant to INH. The ethanol extract inhibited the growth of both the strains in plate and shake cultures with MIC

Fig. 7.5 Structure of allicin



70 μg mL^{-1} for both microorganisms respectively. Moreover, after purifying the allicin over silica gel-G columns, MIC values reduce to 25 μg mL^{-1} for the strains [38]. Allicin was observed to suppress the increased expression of tumor necrosis factor (TNF)-α mRNA and ROS in *M. tuberculosis* H37Rv infected human monocytes in a dose-dependent manner [39]. Hasan and his colleagues also reported that antigen 85B of *M. tuberculosis* is responsible for induction of TNF-α and could be suppressed by allicin. Antigen 85 B complex of *M. tuberculosis* is formed by 85A and 85C components and induces TNF-α by binding to fibronectin in monocytes. Authors concluded that the allicin induced antigen 85B suppression correlated with the reduction in TNF-α release from infected monocytes [40]. Anti-mycobacterial activity of ethanolic extract of garlic against 15 Mdr strains and 5 non-Mdr strains of *M. tuberculosis* was investigated. The ethanolic extract was prepared by maceration method and 7H9 middle brook broth dilution (MBBD) method was used to determine the MIC which was observed to be between 1 and 3 mg mL^{-1} against both types of *M. tuberculosis* strains [41]. Authors proposed that plant extracts could be used as a substitute for reducing the burden of drugs as well as cost of the TB treatment which could in turn help patients to continue the full treatment and prevent development of drug-resistant strains [41].

A very recent study performed by Dwivedi et al. [42] reports the anti-mycobacterial and immunomodulatory activity of both garlic extract and allicin on *M. tuberculosis* H37Rv both in vivo and in vitro. Garlic extract was prepared by grinding 100 g of garlic cloves in 100 mL of water, then filtering it through muslin cloth. The crude extract was centrifuged, dried, then dissolved in water and stored at −20 °C. Their findings revealed that both allicin and garlic extract significantly reduced the mycobacterial burden in murine models by rendering a strong protective Th1 response [42]. These studies validate the strong anti-mycobacterial property of allicin/garlic extract and warrant more investigations.

7.4.6 Propolis

Propolis, also called bee glue, is a bee extract, consisting of wax and resins, used by honeybees to build beehives. This natural resinous mixture is produced by honeybees from secretions collected from plant buds, flowers, and exudates. Propolis has been used as traditional method for curing viral infections, gastrointestinal problems, and TB [43]. The anti-oxidant, antimicrobial, and anti-inflammatory property of propolis has attracted researchers to investigate its therapeutic abilities [44]. The presence of flavonoids in propolis is responsible for the pharmacological effects [45].

Scheller et al. investigated the synergistic effect of ethanolic extracts of propolis (EEP) with anti-TB drugs. They observed that the synergistic effect between EEP and anti-TB drugs reduced the growth rate of 14 out of 17 strains of TB [46]. The consumption of RMP, INH, PZA, and ethambutol over long period of time results in serious side effects like nausea, vomiting, liver damage, loss of weight, etc. in TB patients. Hence, the protective action of bee propolis against anti-TB drugs (RMP

and INH) in Sprague Dawley rats was studied by Bharti et al. [47]. The study suggested that co-administration of propolis with drugs increased the hemoglobin level and body weights of the rats thereby, modulating the toxic effects of the drugs [47].

7.5 Conclusion and Future Directions

Tuberculosis still remains a major world health problem and continues to claim lives despite the efforts of WHO and the governments of various countries. The increased rate of resistance of *M. tuberculosis* against conventional antibiotic treatment have called for an urgent need for development of anti-TB drugs from alternate sources. In such a situation, natural compounds might serve as an unparalleled natural reservoir of chemically and structurally diverse compounds with novel mechanisms of action against the pernicious bacteria. These natural compounds might also be used as an adjunct, to augment the action of standard anti-TB drugs which have become less effective. Their use could also prevent the development of resistant mycobacterial strains. However, these natural compounds with incredible capabilities are not being utilized to their utmost potential due to lack of knowledge, documentation, and significant research. Therefore, isolation, characterization, and elucidation of their properties needs to be done. The various scientific studies reported on the utilization of natural compounds against *M. tuberculosis* strains desires to be replicated and high level clinical trials requires to be performed urgently, only then can this global health issue be controlled.

Acknowledgement Authors would like to acknowledge principal, Poona college of Pharmacy for his consistent encouragement, co-operation and suggestions.

References

1. Dutta NK, Karakousis PC (2012) Tuberculosis chemotherapy: present situation, possible solutions, and progress towards a TB-free world. Indian J Medial Microbiol 30(3):261–263
2. https://www.who.int/campaigns/world-tb-day/2020. Accessed 06 Oct 2020.
3. Sandhu GK (2011) Tuberculosis: current situation, challenges and overview of its control programs in India. J Glob Infect Dis 3(2):143–150
4. Tripathi RP, Tewari N, Dwivedi N, Tiwari VK (2005) Fighting tuberculosis: an old disease with new challenges. Med Res Rev 25(1):93–131
5. https://www.who.int/tb/features_archive/change-treatment-drug-resistant-tb/en/. Accessed 07 Oct 2020
6. Quan D, Nagalingam G, Payne R, Triccas JA (2017) New tuberculosis drug leads from naturally occurring compounds. Int J Infect Dis 56:212–220
7. Meena LS, Rajni (2010) Survival mechanisms of pathogenic *Mycobacterium tuberculosis* H37Rv. Fed Eur Biochem Soc 277:2416–2427
8. Kaur T, Sharma P, Gupta GK, Ntie-Kang F, Kumar D (2019) Treatment of tuberculosis by natural drugs: a review. Plant Arch 19(2):2168–2176

9. Tousif S, Singh DK, Mukherjee S, Ahmad S, Arya R, Nanda R, Das G (2017) Nanoparticle-formulated curcumin prevents Posttherapeutic disease reactivation and reinfection with *Mycobacterium tuberculosis* following isoniazid therapy. Front Immunol 8:739. https://doi.org/10.3389/fimmu.2017.00739
10. Shrestha PM, Dhillion SS (2003) Medicinal plant diversity and use in the highlands of Dolakha district, Nepal. J Ethnopharmacol 86:81–96
11. Rinne E-M (2001) Water and healing: experiences from the traditional healers in Ile-Ife. Niger Nordic J Afr Stud 10:41–65
12. Tabuti JRS, Kukunda CB, Waako PJ (2010) Medicinal plants used by traditional medicine practitioners in the treatment of tuberculosis and related ailments in Uganda. J Ethnopharmacol 127:130–136
13. Semenya SS, Maroyi A (2013) Medicinal plants used for the treatment of tuberculosis by Bapedi traditional healers in three districts of the Limpopo Province, South Africa. Afr J Trad Complement Altern Med 10(2):316–323
14. Nguta JM, Appiah-Opong R, Nyarko AK, Yeboah-Manu D, Addo PGA (2015) Medicinal plants used to treat TB in Ghana. Int J Mycobacteriol 4:116–123
15. Mazlun MH, Sabran SF, Mohamed M, Abu Bakar MF, Abdullah Z (2019) Phenolic compounds as promising drug candidates in tuberculosis therapy. Molecules 24(13):2449. https://doi.org/10.3390/molecules24132449
16. Teixeira ÉW, Message D, Meira RM (2019) An alternative fixing agent for identifying the botanical origin of propolis. Appl Plant Sci 7(12):11309. https://doi.org/10.1002/aps3.11309
17. Ganihigama DU, Sureram S, Sangher S, Hongmanee P, Aree T, Mahidol C, Ruchirawat S, Kittakoop P (2015) Antimycobacterial activity of natural products and synthetic agents: pyrrolodiquinolines and vermelhotin as anti-tubercular leads against clinical multidrug resistant isolates of *Mycobacterium tuberculosis*. Eur J Med Chem 89:1–12. https://doi.org/10.1016/j.ejmech.2014.10.026
18. Prakash S, Bhimba BV (2005) Pharmaceutical development of novel microalgal compounds for Mdr *M. tuberculosis*. Nat Prod Radiance 4(4):264–269
19. Smolarz HD, Swakto-Ossar M, Ginalska G, Medynska E (2013) Antimycobacterial effect of extract and its components from *Rheum rhaponticum*. J AOAC Int 96(1):155–160
20. Yang H, Hu J, Chen Y, Ge B (2019) Role of Sirt1 in innate immune mechanisms against *Mycobacterium tuberculosis* via the inhibition of TAK1 activation. Arch Biochem Biophys 667(30):49–58
21. Charkraborty S, Stalin S, Das N, Choudhury ST, Ghosh S, Swarnakar S (2012) The use of nano-quercetin to arrest mitochondrial damage and MMP-9 upregulation during prevention of gastric inflammation induced by ethanol in rat. Biomaterials 33:2991–3001
22. Shukla H, Kumar V, Singh AK, Rastogi S, Khan SR, Siddiqi MI, Akhtar MS (2015) Isocitrate lyase of *Mycobacterium tuberculosis* is inhibited by quercetin through binding at N-terminus. Int J Biol Macromol 78:137–141
23. Safwat NA, Kashef MT, Aziz RK, Amer KF, Ramadan MA (2018) Quercetin 3-O-glucoside recovered from the wild Egyptian Sahara plant, Euphorbia paralias L., inhibits glutamine synthetase and has antimycobacterial activity. Tuberculosis 108:106–113
24. Butov DO, Zaitseva SI, Pitenko MM, Stepanenko GL, Butova TS (2015) Morphological changes in experimental tuberculosis resulting from treatment with quercetin and polyvinylpyrrolidone. Int J Mycobacteriol 4:296–301
25. Sasikumar K, Ghosh AR, Dusthackeer A (2018) Antimycobacterial potentials of quercetin and rutin against *Mycobacterium tuberculosis* H37Rv. 3 Biotech 8(10):427
26. Pawar A, Jha P, Chpra M, Chaudhury U, Saluja D (2020) Screening of natural compounds that targets glutamate racemase of *Mycobacterium tuberculosis* reveals the anti-tubercular potential of flavonoids. Sci Rep 10:949
27. Srivastava RM, Singh S, Dubey SK, Misra K, Khar A (2011) Immunomodulatory and therapeutic activity of curcumin. Int Immunopharmacol 11:331–341

28. Swarnakar S, Ganguly K, Kundu P, Banerjee A, Maity P, Sharma AV (2004) Curcumin regulates expression and activity of matrix metalloproteinases 9 and 2 during prevention and healing of indomethacin-induced gastric ulcer. J Biol Chem 280(10):9409–9415
29. Gupta PK, Kulkarni S, Rajan R (2013) Inhibition of intracellular survival of multi drug resistant clinical isolates of *Mycobacterium tuberculosis* in macrophages by curcumin. Open Antimicrob Agents J 4:1–5
30. Baldwin PR, Reeves AZ, Powell KR, Napier RJ, Swimm AI, Sun A, Giesler K, Bommarius B, Shinnick TM, Snyder JP, Liotta DC, Kalman D (2015) Monocarbonyl analogs of curcumin inhibit growth of antibiotic sensitive and resistant strains of *Mycobacterium tuberculosis*. Eur J Med Chem 92:693–699
31. Bai X, Oberley-Deegan RE, Bai A, Ovrutsky AR, Kinney WH, Weaver M, Chan ED (2016) Curcumin enhances human macrophage control of *Mycobacterium tuberculosis* infection. Respirology 21(5):951–957
32. Maiolini M, Gause S, Taylor J, Steakin T, Shipp G, Lamichhane P, Deshmukh B, Shinde V, Bishayee A, Deshmukh RR (2020) The war against tuberculosis: a review of natural compounds and their derivatives. Molecules 25:3011
33. Lawal TO, Adenyl BA, Wan B, Franzblau SG, Mahady GB (2011) In-vitro susceptibility of *Mycobacterium Tuberculosis* to extracts of *Uvaria Afzelli* Scott Elliot and *Tetracera Alnifolia* Willd. Afr J Biomed Res 14:17–21
34. Khlifi D, Hamdi M, El Hayouni A, Cazaux S, Souchard JP, Couderc F, Baouajila J (2011) Global chemical composition and antioxidant and anti-tuberculosis activities of various extracts of *Globularia alypum* L. (Globulariaceae) leaves. Molecules 16:10592–10603
35. Fyhrquist P, Laakso I, Marco SG, Julkunen-Tiitto R, Hiltunen R (2014) Antimycobacterial activity of ellagitannin and ellagic acid derivate rich crude extracts and fractions of five selected species of Terminalia used for treatment of infectious diseases in African traditional medicine. S Afr J Bot 90:1–16
36. Reiter J, Levina N, Van der Linden M, Gruhlke M, Martin C, Slusarenko AJ (2017) Diallylthiosulfinate (Allicin), a volatile antimicrobial from garlic (*Allium sativum*), kills human lung pathogenic bacteria, including MDR strains, as a vapor. Molecules 22(10):1711
37. Fatima S, Dwivedi VP (2020) Allicin as an adjunct immunotherapy against tuberculosis. J Cell Immunol 2(4):178–182
38. Ratnakar P, Murthy PS (1995) Purification and mechanism of action of antitubercular principle from garlic (Allium Sativum) active against isoniazid susceptible and resistant *Mycobacterium tuberculosis* H37Rv. Indian J Clin Biochem 10(1):34–38
39. Hasan N, Yusuf N, Toossi Z, Islam N (2006) Suppression of *Mycobacterium tuberculosis* induced reactive oxygen species (ROS) and TNF-α mRNA expression in human monocytes by allicin. FEBS Lett 580:2517–2522
40. Hasan N, Siddiqui U, Toossi Z, Khan S, Iqbal J, Islam N (2007) Allicin-induced suppression of *Mycobacterium tuberculosis* 85B mRNA in human monocytes. Biochem Biophys Res Commun 355:471–476
41. Hannan A, Ullah MI, Usman M, Hussain S, Absar M, Javed K (2011) Anti-mycobacterial activity of garlic (*Allium Sativum*) against multi-drug resistant and non-multi-drug resistant *Mycobacterium Tuberculosis*. Pak J Pharm Sci 24(1):81–85
42. Dwivedi VP, Bhattacharya D, Singh M, Bhaskar A, Kumar S, Fatima S, Sobia P, Kaer LV, Das G (2019) Allicin enhances antimicrobial activity of macrophages during *Mycobacterium tuberculosis* infection. J Ethnopharmacol 243:111634
43. Wagh VD (2013) Propolis: a wonder bees product and its pharmacological potentials. Adv Pharmacol Sci 30:49–82
44. Teixeira ÉW, Message D, Meira RM (2019) Methacrylate: an alternative fixing agent for identifying the botanical origin of propolis. Appl Plant Sci 7(12):e11309
45. Zabaiou N, Fouache A, Trousson A, Baron S, Zellagui A, Lahouel M, Lobaccaro J-MA (2017) Biological properties of propolis extracts: something new from an ancient product. Chem Phys Lipids 207:214–222

46. Scheller S, Dworniczak S, Waldemar-Klimmek K, Rajca M, Tomczyk A, Shani J (1999) Synergism between ethanolic extract of propolis (EEP) and anti-tuberculosis drugs on growth of mycobacteria. Z Naturforschung C, J Biosci 54:549–553
47. Bharti U, Kumar NR, Kaur J (2017) Protective effect of bee propolis against anti-tuberculosis drugs (rifampicin and isoniazid)-induced hematological toxicity in Sprague Dawley rats. Asian J Pharm Clin Res 10:188–190

Medicinal Plants in Targeting Tuberculosis II

8

Niranjan Koirala, Bindu Modi, Romit Kumar Subba, Mamata Panthi, and Jianbo Xiao

Abstract

Tuberculosis is a highly contagious infectious disease triggered by Mycobacterium tuberculosis, which is widely spread by aerosol. The major site of infection is usually the lungs however the disease can attack any extra-pulmonary site as well, which is further diagnosis by necrotizing granulomatous inflammation. World Health Organization reported almost 8.9–10 million people are suffering from tuberculosis in 2019, including 56% men and 32% women, and 12% children. Multidrug-resistant tuberculosis (MDR-TB) is a medical condition in which Mycobacterium tuberculosis strains resistant to at least isoniazid and rifampicin. In-vitro studies suggest that several bioactive compounds and their

N. Koirala (✉)
Department of Natural Products Research, Dr. Koirala Research Institute for Biotechnology and Biodiversity, Kathmandu, Nepal

Laboratory of Biotechnology, Faculty of Science and Technology, University of Macau, Macau SAR, China

B. Modi
Department of Natural Products Research, Dr. Koirala Research Institute for Biotechnology and Biodiversity, Kathmandu, Nepal

Central Department of Chemistry, Tribhuvan University, Kirtipur, Nepal

R. K. Subba · M. Panthi
Department of Natural Products Research, Dr. Koirala Research Institute for Biotechnology and Biodiversity, Kathmandu, Nepal

Department of Pharmacy, Manmohan Institute of Health Sciences, Tribhuvan University, Kathmandu, Nepal

J. Xiao
Institute of Chinese Medical Sciences, State Key Laboratory, University of Macau, Macau SAR, China

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_8

synthetic derivatives obtained from plants, fungi, and marine organism possesses antimycobacterial affinity. Phenolic compounds such as dihydrocubebin, hinokinin, ethoxycubebin possess the antimycobacterial activity. Mycobacterial cell envelope antagonists have been shown to obstruct the synthesis of mycolic acids, arabinogalactan, and peptidoglycan, essential components of the mycobacterial cell wall. The paramount antituberculous drugs hamper the development of mycolic acids or the aid mechanism which links them to the cell membrane. Medicines targeting RNA synthesis encompass those that restrict the assembly of bacterial DNA-dependent RNA polymerases, that are indispensable enzymes for RNA synthesis. Various molecular pathways for the target to cure tuberculosis entail the targets of M. tuberculosis cell wall synthesis, energy metabolism, folate metabolism, DNA replication, and RNA synthesis. Interestingly, in preserving the health of patients diagnosed with tuberculosis, medicinal plants have tremendous advantages with limited side effects as compare to the standard drugs.

Keywords

Tuberculosis · Mycobacterium · Multidrug-resistant tuberculosis · Medicinal plants · DNA replication

8.1 Introduction to Medicinal Plants Used to Treat Tuberculosis

Tuberculosis is a highly contagious infectious disease triggered by Mycobacterium tuberculosis, which is widely spread by aerosol. The major site of infection is usually the lungs; however, the disease can attack any extra-pulmonary site as well, which is further diagnosis by necrotizing granulomatous inflammation [1]. Literature reports that tuberculosis was first found approximately 70,000 years back, followed by the migration of modern human beings outside of Africa [2]. Tuberculosis is listed as among the top ten diseases causing the highest mortality in the globe. Almost 1 billion people throughout the world died from tuberculosis in the past two centuries [3]. World Health Organization reported almost 8.9–10 million people are suffering from tuberculosis in 2019, including 56% men, 32% women, and 12% children [4]. The common symptoms of tuberculosis are prolonging cough with sputum, fever, excessive night sweats, loss of appetite, and weight loss [5].

Currently, two major challenges to the world's tuberculosis treatment are HIV epidemic and the increasing prevalence of drug resistance. In countries most seriously impacted by AIDS, in particular Sub-Saharan Africa, HIV-1 infection has led to a significant rise in the incidence of tuberculosis [6]. Multidrug-resistant tuberculosis (MDR-TB) is a medical condition in which *Mycobacterium tuberculosis* strains resistant to at least isoniazid and rifampicin [7] is one of the major challenges for TB management globally. World Health Organization (WHO) estimates state that approximately 480,000 new cases of MDR-TB occur each year all over the world. Out of them, almost 10% report additional drug resistance and are categorized as

extensively drug-resistant TB. MDR-TB causes approximately 250,000 deaths globally each year, the majority of these being from Asia [7]. The study shows that the MDR-TB care outcomes are very disappointing with up to 45% of patients who have been HIV negative and 85% of HIV patients died within 2 years of the treatment [8].

Literatures regarding tuberculosis and medicinal plant research for its treatment are being published at regular intervals [9–14].

A review paper documented an anti-mycobacteria property from 123 plant species in crude extracts as well as pure compounds [12]. Copp analyzed a broad variety of biologically active products spanning an antimycobacterial activity recorded within 12 years (i.e., from 1990 to 2002) in a review [10]. In vitro studies suggest that several bioactive compounds and their synthetic derivatives obtained from plants, fungi, and marine organism possess antimycobacterial affinity [13]. Different classes of phytochemicals like alkaloids, polyphenols, terpenes, quinones, tannins derived from the Ayurvedic plant were found to be effective in tuberculosis [9]. Many bioactive compounds like allicin, 1-epicatechol, anthocyanidin, ellagic acids, benzophenanthridine alkaloids, hydroxybenzoic acids, beta-sitosterol, gallic acid, glucopyranosides, neolignans, phenylpropanoids, and taraxerol are extracted from several plant species, have been documented to contain antimycobacterial efficacy [15]. The authors have concentrated on further production of anti-TB medications, either as crude extracts that are used for the treatment of tuberculosis as therapeutic or replacement drugs for TB or as potential bioactive compounds. The exclusive review carried out on Southeast Asian medicinal plants revealed 27 plant species encompass 20.5% in vitro anti-TB potential in crude extracts as well as in their bioactive compounds (0–<10μg/ml) [14].

8.2 Biodiversity and Geographical Presence of Plants

Six continental areas, and some regions of the world, such as the Caribbean, Mediterranean, and the Middle East, have dispersed large-scale antituberculous plants. The global delivery of antituberculosis medicines was considered dominant in Asia since it has tropical and subtropical areas. In this section, we listed out different plant families which possess antitubercular efficacy along with their habitat as well as plant part used in the treatment of tuberculosis. Furthermore, these regions have their long established traditional medicine systems.

Those data are documented in Table 8.1. Out of the 50 plants species (from 33 different families) discussed in this review, leaves (44%) were mostly used for antitubercular activity screening, followed by roots (16%), stems (12%), fruits (12%), rhizomes (10%), aerial parts (8%), whole plant (8%), flowers (6%), and seeds (2%) (Table 8.1). Most of the plants in this review have habitat of below 2000 m altitude (92%).

Table 8.1 Geographical presence of medicinal plants

S. No	Plants used (family)	Geographical presence	Parts used	Habitat
1.	Aristolochia taliscana Hook and Arn. (Aristolochiaceae)	Central America—Southern Mexico	Roots	500–2000 m
2.	Aristolochia brevipes Benth. (Aristolochiaceae)	Mexico	Rhizome, ground roots	500–2000 m
3.	Aristolochia elegans Mast. (Aristolochiaceae)	Brazil, Paraguay, Northern Argentina, tropical and temperate regions of the world	Leaves, seeds, and rhizomes	450–2150 msl
4.	Artemisia capillaris Thunb. (Asteraceae)	Central and Southeast Asian countries like China, Cambodia, Indonesia, Japan, Korea, Malaysia, etc.	Aerial parts	100–2700 m
5	Artemisia afra Jacq. ex wild (Asteraceae)	Africa, ranging from South Africa to Ethiopia	Dried leaves	1450–2500 m
6	Azorella compacta Phil., A. madreporica Clos. (Apiaceae)	Peru, Chile, Bolivia, Argentina	Aerial parts	3800–5200 m
7	Beilschmiedia tsangii Merr. (Lauraceae)	Vietnam, Tonkin, Southern Taiwan, Southern and Western China	Leaves	Up to 2200 m
8	Blepharodon nitidum (Vell.) J.F. Macbr. (Asclepiadaceae)	Bolivia, Brazil, Paraguay, Peru, Venezuela Colombia, and Guyana	Whole plant	Up to 1600 m
9	Celastrus vulcanicola Donn. Sm. (Celastraceae)	Central and Southern America	Leaves	1900 m
10	Chamaedorea tepejilote Liebm. (Palmae)	Northwestern S. America—Colombia; C. America—Panama to Mexico	Leaves	Up to 1600 m
11	Citrullus colocynthis (L.) Schrad. (Cucurbitaceae)	Sahara and Arabian deserts, Sudan and Southern part of Asia including Pakistan, India and Southern Islands	Ripe fruit	600–700 msl
12	Citrus sinensis (L.) Osbeck (Rutaceae)	Subtropics and tropic part of the world	Fruit peel	200–2500 msl
13	Chrysactinia mexicana A. Gray (Asteraceae)	New Mexico and Texas south to central Mexico	Roots	350–2950 m
14	Clavija procera B. Ståhl (Theophrastaceae)	Ecuador, Brazil, Colombia, Peru	Stems and bark	450 m
15	Curcuma longa L. (Zingiberaceae)	E. Asia—India, Thailand, Vietnam, Malaysia, Indonesia	Rhizomes	Up to 2000 m
16	Euclea natalensis A. DC. (Ebenaceae)		Roots	800–1580 m

(continued)

Table 8.1 (continued)

S. No	Plants used (family)	Geographical presence	Parts used	Habitat
		Ethiopia and Somalia, southwards to the Western Cape, South Africa		
17.	Foeniculum vulgare Mill. (Apiaceae)	North, Central and South America, Caribbean Islands, India, Argentina, Germany, France, Hungary, Italy, Japan, Romania and Southern Russia	Leaves and stems	Up to 4000 m
18	Justicia adhatoda L. (Acanthaceae)	Indian subcontinent (Assam, Bangladesh, India, Nepal, and Sri Lanka), Laos, and Myanmar	Leaves	Up to 1300 m
19	Kaempferia galanga L. (Zingiberaceae)	E. Asia—Southern China, India, Bangladesh, Myanmar, Thailand, Cambodia, Vietnam	Rhizomes	Up to 1000 m
20	Lantana hispida Kunth (Verbenaceae)	Africa, Australia, India, southeastern Asia	Aerial parts	Up to 1500 m
21	Larrea tridentata Coville. (Zygophyllaceae)	Deserts of western North America, Mexico, Southeastern California, Arizona, Southern Nevada, southwestern Utah, New Mexico, and Texas in the USA	Leaves	Up to 1515 m
22	Plectranthus grandidentatus Gurke (Lamiaceae)	Southern Africa—southern Zimbabwe, Swaziland, S. Africa	Whole plant	Above 1000 m
23	Plumeria bicolor Ruiz & Pav. (Apocynaceae)	Mexico, Central America, Colombia, and Venezuela and all tropical areas of world	Stem bark	0–1500 msl
24	Tabernaemontana elegans Stapf. (Apocynaceae)	East Africa	Roots	Up to 1000 m
25	Diospyros anisandra S.F.Blake (Ebenacea)	Cuba, Guatemala, Mexico Southeast	Roots and bark	Up to 300 m
26.	Piper chaba Hunter (Piperaceae)	South and Southeast Asia	Stems	Up to 1500 msl
27.	Buddleja cordata H.B.K. subsp. cordata (Loganiaceae)	Central Mexican Highlands extending as far north as Chihuahua and south as G Guatemala	Ground stem bark	1500–3000 m
28.	Humulus lupulus (Cannabaceae)	Europe, western Asia and North America	Whole plant	0–2600 m
29.	Oplopanax horridus (Smith) Miq. (Araliaceae)	Northwestern North America	Bark	Up to 1900 m

(continued)

Table 8.1 (continued)

S. No	Plants used (family)	Geographical presence	Parts used	Habitat
30.	Abrus precatorius L. (Leguminosae)	West Indies, South Africa, China, Islands, Brazil, India	Aerial parts	Near sea level to 1000 m
31.	Abutilon indicum (L.) Sweet (Malvaceae)	Tropical and subtropical zones	Leaves	Up to 1200 m
32.	Acanthus ebracteatus Vahl. (Acanthaceae)	Southeast Asia, including northern Australia	Leaves and stems	500–2200 m
33.	Aegle marmelos (L.) Correa (Rutaceae)	Indian subcontinent and Southeast Asia	Fruits and flowers	Up to 1200 m
34.	Aloe vera L. (Aloaceae)	Mediterranean region and subtropical regions of the world	Leaves	1300–2600 msl
35.	Zingiber zerumbet (L.) (Zingiberaceae)	Eastern Asia—Indian subcontinent, Myanmar, Vietnam, Malaysia, Indonesia, Laos, Philippines Thailand, Cambodia	Rhizome	Up to 1300 m
36.	Ziziphus mauritiana Lam. (Rhamnaceae)	Southeastern Asia, Africa, Australia, the Pacific and the Americas	Roots	Up to 1800 m
37.	Voacanga globosa Merr. (Apocynaceae)	Philippines	Leaves	Up to 300 m
38.	Tinospora crispa (L.) Hook. F. & Thomson (Menispermaceae)	Primary rainforests or mixed deciduous forests of South East Asia and Africa including Thailand, Malaysia, and Indonesia	Fruits and flowers	Up to 900 m
39.	Sesbania grandiflora (L.) Poir. (Leguminosae)	Most humid tropical regions of the world	Fruits and roots	Up to 1000 m
40.	Rhoeo spathacea (Sw.) Stearn (Commelinaceae)	West Indies, Puerto Rico, Bahamas, South America and elsewhere in the tropics	Leaves	Sea level to low elevations
41.	Pistia stratiotes L. (Araceae)	Tropical, subtropical, and warmer temperate regions	Whole plant	Up to 1400 m
42.	Petiveria alliacea L. (Phytolaccaceae)	North America, Mexico, Central America, the West Indies, South America and Tropical Africa	Leaves	Up to 360 m
43.	Gynura divaricata (L.) DC. (Asteraceae)	Southeast Asian countries	Leaves	0–1000msl
44.	Morinda citrifolia Linn. (Rubiaceae)	East Indies and Australia. Cultivated in Myanmar	Leaves	Up to 1500 m
45.	Morus alba L. (Moraceae)	USA, Mexico, Australia, Kyrgyzstan, Argentina, Turkey, Iran, Northern China, and India	Leaves and fruit	Up to 3300 m

(continued)

Table 8.1 (continued)

S. No	Plants used (family)	Geographical presence	Parts used	Habitat
46.	Jatropha curcas L. (Euphorbiaceae)	Mexico, Central America, and tropical and subtropical regions	Leaves	Up to 1850msl
47.	Glycosmis pentaphylla (Retz.) DC. (Rutaceae)	Southeast Asia and Australia	Fruits and flowers	Up to 1000 m
48.	Flemingia strobilifera (L.) W. T. Aiton (Fabaceae)	E. Asia—China, India, Sri Lanka, Nepal, Myanmar, Thailand, Cambodia, Laos, Vietnam, Malaysia, Philippines	Leaves	200–1600 m
49.	Croton kongensis Gagnep. (Euphorbiaceae)	E. Asia—China, Myanmar, Thailand, Laos, Vietnam	Whole plants and leaves	Up to 2000 m
50.	Coccinia grandis (L.) Voigt (Cucurbitaceae)	North-central East Africa, Australia The Pacific region, the Caribbean, and southern USA	Leaves	Up to 1100 m

Msl meters above sea level

8.3 Phytochemicals Found in the Antituberculosis Medicinal Plants

Diverse bioactive compounds, extracted from the studied plants, demonstrated strong antitubercular, varying from <1 to 50μg/ml of MIC values. Neolignans, licarin A, isolated from hexane extract showed MIC of 3.12–12.5μg/mL. Eupomatenoid-1, fargesin, and cubebin purified from Aristolochia elegans revealed MIC of 50μg/ml. Isolated ursolic acid (UA) and hydroquinone (HQ) showed 12.5μg/mL. Azorellane and mulinane diterpenoids from Azorella compacta Phil., A. possessed a MIC value of 12.5μg/ml. 24-hydroperoxycycloart-25-en-3β-ol and 25-hydroperoxycycloart-23-en-3β-ol, obtained from Blepharodon nitidum exhibited in vitro anti-Mycobacterium tuberculosis activity with MIC of 25μg/mL and 12.5μg/mL, respectively. Sesquiterpenes derivative 1α-Acetoxy-6β,9β-dibenzoyloxy-dihydro-β-agarofuran showed excellent antimycobacterial efficiency with MIC value of 6.2μg/mL than isoniazid or rifampin.

Caryophyllene oxide, decanal, and palmitic acid from Citrus sinensis (L.) Osbeck exhibited MIC value of 100–200μg/mL, 25–200μg/mL, and 50–100μg/mL, respectively. Demethoxycurcumin and its derivative compound 6 showed MIC value of 200μg/mL and 7.8μg/mL against Mycobacterium tuberculosis H37Rv strains. Diospyrin and 7-methyljuglone isolated from the plant Euclea natalensis comprises MIC of 8.0 and 0.5μg/ml. Compounds isolated from Foeniculum vulgare Mill with their MIC values, linoleic acid, oleic acid both have MIC value 100μg/mL, undecanal (MIC 50–200μg/mL), 1,3-benzenediol (MIC 100–200μg/mL), and 2,4-undecadienal (MIC 25–50μg/mL). Ethyl p-methoxycinnamate (EPMC)

extracted from ethanolic extract of Kaempferia galangal L. shown to impede *M. tuberculosis* H37Ra, H37Rv, drug susceptible, and multidrug-resistant (MDR) clinical isolates (MIC 0.242–0.485 mM). Lignans and flavonoids from Larrea tridentata Coville exhibited MIC in range 12.5–50 mg/mL. From Plectranthus grandidentatus Gurke, royleanone abietanes were isolated with MIC values between 3.12 and 0.39 mg/ml. Plumericin and isoplumericin from chloroform extract Plumeria bicolor Ruiz & Pav. showed MIC values of 2.1 ± 0.12μg/ml and 2.4 ± 0.08μg/ml, respectively. From Diospyros anisandra S.F.Blake, naphthoquinones found to have significant activity with MTB strains (MIC = 1.56–3.33μg/mL). Polyynes neroplomacrol (1), neroplofurol (2), oplopandiol (3), falcarindiol (4), and sesamin (5) were isolated from Oplopanax horridus (Smith) Miq. (Tables 8.2).

8.4 Mechanism of Action of Medicinal Plants in the Treatment of Tuberculosis

8.4.1 Pathophysiology of Tuberculosis

The only recognized source of *Mycobacterium tuberculosis* transmission is human beings. The organism is conveyed through the airborne route through which the lung is the number one target organ for *M. Tuberculosis* [57]. Bacteria are spread via the aerosolization or bacilli-containing droplet nuclei from the infected individual. The macrophages come to be aware of the foreign pathogen and retrieve it via the process called phagocytosis. Then, ensnared and preserved in an enclosed cell membrane referred to as a phagosome [58]. *M. tuberculosis* unexpectedly phagocytized via alveolar macrophages at the same time as it is in the lungs, but they do not kill and wreck the bacterium. Its cellular wall stops the phagosome from integrating with the lysosome, offering some antibacterial components [59]. The gradual development of the *M. tuberculosis* species will attract phagocytic cells in the lungs and rise into premature granulomas. Even so, as the pathogen continues to evolve, the amplified necrotic breakdown of granuloma cells led directly to necrosis, which can escalate to cavitation. When the granuloma cavitates are burst inside the lung, microorganisms migrate out of the body in the atmosphere. Those bacteria are inhaled by healthy people and eventually result in tuberculosis infection [60] (Fig. 8.1).

8.4.2 Current Drugs Therapy and Mechanism of Action

Treatment of tuberculosis over the past couple of years has relied on the use as first-line drugs of antibacterial compounds such as isoniazid, ethambutol, rifampicin, and pyrazinamide and second-line of drugs like fluoroquinolones, thioamides, cycloserine, aminoglycosides, polypeptides, and para-aminosalicylic acid [62]. *M. tuberculosis* pathogens have imparted susceptibility to those antituberculosis drugs. Since *M. tuberculosis* possesses a resistance towards antibiotics and other drugs, it brings a problematic, found to cause mutations

Table 8.2 Plants used for anti-TB activity

Scientific name	Parts used: extract/active compound	Activity	References
Aristolochia taliscana Hook and Arn. (Aristolochiaceae)	Roots: isolation of the Neolignans from hexane extract with bioguided fractionation	Licarin A was isolated which shows excellent MIC of 3.12–12.5μg/mL with M. tuberculosis strains, namely H37Rv, 4 mono-resistant H37Rv, and 12 clinically isolated MDR, and 5 non-tuberculous mycobacterial strains	León-Díaz et al. [16]
Aristolochia brevipes Benth. (Aristolochiaceae)	Rhizome: dichloromethane extract and its fractions yielded eight major compounds	The DCM extract showed antimycobacterial activity with MIC value 12.5μg/mL and extracted bioactive compound, aristolactam observed to have MIC range 12.5 and 25μg/mL	Navarro-García, et al. [17]
Aristolochia elegans Mast. (Aristolochiaceae)	Rhizomes: eupomatenoid-1, fargesin, and cubebin were purified from hexane extract	Fargesin (MIC <50μg/mL) presented antimycobacterial efficiency with H37Rv and an MDR clinically isolated of *M. tuberculosis* (MIC <50μg/mL) strain	Jiménez-Arellanes et al. [18]
Artemisia capillaris Thunb. (Asteraceae)	Aerial parts: ursolic acid UA) and hydroquinone (HQ) were isolated by bioactivity guided fractionation from the methanol extracts	The MIC values of both UA and HQ were found as 12.5μg/ml against the susceptible *M. tuberculosis* strain and 12.5–25μg/ml against MDR/XDR MTB strains	Jyoti et al. [19]
Artemisia afra Jacq. ex wild (Asteraceae)	Dried leaves: artemin and arsubin, sesquiterpene lactones identified from the dichloromethane fractions C8	The isolate fraction C8 reduced replication of M. aurum and M. tuberculosis in a dose-dependent manner with IC50 = 1.9μg/ml and IC50 = 2.0μg/ml, respectively, and an MIC = 10μg/ml	Ntutela et al. [20]
Azorella compacta Phil., A. madreporica Clos. (Apiaceae)	Aerial parts: azorellane and mulinane diterpenoids	Semisynthetic mulinanes and mulinenic acid methyl ester are the excellent mycobacteria tuberculosis inhibitor. Similarly, compound Azorellanes azorellanol, 17-acetoxy-13-α-hydroxyazorellane have MIC values of 12.5μg/mL exhibiting a stronger antimycobacterial effect	María et al. [21]

(continued)

Table 8.2 (continued)

Scientific name	Parts used: extract/active compound	Activity	References
Beilschmiedia tsangii Merr. (Lauraceae)	Leaves: Beilschmin A and B, two lignans isolated exhibited potent antitubercular activities	Beilschmin A and B showed MICs of 2.5 and 7.5 g/mL, respectively	Lenta et al. [22]
Blepharodon nitidum (Vell.) J.F. Macbr. (Asclepiadaceae)	Whole plant: ethanol extract and fractions	In in vitro analysis 24-hydroperoxycycloart-25-en-3β-ol and 25-hydroperoxycycloart-23-en-3β-ol possessed anti-Mycobacterium tuberculosis with MIC of 25μg/mL and 12.5μg/mL, respectively	Aponte et al. [23]
Celastrus vulcanicola Donn. Sm. (Celastraceae)	Leaves: sesquiterpenes and their derivatives exhibited antituberculosis activity against the MDR-TB strain	1α-Acetoxy-6β,9β-dibenzoyloxy-dihydro-β-agarofuran recorded highest antituberculosis activity similar with isoniazid or rifampin with a MIC value of 6.2μg/mL	Torres-romero et al. [24]
Chamaedorea tepejilote Liebm. (Palmae)	Leaves: squalene, farnesol, methylic ester of hexadecanoic acid, beta-sitosterol, and ursolic acid were isolated from hexane extract	Activity against Mycobacterium tuberculosis H37Rv showed ursolic acid, squalene and farnesol to produce a M. tuberculosis growth inhibition of 99% at a concentration of 100 microgram/mL	Jiménez-Arellanes et al. [25]
Citrullus colocynthis (L.) Schrad. (Cucurbitaceae)	Aerial parts and ripe fruit: methanolic extract	Methanolic extract and bioactive fractions IX shown activity against Mycobacterium tuberculosis H37Rv with MIC value of MIC ≤62.5μg/ml and 31.2μg/ml resp	Mehta et al. [26]
Citrus sinensis (L.) Osbeck (Rutaceae)	Fruit peel: monoterpenes, sesquiterpenes, fatty acids, and some other oxygenated non-aromatic compounds were identified from hexane extract	Caryophyllene oxide, decanal, and palmitic acid showed MIC value of 100–200μg/mL, 25–200μg/mL, and 50–100μg/mL, resp	Esquivel-Ferriño et al. [27]
Chrysactinia mexicana A. gray (Asteraceae)	Roots: ethyl extract	The ethyl fraction of roots of C. mexicana was found to have a drug-resistant strain of M. tuberculosis with MIC = 62.5μg/mL	GóMez-CANsiNo et al. [28]
Clavija procera B. Ståhl (Theophrastaceae)		MIC values between 1.6 and 3.12μg/mL versus 37 different sensitive and resistant MTB strains	[29]

	Stems and bark: ethanolic extract yielded oleanane triterpenoid aegicerin as the active constituent		
Curcuma longa L. (Zingiberaceae)	Rhizomes: demethoxycurcumin and its derivatives possess antitubercular activity	Demethoxycurcumin and its derivative compound 6 showed MIC value of 200μg/mL and 7.8μg/mL against mycobacterium tuberculosis H37Rv strain	[30]
Euclea natalensis A.DC. (Ebenaceae)	Roots: naphthoquinones and triterpenes were isolated	Diospyrin and 7-methyljuglone extract observed MIC of 8, 8, and 0.5μg/ml, respectively, with the H37Rv strain of *M. tuberculosis*	[31]
Foeniculum vulgare mill (Apiaceae)	Leaves and stems: bioassay guided fractionation of hexane extract identified 20 compounds in active fractions	Linoleic acid, oleic acid have MIC of 100μg/mL, 1,3-benzenediol reported MIC of 100–200μg/mL, undecanal MIC 50–200μg/mL, and 2,4-undecadienal MIC 25–50μg/mL exhibiting moderate antimycobacterial effect	Esquivel-Ferriño et al. [32]
Justicia adhatoda L. (Acanthaceae)	Leaves: six different quinazoline alkaloids were presented	Alkaloids found to suppress the formation of enzyme β-ketoacyl-acyl-carrier protein synthase III (FabH), which is vital to trigger fatty acid biosynthesis, resulting in poor cell wall synthesis by influencing bacilli survival	Jha et al. [33]
Kaempferia galangal L. (Zingiberaceae)	Rhizomes: ethyl p-methoxycinnamate (EPMC) obtained from ethanolic extract	EPMC demonstrated to suppress strain: *M. tuberculosis* H37Ra, H37Rv, drug susceptible and multidrug-resistant in resazurin microtiter assay, with MIC 0.242–0.485 mM	Lakshmanan et al. [34]
Lantana hispida Kunth (Verbenaceae)	Aerial parts: three pentacyclic triterpenoids with oleanane nucleous were isolated from hexane extracts	Isolated pentacyclic triterpenoids showed MIC value between 25 and 50 mg/mL.	Jiménez-Arellanes et al. [35]
Larrea tridentata Coville. (Zygophyllaceae)	Three lignans and four flavonoids were isolated from chloroformic extract of leaves	Isolated lignans and flavonoids showed MIC value between 12.5 and 50 mg/mL	Favela-Hernández et al. [36]
			Rijo et al. [37]

(continued)

Table 8.2 (continued)

Scientific name	Parts used: extract/active compound	Activity	References
Plectranthus grandidentatus Gurke (Lamiaceae)	Whole plant: royleanone abietanes were isolated from acetone extract	Abietane and its derivatives exhibit against the MDR strain with MIC values between 3.12 and 0.39 mg/ml	
Plumeria bicolor Ruiz and Pav. (Apocynaceae)	Stem bark: plumericin and isoplumericin were extracted from chloroform extract	Plumericin and isoplumericin showed significant activity against H37Rv with MIC values of 2.1 ± 0.12μg/ml and 2.4 ± 0.08μg/ml, resp.	Kumar et al. [38]
Tabernaemontana elegans Stapf. (Apocynaceae)	Roots: ethyl acetate extracts, indole alkaloids are most prominent compound	Ethyl acetate extract portrayed significantly with *M. tuberculosis* H37Rv (MIC 15.6 g/mL)	Luo et al. [39]
Diospyros anisandra S.F. Blake (Ebenacea)	Stem bark: naphthoquinones was from n-hexane crude extract	Plumbagin, 3,3′-biplumbagin, maritinone observed to have efficacy towards both MTB strains with MIC = 1.56–3.33μg/mL	Uc-Cachón et al. [40]
Piper chaba Hunter (Piperaceae)	Stem: n-hexane/chabamide (1) was isolated from the extract	Compound 1 exhibited anti-TB activity with the MIC value of 12.5 μg/ml against H37Ra strain	Rukachaisirikul et al. [41]
Buddleja cordata H.B.K. subsp. cordata (Loganiaceae)	Ground stem and bark: CH2-MeOH (1:1) extract isolated 10 long chain esters	Compound 2[4-hydroxyphenyl]-ethyl behenate exhibited moderate antibacterial activity against mycobacterium tuberculosis (MIC = 64μg/ml)	Acevedo et al. [42]
Humulus lupulus (Cannabaceae)	Whole plant: ethanolic extract	MIC values ranging from 400 to 800μg/ml of alcoholic extract	Serkani et al. [43]
Oplopanax horridus (Smith) Miq. (Araliaceae)	Bark: neroplomacrol, neroplofurol, oplopandiol, falcarindiol, and sesamin isolated from the bark	Polyynes 3 and 4 shown MIC of 61.5 and 6.2μg/mL, respectively	Inui et al. [44]
Abrus precatorius L. (Leguminosae)	Abruquinone B was obtained from the dichloromethane extract of the aerial part	Displays antitubercular activity with MIC of 12.512.5 μg/ml	Limmatvapirat et al. [45]
Abutilon indicum (L.) Sweet (Malvaceae)	Leaves: dichloromethane and methanol/β-amyrin 3-palmitate (1), squalene (2), β-sitosterol (3), and stigmasterol (4) were isolated from the extract	Every compounds exhibited MIC of >128 μg/ml	Macabeo and Lee [46]
Acanthus ebracteatus Vahl. (Acanthaceae)	Chloroform and aqueous methanolic extract of leaves and stem	All extract showed activity with H37Ra strain in MABA at MIC of 1000 μg/ml	Phongpaichit et al. [47]

Aegle marmelos (L.) Correa (Rutaceae)	Fruits and flowers: 90% ethanol	Activities towards H37Rv strain were recorded with 90% ethanol extract in MABA, spanning from 47.8 to >100μg/ml	Elkington et al. [48]
Aloe vera L. (Aloaceae)	Leaves: aqueous methanol extract	The extract revealed activity with the 1600μg/ml MIC against the H37Rv strain	Mohamad et al. [49]
Zingiber zerumbet (L.) (Zingiberaceae)	Rhizome: chloroform, aqueous and methanol extract	Rhizome in MABA asserted repression with MIC of 125, 1000, 1000μg/ml in chloroforms, methanol, water extract versus the H37Ra strain	Phongpaichit et al. [47]
Ziziphus mauritiana Lam. (Rhamnaceae)	Root: mauritine and nummularines extracted from ethanol extracts	The extracted bioactive compound shows activities towards H37Ra with an inhibitory concentration of 72.8μg/ml and 4.5μg/ml, respectively.	Macabeo et al. [50]
Voacanga globosa Merr. (Apocynaceae)	Leaves: dichloromethane and methane/ Globospiramine	The extract shows MIC of 4μg/ml in MABA assay and 5.2μg/ml in low-oxygen recovery assay shows significant antitubercular effect	Macabeo et al. [50]
Tinospora crispa and Thomson (Menispermaceae)	Fruits and flowers: 90% ethanol	The extract observed MIC inhibition of 2.43–96,2μg/ml in micro broth dilution assay	Elkington et al. [48]
Sesbania grandiflora (L.) Poir. (Leguminosae)	Root: methanol/isovestitol (1), medicarpin (2), sativan (3), betulinic acid	The methanol extract showed anti-TB activity against H37Rv with a MIC value of 625μg/ml, compounds 1–3 portrayed MIC of 50μg/ml and compound 4 possessed MIC of 100μg/ml	Hasan et al. [51]
Rhoeo spathacea (Sw.) Stearn (Commelinaceae)	Leaves: 80% methanol	The extract revealed a 100% inhibitory effect with H37Rv and MDR at 5 mg/ml	Radji et al. [52]
Pistia stratiotes L. (Araceae)	Whole plant: 80% methanol	The inhibitory effect towards H37Rv was found to be at MIC 1600μg/ml	Mohamad et al. [49]
Petiveria alliacea L. (Phytolaccaceae)	96% ethanol: leaves	At MIC of 1280μg/ml the ethanol leaf extracts was potent against drug-sensitive and resistant strains of H37Rv	Mulyani et al. [53]
Gynura divaricata (L.) DC. (Asteraceae)	Leaves: hexane, dichloromethane, methanol/ essential oil	The essential oil inhibits H37Ra strain at a MIC of 50 μg/ml	Jiangseubchatveera et al. [54]

(continued)

Table 8.2 (continued)

Scientific name	Parts used: extract/active compound	Activity	References
Morinda citrifolia Linn. (Rubiaceae)	Leaves: ethanol and hexane/(E)-phytol (1), cycloartenol (2), stigmasta-4-en-3-one (3), stigmasta-4-22-dien-3-one(4), β-sitosterol (5), stigmasterol (6), campesta-6,22-dien-5α,8α-epidioxy-3β-ol (7) were isolated from the extract	Both ethanol and hexane extract exhibited 89 and 95% inhibition towards H37Rv strain while conduction bioassay at 100μg/ml concentration. Compound 1, 2, 3, 4, 5, and 6 found to have MIC value 32, 64, 2, 2.5, 128, and 32μg/ml	Saludes et al. [55]
Morus alba L. (Moraceae)	Leaves and fruit: 80% methanol	The extract inhibited H37Rv strain at 1600 mg/ml in the broth microdilution test	Mohamad et al. [49]
Jatropha curcas L. (Euphorbiaceae)	Leaves: 80% methanol	The extract inhibited H37Rv strain at 1600 mg/ml in the broth invivtro test	Mohamad et al. [49]
Glycosmis pentaphylla (Retz.) DC. (Rutaceae)	Fruits and flowers: 90% ethanol	The MIC 93.5 to >100μg/ml in MABA indicated an effect versus H37Rv strain with 90% ethanol extracts of fruit and flowers	Elkington et al. [48]
Flemingia strobilifera (L.) W. T. Aiton (Fabaceae)	Leaves: 80% methanol	The extract demonstrated anti-TB activity in MIC 1600μg/ml versus H37Rv strains	Mohamad et al. [49]
Croton kongensis Gagnep. (Euphorbiaceae)	Whole plants, leaves: ethanol, ethyl acetate, methylene chloride, n-Hexane/ent-1β,7α,14β-triacetoxykaur-16-en-15-one (1), ent-7α,18-dihydroxykaur-16-en-15-one (2), ent-16(S)-18-acetoxy-7α- hydroxykaur-15-one (3), ent-18-acetoxy-7α-hydroxykaur-16-en-15-one (4), ent-1β,14β-diacetoxy-7α-hydroxykaur-16-en-15-one (5), ent-1β-acetoxy-7α,14β-dihydroxykaur-16-en-15-one (6), ent-7α,14β-dihydroxykaur-16-en-15-one (7) were all isolated from ethanol, ethyl acetate, methylene extract of whole plants and leaves	All crude extract fractions of methylene chloride, ethyl acetate, n-Hexane possess an antitubercular effect. Compound 1 was observed to have a stronger affinity with MIC values of 0.78, 1.56, 3.12–12.5μg/ml while the rest of the compound is comprised of MIC spanning between 1.56–6.25μg/ml towards H37Ra and H37Rv and other resistant strains of tuberculosis	Jang et al. [56]
Coccinia grandis (L.) Voigt (Cucurbitaceae)	Leaves: chloroform methanol water	In both extracts, leaves show significant activity towards tuberculosis strain with MIC 1000μg/ml	Phongpaichit et al. [47]

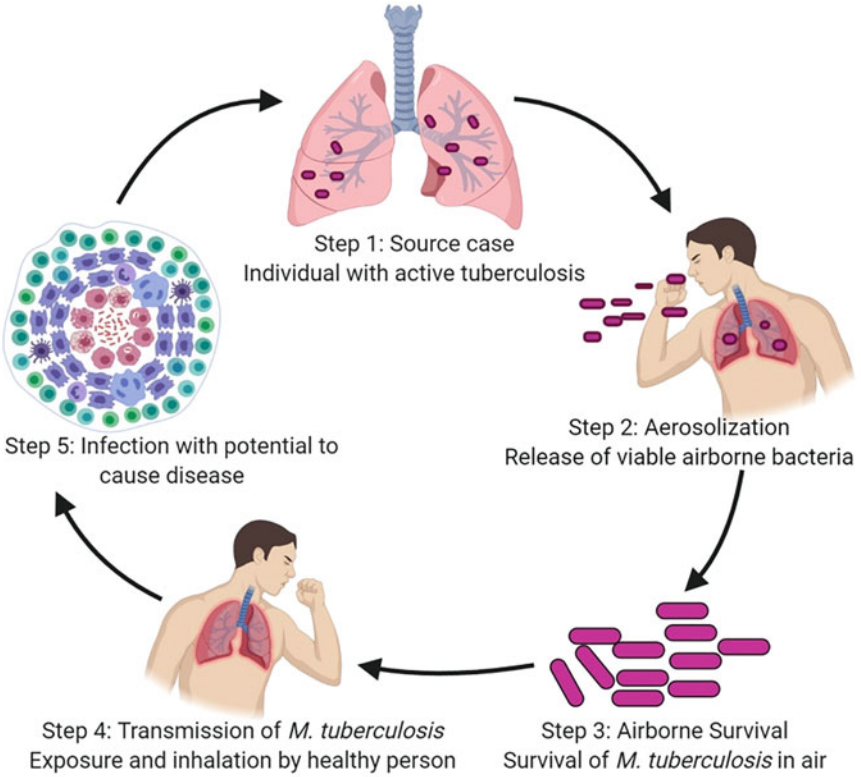


Fig. 8.1 Pathophysiology of tuberculosis [61]

which bring access to a particular form of multidrug-resistant tuberculosis (MDR-TB). Consequently, the cure for the illness is exceedingly complicated [63] (Tables 8.3 and 8.4).

8.4.3 Mode of Actions of Phytochemicals Against Tuberculosis

8.4.3.1 Alkaloids

In the exploration of the novel leading medicinal drug, the screening of the metabolites from the natural products plant extract is a pioneering technique. Alkaloids are the low molecular nitrogen weight compound, solely present in the different parts of the plant. Alkaloids are persistently engaged in the defense system towards pathogens as well as herbivores in plants [66]. The antimycobacterial efficacy is found in several alkaloids such as 3-methylcarbazole, lansine, and 3-formyl-6-methoxycarbazole derived from the bark and stem of *Micromelum hirsutum* employing silica gel chromatography. In fluorometric microplate Alamar

Table 8.3 Classification of antituberculosis drugs. [64]

First-line drugs	Second-line drugs			Third-line drugs
Group 1	Group 2	Group 3	Group 4	Group 5
Rifamycins Isoniazid Rifampicin Rifampin Pyrazinamide Ethambutol Rifapentine Rifabutin	Streptomycin Injectable aminoglycosides Kanamycin Injectable polypeptides Amikacin Injectable polypeptides Viomycin Capreomycin	(Fluoroquinolones) Moxifloxacin Ofloxacin Levofloxacin Ciprofloxacin Gatifloxacin	Cycloserine Para-aminosalicylic acid Ethionamide Prothionamide Terizidone	Clofazimine Clarithromycin Imipenem plus cilastatin Linezolid Thioacetazone Amoxicillin plus clavulanate

blue assay, alkaloids such as 3-formylcarbazole, 3-formyl-6-methoxycarbazole show better antimycobacterial efficacy with the minimum inhibitory concentration (MIC) of 14.3–42.3μg/mL [67, 68].

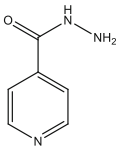
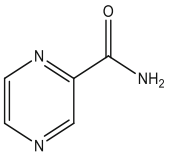
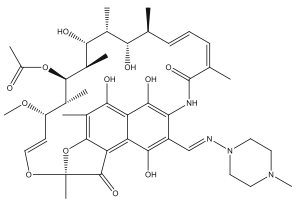
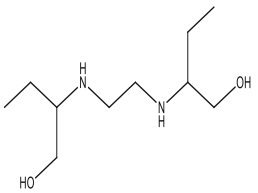
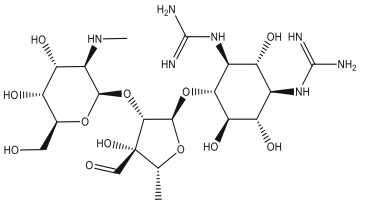
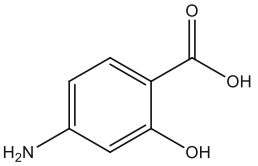
Quinoline alkaloids, such as graveolinine, kokusagine, and 4-methoxy-2-phenylquinoline isolated from the Lunasia amara herb, reported notable in vitro activity towards *M. tuberculosis* H37Rv strain possessed 16μg/mL MIC value. C-2 aryl functionality of the quinoline framework enables the alkaloids to improve inhibitory activity against *M. tuberculosis*. The methoxy group substituted by C-4 boosts the bioactivity of quinoline alkaloids [69]. Bogaine and voacangine are the pentacyclic indole alkaloids extracted from *Tabernaemontana citrifolia* that portrays a significant action versus *M. tuberculosis* which possesses 50–100μg/mL MIC [70]. Metabolite-isolated azaanthraquinone alkaloids from the *Mitracarpus scaber* plant demonstrated action towards *M. intracellulare* with MIC values of 6.25μg/mL. Berberine, an alkaloids is found in several families like Annonaceae, Berberidaceae, Menispermaceae, manifested antimycobacterial efficacy with a MIC of 0.78–1.56μg/mL against *M. intracellulare* [71]. The metabolite hindered the development of *M. tuberculosis* and *M. smegmatis* at a MIC of 25μg/mL. SAR experimental studies on some structurally linked alkaloids of benzo[c]-phenanthridine plants, such as chelirubine, nitidine, sanguinarine, chelerythrine, and macarpine, have shown a substantial inhibitory effect ≥94%at 12.5μg/mL with *M. tuberculosis* H37Rv strain. Convincingly, the addition of alcohol as a functional group of methoxy or methylenedioxy serves a pivotal antitubercular function of alkaloids (Fig. 8.2).

8.4.3.2 Mode of Action of Alkaloids

8.4.3.3 Phenolic and Flavonoids

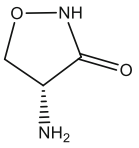
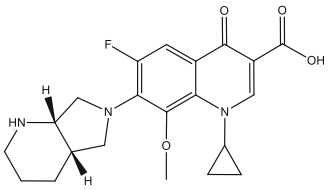
The innate susceptibility in bacteria is due to the permeability of the cell wall as well as efflux pump systems that transfer only selective solutes to penetrate the bacteria and retract foreign compounds in bacteria. In providing inherent resistance against

Table 8.4 Current therapeutic approach use in tuberculosis treatments and their mode of action. [65]

Chemical class of compound (example)	Representative structure	Mode of action
Pyridines (isoniazid)		Isoniazid drugs inhibit the mycolic acid formation
Pyrazines (pyrazinamide)		Pyrazinamide drugs may suppress the synthesis of fatty acids
Rifamycins (rifampin)		Rifampin inhibits the RNA synthesis by binding b-subunit of bacterial DNA–dependent RNA polymerase
Bis-amino alcohols (ethambutol)		Ethambutol inhibits arabinosyl transferases used in arabinoglycan polymerization (cell wall)
Aminoglycosides (streptomycin)		Streptomycin inhibits the protein synthesis by binding with the 30S ribosomal subunit
Phenolic acids (p-aminosalicylic acid)		They suppress folate synthesis

(continued)

Table 8.4 (continued)

Chemical class of compound (example)	Representative structure	Mode of action
Cyclic amino acids (cycloserine)		They have similar actions like D-alanine and act as a barrier to cell wall development
4-quinolones (moxifloxacin)		Moxifloxacin restricts the synthesis of DNA by the inhibitory activity of topoisomerase II/IV

damaging impact, proteasome serves a key role in tuberculosis. Thus, *M. tuberculosis* proteasome is a logical target for novel natural anti-TB drugs against tuberculosis. Phenolic compounds can function as a vector for a proteasome inhibitor [73]. In flavonoids, some natural proteasome inhibitors like baicalein, pectolinarin, quercetin, kaempferol, curcumin, and myricetin are observed [74].

Curcumin has a high pleiotropic property and is a potential activator of apoptosis, resulting from its capacity to modulate multiple signaling molecules. Apoptosis, assessed by an in vitro model of tuberculosis in macrophages, is a mechanism used by the host to suppress intracellular *M. tuberculosis* [75]. The latest studies have shown that curcumin nanoparticles along with isoniazid have substantially reduced hepatotoxicity by improved immunity mediated by T-cells in mice. The analysis found that curcumin nanoparticles were effective in reducing the risk of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) as a beneficial adjuvant treatment [76]. It indicates that curcumin possesses blocking effects against daunorubicin-induced nephrotoxicity in rats by restricting the proliferation of daunorubicin-induced M1 macrophages by a probable mechanism of disrupting cell membranes of *M. tuberculosis* [77].

The vital enzymes in nitrogen metabolism and binding to host cells in *tuberculosis* are glutamine synthase and isocitrate lyase. By using glutamine synthetase, quercetin was reported to inhibit all three strains of Mtb H37Rv, smegmatis, and phlei [78]. By employing fluorescence quenching, pocket detection algorithm, Lineweaver–Burk plots, and blind docking methodologies, quercetin was found to curtail *M. tuberculosis* isocitrate lyase, resulting in an enhanced inhibitory effect on *M. tuberculosis* metabolism [79]. The ethyl acetate leaf fraction of *Piper sarmentosum Roxb* demonstrated to have induced pharmacodynamic effects. This effect was observed by using the microplate tetrazolium (MTT) assay in vitro model with MIC of 3.12μg/mL. The outcome suggests that by exhibiting a promising anti-

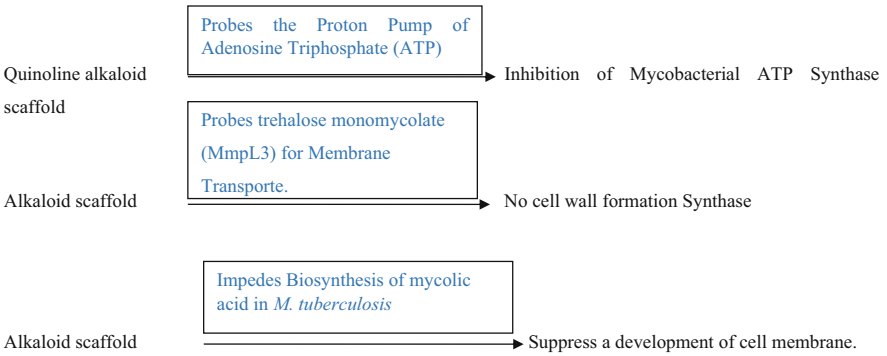


Fig. 8.2 Mode of actions of alkaloids against *M. tuberculosis* [72]

TB function, the ethanol acetate fraction of the methanol leaf extract influences the cellular level [80, 81].

Phenolic compounds such as dihydrocubebin, hinokinin, ethoxycubebin possess antimycobacterial activity. When ethoxycubebin was handled for 24 h against *M. tuberculosis* H37Rv strain bacteria, it induced a spectacular decrease in mycolic acids, supporting the abnormal structure of bacteria with unusual and disorganized form. It concluded that lignans had a promising potential as antimycobacterial agents that had an impact on the metabolism of mycolic acid [82].

The inhibitory action of its constituent polyphenol epigallocatechin gallate (EGCG) on cell signaling has intriguingly included a polyphenolic compound present in green tea, like catechins, theaflavins, and thearubigins. Alternative treatment approaches to treat tuberculosis could be EGCG interfered with the binding of NADH to InhA. The analysis revealed that the oral administration of green tea plant extract in mice diagnosed with *M. tuberculosis* resulted in reduced concentrations of erythrocyte GSH (glutathione) caused by the infection [83].

8.4.3.4 Coumarins

There are various types of coumarins with distinct health capabilities; antituberculosis effectiveness is obtained by dihydrofurano, simple coumarins, and linear coumarin varieties. In the *Fatoua pilosa* plant, the antimycobacterial action of coumarins is shown by the medium pressure liquid chromatography process, which was isolated via thin layer chromatography, found effective in tuberculosis treatment [84]. The antimycobacterial ability of prenylated coumarins and prenylated furanocoumarins has been identified [85]. The results of our antibacterial observations may be linked to the coumarin ring since it is understood that these natural compounds demonstrate their impact by preventing the development of nucleic acid bacteria. It has been shown that the insertion of a prenyl group to the furanocoumarin framework facilitates the lipophilicity of the molecule, enabling its passage via the thick bacterial membrane to its target [86].

8.4.3.5 Quinones

Two compounds obtained from *Artemisia capillaries*, including ursolic acid (UA) and hydroquinone, exemplify in vitro propensity to *M. tuberculosis* strains with a MIC of 12.5μg/mL and an MDR/XDR strain of 12.5–25μg/mL in bioassay fractionation. UA inhibits the biosynthesis of mycolytic acid in strain *M. tuberculosis* H37Ra, resulting in a mycobacterium cell death. Naphthoquinones isolated from *Diospyros anisandra*, specifically 3,30-biplumbagin and, maritinone reveal absence of toxicity in eukaryotic cells and have 32 times greater efficacy with strains of MDR-TB. It has been observed, in aspects of the mode of action, that naphthoquinones influences the mycobacterium electron transport chain since they have similar structure to menaquinone. Furthermore, menaquinone biosynthesis can also be hindered, interfering with the transport of electrons and cellular respiration. Three naphthoquinones 3,3′-biplumbagin, maritinone, and plumbagin recorded the high MIC of 1.56–3.33μg/mL [87, 88].

8.4.3.6 Terpenes

Parthenolide has massive antibacterial properties with a value of MIC 16μg/mL. Parthenolide's better antimycobacterial efficacy can be associated with its molecular framework as it consists of two alkylation sites where the electron-poor center is shaped by transannular cyclization with the donor at C-1 double bond and the nucleophilic receptor at C-5 epoxide [89]. The most efficient terpenoid or diterpenoid 12-demethylmulticauline, derived from the roots of *Salvia multicaulis* possesses 0.46μg/mL MIC. Enthralling, it has greater potential efficacy than the first-line tuberculosis drug ethambutol and almost as active as rifampin in the treatment of tuberculosis [90]. In vitro intracellular and in vivo synergistic effects are shown by the amalgamation of triterpenoid ursolic acid (3β-hydroxy-urs-12-en-28-oic-acid) and oleanolic acid (3β-hydroxy-olea-12-en-28-oic acid). Both acids have an efficacious antilipidic action on eukaryotic cells that generate substantial features in cell wall of the bacterial. A mycobacterium that destroys the lipid-rich complex cell envelope may be impaired by antilipidic action [91].

Diterpenes escobarine A and escobarine B derived from the *Calliandra californica* root, which was further characterized by the use of column chromatography and vacuum liquid chromatography. Both terpenoids exhibited significant inhibitory properties with *M. tuberculosis* strains in the MABA assay [92]. Polyketide synthases (PKSs) have been linked directly to the biosynthesis of composite lipids in mycobacteria or maybe some PKS mutants demonstrate receding in mycobacterial virulence abilities. Molecular docking study reveals the PKS retarding activity of vulgarin and alisiaquinone. In molecular docking, vulgarin exhibited the highest binding affinity potential for PKS with −7.95 Kcal/mol, which is ~1.4 and ~ 6.11 times stronger than that of the standard drug isoniazid −6.00 Kcal/mol and rifampicin −1.3 Kcal/mol, respectively, and comparable binding energy for alisiaquinone A is observed to be −7.86 Kcal/mol. Strong affinity efficiency is attributed to the low value of molecular binding energy. The data demonstrate that inhibiting PKS can require a much lower concentration of vulgarin and alisiaquinone A [93, 94].

8.4.3.7 Mechanism

The different molecular targets against *M. tuberculosis* comprises of synthesis of bacteria cell wall, energy and folate metabolism, DNA replication and RNA synthesis [95]. *M. tuberculosis* complex consists of nine different bacterial members that are responsible for tuberculosis. One of the reasons it can spread more is since it can tolerate some of the common disinfectants and also remain alive in dry states for several weeks. This bacterium can transmit from one person to another via air droplets [96].

The prevalence of mycolic acids is covalently attached to the peptidoglycan surface of the cell wall wrapper (60–90 carbon in length). Mycolic acids and multimethyl-branched fatty acids are prominent in the *M. tuberculosis* cell wall [97]. These incredible longer fatty acids are integral for the survival, pathogenicity, and susceptibility of *M. tuberculosis* to antibiotics. Mycobacterial cell envelope antagonists have been shown to obstruct the synthesis of mycolic acids, arabinogalactan, and peptidoglycan, essential components of the mycobacterial cell wall [98]. The paramount antituberculous drugs hamper the development of mycolic acids or the aid mechanism which links them to the cell membrane. Functional tasks taking part in DNA replication entail initiators of mDNA gyrases and DNA replication. Medicines targeting RNA synthesis encompass those that restrict the assembly of bacterial DNA-dependent RNA polymerases, that are indispensable enzymes for RNA synthesis [99].

The supply of oxygen is requisite for the development of *M. tuberculosis*. *M. tuberculosis* bacteria have an elevated accumulation of lipids in their wall, such that no bacteriological stain is needed. *M. tuberculosis* is also gradually developing and acquiring immunity for pharmaceutical drugs as *M. tuberculosis* is self-equipped; they ingest the drug by modifying their receptor type as per the chemical makeup of medicines [100]. In order to interact with bacterial metabolism, all bacteria consuming energy from nutrient such as folate to work by oxidative phosphorylation (conversion of chemical energy from different sources of ATP) may be changed in *M. tuberculosis* [101]. Diarylquinolones are synthetic compounds extracted from natural quinolones that can interact with the formation of mycobacterial energy by binding and impeding ATP synthase, culminating in a pH homeostasis deficit, and eventually contributing to cell death. A recent, efficient, and effective approach to the development of antimycobacterial drugs is thus aimed at energy metabolism [102]. The DARQ class's exploration depicts a possible route in the analysis of TB drugs. Diarylquinolines directly suppress mycobacterial ATP synthase and show a high degree of action towards both drug and multidrug-resistant *M. tuberculosis* strains [103] (Fig. 8.3).

8.4.3.8 Safety of Medicinal Plants Use in Tuberculosis Treatment

Secondary metabolites are extracted from an herb that has been used widely since ancient times in conventional therapeutic methods for the treatment of different diseases [105]. Plants are enriched in various bioactive phytochemicals like alkaloids, terpenoids, and polyphenols that are important to build immunity. Phytochemicals play a significant role in combating ailments, such as cancer,

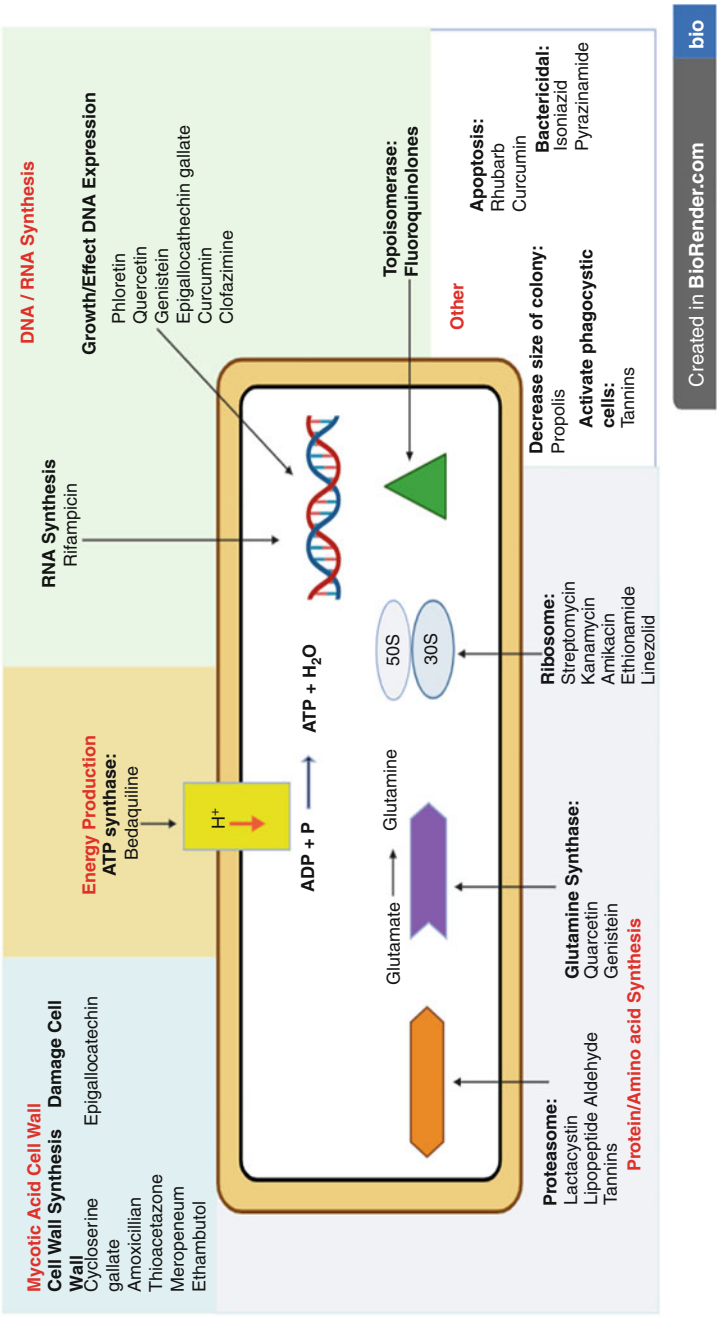


Fig. 8.3 The mechanisms of different anti-TB drugs and natural compounds [104]

Table 8.5 Problems associated with current drug therapy [110]

Compounds	Adverse effect
Isoniazid	Eye problems, neuritis hepatitis
Pyrazinamide	Hepatitis, arthralgia
Cycloserine	Convulsions, headache, depression, dizziness, psychotic reactions
Rifampicin	Pain, nausea, vomiting, hepatitis, thrombocytopenia
Streptomycin	Vestibular and auditory nerve damage, renal damage
Thioacetazone	Skin rash, exfoliative dermatitis
Ethionamide	Eye problems, neuritis
Ethambutol	Diarrhea, hepatotoxicity abdominal pain
Kanamycin	Vertigo, nephrotoxicity, auditory nerve damage

tuberculosis, asthma, coronary heart disease, etc. [106, 107]. In an attempt to allow ability with strains resistant to regular anti-TB medicines, phytochemicals have a couple of modes of action. Both forms of *M. tuberculosis* that predominant in clinical TB (whether extracellular or intracellular and replicating or dormant mycobacteria) are to be eradicated by medicines to create proper therapy [108]. In the early stages of TB, there could be intense oxidative pressure, and antioxidants may play a crucial role in mitigating stress by adjuvant remedies [109]. There are several adverse effects arise due to the standards drugs some of them are listed in Table 8.5.

However, medicinal plants have huge benefits in maintaining the health of tuberculosis patients with very minimal side effects. A polyphenols curcumin is an innovative alternative to tuberculosis treatment since it is affordable and easy-to-obtain from natural ingredients. Relying on several clinical studies, curcumin delivered to individuals at doses of 4–12 g per day has no reported toxicity, and the immunomodulatory impact of curcumin on host cells ought to be generally resistant to the production of *M. tuberculosis* drug resistance [111]. In the treatment of tuberculosis, plant *Annona sylvatica* is often used. Ethyl acetate extract extracted from *A. sylvatica* demonstrated no reported toxicity in Swiss mice when orally fed. Research has also found an increase in the excess weight of mice in treated mice; however, no apparent side effects or toxicity have been detected [112].

Firstly, it is crucial to analyze the levels of cytotoxic effects of medicinal plants to ascertain their effectiveness. The *Cissampelos pareira* root has antimycobacterial effects and is ingested orally. Cytotoxicity (CC50) of 5.22 and 55.0μg/mL, respectively, was found in ethyl acetate and dichloromethane extract of *C. pareira.* Besides that, in the petroleum ether fraction and methanolic fractions cytotoxicity is not reported [113]. It has been shown that many first-line and second-line drugs used in tuberculosis treatment have hepatotoxic effects. Garlic, silymarin, and several other herbal products are taken alone or with synthetic compounds to mitigate the hepatotoxic effect. So without intervening with the therapeutic activities of the drugs, they eradicate the damaging effect. In animal models, both garlic and silymarin are effective, and no substantial toxic effects have been documented in human trials [114].

Antimycobacterial activity is demonstrated by natural terpenes: alpha-pinene, (R)-limonene, (S)-limonene, bisabolol, myrcene, and β-elemene. An experiment to determine cytotoxicity was conducted in GMK cells (monkey kidney epithelial cells) where (R)-limonene and alpha-pinene observed no toxic effect even at high concentrations assessed at 500μg/mL. Whereas bisabolol at a concentration of 71.12μg/mL had mild cytotoxicity against GMK cells [115]. Artemisinin, and its semisynthetic derivatives called artesunate, is derived from the herb *Artemisia annua*. Two separate doses of artesunate (1.75 mg/kg) and artemisinin (3.5 mg/kg) were administered orally for 4 weeks in six-week-old female rats. Two of these compounds exhibit no toxicity in this in vivo model. These compounds, which demonstrated their antituberculosis function, have been found to impair the production of *M. tuberculosis* [116].

8.5 Conclusion

Human beings have been the only known source of *M. tuberculosis* transmission. These bacteria are breathed by healthy individuals and inevitably result in tuberculosis infection. *M. tuberculosis* imparts resistance to first and second-line antituberculosis drugs resultant in complex treatment therapy. Plants are abundant with a myriad of bioactive phytochemicals that are incredibly important for the normal functioning of the immune system, such as alkaloids, terpenoids, and polyphenols. The extraction of metabolites from the plant derives of natural products is a groundbreaking technology in the discovery and exploration of the potential leading medicinal drugs. Various molecular pathways for the target to cure tuberculosis entail the targets of *M. tuberculosis* cell wall synthesis, energy metabolism, folate metabolism, DNA replication, and RNA synthesis. Interestingly, in preserving the health of patients diagnosed with tuberculosis, medicinal plants have tremendous advantages with limited side effects as compared to the standard drugs.

References

1. Dheda K, Barry CE, Maartens G (2016) Tuberculosis. Lancet 387(10024):1211–1226. https://doi.org/10.1016/s0140-6736(15)00151-8
2. Comas I, Coscollá M, Luo T, Borrell S, Holt K, Kato-maeda M et al (2013) Out-of-Africa migration and Neolithic co-expansion of Mycobacterium tuberculosis with modern humans. Nat Genet 45:1176–1182. https://doi.org/10.1038/ng.2744
3. Ryan F (1994) The forgotten plague: how the battle against tuberculosis was won—and lost. Little brown & co, Boston, MA
4. WHO (2020) Global tuberculosis report. https://www.who.int/tb/publications/global_report/TB20_Exec_Sum_20201022.pdf?ua=1
5. Lawn SD, Zumla AI (2011) Tuberculosis. Lancet 378(9785):57–72. https://doi.org/10.1016/s0140-6736(10)62173-3
6. Raviglione M, Harries A, Msiska R, Wilkinson D, Nunn PJA (1997) Tuberculosis and HIV: current status in Africa. AIDS 11(Suppl B):S115–S123

7. Falzon D, Schünemann HJ, Harausz E, González-Angulo L, Lienhardt C, Jaramillo E, Weyer KJERJ (2017) World health organization treatment guidelines for drug-resistant tuberculosis, 2016 update. Eur Respir J 49(3):1602308
8. Nachega JB, Chaisson RE (2003) Tuberculosis drug resistance: a global threat. Clin Infect Dis 36(Suppl_1):S24–S30. https://doi.org/10.1086/344657
9. Arya V, Baba A, Singh A, Memorial J (2011) A review on anti-tubercular plants. Int J PharmTech Res 3(2):872–880
10. Copp BR (2003) Antimycobacterial natural products. Nat Prod Rep 20(6):535–557
11. Mangwani N, Singh PK, Kumar V (2019) Medicinal plants: adjunct treatment to tuberculosis chemotherapy to prevent hepatic damage. J Ayurveda Integr Med 11(4):522–528. https://doi.org/10.1016/j.jaim.2019.02.004
12. Newton SM, Lau C, Wright CWJPR (2000) A review of antimycobacterial natural products. Phytother Res 14(5):303–322
13. Okunade AL, Elvin-Lewis MP, Lewis WHJP (2004) Natural antimycobacterial metabolites: current status. Phytochemistry 65(8):1017–1032
14. Sanusi SB, Abu Bakar MF, Mohamed M, Sabran SF, Mainasara MM (2017) Southeast Asian medicinal plants as a potential source of antituberculosis agent. Evid Based Complement Alternat Med 2017:7185649. https://doi.org/10.1155/2017/7185649
15. Chinsembu KCJAT (2016) Tuberculosis and nature's pharmacy of putative anti-tuberculosis agents. Acta Trop 153:46–56
16. León-Díaz R, Meckes M, Said-Fernández S, Molina-Salinas GM, Vargas-Villarreal J, Torres J et al (2010) Antimycobacterial neolignans isolated from Aristolochia taliscana. Mem Inst Oswaldo Cruz 105(1):45–51
17. Navarro-García V, Luna-Herrera J, Rojas-Bribiesca G, Álvarez-Fitz P, Rios Gomez Y (2011) Antibacterial activity of aristolochia brevipes against multidrug-resistant mycobacterium tuberculosis. Molecules 16:7357–7364. https://doi.org/10.3390/molecules16097357
18. Jiménez-Arellanes A, León-Díaz R, Meckes M, Tapia A, Molina-Salinas G, Luna-Herrera J, Yépez-Mulia L (2012) Antiprotozoal and Antimycobacterial Activities of Pure Compounds from Aristolochia elegans Rhizomes. Evid Based Complement Alternat Med 2012:593403. https://doi.org/10.1155/2012/593403
19. Jyoti MA, Nam KW, Jang WS, Kim YH, Kim SK, Lee BE, Song HY (2016) Antimycobacterial activity of methanolic plant extract of Artemisia capillaris containing ursolic acid and hydroquinone against Mycobacterium tuberculosis. J Infect Chemother 22 (4):200–208. https://doi.org/10.1016/j.jiac.2015.11.014
20. Ntutela S, Smith P, Matika L, Mukinda J, Arendse H, Allie N et al (2009) Efficacy of artemisia afra phytotherapy in experimental tuberculosis. Tuberculosis 1(Suppl 1):S33–S40. https://doi.org/10.1016/s1472-9792(09)70009-5
21. María GMS, Borquez J, Ardiles A, Said-Fernández S, San-Martín A et al (2010) Bioactive metabolites from the Andean flora. Antituberculosis activity of natural and semisynthetic azorellane and mulinane diterpenoids. Phytochem Rev 9:271–278. https://doi.org/10.1007/s11101-010-9162-4
22. Lenta BN, Chouna JR, Nkeng-Efouet PA, Sewald N (2015) Endiandric Acid Derivatives and Other Constituents of Plants from the Genera Beilschmiedia and Endiandra (Lauraceae). Biomol Ther 5(2):910–942. https://doi.org/10.3390/biom5020910
23. Aponte J, Estevez Y, Gilman R, Lewis W, Rojas R, Sauvain M et al (2008) Anti-infective and cytotoxic compounds present in Blepharodon nitidum. Planta Med 74:407–410. https://doi.org/10.1055/s-2008-1034330
24. Torres-romero D, Jiménez I, Rojas R, Gilman R, López M, Bazzocchi I (2011) Dihydro-β-agarofuran sesquiterpenes isolated from Celastrus vulcanicola as potential anti-Mycobacterium tuberculosis multidrug-resistant agents. Bioorgan Med Chem 19:2182–2189. https://doi.org/10.1016/j.bmc.2011.02.034

25. Jiménez-Arellanes A, Meckes M, Alvarez V, Torres J, Parra R (2005) Secondary Metabolites from Chamaedora tepejilote (Palmae) are Active against Mycobacterium tuberculosis. Phytother Res 19:320–322. https://doi.org/10.1002/ptr.1664
26. Mehta A, Srivastva G, Kachhwaha S, Sharma M, Kothari S (2013) Antimycobacterial activity of citrullus colocynthis (L) Schrad against drug sensitive and drug resistant Mycobacterium tuberculosis and MOTT clinical isolates. J Ethnopharmacol 149(1):195–200. https://doi.org/10.1016/j.jep.2013.06.022
27. Esquivel-Ferriño PC, Clemente-Soto AF, Ramírez-Cabriales MY, Garza-González E, Álvarez L, Camacho-Corona MDR (2014) Volatile constituents identified in hexane extract of Citrus sinensis peel and anti-mycobacterial tuberculosis activity of some of its constituents. J Mexican Chem Soc 58(4):431–434
28. GóMez-CANsiNo R, GUZMÁN-GUTIÉRREZ SL, CAMPOS-LARA MG, ESPITIA-PINZÓN CI, Reyes-Chilpa R (2017) Natural compounds from mexican medicinal plants as potential drug leads for anti-tuberculosis drugs. An Acad Bras Cienc 89(1):31–43
29. Rojas R, Caviedes L, Aponte JC, Vaisberg AJ, Lewis WH, Lamas G et al (2006) Aegicerin, the first oleanane triterpene with wide-ranging antimycobacterial activity isolated from Clavija procera. J Nat Prod 69(5):845–846
30. Agrawal D, Saikia D, Tiwari R, Ojha S, Shanker K, Jonnala K et al (2008) Demethoxycurcumin and its semisynthetic analogues as antitubercular agents. Planta Med 74:1828–1831. https://doi.org/10.1055/s-0028-1088335
31. Lall N, Meyer JJM, Wang Y, Bapela NB, van Rensburg CEJ, Fourie B, Franzblau SG (2005) Characterization of Intracellular Activity of Antitubercular Constituents the Roots of Euclea natalensis. Pharm Biol 43(4):353–357. https://doi.org/10.1080/13880200590951829
32. Esquivel-Ferriño PC, Favela-Hernández JM, Garza-González E, Waksman N, Ríos MY, del Rayo Camacho-Corona M (2012) Antimycobacterial activity of constituents from Foeniculum vulgare var. dulce grown in Mexico. Molecules 17(7):8471–8482. https://doi.org/10.3390/molecules17078471
33. Jha D, Panda L, Pandian L, Ramaiah S, Anbarasu A (2012) Detection and confirmation of alkaloids in leaves of justicia adhatoda and bioinformatics approach to elicit its anti-tuberculosis activity. Appl Biochem Biotechnol 168(5):980–990. https://doi.org/10.1007/s12010-012-9834-1
34. Lakshmanan D, Werngren J, Jose L, Kp S, Nair M, Varma R et al (2011) Ethyl p-methoxycinnamate isolated from a traditional anti-tuberculosis medicinal herb inhibits drug resistant strains of Mycobacterium tuberculosis in vitro. Fitoterapia 82:757–761. https://doi.org/10.1016/j.fitote.2011.03.006
35. Jiménez-Arellanes A, Meckes M, Torres J, Luna-Herrera J (2007) Antimycobacterial triterpenoids from Lantana hispida (Verbenaceae). J Ethnopharmacol 111:202–205. https://doi.org/10.1016/j.jep.2006.11.033
36. Favela-Hernández JM, García A, Garza-González E, Rivas-Galindo VM, Camacho-Corona MR (2012) Antibacterial and antimycobacterial lignans and flavonoids from Larrea tridentata. Phytother Res 26(12):1957–1960. https://doi.org/10.1002/ptr.4660
37. Rijo P, Simões MF, Francisco AP, Rojas R, Gilman RH, Vaisberg AJ et al (2010) Antimycobacterial metabolites from plectranthus: royleanone derivatives against Mycobacterium tuberculosis strains. Chem Biodivers 7(4):922–932
38. Kumar P, Singh A, Sharma U, Singh D, Dobhal M, Singh S (2013) Anti-mycobacterial activity of plumericin and isoplumericin against MDR Mycobacterium tuberculosis. Pulm Pharmacol Ther 26(3):332–335. https://doi.org/10.1016/j.pupt.2013.01.003
39. Luo X, Pires D, Aínsa JA, Gracia B, Mulhovo S, Duarte A et al (2011) Antimycobacterial evaluation and preliminary phytochemical investigation of selected medicinal plants traditionally used in Mozambique. J Ethnopharmacol 137(1):114–120. https://doi.org/10.1016/j.jep.2011.04.062
40. Uc-Cachón AH, Borges-Argáez R, Said-Fernández S, Vargas-Villarreal J, González-Salazar F, Méndez-González M et al (2014) Naphthoquinones isolated from Diospyros

anisandra exhibit potent activity against pan-resistant first-line drugs Mycobacterium tuberculosis strains. Pulm Pharmacol Ther 27(1):114–120. https://doi.org/10.1016/j.pupt.2013.08.001
41. Rukachaisirikul T, Prabpai S, Champung P, Suksamrarn A (2002) Chabamide, a novel piperine dimer from stems of Piper chaba. Planta Med 68(9):853–855. https://doi.org/10.1055/s-2002-34410
42. Acevedo L, Martínez E, Castañeda P, Franzblau S, Timmermann B, Linares E, Mata R (2000) New phenylethanoids from Buddleja cordata subsp. cordata. Planta Med 66:257–261. https://doi.org/10.1055/s-2000-8570
43. Serkani JE, Isfahani BN, Safaei HG, Kermanshahi RK, Asghari G (2012) Evaluation of the effect of Humulus lupulus alcoholic extract on rifampin-sensitive and resistant isolates of Mycobacterium tuberculosis. Res Pharm Sci 7(4):235–242
44. Inui T, Wang Y, Nikolić D, Smith D, Franzblau S, Pauli G (2010) Sesquiterpenes from Oplopanax horridus. J Nat Prod 73:563–567. https://doi.org/10.1021/np900674d
45. Limmatvapirat C, Sirisopanaporn S, Kittakoop P (2004) Antitubercular and Antiplasmodial Constituents of Abrus precatorius. Planta Med 70:276–278. https://doi.org/10.1055/s-2004-818924
46. Macabeo APG, Lee CAJPJ (2014) Sterols and triterpenes from the non-polar antitubercular fraction of. Abutilon Indicum 6(4):49–52
47. Phongpaichit S, Vuddhakul V, Subhadhirasakul S, Wattanapiromsakul CJPB (2006) Evaluation of the antimycobacterial activity of extracts from plants used as self-medication by AIDS patients in Thailand. Pharm Biol 44(1):71–75
48. Elkington BG, Sydara K, Newsome A, Hwang CH, Lankin DC, Simmler C et al (2014) New finding of an anti-TB compound in the genus Marsypopetalum (Annonaceae) from a traditional herbal remedy of Laos. J Ethnopharmacol 151(2):903–911
49. Mohamad S, Zin NM, Wahab HA, Ibrahim P, Sulaiman SF, Zahariluddin ASM, Noor SSM (2011) Antituberculosis potential of some ethnobotanically selected Malaysian plants. J Ethnopharmacol 133(3):1021–1026
50. Macabeo APG, Vidar WS, Chen X, Decker M, Heilmann J, Wan B et al (2011) Mycobacterium tuberculosis and cholinesterase inhibitors from Voacanga globosa. Eur J Med Chem 46 (7):3118–3123
51. Hasan N, Osman H, Mohamad S, Chong WK, Awang K, Zahariluddin ASMJP (2012) The chemical components of Sesbania grandiflora root and their antituberculosis activity. Pharmaceuticals 5(8):882–889
52. Radji M, Kurniati M, Kiranasari AJJ o APS (2015) Comparative antimycobacterial activity of some Indonesian medicinal plants against multi-drug resistant Mycobacterium tuberculosis. Pharm Biol 5(1):019–022
53. Mulyani Y, Sukandar E, Adnyana I (2012) Petiveria alliacea: new alternative for the treatment of sensitive and multi-resistant Mycobacterium tuberculosis. J Pharmacog Phtother 4(7):91–95
54. Jiangseubchatveera N, Liawruangrath B, Liawruangrath S, Korth J, Pyne SGJJ o EOBP (2015) The chemical constituents and biological activities of the essential oil and the extracts from leaves of Gynura divaricata (L) DC growing in Thailand. J Essent Oil Bear Plants 18 (3):543–555
55. Saludes JP, Garson MJ, Franzblau SG, Aguinaldo AMJ, Derivatives TE (2002) Antitubercular constituents from the hexane fraction of Morinda citrifolia Linn(Rubiaceae). Phytother Res 16 (7):683–685
56. Jang WS, Jyoti MA, Kim S, Nam K-W, Ha TKQ, Oh WK, Song H-Y (2016) In vitro antituberculosis activity of diterpenoids from the Vietnamese medicinal plant Croton tonkinensis. J Nat Med 70(1):127–132
57. Chaisson RE, Bishai WR (2017) Overview of tuberculosis. In: Handbook of tuberculosis. Adis, London, pp 1–15
58. Flynn JL, Chan J (2003) Immune evasion by Mycobacterium tuberculosis: living with the enemy. Curr Opin Immunol 15(4):450–455. https://doi.org/10.1016/S0952-7915(03)00075-X

59. Karakousis PC, Dutta NK, Manabe YC (2017) Clinical features and diagnosis of tuberculosis: primary infection and progressive pulmonary tuberculosis. In: Handbook of tuberculosis. Adis, Cham, pp 17–34. https://doi.org/10.1007/978-3-319-26273-4_2
60. Habibi P, Daniell H, Soccol CR, Grossi-de-Sa MF (2019) The potential of plant systems to break the HIV-TB link. Plant Biotechnol J 17(10):1868–1891. https://doi.org/10.1111/pbi.13110
61. Churchyard G, Kim P, Shah NS, Rustomjee R, Gandhi N, Mathema B, Dowdy D, Kasmar A, Cardenas V (2017) What we know about tuberculosis transmission: an overview. J Infect Dis 216:S629–S635
62. Gomez-cansino R, Guzman-gutierrez SL, Campos-lara MG, Espitia-pinzon CI, Reyes-Chilpa R (2017) Natural compounds from Mexican medicinal plants as potential drug leads for antituberculosis drugs. Anais Acad Bras Ciencias 89(1):31–43. https://doi.org/10.1590/0001-3765201720160298
63. Widyarti S, Kamaruddin M, Aristyani S, Elvina M, Subagjo S, Rahayu T, Sumitro SB (2019) Bioinorganic chemistry and computational study of herbal medicine to treatment of tuberculosis. In: Medicinal plants-use in prevention and treatment of diseases. IntechOpen, New York
64. Dorman S, Gupta A (2017) Treatment of pulmonary tuberculosis. In: Handbook of tuberculosis. Adis, Cham, pp 35–90. https://doi.org/10.1007/978-3-319-26273-4_3
65. Kerr PG (2013) Plants and tuberculosis: phytochemicals potentially useful in the treatment of tuberculosis. In: Fighting multidrug resistance with herbal extracts, essential oils and their components. Academic Press, Cambridge, MA, pp 45–64. https://doi.org/10.1016/B978-0-12-398539-2.00005-7
66. Kishore N, Mishra BB, Tripathi V, Tiwari VK (2009) Alkaloids as potential anti-tubercular agents. Fitoterapia 80(3):149–163. https://doi.org/10.1016/j.fitote.2009.01.002
67. Ma C, Case RJ, Wang Y, Zhang HJ, Tan GT, Van Hung N, Cuong NM, Franzblau SG, Soejarto DD, Fong HH, Pauli GF (2005) Anti-tuberculosis constituents from the stem bark of Micromelum hirsutum. Planta Med 71(3):261
68. Sharma D, Parkash Yadav J (2017) An overview of phytotherapeutic approaches for the treatment of tuberculosis. Mini Rev Med Chem 17(2):167–183
69. Saga T (2007) First detection of the plasmid-mediated quinolone resistance determinant qnrA in Enterobacteriaceae clinical isolates in Japan. Int J Antimicrob Agents 29:738–748
70. Rastogi N, Abaul J, Goh KS, Devallois A, Philogène E, Bourgeois P (1998) Antimycobacterial activity of chemically defined natural substances from the Caribbean flora in Guadeloupe. FEMS Immunol Med Microbiol 20(4):267–273
71. Okunade AL, Hufford CD, Richardson MD, Peterson JR, Clark AM (1994) Antimicrobial properties of alkaloids from Xanthorhiza simplicissima. J Pharm Sci 83(3):404–406
72. Kittakoop P, Mahidol C, Ruchirawat S (2014) Alkaloids as important scaffolds in therapeutic drugs for the treatments of cancer, tuberculosis, and smoking cessation. Curr Top Med Chem 14(2):239–252
73. Gandotra S, Lebron MB, Ehrt S (2010) The Mycobacterium tuberculosis proteasome active site threonine is essential for persistence yet dispensable for replication and resistance to nitric oxide. PLoS Pathog 6(8):e1001040. https://doi.org/10.1371/journal.ppat.1001040
74. Zheng Y, Jiang X, Gao F, Song J, Sun J, Wang L, Sun X, Lu Z, Zhang H (2014) Identification of plant-derived natural products as potential inhibitors of the Mycobacterium tuberculosis proteasome. BMC Complement Altern Med 14(1):400
75. Chan ED, Oberley-Deegan RE, McGibney M, Ovrutsky A, Bai X (2010) Curcumin enhances macrophage killing of mycobacterium tuberculosis. In: B48. Tuberculosis and non-tuberculous mycobacterium: treatment outcome studies and case reports. American Thoracic Society, New York, pp A3171–A3171
76. Tousif S, Singh DK, Mukherjee S, Ahmad S, Arya R, Nanda R, Ranganathan A, Bhattacharyya M, Van Kaer L, Kar SK, Das G (2017) Nanoparticle-formulated curcumin prevents posttherapeutic disease reactivation and reinfection with Mycobacterium tuberculosis following isoniazid therapy. Front Immunol 8:739

77. Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S, Gordon S, Hamilton JA, Ivashkiv LB, Lawrence T, Locati M (2014) Macrophage activation and polarization: nomenclature and experimental guidelines. Immunity 41(1):14–20
78. Zu Bentrup KH, Miczak A, Swenson DL, Russell DG (1999) Characterization of activity and expression of isocitrate lyase in mycobacterium avium and mycobacterium tuberculosis. J Bacteriol 181(23):7161–7167
79. Safwat NA, Kashef MT, Aziz RK, Amer KF, Ramadan MA (2018) Quercetin 3-O-glucoside recovered from the wild Egyptian Sahara plant, Euphorbia paralias L., inhibits glutamine synthetase and has antimycobacterial activity. Tuberculosis 108:106–113
80. Chaudhari SM, Badole SL (2014) Polyphenols and tuberculosis. In: Polyphenols in human health and disease. Academic Press, Cambridge, MA, pp 723–730
81. Hussain K, Ismail Z, Sadikun A, Ibrahim P (2009) Antioxidant, anti-TB activities, phenolic and amide contents of standardised extracts of Piper sarmentosum Roxb. Nat Prod Res 23 (3):238–249
82. Mazlun MH, Sabran SF, Mohamed M, Abu Bakar MF, Abdullah Z (2019) Phenolic compounds as promising drug candidates in tuberculosis therapy. Molecules 24(13):2449. https://doi.org/10.3390/molecules24132449
83. Frei B, Higdon JV (2003) Antioxidant activity of tea polyphenols in vivo: evidence from animal studies. J Nutr 133(10):3275S–3284S
84. Chiang CC, Cheng MJ, Peng CF, Huang HY, Chen IS (2010) A novel dimeric coumarin analog and antimycobacterial constituents from Fatoua pilosa. Chem Biodivers 7 (7):1728–1736
85. Tan N, Bilgin M, Tan E, Miski M (2017) Antibacterial activities of pyrenylated coumarins from the roots of Prangos hulusii. Molecules 22(7):1098. https://doi.org/10.3390/molecules22071098
86. Widelski J, Popova M, Graikou K, Glowniak K, Chinou I (2009) Coumarins from Angelica lucida L.-antibacterial activities. Molecules 14(8):2729–2734. https://doi.org/10.3390/molecules14082729
87. Gupta R, Thakur B, Singh P, Singh HB, Sharma VD, Katoch VM, Chauhan SVS (2010) Anti-tuberculosis activity of selected medicinal plants against multi-drug resistant Mycobacterium tuberculosis isolates. Indian J Med Res 131(6):809
88. Uc-Cachon AH, Borges-Argaez R, Said-Fernandez S, Vargas-Villarreal J, Gonzalez-Salazar F, Mendez-Gonzalez M, Caceres-Farfan M, Molina-Salinas GM (2014) Naphthoquinones isolated from Diospyros anisandra exhibit potent activity against pan-resistant first-line drugs Mycobacterium tuberculosis strains. Pulm Pharmacol Ther 27(1):114–120
89. Rajab MS, Cantrell CL, Franzblau SG, Fischer NH (1998) Antimycobacterial activity of (E)-phytol and derivatives: a preliminary structure-activity study. Planta Med 64(01):2–4
90. Ulubelen A, Topcu G, Johansson CB (1997) Norditerpenoids and diterpenoids from salvia m ulticaulis with antituberculous activity. J Nat Prod 60(12):1275–1280
91. Jiménez-Arellanes A, Luna-Herrera J, Cornejo-Garrido J, López-García S, Castro-Mussot ME, Meckes-Fischer M, Mata-Espinosa D, Marquina B, Torres J, Hernández-Pando R (2013) Ursolic and oleanolic acids as antimicrobial and immunomodulatory compounds for tuberculosis treatment. BMC Complement Alternat Med 13(1):258. https://doi.org/10.1186/1472-6882-13-258
92. Encarnación-Dimayuga R, Agúndez-Espinoza J, García A, Delgado G, Molina-Salinas GM, Said-Fernández S (2006) Two new cassane-type diterpenes from Calliandra californica with antituberculosis and cytotoxic activities. Planta Med 72(08):757–761. https://doi.org/10.1055/s-2006-931587
93. Barry CE III (2001) Interpreting cell wall 'virulence factors' of Mycobacterium tuberculosis. Trends Microbiol 9(5):237–241
94. Sharma A, Islam MH, Fatima N, Upadhyay TK, Khan MKA, Dwivedi UN, Sharma R (2018) Deciphering the binding of natural terpenoids to mycobacterium tuberculosis type III

polyketide synthase 18 (PKS18): an in-silico approach. J Appl Pharm Sci 8(05):026–034. https://doi.org/10.7324/JAPS.2018.8504
95. Bhat ZS, Rather MA, Maqbool M, Ahmad Z (2018) Drug targets exploited in Mycobacterium tuberculosis: Pitfalls and promises on the horizon. Biomed Pharmacother 103:1733–1747
96. van Ingen J, Rahim Z, Mulder A, Boeree MJ, Simeone R, Brosch R, van Soolingen D (2012) Characterization of mycobacterium orygis as M. tuberculosis complex subspecies. Emerg Infect Dis 18(4):653. https://doi.org/10.3201/eid1804.110888
97. Cole ST, Brosch R, Parkhill J, Garnier T, Churcher C, Harris D, Gordon SV, Eiglmeier K, Gas S, Barry CE 3rd, Tekaia F, Barrell BG (1998) Deciphering the biology of Mycobacterium tuberculosis from the complete genome sequence. Nature 393:537–544. https://doi.org/10.1038/31159
98. Mojumdar M, Paul A, Kabir MSH, Rahman MG, Zohora FT, Hasan MS, Rahman MM (2016) Molecular docking and pass prediction for analgesic activity of some isolated compounds from Acalypha indica L. and ADME/T property analysis of the compounds. World J Pharm Res 5 (7):1761–1770
99. Scharf NT, Molodtsov V, Kontos A, Murakami KS, Garcia GA (2017) Novel chemical scaffolds for inhibition of rifamycin-resistant RNA polymerase discovered from high-throughput screening. SLAS Discov 22(3):287–297. https://doi.org/10.1177/2472555216679994
100. Raju A, Degani MS, Khambete MP, Ray MK, Rajan MGR (2015) Antifolate activity of plant polyphenols against Mycobacterium tuberculosis. Phytother Res 29(10):1646–1651. https://doi.org/10.1002/ptr.5437
101. Minato Y, Thiede JM, Kordus SL, McKlveen EJ, Turman BJ, Baughn AD (2015) Mycobacterium tuberculosis folate metabolism and the mechanistic basis for para-aminosalicylic acid susceptibility and resistance. Antimicrob Agents Chemother 59(9):5097–5106
102. Koul A, Dendouga N, Vergauwen K, Molenberghs B, Vranckx L, Willebrords R, Ristic Z, Lill H, Dorange I et al (2007) Diarylquinolines target subunit c of mycobacterial ATP synthase. Nat Chem Biol 3:323–324. https://doi.org/10.1038/nchembio884
103. Guillemont J, Meyer C, Poncelet A, Bourdrez X, Andries K (2011) Diarylquinolines, synthesis pathways and quantitative structure–activity relationship studies leading to the discovery of TMC207. Future Med Chem 3(11):1345–1360. https://doi.org/10.4155/FMC.11.79
104. Maiolini M, Gause S, Taylor J, Steakin T, Shipp G, Lamichhane P, Deshmukh B, Shinde V, Bishayee A, Deshmukh RR (2020) The war against tuberculosis: a review of natural compounds and their derivatives. Molecules 25(13):3011. https://doi.org/10.3390/molecules25133011
105. Zaynab M, Fatima M, Abbas S, Sharif Y, Umair M, Zafar MH, Bahadar K (2018) Role of secondary metabolites in plant defense against pathogens. Microb Pathog 124:198–202
106. Mugumbate GC (2018) Natural products a reservoir of drugs for treatment of pulmonary tuberculosis. EC Pulmonol Respirat Med 7:545–553
107. Kurmukov AG (2013) Medicinal plants of central asia: Uzbekistan and Kyrgyzstan. Springer, Cham
108. Gupta VK, Kumar MM, Bisht D, Kaushik A (2017) Plants in our combating strategies against Mycobacterium tuberculosis: progress made and obstacles met. Pharm Biol 55(1):1536–1544. https://doi.org/10.1080/13880209.2017.1309440
109. Sivakumar A, Jayaraman G (2011) Anti-tuberculosis activity of commonly used medicinal plants of south India. J Med Plants Res 5(31):6881–6884. https://doi.org/10.5897/JMPR11.1397
110. Shashidhar M, Sandhya MS, Pankaj P, Suhasini B (2015) Herbal drugs as anti-tuberculosis agents. Int J Ayurvedic Herb Med 4:1895–1900
111. Gupta SC, Patchva S, Koh W, Aggarwal BB (2012) Discovery of curcumin, a component of golden spice, and its miraculous biological activities. Clin Exp Pharmacol Physiol 39 (3):283–299

112. Araujo RC, Neves FA, Formagio AS, Kassuya CA, Stefanello ME, Souza VV, Pavan FR, Croda J (2014) Evaluation of the anti-mycobacterium tuberculosis activity and in vivo acute toxicity of Annona sylvatic. BMC Complement Altern Med 14(1):209
113. Njeru SN, Obonyo MA, Nyambati SO, Ngari SM (2015) Bioactivity of Cissampelos pareira medicinal plant against Mycobacterium tuberculosis. J Pharmacog Phytochem 3:167–173
114. Eminzade S, Uras F, Izzettin FV (2008) Silymarin protects liver against toxic effects of anti-tuberculosis drugs in experimental animals. Nutr Metabol 5(1):18. https://doi.org/10.1186/1743-7075-5-18
115. Sieniawska E, Sawicki R, Swatko-Ossor M, Napiorkowska A, Przekora A, Ginalska G, Augustynowicz-Kopec E (2018) The effect of combining natural terpenes and antituberculous agents against reference and clinical Mycobacterium tuberculosis strains. Molecules 23 (1):176. https://doi.org/10.3390/molecules23010176
116. Choi WH (2017) Novel pharmacological activity of artesunate and artemisinin: Their potential as anti-tubercular agents. J Clin Med 6(3):30. https://doi.org/10.3390/jcm6030030

Medicinal Plants in the Treatment of Tuberculosis III

9

Sarita Rawat, Abhay Raizaday, Sachchidanand Pathak, Himmat Singh, Anurag Mishra, Santosh Kumar Singh, Kamal Dua, and Gaurav Gupta

Abstract

Tuberculosis, caused by Mycobacterium tuberculosis, is a significant infectious disease. Even with the fact that the causative organism was already found more than 100 years ago and many successful medicines and vaccines are already provided rendering tuberculosis a preventable and curable disease, tuberculosis still remnants as one of the public health conditions worldwide. The fundamental principles of tuberculosis prevention and control are the same as with all other infectious diseases. The curative part consists of the tuberculosis case finding and treatment and the preventive part involves the BCG vaccination and these serve as the major components of the national tuberculosis initiative to cure the disease and sojourn its transmission. However, case finding and treatment are still considered to be the most effective weapon against tuberculosis. Around world's 1/3rd of the existing population is projected to be asymptomatically infected with tuberculosis and about 5–10% are likely to progress clinical disease during their lifetime. The disease's long-lasting persistence is due to the propensity of the tubercle bacilli to survive for years in the human body. Development of drug-resistant strains, and HIV infection occurrences are the major reasons for high infection rates are prevalent in many countries. There is an urgent need to look for new medicines that are successful and affordable for everyone but in the last 30 years, no new antitubercular drugs have been developed and successfully launched. Due to its large chemical diversity, plant kingdom can look forward to

S. Rawat · A. Raizaday · S. Pathak · H. Singh · A. Mishra · S. K. Singh · G. Gupta (✉)
School of Pharmacy, Suresh Gyan Vihar University, Jaipur, India

K. Dua
Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Sydney, NSW, Australia

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_9

an effective source of new antitubercular agents but the antimycobacterial activity of very limited plant species has been tested so far, even after the occurrence of several plant species worldwide.

Keywords

Tuberculosis · BCG vaccination · HIV infection · Drug-resistant · Antimycobacterial activity · Medicinal plant

9.1 Introduction

The World Health Organization estimates that, annually, around 8 million people develop active tuberculosis globally, and nearly 2 million people die from the disease [1]. Tuberculosis is still being a public health emergency worldwide because the maximum deaths caused by this infectious disease among adults have been reported continuously for the past 25 years [2].

Tuberculosis is well-defined as a bacterial infectious disease that is caused by Mycobacterium tuberculosis (MTB), mainly infect the lung, and can also spire all over the body like brain and spine. It can cause mild to severe illness, and untreated conditions lead to death.

Tuberculosis can be considered as the example of infectious disease and the transmission mode is primarily through the Mycobacterium tuberculosis complex and caused via aerosol of cough and it is having a lung predilection which causes, in almost 85% of cases, necrotizing granulomatous inflammation, although involvement of any extrapulmonary site can also be predicted [3]. The modern treatment for TB consists of a drug regime including ethambutol, isoniazid, rifampicin, and pyrazinamide prescribed for at least over 6 months. Despite having a high recovery rate, the effectiveness of this prescription is still limited by compliance issues, which result in a rise of strains that are resistant to some or all of the first- and second-line antibiotic treatment [2]. A poor prognosis is revealed by these Mycobacterium tuberculosis strains which are known as drug-resistant [TDR] strain, extensively drug-resistant [XDR] strain, and multidrug-resistant [MDR] strains [3, 4]. Tuberculosis-resistant drugs are currently the most dangerous mortal pathogens in the world and are considered to be responsible for countless deaths due to antimicrobial resistance and hence it is treated as one of the world's biggest health problems and there is great desire, enormous need, and urgent action to resolve this problem and totally cure the pathogen [2] (Fig. 9.1).

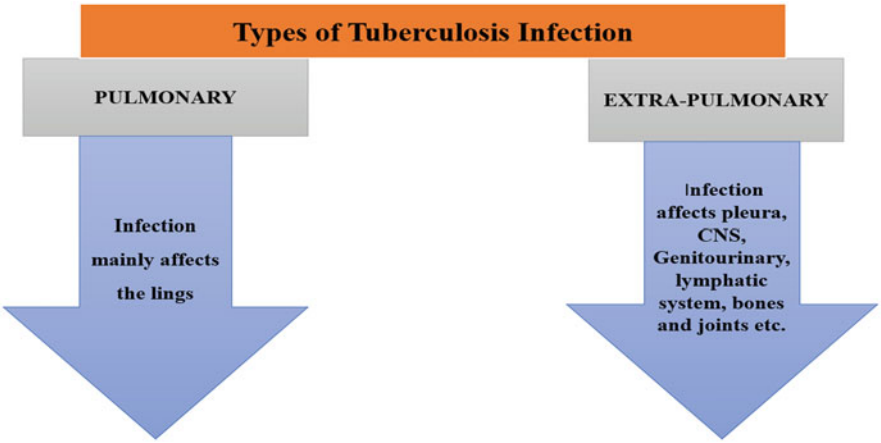


Fig. 9.1 Types of tuberculosis infection

9.2 Tuberculosis: Epidemiology

Tuberculosis has a considerable effect on both morbidity and mortality worldwide. World Health Organization (WHO) reported approximately 10 million new patients of tuberculosis in 2018 and about 1.8 million people died with tuberculosis which include 251,000 patients with HIV. The major cluster was reported in 30 high risk countries containing about 87% of the total number ranging nearly 8.7 million patients. 8 countries for 2/3 of all the new tuberculosis cases include China, South Africa, India, Bangladesh, Indonesia, Pakistan, Philippines, and Nigeria.

Nearly 6.4 million of these were diagnosed with the disease and notified on the record. Mortality due to tuberculosis is estimated to be 1.3 million people each year [2]. Although over the past 13 years there is a decreasing trend at the rate of approximately 2% per year, in the incidence of global tuberculosis the substantiality of disease problem remains remarkable. Tuberculosis infection patients are found all over the world, Southeast Asian regain reported highest number of cases in 2018 followed by 44% new infected cases in African region, and 18% in Western Pacific region.

With an average of 126 cases per 100,000 population, approximately 9 million new cases of mycobacterial tuberculosis were registered in 2013, of which more than 60% were focused in the major 22 high-burden countries [5]. With nearly 13% of the global incident caseload, it is estimated that about 1.1 million people were reported to have tuberculosis with HIV co-infection in 2013 [4, 6]. Nearly 80% of these cases have been concentrated in Africa and HIV-related deaths constitute nearly 25% of all deaths from tuberculosis. In 2013, 480,000 new cases of multidrug-resistant tuberculosis (MDR) have been identified globally leading to approximately 210,000 deaths [3].

There is a slow decrease of about 1.6% per year in the incidence of global tuberculosis, which is far from being 4–5% expected to meet the WHO End TB Strategy targets, but deaths are more rapidly decreasing at a rate of 4.1% per year. Conferring to the Global Burden of Diseases, there is an estimate that around 58 million patients recovered completely through tuberculosis diagnosis and treatment in the year 2000–2018, only a few countries will be able to end this epidemic and achieve the UN Sustainable Development Goals by 2030, completely ending tuberculosis epidemic by 2030 is one of the major health targets [2, 3, 7, 8].

9.3 Who Are Susceptible?

Those who are in close contact with tuberculosis patients are more susceptible to becoming infected and mostly within the initial stage after exposure with contacts [2]. Those who are less than 5 years of age and/or HIV infected have the utmost risk of emerging tuberculosis co-infection [3]. People who are at higher risk of developing tuberculosis can be recognized based on their past medical history and with some simple diagnostic tests [2, 9].

9.4 Tuberculosis: Diagnosis

Tuberculosis is well known as a major public health problem for many years. In the past few years, it is notable that there is a huge change in the epidemiological profile of tuberculosis [10]. The diagnosis of tuberculosis is based on many clinical and radiological opinions but confirmation requires bacteriological and/or histological tests. The culture of bacteria remains the gold standard for the confirmation of tuberculosis [2, 9]. Extrapulmonary tuberculosis is confirmed by examining a sample in normal saline for microscopy and culture. Histopathology can be used to identify characteristic changes like caseation, acid-fast bacilli, and necrotizing granulomas [10].

9.5 Tuberculosis: Aetiology and Pathophysiology.

The existence of Mycobacterium tuberculosis in the body leads to the following sequelae [11–13]:

- Direct clearance of the organism from the body.
- Reactivation disease which is the activation of disease after many years.
- Primary disease which is the onset of active disease.
- Latent infection.

Along with having no underlying medical problems and latent infection, in 5–10% cases, tuberculosis reactivation occurs in patients [1] and relative risk of

reactivation significantly rises with infection of HIV. The communicable droplets of bacteria spread throughout the airways during inhalation and with the support of mucus-secreting goblet cells, most of the bacilli are trapped in airway's upper parts [14, 15].

Mucus helps to easily entrap foreign substances and the mucus regularly shattered by cilia which are present on the cell surface, which also upwards the entrapped particles for removals. The process helps the primary physical defence for the prevention of infection in maximum people exposed to tuberculosis [16]. Phagocytosis of the bacteria, which are present in the droplets and enter the muco-ciliary system reaching the alveoli, are done by alveolar macrophages present in alveolar spaces with the richest immune response. Failure to eliminate the infection by the defence system of host results in the proliferation of bacilli inside alveolar macrophages and eventually it causes the death of the cells in the host system [17].

Cytokines are generated by the infected macrophages and other phagocytic cells attracted, including monocytes neutrophils and other alveolar macrophages, contributing to the formation of a nodular granulomatous structure known as a tubercle. If bacterial replication remains unchecked, tuberculosis will increase and the bacilli will enter the lymph nodes of local host which results in the characteristic primary tuberculosis lymphadenopathy [18]. The Ghon complex is considered as a lesion which is triggered by the formation of the tubercle with the participation of lymph nodes and surrounding lung parenchyma. Bacteraemia can often succeed primary infection, there is a continuous proliferation of the bacilli till an active cell-mediated immune (CMI) response is mounted, which generally takes almost 2–6 weeks to develop [13]. Progressive destruction of the lung is a result of tissue repair process, if an effective CMI response fails to develop. One of the characteristics of tuberculous lesion is caseating necrosis and this is governed by the reactive nitrogen, oxygen intermediates, tumour necrosis factor [TNF]-alpha, and the contents of cytotoxic cells (granzymes and perforin) [19]. Reactivation of tuberculosis is led by the proliferation of a dormant bacterium which was previously seeded during the primary infection and almost 5–10% of individuals having a latent infection and no primary medical problems can develop reactivation of the infection [4, 20].

9.6 Tuberculosis: Transmission

Mycobacterium tuberculosis infection is around one-third of the total infections in world's population and the most widespread of the all is pulmonary tuberculosis. The person's immune status as the latent host itself, the infectiousness of the primary case, and the closeness of contact are the determining factor for the chances of infection [21]. Symptoms like coughing, shouting, sneezing, singing, and any other potent expiratory action that involves any kind of respiratory secretions from the airways with coughing are the most effective in producing infectious aerosols [11, 22]. Mostly the infection may occur due to inhaling droplet nuclei in the respiratory system, which are spread all over the air by the various activity of PTB

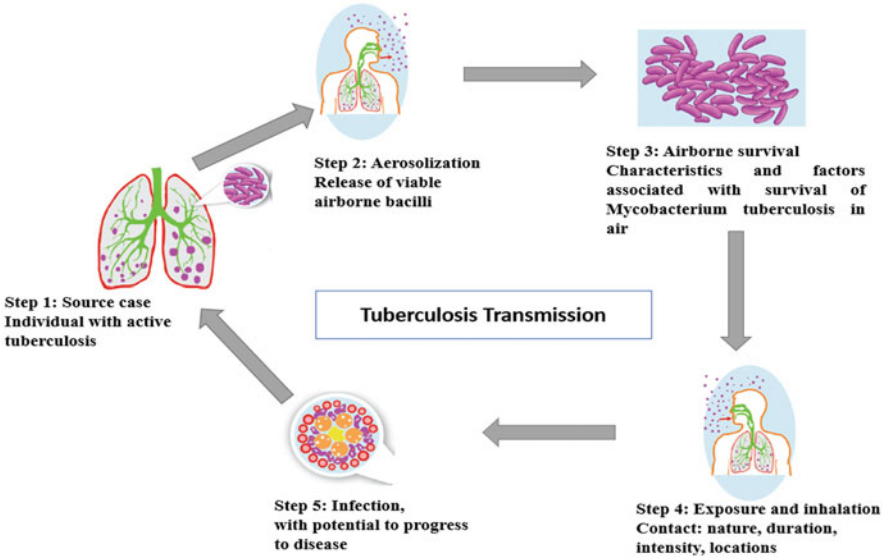


Fig. 9.2 Transmission in pulmonary tuberculosis [3, 9, 18]

[pulmonary tuberculosis] patients when they sing, spit, sneeze, talk, and cough without covering their face [11, 22]. The bronchi's defence mechanism is not able to detect the minute droplet particles and the results contamination is into the terminal alveoli of the lungs, and local lymph nodes become the centre where the tubercle bacilli reproduce and spread and after that, they transfer all over the body [6, 10]. Delayed hypersensitivity is the immune response progressed by the body toward the tubercle bacilli almost 6 weeks after primary infection. Mostly, the additional multiplication of the tubercle bacilli is stopped by the immune responses and a positive result in a tuberculin skin test of the infected person is the only sign of infections [3, 9].

People with index tuberculosis cases, who are HIV infected mostly those with advanced immunosuppression were hypothesized to be less expected than HIV-uninfected entities with tuberculosis to spread to household contacts, possibly because of a more possibility of having smear-negative tuberculosis and a shorter duration of infectiousness due to more speedy progression to death [3, 9]. Primarily, the highest transmission is within the family units but erratic outbreaks can occur in any setting, from factories to schools to the public transportations [3, 9] (Fig. 9.2).

9.7 Treatment for Tuberculosis

The main aim of TB therapy is to minimalize the time interval of illness, certify therapy, reduce mortality rate, stop recurring of the disease, and also stop transmission of the infection, with completely stop the emergence of drug resistance.

[23]. WHO's given a guidelines for all on how to prescribe anti-TB medication, which also includes recommendations on dosages frequency, how to monitoring side effects, how to manage of side effects, and also how to treat in special situations, for example during pregnancy, breastfeeding and also with the patients having liver disorders or renal failure conditions [24].

As a policy to observe, improve, and minimize avoidance the tuberculosis prevention programmes execute directly observed therapy (DOT) without a good indication that it was successful [19]. For drug-sensitive tuberculosis, Rifampicin and Isoniazid are prescribed along with pyrazinamide for 6 months and ethambutol is suggested for first 2 months, and this was established for many years after the evidence-based treatment was accepted, and thus the treatment is vastly effective till now [25, 26]. This regime is called a short course, but still, the treatment's time-interval is its main disadvantage [20]. The complete success of the treatment is well-defined by the accomplishment of therapy with a negative result of the follow-up sputum smears microscopy test. The sputum culture change typically takes approximately 4–6 weeks in the sputum-smear-positive pulmonary tuberculosis test [22, 27].

9.8 Medicinal Plants Having Antituberculosis Activity

Some natural products and their plant-derived entity stand repeatedly a vary vast source of drugs and drug molecules showing limited toxicity, they are having the potential of moderate compliance issues inpatient during prolonged administration of the remedy to cure the disease [24]. Traditional medicines have been used worldwide for years to cure many diseases and these medicines are prepared from many plant-derived sources [24, 28].

For their primary health treatment, roughly 60% of the world's population still relies solely on medicinal plants. Despite the fact that only a few plant species have been systematically studied for their medicinal properties and used for healing diseases, the plant species serve as a rich source for many novel biologically active compounds; therefore, nowadays there is a new interest increased in phytomedicine research [14]. In the particular context of tuberculosis, there are many studies conducted on plants to see the antituberculosis effects by therapists and patients in many kinds of research with the aim of determining the usage of a plant or herbal mixtures to cure tuberculosis diseases and the outcome found the positive supportive use of plant and drugs in the study [15]. The old remedies were carefully evaluated and the parameters in their studies include herbal drug formulation, traditional formulation, treatment duration, and posology [29].

Plants all over the world have been discovered for antituberculosis activity [17]. Few plants those chemical constituents having antimycobacterial activities include Hypericum perforatum L. Kuntze, Curcuma longa L., Salvadora persica L., Plumeria bicolor Seem, Cannabis sativa L., Ocimum basilicum L., Camellia

sinensis (L.), several Vernonia species, and honey/propolis [30]. A popular plant species named widely found in South Africa well known as A. afra is widely distributed towards the northwards of tropical East Africa in the Cape's Cederberg Mountains and commonly used in South Africa for the treatment of coughs, sore throat, diabetes, intestinal worms, malaria, asthma, colds, headache, and gout [31]. The extracts have shown the potential action of antioxidant, antidepressant, cardiovascular, and antimycobacterial activity in some animal studies. Important activities are verified against drug-sensitive and drug-resistant strains of Mycobacterium tuberculosis by the 3 naphthoquinones including shinanolone, diospyrin, and 7-methyljuglone [31, 32]. Knowltonia vesicatoria (Ranunculaceae) found in South Africa traditionally was also used for the treatment of tuberculosis for years and its extracts are used to explore the possibility of synergism effect of antimycobacterial activity along with the isoniazid (INH) [33]. Bolusanthus specious which is broadly distributed in subtropical regions of South Africa including Botswana, Mozambique, Zambia, and Zimbabwe and is the most common plant of Fabaceae family used to cure tuberculosis for a long time, a part that is commonly used is the dry inner bark of the tree [28, 31, 34] (Table 9.1).

9.9 Tuberculosis: Conclusion and Future Prospectus

Because of multi-drug-resistant strain of Mycobacterium tuberculosis and its selection and spread still poses a challenge to global tuberculosis control and can be considered as a Global Health Problem [21]. The re-emergence of infection of tuberculosis has obsessed a widening interest in sympathizing with the mechanisms of drug action and drug resistance, which can contribute significantly to the development and production of new antimicrobials [34]. Plants, in some countries, are the primary source of treatment of tuberculosis. However, plant materials have high antimycobacterial activity and it is well proven that they also have resistance modifying properties, hence certain derives products from a plant can also help combat drug resistance [3]. Unfortunately, till now no plant molecules have yet been marketed or tested to treat mycobacterial infections. Most studies were not expanded much to identify bioactive plant metabolites and were mostly based on the identification of antimycobacterial properties of crude plant extracts [1, 31]. In the future, a combination of modern treatment screening knowledge along with traditional knowledge of plants can lead to the finding of a good anti-tuberculosis treatment. This can prevent further spread of the disease and decrease the morbidity and mortality of the infection and reduce annual deaths occurring during pandemics throughout the world [7].

Table 9.1 Mediational plant with their bioactive compound and parts used in the treatment of tuberculosis [5, 23, 24, 28, 31, 34].

Potentially bioactive compounds found effective against mycobacterium tuberculosis	Plant part used	Botanical name	Plant family
Sulphur compounds	Bulbs and leaves	Tulbaghia violacea Harv.	Alliaceae
Oleanolic and ursolic acids	Whole plant	Leysera gnaphalodes L.	Asteraceae
5,7,2-Trihydroxyflavone	Leaves	Galenia africana L.	Aizoaceae
Chalcone glucosides		Bidens pilosa L.	Asteraceae
Glycosides, alkaloids, flavonoids, and terpenes	Leaves and bulb	Allium cepa.	Amaryllidaceae
Tannins, saponins, flavonoids, and terpenoids	Leaves	Aloe vera var. barbadensis	Asphodelaceae
Oleanolic acid	Leaves, stems	Buddleja saligna L.	Buddlejaceae
Berberine, columbin, chasmanthin, palmarin, inosporon, tinosporic acid, and tinosporol	Stem and leaves	Trichosanthes	Cucurbitaceae
Alkaloids, flavonoids, tannins, and bioflavonoids	Leaves and seeds	Garcinia kola Heckel; Garcinia spp.	Celastraceae
Flavonoids, phenols and their glycosides, glycosylated flavonols, flavanones, isoflavonoids, and flavones	Leaves and stems	Cyclopia intermedia E. Mey	Fabaceae
Hydroxyproline, serine, dimethyl-triptamine, amyrin, and botulin	Bark	Acacia xanthophloea Benth	Fabaceae
Tannins, other phenolic compounds, essential oils, flavonoids, and Phytosterols and fatty acids	Tuber	Pelargonium spp. (notably P. reniforme Curt. And P. sidoides DC.)	Geraniaceae
Coumarins, namely frutinones A, B, and C	Whole plant	Polygala fruticosa berg.	Polygalaceae
Ursolic acid, apigenin, orientin, and luteolin	Leaves and seeds	Ocimum sanctum	Lamiaceae
Alpinumisoflavone, genistein, laburnetin, and luteolin	Stem bark	Ficus chlamydocarpa	Moraceae
Benzophenanthridine, decarine, and 6-acetonyldyhydronitidine	Roots	Zanthoxylum capense	Rutaceae
Anthraquinones, alizarin, asperuloside, nordamnacanthol, ursolic acid, β-Sitosterol, asperuloside, and caproic acid	Roots and leaves	Morinda citrifolia	Rubiaceae

(continued)

Table 9.1 (continued)

Potentially bioactive compounds found effective against mycobacterium tuberculosis	Plant part used	Botanical name	Plant family
Evoxanthine and 1-hydroxy-2,3-dimethoxy-10-methylacridone	Stem bark	Oricia suaveolens	Rutaceae
Flavonoids, sterols, tannins, saponins, and glycosides	Leaves and fruits	Solanum torvum Sw.	Solanaceae

References

1. Knechel NA (2009) Tuberculosis: pathophysiology, clinical features, and diagnosis. Crit Care Nurse 29(2):34–43. https://doi.org/10.4037/ccn2009968
2. Newsletter Article (1990) A cheap and simple diagnosis for tuberculosis. Inpharma Weekly 736:18. https://doi.org/10.2165/00128413-199007360-00048
3. Furin J, Cox H, Pai M (2019) Tuberculosis. Lancet 393(10181):1642–1656. https://doi.org/10.1016/S0140-6736(19)30308-3
4. Harries AD, Dye C (2006) Tuberculosis. Ann Trop Med Parasitol 100(5–6):415–431. https://doi.org/10.1179/136485906X91477
5. Nguta JM et al (2016) In vitro antimycobacterial and cytotoxic data on medicinal plants used to treat tuberculosis. Data Brief 7:1124–1130. https://doi.org/10.1016/j.dib.2016.03.088
6. Cliff JM, Kaufmann SHE, Mcshane H, van Helden P, O'Garra A (2015) The human immune response to tuberculosis and its treatment: a view from the blood. Immunol Rev 264(1):88–102. https://doi.org/10.1111/imr.12269
7. Cruz AT, Starke JR (2007) Clinical manifestations of tuberculosis in children. Paediatr Respir Rev 8(2):107–117. https://doi.org/10.1016/j.prrv.2007.04.008
8. Kanchar A, Swaminathan S (2019) Tuberculosis control: WHO perspective and guidelines. Indian J Pediatr 86(8):703–706. https://doi.org/10.1007/s12098-019-02989-2
9. Dheda K, Barry CE, Maartens G (2016) Tuberculosis. Lancet 387(10024):1211–1226. https://doi.org/10.1016/S0140-6736(15)00151-8
10. Cuevas LE (2014) Diagnosis of tuberculosis. In: Clinical tuberculosis, 5th edn. Taylor & Francis, Abingdon, UK, pp 111–116. https://doi.org/10.1201/b16604
11. Churchyard G et al (2017) What we know about tuberculosis transmission: an overview. J Infect Dis 216:S629–S635. https://doi.org/10.1093/infdis/jix362
12. Farhat MR et al (2013) Genomic analysis identifies targets of convergent positive selection in drug-resistant mycobacterium tuberculosis. Nat Genet 45(10):1183–1189. https://doi.org/10.1038/ng.2747
13. Obakiro SB et al (2020) Ethnobotany, ethnopharmacology, and phytochemistry of traditional medicinal plants used in the management of symptoms of tuberculosis in East Africa: a systematic review. Tropical Medicine and Health 48(1):1–21. https://doi.org/10.1186/s41182-020-00256-1
14. Chinsembu KC (2015) Tuberculosis and Nature's pharmacy of putative anti-tuberculosis agents. Elsevier, Amsterdam, Netherlands. https://doi.org/10.1016/j.actatropica.2015.10.004
15. Gautam R, Saklani A, Jachak SM (2007) Indian medicinal plants as a source of antimycobacterial agents. J Ethnopharmacol 110(2):200–234. https://doi.org/10.1016/j.jep.2006.12.031

16. Barbagallo J, Tager P, Ingleton R, Hirsch RJ, Weinberg JM (2002) Cutaneous tuberculosis: diagnosis and treatment. Am J Clin Dermatol 3(5):319–328. https://doi.org/10.2165/00128071-200203050-00004
17. Katoch VM (2010) Editorial: managing drug-resistant tuberculosis: experiences from India. Expert Rev Anti-Infect Ther 8(5):493–496. https://doi.org/10.1586/eri.10.33
18. Basaraba RJ, Hunter RL (2017) Pathology of tuberculosis: how the pathology of human tuberculosis informs and directs animal models. Microbiol Spectr 5(3):1–13. https://doi.org/10.1128/microbiolspec.tbtb2-0029-2016
19. Serafino RL, Med T (2013) Tuberculosis 2: pathophysiology and microbiology of pulmonary tuberculosis. South Sudan Med J 6(1):10–12
20. Kerry RG et al (2018) Cure of tuberculosis using nanotechnology: an overview. J Microbiol 56 (5):287–299. https://doi.org/10.1007/s12275-018-7414-y
21. Grabauskas V (1983) A World Health Organization perspective. J Rheumatol Suppl 10:5–6. https://doi.org/10.1128/microbiolspec.TNMI7-0036-2016.Correspondence
22. Thomas TA (2019) Tuberculosis in children. Thorac Surg Clin 29(1):109–121. https://doi.org/10.1016/j.thorsurg.2018.09.009
23. Tabuti JRS, Kukunda CB, Waako PJ (2010) Medicinal plants used by traditional medicine practitioners in the treatment of tuberculosis and related ailments in Uganda. J Ethnopharmacol 127(1):130–136. https://doi.org/10.1016/j.jep.2009.09.035
24. Cardona PJ, Ruiz-Manzano J (2004) On the nature of mycobacterium tuberculosis-latent bacilli. Eur Respir J 24(6):1044–1051. https://doi.org/10.1183/09031936.04.00072604
25. Lawal IO, Grierson DS, Afolayan AJ (2014) Phytotherapeutic information on plants used for the treatment of tuberculosis in Eastern Cape Province, South Africa. Evid Based Complement Alternat Med 2014:735423. https://doi.org/10.1155/2014/735423
26. Suárez I, Fünger SM, Rademacher J, Fätkenheuer G, Kröger S, Rybniker J (2019) übersichtsarbeit Diagnostik und Therapie der Tuberkulose. Dtsch Arztebl Int 116 (43):729–735. https://doi.org/10.3238/arztebl.2019.0729
27. Bell LCK, Noursadeghi M (2018) Pathogenesis of HIV-1 and mycobacterium tuberculosis co-infection. Nat Rev Microbiol 16(2):80–90. https://doi.org/10.1038/nrmicro.2017.128
28. Nguta JM, Appiah-Opong R, Nyarko AK, Yeboah-Manu D, Addo PGA (2015) Medicinal plants used to treat TB in Ghana. Int J Mycobacteriol 4(2):116–123. https://doi.org/10.1016/j.ijmyco.2015.02.003
29. Tuyiringire N, Tusubira D, Munyampundu J-P, Tolo CU, Muvunyi CM, Ogwang PE (2018) Application of metabolomics to drug discovery and understanding the mechanisms of action of medicinal plants with anti-tuberculosis activity. Clin Transl Med 7(1):29. https://doi.org/10.1186/s40169-018-0208-3
30. Semenya SS, Maroyi A (2013) Medicinal plants used for the treatment of tuberculosis by Bapedi traditional healers in three districts of the Limpopo Province, South Africa. Afr J Tradit Complement Altern Med 10(2):316–323. https://doi.org/10.4314/ajtcam.v10i2.17
31. Philip Ifesinachi A (2018) African medicinal plants that can control or cure tuberculosis. Int J Pharm Sci Dev Res 4:001–008. https://doi.org/10.17352/ijpsdr.000016
32. Coffee M (2013) Extensively drug-resistant tuberculosis: new strains, new challenges. Microb Drug Resist 6(5):71–89. https://doi.org/10.2217/EBO.12.500
33. Diop EHA et al (2018) Survey on medicinal plants traditionally used in Senegal for the treatment of tuberculosis (TB) and assessment of their antimycobacterial activity. J Ethnopharmacol 216:71–78. https://doi.org/10.1016/j.jep.2017.12.037
34. Sharifi-Rad J et al (2017) Withdrawn: medicinal plants used in the treatment of tuberculosis - Ethnobotanical and ethnopharmacological approaches. Biotechnol Adv 2018:107134. https://doi.org/10.1016/j.biotechadv.2017.07.001

Natural Compounds as Versatile Potential Therapeutic Agents of Lung Cancer

10

Rabia Akram, Haseeb Anwar, Azhar Rasul, Shoaib Ahmad Malik, Javeria Maqbool, Faiqa Sajid, and Ghulam Hussain

Abstract

Cancer is a condition in which cell proliferation becomes unregulated and leads to unchecked and non-terminating growth. It is considered one of the most important causes of death throughout the world. Among all sorts of cancers, lung cancer is the most common and foremost cause of mortality. Late diagnosis and lack of efficient therapeutic intervention are the chief players that cause limitations in the treatment of this type of cancer. Two main types of lung cancer are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Various therapeutic approaches have been evaluated against lung cancer treatment such as radiotherapy, chemotherapy, surgery, and immunotherapy. Cancer cells manifest resistance against chemotherapeutic drugs and become unable to halt the metastasis of tumor cells. In this notion, natural compounds always act as an alternative approach with fewer side effects from history. Natural compounds such as phytochemicals have been shown as promising therapeutic agents due to their apoptotic, antioxidative, and anti-inflammatory activities. In this chapter, the role of these natural compounds is elaborated and well-defined with their therapeutic targets. Flavonoids, phenols, alkaloids, quinones, naphthaquinones, bibenzyl, and carotenoids have been extensively used that may target apoptotic signaling

R. Akram · H. Anwar · J. Maqbool · F. Sajid · G. Hussain (✉)
Neurochemicalbiology and Genetics Laboratory (NGL), Department of Physiology, Faculty of Life Sciences, Government College University, Faisalabad, Pakistan
e-mail: drhaseebanwar@gcuf.edu.pk; ghulamhussain@gcuf.edu.pk

A. Rasul
Department of Zoology, Faculty of Life Sciences, Government College University, Faisalabad, Pakistan

S. A. Malik
Department of Biochemistry, Sargodha Medical College, University of Sargodha, Sargodha, Pakistan

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_10

pathways, halt metastasis, prevent the formation of new blood vessels and invasion of a tumor to the surrounding area. Moreover, the synergistic effect of chemotherapeutic drugs and natural compounds also potentially inhibits the growth and progression of tumor cells. All these aspects have been discussed in the present segment.

Keywords

Natural compounds · Lung cancer · Apoptosis · Tumor · p53

10.1 Introduction

Cancer is a group of disorders that occur due to dysregulated cell proliferation and growth without terminating. Cancer is the second biggest cause of mortality worldwide. In specific organs, more than a hundred divergent types and subtypes of cancer have been found. Several types of cancers such as colorectal, lung, liver, breast, and gastric cancer have been reported in humans. There are commonly six physiological properties that characterized the development of tumors including evasion of apoptosis, growth signals self-sufficiency, growth-inhibitory signals insensitivity, sustained angiogenesis, unlimited replicative potential, and tissue metastasis and invasion [1].

10.1.1 Lung Cancer

Among all lung cancer is the most diagnosed and leading cause of cancer mortality throughout the world with a prevalence rate of 40% [2]. According to a recent estimate, 1.8 million people were diagnosed with lung carcinoma till 2012. The lack of reliable and appropriate therapeutic targets and biomarkers, late diagnosis, and incompetent drugs form a restriction in lung cancer treatment [3]. Lung cancer is further categorized into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) which is three-fourths of all lung cancers. Smoking and older age are accounted for as the main causes of NSCLC [4].

The incidence of lung cancer correlates directly with the pattern of tobacco smoking (predominant risk factor). Greater than 80% of cases in men are reported due to exposure to tobacco, while in women the risk is less: in Northern Europe is about 70% and 45% throughout the world. Besides smoking, numerous other agents are known to increase lung cancer risk including exposure to chromium VI, chloromethyl ethers, nickel, asbestos, radon, or carcinogenic air pollutants, and environmental exposure to tobacco smoke [5]. Apoptosis acts as a defensive system that prevents an unregulated cell cycle. Bcl2 family genes such as Bad, Bax, Bik, and Bak are found to encourage cell death, whereas Bcl-XL halts apoptosis. Dimerization of Bcl-2/Bax is the principal step that regulates apoptosis through caspase

proteins and has a central role to play in induction, amplification, transduction, and execution of apoptotic stimuli within the cellular system [6].

10.1.2 Pathophysiology of Lung Cancer

Lung cancer originates via multiple processes including genetic and epigenetic modifications that drive the uncontrolled proliferation of cells and dysregulated apoptotic machinery. As tumor growth increases, it switches to expand the vascular network of blood vessels (angiogenesis) for oxygen and nutrient supply to the growing tumor. Following it, tumor cells start to invade the nearby surrounding tissues, and distant tissue sites to develop a new secondary tumor (metastasis). Additionally, driver mutations also play a key role in the growth and progression of tumor cells. For example, rearrangements of ROS1 (ROS proto-oncogene 1 receptor tyrosine kinase), ALK (anaplastic lymphoma kinase), and activating mutations in EGFR (epidermal growth factor receptor) contribute to NSCLC progression via activation of multiple signaling pathways including MEK/ERK, PI3K/Akt. These signaling pathways initiate a cascade of reactions and enhance proliferation, angiogenesis, and metastasis of tumor cells [7]. Similarly, VEGF (vascular endothelial growth factor) and MMPs (matrix metalloproteinases) also participate in angiogenesis and metastasis of lung cancer, respectively [8].

10.1.3 Conventional Treatments

Chemotherapy, radiation, immunotherapy, and surgery are mostly used treatment strategies to reduce the growth of lung cancer cells [9]. Radiation and surgery therapies are mostly used to cure early-stage lung cancer; however, these approaches are related to a high risk for cancer recurrence [10]. Chemotherapy is the common most treatment option for lung cancer. The choice of chemotherapeutic agents depends on the severity of tumor proliferation and progression. Platinum-based agents (carboplatin, cisplatin) act as the main component of chemotherapy (first line) despite the stage of lung cancer (Fig. 10.1). Cisplatin is a cytotoxic agent that induces DNA damage and activates the apoptotic pathway and most commonly used at the clinical level. However, cisplatin has been found to cause chemo-resistance and unfortunately unable to cure advanced lung cancer alone [11].

Other treatment agents (targeted therapy) include tubulin inhibitors (paclitaxel, docetaxel), topoisomerase I inhibitors (topotecan, irinotecan), and antimetabolites (pemetrexed, gemcitabine). Additionally, tyrosine kinase inhibitors including anti-VEGF antibodies (bevacizumab), and EGFR inhibitors (gefitinib, erlotinib) have been also used [12]. Unfortunately, the development of resistance in response to chemotherapy is the main obstacle in the treatment of lung cancer. Therefore, most emerging and effective therapy is the use of natural products that has the potential to be used as chemotherapeutic and chemopreventive agents with low or no side effects [13].

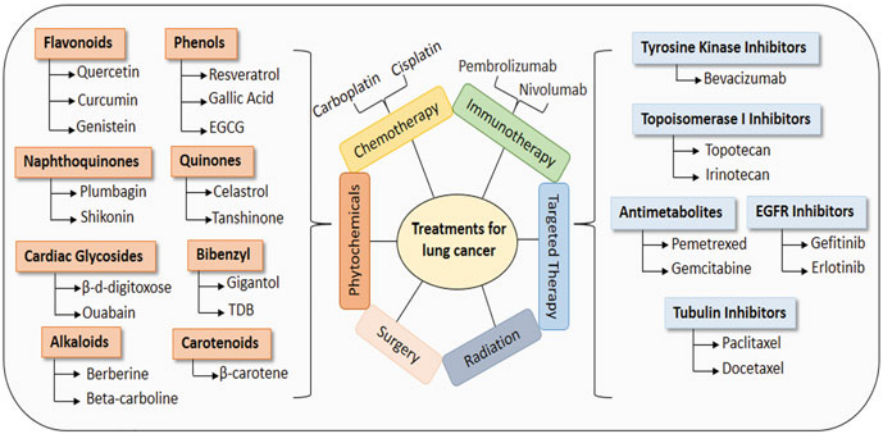


Fig. 10.1 Treatment strategies for lung cancer

10.1.4 Natural Compounds

From the drug discovery history, natural products and their derived compounds are the alternative therapeutic approaches due to their ability to induce apoptosis in malignant cells as compared to normal healthy cells [14]. The main mechanism to control cancer is the induction of apoptosis to halt the proliferation of tumor cells. There are two main pathways targeted to cancer cells which are extrinsic and intrinsic apoptotic pathways [15]. Among natural products, phytochemicals are well known and promising therapeutic agents due to their anti-inflammatory and antioxidative activities. Apples, bananas, tomatoes, fish, herbal tea, white wine, and marine food are sources of phytochemicals that allow lung function recovery [16]. Phytochemicals include alkaloids (berberine, beta-carboline), phenols (resveratrol, EGCG, gallic acid), flavonoids (quercetin, curcumin, genistein), carotenoids (β-carotene), naphthoquinones (shikonin, plumbagin), quinones (celastrol, tanshinone), cardiac glycosides (Ouabain, β-D-digitoxose), and bibenzyl (gigantol, TDB) have been elaborated due to their extensive use in the treatment of lung cancer [17].

Moreover, various active anti-cancer constituents that are derived from vegetables including micronutrients (such as folic acid, vitamin E and C, selenium), and bioactive compounds such as glucosinolates, isothiocyanates, and indoles have been found to contribute in reducing the risk of cancer. These agents either exert direct action through radical scavenging or indirect action via interacting with the body's molecular and metabolic processes to prevent cancer metastasis [5].

This chapter focuses on the molecular targets of natural compounds targeting apoptosis, metastasis, angiogenesis to prevent the progression of lung cancer. In this regard, beneficial constituents of natural compounds with anti-lung cancer activities and their chemotherapeutic potential have been discussed in detail.

10.2 Molecular Targets of Natural Compounds

The unique mechanism of natural compounds provides the knowledge of their useful activity against cancer cells. The molecular mechanism of natural compounds with anticancer properties plays an important part in the development of drug-associated therapeutic approaches for cancer treatment. Target molecules for lung cancer treatment are given below in detail.

10.2.1 Natural Compounds Targeting Apoptotic Pathways

Apoptosis, a series of events involves morphological alterations such as blebbing of plasma and nuclear membrane, shrinkage of the cell, nuclear lamina dissolution, and various biochemical processes responsible for critical activation of apoptosis. Medicinal plants from potent active compounds act as good inducer of apoptosis in lung cancer cells [18]. Different herbs (Thai) such as *Croton oblongifolius*, *Erythrophleum succirubrum,* and *Bridelia ovata* were found to induce cytotoxicity in A549 lung cancer cells [19]. Further, *Citrus aurantium* (a mixture of flavonoids) was reported to mediate p-p53 and cleaved caspase-3 to induce apoptosis in NSCLC (A549) cells [20].

10.2.2 Natural Compounds Arrest Angiogenesis

Angiogenesis is a process of the formation of new blood vessels from pre-existing vessels. It takes the most important part of the growth and spread of lung cancer because it significantly induces the growth and development of novel blood vessels [21]. Hence, blockade of angiogenesis is found as a potent therapeutic target for lung cancer cells. Vascular endothelial growth factors (VEGF) associated with vascular endothelial development contribute a key role in angiogenesis. Along with VEGF, other related indirect angiogenic factors, including platelet-derived growth factor (PDGF), tumor growth factor-alpha (TGF-α), and basic fibroblast growth factor (bFGF) also participate in the spread of a tumor. Various clinical trials have presented VEGF-targeted therapies to prevent the spread of cancer cells via inhibiting angiogenesis [18, 22].

10.2.3 Natural Compounds Attenuating Metastasis

Metastasis is the most important characteristic of malignant neoplasm and the leading cause of mortality in cancer patients. Tumor cell intravasation, dissociation, invasion, spread to distant organs, and increased motility to arrest cells of the small vessels are all related to tumor metastasis. MMPs (Matrix metalloproteinases) are extracellular matrix proteolytic enzymes and related to invasion and metastasis of

cancer. Among all members of the MMP family, MMP-9 and MMP-2 significantly alter the metastatic processes [23, 24].

Several natural product molecules have been reported to target the metastasis of tumor cells to prevent the spread of cancer. Epicatechin-3-gallate derived from green tea was revealed to upregulate E-cadherin and oppose the TGF-β1-induced EMT. Moreover, baicalein and wogonin (flavone component) in *Scutellaria baicalensis* were reported to induce downregulation of MMP-9 and the MMP-2 in both the A549 and H1299 cells [25].

10.2.4 Natural Compounds Targeting ROS

Reactive oxygen species (ROS) signaling is recently considered the main research focuses on lung cancer cells [26]. Few studies mentioned the use of herbal extracts can reduce active oxygen species in lung cancer cells. Histone deacetylase (HDAC) was reported to regulate oxidative stress pathways and can be used with curcumin (*C. longa* L.), and epigallocatechin 3-gallate (*Camellia sinensis*), and sulforaphane (*Brassica oleracea*) to combat NSCLC [18].

10.3 Anti-Lung Cancer Natural Compounds

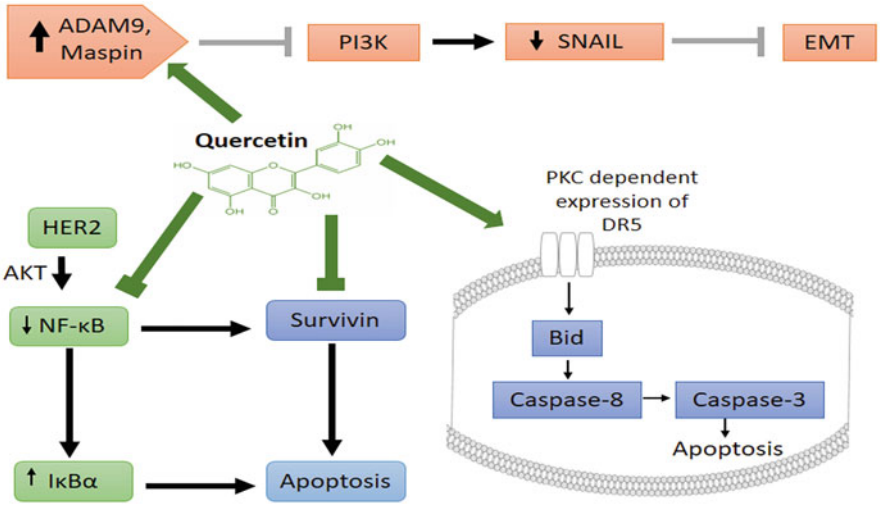
Natural compounds-derived phytochemicals are considered as an alternative approach for therapeutic development against lung cancer. Phytochemicals undeniably have the potential to improve the outcome of lung cancer treatment with fewer side impacts. A brief overview of natural products with non-apoptotic or apoptotic effects is described below.

10.3.1 Flavonoids and Lung Cancer

Flavonoids are polyphenolic compounds associated to reduce the risk factor of different types of lung cancer such as lung cancer and found in vegetables and fruits. Flavonoids have many beneficial effects and altered molecular mechanisms in tumor cells as well as inhibit the production of reactive oxygen species. Of these, some of the important flavonoids are discussed below [27].

10.3.1.1 Quercetin

Quercetin (3,3,4′,5,7-pentahydroxyflavone) is a potent antioxidant and black tea, green tea, vegetables, fruits, and medicinal plants including *Euonymus alatus* (Thunb.) Sieb are a rich source of quercetin. Among all of the above mentioned sources, the apples and onions are excellent derivatives of quercetin. Various studies have reported the beneficial role of quercetin as an anti-inflammatory, anti-hypertensive therapeutic, and preventive agent for cancer cells. Quercetin involved in the cell cycle inhibition and death receptor signaling pathway in H460 cells in NSCLC, as



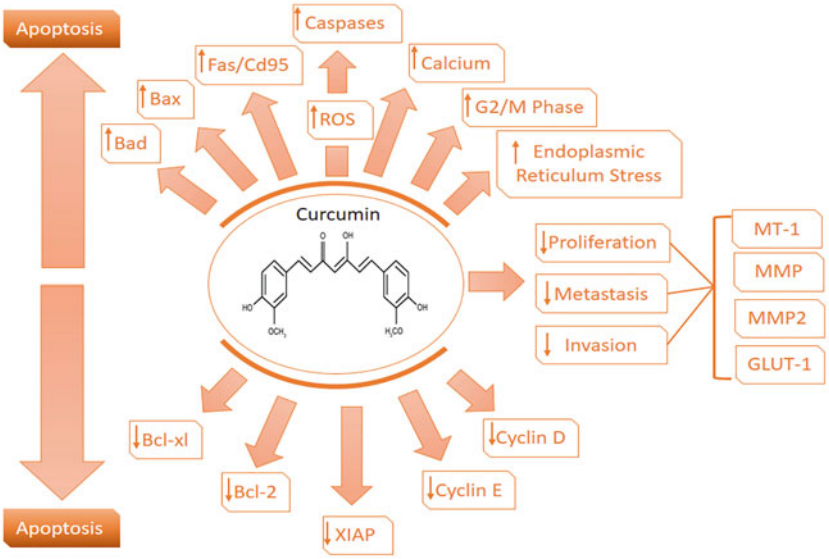
PI3K: Phosphoinositide 3-kinase; PKC: Protein kinase C; AKT: Protein kinase B; SNAIL: Zinc finger transcription factor; NFκB: Nuclear factor kappa B; IκBα: I- kappa B alpha; ADAM-9: Disintegrin and metalloproteinase domain-containing protein 9; Bid: Pro-apoptotic protein; Caspase-3: Protein; Caspase-8: Protein; HER2: human epidermal growth factor receptor-2; DR5: Death receptor-5; EMT: epithelial to mesenchymal transition

Fig. 10.2 Anti-lung cancer mechanistic approach of quercetin

revealed in a recent study. In fact, quercetin sensitizes apoptosis (TRAIL-induced) in NSCLC cells through two main independent pathways including suppression of survivin (Akt-mediated) expression and induction of death receptor-5 (DR5) through PKC (Fig. 10.2). Moreover, quercetin was found to downregulate NF-κB expression and upregulate IκBα (inhibitor of NF-κB) at both protein and mRNA levels and potentiate apoptosis in H460 cancer cells [28, 29]. Cytochrome P450 enzymes including CYP1A1 and CYP3A4 play a crucial role in the bioactivation of polycyclic aromatic hydrocarbons carcinogens in squamous cell lung carcinoma. Since quercetin can modify the CYP1A1 genotype via inhibiting P450 enzymes and it is strongly suggested by clinical studies [30]. Moreover, quercetin has also been found to upregulate Snail independent ADAM9 expressions and maspin to inhibit Snail dependent-Akt activation to suppress EMT in human NSCLC cells [31].

10.3.1.2 Curcumin

Curcumin is a bioactive component of the natural dietary compound turmeric spice and has the potential to exert anticancer effects on several types of cancers including lung cancer [32]. As suggested by in vitro studies via p53 independent and mitochondria-dependent pathways, curcumin induces apoptosis (Fig. 10.3). In the G2/M phase, curcumin strongly upregulates cell cycle arrest, Bad, Bax, FAS/CD95 and downregulates cyclin E, D (cell cycle regulator), Bcl-xL, Bcl-2, XIAP protein



G2/M Phase: Cell cycle phases; Bad: BCL2 associated agonist of cell death; Bax: BCL2 associated X protein; FAS/CD95: Tumor necrosis factor receptor; Cyclin D/E: Cell cycle regulator protein; Bcl-xL: Anti-apoptotic protein; Caspases: Apoptotic protein; Bcl-2: B-cell lymphoma 2; XIAP: X-Linked Inhibitor Of Apoptosis; MT-1: Metallothionein-1 protein; MMP: Matrix metalloproteinases; MMP2: Matrix metalloproteinases-2; GLUT-1: Glucose transporter-1; Ca: Calcium; ROS: Reactive oxygen species

Fig. 10.3 Anti-lung cancer mechanistic approach of curcumin

expression and also able to increase intracellular calcium, endoplasmic reticulum stress, ROS which ultimately leads to interrupt potential of mitochondrial membrane and induces activation of caspases in the cultured H460 cells [33–36]. Besides potent apoptotic effects of curcumin, it also induces an inhibitory effect on tumor survival as well as progression [37]. Additionally, in lung A549 cells curcumin was found to suppress proliferation, metastasis, and invasion via reducing MT-1, MMP, MMP2, and GLUT-1 for cancer intervention [38].

10.3.1.3 Genistein

Genistein (GEN), an isoflavone present in soybeans, soy sauce, soy milk, and tofu, enhances autophagy and apoptosis of cancer cells especially in lung cancer, breast cancer, lymphoma, and gastric cancer [39, 40]. It also enhances the efficacy of radiotherapy in tumor cells and also attenuating inflammatory injuries in normal cells that are caused by ionizing radiation. Autophagy involves the lysosomal degradation pathway which mediates the death of cancerous cells. Similarly, GEN inhibits Bcl-xL translocation and is found to promote apoptosis in NSCLC cells via dissociating Bcl-xL from Beclin-1 as revealed from in vitro and in vivo study [41].

10.3.1.4 Silymarin

Silymarin is obtained commonly from *Silybum marianum* L. Gaertn. (milk thistle) plant and has anticancer properties. Silymarin has no side effects on non-malignant cells but toxic against malignant cells [42]. It is also found that silymarin can restore or reactivate E-cadherin expression in H460 and A549 cells. In fact, E-cadherin expression is directly linked to reducing NSCLC cell migration. Thus, silymarin treatment significantly contributes to regulating HAT activation and HDAC inactivation to control the expression of E-cadherin. Additionally, silymarin also targets transcription factor ZEB1 that downregulates HDAC1/2. Anti-lung cancer activity of silymarin has been explored in NSCLC cell lines (H460 and A549) that potentially correlate to the level of miR-203 (tumor suppressor) expression. Conclusively, silymarin treatment significantly regulates proliferation, invasion as well as metastasis of tumor cells via targeting particular genes [43, 44].

10.3.2 Alkaloids and Lung Cancer

10.3.2.1 Sophoridine

Sophoridine (SRI) being quinolizidine alkaloid possesses a wide range of beneficial properties such as anticancer, anti-inflammatory, antiviral, and also mediates cardiac protection. Extract of *Sophora alopecuroides* L. is a source of sophoridine. Food and Drug Administration (FDA) of China has approved sophoridine injections as a treatment strategy for malignant trophoblastic tumors in 2005. Recently, SRI was also reported to exert an inhibitory effect on malignant tumors. Growing evidence demonstrated that the anticancer activity of SRI is due to its ability to activate p53 signaling in gliomas. Along with p53, the hippo pathway dysregulation also contributes to lung cancer tumorigenesis via regulating the YAP–TEAD complex. MDM2 acts as a down-regulator of p53 and mediates p53 degradation via ubiquitination. SRI inhibited MDM2-mediated p53 ubiquitination that is the potential target site to prevent turnover of the p53 signaling pathway. Of note, a recent study found that SRI promotes apoptosis and suppresses migration and invasion of NCI-H1299 cells independent of p53 and Hippo signaling pathways [45, 46].

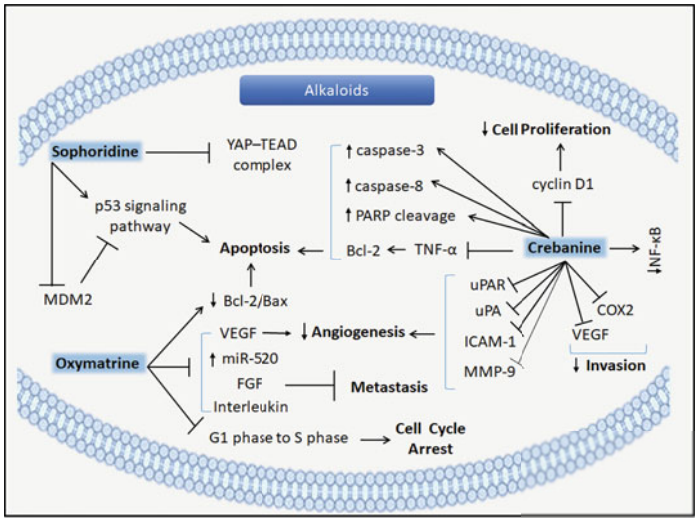
10.3.2.2 Crebanine

Crebanine is one of the aporphine alkaloids isolated from *Stephania venosa* and has many pharmacological activities such as antimicrobial, anticancer, and antiarrhythmic. It presents anticancer properties via suppressing NF-κB activation and sensitizing TNF-α induced cell death of cancer. Of note, NF-κB is a regulator of tumor progression and development as well as a mediator of inflammation and activated by TNF-α which acts as a switch in creating a link between cancer and inflammation. In addition, crebanine also enhances TNF-α mediated apoptosis via activation of caspase-3, caspase-8, and PARP cleavage. It was also revealed that crebanine inhibits TNF-α induced Bcl-2 (anti-apoptotic), cyclin D1 (cell proliferation), MMP-9, uPA, uPAR, and ICAM-1 (invasion) and COX2, VEGF (angiogenesis) gene expression, thus reduces NF-κB activation in human lung adenocarcinoma

cells A549. Hence, crebanine acts as a strong agent in the treatment of lung cancer [47, 48].

10.3.2.3 Oxymatrine

Oxymatrine (OMT) is isolated from "*Sophora flavescens*" and acts as a potent constituent of traditional Chinese medicine. It has multiple beneficial properties including anti-inflammation, anti-tumor, antifibrosis, and antivirus [49, 50]. Numerous in vitro studies have proven that OMT can induce cell cycle arrest, inhibit not only tumor cell proliferation but also differentiation, invasion, metastasis, and promote apoptosis [51]. Experiments showed that OMT blocks A549 lung adenocarcinoma cell line proliferation in vitro and also causes cell cycle arrest via preventing entry from the G1 phase to the S phase and keeps them in the G0 phase. It was found that OMT could decrease the Bcl-2/Bax ratio in the A549 lung cancer cell line (Fig. 10.4). Bioinformatic analysis revealed that OMT has a novel use due to its impact on the regulation of miRNA expression. It may inhibit the major signaling pathways including VEGF, interleukin, cadherin, apoptosis, and FGF to regulate metastasis as well as angiogenic properties of lung tumors. It was also confirmed that OMT treatment upregulates miR-520 significantly, thus strongly associated with the prevention of metastasis and the growth of lung cancer [52].



Bcl-2/Bax: BCL2 associated X protein; Cyclin D 1: Cell cycle regulator protein; uPA: Urokinase; MMP-9: Matrix metalloproteinases-9; PARP: Poly (ADP-ribose) polymerase; COX-2: Cyclooxygenase-2; MDM2: E3 ubiquitin-protein ligase; ICAM-1: Intercellular Adhesion Molecule 1; Caspase-3: Protein; Caspase-8: Protein; NFκB: Nuclear factor kappa B; TNF-α: Tumor necrosis factor-alpha; FAS/CD95: Tumor necrosis factor receptor; Upar: urokinase-type plasminogen activator receptor ; VEGF: Vascular endothelial gowth factor; FGF: Fibroblast growth factor; YAP-TEAD: Yes-associated protein- TEAD transcription factor complex; Interleukin: Protein; p53:Tumor protein; miR-520: tumor-related miRNA

Fig. 10.4 Alkaloids and lung cancer

10.3.2.4 Berberine

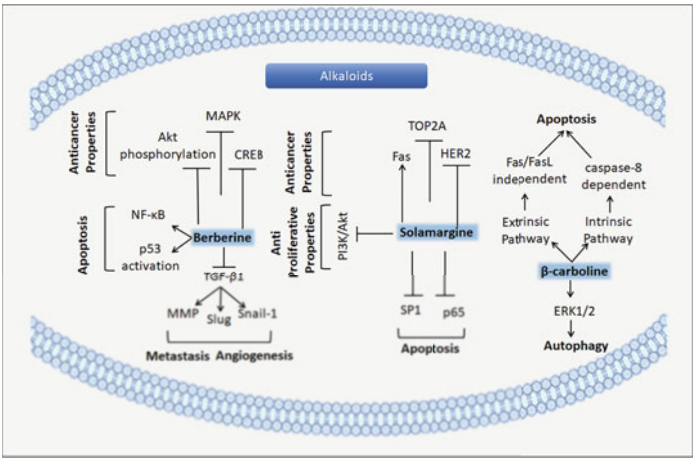
Berberine (2, 3-methylenedioxy-9, 10-dimenthoxyproto-berberine chloride) is isoquinoline alkaloid and derived from berberis species including *Berberis aquifolium* (Oregon grape), *Berberis vulgaris* (barberry), *Tinospora cordifolia*, and *Berberis aristata* (tree turmeric). Berberine (BBR) is widely used as an anti-inflammatory, antifungal, and antibacterial agent [53, 54]. BBR also possess anti-lung cancer activity via inhibition of cell migration, proliferation, apoptosis, and invasion through multiple pathways [55]. BBR is found to treat A549 cell line in a dose and time-dependent manner, as explored by in vitro and in vivo study. Besides, it has also shown that BBR suppresses TGF-β1-induced EMT expression of Slug, Snail-1, and MMP (matrix metalloproteinases), thus inhibits tumor metastasis and angiogenesis. BBR has potential effects on NFκB signal activation, reactive oxygen species generation, RNA or DNA binding, p53 activation, mitochondrial function, MMPs regulation, and inhibition of DNA topoisomerase activity [56]. BBR was also isolated from Rutaceae family plants and exhibited anti-lung cancer properties to treat A549 cancer cells via inhibiting Akt phosphorylation, MAPK, and CREB in a mouse model [57].

10.3.2.5 Solamargine

Solamargine (SM) is a glycoalkaloid and typically extracted from the traditional herb of *Solanum lycocarpum*. It possesses anti-inflammatory, antiproliferative, and antiviral activity and is used against numerous types of cancers including lung cancer. SM downregulates TOP2A (topoisomerase II alpha), HER2 (human epidermal growth factor receptor-2) and upregulates Fas expression to accelerate apoptotic cell death in NSCLC A549 cells [58]. It is found that SM inactivates PI3K/Akt signaling, therefore regulates gene expression and inhibits proliferation and growth of cancer cells. Additionally, SM possesses anti-lung cancer activity by reducing the SP1 transcription factor and p65 level [59, 60].

10.3.2.6 Beta Carboline

Beta-carbolines (β-carboline) are found in various medicinal plants including *Banisteriopsis caapi*, *Peganum harmala*, *Passiflora incarnata*, and *Passiflora edulis*. β-carboline alkaloids have anti-tumor activity and cytotoxic effects on various cancer cells [61]. Harmol is a β-carboline that causes apoptosis in NSCLC H596 cells via the extrinsic pathway (Fas/FasL independent), and the intrinsic pathway (caspase-8 dependent) in humans. In H596 cells, harmol rapidly induces apoptosis within 3 h of treatment [62]. However, recent studies have revealed that harmol kills A549 lung cancerous cells via autophagy instead of apoptosis. Numerous studies reported that the ERK1/2 pathway significantly mediates autophagy (Fig. 10.5). Indeed, harmol also induces autophagy through the ERK1/2 pathway in A549 cells thereby, suggested the key role of harmol in the treatment of lung cancer cells [63, 64].



PI3K:Phosphoinositide 3-kinase; AKT: Protein kinase B; ERK: Extracellular signal-regulated kinase ; MAPK: mitogen-activated protein kinase; MMP: Matrix metalloproteinases: TOP2A: Topoisomerase 2A; Snail-1: Zinc finger transcription factor; Slug: transcription factor; NFκB: Nuclear factor kappa B; TNF-β: Tumor necrosis factor- β ; Caspase-8: Protein; p53:Tumor protein; p65: Protein ; SP1: Specificity proteins; Fas: Protein; CREB: cAMP response element-binding protein; HER2: human epidermal growth factor receptor-2

Fig. 10.5

10.3.3 Polyphenols and Lung Cancer

Polyphenols are commonly present in vegetables, fruits, tea, wine, and whole grains. Till yet, 10,000 polyphenolic natural compounds have been recognized [65]. They are further classified into four groups, including flavonoids, stilbenes, phenolic acids, and lignans [66]. Polyphenols have a high binding affinity with oncogenic molecules and possess anticancer activities. The imperative anti-tumor mechanism of polyphenols in lung cancer vigorously depends on activation or inhibition of certain intrinsic signaling agents such as p53, p21, Bax (pro-apoptotic effectors), miR-622, miR-192-5p (tumor suppressor) and PI3K, MEK, ERK, NFκB (signaling pathways), Bcl2, Bcl-xL (anti-apoptotic effectors), respectively [52].

10.3.3.1 Resveratrol

Resveratrol is a stilbenes phytoalexin and first time isolated from *Veratrum grandiflorum* (White hellebore). Resveratrol (3,5,4′-trihydroxy-trans-stilbene) presented health conferring effects such as anti-inflammatory, antioxidant, anticarcinogenic as well as antidegenerative activities [67, 68]. It inhibits cellular proliferation, induces cell cycle arrest and apoptosis, and also inhibits invasion and metastasis of lung cancer. Moreover, it also exerts inhibitory growth effects on lung cancerous cells through the upregulation of Smad 7 and downregulation of Smad 2/4 that are major components of transforming the growth factor-beta/Smad signaling

pathway. It causes cell cycle arrest in the G1 phase via mediating activation of caspases, suppresses mitochondrial permeability, and increasing p53, p21, and p27 (cyclin-dependent kinase inhibitor) expression at both protein and gene level [69]. In H460 and 16HBE-T bronchial epithelial cells of humans, a previous study found that resveratrol regulated miRNA expression to mediate apoptosis and cell proliferation of tumor cells. Additionally, resveratrol was examined to mediate its anti-tumor effect via regulating miR-520 h in A549 and CL1-4 lung carcinoma cells [70]. Considering the anti-tumor effects; resveratrol, a similar synthetic product BCS (3,4,5-trimethoxy 4 V bromo-cis-stilbene) has been introduced that possesses a more potent effect (1100 times) than resveratrol to cause inhibition of A549 cells [71].

10.3.3.2 Ellagic Acid

Ellagic acid, a phenolic constituent is found in strawberries, raspberries, green tea, pomegranates, grapes, nuts, and has similar potency against lung cancer cells like resveratrol. Among grapes, red wine is the greatest source of higher concentration of ellagic acid [72–74]. Ellagic acid (EA) exhibits both antioxidative and anti-tumor activities [75]. EA indicates in vitro and in vivo anti-tumor activities through inhibiting the proliferative nature of tumor cells via cell cycle arrest. Moreover, EA also induces apoptosis, inhibits angiogenesis, and ameliorates inflammation [76]. Recent research explored that EA has also the ability to control oncoprotein CIP2A (cancerous inhibitor of protein phosphatase 2A) level and induced autophagy in lung cancerous cells. Moreover, EA suppresses p-mTOR, p-Akt, p-P70S6K, Notch, and Shh pathways to mediate cell growth of tumor cells in vivo and in vitro [77].

10.3.3.3 Epigallocatechin-3-Gallate

Epigallocatechin-3-gallate (EGCG) is a principal component of green tea (*Camellia sinensis*), reveals anti-inflammatory, antiproliferative, antioxidative, and antimutagenic activities [78]. EGCG can inhibit the growth rate of tumor cells, as demonstrated in various types of cancers [79]. EGCG has been found to suppress the growth of cancer cells in various NSCLC cell lines [80]. EGCG follows the AMP-activated protein kinase activation pathway to inhibit proliferation, migration, colony formation, and invasion of lung cancer cells (H1299) in human in vivo [81]. Additionally, EGCG also suppresses the growth of lung cancer cells through the upregulation of miR-210 expression [82].

10.3.4 Bibenzyl and Lung Cancer

10.3.4.1 4, 5, 4′-Trihydroxy-3, 3′-Dimethoxybibenzyl (TDB)

Dendrobium ellipsophyllum is a source of 4,5,4′-trihydroxy-3,3′-d imethoxybibenzyl (TDB), that is used for sensitization of lung cancer cells via inhibiting epithelial to mesenchymal transition (EMT) and prevent cancer cell metastasis, invasion, and migration [83]. Snail, vimentin are biomarkers of EMT that are suppressed by TDB non-lethal concentration. This suppression of EMT

leads to induce anoikis as well as causes a reduction in cell growth rate via reducing p-AKT and p-ERK signaling [25, 84]. Moreover, TDB is found to mediate apoptosis in human lung carcinoma through activation of caspase-3 and phosphatidyl-serine localization on the outer surface of the cell membrane. TDB has been reported to restore p53 signaling via activating Bax, Bcl-2 associated X protein, reducing Bcl-2, Mcl-1 in human lung cancer cells including H460, H23, and H292 [83].

10.3.4.2 Gigantol

Gigantol is isolated from the *Dendrobium draconis*, *Thai orchid*, and possesses several pharmacological properties including anti-inflammatory, antiplatelet aggregation, and induces cancer cell death [85–87]. Recent research has clearly mentioned that gigantol follows Cav-1 dependent pathway to suppress cell migration in lung cancer. Cav-1 (caveolin-1), and Cdc42 (cell division cycle 42) are well-known signaling proteins that play a vital role in cell migration. Many cancer types such as lung cancer represent a high level of Cav-1, and it has been seen in human lung carcinoma that overexpression of Cav-1 increases the motility of H460 cancer cells [88, 89]. Interestingly, gigantol is found to be capable of downregulating Cav-1 expression which can lead to the attenuation of Cdc2 expression and Akt phosphorylation and, thereby, suppress filopodia formation. Hence, the results of the study revealed that gigantol has anti-migratory activity in lung cancer cells and can overcome cancer metastasis [90].

10.3.5 Carotenoids and Lung Cancer

10.3.5.1 Crocin

Crocin is abundantly present in saffron (*Crocus sativus*) stigma and possesses anti-tumor activity through mediating growth inhibition of tumor cells. Crocin is water-soluble and presents minor or no side effects, thereby act as a suitable chemotherapeutic agent. Recently, it is revealed that Crocin is the main active carotenoid in saffron that is responsible for anti-lung cancer properties and has shown cytotoxic and antiproliferative effects in A549 cells as compared to L929 (non-malignant) cells [61].

10.3.5.2 Astaxanthin

Astaxanthin is found in abundant amounts in seafood shrimp, salmon, red yeast, and microalgae, possesses several biological activities such as anti-inflammatory, anticancer, antioxidant, and also shows health benefits effects in neurodegenerative, gastrointestinal, and liver diseases [91]. Astaxanthin reduces the Bcl-2 level and enhances the Bax level, as revealed by a recent study. It was also seen that astaxanthin inhibits JAK-1 and STAT-3 phosphorylation that are involved in regulating the cell growth in NSCLC-A549 cells, thus suppresses the growth rate and induces apoptosis [92]. Additionally, astaxanthin has been found to downregulate TS (thymidylate synthase) expression in NSCLC cell lines including H1650 and H1703 via reducing MKK1/2-ERK1/2 activity [93]. Astaxanthin

treatment is found to decrease the p-AKT level, thereby revealed to inhibit cell proliferation and viability of NSCLC cells (A549, H1703) in a dose-dependent manner [94].

10.3.6 Naphthoquinones and Lung Cancer

10.3.6.1 Shikonin

Shikonin (SHK), an active naphthoquinone and main ingredient of purple gromwell (*Lithospermum erythrorhizon*) is a well-known natural product for its pharmacological and biological activity [95]. It has antimicrobial, anti-inflammatory, antiplatelet, antiangiogenic, anti-tumor, and anti-infection actions. SHK has been revealed by clinical studies as well as in vivo and in vitro studies as an anti-lung cancer agent [96, 97]. It exerts cytotoxic effects through the increasing generation of reactive oxygen species that trigger caspase-dependent apoptotic pathways and also downregulates NFκB to mediate MMP levels which ultimately reduce tumor invasion, and survival [98]. SHK has anti-invasive and anti-migratory potential, as significantly suggested by a recent study in lung cancer cells (HCC827). The results of this study mentioned that SHK causes EMT suppression and inhibition of c-Met expression through inhibition of PI3K/Akt and ERK signaling pathway [99]. However, SHK has been explored as a potent cytotoxic agent against lung cancer A549 cells via initiating necrotic and apoptotic pathways [97].

10.3.6.2 Plumbagin

Plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone) is derived naturally from *Plumbago zeylanica* (root) with numerous medicinal properties including anticancer, anti-migratory, and cytotoxic activity. Plumbagin (PLB) has shown antiproliferative activity in A549 cells via arresting tumor cells in S, G2, and M phase and induces apoptosis as well as enhances ROS production via mediating mitochondrial downstream molecules such as caspase-9 and caspase-3 [100, 101]. In addition, a study revealed that PLB treatment inactivates PI3K/Akt signaling, downregulates Bcl2, and upregulates Bax in H23 and A549 lung cancer cells, thus induces autophagic cell death [100]. Another study also explored that PLB suppresses human LCLC (Large cell lung cancer) cell lines including L9981 and NL9980 by inhibiting IL-6/STAT3 signaling [102].

10.3.7 Indole 3-Carbinol and Lung Cancer

Indole 3-carbinol (I3C) belongs to glucobrassicin derivative and found in cruciferous vegetables including cauliflower, brussels sprouts, broccoli, and cabbage. It acts as an anti-tumor agent against various cancers such as liver, gastric, and lung by suppressing tumor cells proliferation, invasion, angiogenesis. Additionally, I3C also modulates carcinogen metabolism and induces apoptosis to prevent the growth of cancer cells. 3,3-diindolylmethane is the main active ingredient of I3C that is

produced when I3C undergoes condensation reactions in the stomach [103]. Various studies highly mentioned the key role of I3C treatment in lung carcinoma [104]. I3C suppresses the level of Cox-2, phospho-NF-κB, FAS, and phospho-Akt but increases proteolytic cleavage of PARP, caspase-3/8, cyclin-D1, p-53, and p21 in lung cancer cells [105, 106]. Further, I3C is also revealed to downregulate overexpression of different microRNAs particularly miR-21 (tumor promoter) as a chemopreventive strategy in lung tumors [107]. ERK, Akt, and NF-κB pathways have been explored to play a key role in the maintenance of cell proliferation, survival, and expression of inflammation-associated genes, respectively. All of these pathways are found to be activated in normal alveolar and bronchial cells and even in NSCLCs. I3C plays a critical role in regulating NFκB, Akt, and ERK pathways, as suggested by not only the A/J mouse model but also by human bronchial epithelial cells (HBECs) and alveolar basal epithelial cells A549 [107, 108].

10.4 Natural Compounds as Chemotherapeutic Drug Sensitizer

Although various natural compounds have been well recognized and well researched about their health-related beneficial effects, it was also strongly suggested that combinatorial treatment of chemotherapeutic drugs and naturally occurring active ingredients can serve as the best therapeutic intervention to eradicate metastasis and apoptosis of lung cancer cells. The synergistic effect of phytochemicals and drugs have been described below.

10.4.1 Genistein-Trichostatin A Combined Effect

Genistein found in soybeans and soybeans related products may possess a protective role against lung cancer and numerous other cancers. Genistein has an enhancing effect on trichostatin A-induced apoptosis, suggesting a strong combination to control cell cycle arrest in A549 cells. Several studies demonstrated that genistein enhances apoptosis via p53 upregulation in NSCLC cells [109]. TSA is a potent HDAC inhibitor, thus contributes to inhibiting tumorigenesis via reducing the HDACs level. Genistein alone at 20 and 50μM concentration has an ability to upregulate histone acetylation (HAT) and p300 expression in A549 cells. However, TSA and genistein synergistic effect upregulate p53 along with HAT in H460 cells in a dose-dependent manner more efficiently than genistein alone [110].

10.4.2 Baicalin-Cisplatin Combined Effect

Cis-diamminedichloroplatinum (cisplatin, DDP) is the first member of anticancer drugs and is used as an intermediate and standard therapy for lung cancer. Cisplatin forms identical cross-links between DNA guanine bases and is used to treat several

other types of cancers including lung carcinoma via triggering apoptotic pathways [111]. However, toxicity and resistance are major side effects of DDP and are widely reported against lung cancer therapy [112]. Natural compound Baicalin belongs to a class of phytochemical flavone glycoside and abundantly found in *Scutellaria lateriflora* and *Scutellaria baicalensis* [113]. Baicalin has been shown as an anxiolytic agent, apoptosis enhancer, inhibitor of prolyl endopeptidase, and malignant tumor proliferation [114]. Downregulation of Microtubule affinity-regulating kinase 2 (MARK2) and p-Akt are the target sites of Baicalin to reduce DDP induced resistance against lung cancer therapy. Indeed, MARK2 directly interacts with Akt that is the main component of PI3K/Akt/mTOR signaling which plays a significant role in the progression and proliferation of cancer. So, Baicalin induced inhibition of MARK2 and Akt suppresses the activation of this signaling pathway and ultimately leads to enhancing the potent effects of DDP to prevent metastasis and invasion of lung cancer cells [115, 116]. Further, in NSCLC, IL-6 signaling also enhances DDP resistance via upregulating Akt expression [117]. Moreover, it has been revealed that the synergistic relation of DDP and baicalin at a dosage of 4 and 8μg/ml after 48 h incubation has an inhibitory effect on tumor cell invasion of A549 lung cancer cell line as compared to alone baicalin or DDP treatment. All these findings strongly suggest that baicalin adjunct of DDP and a candidate for lung cancer therapy [116].

10.4.3 Sophoridine-Cisplatin Combined Effect

Cisplatin is platinum-based chemotherapy and used against advanced lung cancer treatment. Along with beneficial effects, such type therapy has also presented toxic effects and has become a critical challenge for the scientist to develop natural based therapy with no or minimal hazardous effects as discussed in Sect. 4.2. It has also been reported that 85% of patients face neutropenia [118] and 50% were unable to accomplish treatment with cisplatin therapy alone [119]. Based on this, it was evaluated in a recent study that Sophoridine (SRI) and Cisplatin fusion can improve NSCLC cell treatment and diminish the side effects of chemotherapy [46].

10.4.4 Noscapine-Cisplatin Combined Effect

Noscapinoids (Nos) are antimicrotubule agents, suppress the proliferation of cells, and are used in the treatment of various cancers. Noscapine is derived from *Papaver somniferum* L. (opium flower) and used to arrest the G2/M phase in various types of cancers including breast cancer and lung adenocarcinoma (A549 cells) [120, 121]. Nos is found to attenuate microtubule dynamics to halt cell cycle via activating mitotic checkpoints. Further, Nos significantly reduce tumor volume in NSCLC in a dose-dependent manner. Nos-Cis has potential against tumor cells of the lung synergistically, as reported by previous researches. Co-treatment of Cis and Nos showed a significant increase in apoptosis, PAPR cleavage, and caspase 3 as compared to alone. Nos + Cis combination is found to cause cytotoxicity via both

intrinsic and extrinsic apoptotic pathways as well as activation of growth-inhibitory molecules against lung tumor cells [122].

10.5 Lung Cancer Stem Cells

In 1977 the concept of CSCs (cancer stem cells) was familiarized and has become a very concerning topic in cancer study nowadays. CSCs are a minor erratic fraction of the whole population of cancer cells that reveal high tumorigenic potential [123, 124]. Cancer stem cells were first known as "cancer-initiating cells" as they are assumed as the main cause of cancer. The features of CSCs, an essential role in pouring hostility of cancer contain their self-renewal ability, differentiation, migration features, great tumorigenicity, high assault, and conflict to the chemotherapy. According to these features, CSCs are assumed as chief arbitrator of all the malignance hallmarks comprising elevated metastasis potential, elevated tumorigenic, conflict to the chemotherapy, and cancer deterioration [125].

10.5.1 Key Features of Cancer Stem Cells

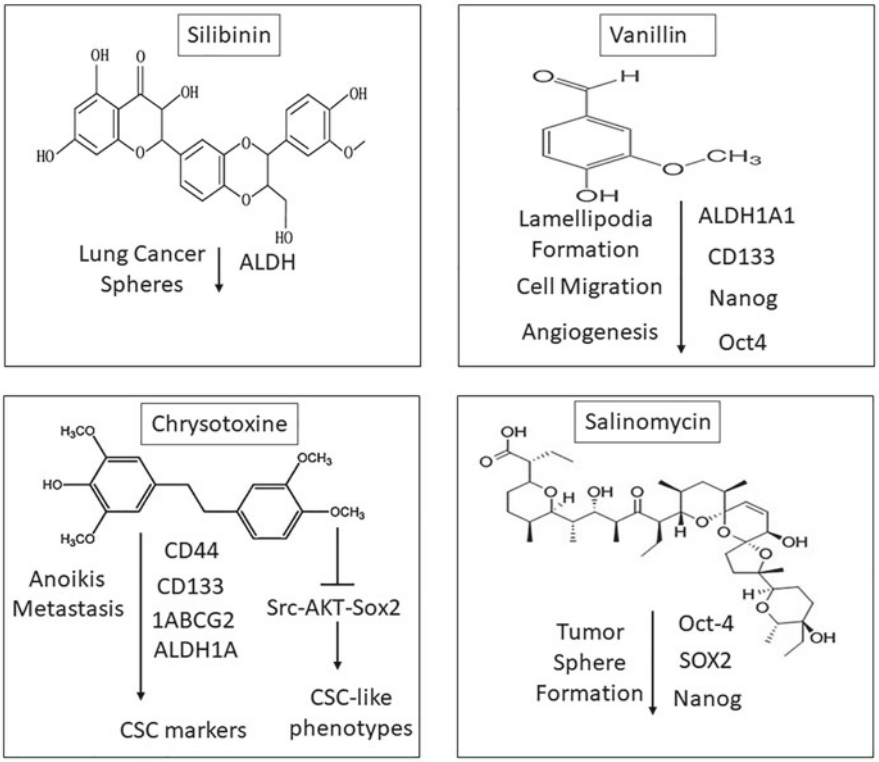
Cancer stem cells (CSCs) are assumed to possess characteristic features such as self-renewal capacity, heterogeneity, and high tumorigenic potential which make it distinguished from normal cells. Detail of each feature is given below:

1. Self-renewal capacity: CSCs have a distinctive ability of self-renewal (like normal stem cells). They divide rapidly and give rise to identical daughter cells. These daughter cells have the same characteristics as like stem cells.
2. Unique ability to direct tumor heterogeneity as well as tumor survival: CSCs can differentiate into various cancer cell lineages, also assist the growth of the tumor cell along with survival.
3. High tumorigenic potential: CSCs have the capability to swiftly proliferate and form non-CSC linages with a new tumor cell.

Different researches (in vivo and in vitro) have been shown that the cancer cells originated from a similar tumor have distinguished features to generate malignant tumor spheroid. Accumulation of genetic and epigenetic modifications in the same tumor derived from cancer cells possesses diverse signaling and cellular properties. These alterations in tumor assets are related to heterogeneity and the plasticity of CSCs that can be identified with certain specialized biomarkers [126].

10.5.2 Natural Compounds and Lung Cancer Stem Cells

Lung malignant growth has been known as a perilous disease from several years. In comparison to other cancers, the expiry rate of such cancer is more



ALDH: Aldehyde dehydrogenase; ALDH1A1: aldehyde dehydrogenase 1 A1; CD133: Antigen; Nanog: Transcription factor; Oct-4: octamer-binding transcription factor 4; SOX-2: Sex determining region Y box 2; CD44: Non-kinase transmembrane glycoprotein; 1ABCG2: Biomarker

Fig. 10.6 Natural compounds targeting lung cancer stem cells

[127]. Therapeutic approaches such as surgery, targeted therapy, chemotherapy, and radiotherapy have failed to get rid of the CSCs population which is the main source of disease relapse. Thus, natural compounds have been found as a therapeutic intervention that specifically targets CSCs in an efficient and precise way to eliminate lung cancer (Fig. 10.6).

10.5.2.1 Chrysotoxine

Chrysotoxine (bibenzyl) is derived from the stem of *Dendrobium pulchellum* and is reported to inhibit metastasis and sensitize anoikis in lung cancer cells via an anchorage-independent manner. Recently, the suppressive role of chrysotoxine was investigated in primary CSCs culture and cell lines H23 and H460 (CSC-rich population). Chrysotoxine has the ability to decrease CSC markers such as CD44,

CD133, ALDH1A, 1ABCG2, and inhibited CSC-like phenotypes through the Src-AKT-Sox2-dependent mechanism [128].

10.5.2.2 Vanillin

Vanillin (4-hydroxy-3-methoxybenzaldehyde) is isolated from *Vanilla planifolia* (seed) and extensively used as a flavoring agent in cosmetics and food. Vanillin induced apoptosis and inhibited angiogenesis, lamellipodia formation, and cell migration in various types of cancer including lung cancer. Additionally, vanillin reduces ALDH1A1 and CD133 expression and associated transcription factor Nanog and Oct4 in H460 cells via reducing Akt and down streaming CSC transcription factors [129, 130].

10.5.2.3 Silibinin

Silibinin, a polyphenolic flavonoid isolated from *Silybum marianum* (milk thistle seed), has the ability to diminish lung cancer. Silibinin abridged aldehyde dehydrogenase (ALDH) expressing CSC-like cells and also prevented the formation of lung cancer spheres in a dose-dependent manner in erlotinib refractory cell populations [131].

10.5.2.4 Salinomycin

Salinomycin, a polyether ionophore antibiotic is obtained from *Streptomyces albus*. Salinomycin treatment has shown to inhibit tumor-sphere formation as well as reduce Oct-4, SOX2, and Nanog expression in aldehyde dehydrogenase A549 lung cells [132]. Both salinomycin-NPs (salinomycin-nanoparticles) and salinomycin have been found to target CSC biomarker CD133 and reduce tumor-sphere formation. Moreover, a combination of gefitinib-NPs and salinomycin-NPs was reported to have an efficient suppressive impact against the growth of tumors than single gefitinib-NPs or salinomycin-NPs or combination of salinomycin and gefitinib [133, 134].

10.6 Conclusion

Cancer is caused by uncontrolled proliferation and growth of cells. Lung cancer is a common type of cancer and is considered the leading cause of mortality throughout the world. Since chemotherapeutic drugs act as an efficient approach for lung cancer treatment, but cancer cells have the potential to exhibit resistance against chemotherapy. Although radiation and immunotherapy are also reported as therapeutic interventions to eradicate cancer cells proliferation and progression, but not exhibit promising treatment approaches. In this regard, molecular targeted therapy of natural compounds with fewer or no side effects has been found as an efficient and alternative treatment strategy for lung cancer. Phytochemicals such as curcumin, quercetin, berberine, resveratrol, gigantol, and indole-3 carbinol are reported to inhibit apoptosis via cell cycle arrest, upregulation of Bax, Bad, and downregulation of anti-apoptotic proteins such as Bcl-2, XIAP, and Bcl-xL. Moreover, this chapter also

highlighted that these natural compounds have also the ability to target intracellular signaling pathways such as PI3K/Akt, ERK1/2, NFκB, and TGF-β1 mediated pathways to inhibit the growth of tumor cell. Conclusively, natural compounds could serve as an ideal anticancer drug for the treatment of lung cancer by regulating the molecular targets involved in apoptosis, angiogenesis, and metastasis of tumor cells.

References

1. Liu T, Liu X, Li W (2016) Tetrandrine, a Chinese plant-derived alkaloid, is a potential candidate for cancer chemotherapy. Oncotarget 7(26):40800–40815. https://doi.org/10.18632/oncotarget.8315
2. Rupa EJ et al (2020) Dendropanax Morbifera extract-mediated ZnO nanoparticles loaded with Indole-3-Carbinol for enhancement of anticancer efficacy in the A549 human lung carcinoma cell line. Materials 13(3197):1–16. https://doi.org/10.3390/ma13143197
3. Mateen S, Raina K, Agarwal R (2013) Chemopreventive and anti-cancer efficacy of silibinin against growth and progression of lung cancer. Nutr Cancer 65(Suppl.1):3–11. https://doi.org/10.1080/01635581.2013.785004
4. Maiuthed A, Chantarawong W, Chanvorachote P (2018) Lung cancer stem cells and cancer stem cell-targeting natural compounds. Anticancer Res 38(7):3797–3810. https://doi.org/10.21873/anticanres.12663
5. van Breda SGJ, de Kok TMCM, van Delft JHM (2008) Mechanisms of colorectal and lung cancer prevention by vegetables: a genomic approach. J Nutr Biochem 19(3):139–157. https://doi.org/10.1016/j.jnutbio.2007.04.002
6. Nair P, Malhotra A, Dhawan DK (2014) Curcumin and quercetin trigger apoptosis during benzo(a)pyrene-induced lung carcinogenesis. Mol Cell Biochem 400(1–2):51–56. https://doi.org/10.1007/s11010-014-2261-6
7. Zhou Q, Pan H, Li J (2019a) Molecular insights into potential contributions of natural polyphenols to lung cancer treatment. Cancers 11(10):1–33. https://doi.org/10.3390/cancers11101565
8. Li J et al (2018) Berberine hydrochloride inhibits cell proliferation and promotes apoptosis of non-small cell lung cancer via the suppression of the MMP2 and Bcl-2/bax signaling pathways. Oncol Lett 15(5):7409–7414. https://doi.org/10.3892/ol.2018.8249
9. Chang WA et al (2016) Laricitrin ameliorates lung cancer-mediated dendritic cell suppression by inhibiting signal transducer and activator of transcription 3. Oncotarget 7(51):85220–85234. https://doi.org/10.18632/oncotarget.13240
10. Howington JA et al (2013) Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. Chest 143(5 Suppl):e278S–e313S. https://doi.org/10.1378/chest.12-2359
11. Chen J et al (2015a) Cisplatin resistance in human cervical, ovarian and lung cancer cells. Cancer Chemother Pharmacol 75(6):1217–1227. https://doi.org/10.1007/s00280-015-2739-2
12. Song X et al (2011) Treatment of lung cancer patients and concomitant use of drugs interacting with cytochrome P450 isoenzymes. Lung Cancer 74(1):103–111. https://doi.org/10.1016/j.lungcan.2011.01.016
13. Mao Z et al (2019) Fucosterol exerts antiproliferative effects on human lung cancer cells by inducing apoptosis, cell cycle arrest and targeting of Raf/MEK/ERK signalling pathway. Phytomedicine 61:152809. https://doi.org/10.1016/j.phymed.2018.12.032
14. Kelloff GJ et al (2000) Progress in cancer chemoprevention: development of diet-derived chemopreventive agents. J Nutr 130(2S suppl):467S–471S. https://doi.org/10.1093/jn/130.2.467s

15. Kim C, Kim B (2018) Anti-cancer natural products and their bioactive compounds inducing ER stress-mediated apoptosis: a review. Nutrients 10(8):1021. https://doi.org/10.3390/nu10081021
16. Zhai T et al (2018) Potential micronutrients and phytochemicals against the pathogenesis of chronic obstructive pulmonary disease and lung cancer. Nutrients 10(7):813. https://doi.org/10.3390/nu10070813
17. Wattanathamsan O, Hayakawa Y, Pongrakhananon V (2019) Molecular mechanisms of natural compounds in cell death induction and sensitization to chemotherapeutic drugs in lung cancer. Phytother Res 33(10):2531–2547. https://doi.org/10.1002/ptr.6422
18. Zhong W, Qin Y, Shuang C, Sun T (2017) Antitumor effect of natural product molecules against lung cancer. In: Adonis M (ed) A global scientific vision – prevention, diagnosis, and treatment of lung cancer. IntechOpen. https://doi.org/10.1016/j.colsurfa.2011.12.014
19. Poofery J et al (2020) Potential of Thai herbal extracts on lung cancer treatment by inducing apoptosis and synergizing chemotherapy. Molecules 25(1):231. https://doi.org/10.3390/molecules25010231
20. Park KIL et al (2014) Flavonoids identified from Korean Citrus aurantium L. inhibit non-small cell lung Cancer growth in vivo and in vitro. J Funct Foods 7(1):287–297. https://doi.org/10.1016/j.jff.2014.01.032
21. Kilarski WW et al (2012) An in vivo neovascularization assay for screening regulators of angiogenesis and assessing their effects on pre-existing vessels. Angiogenesis 15(4):643–655. https://doi.org/10.1007/s10456-012-9287-8
22. Cao Y (2016) Future options of anti-angiogenic cancer therapy. Chin J Cancer 35(2):1–9. https://doi.org/10.1186/s40880-016-0084-4
23. Han M, Song Y, Zhang X (2016) Quercetin suppresses the migration and invasion in human colon cancer caco-2 cells through regulating toll-like receptor 4/nuclear factor-kappa B pathway. Pharmacognosy Magazine 12(46):S237. https://doi.org/10.4103/0973-1296.182154
24. Jiang Q et al (2016) Lunasin suppresses the migration and invasion of breast cancer cells by inhibiting matrix metalloproteinase-2/−9 via the FAK/Akt/ERK and NF-κB signaling pathways. Oncol Rep 36(1):253–262. https://doi.org/10.3892/or.2016.4798
25. Chanvorachote P et al (2016) Potential anti-metastasis natural compounds for lung cancer. Anticancer Res 36(11):5707–5717. https://doi.org/10.21873/anticanres.11154
26. Sznarkowska A et al (2017) Inhibition of cancer antioxidant defense by natural compounds. Oncotarget 8(9):15996–16016. https://doi.org/10.18632/oncotarget.13723
27. Zanoaga O et al (2019) Progress in research on the role of flavonoids in lung Cancer. Int J Mol Sci 20(4291):1–19. https://doi.org/10.1515/biol-2020-0035
28. Chen W et al (2007) Induction of death receptor 5 and suppression of survivin contribute to sensitization of TRAIL-induced cytotoxicity by quercetin in non-small cell lung cancer cells. Carcinogenesis 28(10):2114–2121. https://doi.org/10.1093/carcin/bgm133
29. Youn HS et al (2013) Quercetin potentiates apoptosis by inhibiting nuclear factor-kappaB signaling in H460 lung cancer cells. Biol Pharm Bull 36(6):944–951. https://doi.org/10.1248/bpb.b12-01004
30. Le Marchand L et al (2000) Intake of flavonoids and lung cancer. J Natl Cancer Inst 92(2):154–160. https://doi.org/10.1093/jnci/92.2.154
31. Chang JH et al (2017) Quercetin suppresses the metastatic ability of lung cancer through inhibiting snail-dependent Akt activation and snail-independent ADAM9 expression pathways. Biochim Biophys Acta Mol Cell Res 1864(10):1746–1758. https://doi.org/10.1016/j.bbamcr.2017.06.017
32. Tomeh MA, Hadianamrei R, Zhao X (2019) A review of curcumin and its derivatives as anticancer agents. Int J Mol Sci 20(5):1033. https://doi.org/10.3390/ijms20051033
33. Li Y et al (2013) Curcumin inhibits human non-small cell lung cancer A549 cell proliferation through regulation of Bcl-2/Bax and cytochrome C. Asian Pacific Organiz Cancer Prev 14(8):4599–4602. https://doi.org/10.7314/APJCP.2013.14.8.4599

34. Pillai GR et al (2004) Induction of apoptosis in human lung cancer cells by curcumin. Cancer Lett 208(2):163–170. https://doi.org/10.1016/j.canlet.2004.01.008
35. Saha A et al (2010) Apoptosis of human lung cancer cells by curcumin mediated through up-regulation of "growth arrest and DNA damage inducible genes 45 and 153". Biol Pharm Bull 33(8):1291–1299. https://doi.org/10.1248/bpb.33.1291
36. Yang CL et al (2012) Curcumin induces small cell lung cancer NCI-H446 cell apoptosis via the reactive oxygen species-mediated mitochondrial pathway and not the cell death receptor pathway. DNA Cell Biol 31(2):139–150. https://doi.org/10.1089/dna.2011.1300
37. Jin H et al (2015) Curcumin inhibits cell proliferation and induces apoptosis of human non-small cell lung cancer cells through the upregulation of miR-192-5p and suppression of PI3K/Akt signaling pathway. Oncol Rep 34(5):2782–2789. https://doi.org/10.3892/or.2015.4258
38. Liao H et al (2015) Curcumin inhibits lung cancer invasion and metastasis by attenuating GLUT1/MT1-MMP/MMP2 pathway. Int J Clin Exp Med 8(6):8948–8957
39. Liu GD et al (2014) Genistein alleviates radiation-induced pneumonitis by depressing Ape1/Ref-1 expression to Down-regulate inflammatory cytokines. Cell Biochem Biophys 69(3):725–733. https://doi.org/10.1007/s12013-014-9859-x
40. Rajesh E et al (2015) Naturally occurring products in cancer therapy. J Pharm Bioallied Sci 7(Suppl 1):S181–S183. https://doi.org/10.4103/0975-7406.155895
41. Zhang Z et al (2018) Genistein promotes ionizing radiation-induced cell death by reducing cytoplasmic Bcl-xL levels in non-small cell lung cancer. Sci Rep 8(1):1–9. https://doi.org/10.1038/s41598-017-18755-3
42. Jones V, Katiyar SK (2013) Emerging phytochemicals for prevention of melanoma invasion. Cancer Lett 335(2):251–258. https://doi.org/10.1016/j.canlet.2013.02.056
43. Luzna P et al (2011) Changes of microRNAs-192, 196a and 203 correlate with Barrett's esophagus diagnosis and its progression compared to normal healthy individuals. Diagn Pathol 6(1):114. https://doi.org/10.1186/1746-1596-6-114
44. Singh T, Prasad R, Katiyar SK (2016) Therapeutic intervention of silymarin on the migration of non-small cell lung cancer cells is associated with the axis of multiple molecular targets including class 1 HDACs, ZEB1 expression, and restoration of miR-203 and E-cadherin expression. Am J Cancer Res 6(6):1287–1301
45. Liang L et al (2012) Sophoridine exerts an anti-colorectal carcinoma effect through apoptosis induction in vitro and in vivo. Life Sci 91(25–26):1295–1303. https://doi.org/10.1016/j.lfs.2012.09.021
46. Zhu L et al (2020) Sophoridine inhibits lung cancer cell growth and enhances cisplatin sensitivity through activation of the p53 and hippo signaling pathways. Gene 742:144556. https://doi.org/10.1016/j.gene.2020.144556
47. Lin CH et al (2010) GMI, a Ganoderma immunomodulatory protein, down-regulates tumor necrosis factor α-induced expression of matrix metalloproteinase 9 via NF-κB pathway in human alveolar epithelial A549 cells. J Agric Food Chem 58(22):12014–12021. https://doi.org/10.1021/jf103068w
48. Yodkeeree S, Pompimon W, Limtrakul P (2014) Crebanine, an aporphine alkaloid, sensitizes TNF-α-induced apoptosis and suppressed invasion of human lung adenocarcinoma cells A549 by blocking NF-κB-regulated gene products. Tumor Biol 35(9):8615–8624. https://doi.org/10.1007/s13277-014-1998-6
49. Gao CJ et al (2018) Oxymatrine sensitizes the HaCaT cells to the IFN-γ pathway and Downregulates MDC, ICAM-1, and SOCS1 by activating p38, JNK, and Akt. Inflammation 41(2):606–613. https://doi.org/10.1007/s10753-017-0716-0
50. Liang J et al (2018) Oxymatrine prevents synovial inflammation and migration via blocking NF-κB activation in rheumatoid fibroblast-like synoviocytes. Int Immunopharmacol 55:105–111. https://doi.org/10.1016/j.intimp.2017.12.006

51. Fei ZW et al (2015) Oxymatrine suppresses proliferation and induces apoptosis of hemangioma cells through inhibition of HIF-1a signaling. Int J Immunopathol Pharmacol 28 (2):201–208. https://doi.org/10.1177/0394632015578342
52. Zhou W et al (2019b) Proliferation and migration of lung cancer could be inhibited by oxymatrine through the regulation for miR-520/VEGF. Am J Chin Med 47(4):865–878. https://doi.org/10.1142/S0192415X19500459
53. Singh T et al (2011) Berberine, an isoquinoline alkaloid, inhibits melanoma cancer cell migration by reducing the expressions of cyclooxygenase-2, prostaglandin E2 and prostaglandin E2 receptors. Carcinogenesis 32(1):86–92. https://doi.org/10.1093/carcin/bgq215
54. Tan W et al (2011) Berberine hydrochloride: anticancer activity and nanoparticulate delivery system. Int J Nanomed 6:1773–1777. https://doi.org/10.2147/ijn.s22683
55. Tsang CM et al (2009) Berberine inhibits rho GTPases and cell migration at low doses but induces G2 arrest and apoptosis at high doses in human cancer cells. Int J Mol Med 24 (1):131–138. https://doi.org/10.3892/ijmm_00000216
56. Qi HW et al (2014) Epithelial-to-mesenchymal transition markers to predict response of Berberine in suppressing lung cancer invasion and metastasis. J Transl Med 12(1):1–10. https://doi.org/10.1186/1479-5876-12-22
57. Singh J, Luqman S, Meena A (2020) Emerging role of phytochemicals in targeting predictive, prognostic, and diagnostic biomarkers of lung cancer. Food Chem Toxicol 144:111592. https://doi.org/10.1016/j.fct.2020.111592
58. Liang CH et al (2007) Solamargine upregulation of Fas, downregulation of HER2, and enhancement of cytotoxicity using epirubicin in NSCLC cells. Mol Nutr Food Res 51 (8):999–1005. https://doi.org/10.1002/mnfr.200700044
59. Chen YQ et al (2015b) Inactivation of PI3-K/Akt and reduction of SP1 and p65 expression increase the effect of solamargine on suppressing EP4 expression in human lung cancer cells. J Exp Clin Cancer Res 34(1):1–11. https://doi.org/10.1186/s13046-015-0272-0
60. Schuurbiers OCJ et al (2009) The PI3-K/AKT-pathway and radiation resistance mechanisms in non-small cell lung cancer. J Thorac Oncol 4(6):761–767. https://doi.org/10.1097/JTO.0b013e3181a1084f
61. Samarghandian S, Boskabady MH, Davoodi S (2010) Use of in vitro assays to assess the potential antiproliferative and cytotoxic effects of saffron (Crocus sativus L.) in human lung cancer cell line. Pharmacogn Mag 6(24):309–314. https://doi.org/10.4103/0973-1296.71799
62. Abe A, Yamada H (2009) Harmol induces apoptosis by caspase-8 activation independently of Fas/Fas ligand interaction in human lung carcinoma H596 cells. Anti-Cancer Drugs 20 (5):373–381. https://doi.org/10.1097/cad.0b013e32832a2dd9
63. Abe A et al (2011) The β-carboline alkaloid harmol induces cell death via autophagy but not apoptosis in human non-small cell lung cancer A549 cells. Biol Pharm Bull 34(8):1264–1272. https://doi.org/10.1248/bpb.34.1264
64. Ellington AA, Berhow MA, Singletary KW (2006) Inhibition of Akt signaling and enhanced ERK1/2 activity are involved in induction of macroautophagy by triterpenoid B-group soyasaponins in colon cancer cells. Carcinogenesis 27(2):298–306. https://doi.org/10.1093/carcin/bgi214
65. Chirumbolo S (2014) Dietary assumption of plant polyphenols and prevention of allergy. Curr Pharm Des 20(6):811–839. https://doi.org/10.2174/13816128113199990042
66. Pandey KB, Rizvi SI (2009) Plant polyphenols as dietary antioxidants in human health and disease. Oxidative Med Cell Longev 2(5):270–278. https://doi.org/10.4161/oxim.2.5.9498
67. Aggarwal BB et al (2004) Role of resveratrol in prevention and therapy of cancer: preclinical and clinical studies. Anticancer Res 24(5A):2783–2840
68. Salehi B et al (2018) Resveratrol: a double-edged sword in health benefits. Biomedicines 6 (3):91. https://doi.org/10.3390/biomedicines6030091
69. Whyte L et al (2007) Molecular mechanisms of resveratrol action in lung cancer cells using dual protein and microarray analyses. Cancer Res 67(24):12007–12017. https://doi.org/10.1158/0008-5472.CAN-07-2464

70. Han Z et al (2012) MicroRNA-622 functions as a tumor suppressor by targeting K-Ras and enhancing the anticarcinogenic effect of resveratrol. Carcinogenesis 33(1):131–139. https://doi.org/10.1093/carcin/bgr226
71. Lee EJ et al (2004) G2/M cell cycle arrest and induction of apoptosis by a stilbenoid, 3,4,5-trimethoxy-4′-bromo-cis-stilbene, in human lung cancer cells. Life Sci 75(23):2829–2839. https://doi.org/10.1016/j.lfs.2004.07.002
72. Girish C, Pradhan SC (2008) Drug development for liver diseases: focus on picroliv, ellagic acid and curcumin. Fundam Clin Pharmacol 22(6):623–632. https://doi.org/10.1111/j.1472-8206.2008.00618.x
73. Pereira V et al (2010) HPLC-DAD methodology for the quantification of organic acids, furans and polyphenols by direct injection of wine samples. J Sep Sci 33(9):1204–1215. https://doi.org/10.1002/jssc.200900784
74. Talcott ST, Lee JH (2002) Ellagic acid and flavonoid antioxidant content of muscadine wine and juice. J Agric Food Chem 50(11):3186–3192. https://doi.org/10.1021/jf011500u
75. Heber D (2008) Multitargeted therapy of cancer by ellagitannins. Cancer Lett 269(2):262–268. https://doi.org/10.1016/j.canlet.2008.03.043
76. Zhang HM et al (2014) Research progress on the anticarcinogenic actions and mechanisms of ellagic acid. Cancer Biol Med 11(2):92–100. https://doi.org/10.7497/j.issn.2095-3941.2014.02.004
77. Duan J et al (2019) The red wine component ellagic acid induces autophagy and exhibits anti-lung cancer activity in vitro and in vivo. J Cell Mol Med 23(1):143–154. https://doi.org/10.1111/jcmm.13899
78. Roy M et al (2003) Anticlastogenic, antigenotoxic and apoptotic activity of epigallocatechin gallate: a green tea polyphenol. Mutat Res 523–524:33–41. https://doi.org/10.1016/S0027-5107(02)00319-6
79. Yang CS et al (2009) Cancer prevention by tea: animal studies, molecular mechanisms and human relevance. Nat Rev Cancer 9(6):429–439. https://doi.org/10.1038/nrc2641
80. Sadava D, Whitlock E, Kane SE (2007) The green tea polyphenol, epigallocatechin-3-gallate inhibits telomerase and induces apoptosis in drug-resistant lung cancer cells. Biochem Biophys Res Commun 360(1):233–237. https://doi.org/10.1016/j.bbrc.2007.06.030
81. Chen BH et al (2020) Anticancer effects of epigallocatechin-3-gallate nanoemulsion on lung cancer cells through the activation of AMP-activated protein kinase signaling pathway. Nat Res 10(1):5163. https://doi.org/10.1038/s41598-020-62136-2
82. Wang H, Bian S, Yang CS (2011) Green tea polyphenol EGCG suppresses lung cancer cell growth through upregulating miR-210 expression caused by stabilizing HIF-1α. Carcinogenesis 32(12):1881–1889. https://doi.org/10.1093/carcin/bgr218
83. Hlosrichok A et al (2018) A bibenzyl from Dendrobium ellipsophyllum induces apoptosis in human lung cancer cells. J Nat Med 72(3):615–625. https://doi.org/10.1007/s11418-018-1186-x
84. Chaotham C et al (2014) A bibenzyl from Dendrobium ellipsophyllum inhibits epithelial-to-mesenchymal transition and sensitizes lung cancer cells to anoikis. Anticancer Res 34(4):1931–1938
85. Bhummaphan N, Chanvorachote P (2015) Gigantol suppresses Cancer stem cell-like phenotypes in lung Cancer cells. Evid Based Complement Alternat Med 2015:836564. https://doi.org/10.1155/2015/836564
86. Chen Y et al (2008) Cytotoxic phenolics from Bulbophyllum odoratissimum. Food Chem 107(1):169–173. https://doi.org/10.1016/j.foodchem.2007.07.077
87. Sritularak B, Anuwat M, Likhitwitayawuid K (2011) A new phenanthrenequinone from Dendrobium draconis. J Asian Nat Prod Res 13(3):251–255. https://doi.org/10.1080/10286020.2010.546354
88. Chunhacha P, Chanvorachote P (2012) Roles of caveolin-1 on anoikis resistance in non small cell lung cancer. Int J Physiol Pathophysiol Pharmacol 4(3):149–155

89. Luanpitpong S et al (2010) Regulation of lung cancer cell migration and invasion by reactive oxygen species and caveolin-1. J Biol Chem 285(50):38832–38840. https://doi.org/10.1074/jbc.M110.124958
90. Charoenrungruang S et al (2014) Gigantol, a bibenzyl from Dendrobium draconis, inhibits the migratory behavior of non-small cell lung cancer cells. J Nat Prod 77(6):1359–1366. https://doi.org/10.1021/np500015v
91. Dhankhar J, Kadian SS, Sharma A (2012) Astaxanthin: a potential carotenoid. Int J Pharm Sci Res 3(05):1246–1259. https://doi.org/10.13040/IJPSR.0975-8232.3(5)
92. Wu C et al (2016a) Astaxanthin inhibits proliferation and promotes apoptosis of A549 lung cancer cells via blocking JAK1/STAT3 pathway. Chin J Cell Mol Immunol 32(6):784–788
93. Liao KS et al (2016) Astaxanthin enhances pemetrexed-induced cytotoxicity by downregulation of thymidylate synthase expression in human lung cancer cells. Regulat Toxicol Pharmacol 81:353–361. https://doi.org/10.1016/j.yrtph.2016.09.031
94. Ko JC et al (2016) Astaxanthin down-regulates Rad51 expression via inactivation of AKT kinase to enhance mitomycin C-induced cytotoxicity in human non-small cell lung cancer cells. Biochem Pharmacol 105:91–100. https://doi.org/10.1016/j.bcp.2016.02.016
95. Chen X et al (2002) Cellular pharmacology studies of shikonin derivatives. Phytother Res 16 (3):199–209. https://doi.org/10.1002/ptr.1100
96. Lu L et al (2011) Shikonin extracted from medicinal Chinese herbs exerts anti-inflammatory effect via proteasome inhibition. Eur J Pharmacol 658(2–3):242–247. https://doi.org/10.1016/j.ejphar.2011.02.043
97. Yeh YC, Liu TJ, Lai HC (2015) Shikonin induces apoptosis, necrosis, and premature senescence of human A549 lung cancer cells through upregulation of p53 expression. Evid Based Complement Alternat Med 2015:620383. https://doi.org/10.1155/2015/620383
98. Yeh CC et al (2007) Shikonin-induced apoptosis involves caspase-3 activity in a human bladder cancer cell line (T24). In Vivo 21(6):1011–1020
99. Hsieh YS et al (2017) Shikonin inhibited migration and invasion of human lung Cancer cells via suppression of c-met-mediated epithelial-to-Mesenchymal transition. J Cell Biochem 118 (12):4639–4651. https://doi.org/10.1002/jcb.26128
100. Li YC et al (2014) Plumbagin induces apoptotic and autophagic cell death through inhibition of the PI3K/Akt/mTOR pathway in human non-small cell lung cancer cells. Cancer Lett 344 (2):239–259. https://doi.org/10.1016/j.canlet.2013.11.001
101. Tripathi SK, Rengasamy KRR, Biswal BK (2020) Plumbagin engenders apoptosis in lung cancer cells via caspase-9 activation and targeting mitochondrial-mediated ROS induction. Arch Pharm Res 43(2):242–256. https://doi.org/10.1007/s12272-020-01221-6
102. Yu T et al (2018) Plumbagin suppresses the human large cell lung cancer cell lines by inhibiting IL-6/STAT3 signaling in vitro. Int Immunopharmacol 55:290–296. https://doi.org/10.1016/j.intimp.2017.12.021
103. Dagne A et al (2011) Enhanced inhibition of lung adenocarcinoma by combinatorial treatment with indole-3-carbinol and silibinin in a/J mice. Carcinogenesis 32(4):561–567. https://doi.org/10.1093/carcin/bgr010
104. Song JM et al (2015) Combinations of indole-3-carbinol and silibinin suppress inflammation-driven mouse lung tumorigenesis by modulating critical cell cycle regulators. Carcinogenesis 36(6):666–675. https://doi.org/10.1093/carcin/bgv054
105. Choi HS et al (2010) Indole-3-carbinol induces apoptosis through p53 and activation of caspase-8 pathway in lung cancer A549 cells. Food Chem Toxicol 48(3):883–890. https://doi.org/10.1016/j.fct.2009.12.028
106. Kassie F, Melkamu T et al (2010a) Inhibition of lung carcinogenesis and critical cancer-related signaling pathways by N-acetyl-S-(N-2-phenethylthiocarbamoyl)-l-cysteine, indole-3-carbinol and myo-inositol, alone and in combination. Carcinogenesis 31(9):1634–1641. https://doi.org/10.1093/carcin/bgq139

107. Melkamu T et al (2010) Alteration of microRNA expression in vinyl carbamate-induced mouse lung tumors and modulation by the chemopreventive agent indole-3-carbinol. Carcinogenesis 31(2):252–258. https://doi.org/10.1093/carcin/bgp208
108. Kassie F, Kalscheuer S et al (2010b) Inhibition of vinyl carbamate-induced pulmonary adenocarcinoma by indole-3-carbinol and myo-inositol in a/J mice. Carcinogenesis 31 (2):239–245. https://doi.org/10.1093/carcin/bgp174
109. Hong B et al (2014) Targeting tumor suppressor p53 for Cancer therapy: strategies, challenges and opportunities. Curr Drug Targets 15(1):80–89. https://doi.org/10.2174/1389450114666140106101412
110. Wu TC et al (2016b) The enhancing effect of genistein on apoptosis induced by trichostatin a in lung cancer cells with wild type p53 genes is associated with upregulation of histone acetyltransferase. Toxicol Appl Pharmacol 292:94–102. https://doi.org/10.1016/j.taap.2015.12.028
111. Chen Y et al (2015c) MicroRNAs as regulators of Cisplatin resistance in lung Cancer. Cell Physiol Biochem 37(5):1869–1880. https://doi.org/10.1159/000438548
112. Müller CB et al (2015) Potential crosstalk between cofilin-1 and EGFR pathways in cisplatin resistance of non-small-cell lung cancer. Oncotarget 6(6):3531–3539. https://doi.org/10.18632/oncotarget.3471
113. Kwok MH, Xi HW, Xue H (2000) Interaction of flavones from the roots of Scutellaria baicalensis with the benzodiazepine site. Planta Med 66(1):91–93. https://doi.org/10.1055/s-0029-1243121
114. Takahashi H et al (2011) Baicalein, a component of Scutellaria baicalensis, induces apoptosis by Mcl-1 down-regulation in human pancreatic cancer cells. Biochim Biophys Acta 1813 (8):1465–1474. https://doi.org/10.1016/j.bbamcr.2011.05.003
115. Hubaux R et al (2015) Microtubule affinity-regulating kinase 2 is associated with DNA damage response and cisplatin resistance in non-small cell lung cancer. Int J Cancer 137 (9):2072–2082. https://doi.org/10.1002/ijc.29577
116. Xu Z, Mei J, Tan Y (2017) Baicalin attenuates DDP (cisplatin) resistance in lung cancer by downregulating MARK2 and p-Akt. Int J Oncol 50(1):93–100. https://doi.org/10.3892/ijo.2016.3768
117. Duan S et al (2015) IL-6 signaling contributes to cisplatin resistance in non-small cell lung cancer via the up-regulation of anti-apoptotic and DNA repair associated molecules. Oncotarget 6(29):27651–27660. https://doi.org/10.18632/oncotarget.4753
118. Jiao L et al (2017) Effects of Chinese medicine as adjunct medication for adjuvant chemotherapy treatments of non-small cell lung cancer patients. Sci Rep 7:1–12. https://doi.org/10.1038/srep46524
119. Alam N et al (2005) Compliance with post-operative adjuvant chemotherapy in non-small cell lung cancer: an analysis of National Cancer Institute of Canada and intergroup trial JBR.10 and a review of the literature. Lung Cancer 47(3):385–394. https://doi.org/10.1016/j.lungcan.2004.08.016
120. Habli Z et al (2017) Emerging cytotoxic alkaloids in the battle against cancer: overview of molecular mechanisms. Molecules 22(2):1–22. https://doi.org/10.3390/molecules22020250
121. Landen JW et al (2002) Noscapine alters microtubule dynamics in living cells and inhibits the progression of melanoma. Cancer Res 62(14):4109–4114
122. Chougule M et al (2011) Anticancer activity of Noscapine, an opioid alkaloid in combination with Cisplatin in human non-small cell lung cancer. Lung Cancer 71(3):271–282. https://doi.org/10.1016/j.lungcan.2010.06.002
123. Bonnet D, Dick JE (1997) Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat Med 3(7):730–737. https://doi.org/10.1038/nm0797-730
124. Pardal R, Clarke MF, Morrison SJ (2003) Applying the principles of stem-cell biology to cancer. Nat Rev Cancer 3(12):895–902. https://doi.org/10.1038/nrc1232

125. Nassar D, Blanpain C (2016) Cancer stem cells: basic concepts and therapeutic implications. Annu Rev Pathol: Mech Dis 11:47–76. https://doi.org/10.1146/annurev-pathol-012615-044438
126. Meacham CE, Morrison SJ (2013) Tumour heterogeneity and cancer cell plasticity. Nature 501(7467):328–337. https://doi.org/10.1038/nature12624
127. Ferlay J et al (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136(5):E359–E386. https://doi.org/10.1002/ijc.29210
128. Chanvorachote P et al (2013) Anti-metastatic activities of bibenzyls from Dendrobium pulchellum. Nat Prod Commun 8(1):115–118. https://doi.org/10.1177/1934578x1300800127
129. Bezerra DP, Soares AKN, De Sousa DP (2016) Overview of the role of vanillin on redox status and cancer development. Oxidative Med Cell Longev 2016:973481. https://doi.org/10.1155/2016/9734816
130. Lirdprapamongkol K et al (2010) Vanillin enhances TRAIL-induced apoptosis in cancer cells through inhibition of NF-κB activation. In Vivo 24(4):501–506
131. Corominas-Faja B et al (2013) Stem cell-like ALDHbright cellular states in EGFR-mutant non-small cell lung cancer a novel mechanism of acquired resistance to erlotinib targetable with the natural polyphenol silibinin. Cell Cycle 12(21):3390–3404. https://doi.org/10.4161/cc.26417
132. Gao J et al (2019) Co-delivery of docetaxel and salinomycin to target both breast cancer cells and stem cells by plga/tpgs nanoparticles. Int J Nanomedicine 2019:9199–9216. https://doi.org/10.2147/IJN.S230376
133. Huczynski A (2012) Salinomycin - a new Cancer drug candidate. Chem Biol Drug Des 79 (3):235–238. https://doi.org/10.1111/j.1747-0285.2011.01287.x
134. Wang Y (2012) Effects of Salinomycin on cancer stem cell in human lung adenocarcinoma A549 cells. Med Chem 7(2):106–111. https://doi.org/10.2174/157340611794859307

Exploring the Potential of Medicinal Plants in Lung Cancer

11

Anju Dhiman and Harish Dureja

Abstract

Lung carcinoma is the main cause of death among individuals, accounting for almost 25% of all deaths from cancer. A significant number of individual's perish due to lung cancer per year as compared to the colon, prostate, and breast cancer problem. Smoking and the use of tobacco products have been found to be responsible for nearly 90% of lung cancer cases. However, other factors may lead to lung carcinogenesis, such as air pollution exposures, asbestos, radon gas, and other chronic infections. The most used techniques for the treatment of lung carcinoma are chemotherapy, radiotherapy, and surgery. Standard chemotherapies, however, present severe patient toxicity, side effects and can result in minimal survival benefits. There are many medicinal plants having potential against lung cancer with minimal or no side effects, and, therefore, can be explored scientifically. These plant-derived phytochemicals and antitumor herbs have attracted the investigators/scientists due to their least or no harmful effects to the patient under treatment, as in case of chemotherapy. Studies have reported the covering of different approaches for treatment of lung cancer, however, a cumulative study comprising of the alternative options with natural compounds for lung cancer treatment is in the initial stages and the natural lead molecules responsible for the treatment using herbal medicinal plants are still very scarce. In the present chapter, epidemiology of lung cancer, lung cancer types, its underlying causes, and herbal medicines along with their lead compounds for the treatment of lung carcinoma have been discussed.

A. Dhiman · H. Dureja (✉)
Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, Haryana, India
e-mail: harishdureja@mdu.ac.in

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_11

Keywords

Carcinoma · Chemotherapy · Diagnosis · Herbal medicine · Lung cancer · Natural products

Abbreviations

BAC	Bronchioloalveolar carcinoma
DDP	Diamminedichloroplatinum
EGFR	Endothelial growth factor receptor
HIF	Hypoxia inducing factor
LCNEC	Large cell neuroendocrine carcinoma
nAChR	Nicotinicacetylcholine receptor
NSCLC	Non-small cell lung cancer
PARP	Poly-ADP ribose polymerase
SCLC	Small cell lung cancer
SM	Solamargine
SNP	Single nucleotide polymorphism
TNF	Tumor necrosis factor

11.1 Introduction

The World Health Organization (WHO) reported that the lung cancer (lung carcinoma) is one of the main reasons of deaths around the world [1–3]. The late diagnosis is the major reason of high casualty rate in lung carcinoma patient, with 70% of cases diagnosed at the final stages. This late diagnosis is the rate determining step in the cancer treatment such as radiotherapy and chemotherapy. The occurrence of lung cancer might be due to environmental factors, genetic factors, and lifestyle. The role of genetic factor is little, while environmental and lifestyle factors have an equal and led role in origin of lung cancer [4, 5]. Ionizing radiation, asbestos, tobacco smoking, sulfur mustard, and coal tar pitch are representative of environmental as well as lifestyle factors and responsible for lung carcinogens. Tobacco smoking is the most dominant threat responsible for lung carcinoma in approximately 80% of women and 90% of men. The lung cancer occurrence rate falls very gradually when the smoking is stopped. This concept is signifying that the person who has stopped the smoking is also the considerable carrier for developing lung cancer [6]. A family history increased the two-fold risk for lung cancer which suggests that genetic factors might play a crucial role in the individual's susceptibility to lung carcinoma. Though, only smoking is not responsible for lung cancers, the lung cancer patient's proportion who has by no means smoked may increase in the near future. Exposure to high doses of radiation, air pollution, pre-existing diseases such as tuberculosis or pneumonia and industrial or chemical cancer causing agents

such as silica, arsenic, and asbestos also enhanced the risk of developing lung carcinoma. There are other factors like in-house air pollution during cooking also plays an important part for non-smokers especially for women. As a result, besides cessation of smoking, life style adaptation might be a healthy alternative approach for the management of lung carcinoma [7, 8]. Lung carcinoma is a malign lung tissue marked by unrestricted growth of cells in the lung tissue [9]. Metastatis is the process by which cancer cells migrate throughout the body. Primary cancer of lungs is also called as first stage of lung cancer [10]. The survival rate after surgical treatment for non-small cell lung cancer (NSCLC) at earlier stage is much greater than that at the later stage of disease. Unfortunately, lung cancer is mostly recognized at late stages, because the symptoms are not clear and the observation is difficult at stage I and II of NSCLC. Thus, earlier observation of lung cancer is necessary which may lead to more efficacious management of the disease [3]. Increased life span and exposure to new causing agents made it a deadliest disease [11]. Many environmental factors contribute for the development of lung carcinoma in non-smokers. These factors are second-hand tobacco smoke, exposure of gases like polluted air, radon gas, etc. [12].

The basic symptoms of lung cancer are cough and dyspnea [13]. The possible symptoms of lung cancer include pain, cough, blood in sputum, problem in respiratory tract, fatigue, and loss of appetite. Additionally, many studies revealed that patient's quality of life has been decreased due to more severe form of symptoms. The quality of life has been minimized by the symptoms like pain, loss of appetite, fatigue, dyspnea, etc. [14].

11.2 Epidemiology

The studies on lung cancer have become an extensive subject of interest since last several decades. Lung cancer is more lethal, with greater than 90% mortality rate worldwide [15]. In recent year, the cases of lung cancer were 228,150 and deaths due to this disease was approximately 142,670 as estimated by [16] [17]. It is apparent that genetic and epigenetic pathways are quite different between anti-body drug conjugates and smoking-associated lung cancer. Furthermore, in non-smokers the peripheral cells of bronchioles and alveoli develop the lung cancer. On the other hand, squamous cell carcinomas (SCC), small cell lung cancer, and around 20% of adenocarcinoma developed in the bronchioles [18]. Out of all lung cancer patients, approximately 38.5% suffering from adenocarcinoma, while 20% suffering from squamous cell carcinoma and 2.9% suffering from large cell carcinoma. Since many years, the occurrence of adenocarcinoma has amplified greatly and adenocarcinoma has taken the place of squamous cell carcinoma as the most widespread type of non-small cell lung cancer [19].

Lung cancer detection at the starting point can significantly enlarge the survival chances in 70–90% of patients with non-small cell lung cancer (stage I). A very costly and incursive diagnostic test creates the hindrance in early diagnosis for lung

cancer. Hence, mostly patients have reached to later stage when they are diagnosed [20].

In USA, new cases of lung cancer are 12.9% and 5.3 lakh people survive with this disease. Incidence and mortality rate of lung carcinoma are continuously rising, worldwide [17]. The developed countries like Austria and Germany has faced it as a most regular cancer type. In African countries, smoking prevalent cases of lung cancer is low in both men and women, however at global level, lung carcinoma is less ubiquitous in women compared with men. Now the major reason behind the cancer mortality is lung cancer, accounts 1/fifth deaths by cancer in China and death rate is relatively high as compared to the other countries. Death rate in China is estimated to be increased at 40% from 2015 to 2030.

The developed countries such as North America and European countries are facing lung cancer as a common disease in comparison to developing countries like India and South America. Among men and women, lung cancer remains irregular reflecting gender difference of cigarette smoking pattern. Considering the population of women in China, death rate of lung carcinoma is incongruous because of less smoking, and high adenocarcinoma rate [21].

To trace the path, disease aspects and positive outcomes are assessed by epidemiological processes. In the second half of the twentieth century, the main reason behind the mortalities is lung cancer. Although, tobacco consumption remains globally and smoking cigarette resulted in lung cancer [11]. 16 lakh people had been received a new treatment of lung cancer in 2008 [22]. Incidence trend and deaths in the USA among men and women are 11 lakh and 10 lakh, respectively, and mortality is 84,600 in men and 71,340 in women. This represents reductions of cases and deaths in men in 1980. After 1990 and before 2007, there was 28% decline in men death rate. However, incidence of lung cancer increased in women in 1965 and since 2000 onwards, reduction of around 2% has been observed in comparison to the year 1990. Older patients are highly vulnerable to the lung cancer and show 17% mortality. The vulnerability of African, American race in the USA is more from other ethnic groups. Education level gives an inverse relationship between lung cancer and mortality rate. These groups account approximately 25% of total lung cancer patients with 3 lakh mortality per year. The sub groups of female with cell adenocarcinoma have more lung cancer cases, whereas in 30–40% Asian non-smokers patients have lung cancer with respect to 10–20% of Caucasians [12]. Incidence rate of lung cancer between Hispanic and non-Hispanic young white women is higher between the age group of 30 years and 49 years [17]. In India, lung cancer incidence estimated is approximately 70,275 in both genders. It is also the foremost contributor to cancer-related mortality, resulting in 1.38 million cancer deaths per year globally [23].

11.3 Lung CancerTypes

Lung cancer in the lungs emerges out of the epithelium cells of respiratory tract and can be bifurcated into two broad categories. One is small cell lung cancer (SCLC) that is extremely malignant tumor emerges from cells having neuroendocrine characteristics and 15% of total lung cancer cases are suffering from it. Second one is the non-small cell lung cancer which is further separated to three major pathologic sub types: large cell carcinoma, adenocarcinoma, and squamous cell carcinoma.

Smoking plays an important role in squamous type and small cell type carcinoma, but reduction in cases has been observed since 1970. However, non-smoker has the type of carcinoma called adenocarcinoma and shows increase in incidences globally [24]. Nearly, 85% of all cases of lung cancer are NSCLC type. With the decrease in the smoking prevalence, lung cancer has become more frequent among former than current smokers [25]. NSCLC is now defined by pathological characteristics. The two dominant NSCLC histological phenotypes are squamous cell carcinoma (SCC) and adenocarcinoma (ADC). Generally, ADCs arise in more distal ways, however, SCCs arise in more proximal air route and are more strongly associated with smoking and chronic inflammation than ADCs [26].

A 1/third of squamous cell carcinoma is mainly present in boundary of lungs and 2/third is present in central lungs. It shows certain biological features such as intracellular connection, formation of pearl and singular cell of keratinization [27]. This type of NSCLC is causing ulcers in bronchi and more bleeding than any other form, the cancer cells double itself in every 180 days [28].

The adenocarcinoma begins in the central part of lungs, but about 1/fourth develops along the lung boundaries. The tumors are small but the cells double itself in every 180 days. The cancer developed in alveoli is also called as bronchoalveolar adenocarcinoma and may spread in other parts of the lungs through air route [28]. Minimum invasive adenocarcinoma introduced are second and third subtype, whereas the fourth subtype is micropapillary adenocarcinoma, fifth for "mixed subtype" with a greater component generally known as non-mucinous bronchoalveolar adenocarcinoma and lepidic adenocarcinoma is taken as the sixth cancer generally described as mucinous adenocarcinoma, seventh and final. The small biopsy is a cure for adenocarcinoma and diagnostic criteria purposed recommendation for screening of endothelial growth factor receptor alteration and tissue management in adenocarcinoma patients [27].

The large cell carcinoma contributes 3% in lung cancer. This type of cancer present in the lung boundary and regarded as large necrotic cancer. The cells double itself in about every 100 days and can attack the mediastinum during the disease [28]. Clinical trial had shown that different types of cancer give different response to the different treatment. There is no change in the criteria of treatment of large cell carcinoma that occurs by different ways. Non-smoker cell neuroendocrine carcinoma shows (1) Large cell features—big size, polygonal shape, N/C ratio is low, and regular nucleoli. (2) Neuroendocrine features trabecular growth pattern, etc. (3) Frequent necrosis. (4) High multiplication rate [27]. In past few years, in developed

countries the cases of SCLC has been declined considerably due to the changes in the formation of cigarette [29].

11.4 Causes of Lung Cancer

The most common cause of lung cancer is cigarette smoking but asbestos and other environmental factors like polluted air and passive smoking are other causes of lung cancer [21]. Gene alteration to DNA and genetic changes are responsible for cancer development. These alterations disrupt the normal functioning of cell including proliferation, cell death pathway, and repairing function. The vulnerability of cancer increases with more damage to the cell [30]. Smoke of cigarette contains minimum 73% well-known carcinogen [31]. Approximately 90% and 70% mortality due to lung cancer in men and women has been observed, respectively, in the developed countries due to smoking [32]. Receptive smoking causes lung cancer to the non-smokers and the risk among the receptive smokers has increased significantly in the countries like United states and European Union. The risk increased by 20–30% for those who live with active smoker than those who works in the surroundings of the second-hand smokers. Tobacco smoke is very much similar to cannabis smoke. It is also reported that marijuana smoke increases the risk of lung cancer by two folds; however, many countries use mixture of both tobacco and cannabis [11, 31]. The various factors affecting the lung cancer include the following:

11.4.1 Smoking of Tobacco

International Agency for Research on Cancer (IARC) reported that there are approximately 4000 chemicals identified in cigarette and out of which 60 chemicals cause cancer. Polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and N-nitrosamines are few of the most potent carcinogens found in the cigarette smoke [33]. Smoking is very dangerous and accountable for 90% mortality in men and 80% deaths among women every year. The smoking has relation with lung cancer in two ways. In first way, mutations in the p53genes are provoked by the polycyclic aromatic hydrocarbons which are responsible and essential for deregulation of cell cycle and carcinogenesis. Within the gene, G to T transversions are linked to a molecular signature of tobacco mutagens in lung cancer caused due to smoking. In second way, the N-nitroso compounds, mainly present in tobacco smoke and are potent animal carcinogens. These compounds also found in the urine of smokers [34].

The inhalation of smoke constistuents not only depends on the cigarette but also on the period and amount of smoking, the presence and proficiency of a filter. The nicotine dependence of the smoker is the primary factor that determines the smoking frequency. The cigarettes nowadays contain not as much of nicotine as in the previous time, but smokers are likely to smoke with higher puffs and frequency to

attain a satisfactory level of nicotine. Therefore, the estimation done by smoking machine after measuring the content of tar and nicotine may wrongly estimate individual's exposure. The incidence of adenocarcinoma is mainly increased by the low yield filtered cigarettes. Hence, the peripheral cells in the bronchi are more exposed to carcinogen in smoke as compared to the other portion of the bronchi. Actually, this peripheral part of the bronchi is deficient in protective epithelium and hence exposed to carcinogens that stimulate adenocarcinoma induction [35].

The extent of lung cancer is directly related to cigarette consumption, nicotine and tar quantity in cigarettes, and utilization of unfiltered cigarettes. Approximately 20% deaths of all cancer deaths all over the world might be prevented just by stopping the tobacco smoking. Around 80% or more lung carcinogenesis merely occurs with exposure to tobacco. Passionate smokers who stop smoking or reduce the smoking keep their nicotine content intake by blocking aeration holes, increasing the retention of smoke in the lungs. This may result in augmented circulation of carcinogens to the lung's periphery and enhanced incidence of adenocarcinoma [36].

Repeated exposure of lungs to smoking stimulates inflammatory response in lung's epithelial cells. This leads to the release of chemo static and toxic mediators, reactive oxygen species, and many other pathogenic agents. Such intermediates cause the damage in lung tissues using different mechanisms and promote malignancy. One more marker of lung cancer is cyclooxygenase-2 (COX-2) which regulates the lungs regarding chronic inflammation. It is the marker that is found in malignant and pre-cancerous cells and tells about the signaling of COX-2 for cancer initiation and progression. Smoking also modifies the free radical scavengers in the epithelial cells of lung by way of chronic inflammation induction. In general, reactive oxygen species work as signaling molecules to regulate different pathways. The enhanced generation of reactive oxygen species production in extreme may lead to DNA damage, genetic instability, and replication errors [37].

11.4.2 Genetic Factors

It is found that each and every person who uses tobacco not necessarily develops lung cancer; it indicates that lung malignancy also related to genetics. It may enhance the 1.7-fold risk of lung cancer occurrence in the person having a historical family background with lung cancer. Telomerase reverse transcriptase (TERT) is coded by the 5p15 region and concerned in cell replication. The vulnerability and nicotine dependence for occurrence of lung cancer are related to the 15q25–26 chromosome locus while 6p21 regulates G-protein signaling [38, 39]. Inherited factors contribute about 8% of lung cancers [40]. Many studies have been done on candidate susceptibility of genes that are of high frequency and low penetrance. This approach is presenting the concept that genes are involved in absorption, metabolism, and accumulation of tobacco or carcinogens in tissues of lungs. For instance, many enzymes are involved in the coding of genetic polymorphism for conjugation of tobacco compounds such as aromatic amines, nitrosamines, and polycyclic aromatic hydrocarbons. Phase I (reduction, oxidation, and hydrolysis) and phase II

(conjugation) enzymes are involved in the metabolism of these compounds. There are some commonly studied enzymes in this system that include CYP1A1, myeloperoxidase (MPO), the glutathione S-transferases (GST), microsomal epoxide hydrolase 1, and reduced form of nicotinamide adenine dinucleotide phosphate quinine-oxido-reductase 1 [41].

11.4.3 Gender

It is hypothesized that females have more chances of occurrence of lung cancer as compared to males at the equivalent smoking level. Though, analysis of the hypothesis clears that it not correct because studies demonstrate that it is the similar risks for both at specific degree of smoking history. In fact, women show significantly lesser risk of lung cancer as compared to men for a same level of smoking history. It has also been supposed that women are at lesser risk due to fewer exposures to environmental carcinogens. Hence, at the identical smoking level, the risk of occurrence of lung cancer for women appears to same. However, there are some interesting comparisons regarding the lung cancer occurrence between men and women. First, prognosis is better in women having lung cancer than men. Second, the lung cancer occurrence chance may be enhanced by estrogen. Third, there are a few comprehensible gender differences which have noticed in people who never smoked. The percentage of adenocarcinoma in never smoker women is high as compared to men and women who also have a higher frequency of EGFR mutations as compared to men. These observations observed differentiate the gender specifications regarding the lung carcinogenesis and may prove clinically important [42, 43].

11.4.4 Ethnicity and Race

Race has a strong socioeconomic association and is an important and complex variable that affects the lung cancer occurrence. Americans, Hispanics, and Japanese are less susceptible for lung cancer as compared to blacks, Polynesians, and native Hawaiians who are more susceptible. In the United States, it was observed that the mortality and incidence rate are alike among white women, American women, and African, whereas it is 26% higher rate of incidence and 23% higher the mortality rate in American, African men as compared to white men. The susceptibility of mortality due to lung cancer in Cuban Hispanic men is twice as that of Mexican men which is directly related to cultural trend of smoking [16].

11.4.5 Age

DNA break and telomeres shortening are the biological factors that are mainly responsible for the occurrence of cancer in old age. The average age of lung cancer diagnosis for men and women is 70 years. Around 53% of cases are threatened by lung cancer at the age of 55–74 years old and 37% cases are threatened at the age of 75 years old. The approximate data revealed that the lung cancer occurence rate is 586 per 100,000 in the age group of 85–89 years, while it is approximately 366 per 100,000 at the age of 75–79 years in women. The data also showed that about 10% of cases suffer at or less than the age of 55 years. Non-small cell lung cancer studies have been done in patients with age between 20–46 years and it was observed that the females are more prone to adenocarcinoma. In youth, little complexity of disease is observed and hence genetics is the key factor playing a dominant role in this young patient population. The recovery rate in younger patient population is better and they are more susceptible to receive persistent treatment at every point of the disease, while this becomes very typical at the advanced stage of disease [44].

11.4.6 Occupational and Environmental Causes

Around the 1920s, it was the pervasive air quality that was mainly responsible for the occurrence of lung cancer. Mainly, there are two factors that are responsible for indoor and outdoor quality of air: the first one is burning of fossil fuels which lead to the production of carcinogens and particulate matter in the air. The prolonged exposure to such elements leads to the occurrence of occupation related lung carcinoma. Hence, the workers in the trucking industry are associated with 50% increase in the occurrence of lung cancer. Indoor air quality is affected by the burning of unprocessed fossil fuels like biomass fuels and soft coal, cooking and leads to the chances of increase of lung carcinoma. With the maintenance of proper circulation of air in the cooking area may reduce the 50% risk of lung cancer occurrence [45]. Passive smokers are also at the risk of lung cancer occurrence due to the inhalation of a complex smoke mixture and referred to as “second-hand smoke” or “environmental tobacco smoke.”

It is expected that 5–10% of lung cancers patients increase due to occupational exposure. Asbestos is the major and most common lung carcinogen. It is a naturally occurring silicate mineral and amphibole (amosite, trenolite, crocidolite) and serpentine (chrysotile) subtypes. It is a chrysotile fiber that plays an important role in thoracic malignancies occurrence. Exposure to asbestos at the occupational site may increase lung cancer risk five times more. The synergistic effect of tobacco smoking and asbestos exposure boosts the probability of lung cancer [46].

11.4.7 Radon

Ionizing radiations arise from radon (Rn) are responsible as well as the second most leading factor for mortality due to lung carcinoma. Radon contributes approximately 10% of all deaths caused by lung cancer [12]. Environmental Protection Agency reported that radon is the key reason for deaths due to lung cancer. It is also observed that smoking showed the synergistic effect with radon exposure in case of lung cancer occurrence [47]. The disintegration of radioactive radium creates radon gas, which is colorless and odorless gas. Earth's lithosphere has uranium and decay of uranium produces radium. This radiation decay causes mutations, ionizes genetic material, and becomes cancer causing [48]. When Radon gas concentration increased by 100 bq/m^3, it increases the risk of lung carcinoma by 8% or 16% [48]. The level of radon gas changes with change in the crust composition and surrounding.

11.4.8 Asbestos

It is a silicate mineral, occurs naturally and used as a constructing material and insulating material. In countries having larger industrialization, asbestos is present everywhere in the surrounding. Moreover lung cancer caused by exposure to asbestos has a long duration and heaviness [12]. A person having exposure to asbestos has the higher chances of lung cancer than common public [49]. Mesothelioma a type of pleura cancer also caused by asbestos, and this lung cancer is distinct from other lung cancers [50].

11.4.9 Other Causes

The lung cancer has been associated with the number of other factors such as air pollution, gas concentration, radon, genetics works, and surrounding exposure. There are enough proof to show that some cancer causing substances also include aluminum, cadmium and its derivatives, chromium compounds, beryllium and its derivatives, and few combustion products such as coal, coke production, and coal tar pitch. Radiations such as gamma rays, X-rays; Toxic gases such as methyl ether sulfur mustard and fumes from crystalline silica dust and painting having systematic sclerosis pose a little higher lung cancer risk [51].

11.5 Herbal Alternatives for Lung Cancer

At the present time, surgery, radiation, chemotherapy, immunotherapy, and hormones are the chief approaches used together for the cancer treatment. Though chemotherapy is the most used method but a lot of problems are linked with it like severe toxicity, limited efficacy, and multidrug resistance. Plants have been used

Table 11.1 Some medicinal herbs with their mechanism of action against lung cancer

S. No.	Medicinal herbs	Mechanism of action
1.	*Selaginella tamariscina*	Anti-metastatic effects
2.	*Crocus sativus L.*	Apoptosis induction
3.	*Toona sinensis*	Inhibit the growth of H441 xenograft tumor
4.	*Sesbania grandiflora*	Anti-proliferative effects against cell lines of human lung cancer
5.	*Descurainia sophia*	Regulation of signaling and metabolic pathways
6.	*Panax ginseng*	Increase p53 activity, reduce NF-κB activity, induce apoptosis
7.	*Zingiber officinale*	Reduce lung metastases in animals (mice) in receipt of B16F10 melanoma cells
8.	*Embelia ribes*	Regulate JNK and p38 pathways in apoptosis induced by embelin
9.	*Salvia miltiorrhiza*	Reduce lung adenocarcinoma tumor growth
10.	*Murraya koenigii*	Inhibit cell growth of lung cancer extrinsic and intrinsic pathways of apoptosis
11.	*Lysimachia capillipes*	Induce apoptosis in NSCLC cells
12.	*Scutellaria baicalensis*	Act as complementary in lung cancer chemotherapy
13.	*Cinnamomum subavenium*	Induce cell death of lung cancer by ROS generation followed by apoptosis
14.	*Davallia divaricata*	Induce apoptosis and oxidative stress in cells of lung cancer
15.	*Daphne genkwa*	Inhibit metastasis and tumor growth by defending the viability of host immunocytes
16.	*Curcuma wenyujin*	Inducing tumor cell apoptosis, enhancing radio sensitivity
17.	*Polygala senega*	Cause apoptosis in A549 cell line of lung cancer
18.	*Croton macrostachys*	Inhibit the LLC growth in mice
19.	*Cassia garrettiana*	Inhibit metastasis and tumor growth in LLC bearing mice
20.	*Brucea javanica*	Show the anti-carcinoma effect against lung cancer induced brain metastasis

since ancient time for treatment of cancer and persist to be a chief source of new drugs. Herbal drugs have been documented as smart approach as they have confirmed to be valuable and helpful in sensitizing conventional agents, enhance survival of patient, preventing or reducing the chemotherapy side effects, and life quality improvement in patients of lung cancer. A study conducted on 453 patients of cancer exposed that the approximately 77% of all patients are taking herbal treatment together with conventional chemotherapy. In these cases, the main purpose of using natural products as alternative therapy is to reduce the toxicity, stimulating the immune system, alleviating cancer-related symptoms, and even having direct anticancer effects [52]. Some medicinal herbs with their mechanism of action against lung cancer are listed in Table 11.1 [53].

Chemoprevention is the prophylactic use of non-toxic substances like biological, natural, or synthetic agents for cancer prevention. The occurrence of carcinogenesis is a multifaceted incident and its growth comprises several phases such as initiation, promotion, progression, and lastly metastasis. For instance, in case of lung carcinogenesis, it involves a series of epigenetic and genetic changes in epithelial cells of pulmonary system that direct the cell changes in proliferation, differentiation, invasion, and metastasis. Furthermore, lung carcinogenesis also has "field of cancerization" feature that means tissues near the cancerous lesions would seem to be histologically normal but this tissue has molecular abnormalities at the same time as in the tumors. Example of the "field of cancerization" during lung carcinogenesis is the formation of premalignant in all epithelial cells of airways after exposure to cigarette smoke [54].

This concept is further confirmed because even single mutant epithelial cell in respiratory lining has potential to spread out into surrounding tissues in lung and finally turns into malignancy. Naturally occurring phytochemicals are selectively targeting cancer cells. These chemopreventive phytochemicals play an important role and frequently act on cancer cells even in small doses with no harm on healthy cells. The natural phytochemicals from vegetables and fruits have chemopreventive potentials in case of lung cancer. For example, various studies showed that fruits and vegetables consumption in current smokers may well diminish the risk of occurring lung cancer [55, 56].

Dietary phytochemicals having effective anti-inflammatory or anti-oxidative activities play a vital part in regarding the protection of lung function. Fruits like bananas, apples, and vegetables (tomatoes), fish, herbal tea, white wine, and marine food had shown potential regarding the lung function protection in high risk populations [57].

Tea (*Camellia sinensis*) is the most regular consumed infusion all over the world. There are many studies which showed that consumption of tea has a protective role on carcinogenesis. The protective effect of green tea on carcinogenesis is mainly due to the presence of epigallocatechin gallate which is a chief component of green tea. It may act through various mechanisms like cell cycle arrest and apoptosis induction, modulation of cell-signaling pathways, modulation of carcinogen metabolizing enzymes, and suppression of the activation of transcription factors that result in the cessation of cancer growth. The epigallocatechin gallate (1–40 μM) inhibits the independent growth of human lung cancer cells by regulating p53 expression and also raises the phosphorylation of p53 at Ser15 and Ser20. It plays an important and major part in the improvement of its transcriptional activity and inhibition of MDM2 mediated p53 ubiquitination [58, 59].

Isothiocyanates are present in cruciferous vegetables as glucosinolates. It is myrosinase enzyme that is responsible for the conversion of glucosinolates to isothiocyanates. Phenethyl isothiocyanate, benzyl isothiocyanate, and sulforaphane are extensively studied for their chemo preventive role beside cancer. The benzyl isothiocyanate inhibited gefitinib resistant human NSCLC cells growth by induction of activation of caspase-3, cell cycle arrest at G2/M phase, apoptosis, generation of reactive oxygen species (ROS), depletion of glutathione, suppression of Akt activity,

activation of MAPK, NF-κB transcriptional activation, and activator protein (AP)-1 [60].

Genistein is the most plentiful isoflavone found in soybean and most commonly known for its chemopreventive effects. Genistein (10 μM) has the capacity to enhance trichostatin A apoptosis induction and exert its effect by enhancing the activity of caspase-3 in A549 cells of human lung carcinoma and the normal human lung fibroblasts are unaffected [61].

Fisetin is a naturally occurring flavonoid, occurs in strawberry, grape, persimmon, cucumber, onion, and apple. It has apoptotic, anti-proliferative, and anti-angiogenic properties against cancer cells. Studies had shown that NSCLC cells treatment with fisetin (5–20 μM) restricted cell growth by inhibiting mTOR and PI3K/Akt signaling. It causes declined expression of protein PI3K, phosphorylation of Akt, and mTOR inhibition without affecting normal bronchial epithelial cells [62].

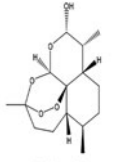
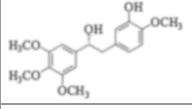
Vitamin C showed the antioxidant activities and found to be protective against lung tissue. Vitamin E is well known for its potent antioxidant property and mainly acts by its membrane repairing, chain breaking, and free radical scavenging activity. The dietary intake of vitamin E is directly correlated with its serum level and lung tissues. A meta-analysis showed that vitamin E and its circulating level is directly associated with lung functioning [63, 64].

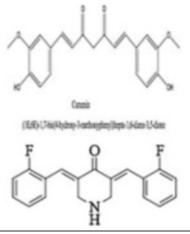
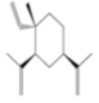
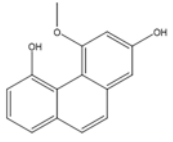
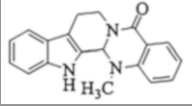
Silibinin is a flavonolignan and found mainly as the chief biological active constituent of silymarin. It is mainly extracted from the dried fruits and seeds of *Silybum marianum*. It plays an important role in the inhibition of initiation and promotion related events in a variety of pre-clinical cancer models for colorectal, skin, lung cancer, and prostate. Among the several cancer models silibinin effects were found to have growth control and prevention of lung cancer through *invitro* and in vivo studies [65].

Phloretin is a flavonoid that is obtained from apples and other plants such as *Pieris japonica*, *Loiseleuria procumbens*, and *Hoveniae lignum*. It was observed a dose of 125–150 μg/mL of phloretin given against Calu-1, NSCLC cell lines A549, H520, and H838 caused reduction in apoptosis induction, proliferation and suppressing the expression of Bcl-2 while increasing cleaved caspase-3 and 9 protein expressions and also downregulating MMP-2 and 9 expression on gene and protein levels [66]. Some plant drugs having potential against the lung carcinoma, along with their active constituents and mechanism involved are listed in Table 11.2.

The compounds like alkaloids, triterpenoids, flavonoids, terpenoids, polysaccharides have been extracted from medicinal plants and some formulas have been combined with chemotherapy for clinical test. *Solanum incanum*, an alkaloidal drug containing solamargine as active constituent is reported to have potential for treatment of four types of lung cancer. Solamargine therapy enhances the combined activity of TNF alpha and beta to the cancer cells. It makes TNF resistant cell lines that are susceptible to alpha and beta TNF. Besides this, solamargine initiates other cell death processes like release of cytochrome C from mitochondria, decrease the level of antiapoptotic Bcl2, Bcl-xl, increase caspase-3 and fragmentation of DNA, thus showing activity against lung cancer.

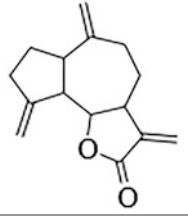
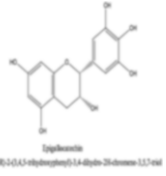
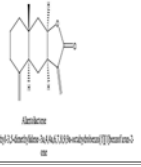
Table 11.2 Some reported medicinal plants useful against lung carcinoma

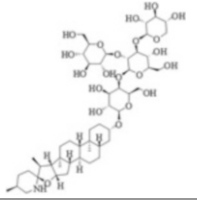
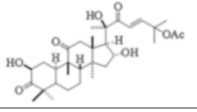
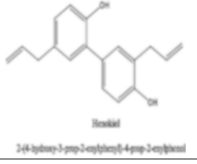
S. No.	Scientific names, common names (family)	Part used	Constituents	Method of preparation (herbal formulation and dosages)	Route of administration	Mechanism	References
1.	Korean angelica, giant angelica, purple parsnip, and dong quai *Angelica gigas* (Apiaceae)	Roots	Decursin (7.3%) 	50 mg/kg/13 days	Intraperitoneal	Cell proliferation, increase apoptosis	Lee et al. [67], Jeong et al. [52]
2.	Sweet sagewort, Sweet wornwood, annual wormwood, annie sweet sagewort, and annual mugwort *Artemisia annua* (Asteraceae)	Flowers and leaves	Dihydroartemisinin (DHA) 	1 μg/ml/72 h	–	Induce cancer cell death through apoptotic pathways	Lu et al. [68], Jeong et al. [52]
3.	South African Bush Willow *Combretum caffrum* (*Combretaceae*)	Bark	Combretastatin (R)-5-(2-hydoxy-2-(3,4,5 trimethoxyphenyl)ethyl-2-methoxyphenol 	Liposome aerosol (40 mg/m^2)	Intramuscular	Act as tubulin-binding agent by preventing polymerization of tubulin	Koshkina et al. [69]
4.	Turmeric *Curcuma longa* (Zingiberaceae)	Rhizomes	Curcumin (2.5–6%) EF24 (3E,5E)-3,5-bis(2 fluorobenzylidene) piperidin-4-one	Curcumin loaded dry powder inhaler 10 μM/L 0.8 μM/72 h	–	Cause apoptosis and inhibit the cell proliferation. Block the NF-Kb, i.e. nuclear factor kappa-B pathway	Alexandrow et al. [70], Zhang et al. [71], Thomas et al. [72]

							
5.	Zedoaria, Zedoary, wild turmeric *Curcuma kwangsiensis* (Zingiberaceae)	Rhizomes	Beta-Elemene 	20 μg/ml/72 h	–	Synergistic effect along with apoptosis	Zhao et al. [73], Jeong et al. [52]
6.	Dendrobium *Dendrobium loddigesii* (Orchidaceae)	Stem	Moscatilin  Moscatilin 4-methoxyphenanthrene-2,5-diol	10–100 μM	Subcutaneous	Inhibit invasion and migration of lung cancer cells, i.e. H23 cells.	Tsai et al. [74]
7.	Evodia fruit *Evodia rutaecarpa* (Rutaceae)	Fruit	Evodiamine 14-methyl-7,8,13b,14 tetrahydroindolo [2′,3′:3,4]pyrido[2,1-b]quinazolin-5(13H)-one 	20–40 μM	–	Cause apoptosis and arrest of cell cycle at G2/M phase.	Fang et al. [75]

(continued)

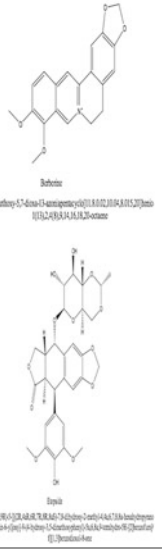
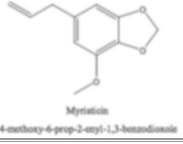
Table 11.2 (continued)

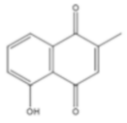
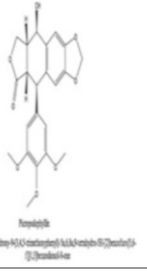
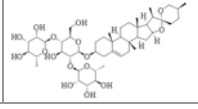
S. No.	Scientific names, common names (family)	Part used	Constituents	Method of preparation (herbal formulation and dosages)	Route of adminis-tration	Mechanism	References
8.	Native cobbler peg *Glossogyne tenuifolia* (Asteraceae)	Woody stem	Glossogin 3,6,9-trimethylenedecahydroazuleno [4,5-b] furan-2(9bH)-one 	12.5 μg/ml/48 h	–	Apoptosis /necrosis that lead to cell death	Hsu et al. [76], Jeong et al. [52]
9.	Green tea *Camellia sinensis* (Theaceae)	Leaves	Epigallocatechin (80%) 	36.03 μM	–	Block the nicotine induced invasion and migration of A549 cells by terminating the level of cyclooxygenase, vascular endothelial growth factor, protein kinase B, phosphoextracellular signal related kinase	Shi et al. [77]
10.	Elecampane *Inula helenium* (Asteraceae)	Root	Alantolactone (1.6338 ± 0.0198% (w/w) 	120 μM	–	Cause apoptosis and arrest of cell cycle at phase G0/G1.	Zhao et al. [78]

11.	Tomato *Lycopersicon esculentum* Linn (Solanaceae)	Fruit	α-tomatine (0.04%) (2S,3R,4S,5S,6R)-2-(((2S,3R,4S,5R,6R)-2-(((2R,3R,4R,5R,6R)-4,5-dihydroxy-2-(hydroxymethyl)-6-(((2aS,2'S,4S,5'S,6aS,6bS,8aS,8bR,9 s,11aS,12aS,12bR)-5′-6a,8a,9-tetramethyloctadecahydrospiro[naptho[2′,1′:4,5]indenol[2,1-b]furan-10,2′-piperidin]-4yl)oxy) tetrahydro-2H-pyran-3-yl)oxy)-5hydroxy-6-(hydroxymethyl)R)-4-(((2S,3R,4S,5R)-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)tetrahydro-2H-pyran-3yl)oxy-5-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol 	1 mg/kg	–	Block the phosphorylation of DNA binding activity of Focal adhesional kinase/ phosphoinositide-3-kinase/protein kinase B, i.e. FAK/P13K/Akt pathway.	Shieh et al. [79]
12.	Ridge gourd *L. graveolens Roxb.* (Cucurbitaceae)	Fruit	Cucurbitacin B (6R,E)-6-((2S,8S,9S,10R,13R,14S,16R,17R)-2,16-dihydroxy-4,4,9,13,14-pentamethyl-3,11-dihydroxadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-6-hydroxy-2-methyl-5-oxohept-3-en-2yl acetate. 	0.5 μM	–	Cause apoptosis and arrest of G2/m phase in cell cycle.	Shukla et al. [80]
13.	Houpu magnolia or magnolia-bark *Magnolia officinalis* (Magnoliaceae)	Bark, seed cones, and leaves	Honokiol (0.25–1.7%) 	Liposomes (10 mg/kg/ 21 days)	Intravenous	Suppression of tumor growth	Jiang et al. [81], Jeong et al. [52]

(continued)

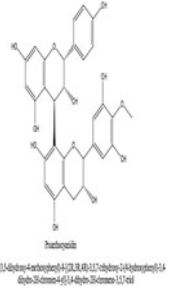
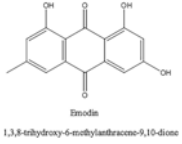
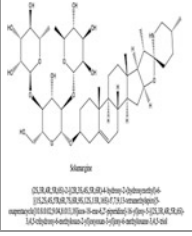
Table 11.2 (continued)

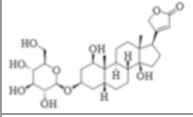
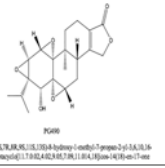
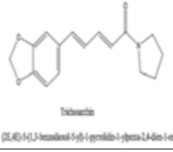
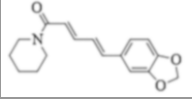
S. No.	Scientific names, common names (family)	Part used	Constituents	Method of preparation (herbal formulation and dosages)	Route of adminis-tration	Mechanism	References
14.	Amur cork tree *Phellodeodendron amurense* (Rutaceae)	Bark	Berberine (33%) Etoposide 	Nanoprecipitation method (1.5 g/kg)	Intraperitoneal	Binds to topoisomerase—ii that cause breaking of single and double strand of DNA and prevent mitosis.	Elgohary et al. [82]
15.	Parsley or garden parsley *Petroselinum sativum* (Apiaceae)	Leaf	Myristicin 	10 mg/mouse/ 20 days	–	Cause cytotoxicity by inhibiting the growth of cancer cells.	Zheng et al. [83], Jeong et al. [52]

16.	Indian leadwort, scarlet leadwort, or whorled plantain *Plumbago indica* (Plumbaginaceae)	Roots	Plumbagin  Plumbagin 5-hydroxy-2-methylnaphthalene-1,4-dione	3 μM/48 h	–	Apoptosis and inhibit cell viability	Gomathinayagam et al. [84], Jeong et al. [52]
17.	American mandrake, ground lemon, mayapple, wild mandrake *Podophyllum peltatum* (Berberidaceae)	Roots	Picropodophyllin 	1–100 μM	–	Terminate the level of protein kinase (p-Akt) and mitogen activated protein (MAPK) and block the expression of insulin like growth factor 1 (IGF-1R).	Zhang et al. [85]
18.	King Solomon's-seal or Solomon's seal *Polygonatum zanlanscianense* (Asparagaceae)	Root	Dioscin (2R,2'R,3S,3'S,4S,4'S,5S,5'S,6R,6'R)-6,6′-(((2R,3S,4S,5R,6R)-4-hydroxy-2-(hydroxymethyl)-6-(((2'R,4S,5'S,6Ar,6Bs,8As,8bR,9R,11aS,12aS,12bS)-5′,6a,8a,9,12b-pentamethyl-1,3,3′,4,4′,5,5′,6,6a,6b,6;,7,8,8a,8b,9,11a,12,12a,12b-icosahydrospiro[naptho[2′,1′,4,5]indeno[2,1-b]furan-10,2′-pyran]-3,5-diyl)bis(oxy))bis(2-methyltetrahydro-2H-pyran-3,4,5,-triol) 	2-20 μM	–	Block the pro-apoptotic protein expression and induce apoptosis.	Wei et al. [86]

(continued)

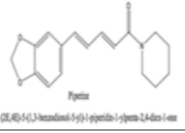
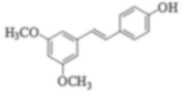
Table 11.2 (continued)

S. No.	Scientific names, common names (family)	Part used	Constituents	Method of preparation (herbal formulation and dosages)	Route of adminis-tration	Mechanism	References
19.	Sessile oak, Cornish oak, Irish Oak, or durmast oak *Quercus petraea* (Fagaceae)		Proanthocyanidin 	0.1% (w/w)/ 58 days	–	Inhibit cellular proliferation	Akhtar et al. [87], Jeong et al. [52]
20.	East Indian rhubarb or Turkey rhubarb, and ornamental rhubarb, Chinese rhubarb, *Rheum palmatum* (polygonaceae)		Emodin 	60 μM/24 h	–	Induce apoptosis by Tribbles 3/nuclear factor kappa light chain enhancer of activated B cells, i.e. TRIB3/NF-Kb pathway and endoplasmic reticulum stress	Su et al. [88], Jeong et al. [52]
21.	Thorn apple, bitter apple, bitter ball, and bitter tomato *Solanum incanum* (Solanaceae)	Fruits, roots, and leaves	Solamargine (62%) 	3 μM/16 h EF24	–	Apoptosis, cell death	Liang et al. [89]

22.	Streptocaulon juventas *Merr.* (Apocynaceae) no common name	Roots	TXA9 4-((1R,3R,5R,8R,9S,10S,13R,14S,17R)-1,14-dihydroxy-10,13-dimethyl-3-(((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl) oxy)hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl) furan-2(5H)-one 	25 mg/kg	Intravenous	Inhibit proliferative activity of small carcinoma cell line of lung	Xue et al. [90]
23.	Thunder god vine *Tripterygium wilfordii* (Celastraceae)	Roots	PG490 (triptolide) 	10 ng/ml/24 h	–	Triptolide is an inhibitor of transcription, proliferation, metastasis of cancer and induce apoptosis.	Frese et al. [91], Jeong et al. [52]
24.	Chinese cucumber *Trichosanthes kirilowii* (Cucurbitaceae)	Root tuber	Trichosanthin 	0.5 mg/ml/48 h	–	Induces apoptosis in tumor cell lines	Li et al. [92], Jeong et al. [52]
25.	Meadow–rue *Thalictrum acutifolium* (Ranunculaceae)	Root	Acutiaporberine (2E,4E)-5-(benzo[d][1,3]dioxol-5-yl)-1-(piperidin-1-yl)penta-2,4-dien-1-one 	0.003 μ mol/ml/ 48 h	–	Apoptosis of the metastatic lung cancer cells	Chen et al. [93], Jeong et al. [52]

(continued)

Table 11.2 (continued)

S. No.	Scientific names, common names (family)	Part used	Constituents	Method of preparation (herbal formulation and dosages)	Route of administration	Mechanism	References
26.	Black pepper *Piper nigrum* (*Piperaceae*)	Flower	Piperine (2–7.4%) 		–	Anti-proliferative activity against A549 cell lines due to arrest at cell cycle phase, i.e. G2/M phase.	Lin et al. [94]
27.	Wine grape, common grape *Vitis vinifera* (Vitaceae)	Leaves, fruit, and blueberries	Pterostilbene (E)-4-(3,5-dimethoxystyryl)phenol 	250 mg/kg	Intraperitoneal	Terminate the expression of epidermal growth factor and also expression of other mediators like extracellular signal regulated protein kinase (ERK1/2), protein kinase (Akt)/ the mammalian target of repamycin (mTOR), signal transducer and activator of transcription 3 (Stat-3), and nuclear factor kappa-B (NF-kB).	Chen et al. [95]

Triterpenoidal compounds like hederacolchicoside A, extracted from *Hedera colchica* and beta hedrin obtained from *Hedera helix* are monodesmoid oleanolic acids and show cytostatic activity against human lung cancer cell line (A549). *Bupleurum falcatum* contains saikosaponin D as one of its active moiety useful for the liver diseases treatment [96].

The root part of *Scutellaria baicalensis* Georgi. possesses flavonoidal constituents like wogonin, baicalein, wogonoside, and neobaicalein. These constituents have been reported to stop the growth of malignant cell lines. Baicalein inhibits the activity of lepooxygenase-12 in several forms of cancer [96].

Antofine and acutiaporberine are medicinal plants that have been tested for their anticancer activity. In India, a poly herbal siddha medicine named "Rasagenthi" is used for cancer treatment. In prostate cancer cell line (PC-3), the Rasagenthi chloroform extract induces apoptosis and reduces the growth of these cell lines as per recent studies. It has been reported that the chloroform extract of Rasagenthi has anti carcinogenic activity on lung cancer cell lines. In recent studies, it has been found that the many dietary phytochemical substances have profound antitumor properties [97].

Chinese herbal medicines (CHMs) clinical performance has good response and shows ability to treat different symptoms of lung cancer. Several traditional Chinese medicines formulae affects synergistically as herb extracts have been reported to stop lung cancer at various stages. It also prevents the patient from adverse side effects of single drug. Research demonstrates that Chinese treatment helps the body to fight against infectious agents that increases the patient's life. Various types of chemical compounds like triterpenoids, alkaloids, terpenoids, flavonoids, and polysaccharides have been reported to possess activity against lung carcinoma [96].

11.6 Conclusion

The traditional ways of treatment using herbal medicinal products are being used for centuries in the treatment of various types of disease. As one of the attractive alternatives to lung cancer treatment, herbal medicines have been recognized and proved to be useful and effective in sensitizing conventional agents, prolonging patient survival, preventing chemotherapy side effects, and enhancing the quality of life of patients with lung cancer. The natural products were primarily used as alternative therapy for the treatment with the goal of reducing toxicity, alleviating symptoms associated with cancer, enhancing the immune system, and also having direct effects on cancer. Herbal treatment has been considered as additional treatment for some malignant disease based on recent scientific research on herbs. Even though several studies have shown an assessment of the potential mechanisms of action of these compounds, many studies have still provided only preliminary screening data and therefore not identified their mechanism of action.

References

1. Merck (2020) Lung carcinoma: tumors of the lungs. http://www.merck.com/mmpe/sec05/ch062/ch062b.html#sec05-ch062-ch062b-1405. Accessed 19 Oct 2020
2. Siegel R, Ward E, Brawley O et al (2011) Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 61 (4):212–236
3. Wang Y, Zhao H, Gao X et al (2016) Identification of a three-miRNA signature as a blood-borne diagnostic marker for early diagnosis of lung adenocarcinoma. Oncotarget 7 (18):26070–26086. https://doi.org/10.18632/oncotarget.8429
4. Howlader N, Noone AM, Krapcho M et al (2010) SEER cancer statistics review, 1975–2008. National Cancer Institute, Bethesda, MD
5. Jemal A, Bray F, Center MM et al (2011) Global cancer statistics. CA Cancer J Clin 61 (2):69–90
6. Bunn PA (2012) Worldwide overview of the current status of lung cancer diagnosis and treatment. Arch Pathol Lab Med 136:1478–1481
7. Amos CI, Xu W, Spitz MR et al (1999) Is there a genetic basis for lung cancer susceptibility. Chemoprevention Cancer 151:3–12
8. Lam WK, White NW, Chan-Yeung MM et al (2004) Lung cancer epidemiology and risk factors in Asia and Africa. Int J Tuberc Lung Dis 8:1045–1057
9. NCI (2015) Non-small cell lung cancer treatment–patient version (PDQ®). http://www.cancer.gov/types/lung/patient/non-small-cell-lung-treatment-pdq. Accessed 12 May 2015
10. World Cancer Report (2014) World Health Organization
11. Alberg AJ, Ford JG, Samet JM et al (2007) Epidemiology of lung cancer: ACCP evidence-based clinical practice guidelines. Chest 132(3):29S–55S
12. De GP, Munden RF (2012) Lung cancer epidemiology, risk factors, and prevention. Radiol Clin N Am 50(5):863–876. https://doi.org/10.1016/j.rcl.2012.06.006
13. Bjerager M, Palshof T, Dahl R et al (2006) Delay in diagnosis of lung cancer in general practice. Br J Gen Prac 56(532):863–868
14. Polanski J, Jankowska PB, Rosinczuk J et al (2016) Quality of life of patients with lung cancer. Onco Targets Ther 9:1023–1028. https://doi.org/10.2147/OTT.S100685
15. Bilello KS, Murin S, Matthay RA et al (2002) Epidemiology, etiology and prevention of lung cancer. Clin Chest Med 23(1):1–25
16. Siegel RL, Fedewa SA, Miller KD et al (2015) Cancer statistics for Hispanics/Latinos, 2015. CA Cancer J Clin 65:457–480
17. Bade BC, Cruz CS (2020) Lung cancer 2020: epidemiology, etiology, and prevention. Clin Chest Med 41(1):1–24
18. Brambilla E, Gazdar A (2009) Pathogenesis of lung cancer signaling pathways: Roadmap for therapies. Eur Respir J 33:1485–1497
19. Dela Cruz CS, Tanoue LT, Matthay RA et al (2011) Lung cancer: epidemiology, etiology, and prevention. Clin Chest Med 32(4):605–644. https://doi.org/10.1016/j.ccm.2011.09.001
20. Walters S, Maringe C, Coleman MP et al (2013) Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007. Thorax 68(6):551–564
21. Alberg AJ, Brock MV, Samet JM et al (2005) Epidemiology of lung cancer: looking to the future. J Clin Oncol 23(14):3175–3185
22. Alberg AJ, Brock MV, Ford JG et al (2013) Epidemiology of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 143(5):e1S–e29S. https://doi.org/10.1378/chest.12-2345
23. Thomas V, Jose B, Rennis D et al (2018) Prevalence of type and etiology of lung cancer among the patients presented to a tertiary care hospital at central Kerala: a descriptive study. Int J Res Med Sci 6:834

24. Hildegard MS (2019) The impact of smoking and the influence of other factors on lung cancer. Expert Rev Respir Med 13(8):761–769. https://doi.org/10.1080/17476348.2019.1645010
25. Molina JR, Yang P, Cassivi SD et al (2008) Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 83(5):584–594. https://doi.org/10.4065/83.5.584
26. Chen Z, Fillmore CM, Hammerman PS et al (2014) Non-small-cell lung cancers: a heterogeneous set of diseases. Nat Rev Cancer 14(8):535–546
27. Travis WD, Rekhtman N (2011) Pathological diagnosis and classification of lung cancer in small biopsies and cytology: strategic management of tissue for molecular testing. Semin Respir Crit Care Med 32(1):22–31. https://doi.org/10.1055/s-0031-1272866
28. National Cancer Institute (2007) Surveillance, epidemiology and end results (SEER) Cancer statistics review 1975–2004. http://SEER.cancer.gov/CSR/1975_2004/results_merged/sect_15_lung_bronchus.pdf
29. Bunn PA, Minna JD, Augustyn A et al (2016) Small cell lung cancer: can recent advances in biology and molecular biology be translated into improved outcomes. J Thorac Oncol 11 (4):453–474
30. Brown KM, Keats JJ, Sekulic A et al (2010) Holland-Frei Cancer Medicine, 8th edn. People's Medical Publishing House USA, Shelton, CT
31. Hecht SS (2012) Lung carcinogenesis by tobacco smoke. Int J Cancer 131(12):2724–2732. https://doi.org/10.1002/ijc.27816
32. Parkin DM (2011) Tobacco-attributable cancer burden in the UK in 2010. Br J Cancer 105 (2):6–13
33. Hecht SS (1999) Tobacco smoke carcinogens and lung cancer. J Natl Cancer Inst 91:1194–1210
34. Vineis P, Alavanja M, Buffler P et al (2004) Tobacco and cancer: recent epidemiological evidence. J Natl Cancer Inst 96(2):99–106
35. Wynder EL, Hoffmann D (1994) Smoking and lung cancer: scientific challenges and opportunities. Cancer Res 54(20):5284–5295
36. Harris JE, Thun MJ, Mondul AM et al (2004) Cigarette tar yields in relation to mortality from lung cancer in the cancer prevention study II prospective cohort, 1982–8. BMJ 328:1–8
37. Bhalla DK, Hirata F, Rishi AK et al (2009) Cigarette smoke, inflammation, and lung injury: A mechanistic perspective. J Toxicol Environ Health 12:45–64
38. Landi MT, Chatterjee N, Yu K et al (2009) A genome-wide association study of lung cancer identifies a region of chromosome 5p15 associated with risk for adenocarcinoma. Am J Hum Genet 85:679–691
39. Lissowska J, Foretova L, Dabek J et al (2010) Family history and lung cancer risk: international multicentre case-control study in Eastern and Central Europe and meta-analyses. Cancer Causes Control 21:1091–1104
40. Yang IA, Holloway JW, Fong KM et al (2013) Genetic susceptibility to lung cancer and comorbidities. J Thorac Dis 5:S454–S462
41. Benhamou S, Lee WJ, Alexandrie AK et al (2002) Meta-and pooled analyses of the effects of glutathione S-transferase M1 polymorphisms and smoking on lung cancer risk. Carcinogenesis 23(8):1343–1350
42. Alberg AJ, Wallace K, Silvestri GA et al (2013) Invited commentary: the etiology of lung cancer in men compared with women. Am J Epidemiol 177:613–616
43. Bain C, Feskanich D, Speizer FE et al (2004) Lung cancer rates in men and women with comparable histories of smoking. J Natl Cancer Inst 96:826–834
44. Arnold BN, Thomas DC, Rosen JE et al (2016) Lung cancer in the very young: treatment and survival in the national cancer data base. J Thorac Oncol 11:1121–1131
45. Dela Cruz CS, Tanoue TL, Matthany RA (2009) Lung cancer: epidemiology and carcinogenesis. In: Shields TW (ed) General thoracic surgery, 7th edn. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia, PA, pp 1281–1298

46. De MS, Consonni D, Bertazzi PA et al (2008) Exposure to occupational carcinogens and lung cancer risk. Evolution of epidemiological estimates of attributable fraction. Acta Biomed 79 (1):34–42
47. EPA (Environmental Protection Agency) (2003) EPA assessment of risks from radon in homes. United States Environmental Protection Agency, Washington, DC
48. Schmid K, Kuwert T, Drexler H et al (2010) Radon in indoor spaces: an underestimated risk factor for lung cancer in environmental medicine. Dtsch Arztebl Int 107(11):181–186. https://doi.org/10.3238/arztebl.2010.0181
49. O'Reilly KM, Mclaughlin AM, Beckett WS, Sime PJ (2007) Asbestos-related lung disease. Am Family Phys 75(5):683–688
50. Davies RJ, Lee YC (2010) "18.19.3". Oxford Textbook Medicine, 5th edn. OUP, Oxford, UK
51. Cogliano VJ, Baan R, Straif K, Grosse Y, Lauby-Secretan B, El Ghissassi F et al (2011) Preventable exposures associated with human cancers. J Natl Cancer Inst 103(24):1827–1839
52. Jeong S, Koh W, Kim B et al (2011) Are there new therapeutic options for treating lung cancer based on herbal medicines and their metabolites. J Ethnopharmacol 138(3):652–661
53. Monteiro L, Bastos K, Filho J et al (2014) Medicinal plants and other living organism with antitumor potential against lung cancer. Evid Based complement Altern Med 2014:604152
54. Siddiqui IA, Sanna V, Ahmad N et al (2015) Resveratrol nano formulation for cancer prevention and therapy. Ann N YAcad Sci 1348(1):20–31
55. Brandes JC, Amin AR, Khuri F et al (2010) Prevention of lung cancer: future perspective with natural compounds. Tuberc Respir Dis 69:1–15
56. Bucher FL, Bueno-de-Mesquita HB, Linseisen J et al (2010) Fruits and vegetables consumption and the risk of histological subtypes of lung cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). Cancer Causes Control 21:357–371
57. Baines KJ, Backer V, Gibson PG et al (2015) Investigating the effects of arctic dietary intake on lung health. Eur J Clin Nutr 69:1262–1266
58. Jin L, Li C, Xu Y et al (2013) Epigallocatechin gallate promotes p53 accumulation and activity via the inhibition of MDM2-mediated p53 ubiquitination in human lung cancer cells. Oncol Rep 29:1983–1990
59. Khan N, Adhami VM, Mukhtar H et al (2009) Review: Green Tea Polyphenols in Chemoprevention of Prostate Cancer: Preclinical and Clinical Studies. Nutr Cancer 61:836–841
60. Shapiro TA, Fahey JW, Wade KL et al (2001) Chemo protective glucosinolates and isothiocyanates of broccoli sprouts: metabolism and excretion in humans. Cancer Epidemiol Biomark Prev 10:501–508
61. Shiau RJ, Chen KY, Wen YD et al (2010) Genistein and beta-carotene enhance the growth-inhibitory effect of trichostatin A in A549 cells. Eur J Nutr 49:19–25
62. Khan N, Afaq F, Khusro FH et al (2012) Dual inhibition of phosphatidylinositol 3-kinase/Akt and mammalian target of rapamycin signaling in human nonsmall cell lung cancer cells by a dietary flavonoid fisetin. Int J Cancer 130:1695–1705
63. Meydani M, Cohn JS, Macauley JB et al (1989) Postprandial changes in the plasma concentration of alpha- and gamma-tocopherol in human subjects fed a fat-rich meal supplemented with fat-soluble vitamins. J Nutrn 119:1252–1258
64. Tsiligianni IG, van der Molen MT (2010) A systematic review of the role of vitamin insufficiencies and supplementation in COPD. Respir Res 11(1):171
65. Mateen S, Tyagi A, Agarwal C et al (2010) Singh RP, Agarwal R. Silibinin inhibits human nonsmall cell lungcancer cell growth through cell-cycle arrest by modulating expression and function of key cell-cycle regulators. Mol Carcinog 49:247–258
66. Ma L, Wang R, Nan Y et al (2016) Phloretin exhibits an anticancer effect and enhances the anticancer ability of cisplatin on non-small cell lung cancer cell lines by regulating expression of apoptotic pathways and matrix metallo proteinases. Int J Oncol 48:843–853
67. Lee HJ, Lee HJ, Lee EO et al (2009) *In vivo* anti-cancer activity of Korean Angelica gigas and its major pyranocoumarin decursin. Am J Chinese Med 37(01):127–142

68. Lu YY, Chen TS, Qu JL et al (2009) Dihydroartemisinin (DHA) induces caspase-3-dependent apoptosis in human lung adenocarcinoma ASTC-a-1 cells. J Biomed Sci 16(1):1–5
69. Koshkina NV, Gilbert BE, Waldrep JC et al (1999) Distribution of camptothecin after delivery as a liposome aerosol or following intramuscular injection in mice. Cancer Chemother Pharmacol 44(3):187–192
70. Alexandrow MG, Song LJ, Altiok S et al (2012) Curcumin: a novel stat 3 pathway inhibitor for chemoprevention of lung cancer. Eur J Cancer Prev 21(5):407
71. Zhang T, Chen Y, Ge Y et al (2018) Inhalation treatment of primary lung cancer using liposomal curcumin dry powder inhalers. Acta Pharma Sin B 8(3):440–448
72. Thomas SL, Zhao J, Li Z et al (2010) Activation of the p38 pathway by a novel monoketone curcumin analog, EF24, suggests a potential combination strategy. Biochem Pharmacol 80 (9):1309–1316
73. Zhao J, Li QQ, Zou B et al (2007) *In vitro* combination characterization of the new anticancer plant drug β-elemene with taxanes against human lung carcinoma. Int J Oncol 31(2):241–252
74. Tsai AC, Pan SL, Liao CH et al (2010) Moscatilin, a bibenzyl derivative from the India orchid Dendrobrium loddigesii, suppresses tumor angiogenesis and growth *in vitro* and in *vivo*. Cancer Lett 292(2):163–170
75. Fang C, Zhang J, Qi D et al (2014) Evodiamine induces G2/M arrest and apoptosis via mitochondrial and endoplasmic reticulum pathways in H446 and H1688 human small-cell lung cancer cells. PloS one 9(12):e115204
76. Hsu HF, Houng JY, Kuo CF et al (2008) Glossogin, a novel phenylpropanoid from Glossogyne tenuifolia, induced apoptosis in A549 lung cancer cells. Food Chem Toxicol 46(12):3785–3791
77. Shi J, Liu F, Zhang W et al (2015) Epigallocatechin-3-gallate inhibits nicotineinduced migration and invasion by the suppression of angiogenesis and epithelial mesenchymal transition in non-small cell lung cancer cells. Oncol Rep 33(6):2972–2980
78. Zhao P, Pan Z, Luo Y et al (2015) Alantolactone induces apoptosis and cell cycle arrest on lung squamous cancer SK-MES-1 cells. J Biochem Mol Toxicol 29(5):199–206
79. Shieh JM, Cheng TH, Shi MD et al (2011) α-Tomatine suppresses invasion and migration of human non-small cell lung cancer NCI-H460 cells through inactivating FAK/PI3K/Akt signaling pathway and reducing binding activity of NF-κB. Cell Biochem Biophys 60(3):297–310
80. Shukla S, Khan S, Kumar S et al (2015) Cucurbitacin B alters the expression of tumor-related genes by epigenetic modifications in NSCLC and inhibits NNK-induced lung tumorigenesis. Cancer Prev Res 8(6):552–562
81. Jiang QQ, Fan LY, Yang GL et al (2008) Improved therapeutic effectiveness by combining liposomal honokiol with cisplatin in lung cancer model. BMC Cancer 8:242
82. Elgohary MM, Helmy MW, Mortada SM et al (2018) Dual-targeted nano-in-nano albumin carriers enhance the efficacy of combined chemo/herbal therapy of lung cancer. Nanomedicine 13(17):2221–2224
83. Zheng GQ, Kenney PM, Zhang J et al (1992) Inhibition of benzopyrene-induced tumorigenesis by myristicin, a volatile aroma constituent of parsley leaf oil. Carcinogenesis 13(10):1921–1923
84. Gomathinayagam R, Sowmyalakshmi S, Mardhatillah F et al (2008) Anticancer mechanism of plumbagin, a natural compound, on non-small cell lung cancer cells. Anticancer Res 28:785–792
85. Zhang Q, Pan J, Lubet RA et al (2015) Targeting the insulin-like growth factor-1 receptor by picropodophyllin for lung cancer chemoprevention. Mol carcinogen 54(S1):E129–E137
86. Wei Y, Xu Y, Han X et al (2013) Anti-cancer effects of dioscin on three kinds of human lung cancer cell lines through inducing DNA damage and activating mitochondrial signal pathway. Food Chem Toxicol 59:118–128
87. Akhtar S, Meeran SM, Katiyar N et al (2009) Grape seed proanthocyanidins inhibit the growth of human non-small cell lung cancer xenografts by targeting insulin-like growth factor binding protein-3, tumor cell proliferation, and angiogenic factors. Clin Cancer Res 15(3):821–831
88. Su J, Yan Y, Qu J et al (2017) Emodin induces apoptosis of lung cancer cells through ER stress and the TRIB3/NF-κB pathway. Oncol Rep 37(3):1565–1572

89. Liang CH, Liu LF, Shiu LY et al (2004) Action of solamargine on TNFs and cisplatin-resistant human lung cancer cells. Biochem Bioph Res Co 322(3):751–758
90. Xue R, Han N, Xia M et al (2015) TXA9, A cardiac glycoside from Streptocaulon juventas, exerts a potent anti-tumor activity against human non-small cell lung cancer cells *in vitro* and *in vivo*. Steroids 94:51–59
91. Frese S, Pirnia F, Miescher D et al (2003) PG490-mediated sensitization of lung cancer cells to Apo2L/TRAIL-induced apoptosis requires activation of ERK2. Oncogene 22(35):5427–5435
92. Li M, Li X, Li JC et al (2010) Possible mechanisms of trichosanthin-induced apoptosis of tumor cells. Ant Rec 293(6):986–992
93. Chen Q, Peng W, Qi S et al (2002) Apoptosis of human highly metastatic lung cancer cell line 95-D induced by acutiaporberine, a novel bisalkaloid derived from Thalictrum acutifolium. Planta Med 68(6):550–553
94. Lin Y, Xu J, Liao H et al (2014) Piperine induces apoptosis of lung cancer A549 cells via p53-dependent mitochondrial signaling pathway. Tumor Biol 35(4):3305–3310
95. Chen RJ, Tsai SJ, Ho CT et al (2012) Chemopreventive effects of pterostilbene on urethane-induced lung carcinogenesis in mice via the inhibition of EGFR-mediated pathways and the induction of apoptosis and autophagy. J Agric Food Chem 60(46):11533–11541
96. Zhou Y, Gao W, Li K et al (2008) Chinese herbal medicine in the treatment of lung cancer. Asian J Tradit Med 3(1):1–11
97. Ranga RS, Sowmyalakshmi S, Burikhanov R et al (2005) A herbal medicine for the treatment of lung cancer. Mol Cell Biochem 280(1–2):125–133. https://doi.org/10.1007/s11010-005-8518-3

Effect of Medicinal Plants against Lung Cancer

12

Suhas Suresh Awati, Gaurav Gupta, Sarita Rawat, Deepa Singh, Sachchidanand Pathak, Yogendra Singh, Santosh Kumar Singh, and Ritu M. Gilhotra

Abstract

Lung cancer is a chronic disease and speaks to one of the greatest health care issues for mankind. It is an illness with a high morbidity and high demise rates. Subsequently, it is regularly connected with a plenty of affliction and general abatement in the quality of life. Just chemotherapy and radiation therapies are now and again effective and in much occasions harmful and deadly. Alternative and less toxic medicine is very considerably essential to this ailment. The goal of this study is to review the medicinal plants having antitumor activity for the management of lung cancer. Medicinal plants are presently standing out as likely wellsprings of anticancer specialists and are broadly utilized because of accessibility of the materials, generally modest, little, or no side effects, wide pertinence, and helpful adequacy which thus have quickened the scientific exploration. The study was directed with lung cancer cell line (Human), on humans and animals, and lung carcinoma (Lewis) was the maximum utilized exploratory model. In this review we have summarized some medicinal plants keep being an abundant wellspring of herbal remedies or bioactive composites against Lung cancer.

S. S. Awati
School of Pharmacy, Suresh Gyan Vihar University, Jaipur, India

Dr. Shivajirao Kadam College of Pharmacy, Kasabe Digraj, Sangli, Maharashtra, India

G. Gupta (✉) · S. Rawat · D. Singh · S. Pathak · S. K. Singh · R. M. Gilhotra
School of Pharmacy, Suresh Gyan Vihar University, Jaipur, India

Y. Singh
Maharishi Arvind College of Pharmacy, Ambabari, Jaipur, India

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_12

Keywords

Lung cancer · Phytoconstituents · Medicinal plant · Antitumor activity · Natural products

12.1 Introduction

Our body is made out of a huge quantity of little cells, each an independent living unit. Normal cells inside the body develop and multiply for a while and afterward stop developing and multiplying. From that point, they only replicate themselves as essential to substitute faulty or dying cells. Malignant growth happens when this cell generation drives out of control. The abnormal development and division saw inside the cancer cells are brought about by harm in these cells DNA (the genetic material inside the cells that decides cellular characteristics and functioning). There is an assortment of ways that cellular DNA gets harmed and defective [1].

Malignancy is an assortment of heterogeneous genetic illnesses joined by collective modifications in multiple cell signal pathways [2]. Numerous trademarks are proposed to cancer cells. Avoidance of modified cell demise or apoptosis remained as principal modifications that dictate malignant growth [3]. Moreover, different trademarks remember independence for development signals, liberating cell energetics, supported angiogenesis, metastasis, evasion immune detection, and tissue intrusion [2–4].

As indicated by the WHO, the malignancy is a non-communicable syndrome liable for 63% of deaths throughout the world, being considered as the second reason for death in the whole globe [5, 6].

Cancer is a main reason for death around the world, representing an expected 96 lakh deaths in 2018. By 2025, 193 lakh new cases are anticipated to develop each year [7]. The most widely recognized cancers are as follows:

- Stomach (1.3 lakh cases)
- Skin cancer (non-melanoma) (1.4 lakh cases)
- Prostate (12.8 lakh cases)
- Colorectal (18 lakh cases)
- Breast (20.9 lakh cases)
- Lung (20.9 lakh cases)

Lung cancer is presently the malignant tumor with the highest rate of mortality around the world, often because it is not recognized till there has been significant growth of the disease, which prompts a huge decline in the personal satisfaction of the patient [8]. The use of tobacco is the most significant danger issue for malignancy and is liable for around 22% of total cancer demise [9].

Various factors are classified as possible reasons for lung cancer, comprising indoor and outside air pollution, cigarette smoking, exposure to passive smoking, radiation, and work-related exposure to composites such as asbestos, arsenic, nickel,

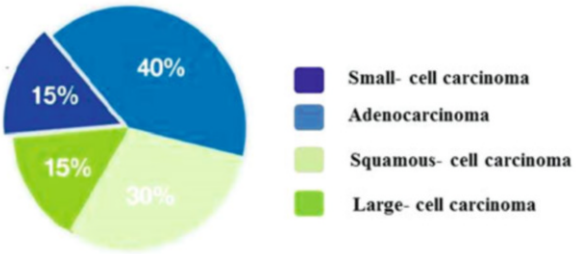


Fig. 12.1 Categories of lung carcinoma by histology

and chromium [10]. The greatest significant reason is smoking [11] besides the occurrence rates of lung carcinoma are usually greater in men than in ladies [12].

There are 2 fundamental forms of lung carcinoma:

(a) Non-small cell lung carcinoma (NSCLC).
(b) Small cell lung carcinoma (SCLC).

(a) *Non-small cell lung carcinoma (NSCLC)*

NSCLC is the furthermost well-known sort of lung cancer. Approximately eight out of ten lung cancers are NSCLC.

There are 3 subclasses of NSCLC:

1. Adenocarcinomas.
2. Squamous cell carcinomas.
3. Large cell carcinomas.

Adenocarcinoma makes up around 40% of entire lung cancers and it is the most widely recognized form of lung carcinoma and arises inside the cells of glands situated on the external aspect of the lungs. It is most oftentimes observed in individuals younger than 45, ladies, and non-smokers.

Squamous cell carcinoma (SCC) makes up about 30% of entire lung carcinoma and also is connected with past filled with smoking. Squamous cell carcinoma is more common in men compared to women. Most instances of SCC establish in the middle of lung. Frequently, and at a prior stage, SCC has indications like coughing up blood.

Large cell carcinoma (LCC) makes up around 15% of entire lung cancers and will in general develop rapidly and is typically undetected until they have metastasized. LCC just shows up in about 1 in each 10 individuals. As new exact diagnostics have opened up any lung carcinoma formerly diagnosed as LCC is recategorized as adenocarcinoma or SCC.

(b) *Small cell lung carcinoma (SCLC)*

SCLC makes up around 15% of entire lung cancers and is a considerably less regular type of lung carcinoma, influencing approximately 1 in each 10 individuals determined to have lung carcinoma. SCLC is especially destructive. It regularly restores after beginning rounds of chemotherapy [12, 13] (Figs. 12.1 and 12.2).

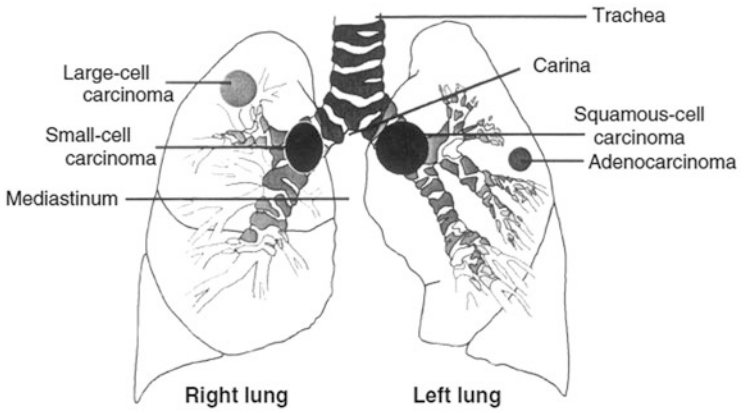


Fig. 12.2 Common Locations for Four major types of Lung Cancer [14]

12.2 Stages of Cancer

"Staging" is a very significant boundary in deciding the seriousness of this illness. Patients can be suggested to medicate appropriately depending on the stage of cancer. There are 4 stages of cancer, each demonstrating various properties and symptoms. These are organized as under:

STAGE ZERO: The physician catches abnormal cells precisely in the upper-most layer of cells coating the aviation paths.

STAGE ONE: This is the primary stage of cancer with no noticeable symptoms. The tumor is not completely developed and has not outspread to different sites of the body. A normal clinical assessment can help identify the existence of first stage disease. If cancer is recognized in this stage, it would be easier to cure it.

STAGE TWO: The tumor in this case is easily visible through scans. There are a few visible symptoms.

STAGE THREE: The benign tumor is fully developed with noticeable symptoms.

STAGE FOUR: This is the terminal stage cancer and no cure is possible in this stage. There is metastasis (spread) of tumor to different parts of the body. There are visible indications of cachexia (unexpected critical weight reduction).

There is another way to categorize cancer based on its severity and expansion as:

T: This is the first stage of cancer and its severity depends on the spread of tumor from its unique position.

N: When the tumor spreads from its original location to lymphatic nodes [15].

These days, surgery, radiation, chemotherapy, hormones therapy, and immunotherapy are the fundamental methodologies for malignant growth therapy, normally enhanced by other correlative and elective medicines, for example, herbal remedies. In spite of the fact that chemotherapy is the technique generally utilized, a few issues are related to its utilization, including restricted adequacy, serious harmfulness, and multidrug opposition [16].

However, in this strategy, on reason of non-selectivity of medications, a high number of healthy cells will be vanished with disease cells. Besides the utmost significant issue in disease treatment is abolishing tumor cells within the sight of normal cells. To treat the cancer by natural sources like plants by examining cytotoxic composites and screening of various extracts of plants are vital [17], Hence, the accessibility of natural products with greater adequacy and minor side effects is anticipated [18]. Medicinal spices are significant for malignancy therapy because of their different chemical composites for finding new dynamic resources against cancer [19].

Various upgrades are accounted for in like manner therapies of malignant growth by ascertaining secondary composites of natural products and herbal remedies. It is assumed that anticancer impacts of plants are established by stimulating the production of antitumor enzymes in the cell, inhibiting cancer's stimulating enzymes, repairing DNA, boosting immunity, and bringing antioxidant impacts [20]. Plants have reliably been a purpose behind the conventional medication frameworks and they have given ceaseless solutions for humanity to a large number of years. Information on the medicinal plants for the provision of several drugs has been of incredible importance [21]. Therapeutic plants are perceived as a rich premise of a wide assortment of components which can be used for medication advancement. Malignancy is the major dangerous sicknesses which are described by unpredictable cell multiplication. It is a significant medical problem in developed and developing nations. The most well-known explanation for malignant growth is changing the approach of life and because of this it becomes an overall issue over the world. Accordingly, there is a demanding need to discover better treatment feasible for this ailment. As chemotherapy and radiation treatment cause different symptoms, so here a need to find novel specialists for the therapy of this sickness; it might be conceivable with the consumption of naturally occurring compounds [22].

Plants have an extensive antiquity of utilization in the therapy of malignant growth and keep on being the primary basis of new medications [23]. Remedies from herbal source have been perceived as one of the striking methodologies for the therapy of lung cancer since they have recognized to be helpful and effectual in alerting conservative agents, extending endurance time, avoiding side effects of chemotherapy, and enhancing personal satisfaction of the sufferer of lung carcinoma [24]. The latest study with plenty of malignancy sufferers uncovered that the ratio of individuals consuming herbal medications in combination with conventional treatment was as high as 77% [25].

This information exhibit the significance of natural composites as a complementary treatment for the therapy of lung carcinoma, principally with the purposes of reduction of toxicity of treatment, improvement of cancer correlated symptoms,

encouragement of the immune system, and direct impact on disease [26]. Numerous natural products or synthetic composites are still broadly utilized clinically, for example, Vinca alkaloids isolated from the *Catharanthus roseus*, i.e. Vincristine, Vinblastine [23]. Also, further promising natural or synthetic composites like flavopiridol [27] and combretastatin A4 are in the clinical development phase [28].

12.3 Methodology

So as to gather evidences about various compounds, keywords "cytotoxicity," "traditional medicine," "medicinal plant," "herbal medicine," "plant compounds," "Lung cancer cell line," "anticancer effect" were looked in domestic databanks and international databases like Scopus Science Direct and PubMed. The search interval was from 1965 to 2020.

12.4 Results and Discussion

12.4.1 Anticancer Impact of Medicinal Plants

Therapeutic plants can be strong anticancer compounds for lung cancer treatment over synthetic items because composites derived from plants are more endured and not toxic to the normal human cells. Effectively accessible ordinary treatments for the therapy of malignant growth are radiotherapy and chemotherapy and they have possess different side effects like neurological, heart, pulmonary, and kidney toxicity, which truly influence the well-being of the individual.

In this manner, an alternative strategy is needed to develop that include slighter toxic and more impactful anticancer drug as compared to the medications accessible throughout the market. Natural medications have a fundamental purpose in the anticipation and therapy of disease. Natural drugs and phytochemicals can act as potent anticancer composites for the lung carcinoma treatment and avoidance by maintaining multi-molecular sites involved in metastasis, angiogenesis, and severe side effects [29, 30]. In this survey, we accomplished antitumor impact of medicinal plants against different kinds of lung tumors dispersed in various regions of the world.

Some of the plants that exhibit anticancer potential against lung cancer are given in Table 12.1.

12.5 Conclusions

Every year, lung cancer takes the lives of billions of peoples. Different treatments are accessible for the treatment but they have a few restrictions, for example, kidney harm, gastrointestinal disorder, and so on, because of which an alternative solution to this problem is required.. A few nations study medicinal plants with antitumor

Table 12.1 List of medicinal plants which exhibit anticancer activity against lung carcinoma

S. no	Botanic name	Family	Portion used	Extract/phytoconstituent	Model/cell line	Mammals tried	Result	References
1.	*Adenosma bracteosum*	Scrophulariaceae	Aerial part	Ethanol extract	NCI-H460	Human lung	Active	[31]
2.	*Allium sativum*	Liliaceae	Cloves	Water–ethanol extract	Lewis lung carcinoma cells LL/2	Human lung	Active	[32, 33]
3.	*Alstonia scholaris*	Apocynaceae	Root bark	O-methyl macralstonine, talcarpine, villalstonine, pleiocarpamine	MOR-P and COR-L23	Human lung	Active	[34]
4.	*Angelica sinensis*	Apiaceae	Whole plant	Aqueous extracts	Lewis lung	Mouse	Active	[35]
5.	*Apis mellifera*	Apidae	Venom	Royal jelly, 10-hydroxydecanoic acid	Lung tumor	Mouse	Active	[36]
6.	*Aristolochia ringens*	Aristolochiaceae	Roots	Ethanol extract	A549	Human lung	Active	[37]
7.	Astragalus cystosus	Fabaceae	Shoot	Lectins, flavonoids, and terpenoids	A549	Human lung	Active	[38]
8.	*Astragalus membranaceus*	Fabaceae	Whole plant	Aqueous extracts	Lewis lung	Mouse	Active	[35]
9.	*Barleria grandiflora*	Acanthaceae	Leaves	Alcohol and aqueous	A549	Human lung	Active	[39]
10.	*Bridelia ovata*	Euphorbiaceae	Whole plant	Ethyl acetate extract	A549	Human lung	Active	[40]
11.	*Brucea javanica*	Simaroubaceae	Seeds	Seeds oil	A549	Human lung	Active	[41]
			Seeds	Seeds oil	Lung carcinoma	Human adult	Active	[42]
			Seeds	Seeds oil	Lung carcinoma	Human adult	Active	[43]

(continued)

Table 12.1 (continued)

S. no	Botanic name	Family	Portion used	Extract/phytoconstituent	Model/cell line	Mammals tried	Result	References
12.	*Bruguiera sexangula*	Rhizophoraceae	Stem bark	Ethanol extract	Lewis lung	Mouse	Active	[44]
13.	*Bupleurum falcatum*	Apiaceae	Whole plant	Saikosaponin D	A-549	Human lung	Active	[45]
14.	*Calamus rotang*	Arecaceae	Aerial parts	Ethanol:Water extract (1:1)	Lewis lung	Mouse	Active	[46]
15.	*Camellia sinensis*	Theaceae	Leaves	Epicatechin gallate, epicatechin, epigallocatechin, theabrownin	Adenocarcinoma cell lines A549, H1299, H1650, H358, HCC827	Human lung	Active	[47]
				Polyphenolic fraction	Lung carcinoma	Mouse	Active	[48]
16.	*Carcharhinus plumbeus*	Carcharhinidae	Serum Chesapeake bay	–	Lewis lung	Mouse	Active	[49]
17.	*Cassia garrettiana*	Fabaceae	Wood	Methanol extract	Lewis lung	Mouse	Active	[50]
18.	*Catharanthus roseus*	Apocynaceae	–	Vinorelbine	NSCL cancer	Human adult	Active	[51]
19.	*Cedrus deodara*	Pinaceae	Wood	Hydroalcoholic extract	A549	Human lung	Active	[52]
20.	*Cenchrus ciliaris*	Poaceae	Aerial parts, roots	Ethanol extract	A549	Human lung	Active	[53]
21.	*Chelidonium majus*	Papaveraceae	Whole plant	Alkaloid fraction	Lung carcinoma	Human adult	Active	[54]
22.	*Chlorella vulgaris*	Chlorellaceae	Dehydrated cells	Chromatographical fraction	Lewis lung-3LL	Mouse	Active	[55]

23.	*Cladonia leptoclada*	Cladoniaceae	Thallus	Ethanol–water extract	Lewis lung	Mouse	Active	[56]
24.	*Coxi lachrymal*	Poaceae	Seed	Methanolic extract	A-549	Human lung	Active	[57]
25.	*Croton bonplandianus*	Euphorbiaceae	Leaves	Acetone extract	A549	Human lung	Active	[58]
26.	*Croton macrostachys*	Euphorbiaceae	Fruits	Ethanol extract	Lewis lung	Mouse	Active	[59, 60]
27.	*Croton oblongifolius*	Euphorbiaceae	Whole plant	Ethyl acetate extract	A549	Human lung	Active	[40]
28.	*Curcuma longa*	Zingiberaceae	Root, rhizome	Curcumin	A549 cells	Human lung	Active	[61]
29.	*Eleutherococcus senticosus*	Araliaceae	Root	Ethanol extract	Chem. induced tumor	Mouse	Active	[62]
30.	*Erythrophleum succirubrum*	Leguminosae	Bark	Ethyl acetate extract	A549	Human lung	Active	[40]
31.	*Euphorbia esula*	Euphorbiaceae	Intact plant	Ethanol extract	Lewis lung	Mouse	Active	[63]
32.	*Euphorbia fischeriana*	Euphorbiaceae	Intact plant	Ethanol extract	Lewis lung	Mouse	Active	[64]
33.	*Ferula gummosa*	Apiaceae	Roots	Acantrifoside E	A-549	Human lung	Active	[65]
34.	*Ferula persica*	Apiaceae	Roots	Farnesiferol A, Acantrifoside E	A-549	Human lung	Active	[65]
35.	*Ganoderma lucidum*	Ganodermataceae	Dried fruit body	Water, ethanol (95%) extract	Ca-Lewis lung	Mouse	Active	[66, 67]
36.	*Glycyrrhiza glabra*	Leguminosae	Roots	Licochalcone-A, Licoagrochalcone	Lung cancer	Mouse	Active	[68]

(continued)

Table 12.1 (continued)

S. no	Botanic name	Family	Portion used	Extract/phytoconstituent	Model/cell line	Mammals tried	Result	References
37.	*Glycyrrhiza uralensis*	Fabaceae	Roots	Isoliquiritigenin	NIH3T3, HCC827, NCI-H1975, 293T, NCI-H1650, A549	Human lung	Active	[69]
38.	*Herba epimedii*	Berberidaceae	Leaves	Icariin, icaritin, icariside	Lung cancer	Mouse	Active	[70]
39.	*Thespesia populnea*	Malvaceae	Fruits	Ethanol–water extract	Lewis lung	Mouse	Active	[46]
40.	*Hypsizigus marmoreus*	Tricholomataceae	Fruits	Aqueous extract	Lewis lung	Mouse	Active	[71]
41.	Lagenaria siceraria	Cucurbitaceae	Fruits	Hydroalcoholic extract	A549	Human lung	Active	[72]
42.	*Lentinus edodes*	Tricholomataceae	Fruits	Aqueous extract	Lewis lung	Mouse	Active	[73]
43.	*Limonia acidissima*	Rutaceae	Ripe fruits	Methanol extract	H460	Human lung	Active	[74]
44.	*Limonium densiflorum*	Plumbaginaceae	Shoots	Ethanol extract	A549	Human lung	Active	[75]
45.	*Lithospermum radix*	Boraginaceae	Whole plant	Hydroxyl isovalerylshikonin	DMS114	Human lung	Active	[76]
46.	*Maytenus serrate*	Celastraceae	Fruits, stemwood, roots	Ethanol extract	Lewis lung	Mouse	Active	[77]
47.	*Morinda citrifolia*	Rubiaceae	Fruits	Ethanol insoluble Portion	Lewis lung	Mouse	Active	[78]
48.	*Moringa oleifera*	Moringaceae	Seed	Pterygospermin 4-(40-oacetyl-a-L-rhamnopyranosyloxy) benzylisothiocyanate, 4 benzyl isothiocyanate	A-549	Human lung	Active	[79]

49.	*Munronia pinnata*	Meliaceae	–	Ganoderiol F	Lewis lung	Mouse	Active	[80]
50.	*Nigella sativa*	Ranunculaceae	Seed	Ethanol–water extract	Lewis lung	Mouse	Active	[46]
				α-hederin	A549, Lewis lung LL/2	Human lung, mouse	Active	[81]
51.	*Oldenlandia diffusa*	Rubiaceae	Leaves, bark, fruit peel	Ursolic acid	A549, ASTC-a-1, Calu-6, H640, and H3255	Human lung	Active	[82]
52.	*Panax ginseng*	Araliaceae	Dried root	Aqueous extract	Benzopyrene induced carcinoma	Mouse	Active	[83]
					Aflatoxin-induced lung adenocarcinoma	Mouse	Active	[84]
					Urethane-induced lung adenocarcinoma	Mouse	Active	[84]
53.	*Pelargonium graveolens*	Geraniaceae	Dried root	–	Lewis lung	Mouse	Active	[85]
54.	*Phellinus linteus*	Hymenochaetaceae	Mycelium	Polysaccharide portion	NCI-H23	Human lung	Active	[86]
55.	*Phyllanthus emblica*	Phyllanthaceae	Fruit	Aqueous extract	A-549	Human lung	Active	[87]
56.	*Podophyllum Peltatum*	Podophyllaceae	Leaves	Podophyllotoxin	NCI-H1299 and A549	Human lung	Active	[88]
57.	*Scutellaria barbata*	Lamiaceae	Whole plant	Ethanol extract	CL1–5	Human lung	Active	[89]
58.	*Solanum incanum*	Solanaceae	Whole plant	Solamargine	B16, A475, and G361	Human lung	Active	[90]

(continued)

Table 12.1 (continued)

S. no	Botanic name	Family	Portion used	Extract/phytoconstituent	Model/cell line	Mammals tried	Result	References
59.	*Solanum nigrum*	Solanaceae	Leaves	Solamargine, solasonine	WM239 and WM115	Human lung	Active	[91]
60.	*Squalus acanthias*	Squalidae	Cartilage	Aqueous extract	Lewis lung	Mouse	Active	[92]
61.	*Syzygium cumini*	Myrtaceae	Fruits	Methanol extract	H460	Human lung	Active	[74]
62.	*Tagetes minuta*	Asteraceae	Aerial parts	Aqueous extract	Lewis lung	Mouse	Active	[93]
63.	*Tecoma stans*	Bignoniaceae	Leaves, flowers	Methanol extract	A549	Human lung	Active	[94]
64.	*Thalictrum acutifolium*	Ranunculaceae	Whole plant	Acutiaporberine	95-D, PLA-801	Human lung	Active	[95]
65.	*Thymbra spicata*	Labiaceae	Whole plant	Hydroalcoholic	SK-Mes-1	Human lung	Active	[96]
66.	*Undaria pinnatifida*	Alariaceae	Thallus pacific	Aqueous extract	Lewis lung	Mouse	Active	[97]
67.	*Viscum album*	Loranthaceae	Whole plant	Aqueous extract	Lewis lung	Mouse	Active	[98]
68.	*Withania somnifera*	Solanaceae	Root and entire plant	Ethanol extract	Lung adenocarcinoma	Mouse	Active	[99, 100]
69.	*Ximenia Americana*	Olacaceae	Leaves	Aqueous extract	A549 & NCI-H460	Human lung	Active	[101]
70.	*Yucca aloifolia*	Agavaceae	Flowers	Methanol extract	Lewis lung	Mouse	Active	[102]
71.	*Ziziphus spina-christi*	Rhamnaceae	Flowers, leaves	Doxorubicin, spinanine-A, rutin, quercetin	Lung cancer	Human adult	Active	[103]

impact on lung cancer. Plants are a significant source of secondary metabolites and a vital source of therapeutic drugs. Natural medication therapy is an ideal decision as it is similarly less expensive and might be strongly prescribed to poor people and country individuals for the viable therapy of cancer of Lung. It is reported that herbal medicines have rich anticancer potency because of their immunomodulatory and antioxidant potential. Numerous species are active in diverse exploratory models. This displays that the natural composites from plants remain being a rich source of herbal remedies or bioactive composites. Bioactive composites altogether impacted the disease research on different perspectives. Secondary metabolites from medicinal plants prevent DNA harm, arrest the cell cycle, inhibit the angiogenesis of tumor cell, and induce apoptosis, hence prevents malignant growth.

There is a requirement for additional investigations on chemical characterization and standardization of the extracts utilized. However, studies with human and cancer cell lines (human Lung) were likewise observed for various species of plants. Moreover, lots of research has to be done on these phytochemicals to assess their potential applications, toxicological and specific genotoxic profile against a wide scope of malignancy in both either in vitro or in vivo. Hence in this section chosen plants have been investigated for their biological action against lung cancer and furthermore efforts are necessary to explore potent anticancer plants from nature to save humans lives across the world from lung cancer.

Conflict of Interest The authors declare no conflict of interest.

References

1. American Cancer Society (2010) Cancer facts & figures. American Cancer Society, Atlanta
2. Luo J, Solimini NL, Elledge SJ (2009) Principles of cancer therapy: oncogene and non-oncogene addiction. Cell 136:823–837
3. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144:646–674
4. Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell 100:57–70
5. Kashfi K (2013) Dysfunctional cell signaling dynamics in oncology: diagnostic, prognostic and treatment opportunities. Biochem Pharmacol 85:595–596
6. Alwan A, Maclean DR, Riley LM, d'Espaignet ET, Mathers CD, Stevens GA, Bettcher D (2010) Monitoring and surveillance of chronic non-communicable diseases: progress and capacity in high-burden countries. Lancet 376:1861–1868
7. CDC—Global Cancer Statistics. http://www.cdc.gov/cancer/international/statistics.htm. Accessed 21 Jan 2016
8. Ford DW, Koch KA, Ray DE, Selecky PA (2013) Palliative and end-of-life care in lung cancer. Chest 143(5 Suppl):498S–512S
9. GBD 2015 Risk Factors Collaborators (2016) Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the global burden of disease study 2015. Lancet 388(10053):1659–1724
10. Alberg AJ, Brock MV, Ford JG, Samet JM, Spivack SD (2013) Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 143:1–29

11. Rom WN, Hay JG, Lee TC, Jiang Y (2000) Molecular and genetic aspects of lung cancer. Am J Respir Crit Care Med 16:1355–1367
12. Duarte RLM, Paschoal MEM (2005) Marcadores moleculares no câncer de pulmão: papel prognóstico e sua relação com o tabagismo. J Braz Pneumol 32:56–65
13. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ, Thun MJ (2005) Cancer statistics, 2005. Cancer J Clin 55:10–30
14. Robert JC (2002) Lung cancer: a review. Am J Health-Syst Pharm 59(1):611–642
15. Rowlands MA, Gunnell D, Harris R, Vatten LJ, Holly JMP, Martin RM (2009) Circulating insulin-like growth factor peptides and prostate cancer risk: a systematic review and metaanalysis. Int J Cancer 124(10):2416–2429
16. Tan W, Huang M et al (2011) Anti-cancer natural products isolated from Chinese medicinal herbs. Chin Med 6(1):1–15
17. Rafieian-Kopaie M, Nasri H (2015) On the occasion of world cancer day 2015: the possibility of cancer prevention or treatment with antioxidants: the ongoing cancer prevention researches. Int J Prev Med 6:108–112. https://doi.org/10.4103/2008-7802.169077
18. Lachenmayer A, Alsinet C, Chang CY, Liovit JM (2010) Molecular approaches to treatment of hepatocellular carcinoma. Dig Liver Dis 42:264–272
19. Newman DJ, Cragg GM (2007) Natural products as sources of new drugs over the last 25 years. J Nat Prod 70:461–477
20. Sakarkar DM, Deshmukh VN (2011) Ethnopharmacological review of traditional medicinal plants for anticancer activity. Int J PharmTech Res 3:298–308
21. Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, Linder T, Wawrosch C et al (2015) Discovery and resupply of pharmacologically active plant-derived natural products: a review. Biotechnol Adv 33(8):1582–1614
22. Dias DA, Urban S, Roessner U (2012) A historical overview of natural products in drug discovery. Meta 2:303–336
23. Cragg GM, Newman DJ (1830) Natural products: a continuing source of novel drug leads. Biochim Biophys Acta 2013:3670–3695
24. Jeong SJ, Koh W, Kim B, Kim SH (2011) Are there new therapeutic options for treating lung cancer based on herbal medicines and their metabolites? J Ethnopharmacol 138:652–661
25. Richardson MA, White JD (2000) Complementary/alternative medicine and cancer research. A national initiative. Cancer Pract 8:45–48
26. Gerber B, Scholz C, Reimer T, Briese V, Janni W (2006) Complementary and alternative therapeutic approaches in patients with early breast cancer: a systematic review. Breast Cancer Res Treat 95:199–209
27. Sedlacek HH (2001) Mechanisms of action of flavopiridol. Crit Rev Oncol Hematol 38:139–170
28. Kapoor S (2013) Combretastatin A4 and its emerging antineoplastic effects. Surgery 153:881
29. Shu-Yi Y, Wen-Chi W, Feng-Yin J, Ning-Sun Y (2013) Therapeutic applications of herbal medicines for cancer patients. Evid Based Complement Alternat Med 302426:1–15
30. Sanjar A, Deepti K, Richa G, Amita V, Ashu M (2013) Role of herbals in cancer management. J Phytopharmacol 2(6):46–51
31. Ngoc HN, Qui THT, Quang TP et al (2020) Anticancer activity of novel plant extracts and compounds from *Adenosma bracteosum* (Bonati) in human lung and liver cancer cells. Molecules 25:2912–2928
32. Kyo E, Uda N, Suzuki A, Kakimoto M, Ushijima M, Kasuga S, Itakura Y (1998) Immunomodulation and antitumor activities of aged garlic extract. Phytomedicine 5:259–267
33. Kyo E, Uda N, Kasuga S, Itakura Y, Sumiyoshi H (1999) In: Wagner H (ed) Garlic as an immuno -stimulant, immuno-modulatory agents from plants. Birkhauser Verlag, Basel, pp 273–288
34. Niwat K, Houghton PJ, Eno-Amooquaye E, Burke PJ (1997) Activity of extracts and alkaloids of Thai Aistonia species against human lung cancer cell lines. Planta Med 63:97–101

35. Wu TH, Yeh KY, Wang CH et al (2019) The combination of *Astragalus membranaceus* and *Angelica sinensis* inhibits lung cancer and cachexia through its immunomodulatory function. J Oncol 3–4:1–15
36. Curic S, Tadic Z, Valpotic I, Sulimanovic D, Basic I (1992) The effect of bee venom on tumor growth and metastasis formation of mammary carcinoma in CBA mice. Vet Arh 62:S31–S35
37. Akindele AJ, Wani Z, Mahajan G, Sharma S, Aigbe FR, Sati N (2015) Anticancer activity of *Aristolochia ringens* Vahl. (Aristolochiaceae). J Tradit Complement Med 5(1):35–41
38. Cassileth BR, Rizvi N, Deng G et al (2009) Safety and pharmacokinetic trial of docetaxel plus an Astragalus-based herbal formula for non-small cell lung cancer patients. Cancer Chemother Pharmacol 65:67–71
39. Manglani N, Vaishnava S, Dhamodaran P, Sawarkar H (2014) *In-vitro* and *in-vivo* anti-cancer activity of leaf extract of *B. grandiflora*. Int J Pharm Sci 6(3):70–82
40. Juthathip P, Patompong K, Subhawat S et al (2020) Potential of Thai herbal extracts on lung cancer treatment by inducing apoptosis and synergizing chemotherapy. Molecules 25:231–260
41. Wu S (1991) Preoperative intravenous drip of an anti-tumor Chinese herb preparation *Brucea javanica* oil emulsion (Ya Dan Zi Emulsion) for lung cancer. Shang-Hai I Hsueh 14:273–275
42. Hu B, Yang N, Liu W, Sha H, Yu D (1991) Estimation of integrations of various functional groups of *Brucea javanica* (L.) Merr. Oil. Bopuxue Zazhi 8:433–440
43. Su S et al (1985) Treatment of lung cancer with brain metastasis by using intravenous drip of 10% emulsion of *Brucea javanica* seminal oil. Chin J Integ Trad West Med 5:86–88
44. Loder J, Russell G (1969) Tumor inhibitory plants. The alkaloids of Bruguiera sexangula and Bruguiera exaristata (Rhizophoraceae). Aust J Chem 22:1271
45. Bochuan Y, Rui Y, Youngsheng M, Shan Z, Xiaodong Z, Ying L (2017) A systematic review of the active saikosaponins and extracts isolated from *Radix Bupleuri* and their applications. Pharm Biol 55(1):620–635
46. Dhar ML, Dhar MM, Dhawan BN, Mehrotra BN, Ray C (1968) Screening of Indian plants for biological activity: part I. Indian J Exp Biol 6:232–247
47. Wu F, Zhou L, Jin W, Yang W, Wang Y, Yan B et al (2016) Antiproliferative and apoptosis-inducing effect of theabrownin against non-small cell lung adenocarcinoma A549 cells. Front Pharmacol 7:465
48. Jiang Y, Chen J, Wu Z, Lin L, Feng S (1998) Inhibitory effect of tea polyphenol on mice lung cancer induced by diethyl stilbestrol combined with urethane. Weisheng Dulixue Zazhi 12:7–9
49. Snodgrass MJ, Burke JD, Meetz GD (1976) Inhibitory effect of shark serum on the Lewis lung carcinoma. J Natl Cancer Inst 56:981–983
50. Kimura Y, Baba K, Okuda H (2000) Inhibitory effects of active substances isolated from *Cassia garrettiana* heartwood on tumor growth and lung metastasis in Lewis lung carcinoma-bearing mice (part 1). Anticancer Res 20:2899–2906
51. Nazir T, Taha N, Islam A, Abraham S, Mahmood A, Mustafa M (2016) Monocytopenia; induction by vinorelbine, cisplatin and doxorubicin in breast, non-small cell lung and cervix cancer patients. Int J Health Sci 10(4):542–547
52. Gaidhani SN, Singh A, Kumari S, Lavekar GS, Juekar AS, Sen S (2013) Evaluation of some plant extracts for standardization and anticancer activity. Indian J Tradit Knowl 12(4):682–687
53. Alothman EA, Awaad AS, Al-Qurayn NA, Al-Kanhal HF, El-Meligy RM, Zain YM (2018) Anticancer effect of *Cenchrus ciliaris* L. Saudi Pharm J 26(7):952–955
54. Staniszewski A, Slesak B, Kolodziej J, Harlozinska-Szmyrka A, Nowicky J (1992) Lymphocyte subsets in patients with lung cancer treated with thiophosphoric acid alkaloid derivatives from *Chelidonium majus* L. (Ukrain). Drugs Exp Clin Res 18:63–67
55. Noda K, Ohno N, Tanaka K, Okuda M, Yadomae T, Nomoto K, Shoyama Y (1998) A new type of biological response modifier from *Chlorella vulgaris* which needs protein moiety to show an antitumour activity. Phytother Res 12:309–319
56. Kupchan SM, Kopperman HL (1975) L-usnic acid: tumor inhibitor isolated from lichens. Experientia 31:625–752

57. Aranya M, Mathukorn S, Chariny C, Worapaka M, Jiradej M (2016) In vitro anti-cancer activities of Job's tears (*Coix lachryma-jobi* Linn.) extracts on human colon adenocarcinoma. Saudi J Biol Sci 23:248–256
58. Bhavna J et al (2016) Cytotoxic and pro-apoptotic activities of leaf extract of Croton bonplandianus Baill. Against lung cancer cell line A549. Indian J Exp Biol 54:379–385
59. Kupchan SM, Hemingway RJ, Coggon P, Mc Phail AT, Sim GA (1968) Crotepoxide, a novel cyclohexane diepoxide tumor inhibitor from *Croton macrostachys*. J Am Chem Soc 90:2982
60. Kupchan SM, Hemingway RJ, Smith RM (1969) Tumor inhibitors. XLV. Crotepoxide, a novel cyclohexane diepoxide tumor inhibitor from *Croton macrostachys*. J Org Chem 34:3898–3902
61. Hiren JM, Vipul P, Ruxana T (2014) Curcumin and lung cancer- a review. Targ Oncol 9 (4):295–310. https://doi.org/10.1007/s11523-014-0321-1
62. Djioev FK (1965) Influence of extract of eleutherococcus on arising of urethane induced lung adenomas in mice. Vopr Onkol 11:51
63. Kupchan SM, Uchida I, Branfman AR, Dailey RG, Fei BY (1976) Antileukemic principles isolated from Euphorbiaceae plants. Science 191:571–572
64. Shentu J, Wei P, Wang A et al (1984) A study of the antitumor effect of *Euphorbia fischeriana* steud on mice with induced tumor. Chin J Integ Trad West Med 4:46–47
65. Seied MV, Mehrdad I, Amirhossein S (2013) Cytotoxic activities of phytochemicals from ferula species. DARU J Pharm Sci 21(39):1–7
66. Furusawa E, Chou S, Furusawa S, Hirazumi A, Dang Y (1992) Antitumor activity of *Ganoderma lucidum*, an edible mushroom, on intraperitoneally implanted Lewis lung carcinoma in syngeneic mice. Phytother Res 6:300–304
67. Kimura Y, Taniguchi M, Baba K (2002) Antitumor and antimetastatic effects on liver of triterpenoid fractions of *Ganoderma lucidum*: mechanism of action and isolation of an active substance. Anticancer Res 22:3309–3318
68. Zhang YY, Huang CT, Liu SM, Wang B, Guo J, Bai JQ et al (2016) Licochalcone A exerts antitumor activity in bladder cancer cell lines and mice models. Trop J Pharm Res 15 (6):1151–1157
69. Jung SK, Lee MH, Kim JE, Singh P, Lee SY, Jeong CH et al (2014) Isoliquiritigenin induces apoptosis and inhibits xenograft tumor growth of human lung cancer cells by targeting both wild type and L858R/T790M mutant EGFR. J Biol Chem 289:35839–35848
70. Yong YL, Tan LT, Ming LC, Chan KG, Lee LH, Goh BH et al (2017) The effectiveness and safety of topical capsaicin in postherpetic neuralgia: a systematic review and meta-analysis. Front Pharm 7:538
71. Saitoh H, Feng W, Matsuzawa T, Ikekawa T (1997) Antitumor activity of *Hypsizigus marmoreus*. II. Preventive effect against lung metastasis of Lewis lung carcinoma. Yakugaku Zasshi 117:1006–1010
72. Shokrzadeh M, Parvaresh A, Shahani S, Habibi E, Zalzar Z (2013) Cytotoxic effects of Lagenaria siceraria Standl. Extract on cancer cell line. J Mazandaran Univ Med Sci 23:225–230
73. Nanba H, Mori K, Toyomasu T, Kuroda H (1987) Antitumor action of shiitake (*Lentinus edodes*) fruit bodies orally administered to mice. Chem Pharm Bull 35:2453–2458
74. Tripathy G, Pradhan D, Pradhan S, Dasmohapatra T (2016) Evaluation of plant extracts against lung cancer using H460 cell line. Asian J Pharm Clin Res 9(2):227–229
75. Medini F, Bourgou S, Lalancette KG et al (2015) Phytochemical analysis, anti-oxidant, anti-inflammatory and anticancer activities of the halophyte *Limonium densiflorum* extracts on human cell lines and murine macrophages. S Afr J Bot 99:158–164
76. Tanawan K (2005) Molecular mechanism of herbs in human lung cancer cells. J Med Assoc Thail 88(11):1725–1734
77. Kupchan SM, Komoda Y, Court WA, Thomas GJ, Smith RM, Karim A, Gilmore CJ, Haltiwanger RC, Bryan RF (1972) Tumor inhibitors. LXXIII. Maytansine, a novel antileukemic ansa macrolide from *Maytenus ovatus*. J Am Chem Soc 94:1354–1356

78. Hirazumi A, Furusawa E, Chou S, Hokama Y (1996) Immunomodulation contributes to the anticancer activity of *Morinda citrifolia* (noni) fruit juice. Proc West Pharmacol Soc 39:7–9
79. Shaban A, Mani GM, Nautiyal R (2012) In vitro cytotoxicity of Moringa oleifera against different human cancer cell lines. Asian J Pharm Clin Res 5:271–272
80. Anchala IK, Priyani P, Charitha LG (2019) Medicinal plants commonly used against cancer in traditional medicine formulae in Sri Lanka. Saudi Pharm J 27:565–573
81. Md. Asaduzzaman K, Han-chun C, Mousumi T, Dian-zheng Z (2011) Anticancer activities of *Nigella sativa* (Black cumin). Afr J Tradit Complement Altern Med 8(S):226–232
82. Wozniak L, Skapska S, Marszalek K (2015) Ursolic acid-a pentacyclic triterpenoid with a wide spectrum of pharmacological activities. Molecule 20:20614–20641
83. Yun YS, Lee YS, Jo SK, Jung IS (1993) Inhibition of autochthonous tumor by ethanol insoluble fraction from *Panax ginseng* as an immunomodulator. Planta Med 59:521–524
84. Yun TK, Yun YS, Han IW (1980) An experimental study on tumor inhibitory effect of red ginseng in mice and rats exposed to various chemical carcinogens. In: Proc. 3rd Int. Ginseng Symp. Seoul, South Korea. pp 87–113
85. Yang C, Lu W, Niu J (1983) Studies on the antitumor action of xiangshenboheyou (a mixture composed of *Pelargonium graveolens* and *Sophora flavescens* and other herbs). Chung Ts'ao Yao 14:409–410
86. Han S, Lee C, Jeon Y, Hong N, Yoo I, Yang K, Kim H (1999) The inhibitory effect of polysaccharides isolated from *Phellinus linteus* on tumor growth and metastasis. Immunopharmacology 41:157–164
87. Ngamkitidechakul C, Jaijo K, Hansakul P, Soonthornchareonnon N, Sireeratawong S (2010) Antitumour effects of phyllanthus emblica l.: induction of cancer cell apoptosis and inhibition of in vivo tumour promotion and in vitro invasion of human cancer cells. Phytother Res 24:1405–1413
88. Choi JY, Hong WG, Cho JH, Kim EM, Kim J, Jung CH et al (2015) Podophyllotoxin acetate triggers anticancer effects against nonsmall cell lung cancer cells by promoting cell death via cell cycle arrest, ER stress and autophagy. Int J Oncol 47:1257–1265
89. Chin-Chuan C, Chun-Pin K, Mei-Miao C, Shu-Huei W (2017) The anti-cancer effects and mechanisms of Scutellaria barbata D. Don on CL1-5 lung cancer cells. Oncotarget 8 (65):109340–109357
90. Sebastian Y, Hamm-Ming S, Chih-Hung L (2017) *Solanum incanum* extract (SR-T100) induces melanoma cell apoptosis and inhibits established lung metastasis. Oncotarget 8 (61):103509–103517
91. Al Sinani SS, Eltayeb EA, Coomber BL, Adham SA (2016) Solamargine triggers cellular necrosis selectively in different types of human melanoma cancer cells through extrinsic lysosomal mitochondrial death pathway. Cancer Cell Int 16(1):11
92. Sorbera L, Castaner R, Leeson P (2000) Ae-941 oncolytic antipsoriatic treatment of age related macular degeneration angiogenesis inhibitor. Drugs Future 25:551–557
93. Ickes GR, Fong HHS, Schiff PL, Perdue JRE, Farnsworth NR (1973) Antitumor activity and preliminary phytochemical examination of *Tagetes minuta* (Compositae). J Pharm Sci 62:1009–1011
94. Robinson JP, Suriya K, Subbaiya R, Ponmurugan P (2017) Antioxidant and cytotoxic activity of *Tecoma stans* against lung cancer cell line (A549). Braz J Pharm Sci 53(3):1–5
95. Qi C et al (2002) Apoptosis of a human non-small cell lung cancer (NSCLC) cell line, PLA-801, induced by acutiaporberine, a novel bisalkaloid derived from Thalictrum acutifolium (Hand.-Mazz.) Boivin. Biochem Pharmacol 63(8):1389–1396
96. Sabzali S, Arman R, Panahi J, Havasian MR, Haghani K, Bakhtiyari S (2014) Investigation on the inhibitory effects of hydroalcoholic extract of *Thymbra spicata* on the growth of lung cancer cell line SK-Mes-1. J Ilam Univ Med Sci 22:153–158
97. Furusawa E, Furusawa S (1989) Anticancer potential of viva-natural, a dietary seaweed extract, on Lewis lung carcinoma in comparison with chemical immunomodulators and on cyclosporine accelerated akr leukemia. Oncology 46:343–349

98. Khwaja T, Dias C, Pentecost S (1986) Recent studies on the anticancer activities of mistletoe (*Viscum album*) and its alkaloids. Oncology 43(Suppl):42–50
99. Mishra L, Singh B, Dagenais S (2000) Scientific basis for the treatment use of *Withania somnifera* (Ashwagandha). Altern Med Rev 5:334–346
100. Singh S, Singh D, Gupta M, Singh N, Kohli R (1979) An experimental evaluation of antitumor activity of *Withania somnifera* (Ashwagandha) and Geriforte. Indian J Pharmacol 11:65b
101. Vedamurthy AB, Shettar AK, Madagi SB (2018) Phytochemical screening and in-vitro antioxidant and Antiproliferative activity of aqueous leaf extract of *Ximenia americana* against non- small cell lung Cancer. Cancer Surg (Los Angel, CA) 3(1):117–124
102. Sokoloff B (1968) The oncostatic and oncolytic factors present in certain plants. Oncology 22:49
103. Jaradat NA, Al-Ramahi R, Zaid AN, Ayesh OI, Eid AM (2016) Ethnopharmacological survey of herbal remedies used for treatment of various types of cancer and their methods of preparations in the West Bank-Palestine. BMC Complement Altern Med 16(93):1–12

Role of Medicinal Plants in Pulmonary Hypertension

13

Deepak Kumar Jindal, Prachi Sah, Dheeraj Bisht, H. Lalhlenmawia, Dharmendra Kumar, and Deepak Kumar

Abstract

Pulmonary hypertension is a chronic and advanced disease associated with increased resistance to the pulmonary vasculature, which causes changes in the morphology of the pulmonary arteries and is a major reason for death worldwide. It is associated more in women than in men. It remains asymptomatic until the harmful effects of hypertension such as stroke, myocardial infarction, etc. are observed. Synthetic drugs are used to overcome this disease, but they produce serious side effects, so alternative medicines from medicinal plants need to be developed. Traditionally, medicinal plants have been used since ancient time and

Deepak Kumar Jindal and Prachi Sah contributed equally.

D. K. Jindal
Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar, Haryana, India

P. Sah
Department of Pharmaceutical Sciences, Sardar Bhagwan Singh University, Dehradun, Uttarakhand, India

D. Bisht
Department of Pharmaceutical Sciences, Kumaun University, Nainital, Uttarakhand, India

H. Lalhlenmawia
Department of Pharmacy, Regional Institute of Paramedical and Nursing Sciences, Aizawl, Mizoram, India

D. Kumar
Department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, UCSI University, Kuala Lumpur, Malaysia

D. Kumar (✉)
Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Shoolini University, Solan, Himachal Pradesh, India

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_13

are shown to be effective. Examples of plants include *Moringa Oleifera* Lam, *Allium sativum L.*, *Terminalia Arjuna*, *Withania Somnifera,* and many more. They act by decreasing SOD, increasing nitric oxide levels, and also lowering the BCL2/BAX ratio. This chapter focuses on the recent discovery of medicinal plants and its phytoconstituents used in the treatment of pulmonary hypertension and the pathways involved.

Keywords

Pulmonary hypertension · chronic disease · Medicinal plant · Anti-hypertension

13.1 Introduction

Pulmonary hypertension (PH) is a chronic and progressive disease related with increased resistance to pulmonary vasculature, which causes alteration in the morphology and structure of the pulmonary arteries and is a major cause of death worldwide. The symptoms include exhaustion, dyspnea, heart trembling, chest pain, anxiety, depression, increased sensitivity to respiratory infections, and retention of fluid [1]. The survival rate without the treatment is for about 2.8 years and can cause oxidative stress, inflammation, permanent hypoxia, and increase of endothelial cells and blockage of apoptosis in pulmonary arteries, which causes pulmonary vascular remodeling and oxygen deficiency in lungs [2, 3]. This occurs when volume of blood increases, right ventricular pressure increases and right ventricular hypertrophy results non-working of the ventricular [4]. The rise in pulmonary arterial pressure causes high blood circulation and right ventricle hypertrophy, when compared to normal conditions. Therefore, the major reason for disruption in O_2 and CO_2 exchange is mainly due to the speedy blood flow channeling through the lung's vasculature [5].

Pulmonary arterial hypertension (PAH) is considered as one of the most common class of PH, can be idiopathic, or may also be due to the result of other causes like collagen vascular disease, portal hypertension, and various toxins/drugs, *viz.* inhaled rapeseed oil, amphetamines, fenfluramine, cocaine, dexfenfluramine, etc. Respiratory diseases or hypoxemia like chronic obstructive pulmonary disease, chronic thrombotic, alveolar-capillary dysplasia and/or embolic diseases, and inflammation like sarcoidosis are linked with pulmonary venous hypertension [6]. The ethology of PH is shown in Fig. 13.1.

13.1.1 Pathophysiology of Pulmonary Hypertension

In the heart development of right ventricular systolic pressure is due to high resistance of the pulmonary vasculature to protect cardiac output. Persistent and continuous enhancement in resistance of the pulmonary vasculature can lead to rise

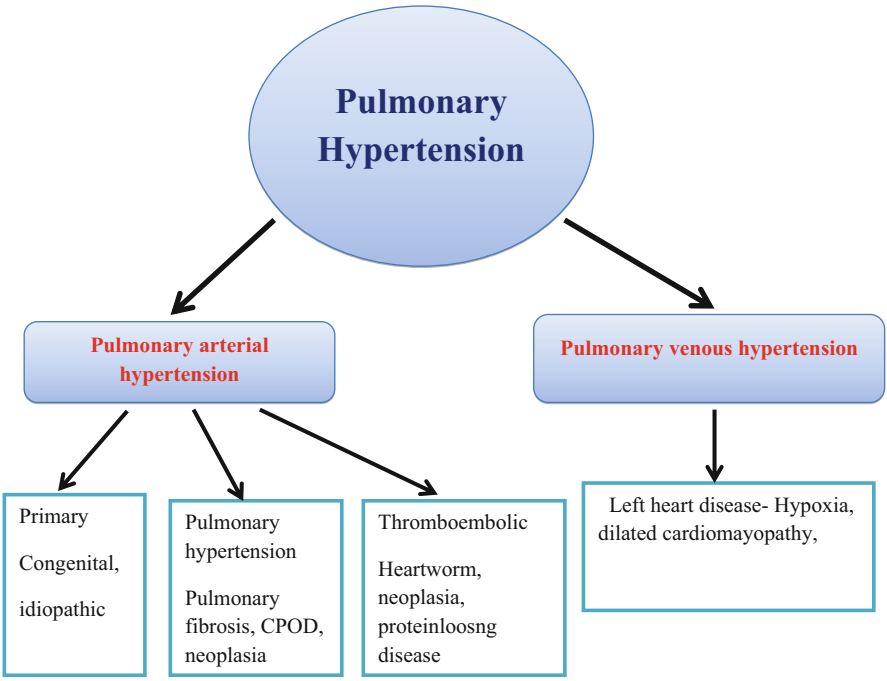


Fig. 13.1 Etiology of pulmonary hypertension

in systemic vascular resistant (SVR) on the right ventricle, thereby increases right ventricular systolic pressure (RVSP), this is pursued by destructive flow in right coronary artery, raised wall stress, and increased oxygen demand. Abnormality of oxygen demand and supply leads to greater SVR and expansion in right ventricular myocardial hypertrophy (RVH) suffering with PH and its frequent compensatory mechanism [3, 7].

Other studies give the impression that in perivascular infiltration and remodeling in PH, the cells are basically derived from bone marrow [8, 9]. Bloodworth et al. observed increase in bone marrow-derived cell exploitation due to PH into the pulmonary parenchyma and also suggested that in perivascular infiltration and remodeling in the lungs of these cells [8]. In the heart transformation of cells into myofibroblast or cardiomyocytes causes cardiac hypertrophy due to bone marrow-derived cells [9].

Further, studies suggest that the patients suffering from hereditary PAH and caveolin mutations in the coding region of bone morphogenic protein receptor 2 can be correlated with cell migration and propagation process which contributes to PAH pathophysiology in 70% of patients [10]. Studies have shown that extracted bone marrow-derived CD133 (+) cells with PAH primarily caused by caveolin mutations or BMPR2 [11].

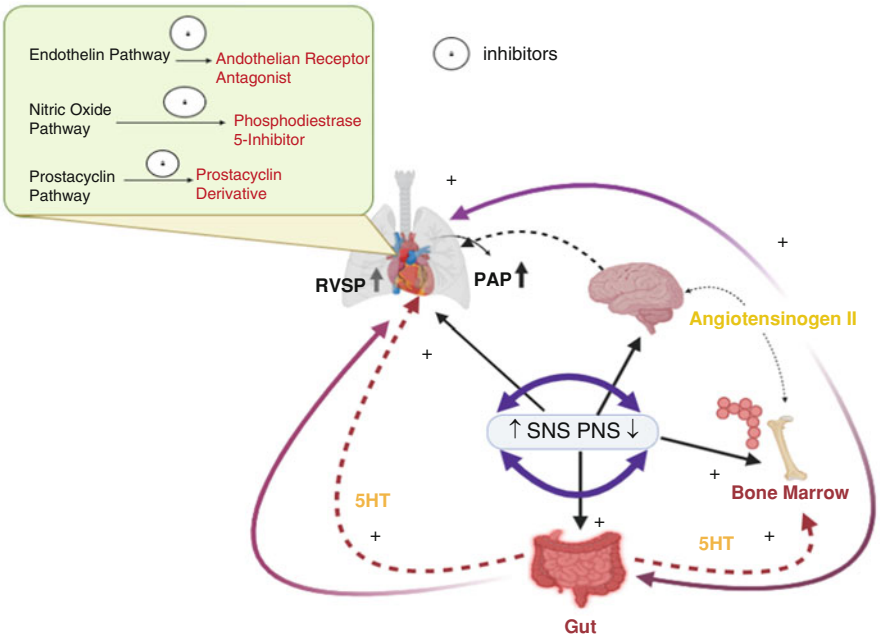


Fig. 13.2 Targets and pathophysiology of pulmonary hypertension

Moreover, in PH bone marrow-derived proangiogenic cells (PACs) promptly give rise to small-vessel remodeling, whereas in RVSP their abscission in the Sugen-Hypoxia model showed a sudden reduction, as it obstructs the muscularization and rigidity of pulmonary arterial vessels with no change in RV remodeling [8]. As suggested by these authors, serotonin plays an important role in functioning and recruitment of PACs in PAH, because it was observed that absence of 5-hydroxytryptamine (serotonin) receptor 2B (5-HT2B) exhibits parallel protective outcomes. Where as an inhibitor of the serotonin reuptake transporter (5-HTT), i.e. Fluoxetine, but not a particular antagonist of the serotonin receptors 5-HT2A or 5-HT2B, 5-HT1D/1B and is helpful in reversing fully antagonized monocrotaline-induced PH or severe PH [12] (Fig. 13.2).

FDA reported certain disorders in PAH patients that were nausea, diarrhea, constipation, etc. [13]. This further signifies that these gut disorders may be considered as a part of a cascade of episode in the PH syndrome and might be independent to treatments side effect.

Histopathological of PAH patients showed remarkable increase in plasma biomarkers for gut intestinal fatty-acid binding protein (iFABP), leakiness zonulin, high mobility group box 1 (HMGB1), gut inflammation lipopolysaccharides (LPS), and tissue inhibitor of metalloproteinase 1 (TIMP1) and higher penetration and gut

swelling. Hypothesis suggest major cause of microbial translocation contribute to chronic inflammation. whereas PH is linked with higher gut permeability [14]. Therefore, different synthetic drugs prove to be very helpful for the treatment of hypertension such as blockers of endothelin receptor (bosentan) [15], prostacyclin agonists (epoprostenol) [16], and phosphodiesterase-5 inhibitors (sildenafil) [17] but due to their side effects natural compounds are preferred over the synthetic drugs.

13.2 Different Plants Used Against Pulmonary Hypertension

13.2.1 *Allium sativum* L.

It is also known as garlic and is traditionally used as a spice as well as for the treatment of different diseases. Chemical constituents of *A. sativum* include sulfur containing compounds such as cysteine sulfoxides mainly responsible for the therapeutic activities. One such cysteine sulfoxide is alliin (Fig. 13.3) [18, 19]. Garlic is also used since older times for various conditions associated with oxygen toxicity, which is attributed to the presence of alliin as it shows strong antioxidant and hydroxyl radical scavenging activities [20].

A. sativum relaxes vascular smooth muscles through increasing the action of endothelial nitric oxide (NO) synthase. Water extract of *A. sativum* has shown the inhibition of the growth of PH caused by hypoxia owing to vasorelaxant action in rats [21]. Other therapeutic activities of *A. sativum* include antidiabetic activity, anti-inflammatory activity, immunity enhancer, anticancer activity, antibacterial activity, and cardiovascular protective activity [22].

13.2.2 *Withania somnifera* L.

It is called as ashwagandha and used in Indian traditional system of medicine [23]. Most important active chemical constituents present in *W. somnifera* are withanolide A and withaferin A (Fig. 13.4) [24]. Treatment of monocrotaline mediated pulmonary hypertension with *W. somnifera* resulted in decrease of right ventricular hypertrophy and pressure, reduction in the expression of protein content of proliferating nuclear cell antigen, increased procaspase-3 expression, reduction of reactive oxygen species, increase of interleukin 10, and decrease of tumor necrosis factor α in rats.

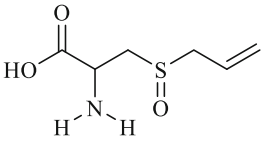


Fig. 13.3 Chemical structure of alliin

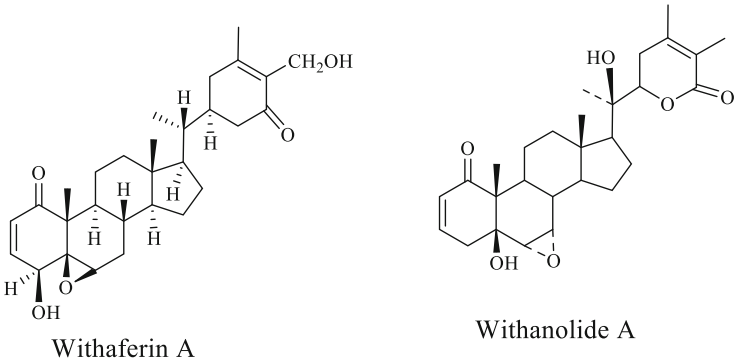


Fig. 13.4 Chemical structure of withaferin A and withanolide A

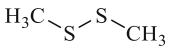


Fig. 13.5 Chemical structure of dimethyl disulfide

This plant also results in increase in endothelial NO synthase expression and decrease in hypoxia inducible factor 1α expression in the tissues of lung, resulting in increased nitric oxide levels causing vasorelaxation [24]. Other activities include antioxidant, anti-inflammatory, antifatigue, antidiabetic, antiaging, antitumor, and anti-Alzheimer [25]. Apart from these, it is also used as antihypertensive and antihyperlipidemic [26].

13.2.3 *Allium macrostemon* Bunge

This plant is traditionally used in Chinese medicine due to its various biological actions like anti-asthmatic owing to its potential to relax the smooth muscles of bronchi, decreasing blood perfusion, and the mean pulmonary arterial pressure apart from antioxidant, anticancer, immunity enhancer activities [27]. Its main active constituent dimethyl disulfide (Fig. 13.5) is reported to have activities such as antihypertensive, anti-inflammatory, melanin formation regulation, thereby making it useful against myocardial ischemia [28].

It has been reported that the volatile oil of *A. Macrostemon* and its phytoactive component dimethyl disulfide mitigates PH by initiating Ca^{2+}/protein kinase A/endothelial NO synthase signaling pathway in endothelial pulmonary arterials [29].

13.2.4 *Terminalia arjuna* Roxb

It is evergreen tree grown in India, used in traditional medicine for its useful effects in cardiovascular diseases [30]. Its active constituents are tannins, flavonoids, and terpenoids [31]. The aqueous extract (stem bark) resulted in prevention of decrease in weight of lung tissues in monocrotaline-induced pulmonary hypertensive rats. This effect was attributed to the reduction of right ventricle hypertrophy and medial wall thickness of pulmonary arteries, decreased lipid peroxidation and NADPH oxidases protein expression in lung, increased superoxide dismutase and catalase, thereby suggesting *T. arjuna* an effective remedy for PH. Other medicinal properties of *T. arjuna* include antioxidant, hypolipidemic, and antihypertensive activity [32, 33].

13.2.5 *Allium ursinum* L.

Commonly known as wild garlic extensively used in ancient system of medicine [34]. The active components of *A. ursinum* responsible for its biological activities are flavonoid glycosides and sulfur compounds. There is upregulation of phosphodiesterase 5 in case of pulmonary hypertension [35] and therefore the actions of *Allium ursinum*, because of saponins and flavonoids, that is linked with inhibition of phosphodiesterase enzyme and decrease blood pressure [36]. Other important activities of *A. ursinum* are inhibitory effect on prostaglandin endoperoxide synthase and 5-lipoxygenase enzyme, plentiful antioxidant activity, antiaggregation effect on platelets downregulation of cholesterol biosynthesis.

13.2.6 *Trifolium pratense* L.

It is a red clover and found in West Asia, Europe, and Africa. Its active chemical constituents are related to the flavonoid class [37]. Administration of isoflavones extracted from *T. pratense* to broiler chickens having PH resulted in reduction of endothelin-1 in serum as well in lung tissues and rise in nitric oxide synthase secretion [38]. In other study, it was also found to increase NO levels and NO synthase in the serum, thereby making it suitable against pulmonary hypertension [39]. Isoflavones present in *T. pratense* may also decrease the contractions of smooth muscle in bladder, uterus, and ileum [40].

13.2.7 *Crataegus rhipidophylla* Gand

Its synonym is *Crataegus oxyacantha* L. and it is inhabitant of Asia, Europe, and Africa [41]. Bioactive compounds of *C. rhipidophylla* include hyperoside, epicatechin, and chlorogenic acid and are shown in Fig. 13.6.

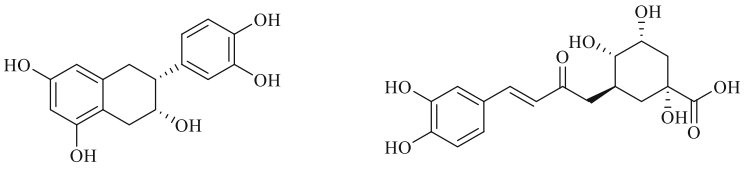


Fig. 13.6 Chemical constituents of *Crataegus rhipidophylla*

This plant has many important medicinal properties like anti-anxiety, antioxidant, anticancer, nephroprotection, neuroprotection, hepatoprotection, and cardioprotection [42, 43]. Its flavonoid extract upon administration in broiler chickens showed augmentation of nitric oxide levels on PH induced by high altitude, probably by overexpression of inducible nitric oxide synthase and superoxide dismutase 1 and by reduction of the expression of endothelin-1 in the tissues of the heart [44].

13.2.8 *Eulophia macrobulbon* Hook.f.

Its synonym is *Corduroy orchid* and traditionally used in Europe, Asia, and America. The ethanolic extract shows the presence of stilbenes and their derivatives, terpenoids, flavonoids, and phosphodiesterase 5 inhibitors, thereby making it useful as a pulmonary vasodilator [45]. Other medicinal activities, *viz.* anti-inflammatory, anticancer, antidiabetic and pulmonary disorders [46]. Ethanolic extract in monocrotaline mediated PH and inhibition of $CaCl_2$ induced contraction in pulmonary arterial rings in rats [47].

13.2.9 *Salvia miltiorrhiza* Bunge

It is also called as red sage and utilized in traditional Chinese medicine for increasing blood flow and cooling the blood in the treatment of abscess, inhibition of the platelet aggregation, protection of myocardium against ischemia, neural cells injuries against anoxia, and hepatic fibrosis [48]. Chemicals constituents responsible for its actions are due to the metabolites of caffeic acid [49, 50]. *Salvia miltiorrhiza* also proved its effectiveness for the protection of vascular endothelial cells [50]. Administration of *S. miltiorrhiza* aqueous extract in pulmonary hypertensive rats resulted in improvement of mean right ventricular systolic and pulmonary arterial pressure, increase in nitric oxide levels, and decrease in endothelin-1, thromboxane A2, and transforming growth factor 1 expression in lung tissues suggesting an effective treatment for PH [51].

13.2.10 *Kelussia odoratissima* Mozzaf

It is commonly known as wild celery and native to Iran, where it is used for the treatment of inflammation and hypertension from ancient times. It contains essential oil, which contains terpenes, phthalides, and (Z)-ligustilide (Fig. 13.7) as active principles [52], while its extract (alcoholic) poses flavonoids and polyphenols with excellent antioxidant activity [53].

Treatment with *K. odoratissima* on broiler chickens with pulmonary hypertension showed increase in wt, decrease in malondialdehyde levels in serum, increase in heterophil/lymphocyte ratio and nitric oxide level apart from overexpression of inducible NO synthase, superoxide dismutase 1, and suppression of the expression of endothelin-1 gene in the tissues of the heart, thereby improvement in the PH [54].

13.2.11 *Moringa oleifera* Lam

A drumstick tree and native of northwest India and grown in tropical and subtropical regions. The active phytoconstituents of *M. oleifera* are nitrile glycosides which have potent antioxidant and hypotensive properties [55]. Administration of *M. oleifera* in monocrotaline-induced PH in rats resulted in increased superoxide dismutase levels and decreased pulmonary pressure as well as pulmonary arterial wall thickness [56]. Also, the active compounds niazirin and thiocarbamates showed antihypertensive effect in rats, thereby making it useful for the treatment of PH [57]. Other therapeutic activities are antihypertensive, decrease in cholesterol levels, potent antioxidant, hypoglycemic and antiproliferative activities [58].

13.2.12 *Rhodiola tangutica* (Maxim.) S.H.Fu

Its synonym is *Sedum algidum* and commonly known as golden root in Tibetan and Qinghai traditional medicine. Chemical constituents responsible for the biological activity of *R. tangutica* are terpenoids, flavonoids, and phenylethanols [59]. Administration of bioactive compounds of *R. tangutica* in hypoxia induced pulmonary hypertension in rats resulted in reduced mean pulmonary arterial pressure and cyclin dependent kinase inhibitor 1B protein expression, resulting in increased expression of protein content of proliferating nuclear cell antigen, cyclin protein kinase 4, and cyclin D and in turn regulation of these factors results in inhibition of cell

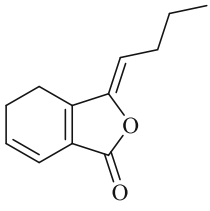


Fig. 13.7 Chemical structure of (*Z*)-ligustilide

proliferation and medial vessel wall thickness, which is responsible for pulmonary hypertension [59]. Also, vessel wall relaxant activity of *R. tangutica* was also confirmed in rat pulmonary artery, thereby indicating an efficient treatment for PH [60]. It is also used for the mitigation of ailments in high altitude for colds [61].

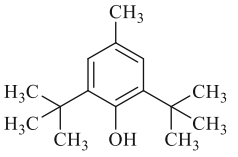
13.2.13 *Mimosa pigra* L.

It is commonly known as giant sensitive tree and traditionally used in Asian, African, and American countries for its medicinal values. Administration of *M. pigra* in hypoxia induced PH caused elevated in NO production, decrease in pulmonary artery pressure and expression of p38 mitogen-activated protein kinase and also phosphorylation of the lung tissue in rats; thereby showing improvement in the symptoms of PH [62]. Other pharmacological activities of *M. pigra* include cardioprotective, antiinfective, and for the treatment of digestive disorders [63].

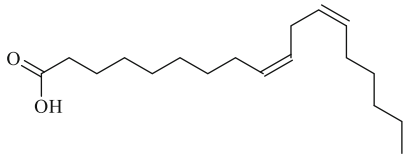
13.2.14 *Securigera securidaca* L.

It is commonly known as goat pea and found in West Asia, Africa, and Europe. Chemical constituents of *S. securidaca* present in alcoholic and aqueous extracts are related to the alkaloids, flavonoids, and saponins [64]. It is traditionally used for ameliorating diabetes, hypertension, obesity, central nervous system, and digestive disorders [65]. Broiler chickens having PH with *S. securidaca* resulted in elevated levels of nitric oxide in plasma also being a vasorelaxant improved the symptoms of PH, apart from improving hemodynamic parameters. Also, the presence of flavonoids prevents nitric oxide inactivation through scavenging superoxide ions (Fig. 13.8).

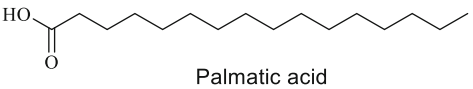
It has been reported that *S. securidaca* can also decrease oxidative stress by reduction of malondialdehyde levels due to chemical constituents such as alkaloids,



2,6-di-*tert*-butyl-4-methylphenol



9,12-octadecadienoic acid



Palmatic acid

Fig. 13.8 Chemical constituents of *S. securidaca*

4-Methyl-2,6-di-tertbutyl phenol, phytosterols, 9,12-octadecadienoic acid, and palmitic acid, thereby indicating an effective treatment for PH by virtue of antioxidant and vasorelaxant properties [66].

13.3 Conclusion

PH is a serious condition in which there is development of high blood pressure in the arteries of lungs of an individual due to hardening and narrowing of the blood vessels. The plants used for the treatment of PH exert their pharmacological actions by virtue of their antioxidant, anti-inflammatory, vasodilatation, antiproliferative activities, and inhibition of vascular remodeling. The reported plants have potential for the treatment of PH and their use overweighs against the chemical compounds owing to their negligible side effects. Many of these plants can prove a boon for making better the quality of life of the patients suffering from PH.

Conflicts of Interest The authors declare no conflict of interest.

References

1. Oliveira AC, Richards EM, Raizada MK (2020) Pulmonary hypertension: pathophysiology beyond the lung. Pharmacol Res 151:104518
2. Reyes RV, Castillo-Galán S, Hernandez I, Herrera EA, Ebensperger G, Llanos AJ (2018) Revisiting the role of TRP, Orai, and ASIC channels in the pulmonary arterial response to hypoxia. Front Physiol 9:486
3. Schermuly RT, Ghofrani HA, Wilkins MR, Grimminger F (2011) Mechanisms of disease: pulmonary arterial hypertension. Nat Rev Cardiol 8(8):443
4. Julian R, Mirsalimi S (1992) Blood oxygen concentration of fast-growing and slow-growing broiler chickens, and chickens with ascites from right ventricular failure. Avian Dis 36 (3):730–732
5. Powell FL, Hastings RH, Mazzone RW (1985) Pulmonary vascular resistance during unilateral pulmonary arterial occlusion in ducks. Am J Physiol Regul Integr Comp Physiol 249(1):R39–R43
6. Lee AJ, Chiao TB, Tsang MP (2005) Sildenafil for pulmonary hypertension. Ann Pharmacother 39(5):869–884
7. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, Arbustini E, Recusani F, Tavazzi L (2001) Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol 37(1):183–188
8. Bloodworth NC, Clark CR, West JD, Snider JC, Gaskill C, Shay S, Scott C, Bastarache J, Gladson S, Moore C, D'Amico R, Brittain EL, Tanjore H, Blackwell TS, Majka SM, Merryman WD (2018) Bone marrow-derived proangiogenic cells mediate pulmonary arteriole stiffening via serotonin 2B receptor dependent mechanism. Circ Res 123:e51–e64
9. Endo J, Sano M, Fujita J, Hayashida K, Yuasa S, Aoyama N, Takehara Y, Kato O, Makino S, Ogawa S, Fukuda K (2007) Bone marrow derived cells are involved in the pathogenesis of cardiac hypertrophy in response to pressure overload. Circulation 116(10):1176–1184
10. Han B, Copeland CA, Kawano Y, Rosenzweig EB, Austin ED, Shahmirzadi L, Tang S, Raghunathan K, Chung WK, Kenworthy AK (2016) Characterization of a caveolin-1 mutation

associated with both pulmonary arterial hypertension and congenital generalized lipodystrophy. Traffic 17(12):1297–1312
11. Asosingh K, Farha S, Lichtin A, Graham B, George D, Aldred M, Hazen SL, Loyd J, Tuder R, Erzurum SC (2012) Pulmonary vascular disease in mice xenografted with human BM progenitors from patients with pulmonary arterial hypertension. Blood 120:1218–1227
12. Guignabert C, Raffestin B, Benferhat R, Raoul W, Zadigue P, Rideau D, Hamon M, Adnot S, Eddahibi S (2005) Serotonin transporter inhibition prevents and reverses monocrotaline-induced pulmonary hypertension in rats. Circulation 111(21):2812–2819
13. Sastry BK, Narasimhan C, Reddy NK, Raju BS (2004) Clinical efficacy of sildenafil in primary pulmonary hypertension: a randomized, placebo-controlled, double-blind, crossover study. J Am Coll Cardiol 43:1149–1153
14. Goel R, Kim S, Rigatto K, Shapiro B, Ray J, Qi Y, Gazzana MB, Knorst MB, Richards EM, Pepine CJ, Raizada MK (2017) Increased gut dysbiosis and leakiness in patients with pulmonary arterial hypertension. In: Council on hypertension. Circulation, San Diego
15. McLaughlin VV, Oudiz RJ, Frost A, Tapson VF, Murali S, Channick RN et al (2006) Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. Am J Respir Crit Care Med 174(11):1257–1263
16. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Hervé P (2002) Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 40(4):780–788
17. Pepke-Zaba J, Gilbert C, Collings L, Brown MC (2008) Sildenafil improves health-related quality of life in patients with pulmonary arterial hypertension. Chest 133(1):183–189
18. Horníčková J, Kubec R, Cejpek K, Velíšek J, Ovesna J, Stavělíková H (2010) Profiles of S-alk (en)yl cysteine sulfoxides in various garlic genotypes. Czech J Food Sci 28(4):298–308
19. Reuter H, Koch H, Lawson L (1996) The science and therapeutic application of *Allium sativum* L. and related species. Williams and Wilkins, Baltimore
20. Kourounakis PN, Rekka EA (1991) Effect on active oxygen species of alliin and *Allium sativum* (garlic) powder. Res Commun Chem Pathol Pharmacol 74(2):249–252
21. Fallon MB, Abrams GA, Abdel-Razek TT, Dai J, Chen S-J, Chen Y-F et al (1998) Garlic prevents hypoxic pulmonary hypertension in rats. Am J Physiol Lung Cell Mol Physiol 275(2): L283–L287
22. Lanzotti V, Scala F, Bonanomi G (2014) Compounds from allium species with cytotoxic and antimicrobial activity. Phytochem Rev 13(4):769–791
23. Mohanty I, Arya DS, Dinda A, Talwar KK, Joshi S, Gupta SK (2004) Mechanisms of cardioprotective effect of *Withania somnifera* in experimentally induced myocardial infarction. Basic Clin Pharmacol Toxicol 94(4):184–190
24. Kaur G, Singh N, Samuel SS, Bora HK, Sharma S, Pachauri SD et al (2015) *Withania somnifera* shows a protective effect in monocrotaline-induced pulmonary hypertension. Pharm Biol 53 (1):147–157
25. Ojha SK, Arya DS (2009) *Withania somnifera* Dunal (Ashwagandha): a promising remedy for cardiovascular diseases. World J Med Sci 4(2):156–158
26. Mohanty IR, Arya DS, Gupta SK (2008) *Withania somnifera* provides cardioprotection and attenuates ischemia–reperfusion induced apoptosis. Clin Nutr 27(4):635–642
27. Tan X, Chai J, Bi S-C, Li J-J, Li W-W, Zhou J-Y (2012) Involvement of matrix metalloproteinase-2 in medial hypertrophy of pulmonary arterioles in broiler chickens with pulmonary arterial hypertension. Vet J 193(2):420–425
28. Chu C-C, Wu W-S, Shieh J-P, Chu H-L, Lee C-P, Duh P-D (2017) The anti-inflammatory and vasodilating effects of three selected dietary organic sulfur compounds from allium species. J Funct Biomater 8(1):5
29. Han C, Qi J, Gao S, Li C, Ma Y, Wang J et al (2017) Vasodilation effect of volatile oil from *Allium macro* stem on Bunge are mediated by PKA/NO pathway and its constituent dimethyl disulfide in isolated rat pulmonary arterials. Fitoterapia 120:52–57

30. Dwivedi S (2007) *Terminalia arjuna* Wight and Arn. A useful drug for cardiovascular disorders. J Ethnopharmacol 114(2):114–129
31. Varghese A, Savai J, Pandita N, Gaud R (2015) In vitro modulatory effects of *Terminalia arjuna*, arjunic acid, arjunetin and arjungenin on CYP3A4, CYP2D6 and CYP2C9 enzyme activity in human liver microsomes. Toxicol Rep 2:806–816
32. Kapoor D, Vijayvergiya R, Dhawan V (2014) *Terminalia arjuna in* coronary artery disease: ethnopharmacology, pre-clinical, clinical and safety evaluation. J Ethnopharmacol 155 (2):1029–1045
33. Pawar R, Bhutani K (2005) Effect of oleanane triterpenoids from *Terminalia arjuna* cardioprotective drug on the process of respiratory oxy burst. Phytomedicine 12(5):391–393
34. Sobolewska D, Podolak I, Makowska-Wąs J (2015) *Allium ursinum*: botanical, phytochemical and pharmacological overview. Phytochem Rev 14(1):81–97
35. Kass DA, Champion HC, Beavo JA (2007) Phosphodiesterase type 5: expanding roles in cardiovascular regulation. Circ Res 101(11):1084–1095
36. Lines T, Ono M (2006) FRS 1000, an extract of red onion peel, strongly inhibits phosphodiesterase 5A (PDE 5A). Phytomedicine 13(4):236–239
37. Boué SM, Wiese TE, Nehls S, Burow ME, Elliott S, Carter-Wientjes CH et al (2003) Evaluation of the estrogenic effects of legume extracts containing phytoestrogens. J Agric Food Chem 51 (8):2193–2199
38. Jiang Y, Yang Y (2016) Trifolium pratense isoflavones improve pulmonary vascular remodelling in broiler chickens. J Anim Physiol Anim Nutr 100(6):1159–1168
39. Simoncini T, Fornari L, Mannella P, Caruso A, Garibaldi S, Baldacci C et al (2005) Activation of nitric oxide synthesis in human endothelial cells by red clove extracts. Menopause 12 (1):69–77
40. Wang L-D, Qiu X-Q, Tian Z-F, Zhang Y-F, Li H-F (2008) Inhibitory effects of genistein and resveratrol on guinea pig gallbladder contractility in vitro. World J Gastroenterol 14(31):4955
41. Chang Q, Zuo Z, Harrison F, Chow MSS (2002) Hawthorn. J Clin Pharm Ther 42(6):605–612
42. Salehi S, Long SR, Proteau PJ, Filtz TM (2009) Hawthorn (Crataegus monogyna Jacq.) extract exhibits atropine-sensitive activity in a cultured cardiomyocyte assay. J Nat Med 63(1):1–8
43. Surai P (2014) Polyphenol compounds in the chicken/animal diet: from the past to the future. J Anim Physiol Anim Nutr 98(1):19–31
44. Ahmadipour B, Kalantar M, Hosseini SM, Ur Rehman Z, Farmanullah F, Kalantar MH et al (2019) Hawthorn (Crataegus oxyacantha) flavonoid extract as an effective medicinal plant derivative to prevent pulmonary hypertension and heart failure in broiler chickens. Kafkas Univ. Vet. Fak Derg 25(3):321–328
45. Temkitthawon P, Changwichit K, Khorana N, Viyoch J, Suwanborirux K, Ingkaninan K (2017) Phenanthrenes from Eulophia macrobulbon as novel phosphodiesterase-5 inhibitors. Nat Prod Commun 12(1):79–82
46. Narkhede AN, Kasote DM, Kuvalekar AA, Harsulkar AM, Jagtap SD (2016) Amarkand: a comprehensive review on its ethnopharmacology, nutritional aspects, and taxonomy. J Intercult Ethnopharmacol 5(2):198–204
47. Wisutthathum S, Demougeot C, Totoson P, Adthapanyawanich K, Ingkaninan K, Temkitthawon P et al (2018) Eulophia macrobulbon extract relaxes rat isolated pulmonary artery and protects against monocrotaline-induced pulmonary arterial hypertension. Phytomedicine 50:157–165
48. Lay S, Chiu JH, Shiao MS, Lui WY, Wu CW (2003) Crude extract of *Salvia miltiorrhiza* and salvianolic acid B enhance in vitro angiogenesis in murine SVR endothelial cell line. Planta Med 69(01):26–32
49. Lu Y, Foo LY (2002) Polyphenolics of salvia—a review. Phytochemistry 59(2):117–140
50. Wang BQ (2010) *Salvia miltiorrhiza*: chemical and pharmacological review of a medicinal plant. J Med Plant Res 4(25):2813–2820

51. Wang Y, Cao S-H, Cui Y-J, Kong L-K, Tian H, Cai H-X et al (2015) *Salvia miltiorrhiza* Bge. f. alba Ameliorates the progression of monocrotaline-induced pulmonary hypertension by protecting endothelial injury in rats. Tohoku J Exp Med 236(2):155–162
52. Shojaei ZA, Ebrahimi A, Salimi M (2011) Chemical composition of three ecotypes of wild celery (*Kelussia odoratissima*). J Herb Spices Med Plants 17(1):62–68
53. Pirbalouti AG, Setayesh M, Siahpoosh A, Mashayekhi H (2013) Antioxidant activity, total phenolic and flavonoids contents of three herbs used as condiments and additives in pickles products. Herb Pol 59(3):51–62
54. Ahmadipour B, Hassanpour H, Asadi E, Khajali F, Rafiei F, Khajali F (2015) *Kelussia odoratissima* Mozzaf a promising medicinal herb to prevent pulmonary hypertension in broiler chickens reared at high altitude. J Ethnopharmacol 159:49–54
55. Gupta R, Dubey D, Kannan G, Flora S (2007) Concomitant administration of *Moringa oleifera* seed powder in the remediation of arsenic-induced oxidative stress in mouse. Cell Biol 31 (1):44–56
56. Chen K-H, Chen Y-J, Yang C-H, Liu K-W, Chang J-L, Pan S-F et al (2012) Attenuation of the extract from *Moringa oleifera* on monocrotaline-induced pulmonary hypertension in rats. Chin J Physiol 55(1):22–30
57. Faizi S, Siddiqui BS, Saleem R, Aftab K, Shaheen F (1998) Hypotensive constituents from the pods of *Moringa oleifera*. Planta Med 64(03):225–228
58. Stohs SJ, Hartman MJ (2015) Review of the safety and efficacy of Moringa oleifera. Phytother Res 29(6):796–804
59. Nan X, Su S, Ma K, Ma X, Wang X, Zhaxi D et al (2018) Bioactive fraction of *Rhodiola algida* against chronic hypoxia-induced pulmonary arterial hypertension and its anti-proliferation mechanism in rats. J Ethnopharmacol 216:175–183
60. Li G, Gai X, Li Z, Chang R, Qi Y, Zhaxi D et al (2016) Preliminary study of active component and mechanism of Rhodiola algida var. tangutica on inducing rat pulmonary artery vasorelaxation. J Qin Med Coll 01:40–45
61. Li H, Sze S, Tong Y, Ng T (2009) Production of Th1-and Th2-dependentcytokines induced by the Chinese medicine herb, Rhodiola algida, on human peripheral blood monocytes. J Ethnopharmacol 123(2):257–266
62. Rakotomalala G, Agard C, Tonnerre P, Tesse A, Derbré S, Michalet S et al (2013) Extract from *Mimosa pigra* attenuates chronic experimental pulmonary hypertension. J Ethnopharmacol 148 (1):106–116
63. Rosado-Vallado M, Brito-Loeza W, Mena-Rejon G, Quintero-Marmol E, Flores-Guido J (2000) Antimicrobial activity of Fabaceae species used in Yucatan traditional medicine. Fitoterapia 71(5):570–573
64. Ahmadi A, Khalili M, Margedari SH, Nahri Niknafs B (2016) The effects of solvent polarity on hypoglycemic and hypolipidemic activities of *Securigera securidaca* (L.) seeds. Drug Res 66 (03):130–135
65. Hosseinzadeh H, Ramezani M, Danaei A (2002) Antihyperglycaemic effect and acute toxicity of *Securigera securidaca* L. seed extracts in mice. Phytother Res 16(8):745–747
66. Ahmadipour B (2018) *Securigera securidaca* seed medicinal herb supplementation of diets improves pulmonary hypertensive response in broiler chickens reared at high altitude. J Anim Physiol Anim Nutr 102(6):1601–1607

Medicinal Plants Used in the Treatment of Pulmonary Hypertension

14

Charles Oluwaseun Adetunji, Olugbemi Tope Olaniyan, Muhammad Akram, Olulope Olufemi Ajayi, Abel Inobeme, Seyi Olaniyan, Fahad Said Khan, and Juliana Bunmi Adetunji

Abstract

Pulmonary hypertension is caused by a rise in the vascular tone thus affecting the structural composition of the pulmonary arteries. There are various symptoms that are associated with pulmonary hypertension, which includes among others, lungs inflammation, apoptosis inhibition, remodeling of pulmonary vascular and hypoxia. It has been established that the application of medicinal plant could be applied for effective management of pulmonary hypertension. Therefore, this chapter intends to provide a detailed information on some medicinal plant that could be applied for effective management of pulmonary hypertension. Detailed information on isolation, purification, and extraction of the active constituents present in plants that are utilized for the treatment of pulmonary hypertension

C. O. Adetunji (✉)
Applied Microbiology, Biotechnology and Nanotechnology Laboratory, Department of Microbiology, Edo State University Uzairue, Iyamho, Edo State, Nigeria;
adetunji.charles@edouniversity.edu.ng

O. T. Olaniyan
Laboratory for Reproductive Biology and Developmental Programming, Department of Physiology, Edo State University Uzairue, Iyamho, Edo State, Nigeria

M. Akram · F. S. Khan
Department of Eastern Medicine, Government College University, Faisalabad, Pakistan

O. O. Ajayi
Department of Biochemistry, Edo State University Uzairue, Iyamho, Edo State, Nigeria

A. Inobeme
Department of Chemistry, Edo State University Uzairue, Iyamho, Edo State, Nigeria

S. Olaniyan · J. B. Adetunji
Nutrition and Toxicology Research Laboratory, Department of Biochemistry, Osun State University, Osogbo, Nigeria

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_14

were also highlighted. Specific techniques for structural elucidation of the active compound were also highlighted. Detailed information on the biochemical pathway involved in the activities of phytochemical in medical plant in the treatment of pulmonary hypertension as well as detailed facts on the modes of action involved in the application of medicinal treatment of pulmonary hypertension were also highlighted.

Keywords

Pulmonary hypertension · Medicinal plants · Structural elucidation · Active compound · Phytochemicals · Lungs inflammation · Apoptosis inhibition

14.1 Introduction

Pulmonary arterial hypertension (PAH) has been identified as a serious ailment that is marked with gradual alteration of the pulmonary arteries and incessant increased pulmonary vascular resistance that could ultimately result in death [1]. In terms of hemodynamics, it is described as mean pulmonary arterial pressure ≥20 mmHg, pulmonary wedge pressure ≥mmHg, and pulmonary vascular resistance of ≥3 wood units [2]. It has a high mortality rate, prevalence of between 11 and 26 cases/million adults as well as a higher incidence in women than men [3].

There are about five categories of PAH based on its etiology; hypertension in the pulmonary arteries resulting in pulmonary arterial hypertension, left-sided heart failure resulting in pulmonary hypertension (PH), hypoxic pulmonary vasoconstriction resulting in PH, elevated pressure in the blood vessels of the lungs that results in chronic embolic pulmonary hypertension and idiopathic PH [4, 5].

Dysfunction of the pulmonary endothelium results in inflammation of the lungs and persistent hypoxia. Oxidative stress is a major contributory factor to vascular remodeling in PAH [6]. Furthermore, pulmonary vascular remodeling that is peculiar to PAH is typified by a buildup of vascular cells in the wall of the pulmonary artery [3]. There are evidences that the aberrant endothelial cell proliferation is genetic. However, hypoxia, oxidative stress allergy to drugs may also be important in the abnormal proliferation of the endothelial cells [4, 5]. There are also indications that individuals with idiopathic PAH have defective genes such as BAX and TGF-b [7]. Mediators of inflammation are involved in the development of PH [8]. Increased levels of IL-1 and IL-6 have been reported in individuals with idiopathic PAH, with elevated expression of CCL5 and fractalkine in severe cases of PH [9].

It is becoming evident that medicinal plants are better alternative to the current therapies in the management of PAH. Serious side effects and high cost are some of the pitfalls in the use of orthodox therapies in the management of PAH. Phosphodiesterase-5 inhibitors (e.g. sildenafil), prostacyclin analogs (e.g. epoprostenol), and antagonists of endothelin receptor (e.g. bosentan) are

some of the currently used drugs [4, 5]. There are evidences that these drugs may not improve patient's quality of life beyond 5 years [10].

Since oxidative stress has been implicated in the progression of PAH, it is believed that food rich in antioxidants may be important in reducing the oxidative damage associated with PAH [11]. Phytochemicals including terpenoids, phytoestrogens, saponins, tetracyclic oxindole alkaloid, isoflavonoids, flavonoids, isoquinoline, monoterpenoid phenolics, etc. have been reported to be efficacious in the management of PAH [4, 5]. Some medicinal plants show potency in the management of pulmonary hypertension such as *Allium sativum*, *Allium macrostemon*, *Allium ursinum* L, *Eulophia macrobulbon*, *Crataegus rhipidophylla Gand*, *Moringa oleifera* Lam, *Rhodiola tangutica*, respectively [4, 5].

14.2 Arterial Pulmonary Hypertension and Medicinal Plants

It has been discovered that inflammation, in situ thrombosis, vasoconstriction, and fibrosis are all associated with the disruption of the physiologic balance. These occurrences result to the contraction of the blood passages bringing about the manifestation of pulmonary hypertension. The pathogenic processes of pulmonary arterial hypertension is comparable to that of chronic pulmonary arterial hypertension as this is also known to include injuries to the endothelial layers and constriction of the blood vessels [6].

Pulmonary hypertension is caused by a rise in the vascular tone thus affecting the structural composition of the pulmonary arteries. Pulmonary hypertension is more common among females that are above the age of 53 [2]. Researchers have documented that in the global population, almost 100 million persons suffer from PH, while for a patient that is not treated, and there is possibility of surviving up to 2.8 years. There are various symptoms that are associated with PH, which includes among others, lungs inflammation, apoptosis inhibition, remodeling of pulmonary vascular and hypoxia. It has been stated that about 100 million people from one place to another in the world are experiencing pulmonary hypertension [12].

The occurrence of pulmonary hypertension is of significant health concern in patients, since this brings about a significant decrease in the volume of oxygen present in the lung, there is a rise in the quantity of blood that is pumped from the heart [13]; the process also bring about the increase in the pressure at the right ventricle which could cause the failure of this chamber of the heart.

There are some major signs that indicate the occurrence of pulmonary hypertension such as dyspnea and serious tiredness during daily endeavors which may generally affect the efficiency in the discharge of daily physical activities. The symptoms of this condition are closely related to those of other diseases of the heart. This therefore makes it not readily possible to detect disease due to pulmonary hypertension hence it gradually results to complications and death [14]. Electrocardiogram plays a dynamic function in the diagnoses of the defects due to HP in the right ventricular region [15].

Pulmonary arterial hypertension (PAH) is a disease that is commonly identified with signs such as a rise in the vascular resistance, thus affecting significantly the functioning of the heart and eventually collapse. The conditions due to this disease have the potential of threatening life. More recently, medicinal plants have been reported to be useful in the treatment of this disease. Findings from various researches documented have shown the therapeutic efficiency of medicinal herbs in the treatment and management of various diseases including the pulmonary arterial hypertension [6].

The essence of using medicinal herbs generally is targeted towards the reduction of acute pulmonary vasoconstriction, decline in the occurrence of vascular remodeling and inducing a reversal of initial vascular remodeling when possible. Basically, most diseases that occur as arterial pulmonary hypertension can result to the failure of the right ventricular heart. This also depends on whether this occurred acutely or chronically with their corresponding associated signs [12].

14.3 Isolation, Extraction of the Active Constituents Present in Plants that Are Utilized for the Treatment of Pulmonary Hypertension

Extracts from plants used for chemotherapy are commonly available either as fluid's extracts or also in their powdery forms obtained after drying. It is also possible to process them into the forms of capsules and tablets and in some other cases they may be fractionated to obtain different active components which could then be used as drugs. There are therefore various techniques of extraction that could be employed in the course of isolating active agents from different medicinal plants use in drugs processing [16].

Right from time immemorial, plants have been engaged in the management of numerous kinds of diseases in humans and animals. This involves the use of various parts of the plants ranging from stem, leaf, bark, flowers, and pods to bark. Basically, the use of herbs in the management of diseases and ailments in human is commonly described as alternative medicines, because unlike the conventional orthodox approach, it does not adhere strictly to the scientific approach to problem solving. It is worth knowing that most of the drugs that are available in pharmaceutical outlets have history that could be traced back to plants based origin, since most of them are obtained as active compounds in plants [17].

Various orthodox drugs have been made available for the management of various PAH. Some of these drugs include the readily inhaled types such as nitric oxide, soluble guanylate that have been formulated more recently as well as various receptor antagonists [18]. Most drugs are used for the management of PAH function through the reduction of the arterial resistance thus bringing about vasodilatation. This implies that mechanisms are not fully in place for the reversal of vascular remodeling which is of immense concern [19]. All medicinal preparations were generally obtained from plants according to history. With recent technology, most of

these plants materials have been processed into drugs that can be used for the treatment of various vascular diseases.

14.4 Extraction and Characterization of Active Constitutes Available in Medicinal Plants

The process of extraction is an indispensable step during the production and characterization of medicinal agents from plants for the management of various diseases. The active substances present in the plants have to be removed through the process of extraction and then purified for proper characterization [20].

Prior to the process of extraction, some of the preliminary processes involve the washing and drying of the plant materials, homogenizing through the process of drying. During the course of purification and processing, it must be ensured that the active ingredients which are usually small are not lost or their chemical nature altered [21]. The choice of the solvent to be employed for the extraction process is influenced greatly by the nature of the active ingredients in focus. Thus there are varying solvents and combinations of solvents in different proportion that can be used during the process of extraction. Generally, polar solvents such as ethyl acetate, alkanols (ethanol and methanol) can be used for compounds that are hydrophilic in nature while non-polar solvents such as dichloromethane are employed for hydrophobic compounds. Chlorophyll can be extracted using hexane as solvent [22].

Various methods of extraction are available, some involve the conventional principles while other are relatively modern. In the traditional methods, water or organic solvents is used as extractant and done under the normal pressure. In modern methods, extraction is achieved under pressure different from atmospheric pressure as well as increased temperature [23]. Among the available approaches in extraction, the most widely employed is solvent extraction. Basically the extraction process goes through the following mechanism: penetrations of the solvent into the solid material, dissolution of the solid material in the extractants, and collection of the solute extracted [24].

Percolation is a process involved during the extraction of plant active components especially for the formulation of tinctures. This involves the use of tube plug where the plant material is put and then covered with a cotton and cock. The suitable solvent is then gradually added inside a closed vessel or container and then cocked. After about four hours at room temperature, the extract is collected and the extractant carefully decanted [25].

Another technique is the application of heat gently at a temperature range of 40 °C to 60 °C. This is known as digestion which is a unique type of maceration. This is good if the active compounds are thermally stable. This technique can further be enhanced through the use of magnetic stirrer. Filtration of the extract is then done after a while, and the process repeated using fresh volume of the extractant until the entire product targeted have been removed from the solid matrix.

Infusion method is another method for extraction of compounds. Here, cold or warm water is used for the maceration of the ground plant material. This process usually lasts for a very short period of time until the active compounds have been transferred into the solvent [26].

In decoction method, the solid plant material is usually soaked in water for a period of time until most of the active materials present have been absorbed into the water. The process is made possible through boiling, after which the mixture is cooled and filtered. The volume of water present in the extract is reduced during the process of boiling. The residual mixture is then filtered. Refluxing can also be used for the process of extraction. This involves a mechanism for the recycling of the solvent around the system through a condenser. This approach is not however suitable for compounds that are readily decomposed on heating.

Tincture is prepared using alcohol as solvent for the extraction process. It is usually carried using a small quantity of the solid material placed in a container. Due to the presence of alcohol it is possible to keep the mixture down for a long period of time. Pressurized liquid extraction is another method that involves acceleration of the process of solvent extraction. Higher temperature and pressure are introduced to achieve this process [23].

There are also non-chromatographic technique which involves the use of monoclonal antibodies as well as phytochemical screening and other related immunoassays. The biological potential and structural elucidation are carried out using the pure compound [4, 5]. There are different methods of separation of natural products which include among others:

Thin layer chromatography: this is a planar chromatographic technique which is very useful in the area of natural products. It is one of the quickest and easiest techniques relevant in the isolation of natural compounds. This is also a useful prerequisite technique for the selection of parameters for the setting of column chromatography. The stationary phase is commonly made of silica while organic solvents are used as mobile phase. Other materials for the stationary phase include alumina [27].

In reverse phase TLC, silica and in some case alumina are used as the adsorbent while a solvent of interest such as water or alcohol which are polar compounds are used as the mobile phase. The most effective method for the separation of components of plants extract is the column chromatography. It involves packing of a material into the column which acts as the adsorbent on which the separation occurs. Silica gel is the most commonly used packing material. The mobile phase or eluent is then applied at the top of the column to induce the process of separation. The basis of the separation is that the mobile phase which is the solvent carries the various components of the extracts to be separated to varying extent hence they are separated [24].

Gas chromatography is another useful analytical procedure for the separation of compounds present in plants extracts. This is mostly applicable to volatile compounds or compounds that can be volatilized. The uniqueness of the instrumental method is that it is capable of providing both quantitative and qualitative feedback on the compounds present in the extracts. The mobile phase is gaseous while the

stationary is liquid. The volatile samples are introduced into the column from where they are carried across by the action of the mobile phase. The column has a stationary phase that is a liquid and adsorbed on the surface of the solid which is inert in nature [28].

High performance liquid chromatography (HPLC) is considered as a robust and versatile technique that is largely employed in the area of natural products analysis. It is useful for the isolation of these compounds. It can be used on any sample whether inorganic or organic in various areas. It has also found useful in quality control for medicinal plants and for finger printing study. Proper choice of mobile and stationary phase is vital in the analysis of a substance using HPLC since this determines the extent of separation and resolution quality. None polar phases that are non-polar is more recently used as solid phases. There is also a requirement of a high pressure, usually up to 400 bars for the efficient elution of the various substances of interest through the column, which then go through the detector where they are detected. Unlike gas chromatography, the use of HPLC is recommended more for compounds which are not readily vaporized or that are thermolabile (decompose at a high temperature) [29].

There is another technique called high performance thin layer chromatography. This is planar in nature where the components of the mixtures are separated using high pressure layer with a data acquisition unit. The layers are coated using an adsorbent material. The efficiency of the plate layer is achieved by reducing the thickness of the layer. The use of the thin layer plates also bring about higher precision and separation.

14.5 High Performance Liquid Chromatography

Presently, there are portable HPLC devices which are made up of a delivery pump for solvent, an introduction component for samples, column, detector, and printer [27].

High performance liquid chromatography (HPLC) can be used for the separation of the various chemical substances present in the extract. This is based on the differences in the rate of migration of different active compounds associated with varying mobile phase and column. Isocratic pattern is vital in the separation and identification of various active ingredients present in the plant extracts. During gradient elution, the ratios of water to the organic solvent are varied if the number of components of interest is more than one and their extent of retention vary. For HPLC analysis, the peak for each of the compound is specific and unique to it for given chromatography conditions. The choice for the most suitable mobile phase depending on the components of interest is vital. The HPLC could be applied for the separation of the pure compound from several impurities. Similarly, the detectors, flow rate, and column have to be carefully chosen too. The functional groups in the compounds available in plant extracts are detected through the use of FTIR. This instrumental approach has proven to be highly valuable in the identification and characterization processes for organic compounds in plants [30].

Like molecular finger printings, the spectra for pure organic compounds obtained from FTIR are significantly specific of that compound. Thus it is possible to identify the spectra of an unknown plant compound found in the extract through a detail comparison with the standards known from existing literature.

There are different methods for the preparation of samples used in FTIR analysis. Basically drops of the samples are placed in between the sodium chloride plate, which then exist as a thin film in between the plates. For solid substances, prior to the analysis, they are grinded with potassium bromide and then they are converted into thin pellet by compression. Dissolution method can also be used in the preparation of solid samples.

Different diseases have been managed with various traditional medicines using numerous medicinal plants which includes Garlic (*Allium sativum*). The active ingredients responsible for the therapeutic potential of garlic are a compound containing sulfur such as sulfoxides as well as cysteine. Also the formation of thiosulfinates from alliin is also a major factor for this activity [31]. Studies have also documented the potencies of garlic in boosting immune system, protection against infectious diseases, and reduction of oxidative stress from free radicals, anti-inflammatory ability, anti-cancer agent as well protection of the heart. A study by Fallon et al. [32] reported that extract of garlic powder using aqueous medium was capable of preventing the occurrence of pulmonary hypertension in rats by relaxing the muscles and vessels in the region.

Tan et al. [33] reported the utilized *Allium maacrostemon* which belongs to Amaryllidaceae as a medicinal plant with unique chemotherapeutic values. This plant was reported to be useful for antioxidant properties. It has the ability to reduce asthmatic diseases due to its potency in the relaxation of the smooth muscles of the bronchus. Treatment of ischemia of myocardial is achieved through the use of the plant *A. macrostemon* which has the active compound dimethyl disulfide (DMDS). The plants are known to be useful due to antihypertensive and anti-inflammatory potential [34].

14.6 Relevant Medicinal Plants for the Treatment of Pulmonary Hypertension

Behnam et al. [35] carried out an investigation to assess the function of *Crataegus* flavonoids on pulmonary hypertensive syndrome prevention and control in chicken at high altitude environment. From their study, it was revealed that the flavonoid extract at different concentrations caused a significant decrease in right ventricular hypertrophy, low mortality, thus the medicinal plant prevented respiratory dysfunction in broiler chickens through there was a decrease in pulmonary blood pressure plus stimulation of the antioxidant defense capacity. Himanshu et al. [36] revealed that traditional medicines are very effective in the management of many chronic pulmonary diseases, thus the authors evaluated the role of stem bark of *Terminalia arjuna* for antihypertensive, anti-ischemic, antioxidant and anti-hypertrophic effects. They discovered that pulmonary hypertension is a serious disease caused by right

heart failure or right ventricular hypertrophy. The authors thus evaluated stem bark of *Terminalia arjuna* as an alternative replacement for the standard drug in the treatment against pulmonary hypertension induced by monocrotaline (MCT) in rodents. Different doses of the extract were administered into the rodents for a period of 25 days and subsequently the results were analyzed with various molecular biology techniques. Form their findings, it was confirmed that *Terminalia arjuna* aqueous extract prevented pulmonary hypertension due to the high level of antioxidant present in the extract.

Masoumeh et al. [37] reported that statistically, about seven million individuals suffer from various form of hypertension yearly across the globe with the prevalent rate in the developing or industrialized area. It is generally known the hypertension is the third cause of mortality across the globe, and the present line of treatment shows gross ineffectiveness due to many side effects, thus herbal medicines have recently gained attention from different quarters. The authors identified various forms of natural constituents proven to be very effective for the treatment or management of hypertension. Jiang and Yang [38] reported that pulmonary arterial remodeling is a serious features of pulmonary arterial hypertension, thus the authors investigated the role of dietary isoflavones available in *Trifolium pratense* in suppressing pulmonary arterial remodeling. Sub-thermo-neutral environmental temperatures were utilized to increase the pulmonary hypertension syndrome, endothelial nitric oxide, or endothelin nitric oxide synthase, in broilers. From the findings, it was discovered that there was significant reduction in pulmonary hypertension syndrome, downregulation of endothelin due to the high presence of isoflavone. Thus, it was recommended that isoflavones present in *Trifolium pratense* isoflavones could serve as alternative drug candidate for the treatment of pulmonary hypertension.

Landazuri et al. [39] reported that hypertension is as a result of pressure difference in the vascular bed which has affected many individuals across the globe. The rate of consumption of herbal regimens for the treatment of this serious ailment among affected individual is alarming, thus there is serious need to quickly evaluate the potency of some of these natural herbs for their antihypertensive properties. The advantages of traditional medicines over the standard drugs are low cost benefits, lowered side effects, and wider acceptance by the people.

Gan [40] reported that poor diagnosis is the major reason why acute pulmonary arterial hypertension wreck serious havoc on the affected individual causing different complications like right ventricular hypertrophy, pulmonary blood pressure, plus thickening of the vascular intima, adventitia, media compounded by ineffective drugs with several adverse effects like apoptosis. Despite several research progress made in biomedical sciences for the development of potent drug for the treatment of pulmonary hypertension, many of the candidate drugs are still very less effective thus many scientists search for alternative molecule with strong effect against many respiratory diseases. Some of the known bioactive molecules are flavonoids, monoterpenoid phenolics DMDS, isoflavonoids, polymethoxylated flavones, phytoesterogens, *C. rhipidophylla*, *S. miltiorrhiza*, *K. odoratissima*, *T. pratense*, baicalin, asiaticoside, punicalagin, ginsenoside Rb1, terpenoids, quercetin, isoquinoline alkaloids, polysaccharides, saponins, A macrostemon, polydatin,

E. macrobulbum, *A. sativum*, *K. odoratissima*, *S. miltiorrhiza*, *M. pigra*, *S. securidaca*, *W. somnifera*, *T. pratense*, Apple polyphenols, baicalin, isorhynchophylline, carvacrol, salidroside, punicalagin, resveratrol, tetracyclic oxindole alkaloid**.** These compounds are found in many herbs and natural plants and are capable of acting on different pathways and receptors to elicit their biological actions like suppression of oxidative stress, repair of tissue damage, decrease in cytosolic Ca^{2+} and TXA2 level, suppression of ET-1 expression, improvement of the antioxidant defense system, suppression of TGF-b1, HIF-1a, AhR or ERK1/2/ STAT3, PI3K/ACT pathways

There studies have also identified different potent molecules like astragalus polysacharides, Berberine, oxymatrine, genistein W. somnifera, baicalin, isorhynchophylline, ginsenoside Rb1, nobiletin, carvacrol, magnesium lithospermate B, punicalagin, polydatin for the management of pulmonary diseases through the reduction in inflammation responses like interleukins, NFkB, pho-IkBa, VEGF, TNF-a, decrease in iNOS expression, caspase-3, plus increase of eNOS expression, enhanced phosphorylation or activation of threonine/ serine protein kinase/eNOS pathway, inhibition of phosphorylated Smad2/3, decrease in mPAP, reduction in collagen I as anti-fibrotic activity, reduction in ERK1/2/Akt/GSK3b/b catenin signaling pathway, reduction in protein phosphatase 2A phosphorylation, decrease in malondialdehyde with enhancement of antioxidant defense system, increase in expression of estrogen receptor-b protein, decrease in apoptosis, oxidative stress, anti-inflammatory or anti-cancer, suppression of Cyclin D1 or CDK6 expression, inhibition of STAT3 plus ERK1/2 signaling, NADPH oxidase, NOX2, and NOX4. Different investigation has established the role of HIF-1a in pulmonary hypertension progression, and increase in nitric oxide and reactive oxygen species could led to activation of HIF-1a, thus antioxidants are capable of suppressing the activation of this pathway and boost the antioxidant pathways like Nrf-2 and Trx-1 expression and subsequently reduce the progression of the disease.

Again, studies have shown that trimethoxystilbene which is a powerful antioxidant possess little side effects compared to other antioxidant molecules. Other bioactive molecules with anti-allergic, anti-proliferative, spasmolytic activity obtained from traditional medicine are apiin, luteolin, and rhoifolin. These molecules tend to reduce capillary pulmonary and aortic pressure. Salidroside from medicinal plant called *Rhodiola rosea* L. is known with strong anti-cancer, antioxidant, immune system enhancer and anti-inflammatory activity. The molecule has the capacity to increase Caspase-3, A2aR, BAX, protein expression thus it is considered to be beneficial to the reduction of pulmonary hypertension progression by modulating apoptosis signaling pathway.

Jasemi et al. [4, 5] discovered that pulmonary arterial remodeling, right ventricular failure, and right ventricle hypertrophy are common feature of pulmonary hypertension, thus the authors evaluated possible medicinal plants and other active constituents that may be of tremendous advantage towards the management of

pulmonary hypertension. They concluded that phytochemicals are the alternative remedy to current synthetic drugs utilized in the management of pulmonary hypertension which has shown to be very grossly inefficient due to numerous side effects.

Ritu et al. [41] reported that the root of Sarpagandha plant has been engaged over the years for the treatment of many ailments such as epilepsy, insanity, insomnia, eclampsia, hysteria, plus hypertension. The authors revealed that, in some few years ago, the root became very popular for the therapeutic property against pulmonary hypertension due to the occurrence of high level of alkaloids and serpine.

Lili et al. [42] revealed that pulmonary hypertension has resulted into many deaths due to progressive arterial remodeling, consistent increase in vascular resistance and right ventricular disorder. Though treatment protocols involve the reduction in the underlining factors, poor results have been achieved so far by many synthetic drugs in the market due to too many side effects. Thus clinical trials for many natural biomolecules are regarded as a useful alternative due to low level of side effects, cheap cost, availability, and potent action against pulmonary hypertension. The authors demonstrated that growing attention has been witnessed over the years for many biomolecules by scientists such as tetrandrine, salidroside, puerarin, polydatin, pyrrolizidine, alkaloids, ligustrazine, ginkgolide B, rhodiola, ergotamine, icariin, pyranocoumarin, cuspidatum, praeruptorin, triptolide, tyrosol, ginseng, liquorice, polygonum, tanshinone IIA, and astragalus. The proposed mechanism of action has been suggested to be through reduction or blockage of endothelin-1, platelet aggregation, prevent thrombosis, reduce Ca2þ channel through dilatation of blood vessels, upregulate hypoxia-inducible factor 1 and increase nitric oxide, downregulate protein kinase B-dependent nuclear factor kB activation signaling and c-Jun N-terminal kinase.

Studies have revealed that biomolecules could modulate cardiovascular function through maintaining the hemodynamics vascular functions, decrease in ventricular preload, sustaining the right ventricular maximum dP/dt, decrease serum angiotensin II, endothelin, thromboxane A2, prostacyclin, prostaglandin F2a, NO/cyclic guanosine monophosphate signaling, downregulate voltage-gated Kþ(Kv)1.5 or Kv2.1, maintain membrane potential.

Meresa et al. [43] reported that one of the major health crises of global concern is pulmonary hypertension particularly in the developing countries where access to good health care facility is poor coupled with high cost of living. Despite the increased efforts by scientists to develop more efficient conventional drug for the management of this condition, many adverse effects are still recorded from the use of these drugs. Thus the authors suggested an alternative with lesser side effects, cost effective, and with potent therapeutic advantage over the conventional ones. Herbal medicines seem to be gaining more popularity among scientific community due to their wide range of biological activity. The authors evaluated many medicinal plants utilized for the treatment of pulmonary hypertension in Ethiopia like *Moringa stenopetala*, *Thymus schimperi*, *Calpurnia aurea*, *Thymus serrulatus*, *Syzygium guineense* so as to create a data and further investigate their biological activity.

Lakshmi et al. [44] revealed that cardiovascular disease particularly pulmonary hypertension is major health crisis that silently kill people across the globe, thus

many scientists have resulted to plant based medicine as alternative to the present synthetic drug due to low efficacy. The authors pointed out that herbal medicines like *Elaeocarpus ganitrus*, *Ginkgo biloba*, *Crataegus monogyna*, *Achillea millefolium*, *Hypericum perforatum*, *Allium sativum*, and many others possess valuable biomolecules with potent biological activity that can provide safety adjuvant against pulmonary hypertension.

Qilian et al. [45] reported that Traditional Tibetan medicine has been effective in ameliorating hypoxia-induced pulmonary hypertension related with high altitude. Thus more research finding on rodents have supported this claim by showing that Tsantan Sumtang modulate nitric oxide-cyclic guanosine monophosphate, K^+ channels, and prostaglandin I2-cyclic adenosine monophosphate pathways with relaxant effects. The authors suggested that Tsantan Sumtang alleviated pulmonary vascular remodeling.

Zhouye and Zhaoqing [46] investigated xiebai capsule compound on pulmonary vascular remodeling in rodents using monocrotaline-mediated pulmonary arterial hypertension. They discovered that the compound significantly reduces most of the complications associated with pulmonary hypertension. Tingting et al. [47] showed that pulmonary hypertension affecting a lot of individuals seem to be on the increase, thus urgent attention is needed to tackle this health condition. The authors suggested that Chinese medical plants like *Rhodiola rosea* Linn. can be explored and analyzed for possible potential ingredient to manage pulmonary hypertension. More research work should be focused on ways to integrate and develop drug candidate and interpreting the modes of action of many of these medicinal plants.

Manish et al. [48] and Thomas et al. [49] stated that many individuals today suffer from pulmonary hypertension with huge amount of money going into the treatment with little effectiveness. They showed that pulmonary hypertension is characterized mainly by enhancing the pulmonary vascular resistance. Therefore, alternative medicines may offer possible solution due to low cost, availability, and efficacy of many of the biomolecules found in these medicinal plants. The authors reviewed some of these plants such as Punarnava, Olive leaf, Rauwolfia, Black cumin seeds, Barberry, Garlic, European mistletoe, Ginseng, Arjuna plus Ginger have all proven to be very effective compared with synthetic drugs against the management of pulmonary hypertension. The authors listed few active constituents found in these medicinal plants such as tannins, saponins, triterpenoid, catechins, flavonoids, proanthocyanidins, sesquiterpene lactone components, ellagic acid, gallic acid, allicin, S-allyl L-cysteine, ajoene, ginsenoside Rb1, ajmaline, serpentinine, rescinnamine, sarpagine, chandrine, deserpidine, amines, oligomeric proanthocyanidins, phenylproamine alkaloids, d-pseudoephedrine, ephedrine, angelicide, ligusticide, hentriacontane, b- ecdysone, triacontanol, alanine, arachidic acid, aspartic acid, behenic acid, boerhavic acid, oxalic acid, hirsutine, punarnavine I&II, rhynchophylline, mitraphylline, beta sitosterol, stigmasterol, campesterol, wedelolactone plus dimethyl wedelolactone, trithienyl aldehyde, ecliptine, kaempferol 3-O-glucoronide, rutin, kaempferol 3-O-rutinosideo, diterpene coleonol, calcium, phytosterols, magnesium, copper plus zinc with the aim of elucidating their biological activity like endothelium-dependent nitric oxide-mediated relaxation,

antispasmodic, reducing triglycerides, blood pressure, plasma viscosity, platelet aggregation, plus fibrinogen, vasodilatory activity and enhance fibrinolysis.

Rakotomalala et al. [50] conducted research on devices related to the vascular effect of MPG by in vitro injection and its steroids and sedative agents, affecting vascular nerves, and in vivo, its activity in blood pressure hypoxia (PAH) in mice. The cellular resistance of MPG particles to hydromethanol is described using the analysis of the 1,1-diphenyl-2-picrylhydrazyl compound in in vitro oxygen uptake. The stabilizers are investigated in TNFα-activated VCAM-1 and endothelial cells. The vasodilating effect of MPG extricate is concentrated in the vasodilators preceding phenylephrine (1 μM) with or without endothelium. MPG particles were split in vivo into polycyclic aromatic hydrocarbons obtained from male Wistar mice, orally with or without MPG (400 mg/kg/day), in low pressure chambers for day 21. The different MPG tablets contain anti-cancer properties and mitigating properties. It moved the adrenal glands, which did nothing to direct the aorta and lung. In vivo, the unstable MPG regimen reduced polycyclic aromatic hydrocarbons in mice by reducing blood pressure by 22.3%, arterial pressure, and heart rate by 20.0% and 23.9%, respectively. This effect is associated with rebuilding of endothelial function and a 2.3 increase in NO synthase. MPG hydromethanolic stearate contains tryptophan and flavonoids, including quercetin glycosides. Likewise, the two compounds effectively block PAHs for hypoxia.

Bai et al. [51] carefully studied the effect of continuous stimulation of the regenerative spirit of Rhodiola and VEGF stimulation on the upper extremities of stimulated PH. The authors showed that the increase in mean myocardial infarction (mPAP) and normal ventricular hypertrophy (RVH) with hypertension decreased in patients receiving Rhodiola. In addition, they examined the airway sample by microscopy and found that this was the most accurate detection of the rat remodeling performed on Rhodiola, as well as the fake tests and treatment sessions. In addition, the authors showed that the increase in VEGF expression due to higher resolution was less when using the herb [51]. It has been thought that Rhodiola pepper can cause an elevation of pH and regeneration of blood vessels, and VEGF inhibition may indicate one of these factors. It has been established that Rhodiola inhibits aortic recurrence which might be linked to atherosclerotic development in rabbits and the influence connected with the combination of VEGF and atherosclerotic tissue. Rhodiola also possesses the ability to inhibit TGF expression and increase the level of stimulated pH in mice.

Huang et al. [52] evaluated the effect of salidroside, a major factor of Rhodiola, on the pH induction in mice. The creators demonstrated an increase in mPAP and RVH, redesign of pneumonia and regular hypoxic regeneration with salidroside treatment, indicating the restorative power of this promise for pH. It is important to note that this concentration may inhibit flat cell proliferation with a flat aspiration passage containing cells under hypoxia, indicating that a decrease in lung acid turnover may be due to inhibitory agents of salidroside.

Zhang et al. [53] confirmed the safety of Rhodiola for patients with severe ALI/dementia. In addition, Rhodiola root extract has been shown to trigger a variety of stimulant effects, such as carrageenan-induced foot swelling, formaldehyde induced joint depletion, and nystatin-induced edema. Since anger is known to play an imperative function in causing PH disease, Rhodiola focuses on the potential benefits of PH by boosting inflammation.

Wang et al. [54] reported that despite the sensation of burning, oxidative stress varies as a critical component in patients with PH, and that there is an experimental effect from experimental studies related to oxidative stress and the pathogenesis of pH. Moreover, herbacetin and kaempferol glycosides are compounds derived from Rhodiola that have cell proliferation and decreased identity. Additionally, Rhodiola extract contains a mixture of other cell compounds, such as natural acids (gallic acids and caffeine), and flavonoids (proanthocyanidins and catechins), p-tyrosol. Undoubtedly, there is evidence that treating hypertensive (SHR) mice with Rhodiola augmented superoxide dismutase action.

Sui et al. [55] established that Rhodiola could inhibit the evolution of the endothelial cell line EVC-304. Studies like these supporting Rhodiola may show an anti-inflammatory effect on neurons, despite promising pregnancy behavior. In addition, Rhodiola ruled out the blocking activity of ACE inhibitors, 41 or so, it is rational to assume that ACE inhibitor inhibition would reduce the rigid vasoconstrictor Ang II production, indicating a plant-specific vasodilation occurrence. Undoubtedly, this means that the ACE barrier has a beneficial effect by adjusting Ang II, which is the inverse of type I in the case of PH.21. The ACE barrier reduces spirit formation of pneumonia manufacturers, Jeffrey and Vanstol explain, however, the creators in their own way realized an impressive effect.

Wang et al. [54] evaluated the levels of Rhodiola on SHR and announced that its positive benefits may be related to NO exercises and cell strengthening. In addition, there is no information on the effect of Rhodiola on ACE inhibitors, as it was later found that the ACP homozygous plays an important role in the cardiovascular system. Hence, there is a need for future studies needs to consider the effect of Rhodiola on the initial flush, especially long-term use.

Yao and Chen [56] GBE has been reported to have positive effects in ameliorating acute lung damage (ALI) by reducing c-Jun regulation of N-terminal kinase and dependent atomic factor B inhibitors of the 38 kB protein. Moreover, they inhibit platelets. It causes platelet clumps to proliferate, and in these areas blood flow can improve. It has been established that ginkgo can decrease potentially harmful pH and reduce RVH, half of which is found in low protein kinase C (PAC) energy [57]. Moreover, Ginkgo Plus was found to significantly reduce the increase in mPAP and PVR induced by hypoxia, as a right ventricular mass component compared to the left ventricle to include septal loads.

GBE facilitates endothelial cell apoptosis (EC) induced by hydrogen peroxide. Moreover, it was also discovered that they possess the potential to balance fire cells and have a powerful effect, which reduces the occurrence of inflammation [58].

Li et al. [59], stated that puerarin can enhance aspiration type development in mice with PH by preventing the presence of collagen. It was also established that

puerarin had an effect on MCT in mice. Additionally, puerarin can stimulate activate caspase-9, cytochrome C, reduce regulation of leukemia / lymphoma 2 (Bcl-2) and increase expression of the protein x (Bax) associated with Bcl-2. It can target oxygen-deficient rebels and reduce the growth of smooth muscle cells (SMCs). Moreover, it has been shown that puerarin promotes apoptosis of venous smooth muscle (PASMC) by the mitochondrial method. Rhodiola can completely prevent VSMC expansion and contraction and reduce ET-1 secretion in pH mice. In addition, Rhodiola is recommended to suppress ET-1 expression and to enhance NO synthesis and infiltration, particularly the effect on the nervous system. Additionally, Rhodiola can relieve unilateral systolic and diastolic vascular pressure. This results in reduced mPAP and RVH improvements and pH improvement, which may be due to skewed VEGF expression in arterial separation. Moreover, Rhodiola has a pronounced effect on highly stimulated RN mice, and blocking changes in beta-1 expression is a potential component.

Polygonum cuspidatum is used in the medical treatment of persistent bronchitis, serious injuries, and warm fluids. Polydatin (PD) is a monocrystal-line compound that has resveratrol extracted *Polygonum cuspidatum*. The polydatin could be used in treating hypertension on myocardium and platelet aggregation, which are antioxidant and anti-shock. In general, PD is believed to reduce PAP to toxic toxins and can increase cardiovascular production and improve fibrin function [60].

It has been established that PD can reduce hypoxic PH and differential reinforcement, providing a protective component for treating oxidative stress damage through PKC transcription. On the other hand, PD reduces PKCa phosphorylation and is initiated by H_2O_2; meanwhile, it causes PKCe phosphorylation, which acts as a cancer prevention agent. Tanshinon IIA is a major ingredient in *Salvia sclarea* L, *Salvia miltiorrhiza* Bge, *Salvia przewalskii* Maxim. Also, it has been validated that Tanshinon IIA may interfere with cell proliferation and the appetite of blood vessels. In addition, it can help reduce Kokot (Kv) Kv2.1 and 1.5 from reduced energy in hourly RNA (mRNA) and protein levels initiated by chronic hypoxia, and to increase p-rate, a process that interferes with Kv in PASMC leads to a decrease in mPAP. 101 Tanshinon IIA has also been reported to suppress PASMC proliferation by hypoxia by blocking the G1/G0 platform, preventing p27 damage by protein B/S protein kinase 2 [61]

Yao and Chen [56] have been reported to have positive effects in ameliorating acute lung damage (ALI) by reducing c-Jun regulation of N-terminal kinase and dependent atomic factor B inhibitors of the 38 kB protein. Moreover, they inhibit platelets. It causes platelet clumps to proliferate, and in these areas blood flow can improve.

14.7 Mechanisms of Action of Some Medicinal Plants in the Treatment of Pulmonary Hypertension

Reports have shown the different mechanisms of action of some medicinal plants in the treatment of pulmonary hypertension. *Allium sativum* was shown to relax the vascular smooth muscles in other to elevate the activity of eNOS [4, 5]. Furthermore, the vaso-relaxant ability of *A. sativum* was observed in another study [32]. Volatile oil obtained from *A. macrostemon* Bunge was also shown to cause relaxation via the activation of Ca^{2+}/PKA/eNOS signaling pathway [62]. Inhibition of PDE5A activity was observed upon the administration of *A. ursinum* L attributed to the polyphenols [4, 5].

Moreover, it has been established that the flavonoids obtained from *Crataegus rhipidophylla* Gand increased the levels of NO caused by elevated altitude in broiler chickens [63]. Ethanolic extract of *Eulophia macrobulbon* halted $CaCl_2$-induced contraction. It also caused relaxation of coronary artery in pigs with hypercholesterolaemia [64]. It was also suggested that hematocrit and expression of p27Kip1 protein were reduced in animals with PH treated with extract of *Rhodiola tangutica* [65]. Table 14.1 shows the biochemical pathway involved in the activities of phytochemical in medicinal plant in the treatment of pulmonary hypertension as well as some phytochemicals that have exhibited medicinal activities.

14.8 Conclusion and Future Recommendation

This chapter has enlighten the potential of different medicinal plants that could be applied for effective management of pulmonary hypertension. Detailed information on isolation, purification, and extraction of the active constituents present in plants that are utilized for the treatment of pulmonary hypertension were provided while the biochemical pathway involved in the activities of phytochemical available in the medical plant in the treatment of pulmonary hypertension as well as detailed facts on the modes of action involved in the application of medicinal treatment of pulmonary hypertension were provided. The application of synthetic biology and genetic engineering could led to the production of some pharmacologically active metabolites with enhanced biologically active that could be used for effective management of pulmonary hypertension. The application of recent averment in the Biotechnology through the application of genomics, bioinformatics, chemoinformatics, and metabolomics will also provide more details on the best biologically active compounds that could be applied for sustainable management of pulmonary hypertension.

Table 14.1 Mode of action of medicinal plants in the treatment of pulmonary hypertension

S/No.	Medicinal plant	Biochemical pathway	Extract	Mode of action	Phytochemicals present	References
1	*Allium macrostemon Bunge*	Ca^{2+}/PKA/eNOS signaling	Macrostemonosides M and N	Activation of Ca^{2+}/PKA/eNOS signaling pathway in PACs	Saponins	Kim et al. [66]
2	*Allium sativum L.*	eNOS	Alliin	Induction of vaso-relaxant activity	Flavonoid and saponins	Hornickova et al. [67]
3	*Allium ursinum L.*	PDE5A signaling pathway	Galactolipids and Phytosterols	Inhibition of PDE5A activity	Saponins and flavonoids	Jasemi et al. [4, 5]
4	*Crataegus rhipidophylla Grand*	Anti-oxidative	Epicatechin, Hyperoxide and Chlorogenic acid	Antioxidant, antianxiety	Flavonoids	Jasemi et al. [4, 5]
5	*Eulophia macrobulbon*	Anti-inhibitory,	Stilbenes	$CaCl_2$ and (RV/LV+S) ratio inhibition	Flavonoids, terpenoids	Jasemi et al. [4, 5]
6	*Kelussia odoratissima Mozzaf*		phthalides	Increase in oxidative stress and decrease in MDA concentration in the blood serum	Flavonoids and polyphenols	Jasemi et al. [4, 5]
7	*Moringa oleifera Lam*	Anti-oxidative	niazirin and thiocarbamates	Increase in SOD levels	Polyphenols	Jasemi et al. [4, 5]
8	*Rhodiola tangutica*	Vaso-relaxant	Polyphenols	Expression of p27Kip1 proteins	Flavonoids and terpenoids	Nan et al. [65]
9	*Salvia miltiorrhiza Bunge*	HO-CO pathway	Caffeic acid	Expression of TGF-b1	Flavonoids	Jasemi et al. [4, 5]
10	*Securigera securidaca L.*		phytosterols	Inhibition of kinase C protein, cyclic AMP- and cGMP-phosphodiesterase	Flavonoids, alkaloids and saponins	Jasemi et al. [4, 5]
11	*Terminalia arjuna*	Anti-oxidative	polyphenols	SOD and CAT inhibition	Flavonoids, terpenoids, and tannins	Meghwani et al. [68]

(continued)

Table 14.1 (continued)

S/No.	Medicinal plant	Biochemical pathway	Extract	Mode of action	Phytochemicals present	References
12	*Withania somnifera L.*		Withaferin A and Withanolide	TNF-α gene inhibition		Jasemi et al. [4, 5]
13	*Centella asiatica L.*	Serine/threonine protein kinase/eNOS pathway	Asiaticoside	Smad2/3 phosphorylation inhibition	Saponins	Wang et al. [69]
14	*Astragalus membranaceus Fisch*		Astragalus polysaccharides	Inflammation synthesis inhibition	Hydrophilic heteropolysaccharides	Yuan et al. [70]
15	*Scutellaria baicalensis Georgi*	AhR pathway	Baicalin	Collagen type 1 inhibition	Flavonoids	Jasemi et al. [4, 5]
16	*Coptidis rhizome*		Berberine	Protein phosphatase 2A (PP2Ac) phosphorylation	Alkaloids	Luo et al. [71]
17	*Oregano*		Carvacrol	PASMCs inhibition	Terpenoid	Jasemi et al. [4, 5]
18	*Panax ginseng*		Ginsenoside Rb1	ET-1 and SOCE expression reduction	G*insenoside*	Jasemi et al. [4, 5]
19	*Uncaria rhynchophylla*		Isorhynchopylline	ERKI/2 and STAT3 signaling pathways inhibition	Alkaloid	Jasemi et al. [4, 5]
20	*Salvia miltiorrhiza*		Magnesium lithospermate B	PASMCs inhibition	Magnesium lithospermate B	Jasemi et al. [4, 5]
21	*Citrus* spp.	Proliferation pathways	Nobiletin	PDGF-BB, Src and STAT3 phosphorylation inhibition	Flavonoids	Jasemi et al. [4, 5]
22	*Sophora flavescens*		Oxymatrine	Inhibition of MCP-1, IL-6, SDF-! hemodynamic indicators	Quinolizidine alkaloid	Jasemi et al. [4, 5]
23	*Polygonum cuspidatum*		Polydatin	Elevation of serum NO levels	Polyphenolic, phytoalexin	Jasemi et al. [4, 5]

24	Pomegranate	NO-cGMP signaling pathway	Punicalagin	NO-cGMP signaling pathway	Ellagitannin	Jasemi et al. [4, 5]
25	Citrus fruits, vegetables, etc.	TrKA/AKT signaling pathway	Quercetin	PASMCs proliferation inhibition	Flavonoid	Jasemi et al. [4, 5]
26	Berries, grapes, chocolate, etc.	PI3K/AKT signaling pathway	Resveratrol	MMP-2 and MMP-9 inhibition	Stilbenoid polyphenol	Jasemi et al. [4, 5]

References

1. Xiang L, Li Y, Xu DX, Kosanovic D, Schermuly RT, Li X (2018) Natural plant products in treatment of pulmonary arterial Hypertension. Pulm Circ 8(3):1–20. https://doi.org/10.1177/2045894018784033
2. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R (2019) Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 53:1801913
3. Sánchez-Gloria JL, Osorio-Alonso H, Arellano-Buendía AS, Carbó R, Hernández-Díazcouder A, Guzmán-Martín CA, Rubio-Gayosso I, Sánchez-Muñoz F (2020) Nutraceuticals in the treatment of pulmonary arterial hypertension. Int J Mol Sci 21:4827. https://doi.org/10.3390/ijms21144827
4. Jasemi SV, Hosna K, Ina YA, Mohammad HF, Javier E (2020) Medicinal plants and phytochemicals for the treatment of pulmonary hypertension. Front Pharmacol 11:145. https://doi.org/10.3389/fphar.2020.00145
5. Jasemi SV, Khazaei H, Aneva IY, Farzaei MH, Echeverria J (2020) Medicinal plants and phytochemicals for pulmonary hypertension. Front Pharmacol 11:145. https://doi.org/10.3389/fphar.2020.00145.
6. Schermuly RT, Ghofrani HA, Wilkins MR, Grimminger F (2011) Mechanisms of disease: pulmonary arterial hypertension. Nat Rev Cardiol 8(8):443. https://doi.org/10.1038/nrcardio.2011.87
7. Yeager ME, Halley GR, Golpon HA, Voelkel NF, Tuder RM (2001) Microsatellite instability of endothelial cell growth and apoptosis genes within plexiform lesions in primary pulmonary hypertension. Circ Res 88(1):E2–E11
8. Dorfmüller P, Perros F, Balabanian K, Humbert M (2003) Inflammation in pulmonary arterial hypertension. Eur Respir J 22(2):358–363
9. Balabanian K, Foussat A, Dorfmüller P, Durand-Gasselin I, Capel F, Bouchet-Delbos L, Portier A, Marfaing-Koka A, Krzysiek R, Rimaniol AC, Simonneau G, Emilie D, Humbert M (2002) CX(3)C chemokine fractalkine in pulmonary arterial hypertension. Am J Respir Crit Care Med 165(10):1419–1425
10. Waxman AB, Zamanian RT (2013) Pulmonary arterial hypertension: new insights into the optimal role of current and emerging prostacyclin therapies. Am J Cardiol 111(5):1–16. https://doi.org/10.1016/j.amjcard.2012.12.002
11. Wong CM, Bansal G, Pavlickova L, Marcocci L, Suzuki YJ (2013) Reactive oxygen species and antioxidants in pulmonary hypertension. Antioxid Redox Signal 18(14):1789–1796
12. Hui-li G (2011) The management of acute pulmonary arterial hypertension. Cardiovasc Ther 29 (3):153–175. https://doi.org/10.1111/j.1755-5922.2009.00095.x
13. Reyes RV, Castillo-Galán S, Hernandez I, Herrera EA, Ebensperger G, Llanos AJ (2018) Revisiting the role of TRP, orai, and ASIC channels in the pulmonary arterial response to hypoxia. Front Physiol 9:486
14. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS et al (2010) Predicting survival in pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL). Circulation 122(2):164–172
15. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery J-L, Barbera JA et al (2009) Guidelines for the diagnosis and treatment of pulmonary hypertension: the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 30(20):2493–2537. https://doi.org/10.1093/eurheartj/ehp297
16. Hussain A, Bennett RT, Tahir Z, Isaac E, Chaudhry MA, Qadri SS, Loubani M, Morice AH (2019) Differential effects of atrial and brain natriuretic peptides on human pulmonary artery: an *in vitro* study. World J Cardiol 11(10):236–243. https://doi.org/10.4330/wjc.v11.i10.236

17. Mintah SO, Asafo-Agyei T, Archer MA, Atta-Adjei Junior P, Boamah D, Kumadoh D, Appiah A, Ocloo A, Boakye YD, Agyare C (2019) Medicinal plants for treatment of prevalent diseases. Intechopen. https://doi.org/10.5772/intechopen.82049
18. Voswinckel R, Reichenberger F, Enke B et al (2008) Acute effects of the combination of sildenafil and inhaled treprostinil on haemodynamics and gas exchange in pulmonary hypertension. Pulm Pharmacol Ther 21:824–832
19. Hoeper MM, Barberà JA, Channick RN et al (2009) Diagnosis, assessment, and treatment of non–pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol 54:85–96
20. Njila NIM, Mahdi E, Lembe MD, Nde Z, Nyonseu D (2017) Review on extraction and isolation of plant secondary metabolites. In: 7th Int'l conference on agricultural, chemical, biological and. Environ Sci 2017:67–72. https://doi.org/10.15242/IIE.C051720
21. Fabricant DS, Farnsworth NR (2001) The value of plants used in traditional medicine for drug discovery. Environ Health Perspect 109:69–75
22. Cosa P, Vlietinck AJ, Berghe DV, Maes L (2006) Anti-infective potential of natural products: how to develop a stronger in vitro 'proof-of-concept'. J Ethnopharmacol 106:290–302
23. Zhang Q, Lin GL, Ye CW (2018) Techniques for extraction and isolation of natural products: a comprehensive review. Chin Med 13(20):1–26. https://doi.org/10.1186/s13020-018-0177
24. Rasul MG (2018) Extraction, isolation and characterization of natural products from medicinal plants. Int J Basic Sci Appl Comput 2(6):1–6
25. Handa SS, Khanuja SPS, Longo G, Rakesh DD (2008) Extraction technologies for medicinal and aromatic plants. ICS UNIDO, Trieste
26. Vidyadhar S, Saidulu M, Gopal TK, Chamundeeswari D, Rao U, Banji D (2010) *In vitro* anthelmintic activity of the whole plant of Enicostemma littorale by using various extracts. Int J Appl Biol Pharma Technol 1(3):1119–1125
27. Fan XH, Cheng YY, Ye ZL, Lin RC, Qian ZZ (2006) Multiple chromatographic fingerprinting and its application to the quality control of herbal medicines. Anal Chim Acta 555:217–224
28. Cannell RJP (1998) Natural products isolation. Human Press Inc., Totowa, pp 165–208
29. Tonthubthimthong SC, Douglas P, Luewisutthichat W (2011) Supercritical CO2 extraction of nimbin from neem seeds an experimental study. J Food Eng 47(4):2
30. Eberhardt TL, Li X, Shupe TF, Hse CY (2007) Chinese tallow tree (Sapium Sebiferum) utilization: characterization of extractives and cell-wall chemistry. Wood Fiber Sci 39:319–324
31. Horníčková J, Kubec R, Cejpek K, Velíšek J, Ovesna J, Stavělíková H (2010) Profiles of S-alk (en) ylcysteine sulfoxides in various garlic genotypes. Czech J Food Sci 28(4):298–308
32. Fallon MB, Abrams GA, Abdel-Razek TT, Dai J, Chen S-J, Chen Y-F et al (1998) Garlic prevents hypoxic pulmonary hypertension in rats. Am J Physiol Lung Cell Mol Physiol 275(2): L283–L287. https://doi.org/10.1152/ajplung.1998.275.2.L283.
33. Tan X, Chai J, Bi SC, Li JJ, Li WW, Zhou JY (2012) Involvement of matrix metalloproteinase-2 in medial hypertrophy of pulmonary arterioles in broiler chickens with pulmonary arterial hypertension. Vet J 193(2):420–425. https://doi.org/10.1016/j.tvjl.2012.01.017
34. Chu MP, Xu ZX, Zhang XL (2007) Changes of expression of ICAM-1 in autoimmune myocarditis in mice and the interfering effect of Panax notoginseng saponin. J Wenzhou Med Coll 37:203–205
35. Behnam A, Majid K, Seyed MH, Zia UR, Farmanullah F, Mohammad HK, LiGuo Y (2019) Hawthorn (Crataegus oxyacantha) flavonoid extract as an effective medicinal plant derivative to prevent pulmonary hypertension and heart failure in broiler chickens. Kafkas Univ Vet Fak Derg 25(3):321–328. https://doi.org/10.9775/kvfd.2018.20930
36. Himanshu M, Pankaj P, Soheb AM, Sandeep S, Milind PH, Sanjay KB, Sudheer A, Ruma R, Subir KM (2016) Beneficial effects of aqueous extract of stem bark of Terminalia arjuna (Roxb.), an Ayurvedic drug in experimental pulmonary hypertension. J Ethnopharmacol. https://doi.org/10.1016/j.jep.2016.07.029
37. Masoumeh P, Reza M, Saber A, Nasrollah N, Siamak N, Fariba B (2017) Medicinal plants used for hypertension. J Pharm Sci Res 9(5):537–541

38. Jiang YB, Yang YR (2015) Trifolium pratense isoflavones improve pulmonary vascular remodelling in broiler chickens. J Anim Physiol Anim Nutr. https://doi.org/10.1111/jpn.12424.1-10
39. Landazuri P, Chamorro NL, Cortes BP (2017) Medicinal plants used in the management hypertension. J Anal Pharm Res 5(2):00134. https://doi.org/10.15406/japlr.2017.05.00134.
40. Gan H (2010) The management of acute pulmonary arterial hypertension. Cardiovasc Ther 29 (2011):153–175. https://doi.org/10.1111/j.1755-5922.2009.00095.x
41. Ritu S, Sakshi J, Jyoti KB, Parul S (2016) The use of rauwolfia serpentina in hypertensive patients. IOSR J Biotechnol Biochem 2(5):28–32
42. Lili X, Ying L, Xu D, Djuro K, Ralph TS, Xiaohui L (2018) Natural plant products in treatment of pulmonary arterial hypertension. Pulm Circ 8(3):1–20. https://doi.org/10.1177/2045894018784033.
43. Meresa A, Fekadu N, Degu S, Tadele A, Geleta B (2017) An ethno botanical review on medicinal plants used for the management of hypertension. Clin Exp Pharmacol 7:228. https://doi.org/10.4172/2161-1459.1000228.
44. Lakshmi T, Anitha R, Durgha K, Manjusha V (2011) Coping with hypertension using safer herbal medicine – a therapeutic review. Int J Drug Dev Res 3(3):31–57
45. Qilian H, Xingmei N, Silin L, Shanshan S, Ke M, Zhanqiang L, Dianxiang L, Rili G (2018) Tsantan sumtang alleviates chronic hypoxia-induced pulmonary hypertension by inhibiting proliferation of pulmonary vascular cells. Biomed Res Int 2018:9504158. https://doi.org/10.1155/2018/9504158
46. Zhouye W, Zhaoqing X (2020) Compound xiebai capsule alleviates pulmonary vascular remodeling in monocrotaline-induced pulmonary arterial hypertension in rats. Trop J Pharm Res 19(1):107–114
47. Tingting W, Jun H, Wenjing X, Yaolei Z, Longfu Z, Li Y, Xiaoqiang Y, Xin C, Yonghe H (2020) Chinese medicinal plants for the potential management of high-altitude pulmonary oedema and pulmonary hypertension. Pharm Biol 58(1):815–827. https://doi.org/10.1080/13880209.2020.1804407.
48. Manish A, Nandini D, Vikas S, Chauhan NS (2010) Herbal remedies for treatment of hypertension. IJPSR 1(5):1–21
49. Thomas FMK, Michael H, Heinrich W, Hagen K, Raimund E (2005) Clinical und pharmacological testing of patients with pulmonary hypertension for treatment decision. Herz 30:286–295. https://doi.org/10.1007/s00059-005-2699-0.
50. Rakotomalala G, Agard C, Tonnerre P, Tesse A, Derbré S, Michalet S, Hamzaoui J, Rio M, Cario-Toumaniantz C, Richomme P, Charreau B, Loirand G, Pacaud P (2013) Extract from Mimosa pigra attenuates chronic experimental pulmonary hypertension. J Ethnopharmacol 148 (1):106–116. https://doi.org/10.1016/j.jep.2013.03.075
51. Bai MK, Guo Y, Bian BD et al (2011) Integripetal rhodiola herb attenuates high altitude-induced pulmonary arterial remodeling and expression of vascular endothelial growth factor in rats. Sheng Li Xue Bao 63:143–148
52. Huang XY, Fan R, Lu YY, Lin QD (2011) The protective effect of salidroside on cor pulmonale rats induced by chronic hypoxia in normal pressure. Chin Arch Tradit Chin Med 29:1868–1871
53. Zhang S, Gao W, Xu K et al (1999) Early use of Chinese drug rhodiola compound for patients with post-trauma and inflammation in prevention of ALI/ARDS. Zhonghua Wai Ke Za Zhi 37:238–240
54. Wang XQ, Wang BH, Li YH, Zhao YL, Wang YY, Wang Y (2012) Regulating effect and its mechanism of Tibet Rhodiola crenulate on blood pressure in spontaneous hypertension rat. Chin J Exp Trad Med Form 18:150–154
55. Sui XL, Yang F, Chen RH et al (2006) Inhibition of rhodiola on the growth of EVC-304 cell line. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi 22:524–525
56. Yao BW, Chen W (2005) Research advances in the pharmacological effects of Ginkgo biloba leaves (in Chinese). Zhejiang J Integr Tradit Chin West Med 15:192–193

57. Young JF, Nielsen SE, Haraldsdottir J, Daneshvar B, Lauridsen ST, Knuthsen P, Crozier A, Sandström B, Dragsted LO (1999) Effect of fruit juice intake on urinary quercetin excretion and biomarkers of antioxidative status. Am J Clin Nutr 69:87–94
58. Tulsulkar J, Shah ZA (2013) Ginkgo biloba prevents transient global ischemia–induced delayed hippocampal neuronal death through antioxidant and anti–inflammatory mechanism. Neurochem Int 62:189–197
59. Li JW, Chen P, Guan XQ et al (2008) Inhibition of Puerarin on pulmonary hypertension in rats with hypoxia and hypercapnia. Zhongguo Zhong Yao Za Zhi 33:544–549
60. Qu HL, Li XY, Wang FY et al (2004) Effect of Polydatin on hypoxic pulmonary hypertension (in Chinese). J Binzhou Med Coll 27:328–329
61. Wei L, Liu T, Liu B et al (2007) Effect of triptolide on the expression of MMP9/TIMP-1 in the lung of expression pulmonary hypertension. Med J 28:828–830
62. Han C, Qi J, Gao S, Li C, Ma Y, Wang J et al (2017) Vasodilation effect of volatile oil from Allium macrostemon Bunge are mediated by PKA/NO pathway and its constituent dimethyl disulfide in isolated rat pulmonary arterials. Fitoterapia 120:52–57. https://doi.org/10.1016/j.fitote.2017.05.007.
63. Ahmadipour B, Hassanpour H, Asadi E, Khajali F, Rafiei F, Khajali F (2015) *Kelussia odoratissima Mozzaf* – A promising medicinal herb to prevent pulmonary hypertension in broiler chickens reared at high altitude. J Ethnopharmacol 159(1):49–54
64. Wisutthathum S, Demougeot C, Totoson P, Adthapanyawanich K, Ingkaninan K, Temkitthawon P et al (2018) Eulophia macrobulbon extract relaxes rat isolated pulmonary artery and protects against monocrotaline-induced pulmonary arterial hypertension. Phytomedicine 50:157–165. https://doi.org/10.1016/j.phymed.2018.05.014.
65. Nan X, Su S, Ma K, Ma X, Wang X, Zhaxi D et al (2018) Bioactive fraction of Rhodiola algida against chronic hypoxia-induced pulmonary arterial hypertension and its anti-proliferation mechanism in rats. J Ethnopharmacol 216:175–183. https://doi.org/10.1016/j.jep.2018.01.010.
66. Kim YS, Cha JM, Kim D, Lee TH (2018) A new steroidal glycoside from Allium macrostemon Bunge. Nat Prod Sci 24(1):54. https://doi.org/10.20307/nps.2018.24.1.54.
67. Hornickova J, Kubec R, Cejpek K, Velisek J, Ovesna J, Stavelikova H (2010) Profile of S-alk (en) ylcysteine sulfoxides in Various garlic genotypes. Czech J Food Sci 28(4):298–308
68. Meghwani H, Prabhakar P, Mohammed SA, Seth S, Hote MP, Banerjee SK et al (2017) Beneficial effects of aqueous extract of stem bark of Terminalia arjuna (Roxb.), An ayurvedic drug in experimental pulmonary hypertension. J Ethnopharmacol 197:184–194. https://doi.org/10.1016/j.jep.2016.07.029.
69. Wang RX, He RL, Jiao HX, Dai M, Mu YP, Hu Y et al (2015) Ginsenoside Rb1 attenuates agonist-induced contractile response via inhibition of store-operated calcium entry in pulmonary arteries of normal and pulmonary hypertensive rats. Cell Physiol Biochem 35(4):1467–1481. https://doi.org/10.1159/000373966.
70. Yuan L-B, Hua C-Y, Gao S, Yin Y-L, Dai M, Meng H-Y et al (2017) Astragalus polysaccharides attenuate monocrotaline-induced pulmonary arterial hypertension in rats. Am J Chin Med 45(04):773–789. https://doi.org/10.1142/S0192415X17500410.
71. Luo J, Gu Y, Liu P, Jiang X, Yu W, Ye P et al (2018) Berberine attenuates pulmonary arterial hypertension via protein phosphatase 2A signaling pathway both in vivo and in vitro. J Cell Physiol 233(12):9750–9762. https://doi.org/10.1002/jcp.26940

Herbal Bioactives for the Treatment of Idiopathic Pulmonary Fibrosis

15

Madhu Sharma, Veera Garg, and Inderbir Singh

Idiopathic pulmonary fibrosis (IPF) is a group of lung disease that mainly affects the interstitium and ultimately results in the inflammation and damaging to the lung tissues [1]. The tissues present around the air sacs are called interstitium. Because of the thickening and scarring, lung tissues become damaged, and make it difficult to work. The scarring gets worse by the time which makes it difficult to breathe and keep the optimum levels of oxygen in the bloodstream. This affects the functioning of the vital organs as they are slowly depriving off oxygen. This disease is characterised by destruction of alveoli along with abnormal accumulation of fibroblasts giving the lungs a "honeycomb" like structure. Generally, this disease is more common in men over 50 years of age and two-thirds are diagnosed after 60 years of age [2]. Approximately 50,000 new cases of IPF are diagnosed each year and the symptoms came first into notice between the age of 50 and 70 years. Earlier the symptoms begin with the shortening of breathe but by the time this condition gets worse by eating or talking. At present, in the USA more than 80,000 adults are suffering from this disease and more than 30,000 cases are diagnosed every year [3]. Here the term "idiopathic" is used because the exact cause of scarring of tissues cannot be figured out (Fig. 15.1).

M. Sharma
Shipra Suncity, Indirapuram, Ghaziabad, Uttar Pradesh, India

V. Garg
S.D. College of Pharmacy, Barnala, Punjab, India

I. Singh (✉)
Chitkara College of Pharmacy, Chitkara University, Patiala, Punjab, India
e-mail: inderbir.singh@chitkara.edu.in

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_15

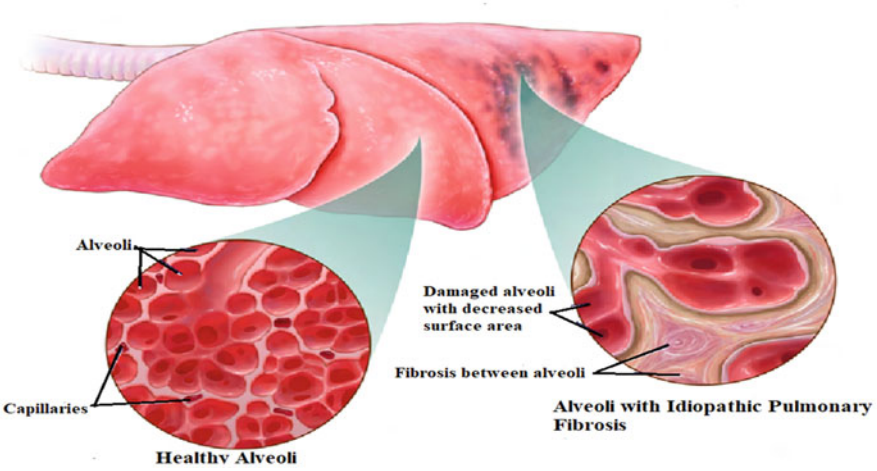


Fig. 15.1 Diagramatic representation of a healthy alveoli and alveoli with idiopathic pulmonary fibrosis

15.1 Aetiology

Although IPF is a lethal disease of unknown aetiology. Various researchers have proposed many theories about what might trigger this disease. But the exact cause is still not known. Some studies revealed that IPF is linked to certain subtypes of certain viruses particularly those which induce somatic mutation. For instance, Epstein Barr Virus (causative organism of glandular fever). Some researchers have suggested Hepatitis C and Herpes virus as one of the causes of IPF. Family history and genetics may also play a role in the occurrence of this disease [4–8]. Some other parameters which are estimated to be one of the reasons of this disease are discussed below:

15.1.1 Environmental Factors

Exposure to hazardous materials such as asbestos and silica makes a person more prone to IPF. Metal workers, farmers and stone cutters are at higher risk of developing this disease. Moreover, animal and bird droppings also make a person more prone to IPF.

15.1.2 Radiation

People who receive the radiation therapy for treatment of lung or breast cancer show the symptoms of IPF either after months or after years of receiving the initial

treatment. The extent of damage further depends on certain factors. For instance, for how long and how much of lung was exposed to the radiations. Whether the patient is already having certain history of lung disease and concomitant use of steroids.

15.1.3 Medications

15.1.3.1 Anti-inflammatory Drugs

Rituximab and sulphasalazine increase the chances of IPF in an individual.

15.1.3.2 Anti-cancer Drugs

Methotrexate and cyclophosphamide which damage the cancer cells further harm the lung tissues also.

15.1.3.3 Antibiotics

Ethambutol and Nitrofurantoin could also damage the lung tissues and make it more prone to IPF.

15.1.3.4 Cardiac Drugs

Especially those which are used to regulate the irregular heartbeat. For example, Amiodarone could harm the lung tissues.

15.1.4 Medical History

A person with a medical history of pneumonia, systemic lupus erythematosus, scleroderma and mixed connective tissue disorder are more susceptible to this disorder.

15.2 Pathophysiology

This has been a subject of debate from the past few decades. Earlier it was believed that IPF is a disorder in which fibrinogenesis plays an important role. Fibrinogenesis begins with the epithelial injury. But the recent studies show that this disease takes place once the homeostasis between the alveolar and the epithelial cells disrupts. This initiates a cascade of changes in the lungs. The homeostasis between the alveolar cells and the epithelial cells may be disrupted by the endogenous factors or because of the environmental stimuli. This results in the activation of the epithelial cells, in response to which aberrant epithelial cell repair takes place [9]. Soit would be appropriate to say that IPF is an epithelial-fibroblastic disease.

According to the current hypothesis, if any susceptible host is exposed to any agent that persuade this disease, (for instance, environmental pollutants, GERD, viral infections, smoke, etc.) then initially alveoli epithelium damage takes place [10]. In normal process of healing, the healing of this damaged alveoli epithelium

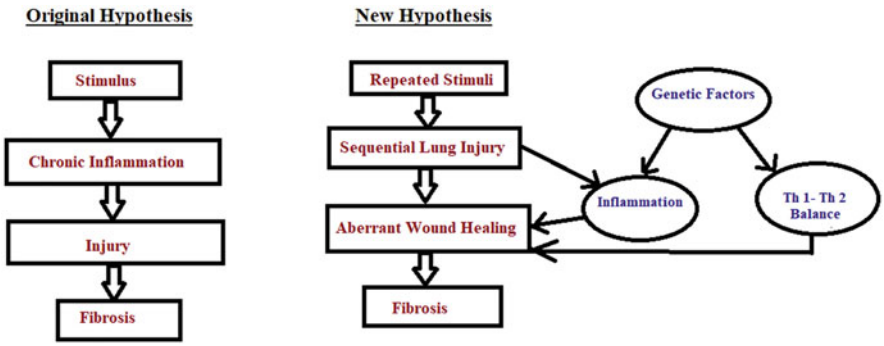


Fig. 15.2 Pathogenesis of idiopathic pulmonary fibrosis according to the original and the new hypothesis

occurs. But in case of IPF, immediately after an injury, aberrant activation of alveolar epithelial cells initiates the migration, proliferation, and activation of mesenchyma cells that leads to the formation of fibroblastic foci. As a result of which there is an excess of accumulation of extracellular matrix. Now there is a possibility that the change in the composition or stiffness of the extracellular matrix. But how the changes in this composition or stiffness affect the epithelial cells, require further study [11]. This ultimately results in the irreversible damage to the lung parenchyma [10] (Fig. 15.2).

Once the alveolar epithelial cells are activated they release certain fibrogenic cytokines and growth factors. For instance, tumour necrosis factor-α (TNF-α), Insulin like growth factor-1, Platelet derived growth factor, endothelin-1 (ET-1), transforming growth factor (TGF-β) are released [10, 13, 14]. These cytokines and growth factors transform the fibroblasts into myofibroblasts and these myofibroblasts further secrete the extracellular matrix proteins [10, 1, 2, 12]. In addition to the cytokines and growth factors, certain prostanoids (for instance, PGE_2) are also synthesised. PGE_2 is a potent inhibitor of fibroblast collagen synthesis [15, 16]. Endothelin-1 also stimulates DNA synthesis in fibroblasts which induce differentiation of fibroblasts into myofibroblasts [17].

In the process of normal wound healing, the myofibroblasts once formed must undergo apoptosis. But if they do not undergo the process of apoptosis, it leads to the accumulation of myofibroblasts which further causes accumulation of extracellular matrix fluid, tissue contraction and scar formation [10]. The studies reveal that TGF-β promotes anti-apoptotic activity in fibroblasts [10].

At a certain stage, the excess apoptosis of the alveolar epithelial cells is taking place and on the other hand, fibroblasts show resistance towards apoptosis. This stage is believed to be the primary factor in contributing to fibroproliferation in IPF. Another important perspective is deficiency of PGE_2. Studies were carried out on the lung tissues of the patients with pulmonary fibrosis revealed that PGE_2 deficiency increases the sensitivity of alveolar epithelial cells to FAS-ligand induced apoptosis, whereas fibroblasts show resistance to FAS-ligand induced apoptosis [18]. So,

apoptosis resistance of fibroblasts and myofibroblasts may be a contributing factor in IPF.

Earlier, eosinophils were also thought to be involved in the pathogenesis of IPF. A significant increase in the BAL fluid eosinophils in the pulmonary fibrosis was observed as compared with the controls [19]. On further investigation, it was revealed that increased eosinophil count in BAL fluid fails to respond to the corticosteroids and it was correlated with the disease progression [20]. Many studies were carried out but the role of eosinophils in fibrogenesis remains unclear. Further investigation revealed that eosinophilic count was higher in patients of IPF than in the patients of scleroderma, which suggests that eosinophils might play a role in the pathogenesis of IPF [21].

The expression of a putative promoter of the gene encoding mucin 5B (MUC 5B) is reported to be 14 times greater than in subjects with IPF as compared to those who did not. So, it is thought to be associated with the pathogenesis of IPF [22].

In the patients with IPF, the mast cells have found to be increase in number [23, 24]. Mast cell products like histamine have also been recovered from BAL fluids of patients with IPF [25]. Electron microscopy samples of the IPF patients show evidences of degranulation. All these evidences show the potential role of mast cells in the pathogenesis of IPF [26].

Mutant telomerase is also correlated with IPF. Telomerase, which is a specialised polymerase, adds telomere to the end of chromosomes so as to prevent the shortening during DNA replication. Telomerase activity is regulated by TGF-β [10]. The studies revealed that IPF patients possess short telomeres which may be due to the loss of alveolar epithelial cells that is further responsible for aberrant repair of epithelial cells. These evidences concluded that telomerase is a potential contributor to the pathophysiology of IPF [27].

The abovementioned factors are thought to be the contributors to the pathogenesis of IPF. Various studies are still carried out to determine the exact contributors to this disease so that novel approaches can be developed to treat IPF (Fig. 15.3).

15.3 Signs and Symptoms

The symptoms may vary from person to person. Some people become ill very quickly [28–30]. In some people, the symptoms may worsen from several weeks to months. IPF includes the non-specific signs and symptoms which can be similar to those involved in pulmonary or cardiac disease. The disease begins either with dyspnea or with non-productive cough. Eventually, dyspnea disables all the activities and it even occurs while standing still. In some rare cases, dyspnea and disability occur within weeks to months (acute exacerbation) as soon as the onset of disease takes place [31, 32]. This form of pulmonary fibrosis is referred to as ‘Hamman Rich Syndrome’. The symptoms usually begin with the time period of 6 months or more.

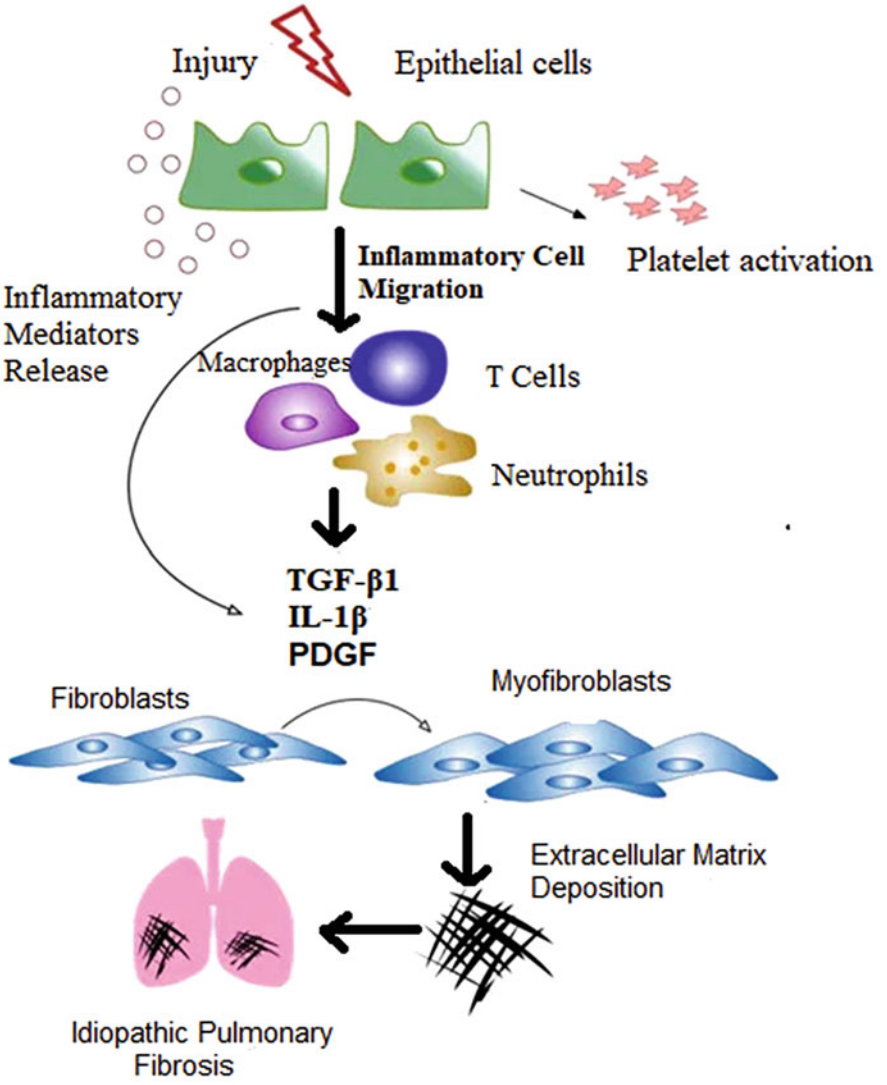


Fig. 15.3 Pathogenesis of idiopathic pulmonary fibrosis

1. Fatigue
2. Unexplained weight loss
3. Clubbing of the fingers or toes
4. Myalgia
5. Shortening of breathe
6. Dry cough
7. Swelling of legs
8. Loss of appetite

This disease when becomes complicated leads to failure of respiratory system and heart [33]. This is because lungs (owing to the formation of scars) could not supply oxygen to the vital organs, thereby leading to further health issues.

15.4 Epidemiology

IPF is a chronic disease. Irrespective of the treatment, it has poor prognosis having survival of mere 3 years. According to a study, in the United Kingdom, an incidence of 6.8 per 100,000 has been reported in the year 2000–2003 [34, 35]. In North America and Europe (3–9 cases per 100,000 person years) its prevalence is high in comparison to South America and East Asia (fewer than four cases per 100,000 person years) [36, 37]. Globally, IPF is affecting 30 in 100,000 [38] with 34,000 new cases per year [39].

15.5 Diagnosis

For the diagnosis, doctor may take a review of the family or medical history. It is very critical to obtain a complete history (including medication history, occupational recreational exposure history and any respiratory exposure history) of the patient [40]. It is better to seek a pulmonologist in case the symptoms worsen. The pulmonologist may conduct some physical tests to rule out that how badly the drugs are damaged. The doctor would also listen to the patient's chest to determine if the patient's lungs are producing some abnormal sounds. These abnormal sounds can be listened carefully using a stethoscope by the doctor. These abnormal sounds can be listened carefully using a stethoscope by the doctor and these sounds are referred as "velco crackles" as it sounds similar to velco being pulled apart. So, it is referred to as "velco crackles". Scarring IPF looks similar to the scarring that occurs due to the other lung disease. So, it is difficult to differentiate between IPF and other lung disease at an early stage. So, certain tests are suggested to rule out the possible causes of IPF and its confirmation.

15.5.1 Imaging Tests

a. *Chest X-ray*: It may show the scar of lungs and also it is useful in determining the course of treatment. But sometimes, in spite of the normal chest X-Ray, further tests are conducted to determine the actual cause behind the shortening of breathe [41]. Typical findings include honeycombing, volume loss in any lobe, netlike, or curvilinear opacities.
b. *Computerized tomography (CT) scan*: A computer is combined with the X-Ray images, taken from different angles. These images are combined with a computer system to obtain cross-sectional images of internal structures of body. CT scan is used to determine the extent of lung damage caused by IPF. For more precision

and detail, high resonance computed tomography (HRCT) scan is used. On HRCT images, IPF is characterised by patches and subpleural opacities. It is a more sensitive technique [42].

c. *Echocardiogram*: It is used to evaluate the amount of pressure experienced by right side of the heart. ECG uses the sound waves to produce the still images of heart's structure [43].

15.5.2 Lung Function Tests

a. *Pulmonary Function Test*: It is used to reveal a parameter named forced vital capacity (FVC). Most basic test used is spirometry which determines how much air lungs can hold and how forcefully air can be emptied from the lungs. In patients with IPF; FVC, total lung capacity, vital capacity all are reduced [44]. It helps the physician to determine if a patient is suffering from mild, moderate, severe or very severe IPF.
b. *Pulse Oximetry*: In this test, a small sensor is attached either to an ear or a finger. This test uses light to determine amount of oxygen in blood.
c. *Exercise Stress Test*: Exercising capacity is evaluated using a six minute exercise test with the help of a treadmill or a stationary bike. Someone will note down the levels of oxygen in the blood through a probe which is either kept either over the forehead or on the finger [45].

15.5.3 Biopsy

If the above-mentioned tests failed to diagnose the disease, then the doctors remove a small portion of lung tissue and examination is done in laboratory to diagnose IPF or any other condition. It is done using the following techniques:

a. *Bronchoscopy*: A very small tissue sample (usually not more than head of a pin) is taken out through a small, flexible tube (bronchoscope) which is inserted either through the mouth or nose into the lungs. But this procedure is associated with certain minor risks. For instance, sore throat, discomfort in nose. Bleeding or deflated lungs are some of the serious complications associated with this technique.

An additional test, known as bronchoalveolar lavage (BAL) is carried out in some cases. Procedure involves the injection of salt water through bronchoscope into a section of a lung. Immediately, it is suctioned out containing cells from air sacs. However, BAL fluid is suggested for patients with newly detected interstitial lung disease and who are under clinical suspicion of IPF and have HRCT pattern of probable usual interstitial pneumonia (UIP) [46].

b. *Surgery biopsy*: Although this technique is more invasive and the large tissue sample is obtained. But the diagnosis of disease would be more accurate than

other techniques. The specimen can be obtained either using open lung surgery or by video-assisted thoracoscopic surgery (VATS).

Surgery biopsy is the best way to distinguish between usual interstitial pneumonia (UIP) from other idiopathic interstitial pneumonias. Among both the techniques, VATS is more preferred as it involves the shorter hospital stay and less morbidity [47].

15.6 Treatment

There are limited treatment options for IPF. This is because lung scarring is permanent and it cannot be reversed in any way. There is only one option, i.e. lung transplantation. However, there are some drugs which are prescribed by the doctors depending upon the severity of the disease. These drugs may either slow down the progression of scarring or improve the quality of life. The following categories of drugs are included in the treatment of IPF.

15.6.1 Anti-fibrotic Drugs/Anti-scarring Drugs: (Pirfenidone, Nintedanib)

FDA has approved two drugs: Pirfenidone and Nintedanib [48]. These drugs slow down the progression of scarring in the lungs. However, monitoring with blood tests is important in patients taking these medications because they are associated with certain side effects. Pirfenidone may result in diarrohea and liver function test abnormalities. Nintedanib may cause rashes and nausea. Because of these potential adverse effects, some patients found it difficult to take this medication.

Antacids are also prescribed by the doctors because of GERD, which is a common problem associated with the patients of IPF.

15.6.2 Corticosteroids: (Prednisone) [49–54]

Corticosteroids can subsequently reduce the inflammation of lungs. Though the steroids cannot completely irradicate the disease. If a patient gives an adequate response to the therapy, steroids can be given for 1–2 years as a maintenance therapy with gradual tapering of the dose. The therapy is initiated with high dose (40–100 mg daily) for 2–4 months with gradual tapering. If responses occur, the improvement can be observed within three months. In case of relapse or deterioration of health, the dose of corticosteroids is escaled or it is given in combination with immunosuppressive agent.

As a maintenance dose, 15–20 mg low dose prednisone every other day is sufficient.

15.6.3 Cytotoxic Agents/Immunosuppressive Agents: (Azathioprine, Cyclophosphamide) [49, 55, 56]

These agents are used for the patients who do not respond to corticosteroid treatment, or experience serious side effects from corticosteroid therapy or patients with diabetes mellitus, hypertension and osteoporosis.

The combination of azathioprine with the corticosteroids is the modest improvement that has enhanced the survival rate in some patients. A high dose (500–1800 mg) of cyclophosphamide was administered i/v for about 2–4 weeks. But the results were impressive. The toxicity associated with cyclophosphamide makes it difficult for the patients to use it in routine for treating IPF.

15.6.4 Other Fibrolytic Agents: (Interferon-ϒ, Interferon-β, Relaxin) [57, 58]

These drugs are tested for the treatment of lung fibrosis by increasing procollagenase. PGE_2 is also being tested for treating lung fibrosis as it inhibits the collagen production. N-acetyl cysteine is a glutathione precursor that can be used in maintenance immunosuppressive therapy for the treatment of IPF [59].

15.7 Herbal Formulations Are Better Alternative for IPF

There are limited treatment options for the treatment of IPF. The prognosis of the disease is also poor. Moreover, there are only two anti-fibrotic drugs which are approved by FDA that actually slow down the process of fibrosis. The drugs (corticosteroids, anti-inflammatory drugs) provide only marginal benefit and are associated with many side effects [60–64] and the other options for living better with this disease are limited. So, the natural or herbal formulations are the best option one could adopt to cope up with this problem. Herbal medicines are used for about 5000 years and it is practised in most of the regions of Asia. Alone in China, there are around 6000 herbal medicines which are available for this therapy [65]. Internet is filled with plethora of information regarding any chronic illness. Indian herbs are considered to be the best in terms of their divinity and purity. Moreover, these herbal formulations are pure as they do not contain any harmful chemicals and they are prepared under the guidance of experts of Ayurveda. The long lasting effect of the herbal formulations is matchless. Broadly, these herbs can be leaves, roots, flowers, seeds, bark or any other segment of plant.

Herbal formulations harmonise ‘the five elements’ (wood, earth, fire, water and metal) in the human body [66, 67]. It is necessary to maintain a balance between these five elements. Every person has a different natural balance, called as individual’s nature. If this balanced state is disturbed, it makes a person, unhealthy. It is also concluded that a mixture of several herbs in a single formula is much more effective than a single constituent. Each formula is divided into four components,

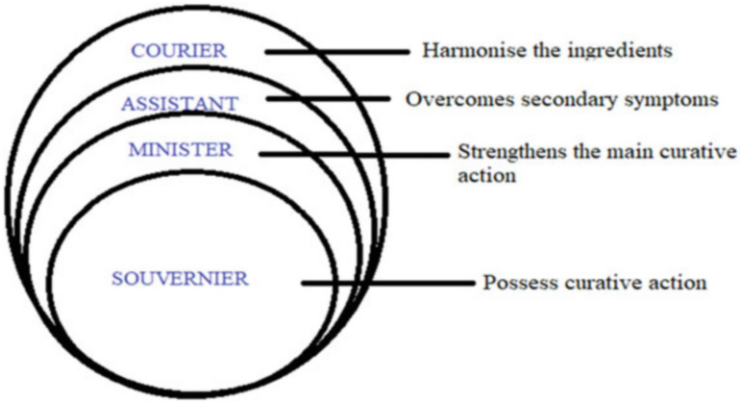


Fig. 15.4 Components of a herbal formulation

namely 'sovereign', 'minister', 'assistant' and 'courier' and has a different role to play. Main curative action is provided by 'sovereign' herb. Minister helps to strengthen the curative action of sovereign herb. Assistant helps to overcome the secondary effects of both sovereign and minister. Courier helps in harmonisation of all the ingredients [68] (Fig. 15.4).

Following are some of the herbal bioactives explained in brief:

1. *Pippali*: The IPF begins with the inflammation and scarring of the lung tissue. The joint pain may also occur in the later stages. So, the common problem that accompanies IPF is rheumatoid arthritis. There is only symptomatic treatment of this problem in conventional system. But Ayurveda offers a better advantage in the form of PippaliVardhamanRasayana [69], which can be used as a rejuvenating therapy [70]. Apart from anti-inflammatory property [71], Pippali also possesses anti-oxidative [72], anti-asthmatic [73], anti-rheumatic [74] and immune-modulatory properties too. A case study was reported for a 55 years old female who was suffering from interstitial lung disease (ILD) with the history of pneumonia. The patient was on corticosteroids and immunosuppressants from past 2 years. Then the patient was treated with Pippali along with Pippali siddha ksheera (medicated milk) with an increasing dose beginning from 3. The dose was then increased to 15 followed by tapering again to 3 pippali for a period of 9 days. After 9 days, satisfactory improvement was seen in the patient and the breathlessness was also reduced from grade 5 to grade 3 on MRC scale [75]. Improvement was also observed in joint pain and body ache which was frequent before the treatment with Pippali Vardhaman Rasayana.

From the study it was concluded that Pippali alleviated the factor 'Ama' (known as endogenous waste material). This factor is responsible for occurrence of autoimmune disease. Pippali thus resulted in the correction of immune system.

2. *Cordyceps sinensis*: Wang et al. carried out a study on bleomycin induced pulmonary fibrosis in mice [76, 77]. Both the preventive and therapeutic effects were studied using C. sinensis which is a fungus used in the traditional Chinese medicines. It is a tonic which soothes the lungs for the treatment of respiratory disorders and fatigue. The preventive effect was studied 48 hours prior to administration of bleomycin and therapeutic effects were studied (4 days after bleomycin administration). It was observed that fibrosis was improved significantly in comparison to placebo. Anti-fibrotic interferon (IFN-ϒ) shows significant increase, whereas transforming growth factor (TGF-β) and IL-ϒ decrease tremendously. From the overall study, it was suggested that Cordyceps sinensis may act through type-I and type-II cytokine imbalance in the lung tissues.
3. *Astragaloside*: Astragaloside possesses anti-fibrotic, immunoregulatory and anti-inflammatory properties [78]. It is obtained from a herb named 'Radix astragali'. The effect was shown in a mouse model with bleomycin administration. Bleomycin is known for its property of inducing inflammation in early stages followed by fibrotic response. When astragaloside was administered 1 day after bleomycin administration, it significantly decreased the amount of hydroxyproline in pulmonary fibrosis in rats mainly through its anti-protease activity [79].
4. *Salviae Miltiorrhizae Radix (SMR) and its extract IH764-3*: This extract was studied for its anti-fibrotic activity over the bleomycin induced fibrosis in rats. When given after day 1 of bleomycin administration, this extract inhibits TGF-β_1 expression and activity of fibroblast growth factor [80–82]. Electron microscopy revealed that before administration of SMR, in the control treated bleomycin group, dense fibrosis was found in the lung interstitium with the presence of the distorted cells. Many abnormal lamellar bodies and cellular structures detached from their basement membrane were present. But in SMR treated animals, less distorted and few abnormal cellular bodies were observed.
5. *Isoliensinine (ILS)*: It is an alkaloid extracted from the seeds of Nelumbo nucifera Gaertn [83]. Bleomycin was administered in animal model followed by the administration of ILS. It was observed that ILS alleviated the lung inflammation by preventing the increase in hydroxyproline [84]. It was suggested that ILS enhanced the activity of superoxide dismutase. It also inhibits the tumour necrosis factor (TNF-α) and TGF-β_1.
6. *Triptolides*: It is a diterpenoid used in the treatment of autoimmune and anti-inflammatory agent against rheumatoid arthritis and encephalomyelitis [85, 86]. From triptolide, a water soluble extract named PG-490-88 was observed. This extract was further evaluated for its anti-fibrotic properties [87]. Mice were used as an animal model and were administered bleomycin. This compound inhibited bleomycin induced fibrosis. Myofibroblasts were also reduced 5 days after administration of bleomycin TGF-β_1 and TGF-β gene expression both were decreased in the animals which were treated with PG 490-88.
7. *Curcumin*: It is one of the most interesting herbs which is used as a dietary herb used in India and China as well. It is a polyphenolic compound obtained from Curcuma longa. It is used as an anti-oxidant [88, 89], anti-inflammatory [90] and anti-carcinogenic [91, 92] agent. Protective effect of curcumin was studied over

bleomycin model [93] and it was concluded that curcumin reduces the hydroxyproline content in lungs [94] when administered after bleomycin. Also, it inhibits TGF-β_1 and TGF-β at transcriptional and translational levels [95].

8. *Rosemary leaves extract*: Bahri Sana et al. investigated the use of Rosmarinus officinalis (RO) which is an aromatic plant belonging to Lamiaceae family. It is a herb that is used as a flavouring agent and an anti-oxidant in food and cosmetic industry. Because it contains polyphenols, so it is widely used in folk medicines. The dried leaves possess anti-oxidant, anti-cancer and anti-inflammatory properties. Carnosic acid and Rosmarinic acid are the phytochemicals of this herb. Carnosic acid can be widely used as an anti-oxidant, anti-microbial and anti-tumour agent [96].

Rosmarinic acid is also widely used as an anti-inflammatory, anti-oxidant, anti-fibrotic, chemoprotective and neuroprotective agent. A study was carried out to investigate the effects of R. officinalis on the lung fibrosis. Fibrosis was induced by bleomycin (BLM). Wistar rats were used as an experimental animal. The rats were administered single dose of bleomycin and R. officinalis was administered intraperitoneally three days later. This was continued for four weeks. This group is named as BLM/RO1-curative group. On the other hand, R. officinalis was administered two weeks before bleomycin administration and this was continued for 15 days. So, it is named as BLM/RO2-prophylactic group. Anti-oxidant activity of R. officinalis on the lungs was studied thereafter.

The bioactives of plant extract are linked to their composition. For instance, tannins, polyphenols, and flavonoids. The study results showed that rosemary extract has better reducing activity than the ascorbic acid which was taken as a positive control. It shows that rosemary extract has high amounts of polyphenols. Also, the study reveals that RO has high free radical scavenging activity than positive control. Because it is believed that in human body, the rate of anti-oxidants must be in equilibrium with the reactive oxygen species. It is important so as to prevent the oxidative stress. So, the levels of some oxidative stress indicators were also evaluated in the study. The level of GSH (reduced glutathione) is linked with the presence of certain enzymes. For instance, glutathione peroxide, glutathione reductase and glutathione-S-transferase (GST). The level of GST and thiol group is significantly decreased after bleomycin administration. GST and catalase are the protective enzymes that have the ability to remove the toxins that result from oxidative stress, chemicals and metabolites from cells. RO when added to both curative and preventive treatment significantly increases the level of GST and thiol group in lungs.

The activated phagocytes in the BLM induced pulmonary fibrosis in rats generate huge amount of reactive oxygen species (ROS), for instance, hydroxyl radicals, superoxide anion, hydrogen peroxide. Although rosemary extract contains large quantity of both the carnosic acid and rosmarinic acid. But it is difficult to conclude which one of these molecules has better anti-fibrotic action or it is due to their synergistic effect. Rosmarinic acid is believed to have anti-fibrotic effect in carbon tetrachloride induced liver fibrosis in rats by inhibiting TGF-β_1 and CTGF

expression in the liver cells, and also it inhibits the hepatic stellate cell proliferation. Carnosic acid, on the other hand, can reduce the increased level of ROS induced by UV which initiates both the anti-oxidant and anti-fibrotic activity.

Catalase plays a vital role in maintaining the hydrogen peroxide homeostasis in cells; as it can convert 6 million molecules of hydrogen peroxide to water and oxygen per minute. Our study revealed that bleomycin induced decrease in the catalase level in the lungs. On the contrary to this, Odajima et al. demonstrated that the decrease in the level of catalase is transient, and it rise up again after 21 days. This suggests that during fibrosis, the cellular dynamics also change which brings drastic changes in the level of catalase. The catalase activity in BLM/RO1 and BLM/RO2 is restored after certain time suggesting that RO might have modulated the cellular dynamics during the on-going process of fibrosis.

9. *Hirsutella sinensis mycelium (HSM)*: Huang et al. carried out a study using a Chinese medicine, Hirsutella sinensis mycelium [97] that is an anamorph of Cordyceps sinensis. C. sinensis possess various therapeutic functions and used as an anti-cancer, anti-diabetic, anti-oxidant, anti-inflammatory and immune-modulatory agent [98–101]. H. sinensis has also emerged as a beneficial therapeutic agent which is used as a substituent of C. sinensis [102]. The ethanolic extract of HSM suppresses IL-1β and IL-18 secretion as suggested by the earlier studies [103]. Studies have also shown that C. sinensis leads to reduction of liver fibrosis by inhibition of TGF-β1, α- smooth muscle actin (α-SMA) and collagen type-I and type-II expression. Chen at al observed that C. sinensis is able to reduce the lung fibrosis too in the rats [104]. In this study, an attempt has been made to study whether the oral intake of ethanolic extract of HSM is able to reduce the lung fibrosis and inflammation in mice.

In general, TGF-β1 is a cytokine that promotes the development of pulmonary fibrosis. TGF-β1 is responsible for differentiation of fibroblasts into myofibroblasts. This helps in the promotion of excessive collagen deposition and leads to inflammation of cells [105]. Expression of α-SMA leads to differentiation of fibroblasts into myofibroblasts. When the study was carried out in animal models, the enhanced expression of TGF-β1 was observed in the lungs of animal models leads to the confirmation of lung fibrosis [106, 107]. So, inhibition of TGF-β1 (fibrogenic cytokine) should be the strategy for treating IPF. Furthermore, NLRP3 inflammasome plays an important role in the development of fibrosis by promoting TGF-β1 signalling. When BLM treatment was given to the mice, it increases the production of reactive oxygen species (ROS) and leads to the development of lung fibrosis [108]. ROS further triggers the formation of NLRP3 inflammasome [109]. Oxidative stress induced by ROS leads to the expression of anti-oxidant enzyme, for example superoxide dismutase (SOD) which is used for conversion of superoxide radicals to hydrogen peroxide [110]. But in case of BLM induced fibrosis, SOD expression is reduced [111].

So, when HSM was administered to animal model, it inhibits TGF-β1 and α-SMA in lung fibroblasts. It was found that it helps in restoring SOD expression in TGF-β1

and this leads to inhibition of reactive oxygen species production. Furthermore, it reduces the expression of NLRP3 inflammasome and enhances the expression of SOD. All these findings lead to the conclusion that HSM can be used in the treatment of pulmonary fibrosis.

10. *Saffron (Crocus sativus)*: Mehrzad Bahtouee et al. investigated the use of a traditional spice which is cultivated in most of the countries like Turkey and Spain [112]. Other than the use of this herb in cooking, it can be used as an anti-depressant, anti-asthmatic, anti-carcinogenic and oxytocic [113, 114]. It is useful in respiratory malignancy due to its cytotoxic effect. Safranal and crocin are the ingredients of saffron which are known to possess anti-tussive effect in guinea pigs [115, 116]. However, it is still not clear how saffron affects the lung fibrosis in spite of having anti-oxidant and radical scavenging property [117].

To evaluate potential of saffron in treatment of lung fibrosis, a study was carried out in bleomycin induced fibrosis involving male Wistar rats as animal model. This is because rats have the same enzymatic and histopathologic changes that take place in human beings in IPF [118, 119]. The rats were instilled with bleomycin intratracheally. The aqueous extract of saffron was given in two different bleomycin treated groups for 28 days.

Fibrotic stage begins after 14 days of bleomycin injection which results in imbalance between free radicals and anti-oxidants in the lungs. Malonidialdehyde (MDA) level was tremendously high in the bleomycin induced group compared to control. MDA level was dramatically decreased in the group receiving saffron. Inflammatory cytokine (TNF-α) level was increased in this study. But the saffron treatment prevented this event. Masson staining is the best indicator of fibrosis which was revealed in bleomycin treated animals. But with the saffron treatment, it was clearly reduced in the lungs of bleomycin treated rats. This study indicated that in future saffron can be one of the promising agents that can be used to treat IPF in human trials.

11. *Citrus alkaline extract (CAE)*: Fanchao Feng et al. conducted a study to investigate the use of citrus in treatment of fibrosis. Citrus is a fruit that is cultivated worldwide and in China it is used as a herbal medicine that is used to expel the phlegm and it is used in the treatment of many pulmonary diseases. The main constituents of citrus are flavonoids, volatile oils and alkaloids [120]. Citrus is used for its anti-microbial, anti-coagulant, anti-oxidant and anti-fibrotic properties. It is used in the treatment of various diseases like hypertension, ulcerative colitis, lung and liver fibrosis [121–123].

IPF can be considered as a age related disease or it occurs primarily at the age of 65 [124] and the various age related mechanisms, for instance, mitochondrial dysfunction, genome instability, cellular senescence, etc. are considered as potential mechanisms that trigger IPF [125].

Cellular senescence is a process in which cells undergo growth arrest, which is triggered by telomere attrition, DNA damage, instability in certain processes. For example, development, ageing and tissue repairing [126]. Senescent cells retain their viability, activation of $P16^{INK4a}$ and P_{21}, increased level of senescence associated β-galactosidase (SA-β-Gal) activity, changes in senescence associated secretory phenotype (SASP). Various cytokines and chemokines are involved in this activity [127, 128]. In this way, senescence is considered detrimental for IPF patients and if these senescent cells are eliminated, it will be very beneficial for treating IPF patients [129, 130]. The mechanism behind the cellular senescence has been related to the tumour suppressor protein (P53) so far. Lung fibroblasts in response to some stimuli differentiate into myofibroblasts and produce cytokines and ECM. The senescent fibroblasts over-secrete α-SMA and exhibit a myofibroblast like phenotype, so as to increase pulmonary fibrosis [131]. So, in order to manage IPF, senescent fibroblasts must be mediated first to treat IPF. The level of PGE_2 is also reduced in IPF patients because the key enzyme (COX-2) fails to be upregulated. COX-2 is also involved in cellular senescence [132, 133].

A study was carried out using CAE to investigate its inhibitory effects over the fibroblasts to modulate the pulmonary fibrosis. For the assessment, the mice were instilled with bleomycin and lung fibrosis was induced. CAE was administered to mice at the calculated doses of 32, 64 or 96 mg/kg/day and Pirfenidone (300 mg/kg/day) for 28 days. Firstly, body weight was monitored which shows weight if mice receiving bleomycin rapidly lose weight in first 10 days, whereas CAE treatment compromised this weight loss within 7 days. The levels of TGF-β_1 and TNF-α increased in the bleomycin instilled mice, but it began to decrease after CAE/pirfenidone treatment. Western blot technique confirms that CAE could decrease expression of α-SMA in the lungs of mouse. Immunofluorescence staining technique was carried out to analyse the senescent biomarkers in fibrotic lungs of mice which shows bleomycin increase the levels of senescence biomarkers P_{21} and $P16^{INK4a}$. This confirms that fibroblasts exhibit senescence in fibrotic lungs. After administration of CAE, the level of these biomarkers was downregulated. CAE significantly decreased the SA.β.Gal activity (Fig. 15.5).

CAE induced COX-2 with time and in a dose dependent manner. But this stimulation reduced to a certain extent with time. Considering these results and the factor that COX-2 is involved in senescence and also stabilises P-53, we can conclude that CAE activates COX-2 and inhibit expression of P-53 and therefore exerts anti-senescence effect. This limits the pathogenesis of IPF. These findings elucidated that CAE can be used as a new agent in treating IPF.

12. *Ginseng Radix Rhizoma*: Bai Yunping et al. carried out an experimental study on rats using a Chinese herbal formula-JinshuiHuanxian formula (JHF). JHF was prepared using 11 medicinal herbs including Ginseng Radix, Ophiopogonis Radix, Rehmanniae Radix, etc. The rats were instilled with bleomycin intratracheally to induce pulmonary fibrosis. After that JHF was orally administered along with Pirfenidone from 1 to 42 days after bleomycin instillation. It was observed that the JHF treated rats possess higher levels of

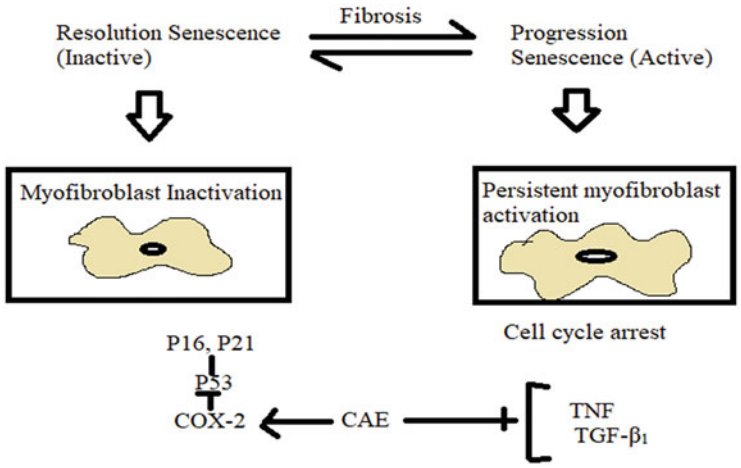


Fig. 15.5 Proposed mechanism of CAE mediated inhibition

superoxide dismutase, catalase and glutathione, whereas JHF has lowered down the collagen deposition. Further it restores the pulmonary function few days after instillation of bleomycin. JHF increased the expression of Nuclear factor erythroid-2-related-factor (Nrf2) and inhibits the expression of NADPH oxidase. JHF inhibited TGF-β_1, which further inhibits differentiation of fibroblasts into myofibroblasts [134]. From the observations, it was concluded that JHF performed long term effects on the pulmonary fibrosis and JHF was proved to be a potential natural drug in the treatment of IPF.

13. *Angelica Sinensis Polysaccharide*: Qian Weibin et al. conducted an investigation using A. sinensis which is a perennial herb. Generally, IPF is associated with accumulation of extracellular matrix and lung fibroblasts. The main active constituent of Angelica sinensis is Angelica sinensis polysaccharide (ASP) that plays a vital role in haemopoiesis, anti-tumour activity and immunomodulation. According to certain evidences, pathophysiology of many processes is dependent on the long non-coding RNAs (LncRNAs). But in case of IPF, the roles of lncRNA and ASP remain unclear. So, an attempt has been made to study the effect of ASP in IPF and its interaction with lncRNA DANCR (Differentiation antagonising non-protein coding RNA). LnRNA's play important roles in cell growth regulation, apoptosis, migration, drug resistance etc. However, lncRNA DANCR is a newly identified lncRNA that plays a vital role in cell proliferation and migration. So, the investigation involves the treatment of Sprague Dawley rats with bleomycin and the treatment of alveolar type-II epithelial cells (RLE-6TN) with TGF-β1. As per the results, ASP treatment leads to suppression of IPF in rats and also it suppresses fibrogenesis in RLE-6TN cells. LncRNA DANCR was downregulated both in the lung tissue of rats and RLE-6TN cells after treatment with ASP. DANCR binds with the AUF-1 (AU binding factor-1). This upregulates the FOXO3 mRNA and finally the protein levels [135]. This

way, DANCR can be served as an important therapeutic target in IPF treatment with ASP.

14. *Feifukang (FFK)*: Li Hongbo et al. demonstrated the amelioration of pulmonary fibrosis using Feifukang (known as pulmonary rehabilitation mixture consisting of eight herbs—Astragalus membranaceus, Codonopsis pilosula, Ophiopogon japonicus, Schisandra chinensis, Panax notosinseng, Bulbus fritillariae thunbergii, Rhizoma anemarrhenae and Glycyrrhiza uralensis. To carry out this study, RNA sequencing was combined to network pharmacology to analyse the multi-pathways of FFK in the treatment of pulmonary fibrosis. Mice were instilled with bleomycin intratracheally followed by administration of FFK on day 2. FFK treatment reduced the collagen deposition and α-SMA. JAK-STAT signalling pathway is also thought to be linked with FFK.

JAK-STAT is a chain of interactions that occur between proteins in a cell and is responsible for various processes. For example, cell division, cell death and tumour formation. This pathway helps in building communication between chemical signals from outside the cell to the nucleus. This results in the activation of various genes through a process called transcription. JAK1, STAT-3 and ADAM-17 are the structural genes of this process [136].

From the findings of the study, it was concluded that the level of those structural genes increases in pulmonary fibrosis whereas FFK remarkably decreases the levels of these structural genes as compared to the level in the bleomycin treated rats. Results remarkably explained the efficacy of FFK in the treatment of pulmonary fibrosis.

15. *Green tea extract*: Marta Figueiredo et al. evaluated the green tea extract to evaluate its efficacy in treating IPF. Epigallocatechin-3-gallate (EGCG) is an anti-oxidant which is present in the green tea extract. The study was carried out in 20 individuals suffering from IPF and scheduled to undergo a biopsy. Half of the patients were given EGCG capsules of dose 600 mg for a period of 14 days. While the other group was left untreated. Also, lung tissue samples of five healthy volunteers were named as 'controls'. The fibrotic proteins (α-SMA, SMAD3 and fibronectic type-1) were found normal in the patients treated with EGCG supplements which suggested the reversion of the fibrotic state of lungs [137].

Cartilage oligomeric matrix protein (COMP) and periostin are the two biomarkers of IPF progression, which show a sufficient drop in patients treated with EGCG capsules.

16. *Arenaria Kansuensis*: Cui Yulei et al. carried out an experimental study of β-carboline (A.kansuensis) to determine its efficacy as an anti-pulmonary fibrotic agent with its possible mechanism. A fraction of A.kansuensis extracted with ethyl acetate was administered daily with dose of 50, 100 and 150 mg/kg in bleomycin induced pulmonary fibrotic rats. An in-vitro study was also carried

out to study epithelial-mesenchymal transition (EMT) effect firstly through lipopolysaccharide induced $RAW_{264.7}$ cell model and secondly through TGF-β1 induced A_{549} cell model [138].

According to the results, a strong anti-pulmonary effect was shown by A. kansuensis at a dose of 150 mg/kg. The body weight and survival rate of rats both were increased after alkaloidal treatment. A total number of 12 β-carboline alkaloids were found in the extract and then all suppress the inflammatory cytokines (TNF-α, IL-6, IL-1β) by inhibiting phosphorylation of NF-Kb/p65 which is the main reason of anti-fibrogenic effect of β-carboline alkaloids. Along with that the extract has significantly inhibited the deposition of collagen and expression of TGF-β1 and α-SMA.

17. *Eliptae Herba*: Xin et al. investigated a traditional Chinese medicine which is used for treatment of lung disorders from the ancient times, for its anti-fibrotic action along with its mechanism. The extract of E. Herba (EXT) was prepared using 80% ethanol. After the intractracheal instillation of bleomycin in rats, EXT was administered orally along with Eclipta Saponin A (ESA). In comparison to BLM group, EXT administration ameliorated the pulmonary fibrosis by increasing superoxide dismutase (SOD) and decreasing the levels of $_{2/3}$were also alleviated with EXT administration. Large amounts of saponins were isolated from E. prostrata and evaluated by BLM induced model [139].
18. *Danshen (Salvia miltiorrhiza Bunge)*: Yongming Pan et al. studied a traditional herb which was used in combination with other herbs to treat various respiratory disorders like pneumonia and pulmonary fibrosis. The active constituent present in Danshen is salvianolic acid A (SAA). Anti-fibrotic activity of SAA was evaluated in bleomycin induced fibrosis in rats. Increased amounts of collagen deposits were observed in bleomycin induced rats. But with the administration of SAA, the proliferation of fibroblasts into myofibroblasts was reduced. This is because of cell cycle arrest and apoptosis. Cell cycle related proteins (Cyclin D_1, Cyclin E_1 and Cyclin B_1) also show decrease in their expression. While the expression of P_{53} and P_{21} in SAA treated cells was increased. BCl-2 protein (apoptotic protein) decrease in a dose dependent manner while caspase-3 protein increase after SAA treatment. The conclusion comes out of the study is that SAA alleviate pulmonary fibrosis by inhibiting the proliferation of fibroblasts and induction of apoptosis which occurs due to P_{53} dependent growth arrest. From the results, we can interpret that SAA should be considered as a novel therapeutic agent in IPF treatment [140].
19. *Dendrobium officinale*: Chen Jianhui et al. elicit the benefits of polysaccharides of Dendrobium officinale (PDO) for the treatment of pulmonary fibrosis. PDO ameliorates the pulmonary fibrosis and inflammation induced by bleomycin instillation in rats. The mechanism was associated with inactivation of TGF-$β_1$-$Smad_{2/3}$signalling pathway. Also it blocked the proliferation of fibroblasts into myofibroblasts by inhibiting total $Smad_{2/3}$, $pSmad_{2/3}$, expression of collagen-1 and fibronectin in a dose dependent manner [141].

20. *Cryptotanshinone (CPT)*: Zhang Qianyu et al. investigated the use of CPT as an anti-fibrotic agent. The expression of NIH/3T3 and HPF cells was measured and it was found out that CPT inhibited their expression in a concentration and time dependent manner. The level of α-SMA, which was upregulated in NIH/3T3 cells was stimulated by TGF-β_1 and afterwards it was decreased after the administration of CPT.

The hydroxyproline content which was higher in bleomycin induced mice was decreased by the treatment of CPT. The levels of collagen-I and α-SMA which rise up during bleomycin induced fibrosis were also downregulated after CPT administration. Flow cytometry analysis was carried out, which indicated that frequency of T-cells, macrophages was increased in BLM induced group and the population of these immunocytes decrease after administration of CPT [142].

21. *Quercetin*: Zhang Xingcai et al. carried out the study on the use of quercetin, which is a flavonoid and found in variety of herbs. It is known for its anti-fibrotic function. The administration of bleomycin or TGF-β in human embryonic lung fibroblasts (HELF), upregulated the level of sphingosine-1-phosphate (S1P), sphingosine kinase 1 (SphK1) and sphingosine-1-phosphate-lyase (S1PL). But this increase in levels of S1P, SphK1 and S1PL was overcome by quercetin administration. From the study, it was concluded that quercetin ameliorates pulmonary fibrosis by inhibition of SphK1/S1P signalling [143].

There is substantial amount of information available regarding herbal formulations for fibrosis mostly published in Chinese or Japanese journal. Most of them demonstrated the herbal medicines that prevent the pulmonary fibrosis in rodents using bleomycin induced lung damage. The reports of clinical trials demonstrate that herbal remedies improvise the symptoms like complications in respiration and lung performance in IPF patients along with increase in survival rate. Nevertheless, the herbal medications must be used with caution for the given reasons:

1. Most of the conclusions are drawn using bleomycin induced fibrosis in rats. But it lacks some of the important features w.r.t the progressive nature of IPF in humans.
2. The detailed investigations of the mechanisms behind herbal formulations are challenging. Because sometimes, polyherbal compositions are used in the treatment of IPF which contain several herbs and each herb contains various bioactive components with different mechanisms.
3. The published trials had either methodological limitations and even some flaws are there that cannot be described. Sometimes, small number of patients are enrolled in a study.

15.8 Marketed Formulations (Table 15.1)

Table 15.1 Herbal marketed formulations for the treatment of pulmonary fibrosis

S. No.	Marketed formulations	Ingredients	Dose	Use
1	Tulsi capsules	Ocimum tenuifloram	1–2 tulsi capsules two times a day, after meals	Breathlessness and dry cough
2	Curcumin capsules	Curcuma longa	2 capsules with plain water twice a day after meals	Chronic cough and shortness of breathe
3	Cap. Aller-G-Care	Neem (Azadirachta indica); Ashwagandha (W. somnifera); Haridra (Curcuma longa); Shirish (Albizia lebbeck)	1–2 capsules taken twice a day after meals	Anti-microbial and anti-inflammatory properties
4	Giloy capsules	Extracts of Tinospora cordifolia	1 capsule with plain water after meals twice daily	Anti-microbial and healing properties
5	Praanrakshak capsules	Anantmool (Tylphora asthamatica); Vasa (Adhatoda vasica); Kantkari (Solanum xanthocarpum); Mulethi (Glycyrrhiza glabra); Bharangi (Clerodendrum serratum); Shirish (Albizia lebbeck); Twak (Cinnamomum zeylanica)	Taken twice, after breakfast and dinner in the form of decoction	Anti-microbial properties and heal lung tissues

References

1. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J et al (2011) An official ATS/ERS/ALAT statement: idiopathic pulmonary fibrosis: evidence based guidelines for diagnosis and management. Am J Respir Crit Care Med 183:788–824
2. Cool CD (2016) Idiopathic interstitial pneumonias: clinical manifestations and pathology (Internet). Update Inc, Waltham MA
3. Nalysnyk L, Cid-Rufaza J, Rotella P, Esser D (2012) Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. Eur Respir Rev 21(126):355–361
4. Navaratnam V, Fleming KM, West J, Smith CJ, Jenkins RG, Fogarty A et al (2011) The rising incidence of idiopathic pulmonary fibrosis in UK. Thorax 66:462–467
5. Raghu G, Chen SY, YVereh WS, Maroni B, Li Q, Lee YC et al (2014) Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence prevalence and survival, 2001-11. Lancet Respir Med 2:566–572
6. Hopkins RB, Burke N, Fell C, Dion G, Kolb M (2016) Epidemology and survival of idiopathic pulmonary fibrosis from national data in Canada. Eur Res 48:187–195

7. Strongman H, Kausar I, Maher TM (2018) Incidence, prevalence and survival of patients with idiopathic pulmonary fibrosis in the UK. Adv Ther 35:724–736
8. Gribbin J, Hubbard RB, le Jeune I, Smith CJ, West J, Tata LJ (2006) Incidence and mortality of Idiopathic Pulmonary Fibrosis and sarcoidiosis in the UK. Thorax 61:980–985
9. Verma S, Slutsky AS (2007) Idiopathic pulmonary fibrosis- new insights. N Engl J Med 356 (13):1370–1372
10. Harari S, Caminati A (2010) IPF: new insight on pathogenesis and treatment. Allergy 65 (5):537–553
11. White ES, Lazar MH, Thannickal VJ (2003) Pathogenetic mechanisms in usual interstitial pneumonia/ idiopathic pulmonary fibrosis. J Pathol 201(3):343–354
12. Gimenez A, Duch P, Puig M, Gabasa M, Xaubet A, Alcaraz J (2017) Dysregulated collagen homeostasis by matrix stiffening and TGF-β in fibroblasts from idiopathic pulmonary patients: role of FAK/Akt. Int J Mol Sci 18:11
13. Visscher DW, Myers JL (2006) Histologic spectrum of idiopathic interstitial pneumonias. Proc Am Thorac Soc 3(4):322–329
14. Chen H, Chen Q, Jiang CM, Shi GY, Sui BW, Zhang W et al (2017) Triptolide suppresses paraquat induced idiopathic pulmonary fibrosis by inhibiting TGFB1-dependent epithelial mesenchymal transition. Toxicol Lett 284:1–9
15. Goldstein R, Polgar P (1982) The effect and interaction of bradykinin and prostaglandins on proteins and collagen production by lung fibroblasts. J Biol Chem 257:8630–8633
16. Lama V, Moore BB, Chistensen P, Toews GB, Peters- Golden M (2002) Prostaglandin E_2 synthesis and suppression of fibroblast proliferation by alveolar epithelial cells is cyclooxygenase-2-dependent. Am J Respir Cell Mol Biol 27:752–758
17. Shahar I, Fireman E, Toilsky M et al (1999) Effect of endothelin-1 on alpha smooth muscles actin expression and on alveolar fibroblast proliferation in interstitial lung diseases. Int J Immunopharmacol 21:759–775
18. Maher TM, Evans IC, Bottoms SE, Mercer PF, Thorley AJ, Nicholson AG (2010) Diminished prostaglandin E_2 contributes to the apoptosis paradox in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 182(1):73–82
19. Reynolds HY, Fulmer JD, Kazmierowski JA, Roberts WC, Frank MM, Crystal RG (1977) Analysis of cellular and protein content of broncho-alveolar lavage fluid from patients with idiopathic pulmonary fibrosis and chronic hypersensitivity pneumonitis. J Clin Invest 59:165–175
20. Rudd RM, Haslam PL, Turner Warwick M (1981) Cryptogenic fibrosing alveolitis. Relationships of pulmonary physiology and bronchoalveolar lavage to response to treatment and prognosis. Am Rev Respir Dis 124:1–8
21. Wells AV, Hansell DM, Haslam PL et al (1998) Bronchoalveolar lavage cellularity. Cryptogenic fibrosing alveolitis compared with the fibrosing alveolitis of systemic sclerosis. Am J Respir Crit Care Med 157:1474–1482
22. Seibold MA, Wise AL, Speer MC, Steele MP, Brown KK, Loyd JE (2011) A common MUC 5B promoter polymorphism and pulmonary fibrosis. N Engl J Med 364(16):1503–1512
23. Hunt LW, Colby TV, Weiler DA, Sur S, Butterfield JH (1992) Immunofluorescent staining for mast cells in idiopathic pulmonary fibrosis: quantification and evidence for extracellular release of mast cell tryptase. Mayo Clin Proc 67:941–948
24. Pesci A, Bertorelli G, Gabrielli M, Olivieri D (1993) Mast cells in fibrotic lung disorders. Chest 103:989–996
25. Walls AF, Bennett AR, Godfrey RC, Holgate ST, Church MK (1991) Mast cell tryptase and histamine concentration in bronchoalveolar lavage fluid from patients with interstitial lung disease. Clin Sci 81:183–188
26. Kawanamio FVJ, Fulmar JD, Crystal RG (1979) Ultrastructure of pulmonary mast cells in patients with fibrotic lung disorders. Lab Investig 40:717–734
27. Armanios MY, Chen JJ, Cogan JD et al (2007) Telomerase mutations in families with idiopathic pulmonary fibrosis. N Engl J Med 356(13):1317–1326

28. Turner Warwick MB, Burrows AJ (1980) Cryptogenic fibrosing alveolitis clinical features and their influence on survival. Thorax 35:171–180
29. Carrington CB, Gaensler EA, Coutu RE, Fitzgerald MX, Gupta RG (1978) Natural history and untreated course of usual and desquamative interstitial pneumonia. N Engl J Med 298:801–809
30. Americal Thoracic Society (2000) Idiopathic pulmonary fibrosis: diagnosis and treatment: International consensus statement. Am J Respir Crit Care Med 161:646–664
31. Kondoh Y, Taniguchi H, Kawabata Y, Yokoi T, Suzuki K, Takag K (1993) Acute exacerbation in idiopathic pulmonary fibrosis. Analysis of clinical and pathologic findings in three cases. Chest 103:1808–1812
32. Tsukamoto K, Cluda K, Hayakawa H, Sato A, Nakajima Y, Doi O et al (1997) Prediction of outcome after acute exacerbation of idiopathic interstitial pneumonia. Nihon KyobuShikkan Gakkai Zasshi 35:746–754
33. Panos RJ, Mortenson RL, Nichol SA, King TE (1990) Clinical deterioration in patients with idiopathic pulmonary fibrosis: causes and assessment. Am J Med 4:396–404
34. Gribben J, Hubbard RB, Le Jeune I, Smith CJP, West J, Tata LJ (2006) Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidiosis in the UK. Thorax 61:980–985
35. Wells AV, Hogaboam CM (2007) Update in diffuse parenchymal lung disease. Am J Respir Crit Care Med 175:655–660
36. Lederer DJ, Martinez FJ (2018) Idiopathic pulmonary fibrosis. N Engl J Med 378:1811–1823
37. Hutchinson J, Fogarty A, Hubbard R (2015) Global incidence and mortality of IPF: a systematic review. Eur Respir J 46:795–806
38. Pardo A, Selman M (2006) Matrix metalloproteases in aberrant fibrotic tissue remodelling. Proc Am Thorac Soc 3:383–388
39. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G (2006) Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Rest Crit Care Med 174:810–816
40. Frankel SK, Schwarz MI (2009) Update in idiopathic pulmonary fibrosis. Curr Opin Pulm Med 15(5):463–469
41. Misumi S, Lynch DA (2006) Idiopathic pulmonary fibrosis/usual interstitial pneumonia: imaging diagnosis, spectrum of abnormalities and temporal progression. Proc Am Thorac Soc 3(4):307–314
42. Lynch DA, Sverzellati N, Travis WD, Brown KK, Colby TV, Galvin JR et al (2017) Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society white paper. Lancet Respir Med 6(2):138–153
43. Patel NM, Lederer DJ, Borczuk AC, Kawut SM (2007) Pulmonary hypertension in idiopathic pulmonary fibrosis. Chest 132(3):998–1006
44. Martinez FJ, Flaherty K (2006) Pulmonary function testing in idiopathic interstitial pneumonias. Proc Am Thorac Soc 3(4):315–321
45. Swigris JJ, Swick J, Wamboldt FS et al (2009) Heart rate recovery after 6 minute walk test predicts survival in patients with idiopathic pulmonary fibrosis. Chest 136(3):841–848
46. Raghu G, Remy-Jardin M, Myers JL et al (2018) Diagnosis of IPF. An official ATS/ERS/JRS/ALAT. Clinical practice guideline. Am J Respir Crit Care Med 198(5):e44–e68
47. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK (2011) An official ATS/ERS/JRS/ALAT statement. Idiopathic pulmonary fibrosis: evidence based guidelines for diagnosis and management. Am J Respir Crit Care Med 183(6):788–824
48. Barggli E, Piccioli C, Rosi E, Torricelli E, Turi L, Piccioli E et al (2019) Pirfenidone and Nintedanib in idiopathic pulmonary fibrosis: real life experience in an Italian referral centre. Pulm J 25(3):149–153
49. Rudd RM, Haslam PL, Turner-Warwick M (1981) Cryptogenic fibrosing alveolitis relationships of pulmonary physiology and bronchoalveolar lavage to treatment and prognosis. Am Rev Respir Dis 124:1–8
50. Panos RJ, Mortenson R, Niccoli SA, King TE Jr (1990) Clinical deterioration in patients with IPF: causes and assessment. Am J Med 88:396–404

51. Johnston ID, Gomm SA, Kalra S, Woodcock AA, Evans CC, Hind CR (1993) The management of cryptogenic fibrosing alveolitis in three regions of United Kingdom. Eur Respir J 6:891–893
52. Meier-Sydow J, M Rust H, Kronenberger C, Thiel M, Amthor H (1979) Long term follow up of lung function parameters in patients with IPF treated with prednisone and azathioprine or D-penicillamine. Prax Pneumol 33:680–688
53. Meier Sydow J, Weiss SM, Buhl R, Rust M, Raghu G (1994) IPF: current clinical concepts and challenges in management. Semin Respir Crit Care Med 15:77–96
54. Raghu G, Depaso WJ, Cain K, Hammar SP, Wetzel CE, Dreis DF et al (1991) Azathioprine combined with prednisone in the treatment of IPF: a prospective, double-blind randomized, placebo controlled clinical trials. Am Rev Respir Dis 137:181–185
55. Winterbauer RH, Hammer SP, Hallman KO, Hays JE, Pardee NE, Morgan EH et al (1978) Diffuse interstitial pneumonitis clinicopathologic correlations in 20 patients treated with Prednisone/Azathioprine. Am J Med 65:661–672
56. Johnson MA, Kwan S, Snell NJC, Nunn AJ, Darbyshire JH, Warwick MT (1989) Randomized controlled trial comparing prednisolone alone with cyclophosphamide and low dose prednisolone in combination in cryptogenic fibrosing alveolitis. Thorax 44:280–288
57. Ziesche R, Hofbauer E, Wittmann K, Petkov V, Block LH (1999) A preliminary study of long term treatment with interferon gamma-1b and low dose prednisolone in patients with IPF. N Engl J Med 341:1264–1269
58. Raghu G, Johnson WC, Lockhart D, Mageto Y (1999) Treatment of IPF with a new antifibrotic agent, Pirfenidone. Results of a prospective, open label phase-II study. Am J Respir Crit Care Med 159:1061–1069
59. Behr J, Maier K, Degenkolb B, Krombach F, Vogelmeier C (1997) Antioxidative and clinical effects of high dose N-acetyl cysteine in fibrosing alveolitis: adjunctive therapy to maintenance immunosuppression. Am J Respir Crit Care Med 156:1897–1901
60. Idiopathic Pulmonary Fibrosis (2000) Diagnosis and treatment. International consensus statement: American Thoracic Society (ATS) and European Respiratory Society (ERS). Am J Respir Crit Care Med 161:646–664
61. Douglas WW, Ryu JH, Schroeder DR (2000) Idiopathic pulmonary fibrosis: impact of oxygen and colchicine, prednisone, or no therapy on survival. Am J Respir Crit Care Med 161:1172–1178
62. Selman M, Carrillo G, Salas J, Padilla RP, Perez-Chavira R et al (1998) Colchicine, D-Penicillamine and prednisone in the treatment of idiopathic pulmonary fibrosis: a controlled clinical trial. Chest 114:507–512
63. Collard HR, Ryu JH, Douglas WW, Schwarz MI, Curran-Everett D et al (2004) Combined corticosteroid and cyclophosphamide therapy does not alter survival in idiopathic pulmonary fibrosis. Chest 125:2169–2174
64. King TE Jr, Albera C, Bradford WZ, Costabel U, Hormel P et al (2009) Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. Lancet 374:222–228
65. Wu J-N (2005) An illustrated Chinese materia medica. Oxford University Press, New York
66. Cohen M (2006) Exploring the other side of acupuncture. J Altern Complement Med 12:707–708
67. Huang ST, Chen AP (2008) Traditional Chinese medicine and infertility. Curr Opin Obstet Gynecol 20:211–215
68. World Health Organisation (2007) WHO International standard terminologies on traditional medicine in the western Pacific region. World Health Organisation, Geneva
69. Laveena K, Rajdip R, Thakar AB (2017) Effect of PippaliVardhamanRasayana in interstitial lung disease- A case report. Int Ayur Med J 5(5):1784–1788
70. Acharya YT, Chikitsa S (2009) Choukhamba orientalia, Agnivesha, Charak, Dradabala, editors. Chapter 1 part 3, verse 40, edition. p 40

71. Kumar S, Arya P, Mukherjee C, Singh BK, Singh N, Parmar VS et al (2005) Novel aromatic ester from Piper longum and its analogues inhibit expression of cell adhesion molecules on endothelial cells. Biochemist 44(6):15944–15952
72. Natarajan KS, Narsimhan M, Shanmugasundaram KR, Shanmugasundaram ER (2006) Antioxidant activity of a salt/spice/ herbal mixture against free radical induction. J Ethnopharmacol 105:76–83
73. Sushruta Samhita SA (2010) Chikitsasthana. Chapter 5, verse 12, edition. p 40
74. Debnath S et al (2015) Clinical study on Amavata (Rheumatoid Arthritis) with Virechana karma (Induced purgation) and rasayana (rejuvenation therapy). Int J Ayur Herb Med 5 (2):1659–17001
75. Fletcher CM (1952) The clinical diagnosis of pulmonary emphysema- an experimental study. Proc R Soc Med 45:577–584
76. Jordan JL, Sullivan AM, Lee TD (2008) Immune activation by a sterile aqueous extract of Cordyceps sinensis: mechanism of action. Immunopharmacol Immunotoxicol 30:53–70
77. Chen JL, Chen YC, Yang SH, K YF, Chen SY (2009) Immunological alterations in lupus-prone autoimmune (NZB/NZW) F_1 mice by mycelia Chinese medicinal fungus Cordyceps sinensis induced redistributions of peripheral mononuclear T-lymphocytes. Clin Exp Med 9 (4):277–284
78. Du Q, Chen Z, Zhou LF, Zhang Q, Huang M et al (2008) Inhibitory effects of astragaloside IV on ovalbumin-induced chronic experimental asthma. Can J Physiol Pharmacol 86:449–457
79. Zhang P, Li JP, Yu XH, He PP, Zhang SJ (2007) Effect of astragaloside on Cathepsin B expression in the lung of rats with experimental pulmonary fibrosis. Prog Mod Biomed 7:860–862
80. Miao WN, Dong J, Liu ST, Chen K (2003) Effect of Salvia miltiorrhiza on the change of pulmonary pathology and expression of transforming growth factor beta in pulmonary fibrosis in mice. Pharmacol Clin Chin Mater Med 19:24–25
81. Liu J (1992) Experimental study of the effect of IH 764-3, a potent component isolated from Salviae miltiorrhiza against pulmonary fibrosis. Zhongguo Yi XueKeXue Yuan Xue Bao 14:250–256
82. Lu SJ, Liu YN, Wang HZ (2005) Study of Salvia miltiorrhiza on bleomycin induced pulmonary fibrosis in mice. Chin J Clin Pharmacol Ther 10:514–517
83. Liu S, Wang B, Li XZ, Qi LF, Liang YZ (2009) Preparation, separation and purification of liensinine, isoliensinine and neferine from seed embryo of Nelumbo nucifera GAERTN using high speed counter current chromatography. J Sep Sci 32:2476–2481
84. Xiao JH, Zhang JH, Chen HL, Feng XL, Wang JL (2005) Inhibitory effects of isoliensinine on bleomycin-induced pulmonary fibrosis in mice. Planta Med 71:225–230
85. Brinker AM, Ma J, Lipsky PE, Baskin L (2007) Medicinal chemistry and pharmacology of genus tripterygium (Celastraceae). Phytochemistry 68:732–766
86. Wang Y, Mei Y, Feng D, Xu L (2008) Triptolide modulates T-cell inflammatory response and ameliorates experimental auto-immune encephalomyelitis. J Neurosci Res 86:2441–2449
87. Krishna G, Liu K, Shigemitsu H, Gao M, Raffin TA et al (2001) PG490-88, A derivative of triptolide blocks bleomycin induced lung fibrosis. Am J Pathol 158:997–1004
88. Reddy AC, Lokesh BR (1994) Effect of dietary turmeric (Curcuma longa) on iron induced lipid peroxidation in rat liver. Food Chem Toxicol 32:279–283
89. Kuchandy E, Rao MNA (1990) Oxygen radical scavenging activity of Curcumin. Int J Pharm 58:237–240
90. Srimal RC, Dhawan BN (1973) Pharmacology of diferuloyl methane (Curcumin) a non-steroidal inflammatory agent. J Pharm Pharmacol 25:447–452
91. Azuine MA, Bhide SV (1992) Chemopreventive effect of turmeric against stomach and skin tumours induced by chemical carcinogens in Swiss mice. Nutr Cancer 17:77–83
92. Aggarwal BB, Kumar A, Bhati AC (2003) Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res 23:363–398

93. Venkatesan N, Punithavathi V, Chandrakasan G (1997) Curcumin protects bleomycin-induced lung injury in rats. Life Sci 61:51–58
94. Punitharathi D, Venkatesan N, Babu M (2000) Curcumin inhibition of bleomycin induced pulmonary fibrosis in rats. Br J Pharmacol 131:169–172
95. Xu M, Deng B, Chow YL, Zhao ZZ, Hu B (2007) Effects of curcumin in treatment of experimental pulmonary fibrosis: a comparison with hydrocortisone. J Ethanopharmacol 112:292–299
96. Sana B, Ali RB, Khaoula G, Mona M, Saloua F, Riadu K et al (2017) Prophylactic and curative effect of rosemary leaves extract in a bleomycin model of pulmonary fibrosis. Pharm Biol 55(1):462–471
97. Huang TT, Lai HC, Ko YF, Ojcius DM, Lan YW, Jan M et al (2015) Hirsutella sinensis mycelium attenuates bleomycin induced pulmonary inflammation and fibrosis in vivo. Sci Rep 5:15282
98. Yamaguchi Y, Kagota S, Nakamura K, Shinozuka K, Kunitomo M (2000) Anti-oxidant activity of the extracts from fruiting bodies of cultured Cordyceps sinensis. Phytother Res 14:647–649
99. Rao YK, Fang SH, Tzeng YM (2007) Evaluation of the anti-fibrotic and anti-proliferation tumoral cells activities of Antrodia camphorate, Cordyceps sinensis and Cinnamomum osmophloeum bark extracts. J Ethnopharmaceut 114:78–85
100. Wu Y, Sun H, Qin F, Pan Y, Sun C (2006) Effect of various extracts and a polysaccharide from the edible mycelia of Cordyceps sinensis on cellular and humoral immune response against ovalbumin in mice. Phytother Res 20:646–652
101. Paterson RR, Lima N (2014) Biomedical effects of mushroom with emphasis on pure compounds. Biom J 37:357–368
102. Chen YQ, Wang N, Qu L, Li T, Zhang W (2001) Determination of anamorph of Cordyceps sinensis inferred from the analysis of ribosomal DNA internal transcribed spacers and 5. Biochem Syst Ecol 29:597–607
103. Huang TT et al (2013) Hirsutella sinensis mycelium suppresses interleukin-1β and interleukin-18 secretion by inhibiting both canonical and non-canonical inflammasomes. Sci Rep 3:1374
104. Chen M et al (2012) Protective roles of cordyceps on lung fibrosis in cellular and rat models. J Ethanopharmacol 143:448–454
105. Fernandez IE, Eickelberg O (2012) The impact of TGF-β on lung fibrosis: from targeting to biomarkers. Proc Am Thorac Soc 9:111–116
106. Tanaka K et al (2010) Therapeutic effect of lecithinized superoxide dismutase on bleomycin induced pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol 298:L348–L360
107. Bao Z et al (2014) Expression of suppressor of cytokine signaling in peripheral blood of patients with Idiopathic pulmonary fibrosis. Chin Med J 127:2117–2120
108. Cheresh P, Kim SJ, Tulasiram S, Kamp DW (1832) Oxidative stress and pulmonary fibrosis. Biochem Biophys Acta 2013:1028–1040
109. Said-Sadier N, Ojcius DM (2012) Alarmins, inflammasomes and immunity. Biom J 35:437–449
110. Kinnula VL, Crapo JD (2003) Superoxide dysmutases in the lung and human lung disease. Am J Respir Crit Care Med 167:1600–1619
111. Santo-Silva MA et al (2012) Redox imbalance and pulmonary function in bleomycin induced fibrosis in C57BL/6, DBA/2 and BALB/C mice. Toxicol Pathol 40:731–741
112. Mehrzad B, Hossein F, Khalil P, Euikyung K, Hamid RR, Zahra T et al (2017) Saffron protection against bleomycin induced pulmonary fibrosis in rats. Iran J Toxicol 11:6
113. Javadi B, Sahebkar A (2013) A survey on saffron in major Islamic traditional medical books. Iran J Basic Med Sci 16(1):1–11
114. Rios J, Recio M, Giner R, Manez S (1996) An update review of saffron and its active constituents. Phytother Res 10(3):189–193

115. Samarghandian S, Borji A, Farahmand SK, Afshari R, Davoodi S (2013) Crocus sativus L. (Saffron) stigma aqueous extract induces apoptosis in alveolar human lung cancer cells through caspase dependent pathways activation. Biomed Res Int 2013:3516010
116. Hosseinzadeh H, Ghenaati J (2006) Evaluation of the anti-tussive effect of stigma and petals of saffron (Crocus sativus) and its components, safranal and crocin in guinea pigs. Fitoterapia 77 (6):1446–1448
117. Assimopoulou A, Sinakos Z, Papageorgiou V (2005) Radical scavenging activity of Crocus sativus L extract and its bioactive constituents. Phytother Res 19(11):997–1000
118. Moore BB, Hogaboam LM (2008) Murine models of pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol 294(2):L152–L160
119. Moeller A, Rodriguez-Lecompte JC, Wang L, Gauldie J, Kolb M (2006) Models of pulmonary fibrosis. Drug Discov Today Dis Model 3(3):243–249
120. Feng F, Wang Z, Li R, Wu Q, Gu C, Xu Y et al (2019) Citrus alkaline extracts prevent fibroblast senescence to ameliorate pulmonary fibrosis via activation of COX-2. Biomed Pharmacother 112:108669
121. Fang T, Liu DD, Ning HM, Dan L, Sun JY, Huang XJ et al (2018) Modified citrus pectin inhibited bladder tumour growth through downregulation of galectin-3. Acta Pharmacol Sin 39:12
122. Gao X, Wang C, Ning C, Liu K, Wang X, Liu Z et al (2018) Hepatoprotection of auraptene from peels of citrus fruits against thioacetamide induced hepatic fibrosis in mice by activating farnesoid X-receptor. Food Funct 9:2684–2694
123. Sharifirad M, Varoni IM, Iriti M, Martorell M, Setzer WN, Del MMC et al (2018) Carvacol and human health: a comprehensive review. Phytother Res 32:1675–1687
124. Ryu JH, Moua T, Daniels CE, Hatman TE, Yi ES, Utz JP et al (2014) Idiopathic pulmonary fibrosis: evolving concepts. Mayo Clin Proc 89:1130–1142
125. Meiners S, Eickelberg O, Konigshroff M (2015) Hallmarks of the ageing lung. Eur Respir J 45:807–827
126. Deursen JMV (2014) The role of senescent cells in ageing. Nature 509:439–446
127. Coppe JP, Desprez PY, Krtolica A, Campisi J (2009) The senescence associated secretory phenotype: the dark side of tumour suppression. Annu Rev Pathol 5:99–118
128. Kuilman T, Michaloglov C, Mooi WJ, Peeper DS (2010) The essence of senescence. Genes Dev 24:2463–2479
129. Lehmann M, Korfei M, Mutze K, Klee S, Ska-Wasek WS, Alsafadi HN et al (2017) Senolytic drugs target alveolar epithelial cell function and attenuate experimental lung fibrosis ex vivo. Eur Respir J 50:1602367
130. Schafer MJ, White TA, Iijima K, Haak AJ, Ligresti G, Atkinson EJ et al (2017) Cellular senescence mediates fibrotic pulmonary disease. Nat Commun 8:14532
131. Lim H, Park H, Kim HP (2015) Effects of flavonoids on senescence associated secretory phenotype formation from bleomycin-induced senescence in BJ fibroblasts. Biochem Pharmacol 96:337–348
132. Kim J, Vaish V, Feng M, Field K, Shim ICM (2016) Transgenic expression of cyclooxygenase-2 (COX-2) causes premature aging phenotypes in mice. Aging 8:2392–2405
133. Da SJ, Abbas M, Benkhiat SK, Burban M, Ribeiro TP, Toti F et al (2017) Replicative senescence promotes prothrombic responses in endothelial cells: role of NADPH Oxidase and cyclooxygenase derived oxidative stress. Exp Gerontol 93:7–15
134. Bai Yunping LJS, Peng Z, Ya L, Meng L, Suxiang F et al (2018) A Chinese herbal formula ameliorates pulmonary fibrosis by inhibiting oxidative stress via upregulating Nrf2. Front Pharmacol 9:628
135. Weibin Q, Xinrui C, Qiuhai Q, Wang D, Lei Z (2019) Angelica sinensis polysaccharide suppresses epithelial mesenchymal transition and pulmonary fibrosis via DANCR/ AUF-1/ FOXO3. Regul Axis 11(1):2152–2250

136. Hongbo L, Wang Z, Jei Z, Wang Y, Yu C, Jinjin Z et al (2018) Feifukang ameliorates pulmonary fibrosis by inhibiting JAK-STAT signaling pathway. BMC Complement Altern Med 18:234
137. Marta F, Hills KN, Scott T, Song WJ (2020) Green tea extract seen to stop fibrotic process of IPF (Lung Scarring) in small study. N Engl J Med 378:1898–1907
138. Yulei C, Lei J, Ruitao Y, Yuin S, Lijuan M, Yanduo T (2019) B-carboline alkaloids attenuate bleomycin induced Pulmonary Fibrosis in mice through inhibiting NF-kb/65 phosphorylation and epithelial- mesenchymal transition. J Ethnopharmacol 243:112096
139. You YY, Qian X, Yue F, Liu Qianyu ZFC, Ceng Z (2015) Preventive effects of ecliptae herba extract and its component, Eclipta saponin A, on bleomycin induced pulmonary fibrosis in mice. J Ethnopharmacol 175:172–180
140. Yongming P, Huiying F, Qing K, Yin X, Qiyang S, Qiang CH et al (2014) Prevention of pulmonary fibrosis with salvianolic acid A by inducing fibroblast, cell cycle arrest and promoting apoptosis. J Ethnopharmacol 155(3):1589–1596
141. Jianhui C, Junhui L, Baolan W, Xiaolei Z, Qiuyang H, Jun Y et al (2018) Polysaccharides from Dendrobium officinale inhibit bleomycin induced pulmonary fibrosis via the TGF-β1-Smad$2_{/3}$ axis. Int J Biol Macromol 118:2163–2175
142. Qianyu Z, Cailing G, Hongyao L, Liqun W, Yali L, Zui T et al (2020) Cryptotanshinone reverses the epithelial mesenchymal transformation process and attenuates bleomycin induced pulmonary fibrosis. Phytother Res 34(10):2685–2696
143. Cai ZX, Yuli C, Wei Z, Xianhai C (2018) Quercetin ameliorates pulmonary fibrosis by inhibiting SphK1/S1P signaling. Biochem Cell Biol 96(6):742–751

Medicinal Plants Used in Treatment of Bronchitis

16

Manish Pathak, Lubhan Singh, Ganesh Prasad Mishra, Kamal Dua, and Sagarika Majhi

Abstract

Owing to the rapidly accelerated growth of resistance to the medications currently in use, respiratory tract infections are health concern worldwide. Inflammation of the membrane of bronchioles, which bring oxygen into and out of lungs, is termed as *bronchitis*. Bronchitis individuals also cough up thickened, sometimes discolored mucus. Bronchitis could be either chronic or acute. Traditionally, many plants are employed for the management of respiratory diseases. Mostly used species in bronchitis were Lamiaceae (23%), Fabaceae and Asteraceae (15%), followed by Solanaceae (11%) and others. The bulk of acute and chronic bronchitis herbal composition was obtained from leaves (39%), followed by bark/stem (10%), whole plant (9%), fruits, nuts, and berries (9%), and roots and rhizomes (9%), while seeds and flowers (9% and 7%) were used less frequently.

The WHO recognizes conventional medicines as an important cornerstone for healthcare services, especially in developing and expansive countries, viz. India. Today, there is an awareness that the vast reservoir of wisdom along with the cultural experience connected with them must be maintained. The biodiversity must not only be preserved, but also the information frequently retained in the

M. Pathak · L. Singh · G. P. Mishra
Kharvel Subharti College of Pharmacy, Swami Vivekanand Subharti University, Meerut, Uttar Pradesh, India

K. Dua
Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Sydney, NSW, Australia

S. Majhi (✉)
I. T. S College of Pharmacy, Muradnagar, Ghaziabad, India

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_16

minds of elderly native and traditional healing practices must be archived. A revival in the utilization of herbal remedies has been seen in the last couple of years. The literature on pharmacological usage of plants for bronchitis and some other respiratory diseases has become expansive by ethnopharmacological research. This chapter aims to offer a description of plant species used in bronchitis in conventional respiratory therapies.

Keywords

Bronchitis · Inflammation · Airway obstruction · Mucus

16.1 Introduction

A widespread and critical cause of sickness and mortality around the globe is respiratory illness. The familiar reasons for hospitalizations among kids were respiratory problems. Acute respiratory infections account for 25–70% of outdoor hospital admissions, including 80% and 20% of upper and lower airway infections, respectively. Common cold, cough, asthma, bronchitis, and whooping cough are frequent respiratory system issues. *Bronchitis* basically is a lung or airway disease and it refers to inflammation of the lungs mainly bronchi [1]. Bronchitis has different major overlapping constructs based on phenotype, duration (acute, sub-acute, chronic), type of inflammation (neutrophilic, eosinophilic, lymphocytic, neurogenic), and lastly clinical syndromes (acute bronchitis, protracted bacterial bronchitis, laryngo-tracheobronchitis, aspiration bronchitis) [2, 3] (Fig. 16.1).

Owing to its remoteness, cold, and extreme environmental conditions, along with restricted medical services, respiratory problems are widespread. In order to manage

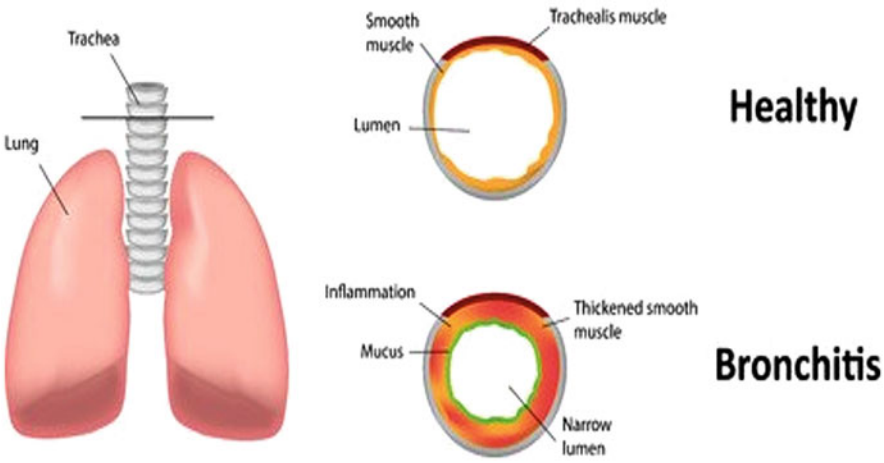


Fig. 16.1 Inflamed and normal bronchial tube

different respiratory conditions, individuals rely on native medicinal plants. In certain parts of the world, natural medicines for the prevention of respiratory disturbances are commonly used. Phyto-therapeutic agents have been used for disease prevention since antiquity, but their use has grown dramatically in recent years. Nearly, 170 herbal medicines gained official approval at the turn of the nineteenth century. According to WHO, through the use of phyto-therapeutic agents, 80% of global population meets their primary health-related concerns and 11% of important medicines are derived from plants.

16.2 Types of Bronchitis

16.2.1 Acute Bronchitis

International Classification of Diseases (ICD) has issued dedicated code for acute bronchitis [4]. Acute bronchitis is a non-precise term and generally it coincides with other symptoms of respiratory tract. The common cause of acute cough, acute bronchitis is caused by viral acute respiratory infections (ARIs) [5, 6]. A review on the history of natural occurring acute cough in children's ranging from 1 day to 4 years of age in primary care revealed that maximum children improve their condition with time but 05–10% progress to develop protracted pneumonia or bronchitis. Around 56% of children with suffering from ARIs are still unwell 4 days after initial consultation. The percentage get lowers down to 26% on the 7th day and up to 6% by the 14th day [7, 8].

16.2.1.1 Etiology of Acute Bronchitis

Pathogenic infection caused by viruses, mycoplasma, bacteria, chlamydia, helminths, and fungi may cause acute bronchitis [9]. Respiratory viruses and bacteria are the common cause of acute bronchitis around 17–33% of infections only because of bacterial or viral infection [10]. Common respiratory viruses are coronaviruses, human rhinovirus, respiratory syncytial virus A and B, influenza, parainfluenza (1–3), adenovirus, human enteroviruses, human parechoviruses, and human metapneumovirus [12, 13]. However, only bacteria, viruses, Chlamydia, mycoplasma are considered in the clinical phenotype of acute bronchitis. Acute bronchitis is caused by any of pathogens listed [11] (Fig. 16.2).

16.2.2 Chronic Bronchitis

Chronic bronchitis is characterized as long-term inflammation of the lungs or bronchi. It is found very common in smokers [14, 15]. Experts agree with that the primary cause of chronic bronchitis is cigarette smoking and somehow air pollution also imparts their role [16]. Person with chronic bronchitis tends to get more easily substile for lung infection and also suffered from episodes of acute bronchitis, when symptoms are getting worse [17, 18].

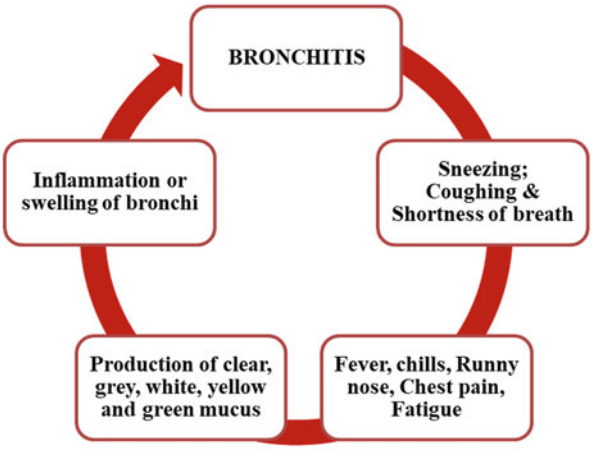


Fig. 16.2 Common sign and symptom of bronchitis

Chronic bronchitis is classified as:

- Person has cough and mucus for at least 2–3 months in a year or for 2 years in a row.
- Person suffering from tuberculosis (TB) or some variant lung infections.

Emphysema and chronic bronchitis are the two main courses of COPD. A broad group of lung diseases, including chronic bronchitis, are chronic obstructive pulmonary disease (COPD) [19]. COPD diseases in the lungs can obstruct the passage of air and cause breathing difficulties [20, 21].

Generally chronic bronchitis arises in those persons who already suffer from other diseases such as:

- Asthma
- Scarring of the respiratory tract (pulmonary fibrosis)
- Pulmonary emphysema
- Sinusitis
- Upper respiratory tract infections
- Tuberculosis

For several years, patients with chronic bronchitis have had cough and phlegm before they suffer from shortness of breath [23].

Chronic bronchitis may cause:

- Wheezing and crackling sounds with breathing
- Narrowing and plugging of your breathing tubes
- Trouble breathing
- Bluish fingernails, lips, and skin because of diminished O_2 levels
- Heart failure

- Swollen feet
- Disability

16.3 Diagnosis of Chronic Bronchitis

Physician will take details of health, history of disease and perform physical examination after these following tests are prescribed:

Pulmonary Function Tests Such measurements help to assess the capacity of the lungs to carry air in/out by using spirometry [24].

- To measure the ability of the lungs to inhale and exhale.
- And keep an eye on respiratory disease.
- To see how well the procedure functions.
- And find out how extreme your lung condition seems to be.
- To figure out whether it is limiting or obstructive to your lung condition.

Peak Flow Monitor This determined accurately how quickly you can push air out of your lungs at the highest speed. The airways are narrowed by inflammation and phlegm in the broad airways in the lungs. This slows the rate of air escaping the lungs [26, 27]. With a flow rate sensor, it can be measured. In saying how well the condition is being managed, this calculation is very important [26].

Arterial Blood Gas This screening test is used to search the blood for the volume of oxygen and carbon dioxide. The acidity in your blood is indeed measured [27].

Pulse Oximetry A simple machine that tests the level of oxygen in the bloodstream is an oximeter. A small sensor is placed or clipped on to a finger or toe to have this measurement. When the device is on, the detector can see a tiny red light. The sensor is pain free and there is no warmth in the red light [28].

Chest X-ray This examination creates photographs of the inner tissues, muscles, and organs [27, 28].

CT Scan To produce pictures of the body, this imaging method uses a combination of X-rays and digital technologies. A CT scan is more detailed and shows clear pictures, including bones, muscles, fat, and organs, of every portion of the body [27–29].

16.3.1 Plastic Bronchitis

Plastic bronchitis is very rare in this present era, it is characterized by the development of bronchial casts that cause obstruction in lungs by affecting airways

[31, 32]. Pathogenesis of cast development is unknown but somehow it arises due to accumulation of mucin with reduced airway clearance and dehydration in a genetically predisposed person [30, 33]. Bronchial casts are of two types:

- Type I: They are inflammatory and made up of fibrin with cellular infiltrates.
- Type II (acellular casts): They consist mainly of mucin with a few cells and usually occur following surgery for congenital cardiac defects. However, analysis of casts may not fit clearly into either category.

Etiologic factors for plastic bronchitis:

- Cardiac defects (after Fontan's procedure).
- Sickle cell disease (acute chest syndrome).
- Asthma, aspergillosis, pneumonia, cystic fibrosis, pulmonary lymphatic disorders, and neoplastic infiltrates.

16.4 Other Causes of and Contributors to Bronchitis

Systematic reviews suggested the link between air pollution cough [34]. It is increasingly appreciated in human and animal studies that environmental pollutants may have additive effects and may influence the respiratory apparatus directly and indirectly through the immune system and neural pathways [35, 36]. However, irrespective of exposure, cough should not be simply ascribed to pollutants (see the "Exacerbation Factors" section) in clinical settings [37].

16.5 Pathophysiology of Bronchitis

Short-term respiratory system infection causes inflammation leading to excessive mucus secretion and initial dry annoying cough which later turns productive. In chronic bronchitis, bronchial inflammation persists. As a result of hypertrophy and hyperplasia of the pulmonary mucus layer and mucous producing goblet cells, the bronchial mucosa induces increased secretion. This further adds chronic leucocyte and lymphocyte invasion of the bronchial walls. Thickened bronchial wall and narrowed bronchial lumen, thereby interfere with the air supply to and from the lungs. With mucus, the shortened lumen is sometimes plugged. There may be damage to the alveoli adjacent to the infected bronchioles, and fibrosis with heightened airway resistance and extreme imbalance in ventilation perfusion occurs. The patient may suffer with fever due to the inflammatory process with associated chills, headache, chest muscle pain, and lack of appetite. The pathophysiology of bronchitis is discussed in Fig. 16.3.

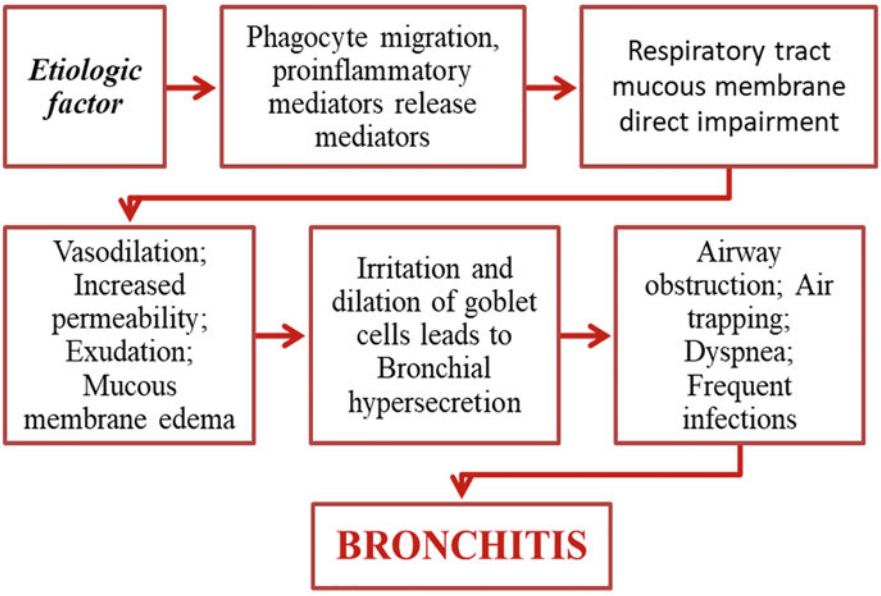


Fig. 16.3 Pathophysiology of bronchitis

16.6 Pharmacotherapy of Bronchitis

The treatment of bronchitis includes airflow optimization and antibiotic therapy along with some other measures. Along with pharmacotherapy, bioactive constituents are used from plant origin listed in Table 16.1.

16.6.1 Airflow Optimization

1. Expectorants: Piperazine, diphenhydramine HCl, acetylcysteine, ephedrine HCl.
2. Bronchodilators:
   - Anticholinergic: Ipratropium bromide
   - Beta-2 agonist: Albuterol, formoterol, salmeterol
   - Corticosteroids: Beclomethasone (inhaled) and prednisone (oral)

16.6.2 Antibiotic Therapy

1. First line agents: Doxycycline, amoxicillin, azithromycin
2. Second line agents: Co-amoxiclav, clarithromycin, cefixime

Table 16.1 List of plant used in treatment of bronchitis

S. no.	Scientific name	Vernacular names	Family	Part used
1	*Abelmoschus esculentus*	Okra, ladies' finger	Solanaceae	Fruit [49]
2	*Abrus precatorius L.*	Indian licorice, crab's eye	Fabaceae	Root, leaves, seeds [49, 50]
3	*Adhatoda vasica nees*	Bansa, Malabar nut, white vasa	Acanthaceae	Leaves, whole plant [49]
4	*Adiantum capillus-veneris*	Maidenhair fern, Venus maidenhair	Pteridaceae	Whole plant [49]
5	*Aframomum melegueta*	Grains of paradise, alligator pepper	Zingiberaceae	Seeds, leaves [50]
6	*Ageratum conyzoides*	Chick weed, goat weed, whiteweed	Asteraceae	Leaves, whole plant [50]
7	*Agrimonia eupatoria*	Church steeples, sticklewort	Rosaceae	Leaves, flower, stem [49]
8	*Ajuga Iva*	Herb ivy, Chendgoura/ Shandgoura	Lamiaceae	Whole plant [49]
9	*Allium ascalonicum L.*	Wild onion	Liliaceae	Whole plant, bulbs [50]
10	*Allium sativum*	Garlic, lahsan, lehsun	Amaryllidaceae	Bulb [49, 50]
11	*Alpinia officinarum*	Lesser galangal	Zingiberaceae	Flowers, leaves [49]
12	*Alstonia boonei*	Pattern wood, stool wood	Apocynaceae	Stem, bark, leaves [50]
13	*Althaea officinalis*	Marshmallow, common marshmallow	Malvaceae	Flowers, leaves, roots, fruits, seed [49]
14	*Amaranthus spinosus L.*	Spiny amaranth, spiny pigweed, prickly amaranth	Amaranthaceae	Root, leaves, whole plant [49, 50]
15	*Anacardium occidentale L.*	Cashew apple, caju, cashewnut	Anacardiaceae	Leaves, fruit, stem, bark [50]
16	*Ananas comosus*	Crowa, pineapple, Ananas	Bromeliaceae	Unripe fruit, whole plant [50]
17	*Andrographis paniculata*	Kirayat, kariyat, Kalmegh	Acanthaceae	Leaves, root [49]
18	*Anemone hepatica*	Liverwort, kidneywort	Ranunculaceae	Leaves [49]
19	*Anethum graveolens L.*	Dill, soya	Apiaceae	Seeds [49]
20	*Angelica archangelica*	Garden angelica, wild celery	Apiaceae	Stem, root [49]
21	*Annickia chlorantha*	Epfoué	Annonaceae	Stem, bark [50]
22	*Antiaris toxicaria*	Barkcloth tree, antiaris, false iroko	Moraceae	Leaves, fruit [50]

(continued)

Table 16.1 (continued)

S. no.	Scientific name	Vernacular names	Family	Part used
23	*Apium Graveolens L.*	Celery, wild celery, Bari ajmod	Apiaceae	Seed and root [49]
24	*Artemisia vulgaris*	Mugwort, wild wormwood, felon herb	Asteraceae	Aerial part, root [49]
25	*Asarum europaeum*	European wild ginger, hazelwort, wild spikenard	Aristolochiaceae	Flower, leaves [49]
26	*Asclepias tuberosa*	Butterfly weed, Indian paintbrush, orange milkweed	Apocynaceae	Root [49]
27	*Avena sativa L.*	Oats, common oat	Poaceae	Seeds [49]
28	*Azadirachta indica A. Juss*	Neem, nimtree, or Indian lilac	Meliaceae	Leaf extract [49]
29	*Bambusa vulgaris*	Bamboo	Poaceae	Leaves, young shoot [50]
30	*Berberis vulgaris*	Common barberry, European barberry	Berberidaceae	Root bark, stem bark [49]
31	*Bistorta vivipara*	Alpine bistort, alpine knotweed	Polygonaceae	Root and stem [49]
32	*Bletilla striata*	Hyacinth orchid, urn orchid	Orchidaceae	Rhizome [49]
33	*Borago officinalis*	Burrage, bee bread, ox's tongue	Boraginaceae	Leaves, flower [49]
34	*Bridelia ferruginea*	Asas, Assas	Phyllanthaceae	Stem bark [50]
35	*Bryophyllum pinnatum*	Air plant, cathedral bells, life plant, miracle leaf	Crassulaceae	Leaves [50]
36	*Cajanus cajan*	Pigeonpea, red gram, tur	Fabaceae	Leaves [50]
37	*Calamintha officinalis*	Moench	Lamiaceae	Aerial parts [49]
38	*Calotropis procera*	Sodom apple, stabragh, king's crown, rubber bush	Apocynaceae	Leaves [50]
39	*Capsicum annuum L.*	Capsicum, bell pepper	Solanaceae	Leaves, fruit [50]
40	*Carica papaya L.*	Papaya, pawpaw, melon tree	Caricaceae	Leaves, unripe fruit [50]
41	*Carum copticum L.*	Ajwain, ajowan, bishop's weed	Apiaceae	Seeds, leaves, and flowers [49]
42	*Carum carvi L.*	Wild caraway. Caraway	Apiaceae	Stem and leaves [49]
43	*Cassia occidentalis*	Coffee senna, coffeeweed, Kasunda	Fabaceae	Leaves, flowers [49]
44	*Cassia tora Linn*	Pavand, Punwad, Punwadia	Fabaceae	Shoot and leaves [49]
45	*Centaurium Erythraea Rafn*	Centauro maggiore, Erba-China	Gentianaceae	Aerial parts [49]

(continued)

Table 16.1 (continued)

S. no.	Scientific name	Vernacular names	Family	Part used
46	*Chasmanthera dependens*	Ato	Menispermaceae	Leaves [50]
47	*Chimaphila umbellata*	Umbellate wintergreen, pipsissewa, prince's pine	Ericaceae	Leaves, root [49]
48	*Chromolaena odorata*	Siam weed, Christmas bush, devil weed	Asteraceae	Leaves [50]
49	*Chrysophyllum albidum*	White star apple	Sapotaceae	Leaves, seeds [50]
50	*Cichorium intybus L.*	Chicory, French endive, succory	Asteraceae	Whole plants [49]
51	*Cinnamomum camphora*	Camphor tree, camphorwood, Kapur	Lauraceae	Leaves, flower [49]
52	*Cissampelos owariensis*	Akuraso (mouse's ear)	Menispermaceae	Leaves [50]
53	*Citrullus colocynthis*	Bitter apple, bitter cucumber, desert gourd	Cucurbitaceae	Leaves, fruit [49, 50]
54	*Citrus aurantiifolia*	Lime, Kagzi nimbu	Rutaceae	Leaves, fruit [50]
55	*Citrus sinensis*	Naval orange, sweet orange	Rutaceae	Peel, flower, leaves [49]
56	*Cocos nucifera L.*	Coconut tree, coconut palm	Arecaceae	Nuts, epicarp, leaves [50]
57	*Cola acuminata*	Cola nut, abata cola	Malvaceae	Leaves [50]
58	*Colchicum luteum*	Suranjan, Hirantutiya	Colchicaceae	Coms [49]
59	*Coleus aromaticus Benth*	Indian borage, French thyme, Indian mint	Lamiaceae	Leaves [49]
60	*Combretum bracteatum*	Bushwillows	Combretaceae	Stem, bark [50]
61	*Combretum micranthum*	Kinkeliba, Burkina Faso, Senegal	Combretaceae	Stem, bark [50]
62	*Commiphora myrrha*	Bola, heerabola, hirabol	Burseraceae	Resin [49]
63	*Conyza bonariensis*	Asthmaweed, wavy-leaf fleabane	Asteraceae	Whole plants [49]
64	*Corchorus olitorius L.*	Tossa jute, Jew's mallow, Kostha	Malvaceae	Whole plant [50]
65	*Coronopus didymus*	Pitpapra, Jangli Hala	Brassicaceae	Leaves and tender parts [49]
66	*Crataegus oxyacantha L.*	Haw, whitehorn, Pingyat, Phindak	Rosaceae	Leaves, flower [49]
67	*Crinum jagus*	St. Christopher, Harmattan lily	Amaryllidaceae	Shoot, roots [50]
68	*Crotalaria retusa L.*	Devil-bean, rattleweed, wedge-leaf rattlepod	Fabaceae	Leaves [50]

(continued)

Table 16.1 (continued)

S. no.	Scientific name	Vernacular names	Family	Part used
69	*Crudia klainei*	Haratou	Leguminosae	Leaves [50]
70	*Cymbopogon citratus*	Lemongrass, barbed wire grass, silky heads	Poaceae	Leaves [50]
71	*Cynoglossum lanceolatum*	Hathipendi	Boraginaceae	Whole plant [49]
72	*Daucus carota*	Wild carrot, bird's nest, bishop's lace	Apiaceae	Stem, root, carrot [49]
73	*Dioclea reflexa*	Bapiana, dauwa	Leguminosae	Seeds [50]
74	*Dioscorea dumetorum*	Bitter yam, cluster yam	Dioscoreaceae	Leaves, roots [50]
75	*Echinacea angustifolia*	Purple coneflower	Asteraceae	Flower, leaves [49]
76	*Elaeis guineensis*	Oil palm, macaw-fat	Arecaceae	Fruit, roots [50]
77	*Erythrophleum suaveolens*	Forest ordeal tree, red water tree, sasswood tree	Fabaceae	Stem, bark, leaves [50]
78	*Eucalyptus globulus Labill*	Australian fever tree, blue gum, southernblue gum	Myrtaceae	Leaves [49]
79	*Eugenia caryophyllata Thunb*	Lavangaha, Laung	Myrtaceae	Flower [49]
80	*Eugenia jambolana*	Jaman, black plum, damson plum, Indian blackberry	Myrtaceae	Bark [49]
81	*Euphorbia helioscopia Linn.*	Wart spurge, umbrella milkweed, and madwoman's milk	Euphorbiaceae	Whole plant [49]
82	*Evolvulus alsinoides*	Dwarf morning-glory, Vishnukranta, Vishnu Krantha	Convolvulaceae	Whole plant [49]
83	*Ficus exasperate*	Sandpaper tree, Brahma's banyan, white fig	Moraceae	Leaves, stem, bark, roots [50]
84	*Ficus platyphylla*	Flake rubber tree; red Kano rubber tree	Moraceae	Stem, roots, bark [50]
85	*Garcinia kola*	Bitter kola, false kola	Clusiaceae	Roots, seeds, stem, bark [50]
86	*Geranium rotundifolium L.*	Round-leaved crane's-bill	Geraniaceae	Leaves [49]
87	*Glycyrrhiza glabra L.*	Liquorice, sweetwood, mithilakdi	Fabaceae	Stem, bark, roots [49]
88	*Gossypium barbadense L.*	Creole cotton, pima cotton	Malvaceae	Roots, seeds [50]
89	*Grindelia squarrosa*	Curlycup gumweed, rosin weed	Asteraceae	Leaves [49]
90	*Hedera helix*	English ivy, needlepoint ivy	Araliaceae	Leaves, berries [49]

(continued)

Table 16.1 (continued)

S. no.	Scientific name	Vernacular names	Family	Part used
91	*Helianthus tuberosus*	Sunroot, sunchoke, earth apple	Asteraceae	Tubers [49]
92	*Hybanthus enneaspermus*	Spade flower, Ratan Purush	Violaceae	Leaves [50]
93	*Hydrastis canadensis*	Orangeroot, yellow puccoon	Ranunculaceae	Leaves [49]
94	*Hyoscyamus niger*	Henbane, black henbane and stinking nightshade	Solanaceae	Leaves, seeds [49]
95	*Hyssopus officinalis*	Hyssop, Jupha	Lamiaceae	Aerial part [49]
96	*Inula helenium*	Elecampane, Scabwort	Asteraceae	Root, rhizome [49]
97	*Inula racemosa hook*	Puskarmool, Pokharmul	Asteraceae	Root [49]
98	*Ipomoea batatas*	Sweet potato, Brazilian arrowroot	Convolvulaceae	Leaves [50]
99	*Iris hookeriana*	Hooker's iris	Iridaceae	Flower [49]
100	*Jatropha curcas L.*	Physic nut, poison nut	Euphorbiaceae	Seeds [50]
101	*Jatropha gossypiifolia*	Bellyache bush, black physic nut	Euphorbiaceae	Leaves [50]
102	*Jatropha multifida*	Coral bush, physic nut	Euphorbiaceae	Sap latex [50]
103	*Juniperus communis*	Aaraar, Havusha	Pinaceae	Leaves [49]
104	*Khaya grandifoliola*	Benin mahogany, Benin wood	Meliaceae	Stem, bark [50]
105	*Kigelia africana*	Sausage tree, Balam khira, Jhar fanoos	Bignoniaceae	Seeds, leaves [50]
106	*Lagenaria breviflora*	Wild colocynth	Cucurbitaceae	Whole plant [50]
107	*Launaea taraxacifolia*	African lettuce	Asteraceae	Stem, bark [50]
108	*Laurus nobilis*	Bay tree, sweet bay	Lauraceae	Leaves [49]
109	*Lavandula angustifolia*	English lavender	Lamiaceae	Leaves [49]
110	*Lavandula dentata L.*	French lavender, fringed lavender	Lamiaceae	Flower [49]
111	*Lawsomia alba lam*	Henna, Mehendi	Lythraceae	Leaves [49]
112	*Lawsonia inermis alba*	Henna, mignonette tree	Lythraceae	Powdered leaves, seeds, bark [49]
113	*Lawsonia inermis L.*	Hina, henna	Lythraceae	Leaves, whole Plant [50]

(continued)

Table 16.1 (continued)

S. no.	Scientific name	Vernacular names	Family	Part used
114	*Linum usitatissimum*	Flaxseed, linseed	Linaceae	Seeds [49]
115	*Lobelia Inflata*	Indian tobacco, puke weed	Campanulaceae	Leaves [49]
116	*Luffa cylindrica*	Dishrag gourd, rag gourd, sponge gourd, Ghia torai	Cucurbitaceae	Seeds [50]
117	*Malva sylvestris*	Common mallow, tall mallow	Malvaceae	Leaves, whole plant [49]
118	*Mangifera indica*	Mango, amra	Anacardiaceae	Leaves, stem, bark, roots [50]
119	*Marrubium vulgare L.*	White horehound, Pahari gandana	Lamiaceae	Shoots and leaves [49]
120	*Melilotus indica L.*	Indian sweet-clover, Senji Methi, ban Methi	Fabaceae	Annual herb [49]
121	*Mentha pulegium L3*	Pennyroyal, squaw mint	Lamiaceae	Leaves [50]
122	*Mentha suaveolens*	Apple mint, round-leaved mint	Lamiaceae	Leaves [49]
123	*Mentha viridis L.*	Spearmint, lamb mint	Lamiaceae	Leaves [49]
124	*Mimosa pudica L.*	Shame plant, humble plant, Chui Mui, Lajvanti	Fabaceae	Leaves [50]
125	*Momordica charantia L.*	Bitter apple, bitter gourd, Karela	Cucurbitaceae	Fruit, whole plant [50]
126	*Morinda lucida*	English brimstone tree	Rubiaceae	Leaves, stem, bark, roots [50]
127	*Mucuna pruriens*	Monkey tamarind, velvet bean, Kiwach	Fabaceae	Leaves [50]
128	*Myristica dactyloides Gaert.*	Bitter nutmeg, Pasupathi	Myrtaceae	Leaf and fruit [49]
129	*Myrtus communis L.*	Common myrtle, foxtail Myrtle	Myrtaceae	Leaves [49]
130	*Nicotiana tabacum L.*	Tobacco	Solanaceae	Leaves [50]
131	*Nigella sativa L.*	Black cumin, nigella, kalojeera	Ranunculaceae	Seeds [49]
132	*Ocimum americanum L.*	Hoary basil, Kali tulasi	Lamiaceae	Leaves [50]
133	*Ocimum basilicum L.*	Great basil, hebak	Lamiaceae	Leaves, seeds [49]
134	*Ocimum gratissimum L.*	Clove basil, African basil, ram tulsi	Lamiaceae	Leaves [50]
135	*Ocimum sanctum L.*	Holy basil, tulsi	Lamiaceae	Leaves [49]

(continued)

Table 16.1 (continued)

S. no.	Scientific name	Vernacular names	Family	Part used
136	*Olea europaea L.*	Wild olive, brown olive	Oleaceae	Seeds [49]
137	*Onosma bracteatum wall*	Goaza, Ganjaba Goziya	Moraceae	Whole plant [49]
138	*Opuntia monacantha haw*	Drooping prickly pear, nagphani, chhitaar thohar	Cactaceae	Whole plant [49]
139	*Origanum compactum Benth*	Zaatar	Lamiaceae	Leaves [49]
140	*Origanum majorana L.*	Sweet marjoram, murwa, sathra	Lamiaceae	Leaves [49]
141	*Origanum vulgare*	Oregano, Sathra	Lamiaceae	Leaves [49]
142	*Panax quinquefolius*	American ginseng	Araliaceae	Root [49]
143	*Pergularia daemia L.*	Hair knot plant, stinking swallowwort, trellis-vine	Apocynaceae	Leaves [49]
144	*Persea americana*	Avocado, alligator pear, Makhanphal	Lauraceae	Leaves [50]
145	*Phyllanthus amarus*	Black catnip, hurricane weed	Phyllanthaceae	Whole plant [50]
146	*Phyllanthus emblica*	Indian gooseberry, Amla, Amlaki	Phyllanthaceae	Fresh fruits, seeds, flowers, [49]
147	*Picralima nitida*	Akuamma	Apocynaceae	Stem, bark [50]
148	*Pimpinella anisum*	Aniseed, sweet cumin	Apiaceae	Seeds [49]
149	*Pimpinella saxifraga*	Burnet-saxifrage	Apiaceae	Leaves [49]
150	*Piper betle L.*	Betel pepper, kava	Piperaceae	Leaves [49]
151	*Piper guineense*	Ashanti pepper, Benin pepper	Piperaceae	Leaves, seeds [50]
152	*Plantago major*	Great plantain, Lahuriya	Plantaginaceae	Aerial part [49]
153	*Platycodon grandiflorus*	Balloon-flower, Korean bellflower	Campanulaceae	Root [49]
154	*Plectranthus amboinicus*	Indian borage, Karpuravalli	Lamiaceae	Leaves [49]
155	*Plukenetia conophora*	Nigerian walnut, conophor	Euphorbiaceae	Leaves, fruit, bark [50]
156	*Polygala amarella*	Dwarf milkwort, Kentish milkwort	Polygalaceae	Aerial part [49]
157	*Polygonum aviculare*	Common knotgrass, buckwheat	Polygonaceae	Seed [49]
158	*Primula veris L.*	Cowslip, cowslip primrose	Primulaceae	Flower [49]

(continued)

Table 16.1 (continued)

S. no.	Scientific name	Vernacular names	Family	Part used
159	*Psidium guajava L.*	Yellow guava, lemon guava	Myrtaceae	Fruit, leaves, seeds, pulp [49, 50]
160	*Punica granatum L.*	Pomegranate, Anar	Lythraceae	Juice of fruit [49]
161	*Quercus incana Bartram*	Bluejack oak, cinnamon oak	Fagaceae	Bark and fruits [49]
162	*Rheum spiciforma Royle*	Pamb-Chalan, Pamb-Hak	Polygonaceae	Roots [49]
163	*Rosa damascene*	Damask rose	Amaranthaceae	Leaves [49]
164	*Rosmarinus officinalis L.*	Rosemary	Lamiaceae	Leaves [49]
165	*Saccharum officinarum L.*	Sugarcane, ganna	Poaceae	Stem [50]
166	*Salvia officinalis L.*	Common sage, culinary sage	Lamiaceae	Leaves [49]
167	*Sarcocephalus latifolius*	African peach, Guinea peach	Rubiaceae	Roots [50]
168	*Saussurea ceratocarpa*	Saw-wort and snow lotus	Asteraceae	Whole plant [49]
169	*Serenoa repens*	Saw palmetto	Arecaceae	Fruit [49]
170	*Sisymbrium officinale*	Hedge mustard, oriental mustard	Brassicaceae	Leaves [49]
171	*Solanum americanum*	American black nightshade	Solanaceae	Whole plant [50]
172	*Solanum incanum L.*	Thorn apple, bitter apple, bitterball	Solanaceae	Leaves, seeds [49]
173	*Solanum melongena L.*	Brinjal, eggplant, baingan	Solanaceae	Fruit, leaf, root [49]
174	*Solanum nigrum L.*	Blackberry nightshade, makhoi; nununia	Solanaceae	Leaf, berries, flowers, root [49]
175	*Sorghum bicolor*	Black amber, broom-corn, jowar	Poaceae	Leaves, pods, seeds [50]
176	*Spondias mombin L.*	Yellow mombin, hog plum	Anacardiaceae	Leaves, stem, bark [50]
177	*Stacia integerrima*	Peregrina, spicy Jatropha, kakar singhi, kakra	Euphorbiaceae	Bark and fruit [49]
178	*Sterculia rhinopetala*	Munone, brown sterculia	Malvaceae	Stem, bark [50]
179	*Strombosia grandifolia*	Afina, bokyi keshu	Olacaceae	Roots, leaves, fruit [50]
180	*Styrax benzoin*	Gum Benjamin tree, loban	Styracaceae	Resin [49]
181	*Succisa pratensis*	Devil's-bit, scabious	Caprifoliaceae	Flower [49]

(continued)

Table 16.1 (continued)

S. no.	Scientific name	Vernacular names	Family	Part used
182	*Swertia petiolata*	Tikta, chuck theek kar poh, Chirayata	Gentianaceae	Fruit [49]
183	*Synsepalum dulcificum*	Miracle fruit, miracle berry	Sapotaceae	Leaves, seeds [50]
184	*Talinum fruticosum*	Nela basale, Ceylon spinach	Talinaceae	Roots, leaves [50]
185	*Taraxacum officinale*	Common dandelion, Dudhi, Baran, dudal	Asteraceae	Leaves, root [49]
186	*Taxus baccata Linn.*	Common yew, English yew, Sukapuspa, Vikarna	Taxaceae	Bark [49]
187	*Taxus wallichiana Zucc.*	Himalayan yew	Taxaceae	Leaves and fruits [49]
188	*Tetrapleura tetraptera*	Aridan	Fabaceae	Pods, bark [50]
189	*Theobroma cacao L.*	Cacao tree	Malvaceae	Leaves [50]
190	*Thymus serpyllum*	Breckland thyme, wild thyme	Lamiaceae	Aerial parts [49]
191	*Thymus vulgaris*	Common thyme, German thyme	Lamiaceae	Leaves [49]
192	*Trachyspermum ammi*	Ajwain, caraway	Apiaceae	Seeds and oil [49]
193	*Trifolium pratense L.*	Red clover, Tripatra	Fabaceae	Dried flowers [49]
194	*Trigonella foenum-graecum L.*	Fenugreek, Methi	Fabaceae	Seeds [49]
195	*Tussilago farfara*	Coltsfoot, horsefoot	Asteraceae	Flowers [49]
196	*Ulmus rubra*	Slippery elm	Ulmaceae	Leaves, flower [49]
197	*Urtica dioica*	Stinging nettle, Bichchhu buti	Urticaceae	Leaves [49]
198	*Uvaria afzelii*	Finger root, bush banana	Annonaceae	Roots [50]
199	*Viola betonicifolia Sm*	Arrowhead violet, mountain violet	Violaceae	Whole herb and flowers [49]
200	*Vitis vinifera L.*	Grape, Angoor	Vitaceae	Flowers [49]
201	*Zea mays L.*	Maize, corn, Makka	Poaceae	Fruits [50]
202	*Ziziphus jujube mill.*	Bari, jujube	Rhamnaceae	Fruits [49]
203	*Zizyphus nummularia*	Jhar Beri, adbaubordi	Rhamnaceae	Fruit [49]
204	*Zizyphus sativa G*	Chinese jujube	Rhamnaceae	Fruit and leaves [49]

16.6.3 Other Measures To Be Taken

Smoking cessation, aerobic physical exercise (walking 20 min or bicycling), adequate systemic hydration increases the mobilization of secretions, oxygen therapy (supplemental oxygen for patients with resting hypoxemia).

16.6.4 Plant Used in Management of Bronchitis

Plants have been used in traditional medicine for several thousand years. From the time immemorial, human civilizations have been exploring and using various plants and plant products to cure the lethal diseases [38–40]. Different plant species and their uses as medicine are greatly well-known to indigenous communities in different parts of the world. Regional people, in particular, are experts in mounting innovative methods and goods from their surrounding environment. Several medications have plant origin and maybe some plants are presently under study to determine their medicinal effectiveness [41]. While some of the traditional tribal groups and some human beings who believed in the use of herbal medicines still exercise the knowledge about the use of traditional herbal medicines [42]. Some common plant parts and families used in bronchitis are depicted in Figs. 16.4 and 16.5, respectively.

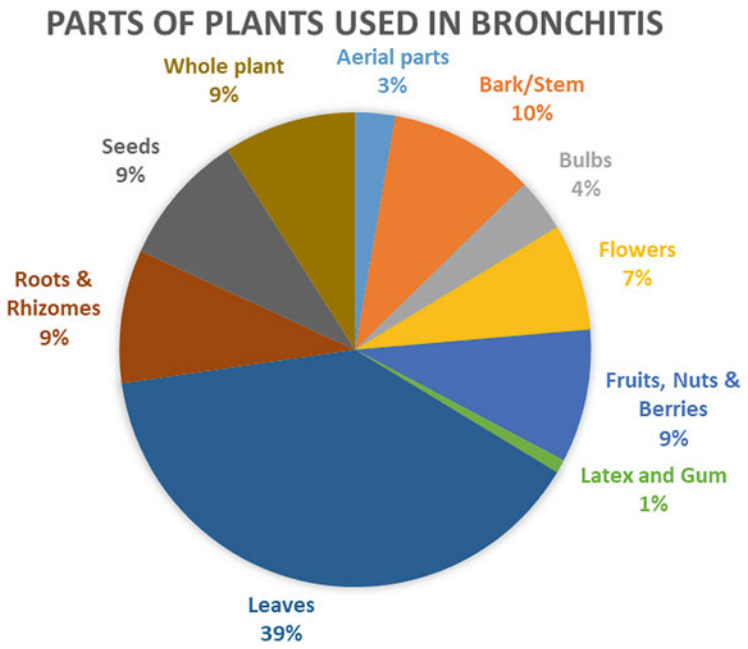


Fig. 16.4 Parts of plants used in bronchitis

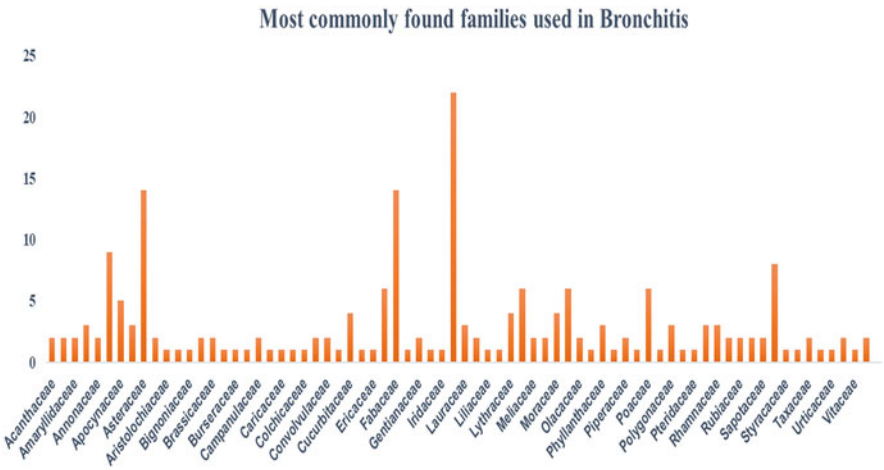


Fig. 16.5 Most commonly found families used in bronchitis

Today, as many as 80% of the world's population rely on conventional medicine for their basic medical needs, according to the World Health Organization (WHO) [43, 44]. The production of indigenous medicines and the use of medicinal plants for the treatment of different diseases have significant economic benefits. The lack of primary health care facilities and transit services, the unaffordable cost of treatment, the health risks of many allopathic medications have led to increased focus on the use of plant materials [45, 46]. It has been estimated that 1.5 billion populations of developing countries use traditional medicines either because the people cannot afford synthetic medicine or because traditional medicines are more acceptable [46–48].

16.7 Conclusion

Herbal medicinal plants can be a good alternative for the treatment of bronchitis with the growing interest in health and wellness; alternative medicines are becoming increasingly popular worldwide. Plant products are economical and tend to have lesser side effects. In addition, several scientific research data shows that herbal medicines can be highly effective in treatment of acute and chronic bronchitis. In addition, as study in this field grows, the optimal doses for herbal remedies are gradually considered to be more reliable.

This summary would not only offer benchmark evidence for selection process of potential plants used in respiratory problems preferentially bronchitis, but will also be useful by the implementation of ethno-botanical indices for the conduct of bioactive compounds studies. It requires time to introduce productive strategies for the careful usage of the world's precious ethno-botanical heritage and to fill the void between ethno-medicine and pharmacological science to completely clarify the

promising public health effects of plant-based medicines. This chapter also sets out suggestions for the regions to be explored in future ethno-botanical studies.

References

1. Reddy KN, Reddy CS, Trimurthulu G (2006) Ethnobotanical survey on respiratory disorders in eastern Ghats of Andhra Pradesh. Ethnobot Leafl 1:16
2. Taur DJ, Patil RY (2011) Antiasthmatic activity of *Ricinus communis* L. roots. Asian Pac J Trop Biomed 1(1):S13–S16
3. Taur DJ, Patil RY (2011) Mast cell stabilizing and antiallergic activity of *Abrus precatorius* in the management of asthma. Asian Pac J Trop Med 4(1):46–49. https://doi.org/10.1016/S1995-7645(11)60030-8
4. Taur DJ, Patil RY (2011) Some medicinal plants with anti-asthmatic potential: a current status. Asian Pac J Trop Biomed 1(5):413–418
5. Haq I (2004) Safety of medicinal plants. Pak J Med Res 43(4):203–210
6. Singh P, Shukla R, Kumar A, Prakash B, Singh S, Dubey NK (2010) Effect of *Citrus reticulata* and *Cymbopogon citratus* essential oils on *Aspergillus flavus* growth and aflatoxin production on *Asparagus racemosus*. Mycopathologia 170(3):195–202
7. Ali SI, Qaiser M (1986) A phytogeography analysis of the phanerogames of Pakistan and Kashmir. Proc R Soc Edinb 89:89–101
8. Shinwari ZK, Qaiser M (2011) Efforts on conservation and sustainable use of medicinal plants of Pakistan. Pak J Bot 43:5–10
9. Haq I (1983) Medicinal plants. Hamdard Foundation Press, Karachi
10. Karou D, Nadembega WMC, Ouattara L, Ilboudo DP, Canini A, Nikiéma JB, Simpore J, Colizzi V, Traore AS (2007) African ethnopharmacology and new drug discovery. Med Aromat Plant Sci Biotechnol 1(1):61–69
11. Hussain K, Shahazad A, Zia-ul-Hussnain S (2008) An ethnobotanical survey of important wild medicinal plants of Hattar district Haripur, Pakistan. Ethnobot Leafl 1:5
12. Hamayun M, Khan SA, Sohn EY, Lee IJ (2006) Folk medicinal knowledge and conservation status of some economically valued medicinal plants of district swat. Pakistan Lyonia 11 (2):101–113
13. Bremer K, Anderberg AA (1994) Asteraceae: cladistics and classification. Timber Press, Portland
14. Jeffrey C (2007) Introduction with key to tribes. In: Kadereit JW, Jeffrey C (eds) The families and genera of vascular plants, vol. 8, flowering plants. Eudicots: Asterales, vol 2006. Springer, Berlin, pp 61–87
15. Barker MS, Kane NC, Matvienko M, Kozik A, Michelmore RW, Knapp SJ, Rieseberg LH (2008) Multiple paleopolyploidizations during the evolution of the Compositae reveal parallel patterns of duplicate gene retention after millions of years. Mol Biol Evol 25(11):2445–2455
16. Cronquist A (1982) An integrated system of classification of flowering plants. Columbia University Press, New York
17. Adekenov SM (1995) Sesquiterpene lactones from plants of the family Asteraceae in the Kazakhstan flora and their biological activity. Chem Nat Compd 31(1):21–25
18. Uysal T, Ozel E, Bzkurt M, Ertuğrul K (2012) Genetic diversity in threatened populations of the endemic species *Centaurea lycaonica* Boiss. Heldr. (Asteraceae). Res J Biol 2(3):110–116
19. Stepp JR, Moerman DE (2001) The importance of weeds in ethnopharmacology. J Ethnopharmacol 75(1):19–23
20. Daehler CC (1998) The taxonomic distribution of invasive angiosperm plants: ecological insights and comparison to agricultural weeds. Biol Conserv 84(2):167–180
21. Ahmed AA, Bassuony NI (2009) Importance of medical herbs in animal feeding. World J Agric Sci 5(4):456–465

22. Khan SM, Page S, Ahmad H, Harper D (2013) Identifying plant species and communities across environmental gradients in the Western Himalayas: method development and conservation use. Eco Inform 14:99–103
23. Kumar D, Trivedi N, Dixit RK (2015) Herbal medicines used in the traditional Indian medicinal system as a therapeutic treatment option for diabetes management: a review. World J Pharm Pharm Sci 4(4):368–385
24. Koffi N, Marie-Solange T, Emma AA, Noel ZG (2009) Ethnobotanical study of plants used to treat arterial hypertension in traditional medicine, by abbey and Krobou population of Agboville (Cote d'ivoire). Eur J Sci Res 35:85–98
25. Adeyemi OO, Akindele AJ, Nwumeh KI (2010) Acute and subchronic toxicological assessment of *Byrsocarpus coccineus* Schum. and Thonn. (Connaraceae) aqueous leaf extract. Int J Appl Res Nat Prod 3(2):1–11
26. Ghorbani A (2005) Studies on pharmaceutical ethnobotany in the region of Turkmen Sahra, north of Iran: (part 1): general results. J Ethnopharmacol 102(1):58–68
27. Bhat JA, Kumar M, Bussmann RW (2013) Ecological status and traditional knowledge of medicinal plants in Kedarnath wildlife sanctuary of Garhwal Himalaya. Ind J Ethnobiol Ethnomed 9(1):b5
28. Sosnowska J, Balslev H (2013) American palm ethnomedicine: a meta-analysis. J Ethnobiol Ethnomed 5(1):43
29. Adnan M, Begum S, Latif A, Tareen AM, Lee LJ (2012) Medicinal plants and their uses in selected temperate zones of Pakistani Hindukush-Himalaya. J Med Plant Res 6(24):4113–4127
30. Adnan M, Ullah I, Tariq A, Murad W, Azizullah A, Khan AL, Ali N (2014) Ethnomedicine use in the war affected region of Northwest Pakistan. J Ethnobiol Ethnomed 10(1):16
31. Maroyi A (2011) An ethnobotanical survey of medicinal plants used by the people in Nhema communal area, Zimbabwe. J Ethnopharmacol 136(2):347–354
32. Verma AK, Kumar M, Bussmann RW (2007) Medicinal plants in an urban environment: the medicinal flora of Banares Hindu University, Varanasi, Uttar Pradesh. J Ethnobiol Ethnomed 3 (1):35
33. Merzouki A, Ed-Derfoufi F, Mesa JM (2000) Contribution to the knowledge of Rifian traditional medicine. II: folk medicine in Ksar Lakbir district (NW Morocco). Fitoterapia 71 (3):278–307
34. Jayanthy A, Prakash KU, Remashree AB (2013) Seasonal and geographical variations in cellular characters and chemical contents in *Desmodium gangeticum* (L.) DC - an ayurvedic medicinal plant. Int J Herbal Med 2(3):34–37
35. Savithramma N, Sulochana C, Rao KN (2007) Ethnobotanical survey of plants used to treat asthma in Andhra Pradesh, India. J Ethnopharmacol 113(1):54–61
36. Ritch R (2000) Potential role for *Ginkgo biloba* extract in the treatment of glaucoma. Med Hypothesis 54(2):221–235
37. Shinwari ZK, Watanabe T, Rehman M, Youshikawa T (2006) A pictorial guide to medicinal plants of Pakistan. KUST, Kohat
38. Shah M, Hussain F (2012) Conservation assessment of plant resources of chakesar valley, district Shangla, KPK, Pakistan. Pak J Bot 44:179–186
39. Shah SM, Hussain F (2012) Ethnomedicinal plant wealth of Mastuj valley, Hindukush range, district Chitral, Pakistan. J Med Plant Res 6(26):4328–4337
40. Sher H, Hussain F (2009) Ethnobotanical evaluation of some plant resources in northern part of Pakistan. Afr J Biotechnol 8(17):4066–4076
41. Sher H, Aldosari A, Ali A, de Boer HJ (2014) Economic benefits of high value medicinal plants to Pakistani communities: an analysis of current practice and potential. J Ethnobiol Ethnomed 10(1):71
42. Hamayun M, Khan MA, Begum S (2003) Marketing of medicinal plants of Utror-Gabral valleys, Swat, Pakistan. Ethnobot Leafl 2003(1):13
43. Khan SW, Khatoon SU (2008) Ethnobotanical studies on some useful herbs of Haramosh and Bugrote valleys in Gilgit, northern areas of Pakistan. Pak J Bot 40:43

44. Hussain AM, Abbasi MS, Hussain N, Majid SA (2013) A survey of important indigenous medicinal plants of district Bhimber Azad Jammu Kashmir, Pakistan. Int J Adv Res 1:635–644
45. Mughal TA (2009) Ethnomedicinal studies of flora of southern Punjab and isolation of biologically active principles. Doctoral dissertation. Lahore College for Women University, Lahore
46. Ahmad M (2006) Checklist of medicinal flora of tehsil Isakhel, District Mianwali-Pakistan. Ethnobot Leafl 10:41–48
47. Ahmad M, Sultana S, Fazl-i-Hadi S, Ben Hadda T, Rashid S, Zafar M, Yaseen G (2014) An ethnobotanical study of medicinal plants in high mountainous region of Chail valley (district Swat-Pakistan). J Ethnobiol Ethnomed 10:36
48. Jabeen A, Khan MA, Ahmad M, Zafar M, Ahmad F (2009) Indigenous uses of economically important flora of Margalla hills national park, Islamabad, Pakistan. Afr J Biotechnol 8 (5):763–784
49. Alamgeer, Younis W, Asif H, Sharif A, Riaz H (2018) Traditional medicinal plants used for respiratory disorders in Pakistan: a review of the ethno-medicinal and pharmacological evidence. Chinas Med 13:48
50. Lawal IO, Olufade II, Rafiu BO (2020) Ethnobotanical survey of plants used for treating cough associated with respiratory conditions in Ede South local government area of Osun State. Plants 9:647

Role of Medicinal Plants in Treatment of Pulmonary Edema

17

Piyush Mittal, Anurag Verma, and Manjari Mittal

Abstract

Pulmonary oedema is a manifestation of both cardiogenic and non-cardiogenic reasons. The clinical picture of Pulmonary oedema mainly include dyspnoea, orthopnoea, chest tightness and coughing. Although, the majority of patients admitted with Pulmonary oedema show rapid clinical improvement as result of intravenous (IV) Inotropes, blood pressure lowering drugs, diuretics etc. but, there is a general lack of good evidence to guide therapy. A number of studies showed efficacy of various natural plants such as garlic, rosemary, turnip etc. and their constituents to reduce lung inflammation. Future research is required to develop innovative pharmacotherapies based on natural medicinal plants capable of relieving symptoms of pulmonary oedema.

17.1 Pulmonary Edema

Pulmonary edema is a condition of the lungs where the lungs are filled with excessive amount of fluids. In this condition patients feel breathing difficulty or shortness of breath. Most often, this condition arises because of heart related problems and other non-cardiogenic reasons may include chemical exposure, toxins, medication overdose, infections, and trauma to chest. Pulmonary edema can be fatal if not diagnosed and treated timely.

P. Mittal (✉) · A. Verma
Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad, India

M. Mittal
Moradabad Institute of Technology, Moradabad, India

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_17

17.2 Clinical Manifestations

The clinical manifestations for pulmonary edema may develop suddenly or sometimes develop over time depending on the etiology of pulmonary edema. The major signs and symptoms include

- Difficulty in breathing (dyspnea)
- Difficulty in breathing when lying flat (orthopnea)
- Chest tightness
- Cyanosis
- Coughing with frothy/pink sputum
- Wheezing
- Fatigue
- Swelling in lower extremities

17.3 Etiology

Pulmonary edema is most often caused by cardiogenic reasons like coronary artery disease, cardiomyopathy, heart valve problems, heart failure, and hypertension. Sometimes it is due to non-cardiogenic reasons depicted in Fig. 17.1. Other risk factors causing pulmonary edema may include diabetes, acute severe asthma, obesity, alcohol/drug abuse, blood transfusion, and central nervous system injury.

17.4 Diagnosis and Treatment Options

Clinical diagnosis of pulmonary edema is made on the basis of signs and symptoms, chest X-ray, chest CT, atrial blood gas test, fine inspiratory crackle sound on auscultation, ECG, echocardiogram, pulse oximetry, and blood test.

The immediate treatment of pulmonary edema is supplemental oxygen in emergency department and certain medications like diuretics and blood pressure lowering medications used to treat cardiogenic pulmonary edema depending on the severity of the case. The treatment for non-cardiogenic pulmonary edema to take the corrective measures for the cause of pulmonary edema, supportive care and to treat underlying conditions, supplemental oxygen and mechanical ventilation. Some lifestyle tips like weight management, regular exercise, balanced diet, quit smoking, reduction in salt intake, management of other medical conditions like blood pressure control can help the patient to manage pulmonary edema.

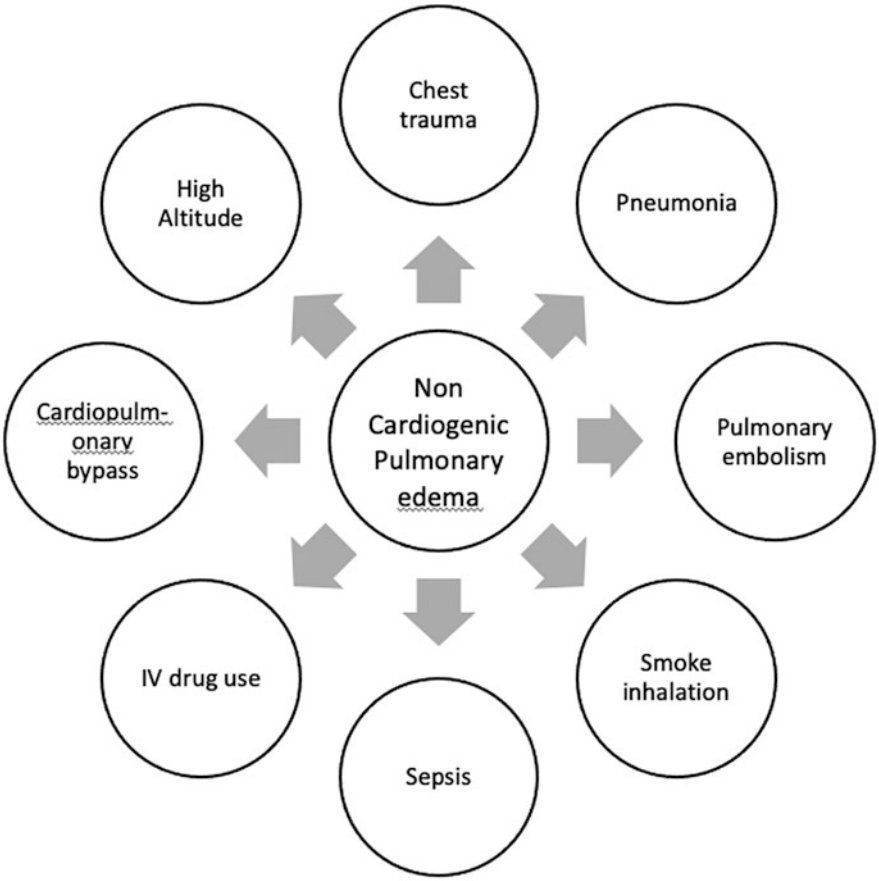


Fig. 17.1 Non-cardiogenic causes of pulmonary edema

17.5 Medicinal Plants Role in Pulmonary Edema

From ancient time plants, herbs, condiments are used to treat medical conditions as home remedies. Around 80% of the world's population have reliance on medicinal plants for their minor ailments. As we know the pulmonary edema is an inflammatory condition of lungs, few herbs/supplements and medicinal plants are found to be useful in treating the conditions. Many studies have shown the effectiveness of CAM (complementary and alternative medicines) like Ayurveda, siddha, Unani, and Tibbi medicines, homeopathy, and traditional Chinese medicines (TCM) in treating cardiovascular and respiratory conditions with the help of different plant-based formulations like tinctures and dried extracts.

There are many herbs and medicinal plants used for cardiovascular and pulmonary pathological conditions but very few are indicated for pathological conditions

Table 17.1 List of plants used in treating pulmonary edema

S. No.	Name of plant	Family	Part used
1	*Allium sativum* (garlic)	Amaryllidaceae	Whole plant
2	*Rosmarinus officinalis* (rosemary)	Lamiaceae	Leaves
3	*Brassica rapa* (turnip)	Brassicaceae	Tubers
4	*Rhodiola rosea* (golden root)	Crassulaceae	Whole grass
5	*Hippophae rhamnoides* (sea buckthorn)	Elaeagnaceae	Leaves
6	*Pueraria lobata* (Asian arrowroot)	Fabaceae	Roots
7	*Ginkgo biloba* (ginkgo)	Ginkgoaceae	Leaves
8	*Aesculus hippocastanum* (horse chestnut)	Hippocastanaceae	Whole plant

such as pulmonary edema in literature, a list of those medicinal plants is depicted in Table 17.1.

17.5.1 *Allium sativum* (Garlic)

Garlic is used as a dietary supplement in our daily food preparation and it is cultivated throughout the world. The medicinal properties of garlic are well documented in various traditional medicinal systems and cultures. Garlic possesses medicinal properties like antimicrobial, cardiovascular, anti-inflammatory, antidiabetic, hypolipidemic, anticancer, immunomodulatory effect. Garlic has shown the effectiveness in treating pulmonary edema in the studies. The possible mechanism is that the organosulfur compounds present in garlic interact with the epithelial sodium channel (ENaC). The ENaCs generally regulate salt and water regulations in various organs. In the lungs, the alveolar fluid clearance through the epithelium is regulated through ENaCs. The compound in garlic allicin inhibits the ENaCs activity, therefore possible role in the reduction of pulmonary edema.

17.5.2 *Rosmarinus officinalis* (Rosemary)

Rosemary is a popular culinary agent in European cousin and used as medicinal herb from ages. It is originated from Mediterranean region and nowadays found all over the world. It is used as spice, natural preservative, ornamental, and medicinal plant at home. Its pharmacological properties include antimicrobial, anti-inflammatory, antioxidant, antitumor, neuroprotective, hypoglycemic, immunomodulatory effects. It is evidenced that rosemary may help to reduce body fluids. The exact mechanism is not known but one study suggested that the antioxidant properties can help to reduce lung fibrosis and inflammation.

17.5.3 *Brassica rapa* (Turnip)

Turnip is a popular vegetable of winter and easy to grow and store. Turnip is low in calories and good for health for many reasons like detoxifying the body, rich in calcium, iron, and vitamin C. It is traditionally used as anti-hypoxia medicine in Tibetan communities. Turnip is rich in polysaccharides, flavonoids, terpenes, and bioactive compounds. Turnip reduces oxidative stress, it also has immunomodulatory, antiulcer, anticancer, antimicrobial activities. Turnip may help to reduce pulmonary edema by its activity on lung barriers, it improves the integrity of lung barriers, reduces the leakage of protein in alveolar fluids, and also inhibits oxidative stress and inflammation.

17.5.4 *Rhodiola rosea* (Golden Root)

Golden root is traditionally used in Europe and China and has shown health benefits like ginseng, and it improves stamina, mood, fatigue, memory. It also demonstrates antiaging, anti-inflammatory, immunostimulant. Golden root is used for mountain sickness as it is a blood tonic and prevents high altitude sickness, it also treats malhypoxia and anoxia.

17.5.5 *Hippophae rhamnoides* (Sea Buckthorn)

Sea buckthorn is used as Tibetan folk medicine, almost all parts of the plants are used as medicine, it is used in dermatitis, cardiovascular conditions, chronic kidney disease, liver problems, indigestions, digestive tract infections, cold, dry eyes, skin conditions, asthma, cancer, immunomodulator agents. Sea buckthorn is also called as gold mine, wonder plant, and golden bush because of these medicinal properties. Sea buckthorn exerts pulmonary edema control by decrease in vascular permeability and oxidative stress.

17.5.6 *Pueraria lobata* (Asian Arrowroot)

Asian arrowroot is commonly known as Kudju in east Asian countries. Its root flower and leaves are used to make medicines. Arrowroot is generally used for alcoholism, diabetes, heart conditions, menopause, obesity, flu, and fever. Arrowroot is found to be effective in pulmonary edema in the study where puerarin a chemical found in arrowroot can prevent lung injury due to hypoxia in animal model. This protective activity is shown as puerarin downregulated the inflammatory cytokines, aquaporins (AQP), and Nf-kB signaling pathway.

17.5.7 *Ginkgo biloba* (Ginkgo)

Ginkgo is a very popular herbal medicine for ages especially in Asian culture. Ginkgo is rich in flavonoids and terpenoids and antioxidants. It is used for memory enhancement, dementia, Alzheimer's disease, anxiety, blood disorders. It has antioxidant, anti-inflammatory, anxiolytic activity and it improves glaucoma, acute mountain sickness. The study suggested that the ginkgo biloba prevents the development of pulmonary edema in experimental rats.

17.5.8 *Aesculus hippocastanum* (Horse Chestnut)

Horse chestnut is widely used as a phytomedicine from ancient times, this plant is native of east Europe. Horse chestnut is widely used for its activity on varicose vein, leg ulcer, bruises. As a folk medicine, it is used for hematoma, cardiac venous insufficiency, hemorrhoids, pain, phlebitis, diarrhea, anorexia, antiseptic, antiaging. It is evident that use of horse chestnut in gastric ulcer, stroke, venous congestion, skin inflammation, and frostbite. Horse chestnut is used for lung cancer and it is used as an ingredient in the polyherbal formulation for the treatment of pulmonary edema.

References

1. Alena (2019) 7 health benefits of horse chestnut extract https://www.healthline.com/nutrition/horse-chestnut-benefits. Accessed 30 Oct 2020
2. Bahria et al (2017) Prophylactic and curative effect of rosemary leaves extract in a bleomycin model of pulmonary fibrosis. Pharm Biol 55(1):462–471
3. Banerjee et al (2002) Effect of garlic on cardiovascular disorders: a review. Nutr J 1:4
4. Berg JT (2004) Ginkgo biloba extract prevents high altitude pulmonary edema in rats. High Alt Med Biol 5(4):429–434
5. Clark SB, Soos MP (2020) Noncardiogenic pulmonary edema. StatPearls Publishing, Treasure Island. https://www.statpearls.com/ArticleLibrary/viewarticle/28023 [Updated 2020 Oct 1]
6. Du et al (2017) Sea buckthorn paste protects lipopolysaccharide-induced acute lung injury in mice through attenuation of oxidative stress. Oxid Med Cell Longev:1–9
7. Steven D. Ehrlich (2016) Pulmonary edema. http://pennstatehershey.adam.com/content.aspx?productid=107&pid=33&gid=000137. Accessed 25 Sept 2020
8. Eva et al (2015) Sea buckthorn (Hippophae rhamnoides L.) as a potential source of nutraceutics and its therapeutic possibilities—a review. Acta Vet Brno 84:257–268
9. Fallon et al (1998) Garlic prevents hypoxic pulmonary hypertension in rats. Lung Cell Mol Physiol 19:283–287
10. Health benefits of Ginkgo biloba (2017). https://www.medicalnewstoday.com/articles/263105. Accessed 29 Oct 2020
11. Idris et al (2020) Phytochemical, ethanomedicinal and pharmacological applications of escin from *Aesculus hippocastanum* L. towards future medicine. J Basic Clinic Phys Pharmacol 31 (5):20190115
12. Jayamurthy et al (2011) Modulation of hypoxia-induced pulmonary vascular leakage in rats by sea buckthorn (Hippophae rhamnoides L.). Evid Based Complement Alternat Med:1–13
13. Jin et al (2012) Anti-inflammatory and antioxidant activities of constituents isolated from Pueraria lobata roots. Arch Pharm Res 35(5):823–837

14. Kudju (n.d.). https://www.webmd.com/vitamins/ai/ingredientmono-750/kudzu. Accessed 29 Oct 2020
15. Li et al (2018) P-coumaric acid as a prophylactic measure against normobaric hypoxia induced pulmonary edema in mice. Life Sci 211:215–223
16. Mayo Clinic (n.d.) Pulmonary edema. https://www.mayoclinic.org/diseases-conditions/pulmonary-edema/symptoms-causes/syc-20377009. Accessed 25 Sept 2020
17. Moraga FA et al (2007) Ginkgo biloba decreases acute mountain sickness in people ascending to high altitude at Ollague (3696 m) in northern Chile. Wilderness Environ Med 18:251–257
18. Oliveira d et al (2019) Rosmarinus officinalis L. (rosemary) as therapeutic and prophylactic agent. J Biomed Sci 26:5
19. Qian et al (2012) Salidroside protects human erythrocytes against hydrogen peroxide-induced apoptosis. J Nat Prod 75:531–537
20. Science-Backed Health Benefits of Rhodiola rosea (n.d.). https://www.healthline.com/nutrition/rhodiola-rosea. Accessed 15 Oct 2020
21. Sea Buckthorn (n.d.). https://www.webmd.com/vitamins/ai/ingredientmono-765/sea-buckthorn. Accessed 25 Oct 2020
22. Sandra Tonn (n.d.) Turnips are tops for health. https://www.alive.com/food/turnips-are-tops-for-health/. Accessed 15 Oct 2020
23. Wang et al (2016) Protective effects of puerarin on acute lung and cerebrum injury induced by hypobaric hypoxia via the regulation of aquaporin (AQP) via NF-κB signaling pathway. Int Immunopharmacol 40:300–309
24. Wang T et al (2020) Chinese medicinal plants for the potential management of high-altitude pulmonary oedema and pulmonary hypertension. Pharm Biol 58(1):815–827
25. Ware LB et al (2005) Acute pulmonary edema. N Engl J Med 353:2788–2796
26. Zampieron ER (2017) Horse chestnut (Aesculus Hippocastanum) for venous insufficiency. Int J Complement Alt Med 5(3):00153

Medicinal Plants Used in the Treatment of Influenza A Virus Infections

18

Shivraj Popat Jadhav, Himmat Singh, Ritu M. Gilhotra, Anurag Mishra, Yogendra Singh, Anand Krishnan, Kamal Dua, and Gaurav Gupta

Abstract

All over the world, different types of influenza viruses are responsible for seasonal pandemics annually. The influenza virus is responsible for 0.3–0.5 million deaths every year. Influenza A, B, and C are the three main types of influenza virus. Influenza A virus is the most infectious one among different types as it has the ability to change genetic shift and transfer from animal to human. Various synthetic drugs are prescribed for the treatment of influenza. But these drugs have their own drawbacks like the production of resistance and side effects. Hence remedies for influenza A can be obtained from nature. Different studies are carried over different plant extracts in the discovery of effective anti-influenza treatments. Various phytochemicals are being screened for effective and safe anti-

S. P. Jadhav
School of Pharmacy, Suresh Gyan Vihar University, Jaipur, India

Divine College of Pharmacy, Baglan, Nashik, Maharashtra, India

H. Singh · R. M. Gilhotra · A. Mishra · G. Gupta (✉)
School of Pharmacy, Suresh Gyan Vihar University, Jaipur, India

Y. Singh
Maharishi Arvind College of Pharmacy, Ambabari, Jaipur, India

A. Krishnan
Department of Chemical Pathology, School of Pathology, Faculty of Health Sciences and National Health Laboratory Service, University of the Free State, Bloemfontein, South Africa

K. Dua
Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Sydney, NSW, Australia

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_18

influenza treatment. This chapter includes an overview of different plants and phytochemicals screened for anti-influenza A activity.

Keywords

Influenza A virus infections · Epidemiology · Etiology · Medicinal plants · Phytochemicals

18.1 Influenza A Virus Infections: Introduction and Epidemiology

Viral infections have prevailed throughout the world among humans as well as animal populations and will remain one of the foremost causes of mortality and morbidity. Some of the examples of these viruses are Human Immunodeficiency Virus (HIV), Influenza virus, Ebola virus, SARS, and Coronavirus. There are about 219 virus species that are capable to infect humans. In 1901 yellow fever virus was first to be discovered and three to four new species are still being discovered every year [55]. The influenza virus is one of the viruses which is accountable for more than three million new cases every year and 0.3–0.5 million deaths every year [13, 36]. The influenza virus causes human respiratory infection and has a high morbidity and mortality rate. Influenza viruses can be classified in subspecies like A, B, and C virus. At a times there can be several influenza viruses circulating in humans, which cause seasonal flu having mild symptoms.

Some of the biggest and most dangerous disease outbreaks of humankind are caused by the influenza virus. Spanish flu pandemic originated in 1918 and responsible for killing more than 60 million people all over the world; followed by more pandemics in 1957, 1968, 1977, and 2009 killing millions more. Still, in a year around 0.4 million people probably die because of recurring flu [1, 26, 48].

Influenza is defined as "a contagious respiratory illness caused by influenza viruses that infect the nose, throat, and lungs. It can cause mild to severe illness, and at times can lead to death" by the Centers for Disease Control and Prevention of the USA [18].

Sneezing or coughing by an infected person blows out fine droplets into the air. Inhalation of these droplets by a healthy person is enough to cause infection. The average incubation period is about 48 h. Initially, cells of the upper respiratory tract are infected followed by lower parts of the respiratory tract. Various symptoms observed in an infected person rages from fever, sore throat, cough, rhinitis, muscle aches, tiredness, headache, vomiting, and diarrhea [33].

18.2 Classification and Etiology of Influenza Virus

The influenza virus is from the Orthomyxoviridae family. This family contains viruses having segmented single sense single-strand RNA inside the envelope. Influenza A, Influenza B, and Influenza C are the types of influenza virus. Among

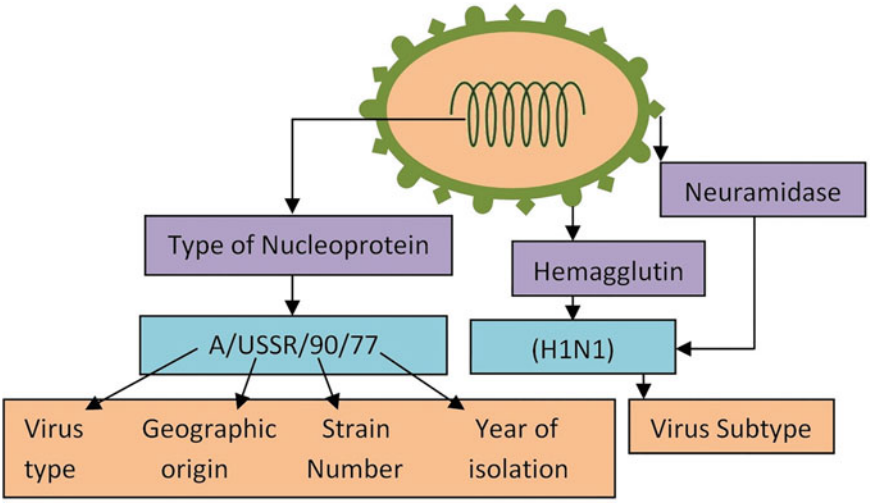


Fig. 18.1 Nomenclature of influenza virus

these four only two are clinically relevant to humans [3]. World Health Organization (WHO) laid certain norms regarding the nomenclature of the influenza virus in 1980. These norms include factors such as [32] (Fig. 18.1);

- Virus type (either A, B, C).
- The country or geographic place where the virus is first secluded.
- Strain.
- Isolation year.
- Proteinous antigenic structure present on the virus indicated by letter and number like H1 to H6 and N1 to N9.

Among these types, Influenza A is the most hazardous one and it can infect a variety of hosts like swine, horses, domestic as well as wild birds, fowl, and dogs [38]. Influenza A viruses contain multiple-segmented genomes, which indicates that the genome is separated in different sections which are joined together. These genome segments rearrange to produce a new combination, producing a new virus subtype [28]. Each year, seasonal outbreaks of influenza viruses occur because of different subtypes of influenza A viruses. Sometimes these subtypes can cause huge pandemic outbreaks like the 2009 H1N1 pandemic influenza, also called swine flu. Human, avian, and swine influenza viruses' genomic parts are combined in this subtype [45]. The most challenging thing about the influenza virus is its ability to cause a genetic shift, which causes constant evolution and production of new subtypes (Table 18.1).

Table 18.1 Characteristics of different Influenza Virus types

Type of influenza virus	Features
Type A	• Responsible for causing mild to severe sickness • All age groups are susceptible to infection • Human, as well as animal species, are affected
Type B	• Responsible for causing milder illness than type A • Children are more susceptible to infection • Humans are only affected
Type C	• Hardly reported in humans • Caused no epidemics till date

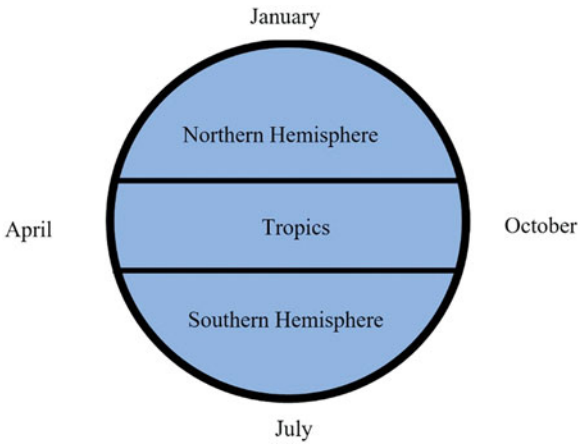


Fig. 18.2 General pattern of influenza annual season [44]

18.3 Epidemiology

Wild birds and domestic birds act as a reservoir of Influenza A virus in which all HA and NA types occur [52, 53]. Avian plague, also called bird flu occurs in chicken due to highly infectious subtypes H5 and H7. This virus can replicate very fast inside the bird body and may have a maximum death rate. Type A/H3N2 and A/H1N1 are observed to be cocirculated in humans since 1977. Viruses of subtype H1N2 were first observed in 1977. Then in 2001 and 2002 outbreak was observed in some countries [16]. In each winter periodic influenza epidemics can arise in both the southern and northern hemispheres. Due to Influenza, it is estimated that, per year, approximately 500,000 deaths occur worldwide [11] (Fig. 18.2).

Slight is identified about influenza's tropical epidemiology, but it is considered that influenza can arise around the year. Apart from seasonal dependency, infections can also occur around the year in temporarily limited areas. It is estimated that during the annual outbreaks of influenza around 10–15% of the population is affected. The majority of deaths associated with Influenza are over 60 years old [49, 60]. In the past century, three big pandemics strike the human race, in 1918 Spanish flu (H1N1)

is responsible for nearly 40 million deaths, in 1957 Asian influenza (H2N2) caused the death of 1–2 million population and 1968 Hong Kong flu (H2N3) caused the death of 0.75–1 million population [11].

18.4 Treatment/Management of Influenza Virus Disease

The influenza virus is self-limiting and symptoms are mild in most individuals. If infections are mild, then there is no need for antiviral treatment. Antiviral treatment is necessary during outbreaks. Several medications belonging to the neuraminidase inhibitor family-like Oseltamivir, Zanamivir, and Peramivir are used in the treatment of Influenza A as well as B. Other medications like Amantadine and Rimantadine are effective versus type A, however, not against type B. Along with this vaccination is highly recommended before the seasonal outbreak [21, 23, 57]. These drugs have their own drawbacks like side effects, specific activity. Remedies over Influenza A can be obtained from nature. Nature is acting as a reservoir of medicines since human civilization. Various plants are found to be active against the Influenza A virus. Alternative therapy against Influenza A virus is necessary for several reasons like resistance to already present drugs, the emergence of new virus types, unpredictable availability of the vaccine, and the cost of available drugs.

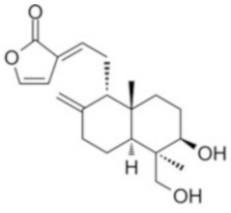
18.5 Medicinal Plants Used in the Treatment of Influenza A Virus Infections

Plants across the world have been explored for Anti-Influenza activity.

(a) *Ribes nigrum* L. [10, 25]: This plant is also recognized as black currant or cassis. It is a woody shrub from the family Grossulariaceae. Crude fruit and leave extract of this plant is found to be active against Influenza A as well as B. Crude fruit extract was rich in anthocyanins like delphinidin, peonidin, and cyanidin along with organic acids like ascorbic acid and citric acid. The concentration of plant fruit extract to inhibit plaque formation by 50% (Also termed as IC_{50}) for Influenza virus A (IVA) was found to be 3.2 μg/mL. The dose of 10 μg/mL directly inactivates 99.9% IVA at a pH of 2.8 [25]. Plant extract is found to have broad antiviral activity towards IVA. One of the studies indicates that extract mainly acts by suppressing the late stage of growth of the virus in the cell [25] while another study indicates that the early stage of the infection process is blocked [10]. Experimental results indicate that plant constituents inhibit viral internalization but do not interfere with cellular activity [10]. The mechanism may involve direct antiviral effects of the extract by a combination of constituents of an extract with haemagglutinin on the viral envelope. In vivo studies also indicated antiviral activity of leave extract in mice [10].

(b) *Cistus incanus* P. [9]: This plant is a hybrid between *Cistus albidus* and *Cistus crispus*. It is a shrub with pink to red flowers belonging to the family Cistaceae. CYSTUS052 is the extract obtained from this plant and high in polyphenolic content (more than 26%) and other constituents like gallocatechin, gallic acid, catechin, and epicatechin [9]. The Anti-Influenza effect of CYSTUS052 was studied using Madine Darby Canine Kidney (MDCK) cell line. These cell lines were infected with A/Puerto-Rico/8/34 (H1N1) (PR8), the extremely infective avian influenza virus (HPAIV), A/FPV/Bratislava/79 (H7N7) (FPV) along with a human isolate of the HPAIV of the H5N1 subtype (A/Thailand/1(KAN-1)/2004 (H5N1)). Dose-dependent reduction of progeny virus was showed by the extract. At a concentration of 50 μg/mL CYSTUS052 showed a maximum reduction in progeny virus. Cell morphology and viability was not affected by CYSTUS052 and does not undesirably affect cellular production and metabolism. The mechanism of action of extract indicates that it may hinder the virus itself and avoid infection by a reduction in virus uptake by the cell. Cells pretreated with CYSTUS052 showed the inability of the virus to bind with RBC which indicates that components of the extract are able to interact directly with viral Hemagglutinin and block binding of the virus to cellular receptors. Also, IVA does not show resistance easily to CYSTUS052.

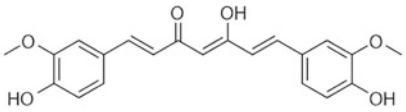
(c) *Andrographis paniculate* [4]: This plant belongs to the family Acanthaceae. Diterpenoid lactones such as andrographolide, dehydroandrographolide (DAP), and neoandrographolide are major components of the plant. DAP showed strong anti-influenza A virus action towards the A/chicken/Hubei/327/2004 (H5N1), A/duck/Hubei/XN/2007 (H5N1), A/PR/8/34 (H1N1), A/NanChang/08/2010 (H1N1), and A/HuNan/01/2014 (H3N2) in vitro. The mechanism of action of DAP was found to be inhibition of H5N1 replication by a reduction in the construction of viral nucleoprotein (NP) mRNA, NS1 proteins. DAP does not affect the absorption and release of the virus. DAP also efficiently controlled the nuclear transfer of viral ribonucleoprotein (vRNP) complexes which is significant for Anti-IVA activity. The selectivity index of DAP was found to be close to ribavirin in A549 cell line. Also, DAP showed a marked effect against the production of viral progeny.



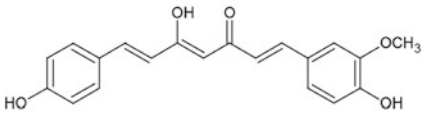
Dehydroandrographolide

(d) *Curcuma Longa* [6, 8]: Curcuma longa is a traditional plant used for various purposes belongs to the family Zingiberaceae and found in south to southeast tropical Asia. Rhizomes of *C. longa* are used for the extraction of active

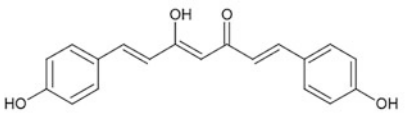
components and to study antiviral activity. Curcumin rhizome contains diarylheptanoids (class of curcuminoids) like curcumin, demethoxycurcumin, and bisdemethoxycurcumin with different essential oils [14]. Anti-Influenza A study was carried out in the MDCK cell line against Human influenza virus PR8, A/Puerto-Rico/8/34 (H1N1), and avian influenza virus A/chicken/Taiwan/NCHU0507/99 (H6N1). Initially, the cell culture medium was provided with different levels of curcumin. The virus population was determined at 12, 18, 24, and 30 h post-infection. After treatment with curcumin, it was observed that the synthesis of the virus was drastically decreased in a dose-dependent manner. Various viral protein synthesis was affected like haemagglutinin (HA), neuraminidase (NA), and matrix protein. Curcumin showed an antiviral effect in the early stages of viral infection like virus attachment but not against penetration. This can be attributed to the blockade of HA activity by curcumin which was confirmed by HA inhibition assay. Loss of the HA activity suggested that curcumin intrudes the connection between the viral HA protein and its cellular receptor by already occupying the binding position on HA protein or by alteration of the virus envelope.



Curcumin



Demothoxycurcumin



Bisdemethoxycurcumin

(e) *Ginkgo biloba* [14]: This tree is also called as maidenhair and native to china belonging to the family Ginkgoaceae. Extracts from leaves of *G. biloba* contain flavonoids, namely kaempferol, quercetin, isorhamnetin along with terpene lactones such as bilobalide, ginkgolide A, B, C, and J [30]. The anti-Influenza activity of plant leaf extract was studied by using MDCK cells. Leaf extract was found to be nontoxic to MDCK cells. The extract showed no effect on the multiplication of cells as indicated by plaque assay, however, when MDCK cells were first exposed to leaf extract, anti-influenza activity was markedly

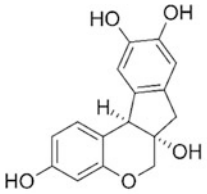
enhanced as dose is increased. Plant leaf extract at 5 μg/mL completely inhibited plaque formation. This suggests that plant extract inhibits the virus in the early stages before entering the virus in the cytoplasm of the cell. The mechanism of action of plant extract is based on the inhibition of HA on virus-cell and prevents virus adsorption on the surface of the cell. Leaf extract inhibited different types of influenza viruses like influenza A/PR/8/34 (H1N1), A/Udorn/72 (H3N2), and B/Lee/40.

(f) *Psidium guajava* Linn [46].: *Psidium guajava* Linn belongs to the family Myrtaceae with different chemical constituents like tannins, alkaloids, saponins, triterpenoids, glycosides, flavonoids, and phenolic compounds. Different polyphenols like catechin, myricetins, quercetin, gallic and ellagic acids are present in leaf extract [35]. Extract of leaves of *P. guajava* showed 111 mg of tannin per 100 mL. It was observed that the tea leaf extract of the plant does not show any cytotoxic effect on AX4 cells. Leaf extract showed an inhibitory effect on the growth of different species of resistance seasonal viruses with IC_{50} values of $0.58 \pm 0.14\%$ versus A/Yamaguchi/20/06 and $0.23 \pm 0.05\%$ versus A/Kitakyushu/10/06. The mechanism of action of leaf extract involves inhibition of hemagglutinin and Neuraminidase of the Influenza virus at a concentration of 0.1%. This prevents the entry of the viral particle. This overall concludes that leaf extract (tea) has potent anti-influenza activity.

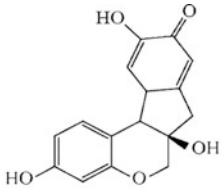
(g) *Echinacea purpurea* [37]: It is a North American species also called as purple coneflower belongs to the daisy family or Asteraceae family. A standardized extract of a plant called Echinaforce® was tested for Anti-Influenza A virus action. Echinaforce consists of an extract in ethanol of herb and root (95:5) of plant *E. purpurea.* The extract contains most of the caffeic acid derivatives and alkyl amides and traces of polysaccharide [42]. Human H1N1-type IV, extremely infectious avian IV (HPAIV) of the H5- and H7-types and swine-origin IV (S-OIV, H1N1), were all deactivated in MDCK cell culture assays by the Echinaforce extract at recommended doses for oral ingestion. A thorough study indicated that with the H5N1 HPAIV strain, before infection, straight interaction between Echinaforce and virus was compulsory for utmost suppression in virus replication. The extract hinders with the viral entry into cells as indicated by Hemagglutination assay that the extract suppressed the receptor-binding action of the virus. Echinaforce did not produce any type of resistance as compared to Tamiflu which produced resistance in viruses.

(h) *Caesalpinia sappan* L. [31]: *C. sappan* is a plant belonging to the Leguminosae family, also known as Brazil or Sappan wood having distribution in Asia. The heartwood of this plant has been used traditionally for various medicinal purposes. Chemical constituents present sappan wood includes various phenolic compounds like xanthone, coumarin, chalcones, flavones, homoisoflavonoids, protosappanin A, 3-deoxysappanchalcone, sappanchalcone, rhamnetin, brazilein, and brazilin. The anti-influenza activity of these constituents was studied with help of the cytopathic effect (CPE) reduction method in vitro on the A/Guangdong/243/72 (H3N2) virus strain with the help of using MDCK cell line. Antiviral actions of brazilein, brazilin,

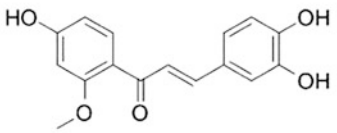
and protosappanin A were <50% at their maximal non-cytotoxic concentrations (MNCC) as indicated by results of the CPE assay, while rhamnetin showed anti-influenza activity lesser than that of ribavirin and oseltamivir acid. 3-deoxysappanchalcone showed substantial in vitro anti-influenza virus activity. IC_{50} value was approximately eight times lesser than ribavirin and almost 15 times more than oseltamivir acid. Sappanchalcone showed a potency similar to that of 3-deoxysappanchalcone. Oxysappanchalcone and sappanchalcone displayed the maximum anti-influenza virus (H3N2) activity with IC_{50} values of 1.06 and 2.06 μg/mL, correspondingly.



Brazilin

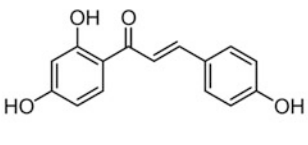


Brazilein

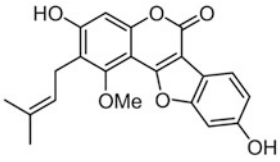


Sappanchalcone

(i) *Glycyrrhiza uralensis* [39, 51]: *Glycyrrhiza uralensis* is a member of the Leguminosae family commonly called as licorice has been used for various medicinal purposes traditionally like treatment of fever, liver diseases, constipation, ulcer, etc. The major constituents present in the root are flavonoids, pentacyclic triterpene saponins like liquiritin, isoliquiritin, glycyrrhizin, and glycyrrhizic acid. Among 18 isolated polyphenols from methanol extract of roots of the plant shown neuraminidase inhibitory activity. 18 polyphenols are from different groups like chalcones, flavonoids, coumarins, and phenylbenzofuran. Among these 18 polyphenols isoliquiritigenin (IC_{50} = 9.0 lM) and glycyrol (IC_{50} = 3.1 lM) had strong inhibitory activity. From the structure-activity relationship, it became clear that the furan ring present in polyphenols is essential for the activity of neuraminidase inhibition. Also, this activity is increased by the apioside group on the chalcone and flavone backbone. Also, in another study, glycyrrhizin present in licorice root protected mice exposed to a lethal amount of influenza virus through stimulation of IFN-Y production by T cells.

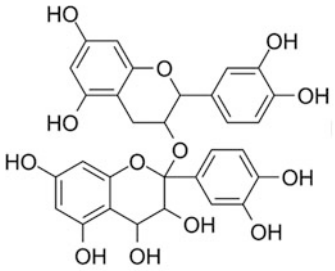


Isoliquiritigenin

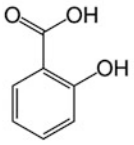


Glycyrol

(j) *Sambucus nigra L.* [24]: Elderberry has been used traditionally for the treatment of influenza and colds. *S. nigra* belongs to the family Caprifoliaceae. Elderberry is known to have a high content of polysaccharides and phenolic compounds like phenolic acid, flavonoids, proanthocyanidins, and catechins [56]. The anti-influenza activity of these phenolic compounds is suggested due to their direct action on IVA. The study reported IC50 value of elderberry concentrated juice is 720 ± 79 μg/mL and the selectivity index is 36 ± 6.7. The anti-IVA mechanism of action of elderberry juice can be through inhibition of haemagglutination and viral proliferation. The constituent from elderberry juice said to stop the adhesion of the virus-cell to the host cell receptors. In addition to this, it also stimulates the production of cytokines and monocytes.



Proanthocynidines



Phenolic Acid

(k) Ma-Huang-Tang [54]: Also known as ephedra in common language belongs to the family Ephedraceae. Ma-Huang-Tang (MHT) is used for various purposes like bronchitis, asthma, and influenza. Various chemical constituents present in MHT include L-methylephedrin (LMEP), L-ephedrine (LEP), and D-pseudo-ephedrine (DPEP). These chemicals were found to be safe in cytotoxic studied on MDCK cells. These constituents are said to hinder the proliferation of influenza A virus in vitro. These ingredients significantly inhibited different gene signaling pathways related to mRNAs like TLR3, TLR4, and TLR7. Hence three ephedra alkaloids were found to be effective against virus in vitro. Animal research indicated that LEP and DPEP significantly decreased lung index, lung injury, virus load in the lung, level of IL-1β, and stopped viral mRNA expression and protein expression. These all findings suggest that MHT alkaloids can be used for effective management of the Influenza A virus.

(l) *Syzygium nervosum* [19]: This plant is also known as *Cleistocalyx operculatus* native to Asia belonging to the family Myrtaceae. During the study neuraminidase, inhibitory activity was shown by ethanolic extract of leaves. Chemical constituents of leaves include acetophenones, flavanones, and others. Isolated components showed maximum enzymatic prohibition on several neuraminidases from diverse influenza viruses, like H1N1, H9N2, and

oseltamivir-resistant novel H1N1 with H274Y mutation expressed in HEK293 cells. IC_{50} values of these constituents' ranges from 5.07 ± 0.94 μM to 9.34 ± 2.52 μM.

(m) *Pinus densiflora* [20]: Plant is usually recognized as Korean red pine and from the family Pinaceae. The plant is extensively spread to East Asia, Korea, China, and Japan. Traditionally *P. densiflora* is used for the treatment of stroke, fatigue, depression, anxiety, and cancer. Chemical components present in the leaves of the plant include essential oil (α-pinene, β-pinene, camphene, limonene), bornyl acetate, borneol, benzoic acid, cinnamic acid, flavonoids, diterpenoids, and stilbenoid. Cytotoxic and cytopathic studies of plant leave extract were performed on DCK cells. Extracted components were studied for Anti-influenza activity by CPE inhibition and NA inhibition assay method. The mechanism of these components includes a decrease in the synthesis of HA and NA depending upon the dose, which was supported by immunofluorescence assay. In the viral infected cell, green fluorescence was observed of tagged NA while fluorescence was not found in the treated cell. Flavonoids exerted anti-influenza activity by direct NA inhibition while diterpenoids affect the gene expressions of various proteins which are essential for viral replication.

(n) *Mosla scabra* [58]: *M. scabra* is a tomentose plant of the family Labiatae native to southeast China. It is used for antiviral, antipyretic effects for lung disease and demonstrated to be useful in cold, fever, inflammation, and bronchitis. Crude drug extract primarily contains flavonoids, such as apingenin, 5-hydroxy-6,7-dimethoxyflavone, 5,7-dihydroxy-4-methoxyflavone, and acacetin. In this study antiviral effect of M. scabra herbal extract is studied against the influenza virus A/PR/8/34 virus (H1N1 subtype). After administration of the extract at a concentration of 0.3–30.0 mg/kg in allantoic fluid of egg showed a survival rate of more than 80%. This suggested no toxic effect at the therapeutic dose. The IC_{50} value of extract was determined to be 0.15 μg/mL. Flavonoids present in the extract are mainly responsible for the antiviral activity which can affect the membrane synthesis and budding of viral particles by the prohibition of IVA sialidase.

(o) *Alpinia katsumadai* [17, 27]: *A. katsumadai* is a traditional Chinese medicine belonging to the Zingiberaceae family used as anti-emetic and stomachic. Major constituents present in the plant include diarylheptanoids, monoterpenes, flavonoids, sesquiterpenes, and chalcones. A study was performed to find out the anti-influenza outcome of two plant seed extract and five fractions on virus strains like A/PR/8/34 (H1N1) and A/Chicken/Korea/MS96/96 (H9N2) in MDCK cells. One of the extracts demonstrated dose-dependent antiviral activity against A/PR/8/34 (H1N1) at a dose of 12.5 μg/mL. From quantitative real-time PCR, the extract showed activity by the mechanism of obstruction of viral attachment and virus replication after entry.

18.6 Phytochemicals Used in Influenza A Virus Infections

(a) *Polyphenols*:
Polyphenols show a wide range of antiviral activity through various mechanisms like the prohibition of NA activity, inhibition of viral protein or mRNA synthesis, or inhibition of membrane fusion. Polyphenols show activity in the early stages of viral infection. Polyphenols extracted from fruits of *Chaenomeles sinensis* showed activity against influenza A by inhibition of HA activity as well as by suppression of NS2 protein synthesis [40]. Polyphenols from leaves extract of *Folium isatidis* cause a reduction in the pulmonary index and reduced mortality rate in mice [22]. Polyphenols from plant extract *Reynoutria elliptica* showed high inhibitory activity for NA [29]. Extract of plant *Geranium sanguineum* is rich in polyphenolic complexes showed strong anti-influenza activity in vitro as well as in vivo in mice [15]. *Cistus incanus* extract having polyphenolic content showed strong antiviral activity in MDCK and A549 cell cultures infested with avian and human influenza strains [9]. Flavonoids are a group of polyphenols that have shown antiviral activity against the influenza virus. *Houttuynia cordata* contains flavonoid quercetin 3-rhamnoside which is reported to have an inhibitory result on the replication of Influenza A virus [7]. Juice of the root of plant *Agrimonia pilosa* has been used for the treatment of cough and colds traditionally, later the juice was found to contain different flavonoids like catechin, hyperoside, quercitrin, quercetin, and rutin and are useful for the treatment of influenza A virus [43].

(b) *Alkaloids*:
Alkaloids are present abundantly in different medicinal plants. Alkaloids possess a variety of pharmacological activities. The isoquinoline alkaloid thalimonine which is isolated from the *Thalictrum simplex* has exhibited antiviral activity against influenza strain H7N7 and H7N1 in cell cultures. Thalimonine distinctly stopped the influenza virus replication in vitro by decreasing the activity of viral glycoproteins HA and NA on the surface of infected cells [41]. Extract of plant *Commelina communis* contains alkaloids which shown antiviral activity against the influenza virus H1N1 in vitro as well as in vivo [2]. Total alkaloids like β-carbolines: harmine, harmalol, harmaline, and harman and quinazoline derivatives: vasicine and vasicinone present in the extract of *Peganum harmala* seeds exhibited in vitro anti-influenza activity [34]. Isoquinoline alkaloid berberine derived from plant *Hydrastis canadensis* strong inhibitory effect on the growth of H1N1 influenza A strains PR/8/34. Berberine acts post-transitionally and stops virus protein maturation and hence stop viral growth [5]. Hirsutine is a type of corynanthe indole alkaloid derived from the plant *Uncaria rhynchophylla*. Hursutine showed a potent anti-influenza activity [47].

(c) *Aromatic organic compounds*
Roots of plant *Cynanchum stauntonii,* belonging to the family Apocynaceae contain different volatile oils like decadienal, methypentanol, furanone, and dihydro-5-pentyl which showed antiviral action against the influenza virus

in vivo and stopped deaths because of the virus in a dose-dependent manner [59]. *Ferula assafoetida* contains anti-influenza A components sesquiterpene coumarins and diterpenes. These components showed greater activity against Influenza A virus as compared to amantadine [50]. Glycyrrhizin is triterpenoid saponin present in roots of plant licorice. This triterpenoid saponin is found to have a protective action on the cells against influenza virus A, H3N2. Treatment with glycyrrhizin showed a strong decrease in the number of infested human lung cells [51].

(d) *Proteins/sugar derivatives*

Sugar and sugar analogs have been tested for anti-influenza activity. These sugars act by disruption of glycosylation which is required for the synthesis of glycoprotein. These sugars inhibit various enzymes required for the synthesis of sugar chains inside the virus. Benzyl group attached sugar molecule has an antiviral effect against influenza A virus [50]. *Codiaeum variegatum* leaves contain bioactive cynoglucoside which is reported to have anti-influenza A activity [12] (Fig. 18.3).

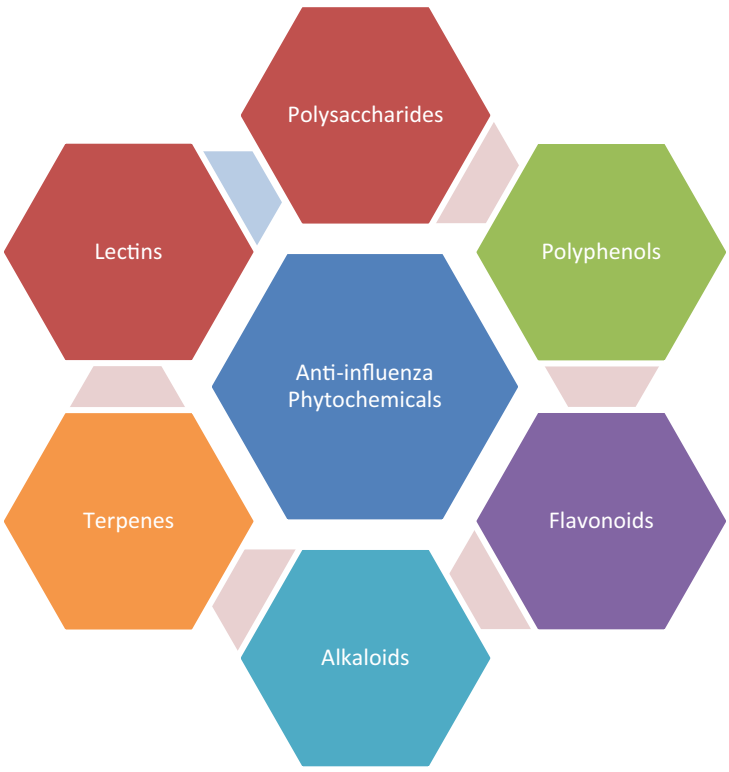


Fig. 18.3 Groups of different phytochemicals having anti-influenza activity

Plant extracts and phytochemicals show anti-influenza activity by various mechanisms such as inhibition of acidification of viral membrane, by inhibition of viral attachment to host cell, by inhibition of entry of viral cell in a host cell, by inhibition of NA and HA present on viral cell, and by inhibition of viral replication through suppression of viral mRNA.

18.7 Conclusion and Future Prospectus

Influenza virus A is responsible for the pandemic in human history and it holds the dangerous potential to cause major pandemics and deaths in the future also. Influenza virus causes an acute respiratory infection which contributes to noteworthy morbidity and mortality in seasonal epidemics and pandemic eruptions throughout the world. Many new antiviral agents have been synthesized like oseltamivir and ribavirin for the cure of influenza infection. But these synthetic drugs have their own drawbacks like the development of resistance and side effects. Vaccination is another remedy for the stoppage of influenza virus contagion but the delay in the development of vaccines and changes in the genetic structure of the virus is a major problem associated with vaccination. Hence an effective and universal treatment against influenza virus species is still necessary. Such treatment against influenza A virus can be obtained from plants as plants hold a history of providing remedies against various diseases. Various studies are carried out concerning the anti-influenza virus potential of a number of plants and found to be effective. Physiological activities of various phytochemicals like polyphenols, flavonoids, alkaloids extracted from plant sources have shown promising activity against different strains of Influenza A virus in vitro and in vivo. In the future, a combination of modern high-throughput screening knowledge along with traditional knowledge of plants can lead to the discovery of a good anti-influenza candidate. This can prevent annual deaths occurring during pandemics throughout the world.

References

1. Beveridge WIB (1977) Influenza: the last great plague. An unfinished story of discovery. Heinemann Educational Books, London
2. Bing FH, Liu J, Li Z, Zhang GB, Liao YF, Li J, Dong CY (2009) Anti-influenza-virus activity of total alkaloids from Commelina communis L. Arch Virol 154(11):1837–1840. https://doi.org/10.1007/s00705-009-0503-9
3. Blümel J, Burger R, Drosten C, Gröner A, Gürtler L, Heiden M, Hildebrandt M, Jansen B, Klamm H, Montag-Lessing T, Offergeld R, Pauli G, Seitz R, Schlenkrich U, Schottstedt V, Willkommen H, Von König CHW, Schweiger B (2009) Influenza virus. Transfus Med Hemother 36(1):32–39. https://doi.org/10.1159/000197314
4. Cai W, Li Y, Chen S, Wang M, Zhang A, Zhou H, Chen H, Jin M (2015) 14-Deoxy-11,12-dehydroandrographolide exerts anti-influenza A virus activity and inhibits replication of H5N1 virus by restraining nuclear export of viral ribonucleoprotein complexes. Antivir Res 118 (March):82–92. https://doi.org/10.1016/j.antiviral.2015.03.008

5. Cecil CE, Davis JM, Cech NB, Laster SM (2011) Inhibition of H1N1 influenza A virus growth and induction of inflammatory mediators by the isoquinoline alkaloid berberine and extracts of goldenseal (Hydrastis canadensis). Int Immunopharmacol 11(11):1706–1714. https://doi.org/10.1016/j.intimp.2011.06.002
6. Chen DY, Shien JH, Tiley L, Chiou SS, Wang SY, Chang TJ, Lee YJ, Chan KW, Hsu WL (2010) Curcumin inhibits influenza virus infection and haemagglutination activity. Food Chem 119(4):1346–1351. https://doi.org/10.1016/j.foodchem.2009.09.011
7. Choi HJ, Song JH, Park KS, Kwon DH (2009) Inhibitory effects of quercetin 3-rhamnoside on influenza A virus replication. Eur J Pharm Sci 37(3–4):329–333. https://doi.org/10.1016/j.ejps.2009.03.002
8. Dao TT, Nguyen PH, Won HK, Kim EH, Park J, Won BY, Oh WK (2012) Curcuminoids from Curcuma longa and their inhibitory activities on influenza A neuraminidases. Food Chem 134 (1):21–28. https://doi.org/10.1016/j.foodchem.2012.02.015
9. Ehrhardt C, Hrincius ER, Korte V, Mazur I, Droebner K, Poetter A, Dreschers S, Schmolke M, Planz O, Ludwig S (2007) A polyphenol rich plant extract, CYSTUS052, exerts anti influenza virus activity in cell culture without toxic side effects or the tendency to induce viral resistance. Antivir Res 76(1):38–47. https://doi.org/10.1016/j.antiviral.2007.05.002
10. Ehrhardt C, Dudek SE, Holzberg M, Urban S, Hrincius ER, Haasbach E, Seyer R, Lapuse J, Planz O, Ludwig S (2013) A plant extract of Ribes nigrum folium possesses anti-influenza virus activity in vitro and in vivo by preventing virus entry to host cells. PLoS One 8(5):e63657. https://doi.org/10.1371/journal.pone.0063657
11. Fauci AS (2006) Seasonal and pandemic influenza preparedness: science and countermeasures. J Infect Dis 194(SUPPL. 2):73–76. https://doi.org/10.1086/507550
12. Forero JE, Avila L, Taborda N, Tabares P, López A, Torres F, Quiñones W, Bucio MA, Mora-Pérez Y, Rugeles MT, Joseph-Nathan P, Echeverri F (2008) In vitro anti-influenza screening of several Euphorbiaceae species: structure of a bioactive Cyanoglucoside from Codiaeum variegatum. Phytochemistry 69(16):2815–2819. https://doi.org/10.1016/j.phytochem.2008.09.003
13. Gasparini R, Amicizia D, Lai PL, Panatto D (2012) Clinical and socioeconomic impact of seasonal and pandemic influenza in adults and the elderly. Human Vaccines Immunother 8 (1):21–28. https://doi.org/10.4161/hv.8.1.17622
14. Goel A, Kunnumakkara AB, Aggarwal BB (2007) Curcumin as "Curecumin": from kitchen to clinic. Biochem Pharmacol 75(4):787–809
15. Govorkova EA, Webster RG (2010) Combination chemotherapy for influenza. Viruses 2 (8):1510–1529. https://doi.org/10.3390/v2081510
16. Gregory V, Bennett M, Orkhan MH, Al Hajjar S, Varsano N, Mendelson E, Lin YP (2002) Emergence of influenza A H1N2 reassortant viruses in the human population during 2001. Virology 300(1):1–7. https://doi.org/10.1006/viro.2002.1513
17. Grienke U, Schmidtke M, Kirchmair J, Pfarr K, Wutzler P, Dürrwald R, Wolber G, Liedl KR, Stuppner H, Rollinger JM (2010) Antiviral potential and molecular insight into neuraminidase inhibiting diarylheptanoids from Alpinia katsumadai. J Med Chem 53(2):778–786. https://doi.org/10.1021/jm901440f
18. Grohskopf LA, Alyanak E, Broder KR, Walter EB, Fry AM, Jernigan DB (2019) Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices - the United States, 2019-20 influenza season. MMWR Recomm Rep Morb Mortal Wkly Rep Recomm Rep 68(3):1–21. https://doi.org/10.15585/mmwr.rr6803a1
19. Ha TKQ, Dao TT, Nguyen NH, Kim J, Kim E, Cho TO, Oh WK (2016) Antiviral phenolics from the leaves of Cleistocalyx operculatus. Fitoterapia 110:135–141. https://doi.org/10.1016/j.fitote.2016.03.006
20. Ha TKQ, Lee BW, Nguyen NH, Cho HM, Venkatesan T, Doan TP, Kim E, Oh WK (2020) Antiviral activities of compounds isolated from Pinus densiflora (pine tree) against the influenza A virus. Biomol Ther 10(5):711. https://doi.org/10.3390/biom10050711

21. Haber P, Moro PL, Ng C, Dores GM, Lewis P, Cano M (2019) Post-licensure surveillance of trivalent adjuvanted influenza vaccine (aIIV3; Fluad), vaccine adverse event reporting system (VAERS), United States, July 2016–June 2018. Vaccine 37(11):1516–1520. https://doi.org/10.1016/j.vaccine.2019.01.052
22. Jiang LL, Lu YL, Jin JH, Dong LL, Xu FL, Chen SS, Wang ZY, Liang G, Shan XO (2015) n-Butanol extract from folium isatidis inhibits lipopolysaccharide-induced inflammatory cytokine production in macrophages and protects mice against lipopolysaccharide-induced endotoxic shock. *Drug Design*. Dev Ther 9:5601–5609. https://doi.org/10.2147/DDDT.S89924
23. Kenmoe S, Tcharnenwa C, Monamele GC, Kengne CN, Ripa MN, Whitaker B, Alroy KA, Balajee SA, Njouom R (2019) Comparison of FTD® respiratory pathogens 33 and a singleplex CDC assay for the detection of respiratory viruses: A study from Cameroon. Diagn Microbiol Infect Dis 94(3):236–242. https://doi.org/10.1016/j.diagmicrobio.2019.01.007
24. Kinoshita E, Hayashi K, Katayama H, Hayashi T, Obata A (2012) Anti-influenza virus effects of elderberry juice and its fractions. Biosci Biotechnol Biochem 76(9):1633–1638. https://doi.org/10.1271/bbb.120112
25. Knox YM, Suzutani T, Yosida I, Azuma M (2003) Anti-influenza virus activity of crude extract of Ribes nigrum L. Phytother Res 17(2):120–122. https://doi.org/10.1002/ptr.1053
26. Krau SD (2013) The impact of heat on morbidity and mortality. Crit Care Nurs Clin North Am 25(2):243–250. https://doi.org/10.1016/j.ccell.2013.02.009
27. Kwon HJ, Kim HH, Yoon SY, Ryu YB, Chang JS, Cho KO, Rho MC, Park SJ, Lee WS (2010) In vitro inhibitory activity of Alpinia katsumadai extracts against influenza virus infection and hemagglutination. Virol J 7:1–9. https://doi.org/10.1186/1743-422X-7-307
28. Lamb R, Krug R (2001) Orthomyxoviridae: the viruses and their replication. In: Field's virology. Lippincott-Raven Press, Philadelphia, pp 1487–1532
29. Lee CH, Kim SI, Lee KB, Yoo YC, Ryu SY, Song KS (2003) Neuraminidase inhibitors from Reynoutria elliptica. Arch Pharm Res 26(5):367–374. https://doi.org/10.1007/BF02976693
30. Lichtblau D, Berger JM, Nakanishi K (2002) Efficient extraction of ginkgolides and bilobalide from Ginkgo biloba leaves. J Nat Prod 65(10):1501–1504. https://doi.org/10.1021/np0201974
31. Liu AL, Shu SH, Qin HL, Lee SMY, Wang YT, Du GH (2009) In vitro anti-influenza viral activities of constituents from Caesalpinia sappan. Planta Med 75(4):337–339. https://doi.org/10.1055/s-0028-1112208
32. Memorandum WHO (1980) A revision of the system of nomenclature for influenza viruses: a WHO memorandum. Bull World Health Organ 58(4):585–591
33. Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J (2000) Clinical signs and symptoms predicting influenza infection. Arch Intern Med 160(21):3243–3247. https://doi.org/10.1001/archinte.160.21.3243
34. Moradi MT, Karimi A, Rafieian-Kopaei M, Fotouhi F (2017) In vitro antiviral effects of Peganum harmala seed extract and its total alkaloids against influenza virus. Microb Pathog 110:42–49. https://doi.org/10.1016/j.micpath.2017.06.014
35. Morais-Braga MFB, Carneiro JNP, Machado AJT, Sales DL, dos Santos ATL, Boligon AA, Athayde ML, Menezes IRA, Souza DSL, Costa JGM, Coutinho HDM (2017) Phenolic composition and medicinal usage of Psidium guajava Linn.: antifungal activity or inhibition of virulence? Saudi J Biol Sci 24(2):302–313. https://doi.org/10.1016/j.sjbs.2015.09.028
36. Nováková L, Pavlík J, Chrenková L, Martinec O, Červený L (2018) Current antiviral drugs and their analysis in biological materials – part II: antivirals against hepatitis and HIV viruses. J Pharm Biomed Anal 147:378–399. https://doi.org/10.1016/j.jpba.2017.07.003
37. Pleschka S, Stein M, Schoop R, Hudson JB (2009) Anti-viral properties and mode of action of standardized Echinacea purpurea extract against highly pathogenic avian influenza virus (H5N1, H7N7) and swine-origin H1N1 (S-OIV). Virol J 6:1–9. https://doi.org/10.1186/1743-422X-6-197
38. Rumschlag-Booms E, Rong L (2013) Influenza A virus entry: implications in virulence and future therapeutics. Adv Virol 2013:121924. https://doi.org/10.1155/2013/121924

39. Ryu YB, Kim JH, Park SJ, Chang JS, Rho MC, Bae KH, Park KH, Lee WS (2010) Inhibition of neuraminidase activity by polyphenol compounds isolated from the roots of Glycyrrhiza uralensis. Bioorg Med Chem Lett 20(3):971–974. https://doi.org/10.1016/j.bmcl.2009.12.106
40. Sawai R, Kuroda K, Shibata T, Gomyou R, Osawa K, Shimizu K (2008) Anti-influenza virus activity of Chaenomeles sinensis. J Ethnopharmacol 118(1):108–112. https://doi.org/10.1016/j.jep.2008.03.013
41. Serkedjieva J, Velcheva M (2003) In vitro anti-influenza virus activity of the pavine alkaloid (−)-thalimonine isolated from Thalictrum simplex L. Antivir Chem Chemother 14(2):75–80. https://doi.org/10.1177/095632020301400202
42. Sharma M, Anderson SA, Schoop R, Hudson JB (2009) Induction of multiple pro-inflammatory cytokines by respiratory viruses and reversal by standardized Echinacea, a potent antiviral herbal extract. Antivir Res 83(2):165–170. https://doi.org/10.1016/j.antiviral.2009.04.009
43. Shin WJ, Lee KH, Park MH, Seong BL (2010) Broad-spectrum antiviral effect of Agrimonia pilosa extract on influenza viruses. Microbiol Immunol 54(1):11–19. https://doi.org/10.1111/j.1348-0421.2009.00173.x
44. Simonsen L (1999) The global impact of influenza on morbidity and mortality. Vaccine 17 (Suppl 1):S3–S10
45. Smith GJD, Vijaykrishna D, Bahl J, Lycett SJ, Worobey M, Pybus OG, Ambaut A (2009) Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza an epidemic. Nature 459(7250):1122–1125. https://doi.org/10.1038/nature08182
46. Sriwilaijaroen N, Fukumoto S, Kumagai K, Hiramatsu H, Odagiri T (2012) Antiviral effects of Psidium guajava Linn. (guava) tea on the growth of clinical isolated H1N1 viruses: its role in viral hemagglutination and neuraminidase inhibition. Antivir Res 94(2):139–146. https://doi.org/10.1016/j.antiviral.2012.02.013
47. Takayama H, Iimura Y, Kitajima M, Aimi N, Konno K, Inoue H, Fujiwara M, Mizuta T, Yokota T, Shigeta S, Tokuhisa K, Hanasaki Y, Katsuura K (1997) Discovery of anti-influenza A virus activity of a corynanthe-type indole alkaloid, hirsutine, in vitro and the structure-activity relationship of natural and synthetic analogs. Bioorg Med Chem Lett 7(24):3145–3148. https://doi.org/10.1016/S0960-894X(97)10154-8
48. Taubenberger JK, Morens DM (2006) 1918 influenza: the mother of all pandemics. Emerg Infect Dis 12(1):15–22. https://doi.org/10.3201/eid1209.05-0979
49. Thompson WW, Shay DK, Weintraub E, Cox N, Anderson LJ, Fukuda K (2003) Mortality associated with influenza and respiratory syncytial virus in the United States. J Am Med Assoc 289(2):179–186. https://doi.org/10.1001/jama.289.2.179
50. Tyrrell BE, Sayce AC, Warfield KL, Miller JL, Zitzmann N (2017) Iminosugars: promising therapeutics for influenza infection. Crit Rev Microbiol 43(5):521–545. https://doi.org/10.1080/1040841X.2016.1242868
51. Utsunomiya T, Kobayashi M, Pollard RB, Suzuki F (1997) Glycyrrhizin, an active component of licorice roots, reduces morbidity and mortality of mice infected with lethal doses of influenza virus. Antimicrob Agents Chemother 41(3):551–556. https://doi.org/10.1128/aac.41.3.551
52. Webster RG (1998) Influenza: An emerging disease. Emerg Infect Dis 4(3):436–441. https://doi.org/10.3201/eid0403.980325
53. Webster RG (2002) The importance of animal influenza for human disease. Vaccine 20(SUPPL. 2):16–20. https://doi.org/10.1016/S0264-410X(02)00123-8
54. Wei W, Du H, Shao C, Zhou H, Lu Y, Yu L, Wan H, He Y (2019) Screening of antiviral components of Ma Huang Tang and investigation on the ephedra alkaloids efficacy on influenza virus type A. Front Pharmacol 10(September):1–22. https://doi.org/10.3389/fphar.2019.00961
55. Woolhouse M, Scott F, Hudson Z, Howey R, Chase-Topping M (2012) Human viruses: discovery and emergence. Philos Trans R Soc B Biol Sci 367(1604):2864–2871. https://doi.org/10.1098/rstb.2011.0354
56. Wu X, Gu L, Prior RL, McKay S (2004) Characterization of anthocyanins and proanthocyanidins in some cultivars of Ribes, Aronia, and Sambucus and their antioxidant capacity. J Agric Food Chem 52(26):7846–7856. https://doi.org/10.1021/jf0486850

57. Yang L, Chan KP, Wong CM, Chiu SSS, Magalhaes RJS, Thach TQ, Peiris JSM, Clements ACA, Hu W (2019) Comparison of influenza disease burden in older populations of Hong Kong and Brisbane: the impact of influenza and pneumococcal vaccination. BMC Infect Dis 19 (1):1–8. https://doi.org/10.1186/s12879-019-3735-7
58. Yu C, Yan Y, Wu X, Zhang B, Wang W, Wu Q (2010) Anti-influenza virus effects of the aqueous extract from Mosla scabra. J Ethnopharmacol 127:280–285. https://doi.org/10.1016/j.jep.2009.11.008
59. Zai-Chang Y, Bo-Chu W, Xiao-Sheng Y, Qiang W (2005) Chemical composition of the volatile oil from Cynanchum stauntonii and its activities of anti-influenza virus. Colloids Surf B: Biointerfaces 43(3–4):198–202. https://doi.org/10.1016/j.colsurfb.2005.05.003
60. Zucs P, Buchholz U, Haas W, Uphoff H (2005) Influenza associated excess mortality in Germany, 1985 - 2001. Emerg Themes Epidemiol 2(August 1992):1–9. https://doi.org/10.1186/1742-7622-2-6

Medicinal Plants Used in the Treatment of Influenza A Virus Infections

19

Charles Oluwaseun Adetunji, Olulope Olufemi Ajayi, Muhammad Akram, Olugbemi Tope Olaniyan, Muhammad Amjad Chishti, Abel Inobeme, Seyi Olaniyan, Juliana Bunmi Adetunji, Mathew Olaniyan, and Samson Oluwasegun Awotunde

Abstract

Influenza A virus has been identified as a major factor responsible for most critical respiratory disease of the Influenza viruses around the globe. Moreover,

C. O. Adetunji (✉)
Applied Microbiology, Biotechnology and Nanotechnology Laboratory, Department of Microbiology, Edo State University Uzairue, Iyamho, Edo State, Nigeria;
adetunji.charles@edouniversity.edu.ng

O. O. Ajayi
Department of Biochemistry, Edo State University Uzairue, Iyamho, Edo State, Nigeria

M. Akram
Department of Eastern Medicine, Government College University, Faisalabad, Pakistan

O. T. Olaniyan
Laboratory for Reproductive Biology and Developmental Programming, Department of Physiology, Edo State University Uzairue, Iyamho, Nigeria

M. A. Chishti
Department of Basic Clinical Sciences Faculty of Eastern Medicine, Hamdard University, Karachi, Pakistan

A. Inobeme
Department of Chemistry, Edo State University Uzairue, Iyamho, Nigeria

S. Olaniyan · J. B. Adetunji
Nutrition and Toxicology Research Laboratory, Department of Biochemistry Sciences, Osun State University, Osogbo, Nigeria

M. Olaniyan
Department of Medical Laboratory Science, Edo State University Uzairue, Iyamho, Edo State, Nigeria

S. O. Awotunde
Department of Biochemistry School of Health Sciences, Soroti University, Soroti, Uganda

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_19

it has been validated that several medicinal plants could be applied in the management of Influenza when compared to several synthetic drugs which has been acclaimed with several adverse effect A virus. This might be linked to several factors such as their low toxicity, ease of access, low cost, and cultural acceptance. Hence, this chapter intends to provide a detailed information on the application of medicinal plant on the treatment of Influenza A virus. Detailed information was also provided on the mechanism of action utilized by these medicinal plants against Influenza A virus.

Keywords

Influenza A virus · Medicinal plants · Inhibition · Microorganism · Low toxicity · Low cost · Adverse effect · Synthetic drugs

19.1 Introduction

Influenza A virus is a member of the Orthomyxoviridae which is the main causes of most critical respiratory disease of the influenza viruses. It is responsible for high morbidity and mortality [1–4]. Its common symptoms are; high fever, cold, and sore eyes [5]. There are limitations in the use of vaccines and drugs in the prevention and management of Influenza A virus infections. This includes resistance to antiviral drugs and drug side effects which are often unpleasant. The common drugs used are Zanamivir, Oseltamivir, Amantadine, and Rimantadine. Reports showed that their mode of action differs from one another. For instance, Amantadine and rimantadine inhibited cell entry of the virus via the inhibition of ion channel M2 protein. Moreover, Oseltamivir and zanamivir blocked neuraminidase, thereby preventing the release of the viral contents [6–8]

Studies have indicated the potency of medicinal plants in the management of Influenza A virus. Their preference to orthodox drugs is premised on their low toxicity, ease of access, low cost, and cultural acceptance [5]. There are evidences that they act by boosting the immune system. These medicinal plants include; *Glycyrrhiza glabra*, *Ocimum sanctum*, *Ocimum tenuiflorum*, *Allium sativum*, *Cocos nucifera*, *Zingiber officinale*, *Tinospora cordifolia* among others.

Glycyrrhiza glabra, commonly called Licorice contains phenolic compounds such as flavonoids, coumarin, derivatives of cinnamic acids, which have been described to have potent antiviral features [9]. There are evidences that its roots have been used for infections of the upper respiratory tract. *Ocimum sanctum* is another medicinal plant with a long history of use. It is a member of the Lamiaceae family. Its antimicrobial, antifungal, and antiviral properties are well documented [9]. Its principal constituent is eugenol, rosmarinic acid, carvacrol, ursolic acid, linalool oleanolic acid, beta-caryophyllene [10]. The immunomodulatory effects of *Ocimum tenuiflorum* have also been reported [11].

Allium sativum also known as garlic, has a record of long years of human use in the management of infections, particularly, viral infections. Tsai et al. [12] reported

that it killed influenza virus. Coconut, *Cocos nucifera* is another medicinal plant whose use dated back to centuries. Its medium-chain fatty acids and their derivatives have been reported t have potent antiviral potentials [13]. It is believed that the consumption of coconut oil could results in the degradation of the medium-chain triglycerides into chain fatty acids which have a greater potential of killing pathogenic microbes. Monolaurin, a derivative of lauric acid confers antiviral ability on coconut. It acts by dissolving lipid components of the viral envelope membrane. Furthermore, MCFA inhibits viral signal transduction [14].

Zingiber officinale. Commonly called ginger. It is a member of Zingiberaceae family. It contains allicin, ajoene, alliin which are sulphur compounds. It also contains enzyme such as myrosinase, alliinase, and peroxidase. Each of these compounds has specific bio-functions. Allicins boosts the activities of antioxidant enzymes. TNF-α, referred to as antiviral cytokine is found in Ginger [15]. *Tinospora cordifolia*. This is commonly called Guduchi. It is a native to Sri Lanka and Myanmar. Some typical examples of such phytochemicals present in Zingiber officinale includes tinosponone, arabinogalactan polysaccharide, tinosporic acid, crude Giloininand, cordifolisides A to E, syringen, berberine, Giloin [16, 17]. Its immunomodulatory properties could be explored in the management of influenza A virus [18].

Influenza viruses are highly contagious and are a significant causative agent for pandemics and recurrent epidemics. Around 10% of the population of the world is on average, contaminated by the virus annually causes about 250,000 deaths, posing a significant health threat [1, 3, 19, 20]. The Orthomyxoviridae family comprises three groups of influenza viruses—A, B, and C. The main causes of animal and human infections are known to be types A and B [2, 4]. However, the most serious respiratory diseases are caused by the influenza A virus, resulting in substantial morbidity and often high mortality [2, 4]. Chills, elevated fever, watering and sore eyes, and rash are the typical unfavourable symptoms of influenza that typically begin 1–2 days after infection [21].

These viruses are spread through the air from infected mammals through sneezes or cough, producing aerosols containing the virus, and through their droppings from infected birds. It is also possible to spread the swine flu virus via nasal secretion, saliva, urine, and blood. These fluids are the main cause of infection [22]. Flu epidemics occur annually in temperate areas during autumn and winter, causing substantial mortality and morbidity every year [23].

Actually, treatment of patients infected with the influenza virus is primarily based on supportive care, depending on the patient's situation, along with the use of antiviral drug therapy [24, 25]. To date, licenced medicines of influenza have been categorized into classes of inhibitors of neuraminidase, such as oseltamivir and zanamivir, and M2 ion channel inhibitors including rimantadine and amantadine [26–28].

While anti-influenza drugs have been used successfully against human infection with influenza A viruses, increased reports of drug-resistant influenza viruses have brought the disease back to public attention [29–31]. The question for alternative anti-influenza agents is therefore required and is of interest in the development of

potential strategies for the management of influenza diseases. The objective this paper is to discuss the antiviral potential of herbs used for the management of Influenza A virus.

Therefore, this chapter intends to provide a detailed information on typical examples of medicinal plants that could be applied for effective treatment of influenza A while detailed facts regarding the mechanisms of action of some medicinal plants in the treatment of influenza A virus was discussed extensively.

19.2 Typical Examples of Medicinal Plant with Anti-influenza Virus Activity

Natural inhibitors for influenza virus have been sought for so long. Scientist has carried out several studies with regard to plant-based chemical compounds that can be utilized for the inhibition of influenza virus [32]. It has been reported that there are different phytochemicals that have been used in vivo and in vitro for influenza virus [33]. Several photochemical obtained from plants around have shown anti-influenza potential which has been linked to the occurrence of active agents such as saponin, flavonoids, alkaloids, and glycosides [15]. This has raised hope for the possibility of obtaining a phytochemical for the control of influenza virus.

Plant-based natural substances are the backbone for the new discovery of drugs. They are used as purified compounds or extracts [34]. It has been reported that 80% of the global population use medicinal herbs for treatment and rely on other traditional approach to treatment using herbs. This has made it possible to treat varieties of diseases including infectious and chronic types [35].

Jung and Lee [36] reported that influenza viruses causes serious respiratory tract infection characterized by fever, congestion or myalgia. Though there has been some great effort to prevent and manage influenza infections, little success has been recorded so far as a result of rapid genetic mutation of influenza viruses making therapeutic regime slow and ineffective. Studies have revealed that influenza infections are a major public health crisis with several cases of death related flu-linked complications across the globe annually. Looking at the alarming rate of death with little or no effective therapy at sight, vaccination against these viruses may be the alternative approach to reduce the burden. The application of molecular biology techniques could help in the identification of influenza virus.

Studies have demonstrated that immunogenicity is a major challenge in vaccine development against influenza virus and many of the well-developed vaccine like recombinant vaccines, mRNA vaccines, and DNA vaccines have poor immunogenicity though their potency could be enhanced. Different approaches have been deployed to increase their potency, such as addition of a TLR5 agonist—flagellin could boost the efficacy of the recombinant vaccines, likewise addition of RIG-I agonist could enhance humoral responses to DNA vaccines. Basically, a study on the relationship between influenza virus pathophysiological mechanism and the host immune reaction would shed more light on the complex interactions of vaccine physiology. Rapid mutation rate escaping proper proofreading changes the viral

protein target for the anti-influenza drugs thus developing drug resistance due to alteration in viral genome, thus, there is still lack of standard stratagems for the inhibition or management of these influenza viruses. The current medications could only reduce the severity of the infections; hence more studies should be done to elucidate the virus–host interactions so as to support the development of effective therapy.

Diana and Juan [37] reported that influenza viruses have three main glycoproteins proteins, Matrix 2, hemagglutinin, and neuraminidase. These are surface proteins that are utilized for their classification into numerous subtypes based on serological recognition. These viruses particularly hemagglutinin subtypes are very pathogenic to human which can occur through animals to human or human to human transmission to cause serious epidemic, thus control measure utilizing vaccination may be the best approach to address this threat. Jeffery and David [38] revealed that the worst pandemic ever recorded to affect about 50 million individuals worldwide in 1918 was caused influenza viruses by the hemagglutinin subtypes avian influenza viruses. Scientists have suggested rapid development of vaccines as advanced therapy to prevent the occurrence of such pandemic in the future. Zambon [39] discovered that the presence of influenza A viruses present could cause respiratory infections in children in numerous many communities with explosive outbreaks. Across the globe, influenza A transmissions particularly of the hemagglutinin subtypes have resulted into serious epidemic coupled with some other respiratory viruses, thus rapid development of molecular biology technology that can enhance diagnostic outcomes against these pathogens would be a major landmark progress. The authors suggested that advanced development of antiviral drug candidate like neuraminidase inhibitors and vaccines would provide beneficial approach to reduce the epidemic.

Ahsan et al. [40] showed that there are about 11 coded proteins in influenza virus genome and insertion of basic amino acid residue to the cleavage site of this protein makes them more virulent. Viral re-assortment due to immune evasion create pressure on the antibodies due to mutation in virus specific T cell receptors generating interferons which are potential vaccine candidate against influenza viruses by manipulation of interferon and the viral genome. Studies have demonstrated that influenza virus have a very unstable antigen to evade the immunity thus hijacking the molecular machinery in the host cells. Cavallazzi and Ramirez [41] reported that respiratory viruses are common cause of immunosuppression in a community acquired pneumonia. Though the diagnosis is a major concern for now, very little accuracy is recorded with the present clinical prediction. Peteranderl et al. [42] suggested that respiratory infections in human caused by viral influenza can be grouped into pandemic and seasonal influenza which can be closely monitored through vaccination in the target population. The authors noted that this infection may be complicated by co-infection with bacteria particularly in a population with very low immunity resulting into severe mortality and economic downturn. Advancement in research to study the biology of viruses especially in human host may be a key strategy to develop efficient antiviral drugs against influenza virus. They concluded that in the development of novel therapy against influenza virus, host-based agent for lung regeneration and immune booster should be considered.

Mousa [43] demonstrated that in an attempt to develop a potent vaccine against influenza viruses, alteration in viral antigenic protein structure should be factored particularly the RNA viruses which makes the current antiviral drug grossly ineffective. The authors suggested the utilization of plant-based active constituents as an alternative to the synthetic drugs due to the presence of strong neuraminidase inhibitors, polyphenol, glycyrrhizin, plus baicalin with well-established mechanism of action, thereby inhibiting viral budding, hemagglutination, penetration, immunoglobulin production, stimulation of interferon-gamma generation by T cells, and subsequent virion exertion structural impairment.

19.3 Medicinal Plants for the Treatment of Influenza A Virus Infections

Ganjhu et al. [44] reported that due to the present inefficient synthetic drug adopted in the treatment of influenza virus infection, medicinal plant phytoconstituents could offer a beneficial remedy particularly those with antiviral properties. The authors evaluated various medicinal plants used for other viral infections such as Human immunodeficiency virus, rabies virus, Chandipura virus, Enterovirus, and Japanese Encephalitis Virus for possible therapeutic effect on Influenza viruses. It is believed that phytochemicals from medicinal plants strengthens the immune system which enables the body to combat any infectious diseases. The plant antiviral components have emerged as an alternative solution to many of the present synthetic antiviral drug resistance with proven safety and efficacy through clinical trials. Nonetheless, further evaluation needs to be carried out to establish the right dosage, optimal treatment protocol and concentration. The authors revealed that herbal formulations are adopted across different parts of the world in combination or individual active biomolecules, and report on their biological mechanisms should be identified.

Jassim and Naji [45] reported that diverse plant species with huge potential antiviral molecules such as terpenoids, thiophenes, polyines, peptides, flavonoids, lignans, polysaccharides, naphtho- and anthraquinones, polyphenolics, sulphides, coumarins, furyl compounds, volatile essential oils, saponins, alkaloids, have been evaluated for possible alternative to the synthetic present antiviral drug with numerous side effects and high cost. However, their individual mechanism of action is yet to fully elucidated, though some seems to have overlapping mechanisms. The authors suggested that molecular biology approach and assays such as compromised designs, randomized crossover studies, multiple-arm trials, pre and post-treatment analyses, nonrandomized crossovers, should be deployed to evaluate the efficacy and relative actions against functional or genetically diverse viruses.

Mehrbod et al. [5] reported that people across globe are constantly being faced with the threat of influenza virus infection requiring an effective antiviral agent to tackle. The authors revealed that many of the synthetic drugs available are very expensive, less effective and produce numerous side effects upon use. Therefore, they suggested medicinal plants active constituents as an alternative approach to treat influenza viral infection. They screened and evaluated five antiviral plants in

South African like *Tabernaemontana ventricosa*, *Rapanea melanophloeos*, *Cussonia spicata*, *Clerodendrum glabrum*, plus *Pittosporum viridiflorum* species against influenza virus. These plants have been utilized in the treatment of many infection and inflammatory diseases, thus the cytotoxicity, and concentrations, were equally established. From their results it was observed that the medicinal plants *Rapanea melanophloeos*, and *Pittosporum viridiflorum* significantly produced antiviral activity compared with the rest. Thus further study was suggested to establish the mechanism of action and isolate, characterize the main active constituents responsible for these biological effects.

Mousa [46] showed that in the past few years, the prevalence of respiratory influenza viral infection across the world is unprecedented due to the lack of adequate effective synthetic drug candidate to treat this infection. Also, studies have revealed that the viral antigenic structures are very unstable especially the RNA viruses, thus an alternative solution is eminently required. Natural therapies such as the utilization of herbal remedies like antiwei, licorice roots, ginseng, Echinacea, berries, carnosic acid, guava tea, pomegranate, Bai Shao plus maoto have been identified by many authors for the treatment against respiratory influenza viral infections. The author revealed that dietary supplements such as zinc, vitamin C, selenium, probiotics, yeast-based product, seaweed extract, garlic extract have equally proven to be effective against influenza viruses.

Other studies have pointed attention of many scientists to the role of natural antiviral remedies like herbal medications as alternatives to synthetic chemical formulations against influenza viral infections. Ding et al. [47] reported that Lianhuaqingwen Capsule which is a Chinese medicine formulation is very potent against respiratory tract infections. The antiviral and cytotoxicity activity of this formulation was evaluated and other molecular signaling pathways using molecular biology techniques. From their results, it was demonstrated that Lianhuaqingwen Capsule significantly inhibited the influenza virus proliferation, suppressed NF-kB activation, cytokines in a dose-dependent manner. Thus, the experimental study demonstrated that Lianhuaqingwen Capsule is effective against broad spectrum of influenza viruses and could serve as alternative to the synthetic drugs with very low side effects.

Hudson [48] showed that influenza viruses have caused serious pandemics in the past with huge burden placed on animals and human's health. Thus, characterization of the virus genome could be used in developing appropriate candidate drugs for treatment against viral infections due to influenza viruses. Many herbal remedies have been suggested in the past by several authors, hence active ingredients such as polyphenols could display a crucial benefit in alleviating many symptoms due to respiratory tract infections. The active constituents have been shown to interact with the viral protein and also synergistically work together to offer anti-inflammatory, antioxidant or antibacterial properties against influenza infection. The authors revealed that in the course of viral respiratory tract infections, there is an increased secretion of pro-inflammatory chemokines and cytokines, thus inhibition of this process through plant-based therapy may help to alleviate the conditions.

Al-garawyi et al. [49] reported that some of the major symptoms displayed by individual infected by respiratory viral infection include cough, cold, sneezes, sore throat, and fever. The authors noted that influenza virus infection can be transfer or transmitted among individuals through droplets or direct contact. Natural remedies are beginning to gain massive attention from the scientific communities as a result of low side effects, readily available, and highly effective. Many of these active ingredients such as Lavender, Cinnamon, Peppermint, Thyme oils, and Eucalyptus are now being considered as alternatives to the synthetic drugs.

19.4 Modes of Action of the Active Constituents Present in Plants that Are Utilized for the Management of Influenza A Virus Infections

There is variation in the mode of action of various extracts of plants in the management of viral diseases. Similarly, there are different routes for the boosting of the immune system and body defence mechanism. Some investigations have been carried out to assess the features of these extracts in stimulating the immune system of the body [50]. It has been reported that stimulation of interleukin 6 production was brought about by the extracts from the roots of *Heracleum maximum*, a medicinal plant. This plant was observed to have unique antifungal and antibacterial potentials [50].

It was reported that several infectious diseases have been managed successfully in Taiwan through the use of *P. Asiatica*. They were found to show proliferation of lymphocyte, with the potential of producing interferon—gamma. Basically, cell mediation of immune responses is commonly shown by production of interferon gamma and proliferation of lymphocytes [51]. Immune response boosting has also been documented in the use of extract from *Sambucus nigra*, a medicinal plant. This was found to have potency for some microbial strains.

Extracts from plants have been established to have broad spectrum antiviral potential apart from their ability in modulating the immune system. These unique properties are due to the various bioactive agents present in the plant extracts. In a related study, Kotwal et al. [52] reported that extracts from *Trifollium* specie show unique potencies against various viral agents including Marburg, influenza, papillomavirus, and HIV.

Buckwold et al. [53] documented that lectin, an isolate from leaves of *Pandanus* specie using saline medium showed antiviral potential against influenza virus, HSV-1. Also, the crude extract of Pandanus displayed antiviral effectiveness against different groups of viruses which showed the presence of different antiviral agents in various parts of the plant. Table 19.1 indicates the mode of action of some medicinal plants that have been utilized for effective treatment of Influenza A virus

Table 19.1 Mode of action of medicinal plants in the treatment of Influenza A virus

S/N	Medicinal plant	Major antiviral active ingredients	Mode of action	Reference
1	*Glycyrrhiza glabra*	Triterpene and Glycyrrhizinic acid	Inhibition of viral replication	Arora et al. [9]
2	*Ocimum sanctum*	Eugenol, oleanolic acid, ursolic acid, rosmarinic acid	Immunomodulation, anti-inflammatory	Arora et al. [9]
3	*Allium sativum*	Ajoene	It kills influenza virus	[9]
4	*Cocos nucifera*	Monolaurin	It dissolves lipid components of the viral envelope membrane and inhibit viral signal transduction	Arora et al. [9]
5	*Zingiber officinale*	Allicin, ajoene, alliin, myrosinase, 6alliinase and p7eroxidase	It boosts antioxidant enzymes' activities	Arora et al. [9]
6	*Tinospora cordifolia*	Tin8osporone, tinosporic acid, cordifolisides, syringen, berberine, Giloin, crude Giloininand	Immunomodulation	Arora et al. [9]
7	*Aristolochia bracteolata*		Inhibition of RBC hemagglutination caused by viruses	Mohamed et al. [54]
8	*Boscia senegalensis*		Inhibited RBC hemagglutination induced by influenza virus	Mohamed et al. [54]
9	*Leptadenia arborea*		Inhibited RBC hemagglutination induced by influenza virus	Mohamed et al. [54]
10	*Cordia africana*		Inhibited RBC hemagglutination induced by influenza virus	Mohamed et al. [54]
11	*Balanites aegyptiaca*		Inhibited RBC hemagglutination induced by influenza virus	Mohamed et al. [54]
12	*Mentha piperita*	Aetheroleum menthae piperitae, flavonoids, polymerized polyphenols, carotenes, tocopherols, betaine, and choline	It kills Influenza viruses	Arora et al. [9]
13	*Clerodendrum glabrum*	Flavonoids	Anti-inflammatory	Mehrbod et al. [5]
16	*Pittosporum viridiflorum*		Antioxidant	Mehrbod et al. [5]
17	*Rapanea melanophloeos*	Tannins, terpenoids, alkaloids, saponins, cardiac glycosides, flavonoids and phlobatannins	Antioxidant	Mehrbod et al. [5]

(continued)

Table 19.1 (continued)

S/N	Medicinal plant	Major antiviral active ingredients	Mode of action	Reference
18	*Azadirachta indica*	Azadirachtin, nimbin, and nimbidin	They probably inhibit viral reproduction	Arora et al. [9]
19	*Aegle marmelos*	Alkaloids, coumarins, and steroids		Arora et al. [9]

19.5 Herbal Formulations for the Management of Influenza A Virus Infections

Majority of the people from developed nations depends on medicinal plants for management of various ailments [55]. Herbs that are effective in treating swine flu include *Taraxacum officinale*, *Allium fistulosum* L., *Sambucus nigra* L., *Ocimum basilicum*, *Cynodon dactylon*, *Emblica officinalis* are very effective antiviral herbs that are immune to bacterial and biological chemical stressors. It has been discovered that many herbs are effective in the treatment of flu, but they have not been explored scientifically. The medication for these plants/herbs is highly used by the natives as an alternative therapeutic options for their action against the H1N1 influenza virus for the human race, formulating, and helping [56].

The dandelion is commonly known as *Taraxacum officinale*. This genus contains more in the family Asteraceae, the number of plants. The use of plants has been considered for many decades in conventional medicine, to relieve various diseases. This plant is used in the treatment of various ailments such as pyrexia, viral infection, lymphadenitis, hepatic disorders, flu, and acute mastitis. Dandelion flower ethanol extracts were discovered. SK-OV-3 cells suppress proliferation of cells and result in human ovarian cancer apoptosis [57]. In solvent-fractionated solvents, cytotoxic, pro-oxidant, and antioxidant were observed by [58]. The components of the plant extract have been reported with anti-influenza virus properties when tested in vitro using dandelion flower extracts [58].

The *Allium fistulosum L.* is an essential plant which is grown internationally. They have several nutritional benefits, as medicinal and functional foods. Indeed, there have been frequent studies headed for assessment of natural activities comprising which are antimicrobial effects, antioxidants, antifungal agents. *Allium fistulosum* L be an extremely common herb in the East Asia state, and it was documented in Oriental medical dictionaries for Asian countries as a crude drug for Pain and phlegm in the abdomen. Furthermore, in Japan welsh onion was used as a traditional medicine for the management of common cold. Such conventional uses of *Allium Fistulosum* suggest it may be possible to accommodate dynamic materials that donate for the avoidance and/or treatment of communicable respiratory ailments, like influenza. It has been studied that the plant species fructan is considered as an active component of the theory which could exert viral anti-influenza

properties. Furthermore, several studies have stated that insulin works against viruses as a possible factor [59].

Black elderberries have been prescribed in the treatment of sinusitis, colds, and influenza in eastern system of medicine and it also have several antiviral potential. It has been documented that the standardized plant extract formulations could led to reduction of hemagglutination and inhibition of influenza virus multiplication [60]. The efficacy of black elderberries has been proved in the treatment of influenza-like symptoms chimpanzees, has also been seen in the Zoo in Jerusalem, Israel [61]. Black elderberries extract have been shown to possess an antimicrobial activity against *Streptococcus pyogenes* and *Branhamella catarrhalis*. These organism responsible for various ailments of respiratory tract [62].

In Ayurvedic and Unani medicine, *Justicia adhatoda* is a renowned herb, a shrub that is widespread across South-East Asia's tropical regions. The plant's leaves have been used widely to treat respiratory disorders. Simultaneous leaf assays reported a 33% reduction in aqueous extract at a fraction of 10,000 lg/ml and a 16.67% reduction in aqueous extract from 1000 to 5000 lg/ml, while a 100% diminution in methanolic extract was examined at a fraction of 10,000 lg/ml. The result obtained showed that there was an inhibition observed which decrease from 33.34% at 1 mg/ml to 16.67% at 5000 lg/ml as the concentration decreased. The result obtained indicates that aqueous and methyl alcohol extracts can interact straight through the protein covering of diseases through the sialic acid receptor on the cell surface. Moreover, the methyl alcohol extract could inhibit the flu virus infection, and hindered the viral hemagglutinin (HA) protein. It has been observed that the vasicine alkaloids were extracted among leaves with a proportion masterpiece of 0.026% in methanol furthermore 0.023% in watery extract [63]

Moreover, the sesquiterpenoid compounds derived from *Ocimum basilicum* such as caryophyllene, farnesol, and flavonoids such as apigenin, as well as monoterpenes such as linalool cineole, carvone, geraniol, fenchone, myrcene, thujone, and triterpenoids such as ursolic acid have all been demonstrated to possess anti-influenza attributes. Most of the secondary metabolites are involved in inhibition of different DNA and RNA viral infection [64]. Only three forms of apigenin secondary metabolites, linalool, and the various kinds of human being adenovirus engaged in bronchitis have been directly checked for ursolic acid and ursolic acid. Maximal inhibition was shown among these ursolic acids (50%) at a lowest fraction (4.2 lg/ml) against adenovirus (ADV-8). The composition of all the compounds isolated is >95%. 2,3-Dideoxycytidine has been identified as one on the crucial active ingredient in formulation and also possess ursolic acid action. The viral activity was inhibited by triterpenoid saponins of the oleanane group through hindering DNA production, whereas the urasane faction hampered capsidide viral protein group (Lizarzaburu et al. 2000) [65].

Five groups of biologically active compounds are found in phytochemicals isolated from *Plantago major*: aucubin could be classed among the iridoid glycoside class, baicalin, baicalein, and luteolin are flavonic initiatives. It has been demonstrated during in vitro antiviral activity of these compounds was observed with ursolic acid and oleanolic acid tested in opposition to three forms of individual

adenovirus at various proportions. Also, caffeic acid and chlorogenic acid showed 50% adenovirus hindrance at least fractions of approximately 13.3 and 14.2 lg/ml, correspondingly. Powerful antiviral action of phenolic compounds could be associated through the existence of two hydroxyl groups on ferulic acid and caffeic acid as opposed to ferulic acid and p phenolic acid. Phenolic compounds have been found effective to be effective for the inhibition against all the tested virus most especially their antiviral activity against adenovirus [66].

Several bioactive chemical groups have been investigated for their antiviral activity, such as sesquiterpenes, triterpenes, flavonoids, phenolic and benzoic compounds secluded from several additional herbs [67]. Toxicological tests have shown no toxicity of these compounds opposing to this outcome, a further study indicated through oral route of aqueous leaf extract (1000 mg/kg body weight) showed the greatest decrease in total gastric fluid acidity in rats [68].

Various pharmacologically derivatives were isolated from *Z. officinale* such as b-bisabolene, a-zingiberene, b-sesquiphellandrene, ar-curcumene, favan, lavonoids, flavan, and 4,6-dichloroflavan were examined for its antiviral activity. It was discovered that at various concentrations, all of these phytochemical constituents demonstrated 50% inhibition to against all the tested viral pathogens. 4,6-Dichloroflavan was perceived as it was the mainly efficient compound because it illustrated 50% rhinovirus inhibition at the smallest fraction of about 0.02 lg/ml. 4,6-dichloroflavan was attributed to the lipophilic nature of its antirhinoviral activity as different lipophilic secondary metabolites are known to contain *Z. officinale*. Dichloroflavan separated from further natural products was as well examined in opposition to rhinovirus and demonstrated its powerful capability to attach with the majority responsive products on their receptor spots, Rhinovirus IB. Especially for their antirhinoviral activity, several bioactive compounds segregated from superior plants have been tested for their antiviral action. It has been established through statistics illustrated that the majority of plant antirhinoviral action was due to the existence of compounds of flavonoids.

Moreover, the methanolic extract derived from *Verbascum thapsus* demonstrated a high efficacy of approximately 50% against the influenza A virus at a lowest proportion of 6.25 lg/ml. Phenylethanoid and lignin glycosides were isolated from *V. thapsus* methanolic extract. The phytoconstituents responsible for the viral activity of anti-influenza rely on the quantity of dynamic compounds found in the vegetation, that otherwise depend on the biological division, the period collected, the weather and environmental state of the collection place. Additional proportion and isolation of extract(s) from this plant will expose strong antiviral action. Toxicity at higher doses was not found [69].

Various studies have shown that many bioactive ingredients are isolated from medicinal herbs, such as *Geranium sanguineum* L. A medicinal plant that decreases the in vitro and in vivo infectivity of different strains of the influenza virus [33]. In Bulgaria (and possibly other countries), watery and alcoholic extracts from the dehydrated aerial cores of geranium have common utilizes to work against different disorders of gastrointestinal system, contaminations, and provocative situations. The antiviral effect of Geranium sanguineum L has been established against individual,

equine and avian influenza A virus strains, including the amantadine-resistant virus using cell culture and animal model laboratory experiments [70].

Also, the aqueous extracts of *C. sinensis* has been demonstrated to possess antimicrobial, antioxidant and other bioactivity actions. These actions tend to be there mainly as a result of the leading polyphenolic constituents, the catechin and their theaflavins, that jointly can account for 10% of the dry weight of the leaves. Some authors have also stated the pharmacodynamics activity and bioavailability of tea polyphenols in intestinal tissues as well as their antiviral activity against several influenza virus [71].

On the other hand, intestinal bioavailability is not inherently influenced by upper respiratory viruses and bacteria, as contact of the species would firstly happen in mucosal tissues; thus in vivo oral cavity clean or rinse throat will be extra efficient than conventional tea consumption. A first round testing with a rinsed solution of green tea catechins for its capability to inhibit influenza infection [72]. In another study focused on subjective "cold and flu" symptom ratings, individuals drank either capsules made from polyphenol-rich standardized green tea every day, equivalent to around 10 cups of tea a day or placebo. Around one-third fewer symptoms were registered by the green tea group [73].

Cistus incanus extracts have been the subject of recent anti-bioactivity investigations. The presence of catechins and polyphenolic have been affirmed to exhibit anti-influenza activities. The extract was very successful at non-cytotoxic concentrations in inhibiting the reproduction of numerous strains of human being and avian influenza viruses in cell culture (50μg/ml consequential in a diminution of 99% devoid of harmfully disturbing a number of cell viability and meaning parameters) [74].

Recently, polyphenol-rich pomegranate extracts have been documented for anti-influenza virus activity. They could inhibit virus replication cycle at a very early stage, possibly as a result of its capability to obstruct viral HA and enter cells. The antiviral activity could be linked to the presence of polyphenol punicalagin. However, punicalagin could inhibit any viral activity through the neuraminidase inhibitor oseltamivir [75].

In North America, different forms of extract derived from aerial pieces and numerous types of *Echinacea* spp. have been utilized historically in the management of respiratory diseases, abrasions, and further inflammatory situations [76]. In last 10 years, as "cold and flu" remedies, they have become very common. The key bioactive constituents were initially suggested to be polysaccharides; however, additional modern researches have identified the presence on alkyl amides and some other derivatives of caffeic acid as the main active ingredients [77].

Also, crushed Glycyrrhiza root has been established as an efficient medicinal part of plant for removing phlegm and has been utilized from the very old eras, principally in *Ayurvedic* system of healing, for this reason; the plant's derivations were used for the treatment of several infections related to the superior respiratory tract. Several phenolic constituents, for instance, flavonoids and their derivatives of glycosides, glucosides, coumarin, cinnamic acid, liquiritin, and isoliquiritin have also been segregated from the Indian species in particular. The antiviral activity

could be linked to the presence of active compounds such as triterpine, saponins, and in particular glycyrrhizinic acid [13].

Furthermore, some fatty acids have been reported to possess some antiviral properties [13]. The middle-chain triglycerides may destroy infectious microorganisms within the physique. The antiviral achievement endorsed to lauric acid monoglyceride is to solubilise phospholipids in the killing of the infectious microorganisms'. Several evidence have affirms that the presence of middle-sequence fatty acids could interferes through the indicator movement of the organism and that the antimicrobial outcome on viruses is as a result of virus assembly intervention and viral suppuration [78].

The methanol extract of *Emblica officinalis* fruit have a powerful hampering commotion adjacent to reverse transcriptase of human immunodeficiency virus. In Cuban traditional medicine, *Emblica officinalis* watery extracts are utilized for their antiviral action against Hepatitis B virus, Influenza A and B Virus. The extract's cytotoxicity was experienced with wealth of outpost appearance capacity and development embarrassment assays, in addition to through mitotic directory calculation. Cytofluorimetric approaches have investigated programmed cell death induction and cell rotation kinetics [79]. In Ayurvedic system of treatment *Emblica officinalis* is a general ingredient of Polyherbal formulations, and Chyawanprash is mainly remarkably component that is an important adaptogen and protection inoculation that could be applied for effective management of infection with swine flu [80].

There have been studies that have established the antimicrobial antiviral activity in *Mentha piperita* most especially from the menthol extract during in vitro antiviral activity against flu virus and herpes as well as many other viruses. The aqueous extracts derived from peppermint leaves have been shown to demonstrate antiviral activities against influenza A and Herpes simplex virus [81]. The oil produced from *Mentha piperita* is full of terpenoids, for instance, alpha-pinene or beta-pinene, alpha-phellandrene, as well as menthol-linked ester or liberated isovaleric acid and acetic acid that are primarily accountable for the herb's antimicrobial action [82].

The dynamic attitudes of *Tinospora cordifolia* have been shown to have immunostimulant efficacy and protend the capability to trigger and enhances the activities of serum IgG antibodies together with the stimulation of macrophages [18]. In the leukocyte migration inhibition experiments, improvement in humoral protection, indicated through the hemagglutination, was observed together with motivation of cell-mediated resistance. This affirms the immunostimulant potentials of these herb against H1N1 flu [83].

Furthermore, studies on cellular development and intentions adjusted through andrographolide protected cell therapy have been carried out in clinical trials. The outcome obtained suggested that andrographis has been shown to minimize indications and protends the potentials to shorten the duration of chills. Flu manifestations symptoms includes weakness, pain in throat, painful muscles, watery nose, pain in head, and swelling of the lymph nodes could also be decreased by *Andrographis paniculata* [84].

19.6 Conclusion and Future Recommendation

This chapter has provided a detailed information on several medicinal plants that could be applied for effective management of Influenza A virus which has been identified as a major factor responsible for most critical respiratory. Detailed information on the mechanism of action by which these medicinal plants exhibit their antiviral activities against Influenza A virus were also provided. There is a need to establish the best formulation that will entails different pharmacological active constitutes derived from unexploited bioresources majorly from diverse environment such as marine environment. This will enable the identification of novel biologically active substance that could be applied for effective management of Influenza A virus. Moreover, there is need to also identify biologically active metabolites that could be derived from beneficial microorganism which could serve as an antiviral agent against Influenza A virus. This will go a long way towards the elimination of several adverse effects involved in synthetic drugs as well as improves the effectiveness of these biogenic derived anti-Influenza A virus drug.

References

1. Rajasekaran D, Palombo EA, Chia YT, Lim SLD, Lee TC, Malherbe F et al (2013) Identification of traditional medicinal plant extracts with novel antiinfluenza activity. PLoS One 8:e79293
2. Webster R, Bean WGO, Chambers T, Kawaoka Y (1992) Evolution and ecology of influenza a virus. Microbiol Rev 56:152–179
3. Rajasekaran D, Palombo EA, Yeo TC, Ley DLS, Tu CL, Malherbe F, Grollo L (2013) Identification of traditional medicinal plant extracts with novel anti-influenza activity. PLoS One 8(11):e79293
4. Webster RG, Bean WJ, Gorman OT, Chambers TM, Kawaoka Y (1992) Evolution and ecology of influenza A viruses. Microbiol Mol Biol Rev 56(1):152–179
5. Mehrbod P, Abdalla MA, Njoya EM, Ahmed AS, Fotouhi F, Farahmand B, Gado DA, Tabatabaian M, Fasanmi OG, Eloff JN, McGaw LJ, Fasina FO (2018) South African medicinal plant extracts active against influenza A virus. BMC Complement Altern Med 18:112. https://doi.org/10.1186/s12906-018-2184-y.
6. Beringer P, Troy A, David A, Remington JP (2006) The science and practice of pharmacy. Lippincott Williams & Wilkins, Philadelphia, p 1419
7. Pathumwadee I, Chittima L, Thanyada R, Arthorn L, Maturos M, Panita D et al (2008) How amantadine and rimantadine inhibit proton transport in the M2 protein channel. J Mol Graph Model 27:342–348
8. Sarah CD, Hong M (2008) Amantadine-induced conformational and dynamical changes of the influenza M2 transmembrane proton channel. Proc Natl Acad Sci U S A 105:1483–1488
9. Arora R, Chawla R, Marwah R, Arora P, Sharma RK, Kaushik V, Goel R, Kaur A, Silambarasan M, Tripathi RP, Bhardwaj JR (2011) Potential of complementary and alternative medicine in preventive management of novel H1N1 Flu (swine flu) pandemic: thwarting potential disasters in the bud. Evid Based Complement Alternat Med 2011:586506. https://doi.org/10.1155/2011/586506
10. Kuhn M, Winston D (2007) Winston & Kuhn's herbal therapy &supplements: a scientific and traditional approach. Lippincott Williams & Wilkins, Philadelphia
11. Gupta S, Sharma P, Saini BM (2007) Immunomodulatory potential of Ocimum tenuiflorum extracts in bovine peripheral blood mononuclear cells in vitro. J Immunol Immunopathol 9:31–36

12. Tsai Y, Cole LL, Davis LE, Lockwood EJ, Simmons V, Wild GC (1985) Antiviral properties of garlic: in vitro effects on influenza B, herpes simplex and Coxsackie viruses. Planta Med 5:460–461
13. Duke W (2009) Medicine: Cocos nucifera Folk Medicine, 2009
14. Kabara JJ (1978) The pharmacological effect of lipids. American Oil Chemist's Society, Champaign
15. Wang X, Jia W, Zhao A, Wang X (2006) Anti-influenza agents from plants and traditional Chinese medicine. Phytother Res 20(5):335–341
16. David W, Steven M (2007) Adaptogens: herbs for strength, stamina, and stress relief. Healing Arts Press, Rochester
17. Singh SS, Pandey SC, Srivastava S, Gupta VS, Patro B, Ghosh AC (2003) Chemistry and medicinal properties of Tinospora cordifolia (Guduchi). Indian J Pharm 35(2):83–91
18. Kapil A, Sharma S (1997) Immunopotentiating compounds from Tinospora cordifolia. J Ethnopharmacol 58(2):89–95
19. McCaughey C (2010) Influenza: a virus of our times. Ulster Med J 79(2):46
20. Ng WF, To KF (2007) Pathology of human H5N1 infection: new findings. Lancet 370 (9593):1106–1108
21. Whitley RJ, Monto AS (2006) Prevention and treatment of influenza in high-risk groups: children, pregnant women, immunocompromised hosts, and nursing home residents. J Infect Dis 194(Supplement_2):S133–S138
22. Khan MZA, Gajamer VR (2015) Epidemical disease: a review on swine flu. Int J Pharm Biomed Res 2:11–19
23. Shrestha S, Foxman B, Berus J, Van Panhuis WG, Steiner C, Viboud C, Rohani P (2015) The role of influenza in the epidemiology of pneumonia. Sci Rep 5:15314
24. Khazeni N, Bravata DM, Holty J-EC, Uyeki TM, Stave CD, Gould MK (2009) Systematic review: safety and efficacy of extended-duration antiviral chemoprophylaxis against pandemic and seasonal influenza. Ann Intern Med 151(7):464–473
25. Stephenson I, Clark TW, Pareek M (2008) Antiviral treatment and prevention of seasonal influenza: a comparative review of recommendations in the European Union. J Clin Virol 42 (3):244–248
26. Kurtz S, Luo G, Hahnenberger KM, Brooks C, Gecha O, Ingalls K, Numata K i, Krystal M (1995) Growth impairment resulting from expression of influenza virus M2 protein in Saccharomyces cerevisiae: identification of a novel inhibitor of influenza virus. Antimicrob Agents Chemother 39(10):2204–2209
27. Muthuri SG, Myles PR, Venkatesan S, Leonardi-Bee J, Nguyen-Van-Tam JS (2013) Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009–2010 influenza A (H1N1) pandemic: a systematic review and meta-analysis in hospitalized patients. J Infect Dis 207(4):553–563
28. Nicholson K, Aoki F, Osterhaus A, Trottier S, Carewicz O, Mercier C, Rode A, Kinnersley N, Ward P (2000) Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Lancet 355(9218):1845–1850
29. Hurt AC (2014) The epidemiology and spread of drug resistant human influenza viruses. Curr Opin Virol 8:22–29
30. Okomo-Adhiambo M, Fry AM, Su S, Nguyen HT, Abd Elal A, Negron E, Hand J, Garten RJ, Barnes J, Xiyan X (2015) Oseltamivir-resistant influenza A (H1N1) pdm09 viruses, United States, 2013–14. Emerg Infect Dis 21(1):136
31. Piñón A, Acosta B, Valdés O, Pérez A, Muné M, Arencibia A, Savón C, Goyenechea A, Oropesa S, González G (2013) Adamantane and neuraminidase inhibitor resistance among circulating human influenza A viruses in Cuba during 2006-2010. Int J Antimicrob Agents 42 (1):97
32. May G, Willuhn G (1978) Antiviral effect of aqueous plant extracts in tissue culture. Arzneimittelforschung 28(1):1–7

33. Ivanova E, Toshkova R, Serkedjieva J (2005) A plant polyphenol-rich extract restores the suppressed functions of phagocytes in influenza virus-infected mice. Microbes Infect 7(3):391–398
34. Cosa P, Vlietinck AJ, Berghe DV, Maes L (2006) Anti-infective potential of natural products: how to develop a stronger in vitro 'proof-of-concept. J Ethnopharmacol 106:290–302
35. Duraipandiyan V, Ayyanar M, Ignacimuthu S (2006) Antimicrobial activity of some ethnomedicinal plants used by Paliyar tribe from Tamil Nadu, India. BMC Complement Altern Med 6:35–41
36. Jung HE, Lee HK (2020) Host protective immune responses against influenza A virus infection. Viruses 12:504. https://doi.org/10.3390/v12050504.
37. Echeverry DM, Rodas JD (2011) Influenza virus A H5N1 and H1N1: features and zoonotic potential. Rev Colomb Cienc Pecu 24:647–662
38. Taubenberger JK, Morens DM (2008) The pathology of influenza virus infections. Annu Rev Pathol Mech Dis 3:499–522
39. Zambon M (2014) Influenza and other emerging respiratory viruses. Medicine 42(1):45–51
40. Ahsan N, Sabahat A, Muhammad AN (2019) A review of strategic immune evasion by influenza virus and antiviral response of interferon. Adv Biotechnol Micro 12(5):555848. https://doi.org/10.19080/AIBM.2019.12.555848
41. Cavallazzi R, Ramirez JA (2018) Influenza and viral pneumonia. Clin Chest Med 39:703–721. https://doi.org/10.1016/j.ccm.2018.07.0050272-5231/18
42. Peteranderl C, Herold S, Schmoldt C (2016) Human influenza virus infections. Semin Respir Crit Care Med 37:487–500
43. Mousa HA-L (2015) Herbal therapies for prevention and treatment of influenza and influenza-like illness. J Infect Dis Ther 3:215. https://doi.org/10.4172/2332-0877.1000215
44. Ganjhu RK, Mudgal PP, Maity H, Dowarha D, Devadiga S, Nag S, Arunkumar G (2015) Herbal plants and plant preparations as remedial approach for viral diseases. Virus Dis 26 (4):225–236. https://doi.org/10.1007/s13337-015-0276-6
45. Jassim SAA, Naji MA (2003) Novel antiviral agents: a medicinal plant perspective. J Appl Microbiol 95:412–427. https://doi.org/10.1046/j.1365-2672.2003.02026.x
46. Mousa HA-L (2017) Prevention and treatment of influenza, influenza-like illness, and common cold by herbal, complementary, and natural therapies. J Evid Based Complement Alternat Med 22(1):166–174. https://doi.org/10.1177/2156587216641831
47. Ding Y, Zeng L, Li R, Chen Q, Zhou B, Chen Q, Cheng P l, Yutao W, Zheng J, Yang Z, Zhang F (2017) The Chinese prescription lianhuaqingwen capsule exerts anti-influenza activity through the inhibition of viral propagation and impacts immune function. BMC Complement Altern Med 17:130. https://doi.org/10.1186/s12906-017-1585-7
48. Hudson JB (2009) The use of herbal extracts in the control of influenza. J Med Plants Res 3 (13):1189–1195
49. Al-garawyi AMA, Hussein TA, Jassim MMA (2020) Inhibition of viral infection by using of natural herbal remedies as alternative treatment. Syst Rev Pharm 11(6):416–419. https://doi.org/10.31838/srp.2020.6.66
50. Webster D, Taschereau P, Lee TD, Jurgens T (2006) Immunostimulant properties of Heracleum maximum Bartr. J Ethnopharmacol 106(3):360–363
51. Chiang LC, Chiang W, Chang MY, Lin CC (2003) In vitro cytotoxic, antiviral and immunomodulatory effects of Plantago major and Plantago asiatica. Am J Chin Med 31(2):225–234
52. Kotwal GJ, Kaczmarek JN, Leivers S, Ghebremariam YT, Kulkarni AP, Bauer G, C DEB, Preiser W, Mohamed AR (2005) Anti-HIV, anti-poxvirus, and anti-SARS activity of a non-toxic, acidic plant extract from the trifollium species secomet-V/anti-Vac suggests that it contains a novel broad-spectrum antiviral. Ann N Y Acad Sci 1056:293–302
53. Buckwold VE, Wilson RJ, Nalca A, Beer BB, Voss TG, Turpin JA, Buckheit RW III, Wei J, Wenzel-Mathers M, Walton EM, Smith RJ, Pallansch M, Ward P, Wells J, Chuvala L, Sloane S, Paulman R, Russell J, Hartman T, Ptak R (2004) Antiviral activity of hop constituents against a series of DNA and RNA viruses. Antivir Res 61(1):57–62

54. Mohamed MS, Idriss MT, Alruwaili NK, Alotaibi NH, Elsaman T, Mohamed MA (2020) Investigation of the potential anti-influenza activity of five plants grown in Sudan and used folklorically for respiratory infections. J Appl Pharm Sci 10(06):054–061
55. Goleniowski ME, Bongiovanni G, Palacio L, Nuñez C, Cantero J (2006) Medicinal plants from the "Sierra de Comechingones", Argentina. J Ethnopharmacol 107(3):324–341
56. Maria John KM, Enkhtaivan G, Ayyanar M, Jin K, Yeon JB, Kim DH (2015) Screening of ethnic medicinal plants of South India against influenza (H1N1) and their antioxidant activity. Saudi J Biol Sci 22(2):191–197. https://doi.org/10.1016/j.sjbs.2014.09.009
57. Choi EJ, Kim G-H (2009) Dandelion (Taraxacum officinale) flower ethanol extract inhibits cell proliferation and induces apoptosis in human ovarian cancer SK-OV-3 cells. Food Sci Biotechnol 18(2):552–555
58. Hu C, Kitts DD (2003) Antioxidant, prooxidant, and cytotoxic activities of solvent-fractionated dandelion (Taraxacum officinale) flower extracts in vitro. J Agric Food Chem 51(1):301–310
59. Lee JB, Miyake S, Umetsu R, Hayashi K, Chijimatsu T, Hayashi T (2012) Anti-influenza A virus effects of fructan from Welsh onion (*Allium fistulosum* L.). Food Chem 134(4):2164–2168. https://doi.org/10.1016/j.foodchem.2012.04.016
60. Zakay-Rones Z, Varsano N, Zlotnik M, Manor O, Regev L, Schlesinger M, Mumcuoglu M (1995) Inhibition of several strains of influenza virus in vitro and reduction of symptoms by an elderberry extract (*Sambucus nigra* L.) during an outbreak of influenza B Panama. J Altern Complement Med 1(4):361–369. https://doi.org/10.1089/acm.1995.1.361
61. Burge E, Mumcuoglu M, Simmons T (1999) The effect of Sambucol on flu-like symptoms in chimpanzees: prophylactic and symptom-dependent treatment. Int Zoo News 46:16–19
62. Krawitz C, Mraheil MA, Stein M, Imirzalioglu C, Domann E, Pleschka S, Hain T (2011) Inhibitory activity of a standardized elderberry liquid extract against clinically-relevant human respiratory bacterial pathogens and influenza A and B viruses. BMC Complement Altern Med 11:16. https://doi.org/10.1186/1472-6882-11-16
63. Chavan R, Chowdhary A (2014) In vitro inhibitory activity of Justicia adhatoda extracts against influenza virus infection and hemagglutination. Int J Pharm Sci Rev Res 25(2):231–236
64. Chiang LC, Ng LT, Cheng PW, Chiang W, Lin CC (2005) Antiviral activities of extracts and selected pure constituents of Ocimum basilicum. Clin Exp Pharmacol Physiol 32(10):811–816
65. Chang M-Y, Shen Y-L (2014) Linalool exhibits cytotoxic effects by activating antitumor immunity. Molecules 19(5):6694–6706
66. Chiang L, Chiang W, Chang M, Ng L, Lin C (2002) Antiviral activity of Plantago major extracts and related compounds in vitro. Antivir Res 55(1):53–62
67. Pushpa R, Nishant R, Navin K, Pankaj G (2013) Antiviral potential of medicinal plants: an overview. Int Res J Pharm 4(6):8–16
68. García MG, Coto TM, Soto GR, Pazos L (2003) Sub-chronic toxicity and test of eye irritability of leaf aqueous extract from Plantago major (Plantaginaceae). Rev Biol Trop 51(3-4):635–638
69. Escobar FM, Sabini MC, Zanon SM, Cariddi LN, Tonn CE, Sabini LI (2011) Genotoxic evaluation of a methanolic extract of Verbascum thapsus using micronucleus test in mouse bone marrow. Nat Prod Commun 6(7):989–991
70. Serkedjieva J, Gegova G, Mladenov K (2008) Protective efficacy of an aerosol preparation, obtained from Geranium sanguineum L, in experimental influenza infection. Pharmazie 63 (2):160–163
71. Friedman M (2007) Overview of antibacterial, antitoxin, antiviral, and antifungal activities of tea flavonoids and teas. Mol Nutr Food Res 51(1):116–134
72. Yamada H, Takuma N, Daimon T, Hara Y (2006) Gargling with tea catechin extracts for the prevention of influenza infection in elderly nursing home residents: a prospective clinical study. J Altern Complement Med 12(7):669–672
73. Rowe CA, Nantz MP, Bukowski JF, Percival SS (2007) Specific formulation of Camellia sinensis prevents cold and flu symptoms and enhances γδ T cell function: a randomized, double-blind, placebo-controlled study. J Am Coll Nutr 26(5):445–452

74. Ehrhardt C, Hrincius ER, Korte V, Mazur I, Droebner K, Poetter A, Dreschers S, Schmolke M, Planz O, Ludwig S (2007) A polyphenol rich plant extract, CYSTUS052, exerts anti influenza virus activity in cell culture without toxic side effects or the tendency to induce viral resistance. Antiviral Res 76(1):38–47
75. Haidari M, Ali M, Casscells SW III, Madjid M (2009) Pomegranate (Punica granatum) purified polyphenol extract inhibits influenza virus and has a synergistic effect with oseltamivir. Phytomedicine 16(12):1127–1136
76. Barnes J, Anderson LA, Gibbons S, Phillipson JD (2005) Echinacea species (Echinacea angustifolia (DC.) Hell., Echinacea pallida (Nutt.) Nutt., Echinacea purpurea (L.) Moench): a review of their chemistry, pharmacology and clinical properties. J Pharm Pharmacol 57(8):929–954
77. Curreli F, Friedman-Kien AE, Flore O (2005) Glycyrrhizic acid alters Kaposi sarcoma–associated herpesvirus latency, triggering p53-mediated apoptosis in transformed B lymphocytes. J Clin Investig 115(3):642–652
78. Projan SJ, Brown-Skrobot S, Schlievert PM, Vandenesch F, Novick RP (1994) Glycerol monolaurate inhibits the production of beta-lactamase, toxic shock toxin-1, and other staphylococcal exoproteins by interfering with signal transduction. J Bacteriol 176(14):4204–4209
79. Sanchez-Lamar A, Fiore M, Cundari E, Ricordy R, Cozzi R, De Salvia R (1999) Phyllanthus orbicularis aqueous extract: cytotoxic, genotoxic, and antimutagenic effects in the CHO cell line. Toxicol Appl Pharmacol 161(3):231–239
80. Fortunatov M (1952) Experimental use of phytoncides for therapeutic and prophylactic purpose. Voprosy Pediatrii i Okhrany Materinstva 20(2):55–58
81. Herrmann EC Jr, Kucera LS (1967) Antiviral substances in plants of the mint family (Labiatae). III. Peppermint (Mentha piperita) and other mint plants. Proc Soc Exp Biol Med 124(3):874–878
82. Valsaraj R, Pushpangadan P, Smitt U, Adsersen A, Nyman U (1997) Antimicrobial screening of selected medicinal plants from India. J Ethnopharmacol 58(2):75–83
83. Sohni YR, Bhatt RM (1996) Activity of a crude extract formulation in experimental hepatic amoebiasis and in immunomodulation studies. J Ethnopharmacol 54(2-3):119–124
84. Melchior J, Palm S, Wikman G (1997) Controlled clinical study of standardized Andrographis paniculata extract in common cold—a pilot trial. Phytomedicine 3(4):315–318

20

COVID-19 Pandemic Panic: Prophylactic as Well as Therapeutic Management with Traditional Ethnic Phytopharmaceuticals with Challenging Nano-spray Inhaler and Advanced Drug Delivery System

Gaurav Gupta, Abhishek Bhattacharjee, Amit Ladha, Adity Sarbajna, Mridul Pokhrel, Partha Palit, and Subhash C. Mandal

Abstract

SARS-CoV-2 virus is the causative agent of COVID-19 pandemic which has led to a massive health crisis needing in-depth understanding of the disease including its clinical pathology, diagnosis, and immune response, which can be used for

Gaurav Gupta, Abhishek Bhattacharjee and Partha Palit contributed equally with all other contributors.

The original version of this chapter was revised: authorship has been amended. A correction to this chapter can be found at https://doi.org/10.1007/978-981-33-6850-7_27

G. Gupta · A. Ladha
Present Address: Area of Biotechnology and Bioinformatics, NIIT University, Neemrana, Rajasthan, India

A. Bhattacharjee · P. Palit (✉)
Present Address: Department of Pharmaceutical Sciences, Drug Discovery and Novel Drug Delivery Research Laboratory, Assam University, Silchar, Assam, India

A. Sarbajna
Department of Zoology, Surendranath College, Kolkata, India

M. Pokhrel
Department of Pharmaceutical Science, Assam University, Silchar, India

P. Palit
Department of Pharmaceutical Sciences, Drug Discovery and Novel Drug Delivery Research Laboratory, Assam University, Silchar, Assam, India

S. C. Mandal
Pharmacognosy and Phytotherapy Research Laboratory, Division of Pharmacognosy, Department of Pharmaceutical Technology, Jadavpur University, Kolkata, India

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_20

designing an effective therapy against this virus. Treatment modalities based on plants or plant-derived compounds can offer a wide range of options for targeting the SARS-Cov2 virus directly or indirectly. At the same time, plant-derived compounds have the capacity to bolsters host immunity thereby resisting viral growth. Here in this review, we have systematically discussed about the importance of medicinal plants and phytopharmaceuticals, in various formulations, for the treatment of COVID-19 and its associated pathologies.

Keywords

COVID-19 · Potential phytometabolites · Immune regulation · Nano-phyto-formulation · Advanced drug delivery system

20.1 Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes Coronavirus disease (COVID-19), which has emerged as a universal health crisis. The epicenter of this global disease was believed to be Wuhan, China [1–3] that resulted in the infection of over 4 million people and causing over 280,000 fatalities [4].

Broadly speaking, positive-stranded RNA coronaviruses are enveloped viruses capable of infecting multiple animals including humans and display zoonotic transmission from animal reservoirs [5–7]. Mild upper respiratory illness is one of the major pathologies caused by many human coronaviruses. SARS-CoV-2, SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) belonging to Beta coronaviruses group, usually infects the lower respiratory tract of humans resulting in severe and mostly fatal respiratory syndrome [8, 9].

SARS-CoV-2 shares its genome organization with other beta coronaviruses. It has been observed that both SARS-CoV-1 and SARS-CoV-2 have 79% genome homology, while SARS-CoV-2 and MER-COV have 50% homology [10]. The major structural proteins of SARS CoV-2 are replicase (ORF1a/ORF1b), spike (S), envelope (E), membrane (M), and nucleocapsid (N). The genes encoding the structural proteins are interspersed between seven putative ORFs encoding accessory proteins [11].

Bats are the natural host of SARS-CoV-2. Moreover, studies have shown a significantly high 96.2% homology between SARS-CoV-2 and bat coronavirus (RaTG13) isolated from Yunnan province, China [12–14]. Other than bats, pangolins are another wildlife host for SARS-CoV-2 [15–18].

Initiation of virus infections requires binding of virions to surface receptors present on the host cells. Therefore, these host receptors recognized by the virus are critical in determining the host cells and tissues thats are being infected with the virus [19]. SARS-Cov2 enters the host cells by utilizing its surface transmembrane spike (S) glycoprotein [20]. This S glycoprotein is made up of two functional subunits, S1 and S2, which participates in attachment to the host cell receptor and fusion of the host and viral membranes, respectively. SARS-CoV-2-S, in turn, uses

the host angiotensin-converting enzyme 2 (ACE2) to gain entry in the host cell [12–14, 21, 22]. Other than human ACE2, SARS-CoV-2 can also bind to ACE2 from other animals such as pig, ferret, rhesus monkey, civet, cat, pangolin, rabbit, and dog [6, 7, 12–14, 21–24].

Novel therapeutic strategies are needed to combat the SARS-COV-2. Here in this book chapter, we will be discussing the various plant-based modalities that can be developed as potential drugs in various formulation for combating COVID 19.

20.2 Pathological Characterization of SARS-COV-2 Infection

Host ACE 2 protein which participates in SARS-Cov-2 entry is significantly expressed on different human cells including type II alveolar cells, oral, esophageal, ileal epithelial cells, myocardial cells, proximal tubule cells of the kidneys as well as urothelial cells of the bladder [25]. S protein of SARS-CoV-2 is cleaved into S1 and S2 proteins by host enzyme, furin, which is critical for the virus to gain entry in the lung cells [21, 22].

ACE 2/angiotensin axis plays a pivotal role regulation of inflammation and signaling pathways that contributes to tissue injury [26] and has also been accounted for COVID-19 associated clinical manifestations such as hypokalemia, vasoconstriction [27], and development of acute respiratory distress syndrome (ARDS) [28]. It should be noted that the ACE 2 expression in the gastrointestinal, cardiovascular, endocrine, and genitourinary systems is significantly higher than the respiratory system, which serves as the primary target of the virus [25]. Moreover, there is an increase in the number of COVID-19 cases in men, which could be accounted for attenuated expression of ACE 2 in females [6, 7, 29]. Interestingly, a study has shown that ACE 2 expression is also age-dependent [30]. However, COVID-19 infection affects people of all ages. Young individuals under 18 years account for nearly 2% of the reported COVID-19 incidences [31]. Interestingly, the majority of the infected young individuals having COVID-19 were either not exhibiting symptoms or experienced milder symptoms [32]. Severity to COVID19 increases with accompanying health conditions that affect vital organs such as heart, kidney, lung, and others [33–35].

COVID-19 causes major clinical manifestation of the respiratory system where patients display various pathologies such as single ground-glass opacity (GGO), bilateral diffuse heterogeneous consolidation with air bronchogram and bronchiectasis, the "white lung." During the initial phase of COVID19, GGO is prevalent in lower right lobes of the lungs having significant inter or intralobular septal thickening. Moreover, disease progression is marked by formation of sub-segments and bilateral multiple lobes in the lungs [12–14, 28]. Interestingly, there is a trend of increasing number of neutrophils in COVID-19 cases, which bears direct forbearance to damage associated with the lungs [36]. During severe COVID-19 infection, several characteristics of acute respiratory distress syndrome are observed such as diffuse alveolar damage, desquamation of pneumocytes, development of hyaline membranes, edema, and others [33, 37].

The mortality rate of COVID-19 is significantly higher in patients with cardiovascular diseases [38–40]. Some of the patients with severe COVID-19 infection suffer from cardiac failure. However, inflammatory cardiomyopathy has also been observed in a few COVID-19 patients [41–43].

COVID-19 also affects the kidney by causing acute injury to it resulting in increased mortality [44]. SARS-COV2 can target the cellular components of kidney as podocytes and proximal tubular epithelial cells that express significant levels of ACE 2 receptors [45, 46]. Some of the clinical pathologies associated with kidney damage resulting in increased mortality in COVID-19 patients include proteinuria, hematuria, increased levels of blood urea nitrogen, and serum creatinine [47–51]. Urine analysis of COVID-19 patients shows glomerular and tubular injury that substantiates kidney damage [52].

COVID19 is capable of infecting the gastrointestinal tract leading to diarrhea, which is evident from clinical biopsy analysis [53]. This is because epithelial cells of the GI tract express high levels of ACE 2 receptors [17, 18].

SARS-CoV2 targets the central nervous system and the cerebrospinal fluid [54, 55]. Therefore, this neuroinvasive potential of SARS-CoV-2 might have a role in initiating acute cardiac and respiratory failure of COVID-19 [47–51]. This can be substantiated by identification of acute ischemic stroke during SARS-CoV2 infection as a neurologic complication [56].

Thus SARS-CoV-2 targets multiple organs to mediate disease pathology, which in the later stages or the presence of comorbidity, could be detrimental, leading to multiple organ failure and death.

20.2.1 Signs and Symptoms

COVID-19 infection is associated with a wide range of symptoms, which varies from mild symptoms to severe illness. Once an individual has come in contact with SARS-CoV2, it usually takes around 2–14 days for the symptoms to show up. COVID-19 pneumonia in adults is associated with symptoms such as fever, dry cough, loss of smell or taste sore throat, headache, fatigue, myalgia, and breathlessness (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html; [8, 9, 38–40]). Infected patients usually show mild pneumonia to moderate pneumonia which could be associated with critical illness, hospitalization, mechanical ventilation, multiorgan failure, and death. Moreover, critically ill patients with accompanying comorbidities run a high risk of death [33].

20.2.2 Laboratory Diagnosis for COVID-19

Viral and host factors such as virus associated antigens, nucleic acid, and virus-specific antibodies are the essentials for diagnosis of SARS-CoV-2. Moreover, these host generated anti-SARSCoV-2 antibodies are critical for identifying previous exposure to SARS-CoV2 (Laboratory testing for coronavirus disease; [1]).

Detection of SARS-CoV2 RNA from the naso-pharynx or lower respiratory swabs is used for detecting active infection and is also used for direct diagnosis of SARS-CoV-2 infection [57].

Different analytical techniques such as real-time PCR, reverse-transcription-loop-mediated isothermal amplification (RT-LAMP) are used for detection of SARS-COv2 nucleic acid.

The high sensitivity and specificity of Real-time PCR make it the most commonly used tool in SARS-CoV-2 RNA detection and the same can be employed for screening symptomatic and asymptomatic patients. Envelope (E) and RNA-dependent RNA polymerase (RdRp) of SARS-COv-2 serves as targets for the initial and confirmatory test for COVID-19. Moreover, another variation of Real-time PCR termed as one-step Real-time PCR assay has been employed for detecting SARS-CoV-2 [58], where the N region is employed for screening and ORF1b serves as a confirmatory test for the virus [59].

Real-time PCR can also be combined with LAMP, which uses exponential amplification of specific nucleic acid at constant temperature, for screening SARS-CoV-2 RNA. The technique is advantageous as it avoids certain pitfalls such as ultra-pure samples, trained laboratory personnel, and costly analytical instruments. It has the lowest turnaround time indirect methods and has high sensitivity making it a practical substitute for Real-time PCR in situations where time is of the essence.

Detection of viral antigens using enzyme-linked immunoassay (ELISA), chemiluminescent immunoassay (CLIA), and rapid serological tests has also been employed for screening. ELISA is used for the detection of IgG and IgM that are specific for SARS-CoV-2 N and S proteins. However, antibody ELISA does not completely satisfy the diagnostic efficacy in absence of suitable standards [60]. Due to its medium turnaround time, ease of sample collection and inexpensive nature, this diagnostic technique is widely used for screening a large cohort.

On the other hand, the shortcomings in ELISA are compensated by CLIA. It offers a reliable way for quantification of antibodies by relying on chemiluminescence reaction that permits evaluation of IgG and IgM titers [61]. Major advantages associated with it include high throughput screening, increased sensitivity, and early detection of suspicious cases with false negative nucleic acid diagnosis.

Other diagnostic technique based on immunoassay technology such as rapid serological tests provides a quick and reliable method for evaluating IgM and IgG [47–51]. This technique utilizes colloidal gold-labeled SARS-CoV-2 recombinant protein and murine anti-human IgG, IgM, and control antibodies immobilized in different demarcated areas. However, one of the major disadvantages of this technique is lack of stringent test for clinical accuracy before using it for large cohort screening of COVID-19.

20.2.3 Asymptomatic, Pre-symptomatic and Mild-Symptomatic and Acute Symptomatic Profile

Clinical spectrum of COVID-19 disease has shown the emergence of pre-symptomatic, mild-symptomatic, acute symptomatic, and asymptomatic patients, which presents different clinical manifestations of the disease.

Out of the total SARS-CoV-2 infections, asymptomatic individuals account for approximately 40–45% cases. These asymptomatic patients can transmit the virus to others for an extended period, where the mean duration of virus shedding was 19 days and was much longer than the symptomatic group. Moreover, the asymptomatic infection may be associated with subclinical lung abnormalities, as detected by computed tomography [62–64]. Asymptomatic individuals have lower levels of virus-specific IgG levels and neutralizing antibodies compared to symptomatic group [62, 63]. Major inflammatory and anti-inflammatory cytokines such as IL-6, IFN-γ, IP-10, IL-10, IL-15, IL-2, and others were significantly lower in asymptomatic individuals compared to symptomatic groups [62, 63]. The above findings clearly show that asymptomatic individuals pose a weak immune response to SARS-CoV-2.

On the other hand, mild-symptomatic patients exhibit mild symptoms such as cough, similar to mild pneumonia [8, 9]. However, patients which do not show disease severity are able to eliminate the virus quickly. In conclusion, patients without symptoms are able to eliminate the virus within five days than patients with mild symptoms [33].

Immunological changes such as marked reduction in lymphocytes, selective loss of CD^{4+} T cells, CD^{8+} T cells, and NK cells, hyper activated T cells along with significant expression of energy markers on T cells are commonly associated with individuals having acute symptoms in comparison to those harboring mild or no symptoms [47–51].

20.2.4 Immunopathological Syndrome

Critical immunopathology associated with COVID-19 are sharp decline in lymphocyte count, hyperactivation and energy of lymphocytes, defects in granulocytes and monocytes, enhanced production of cytokines and antibodies [65].

Lymphopenia is associated with disease severity [47–51, 63] and shows a remarkable reduction in $CD4^+$ T cells, $CD8^+$ T cells, NK cells, and B cells [37, 67–70]. In particular, lymphocyte levels fall below 20% during severe infection, accompanied by a sharp drop in $CD8^+$ T cells and memory helper T cells [47–51, 69, 70]. COVID-19 associated lymphopenia can be explained by the fact that S protein of SARS CoV-2 binds to ACE2 receptors on T cells, macrophages, and others, to directly infect these immune cells [65, 71]. Additionally, SARS-CoV2 has been shown to destroy immune organs such as lymph and spleen [47–51, 72], which could also be accounted to COVID 19 associated lymphopenia.

Granulocytes and monocytes show abnormality in cell count in COVID-19 patients. Typically, the severity of COVID-19 is associated with a higher number of neutrophils, and reduced numbers of eosinophils, basophils, and monocytes [68, 73]. Moreover, a significantly higher ratio of neutrophils to lymphocytes also indicates disease severity and poor clinical outcome [47–51, 66, 68, 73]. This increase in neutrophil numbers might be due to SARS-CoV-2 mediated recruitment of neutrophils to the infected tissues [65, 74, 75].

$CD8^+$ T cell responses are more frequent than $CD4^+$ T cells responses during COVID-19. SARS CoV-2 antigen-specific T cells from severe cases have a central memory phenotype and show significant expression of inflammatory cytokines such as interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and others [76, 77]. Moreover, significantly enhanced expression of activation markers such as CD44, CD69, CD38, and others, on $CD4^+$ T cells and $CD8^+$ T cells was observed in COVID-19 patients [12–14]. Whereas patients with severity showed remarkably higher expression of cell priming and clonal expansion markers such as OX40 and 4-1BB. In addition, $CD8^+$ T cells of patients with COVID-19 show increased expression of exhaustion phenotypes such programmed cell death protein-1 and T cell immunoglobulin domain and mucin domain-3 [78].

Increased cytokine production, also known as cytokine storm, is characteristic of disease severity. This cytokine storm during COVID-19 is marked by an alarming increase in the secretion of inflammatory cytokines, including IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), interferon-inducible protein-10 (IP10), monocyte chemotactic protein 1 (MCP1), macrophage inflammatory protein-1α, IFN-γ, and TNF-α [8, 9, 47–51, 67, 68, 79]. Interestingly, severe cases of COVID19 show elevated levels of IL-1β, IL-6, and IL-10 [78, 80]. Mechanistically, SARS-CoV-2 initiates the cytokine storm by activating pathogenic T helper cells, which secretes GM-CSF leading to the induction of $CD14^+$ $CD16^+$ monocytes. These monocytes, in turn, release IL-6 leading to excessive inflammation [12–14]. Another class of $CD14^+$ $IL\text{-}1\beta^+$ monocytes also participates in cytokine storm by secreting IL-1β [81]. Additionally, the IL-6 produced during SARS-CoV-2 infection is known to induce Th17 cells during COVID-19 [82]. This Th17 cell-derived IL-17 promotes recruitment of macrophages, neutrophils, and monocytes at the site of infection [33, 83].

B cell activation and proliferation affect the outcome of COVID-19. In particular, IgG produced by activated B cells are increased in patients with severity [65, 78]. Antibodies can be detected in the first seven days of infection, and the antibody levels would peak around 15–19 days post the onset of the disease [6, 7, 62, 63]. This increased antibody levels promote virus infectivity due to enhanced virus entry into cells via the Fc portion of the antibody bound to the Fc receptor on host cells [72].

20.3 Treatment Modality of COVID-19 in the Context of Phytopharmaceuticals

The traditional mode of treatments has been considered to be highly promising due to extensive application of aromatic herbs, culinary spices, and herbal teas. As they are safe, effective and naturally gifted, readily available as per requirement. Moreover, several bioactive leads like glycyrrhizin, andrographolide, silymarin, Baicalin, Theaflavin, Azadirachtin, Curcumin, Lycorine, Galantamine, Saikosaponin, Ursolic acid, Rosmarinic acid, Emodin have revealed promising effect against different deadly viral infection. During the 2003 SARS outbreak, the effectiveness of phytomedicine as anti-viral agent were note-worthy. The use of herbs and spices towards fighting SARS-CoV-2 infection is quite encouraging around the countries, including China, Japan, Korea, Algeria, are inspiring [8, 9, 84, 85]. After the outbreak of SARS-CoV-1 (2003) and MERS-CoV in 2015, researchers have been attempting to explore different anti-viral extracts and Phytomolecules against SARS-CoV. This information had guided a group of researchers to identify more than 200 medicinal plants & spices for their anti-viral properties against this SARS-CoV-2 strain [86]. The dose-dependent anti-viral response of these extracts and lead Phytomolecules were significant, depending on the requirement, the screened-out extracts were ranging from low to high concentrations [86]. However, selection of appropriate extract, fraction, and lead phytomarker compounds is very important to tackle the covid-19 infection in the right dose and the right time of onset of infection with standardized phytopharmaceuticals. The treatment modality of covid-19 could be fixed based on the severity of the infection and its subsequent phase of the symptoms. On the basis of different degrees of severity and the respective symptoms of Covid-19, phytopharmaceuticals can be applied based on its pharmacological property as depicted in Table 20.1.

20.3.1 Anti-viral Medicinal Plants and Its Phytopharmaceuticals

Traditional ethnic Phyto molecules, bio-active extracts, and bioactivity guided fraction demonstrated very promising viricidal or blocking of host-virus interaction in the respiratory viral infection particularly in influenza, SARS, and MERS coronavirus as suggested by earlier study. Especially, L. radiata displayed the most potent anti-viral activity against the virus strain [76, 94]. These data were as per the two other research teams, who validated that an active compound of liquorice roots, i.e., glycyrrhizin, conferred an anti-SARS-CoV effect by stopping viral replication [95]. In another study, glycyrrhizin (Glycyrrhiza glabra, Fabaceae family) also exhibited anti-viral property when tested for its in vitro anti-viral activity on ten different clinical strains of SARS-CoV. Baicalin, a constituent of the plant Baikal skullcap (*Scutellariabaicalensis*), has been demonstrated encouraging anti-viral potential against SARS-CoV. So far, the in vitro results of Baicalin could not relate with in vivo clinical efficacy. As the oral bioavailability was not satisfactory as expected. Lycorine, an Amaryllidaceae alkaloid, has also confirmed a powerful anti-viral effect

Table 20.1 Probable treatment modality via phytotherapy and recommended plants

Pre-symptomatic or asymptomatic phase of covid-19	Mild-symptomatic	Moderate symptomatic	Acute symptomatic
Immune-boosting nutraceuticals enriched with minerals, amino acids, vitamins and anti-oxidants derived from plants extract and edible beverages It has been applied to strengthen or stimulate the body immunity to fight against virus for controlling the further viral infection through innate and cell mediated immunity	Mild fever, cough, sneezing, mild body aches	Moderate fever, cough, decongestion of nose, shortness of breath, moderate headache, moderate back pain Deposition of sputum and mucous in the upper respiratory tract, infection in the throat and pain	High fever, severe shortness of breath, gradual falling of oxygen saturation in body, high cough, infection in lower respiratory tract, severe whole-body aches, Acute respiratory distress syndrome, internal blood coagulation, vasculitis
Observation or monitoring required	Observation, monitoring plus anti-infective therapy with anti-oxidant, nutraceuticals recommended	Bronchodilator and expectorant, anti-viral drug, anti-pyretic, anti-oxidant, nutraceuticals	Severe anti-anti-inflammatory drugs plus anti-coagulant, anti-pyretic, expectorant or mucolytic agents plus Intensive care unit may be recommended
Probable medicinal plants, herbs and spices such as nutmeg turmeric, cinnamon, oregano, cumin and caraway, citrus fruit, berry, tulsi, ashwagandha, pipul, giloy, etc. [87, 88]	Potential choice of herbs for treatment Like vasaka, tulsi, pipul, clove, cinnamon, garlic, ginger, eucalyptus, Nigella sativa, berry, nutritional tea and spicy beverages, Thymus vulgaris, Echinacea spp., Mentha, Glycyrrhiza glabra and Habbe Bukhar, Sharbat Khaksi, bromhexine hydrochloride, Sharbat Zanjabeel, Naqu Nazla, Majun Chobchini, Jawrish Jalinus, and Khamira Marvareed claimed to be blood purifier, cardio-protective ([89]; theherbalacademy.com) Ma-Xing-Gan-Shi-Tang, Chinese herbal formulation as anti-pyretic [84]	Vasaka, tulsi, turmeric, black pepper, liquorice, vitex negundo, euphorbia species	Withania, ginseng, kalmegh, euphorbia species, vitex negundo and higher doses of turmeric for the management of acute inflammatory disorders in response to acute viral infection [90–93] Garlic, gingko biloba, Grape seed extract, peppers, Bromelain, feverfew extract www.openanesthesia.org/herbal_medicines_anticoagulation_Effects

against SARS-CoV. Several previous investigations suggest that lycorine seems to have broad anti-viral properties and has been reported to have an inhibitory action on the Herpes simplex virus (HSV, type I) [96] and Poliomyelitis virus [97]. Other traditional herbs and plants possessing anti-viral properties against SARS-CoV, Influenza, and MERS are Japanese honeysuckle (Lonicera japonica), the commonly known Eucalyptus tree, and Korean ginseng (Panax ginseng) the last one through its active secondary metabolite, ginsenoside-Rb1. Sinigrin and Hesperidin have demonstrated impressive anti-viral property against SARS-COV-1 and MERS-COV, as well. Berberine, Quercetin, hypericin, rutin, isoquercetin, Epigallocatechin 3-gallate, Silymarin, Bromhexine, Coumarins, Gingerols, Curcumin are the potential leads derived from various traditional herbs and spices, showed very outstanding anti-viral efficacy against respiratory viral infection caused by Influenza virus (Yang et al., 2020) [65].

20.3.2 Anti-inflammatory Herbal Leads for Management of Moderate and Acute Symptomatic Covid-19 Patient

Anti-inflammatory treatment seems to be effective in immuno-regulation for controlling viral infections mediated cytokine storm induced by SARS-Cov-2. This inflammatory disorder has been created in some individuals due to immune dysregulations and aberrant immune response in connection to cellular viral infection and replication [38–40]. An excessive immune response may cause inflammatory disorders followed by organ damage and immune disorders, even life-risk for the patient. In those cases, moderate viral infection may induce severe and acute stages of viral infection [98, 99]. It is needless to say that viral diseases, patients infected with COVID-19 showed inflammatory responses possessing significant levels of plasma cytokines and leucocytes in response to the JAK-STAT pathway [100] that led to the activation of $CD4^+$ T cells, responsible for inflammation [101, 102]. Therefore, strong and potential anti-inflammatory agents significantly may handle such inflammatory disorders by suppressing the inflammatory cytokine upregulation and storm. This approach may reduce the hospitalization time and recovery time of the covid-19 patient. Severe Covid-19 patients have levels of pro-inflammatory cytokines such as IL-10, IL-2, IL-7, MCP-1, G-CSF, MIP-1A, and TNF-α [103]. It is well reported that aromatic herbs and medicinal plants are the bio-resources and factory for the production of several anti-inflammatory and immune-suppressants secondary-metabolites such as steroids, terpenoids, flavonoids, coumarins, and plant lignans that could be explored to check and control the inflammatory crises of covid-19 patients in response to viral replication [104]. However, pre-clinical and clinical trials need to be undertaken for the evaluation of the safety and efficacy of such polyherbal formulation and lead phytopharmaceuticals [99].

20.3.3 Anti-coagulant Phytopharmaceuticals for COVID-19 Treatment

Patients infected with SARS-CoV-2 who manifest severe disease syndrome have induced a high degree of coagulopathy. It is well reported that poor clinical outcomes can be possible in the context of the extent of the coagulopathy [105]. Even mild covid-19 patient suffers severe ventricular thrombus with pre-existing dilatated cardiomyopathy. In contrast, anti-coagulant treatment recovers the severity of the illness very quickly and improves the mortality of the covid-19 [106]. In view of such perspective, it could be inferred that medicinal plants and spices derived Phyto-lead compounds could be explored as significant antiplatelet and anti-coagulant agents [107, 108] for the management of few severe cases of pulmonary coagulopathy and blood clotting complications triggered by covid-19 [99]. Because, in order to prevent thromboembolic manifestations associated with the moderate to acute covid-19, prophylactic antithrombotic medications are fruitful and beneficial during the acute stages. Herbs and spices derived phytoconstituents like Cinnamaldehyde and Cinnamophilin have been found to be an anticoagulative, thromboxane A2 receptor antagonist, anti-atherosclerotic agents. They can prevent unprecedented clumping of platelet and atherosclerotic cardiac disorders due to blood coagulation in the covid-19 patient. So, these types of marker compounds enriched phytoformulation can be highlighted to reduce inflammatory and thrombotic complications in COVID-19 patients subjected to in-depth clinical research [109, 110].

20.3.4 Recovered Covid-19 Patient Management via Phytopharmaceuticals

Management of recovered patient from 2019-nCoV infection to avoid the post-infective health complications like vasculitis, carditis, glaucoma in the eye is quite needful and mandatory. In order to achieve this goal follow-up checks, health monitoring, and rehabilitation, medicine management particularly with phytopharmaceutical and 14 days home quarantine are required by following the general protocol to give the better life of the Covid-19 recovered patients. This approach should be adopted to the patients being discharged from hospital with acute and subacute viral infection-related complications.

Vasculitis has been reported frequently to the recovered patients after returning from Hospitals, which needs to be carefully handled by the therapeutic approaches of medicine. Particularly traditional plants derived phytotherapy could be the promising option to alleviate and control the vasculitis [111–113].

Only 10.8% of the patients have no post-covid-19 complications, while a large proportion of subjects affected by several symptoms and diseases. The most common reported symptoms were fatigue (72.8%), more severe displays like stroke, renal failure, myocarditis, and pulmonary fibrosis. There was an association between the presence of other pre-existing comorbidities and severity of the disease. Also, the

severity of COVID-19 was related to the severity of post-COVID-19 manifestations. So, recovered COVID-19 must undergo long-term monitoring for evaluation and treatment is highly appreciated with herbal therapy [90] based on the symptoms and conditions that might be precipitated with the new coronavirus infection [114]. Potential anti-oxidant and anti-inflammatory possessing herbs could be the best choice for the treatment of such post-covid-19 recovered health difficulties.

20.4 Better Management of Covid-19 Patient via Advanced Nano Formulation-Based Drug Delivery of Active Phytopharmaceuticals

Viral infection has always proven to be the leading cause of wide spread infections and deaths worldwide and has resulted in significant economic losses. Treatment approaches mainly rely on vaccination and therapeutics. It is based on targeting critical processes in the virus life cycle. However, many viruses are often becoming drug-resistant, which requires additional resources for the development of new drugs and designing novel site-specific targeted drug delivery system.

Research in the field of phytopharmaceutical based formulation technology for the development of noval trends in this field is the need of the hour. Academicians are expected to play a vital role in developing new phyto medicines from varied diversity of flora and fauna across the globe. It necessitates us to catch up fast to the new technologies in modern pharmaceutical technology era and explore their tremendous scope in phytochemistry. It is high time to work together!

20.4.1 Implification of Nanosuspension via Nasal Inhaler

Nanosuspensions are biphasic colloidal dispersions in which the drug particle is dispersed uniformly throughout the dispersion medium commonly a solvent. They are stabilized using surfactants, polymers, other excipients and are prepared by suitable methods. The size of the finely size reduced drug particles is below 1μm. They find varied applications in designing novel formulations to be delivered by various routes of administration like oral, transdermal, injectable, ophthalmic, and pulmonary [115].

Nanosuspension based inhalers offer potential applications in minimizing many problems associated with microparticulate suspension type aerosols in pulmonary drug delivery [34]. Limited diffusion and dissolution in alveolar fluids along with rapid clearance due to short residence time are the problems associated with these suspensions. This is attributed to the agglomeration and aggregation of particles which results in the deposition of particles in the pharynx and upper respiratory tract along with the ciliary movement of particles [116].

In case of nanosuspension based inhalers, the nano-size range of particles results in quick onset of action due to fast diffusion and also dissolution in alveolar fluids owing to their large surface area which increases affinity with mucosal surface.

Further, it can prolong the residence time of the drug in target site resulting in sustained release and reduction in dosing frequency.

The nanosuspension inhalers, unlike microparticulate inhalational aerosols, possess unique physicochemical properties like uniform and narrow particle size distribution characteristics of nanoparticles which will prevent them from uneven distribution of a drug in pulmonary drug delivery [117]. Moreover, the physical instability of nanosuspensions owing to their liquid state can be minimized by converting them to solid-state oral and inhalable dosage forms. Spray drying and freeze-drying technique can be used for their solidification purpose to convert them to dry state. Spray drying technique improves the porosity of nanoparticles, whereas the freeze-drying technique can be utilized for solidification of thermolabile drug candidates. Further, dispersibility of dry powder formulation is essential for its functionality in oral and pulmonary clinical implications [118].

Dry Powder Inhalers (DPIs)

DPIs are specially designed devices which are used to deliver dry powders in aerosolized form. Dry powder formulations have more excellent physicochemical stability than liquid formulations. Their performance, effectiveness, and efficiency depend on formulation characteristics and designing of the device [119]. For aerosolization of a drug in dry powder state single particles are deagglomerated using external force which is possible via impaction between particle-particle or between particles and device or particles and shearing force exerted by airflow and thus achieve respirable fraction. Clickhaler, Multi-haler, and Diskus are commercially available DPIs which deaggumerates the dry powders via impact between particles and airflow shear whereas other devices like Turbuhaler and Spinhaler deagglomerate the dry powders via impact between particles and surface of the device [120, 121].

Pressurized Metered-Dose Inhalers (pMDIs)

pMDIs, the most popular category of the inhaler device used commonly in case of respiratory diseases like chronic obstructive pulmonary disease and asthma and thus may be a suitable choice of device for COVID-19 19 pandemics. These devices generally consist of a mouthpiece, actuator, and a metering cup in the aerosol valve assembly [122]. The metering cup can deliver 20–100μL of product each time the valve seat is pressed.

20.4.2 Drug Delivery via Nebulizer with Active Medicament

The inhaler is different from nebulizer in the ease of use. A nebulizer can directly deliver the medicament into the lungs and requires the patient's cooperation. Therefore, they are suitable drug delivery device for pediatric, geriatric ventilated and unconscious patients or those who are unable to use pressurized metered-dose inhalers (pMDIs) and DPIs [123]. Another drawback for the users is that they need to be assembled, loaded with medication and de-assembled before and after

Table 20.2 Novel technology marketed nebulizers

Nebulizer	Type	References
Aero Eclipse II, BAN	Breath nebulizer	Davies et al. [125], Sabato et al. [126]
Micro Air NE-U22	Vibrating nebulizer	Najlah et al. [127]
AKITA, APIXNEB	Vibrating nebulizer	Zhou et al. [128]
CompAIR, NEC-C801	Jet nebulizer	Luisetti et al. [129, 130]
PARI LC Plus	Breath enhanced jet nebulizer	www.omron-healthcare.com; Govoni et al. [131]
I-neb ADD system	Vibrating nebulizer with metered chamber	Hodson et al. [132], Geller and Kesser [133]

each use. They have to be cleaned before reuse [124]. All these procedures may be challenging to follow for an untrained person.

Nebulizers are basically of two types, namely jet and ultrasonic nebulizers. They differ in force required to dispense the aerosol product onto the site of application. Nebulizers generate 1–5μm size particles depending on the make and model.

In case of jet nebulizer type device, when the valve seat is pressed the fluid pressure inside decreases as the product concentrate passes through the narrow cross-sectional area of the capillary tube with high velocity under reduced pressure which is based on Venturi's principle. In designing of such nebulizers, multiple baffles are suitably placed in the aerosol valve assembly. These baffles help in reducing the velocity and breakdown of the larger droplet into finer droplets on the impact of product concentrate with them [125]. This reduces the possibility of impaction of the product concentrate on the oropharyngeal region of the patient.

In case of ultrasonic nebulizer type device, the high-frequency piezoelectric crystals vibrate at high frequency due to the ultrasonic waves which are responsible for the breakdown of larger droplets of product concentrate into finer droplets. Compared to the jet nebulizer, ultrasonic nebulizers are costly and have a demerit of not suitable devices for heat sensitive and thermolabile substances [126].

For proper, accurate and reproducible product delivery through these nebulizer devices, the following process variables must be optimized

1. Fill volume of the product concentrate to be loaded in the device.
2. The viscosity of the formulated product concentrates.
3. Airflow rate and pressure in case of jet nebulizers.
4. Components of the nebulizer valve assembly.

Recent advancement in nebulizer technology is summarized in Table 20.2.

20.4.3 Oral Lozenges of Phytometabolites for Prophylaxis and Treatment

As we are aware that till date, there is no drug or vaccine in the market to treat SARS-CoV-2, although various pre-clinical and clinical trials are going on worldwide. Currently, anti-retroviral drugs like redeliver, lopinavir, ritonavir, oseltamivir, and alternative approaches from traditional medicine have been reported [38–40, 102, 134, 135]. Treatment is based mainly on symptom-based therapies [134, 135]. The concept of drug repurposing came into the spotlight for several reasons [136]. The systematic approach for drug development is, however, much broader in a sense that natural products from medicinal plants and marine compounds, phytochemicals represent a broad chemical basis for drug development. Hence, chemical scaffolds from natural sources are indispensable for drug development.

Lozenges are solid unit dosage form intended to be sucked in the oral cavity to release the medicament for a prolonged time period in local site of action by producing local or systemic effect and thereby maybe a right choice of drug delivery designing for treatment in COVID-19 pandemic. They are generally flavored dosage form and may be medicated or unmedicated. However, if medicated and prepared with active phytometabolites may result in constant level of active drug in the oral cavity, oropharynx, and throat tissues. Lozenges are excellent alternative for drug delivery for those patients who face difficulty in swallowing the intact tablet or capsule-like in case of a pediatric or geriatric group of patients. Drugs incorporated in lozenges include analgesics, anaesthetics, antiseptics, antitussives, antimicrobials, astringents, decongestants, demulcents, and corticosteroids, Lozenges may be compounded with single or multiple ingredients depending on the patient's needs. Sore throats and other irritations in mouth and pharynx are common ailments that can cause pain and discomfort in patients [137, 138].

Advantages of Lozenge [139, 140]

1. They avoid first-pass metabolism.
2. They offer increased bioavailability.
3. They may be used for designing local as well as systemic drug delivery.
4. They are a suitable alternative of dosage form for patient groups with difficulty in swallowing intact dosage form.
5. They release medicament slowly over a prolonged period of time.
6. They provide distribution of drugs in the oral cavity and pharynx.
7. They are easy to manufacture and store.

20.4.4 3D Printing Tablets of Phytocompounds for Covid-19 Management

Three-dimensional printing is a fast-growing technology that is designed on concept of additive manufacturing in the field of both biomedical as well as pharmaceutical [141–145]). 3D printing has currently become attractive to scientists that currently

are limited to producing fixed-dose tablets with fewer possibilities of personalization [146–150]. Small batch size or even a unit dose manufacturing utilizing 3D printing is considered to be a cost-effective method [135, 142, 151].

Various 3D printers like polylactic acid, acrylonitrile butadiene styrene, and polycaprolactone have shown promising characteristic features for designing 3D printed dosage forms [150, 152, 153]. Therefore, it is the need of the hour to move towards studying polymers with potential for 3D printing of oral dosage forms.

3D printed tablets contain active drugs that are prepared by 3D printing technique which can deliver drugs safely and effectively in a customized manner to patients. Drugs contained in 3D printed tablets have a unitary porous structure because of which when orally administered, they tend to settle in the oral cavity. Thus, these tablets rule out the requirement of these tablets to be swallowed orally and minimize the dose requirement by producing a therapeutic effect in the site of administration over a prolonged period of time. It aids the manufacturers to easily customize the size, shape, appearance, and rate of release of wide array of medicines. Thus, these drugs can be personalized as per patient requirements [154].

3D printing technique has vast growth potential in the market as they offer manufacturers with ample scope in research and development activities and opportunity to personalize medicines. They also provide an exciting opportunity in improving patient care and may be sought for drug delivery in COVID-19 19 pandemic because of their excellent properties. Recently research has highlighted that $>$50% of consumers have expressed their interest in using customized medicines and experts forecast a scaffold increase in their market size by next 5–7 years. Moreover, after the Precision Medicine's initiative was published in the USA in 2015, various research organizations are working for the development of more and more tailored treatment options to make medicines safer and more useful than ever before.

20.5 Conclusion

In view of the current context of covid-19 pandemic around the globe and its corresponding panic created among the community people, we have discussed thoroughly different aspects of these highly contagious viral diseases in the above-mentioned different segments of the chapter. It has been concluded that covid-19 caused by the newly natural originated zoonotic strain have paralyzed the standard lifestyle of the community people of 215 countries and its associated territory. Our reviewed discussion could be suggested that early diagnosis of the SARS-CoV-2 may resolve the issue of fatality subjected to appropriate therapy with suitable active, safe, and effective potential anti-viral lead molecule. The treatment modality could be improved by applying phytopharmaceutical formulation loaded with potential Phyto-extract or phytometabolites subjected to pre-clinical and clinical validation with enhanced stability. Formulation can be developed with achievable success and novel strategy of inhaler, nebulizer, oral lozenges, and 3D printing tablet formulation. This approach could reduce the stability and other pharmacokinetic

issues associated with the Phytocompounds and mediate the target-oriented drug delivery with safe and reduced dose of the active phyto-medicament.

Moreover, the nature and phytopharmacological properties of phytocompounds should be considered during the Phyto formulation development against the SARS-COV-2 infection based on the clinical pathophysiological pre-existing complications and comorbidities of the affected syndromes for successful treatment modality developments for effective therapeutic management of covid-19, as explained in Table 20.1.

References

1. World Health Organization (2020) Coronavirus disease (COVID-19) pandemic. https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J et al (2020) A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 382:727–733
3. Wu Z, McGoogan JM (2020) Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China. JAMA 323(13):1239
4. Johns Hopkins Coronavirus Resource Center (2020) COVID-19 map. Johns Hopkins Coronavirus Resource Center. Available online at: https://coronavirus.jhu.edu/map.html. Accessed May 11, 2020
5. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF (2020) The proximal origin of SARS-CoV-2. Nat Med 26:450–452
6. Zhao X et al (2020a) Broad and differential animal angiotensin-converting enzyme 2 receptor usage by SARS-CoV-2. J Virol 94:e00940–e00920
7. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W (2020b) Single-cell RNA expression profiling of ACE 2, the receptor of SARS-CoV-2. Am J Respir Crit Care Med. https://doi.org/10.1164/rccm.202001-0179LE
8. Chen N, Zhou M, Dong X et al (2020a) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395(10223):507–513
9. Chen Y, Liu Q, Guo D (2020c) Emerging coronaviruses: genome structure, replication, and pathogenesis. J Med Virol 92:418–423
10. Lu R et al (2020) Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395:565–574
11. Chan JF et al (2020) Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect 9:221–236
12. Zhou S, Wang Y, Zhu T, Xia L (2020a) CT features of Coronavirus disease 2019 (Covid-19) pneumonia in 62 patients in Wuhan, China. Am J Roentgenol 214(6):1287–1294
13. Zhou Y et al (2020b) Aberrant pathogenic GM-CSF+T cells and inflammatory CD14+CD16+monocytes in severe pulmonary syndrome patients of a new coronavirus. Preprint at https://www.biorxiv.org/content/10.1101/2020.02.12.945576v1
14. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W et al (2020c) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579:270–273
15. Lam TT et al (2020) Identifying SARS-CoV-2 related coronaviruses in Malayan pangolins. Nature 583:282–285
16. Liu P, Chen W, Chen JP (2019) Viral metagenomics revealed Sendai virus and coronavirus infection of Malayan pangolins (Manis javanica). Viruses 11:979

17. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H (2020a) Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology 158(6):1831–1833. https://doi.org/10.1053/j.gastro.2020.02.055
18. Xiao K et al (2020b) Isolation of SARS-CoV-2-related coronavirus from Malayan pangolins. Nature 583:286–289
19. Lu G, Wang Q, Gao GF (2015) Bat-to-human: spike features deter- mining 'host jump' of coronaviruses SARS-CoV, MERS-CoV, and beyond. Trends Microbiol 23:468–478
20. Tortorici MA, Veesler D (2019) Structural insights into coronavirus entry. Adv Virus Res 105:93–116. https://doi.org/10.1016/bs.aivir.2019.08.002
21. Hoffmann M et al (2020a) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181:271–280
22. Hoffmann M, Kleine-Weber H, Pohlmann S (2020b) A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. Mol Cell 78(4):779–784
23. Chandrashekar A et al (2020) SARS-CoV-2 infection protects against rechallenge in rhesus macaques. Science 369:812–817
24. Shi J et al (2020) Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2. Science 368:1016–1020
25. Zou X, Chen K, Zou J, Han P, Hao J, Han Z (2020) Single-cell RNA-seq data analysis on the receptor ACE 2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med 14:185–192
26. Rodrigues Prestes TR, Rocha NP, Miranda AS, Teixeira AL (2017) The anti-inflammatory potential of ACE 2/angiotensin–(1–7)/Mas receptor axis: evidence from basic and clinical research. Curr Drug Targets 18(11):1301–1313
27. Gheblawi M, Wang K, Viveiros A et al (2020) Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE 2. Circ Res 126(10):1456–1474
28. Pal R, Bhansali A (2020) COVID-19, diabetes mellitus and ACE 2: the conundrum. Diabetes Res Clin Pract 162:108132
29. Dashraath P, Wong JLJ, Lim MXK, Lim LM, Li S, Biswas A, Choolani M, Mattar C, Su LL (2020) Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol 222(6):521–531. https://doi.org/10.1016/j.ajog.2020.03.021
30. Bunyavanich S, Do A, Vicencio A (2020) Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. JAMA 323(23):2427–2429
31. Dong Y, Mo X, Hu Y et al (2020) Epidemiology of COVID-19 among children in China. Pediatrics 145(6):e20200702
32. Bialek S, Gierke R et al (2020) Coronavirus Disease 2019 in Children – United States, February 12–April 2, 2020. MMWR Morb Mortal Wkly Rep 69(14):422–426
33. Wu C, Chen X, Cai Y et al (2020) Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 180(7):1–11
34. Dolovich MB, Dhand R (2011) Aerosol drug delivery: developments in device design and clinical use. Lancet 377(9770):1032–1045
35. Liu Y, et al (2020a) Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. Preprint at https://www.medrxiv.org/content/10.1101/2020.02.17.20024166v3
36. Ng D, Hosani FA, Keating MK et al (2016) Clinicopathologic, immunohistochemical, and ultrastructural findings of a fatal case of Middle East Respiratory Syndrome Coronavirus Infection in the United Arab Emirates, April 2014. Am J Pathol 186(3):652–658
37. Xu Z, Shi L, Wang Y et al (2020) Pathological findings of Covid-19 associated with acute respiratory distress syndrome. Lancet Respir Med 8(4):420–422
38. Wang F, Hou H, Luo Y, Tang G, Wu S, Huang M, Liu W, Zhu Y, Lin Q, Mao L, Fang M, Zhang H, Sun Z (2020a) The laboratory tests and host immunity of COVID-19 patients with different severity of illness. JCI Insight 5(10):e137799

39. Wang Z, Chen X, Lu Y, Chen F, Zhang W (2020b) Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. Biosci Trends 14(1):64–68
40. Wang D, Hu B, Hu C et al (2020c) Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 323(11):1061–1069
41. Inciardi RM, Lupi L, Zaccone G et al (2020) Cardiac involvement in a patient with coronavirus disease 2019 (Covid-19). JAMA Cardiol 5(7):1–6
42. Juusela A, Nazir M, Gimovsky M (2020) Two cases of Coronavirus 2019–related cardiomyopathy in pregnancy. Am J Obstet Gynecol 2(2):100113
43. Zeng J-H, Liu Y-X, Yuan J et al (2020) First case of Covid-19 complicated with fulminant myocarditis: a case report and insights. Infection. https://doi.org/10.1007/s15010-020-01424-5
44. Cheng Y, Luo R, Wang K et al (2020) Kidney disease is associated with in-hospital death of patients with Covid-19. Kidney Int 97(5):829–838
45. Pan F, Ye T, Sun P et al (2020a) Time course of lung changes at chest CT during recovery from Coronavirus Disease 2019 (Covid-19). Radiology 295(3):715–721
46. Pan X-W, Xu D, Zhang H, Zhou W, Wang L-H, Cui X-G (2020b) Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis. Intensive Care Med 46:1114–1116
47. Li D et al (2020a) Immune dysfunction leads to mortality and organ injury in patients with COVID-19 in China: insights from ERS-COVID-19 study. Signal Transduct Target Ther 5:62
48. Li YC, Bai WZ, Hashikawa T (2020b) The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 92(6):552–555
49. Li Y, Shi J, Xia J, Duan J, Chen L, Yu X, Lan W, Ma Q, Wu X, Yuan Y, Gong L, Yang X, Gao H, Wu C (2020c) Asymptomatic and symptomatic patients with non-severe coronavirus disease (COVID-19) have similar clinical features and virological courses: a retrospective single center study. Front Microbiol. https://doi.org/10.3389/fmicb.2020.01570
50. Li Z, Yi Y, Luo X et al (2020d) Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. J Med Virol. https://doi.org/10.1002/jmv.25727
51. Li Z, Wu M, Guo J et al (2020e) Caution on kidney dysfunctions of 2019-nCoV patients. Preprint from MedRxiv. https://doi.org/10.1101/2020.02.08.20021212
52. Hong X-W, Chi Z-P, Liu G-Y et al (2020) Analysis of early renal injury in COVID-19 and diagnostic value of multi-index combined detection. Preprint from MedRxiv. https://doi.org/10.1101/2020.03.07.20032599
53. Villapol S (2020) Gastrointestinal symptoms associated with COVID-19: impact on the gut microbiome. Transl Res 226:57–69. https://doi.org/10.1016/j.trsl.2020.08.004.
54. Baig AM, Khaleeq A, Ali U, Syeda H (2020) Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci 11(7):995–998
55. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B (2020) COVID-19–associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. Radiology 296(2):E119–E120
56. Oxley TJ, Mocco J, Majidi S et al (2020) Large-vessel stroke as a presenting feature of Covid-19 in the young. N Engl J Med 382(20):e60
57. Corman VM, Landt O, Kaiser M et al (2020) Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill 25(3):2000045. https://doi.org/10.2807/1560-7917.ES.2020.25.3.2000045
58. Chu DKW, Pan Y, Cheng SMS et al (2020) Molecular diagnosis of a novel coronavirus (2019-nCoV) causing an outbreak of pneumonia. Clin Chem 66(4):549–555. https://doi.org/10.1093/clinchem/hvaa029.

59. Baek YH, Um J, Antigua KJC et al (2020) development of a reverse transcription-loop-mediated isothermal amplification as a rapid early-detection method for novel SARS-CoV-2. Emerg Microbes Infect 2020:1–31. https://doi.org/10.1080/22221751.2020.1756698.
60. Castro R, Luz PM, Wakimoto MD, Veloso VG, Grinsztejn B, Perazzo H (2020) COVID-19: a meta-analysis of diagnostic test accuracy of commercial assays registered in Brazil. Braz J Infect Dis S14138670(20):530029. https://doi.org/10.1016/j.bjid.2020.04.003
61. Vashist SK (2020) In vitro diagnostic assays for COVID-19: recent advances and emerging trends. Diagnostics 10(4):E202. https://doi.org/10.3390/diagnostics10040202
62. Long QX, Tang XJ, Shi QL, Li Q, Deng HJ, Yuan J, Hu JL, Xu W, Zhang Y, Lv FJ, Su K, Zhang F, Gong J, Wu B, Liu XM, Li JJ, Qiu JF, Chen J, Huang AL (2020a) Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med 26 (8):1200–1204
63. Long QX et al (2020b) Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med 26:845–848
64. Oran DP, Topol EJ (2020) Prevalence of asymptomatic SARS-CoV-2 infection: a narrative review. Ann Intern Med 173(5):362–367. https://doi.org/10.7326/M20-3012
65. Yang L, Liu S, Liu J, Zhang Z, Wan X, Huang B, Chen Y, Zhang Y (2020) COVID-19: immunopathogenesis and Immunotherapeutics. Signal Transduct Target Ther 5(1):128
66. Lippi G, Plebani M (2020) Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med 58:1131–1134
67. Huang C et al (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395:497–506
68. Qin C et al (2020) Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis. https://doi.org/10.1093/cid/ciaa248
69. Tan M et al (2020a) Immunopathological characteristics of coronavirus disease 2019 cases in Guangzhou, China. Immunology 160:261–268
70. Tan L et al (2020b) Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Target Ther 5:33
71. Perlman S, Dandekar AA (2005) Immunopathogenesis of coronavirus infections: implications for SARS. Nat Rev Immunol 5:917–927
72. Cao X (2020) COVID-19: immunopathology and its implications for therapy. Nat Rev Immunol 20:269–270
73. Zhang B, et al (2020) Immune phenotyping based on neutrophil-to-lymphocyte ratio and IgG predicts disease severity and outcome for patients with COVID-19. Preprint at https://www.medrxiv.org/content/10.1101/2020.03.12.20035048v1
74. Deshmukh HS et al (2014) The microbiota regulates neutrophil homeostasis and host resistance to Escherichia coli K1 sepsis in neonatal mice. Nat Med 20:524–530
75. Smith CK, Trinchieri G (2018) The interplay between neutrophils and microbiota in cancer. J Leukoc Biol 104:701–715
76. Li CK et al (2008) T cell responses to whole SARS coronavirus in humans. J Immunol 181:5490–5500
77. Ni L, Ye F, Cheng M-L (2020) Detection of SARS-CoV-2-specific humoral and cellular immunity in COVID-19 convalescent individuals. Immunity 52:971–977
78. Diao B et al (2020) Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol 11:827
79. Liu J et al (2020b) Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine 55:102763
80. Wan S, et al (2020) Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). Preprint at https://www.medrxiv.org/content/10.1101/2020.02.10.20021832v1
81. Wen W et al (2020) Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. Cell Discov 6:31

82. Hotez PJ, Bottazzi ME, Corry DB (2020) The potential role of Th17 immune responses in coronavirus immunopathology and vaccine-induced immune enhancement. Microbes Infect 22(4-5):165–167
83. Wu D, Yang XO (2020) TH17 responses in cytokine storm of COVID-19: an emerging target of JAK2 inhibitor Fedratinib. J Microbiol Immunol Infect 53:368–370
84. Lin YC, Chang CW, Antitussive WCR (2016 Nov 10) Anti-pyretic and toxicological evaluation of Ma-Xing-Gan-Shi-Tang in rodents. BMC Complement Altern Med 16(1):456
85. McCutcheon JP, McDonald BR, Moran NA (2009) Convergent evolution of metabolic roles in bacterial co-symbionts of insects. Proc Natl Acad Sci U S A 106(36):15394–9. https://doi.org/10.1073/pnas.0906424106
86. Boukhatem MN, Setzer WN (2020) Aromatic herbs, medicinal plant-derived essential oils, and phytochemical extracts as potential therapies for coronaviruses: future perspectives. Plants 9(6):800. https://doi.org/10.3390/plants9060800
87. Leal LN, Jordán MJ, Bello JM, Otal J, den Hartog LA, Hendriks WH, Martín-Tereso J. Dietary supplementation of 11 different plant extracts on the antioxidant capacity of blood and selected tissues in lightweight lambs. J Sci Food Agric 2019;99(9):4296-4303. doi: https://doi.org/10.1002/jsfa.9662.
88. Rubió L, Motilva MJ, Romero MP (2013) Recent advances in biologically active compounds in herbs and spices: a review of the most effective antioxidant and anti-inflammatory active principles. Crit Rev Food Sci Nutr 53(9):943–953
89. Fatima S, Haider N, Alam MA, Gani MA, Ahmad R, Taha M (2020) Herbal approach for the management of COVID-19: an overview. Drug Metab Pers Ther. https://doi.org/10.1515/dmdi-2020-0150
90. Tang B, Lo HH, Lei C, U KI, Hsiao WW, Guo X, Bai J, Wong VK, Law BY (2020a) Adjuvant herbal therapy for targeting susceptibility genes to Kawasaki disease: an overview of epidemiology, pathogenesis, diagnosis and pharmacological treatment of Kawasaki disease. Phytomedicine 70:153208
91. Jalali A, Dabaghian F, Akbrialiabad H, Foroughinia F (2020) A pharmacology-based comprehensive review on medicinal plants and phytoactive constituents possibly effective in the management of COVID-19. Phytother Res. https://doi.org/10.1002/ptr.6936
92. Lindler BN, Long KE, Taylor NA, Lei W (2020) Use of herbal medications for treatment of osteoarthritis and rheumatoid arthritis. Medicine 7(11):E67
93. Palit P, Mandal SC, Bhunia B (2016) Total steroid and terpenoid enriched fraction from Euphorbia neriifolia Linn offers protection against nociceptive-pain, inflammation, and in vitro arthritis model: An insight of mechanistic study. Int Immunopharmacol 41:106–115
94. Palit P, Chattopadhyay D, Thomas S, Kundu A, Kim HS, Rezaei N (2020) Phytopharmaceuticals mediated furin and TMPRSS2 receptor blocking: can it be a potential therapeutic option for Covid-19? Phytomedicine 2020:153396. https://doi.org/10.1016/j.phytomed.2020.153396
95. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW (2003) Treatment of SARS with human interferons. Lancet 362(9380):293-4. https://doi.org/10.1016/s0140-6736(03)13973-6. Erratum in: Lancet. 2003 Aug 30;362(9385):748
96. Renard-Nozaki J, Kim T, Imakura Y, Kihara M, Kobayashi S (1989) Effect of alkaloids isolated from Amaryllidaceae on herpes simplex virus. Res Virol 140(2):115–28. https://doi.org/10.1016/s0923-2516(89)80089-5
97. Ieven M, Vlietinck AJ, Vanden Berghe DA, Totte J, Dommisse R, Esmans E, Alderweireldt F (1982) Plant antiviral agents. III. Isolation of alkaloids from Clivia miniata Regel (Amaryllidaceae). J Nat Prod 45(5):564–573. https://doi.org/10.1021/np50023a009
98. Song JW, Zhang C, Fan X, Meng FP, Xu Z, Xia P, Cao WJ, Yang T, Dai XP, Wang SY, Xu RN, Jiang TJ, Li WG, Zhang DW, Zhao P, Shi M, Agrati C, Ippolito G, Maeurer M, Zumla A, Wang FS, Zhang JY (2020) Immunological and inflammatory profiles in mild and severe cases of COVID-19. Nat Commun 11(1):3410

99. Gautam S, Gautam A, Chhetri S, Bhattarai U (2020) Immunity against COVID-19: potential role of Ayush Kwath. J Ayur Integr Med. https://doi.org/10.1016/j.jaim.2020.08.003
100. Luo W, Li YX, Jiang LJ, Chen Q, Wang T, Ye DW (2020) Targeting JAK-STAT signaling to control cytokine release syndrome in COVID-19. Trends Pharmacol Sci 41(8):531–543. https://doi.org/10.1016/j.tips.2020.06.007
101. Aras A, Gohar KS, Jabeen S, Farooqi A, Xu B (2018) Regulation of cancer cell signaling pathways by mushrooms and their bioactive molecules: Overview of the journey from benchtop to clinical trials. Food Chem Toxicol 119:206–214. https://doi.org/10.1016/j.fct.2018.04.038
102. De Biasi S, Meschiari M, Gibellini L et al (2020) Marked T cell activation, senescence, exhaustion and skewing towards TH17 in patients with COVID-19 pneumonia. Nat Commun 11(1):3434. https://doi.org/10.1038/s41467-020-17292-4.
103. Prompetchara E, Ketloy C, Palaga T (2020) Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol 38. https://doi.org/10.12932/AP-200220-0772.
104. Bagad AS, Joseph JA, Bhaskaran N, Agarwal A (2013) Comparative evaluation of anti-inflammatory activity of curcuminoids, turmerones, and aqueous extract of curcuma longa. Adv Pharmacol Sci 2013:80575
105. Imaeda S, Kabata H, Shiraishi Y, Kamata H, Tsuruta H, Yuasa S, Ishii M, Fukuda K, Fukunaga K (2020) Left ventricular thrombus with COVID-19 complication in a patient with dilated cardiomyopathy. CJC Open 3(1):124–126. https://doi.org/10.1016/j.cjco.2020.09.014
106. Van Haren FMP, Page C, Laffey JG, Artigas A, Camprubi-Rimblas M, Nunes Q, Smith R, Shute J, Carroll M, Tree J, Carroll M, Singh D, Wilkinson T, Dixon B (2020) Nebulized heparin as a treatment for COVID-19: scientific rationale and a call for randomized evidence. Crit Care 24(1):454
107. Akram M, Rashid A (2017) Anti-coagulant activity of plants: mini review. J Thromb Thrombolysis 44(3):406–411. https://doi.org/10.1007/s11239-017-1546-5
108. Chua TK, Koh HL (2006) Medicinal plants as potential sources of lead compounds with antiplatelet and anti-coagulant activities. Mini Rev Med Chem 6(6):611–624
109. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H (2020) Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 191:145–147. https://doi.org/10.1016/j.thromres.2020.04.013.
110. Tsui PF, Lin CS, Ho LJ, Lai JH (2018) Spices and atherosclerosis. Nutrients 10(11):1724. https://doi.org/10.3390/nu10111724
111. Ingraffea A, Donohue K, Wilkel C, Falanga V (2007 May) Cutaneous vasculitis in two patients taking an herbal supplement containing black cohosh. J Am Acad Dermatol 56 (5 Suppl):S124–S126
112. Nasiri S, Dadkhahfar S, Abasifar H, Mortazavi N, Gheisari M (2020) Urticarial vasculitis in a COVID-19 recovered patient. Int J Dermatol. https://doi.org/10.1111/ijd.15112
113. Wu D, Lin W, Wong KW (2018) Herbal medicine (Gancao Xiexin decoction) for Behcet disease: a systematic review protocol. Medicine 97(37):e12324. https://doi.org/10.1097/MD.0000000000012324.
114. Kamal M, Abo Omirah M, Hussein A, Saeed H (2020) Assessment and characterization of post-COVID-19 manifestations. Int J Clin Pract 2020:e13746. https://doi.org/10.1111/ijcp.13746.
115. Prabhakar C, Krishna KB (2011) A review on nanosuspensions in drug delivery. Int J Pharm BioSci 2(1):549–558
116. Jacobs C, Müller RH (2002) Production and characterization of a budesonide nanosuspension for pulmonary administration. Pharm Res 19(2):189–194

117. Zhang Y, Zhang J (2016) Preparation of budesonide nanosuspensions for pulmonary delivery: characterization, in vitro release and in-vivo lung distribution studies. Artif Cells Nanomed Biotechnol 44(1):285–289
118. Malamatari M, Somavarapu S, Taylor KM, Buckton G (2016) Solidification of nanosuspensions for the production of solid oral dosage forms and inhalable dry powders. Expert Opin Drug Deliv 13(3):435–450
119. Sanchis J, Corrigan C, Levy ML, Viejo JL (2013) Inhaler devices – from theory to practice. Respir Med 107(4):495–502
120. Begat P, Morton DA, Shur J, Kippax P, Staniforth JN, Price R (2009) The role of force control agents in high-dose dry powder inhaler formulations. J Pharm Sci 98(8):2770–2783
121. Islam N, Cleary MJ (2012) Developing an efficient and reliable dry powder inhaler for pulmonarydrug delivery-a review for multidisciplinary researchers. Med Eng Phys 34 (4):409–427
122. Vaswani SK, Creticos PS (1998) Metered dose inhaler: past, present, and future. Ann Allergy Asthma Immunol 80(1):11–19
123. Hess DR (2000) Nebulizers: principles and performance. Respir Care 45(6):609–622
124. Hess DR (2008) Aerosol delivery devices in the treatment of asthma. Respir Care 53 (6):699–723
125. Davies LA, Nunez-Alonso GA, McLachlan G, Hyde SC, Gill DR (2014) Aerosol delivery of DNA/liposomes to the lung for cystic fibrosis gene therapy. Hum Gene Ther Clin Dev 25 (2):97–107
126. Sabato K, Ward P, Hawk W, Gildengorin V, Asselin JM (2011) Randomized controlled trial of a breath-actuated nebulizer in pediatric asthma patients in the emergency department. Respir Care 56(6):761–770
127. Najlah M, Parveen I, Alhnan MA et al (2014) The effects of suspension particle size on the performance of air-jet, ultrasonic and vibrating-mesh nebulizers. Int J Pharm 461(12):234–241
128. Zhou QT, Tang P, Leung SS, Chan JG, Chan HK (2014) Emerging inhalation aerosol devices and strategies: where are we headed? Adv Drug Deliv Rev 75C:3–17
129. Luisetti M, Kroneberg P, Suzuki T et al (2011) Physical properties, lung deposition modeling, and bioactivity of recombinant GM-CSF aerosolized with a highly efficient nebulizer. Pulm Pharmacol Ther 24(1):123–127
130. CompAIR NE-C801 (2014) OMRON Healthcare Europe BV; August 19. Available from: http://www.omron-healthcare.com/eu/en/our-products/respiratory-therapy/compair-ne-c801
131. Govoni M, Poli G, Acerbi D et al (2013) Pharmacokinetic and tolerability profiles of tobramycin nebulizer solution 300 mg/4 ml administered by PARI eFlow (®) rapid and PARI LC Plus (®) nebulizers in cystic fibrosis patients. Pulm Pharmacol Ther 26(2):249–255
132. Hodson ME, Gallagher CG, Govan JR (2002) A randomized clinical trial of nebulized tobramycin or colistin in cystic fibrosis. Eur Respir J 20(3):658–664
133. Geller DE, Kesser KC (2010) The I-neb adaptive aerosol delivery system enhances delivery of alpha1-antitrypsin with controlled inhalation. J Aerosol Med Pulm Drug Deliv 23(Suppl 1): S55–S59
134. Arabi YM, Fowler R, Hayden FG (2020) Critical care management of adults with community-acquired severe respiratory viral infection. Intensive Care Med 46(2):315–328
135. Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ et al (2020) Case of the index patient who caused tertiary transmission of COVID-19 infection in Korea: the application of lopinavir/ritonavir for the treatment of COVID-19 infected pneumonia monitored by quantitative RT-PCR. J Korean Med Sci 35(6):e79
136. Ashburn TT, Thor KB (2004) Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug Discov 3(8):673–683
137. Deepak R, Sanjay S (2012) Formulation and evaluation of antianthalmentic chewable tablet. Int Pharma Sci 2(1):13–26

138. Mahalaxmi R, Rajesh K, Deepak K (2011) Investigating the suitability of Isomalt and liquid glucose as sugar substitute in the formulation of salbutamol sulphate hard candy lozenges. J Chem Pharm Res 3(4):69–75
139. Allen LV (2001) Troches and lozenges, secundum artem. Curr Pract Compd Inf Pharm 4 (2):23–25
140. Peters D (2005) Medicated lozenges. In: Lieberman HA, Lachman L, Schwartz JB (eds) Pharmaceutical dosage forms: tablets, 2nd edn. Marcel Dekker, Inc, New York, pp 419–577
141. Holländer J, Hakala R, Suominen J, Moritz N, Yliruusi J, Sandler N (2018) 3D printed UV light cured polydimethylsiloxane devices for drug delivery. Int J Pharm 544(2):433–442
142. Jamróz W, Kurek M, Łyszczarz E, Brniak W, Jachowicz R (2017a) Printing techniques: recent developments in pharmaceutical technology. Acta Pol Pharm 74(3):753–763
143. Ligon SC, Liska R, Stampfl J, Gurr M, Mülhaupt R (2017) Polymers for 3D printing and customized additive manufacturing. Chem Rev 117(15):10212–10290
144. Solanki NG, Tahsin M, Shah AV, Serajuddin ATM (2018) Formulation of 3D printed tablet for rapid drug release by fused deposition modeling: screening polymers for drug release, drug-polymer miscibility and printability. J Pharm Sci 107(1):390–401
145. Yu DG, Zhu LM, Branford-White CJ, Yang XL (2008) Three-dimensional printing in pharmaceutics: promises and problems. J Pharm Sci 97(9):3666–3690
146. Khaled SA, Burley JC, Alexander MR, Roberts CJ (2014) Desktop 3D printing of controlled release pharmaceutical bilayer tablets. Int J Pharm 461(1–2):105–111
147. Sandler N, Preis M (2016) Printed drug-delivery systems for improved patient treatment. Trends Pharmacol Sci 37(12):1070–1080
148. Water JJ, Bohr A, Boetker J, Aho J, Sandler N, Nielsen HM (2015) Three-dimensional printing of drug-eluting implants: preparation of an antimicrobial polylactide feedstock material. J Pharm Sci 104(3):1099–1107
149. Yu DG, Branford-White C, Ma ZH, Zhu LM, Li XY, Yang XL (2009) Novel drug delivery devices for providing linear release profiles fabricated by 3DP. Int J Pharm 370(1-2):160–166
150. Zema L, Melocchi A, Maroni A, Gazzaniga A (2017) Threedimensional printing of medicinal products and the challenge of personalized therapy. J Pharm Sci 106(7):1697–1705
151. Palo M, Holländer J, Suominen J, Yliruusi J, Sandler N (2017) Expert review of medical devices 3D printed drug delivery devices: perspectives and technical challenges 3D printed drug delivery devices: perspectives and technical challenges. Expert Rev Med Devices 14 (9):685–696
152. Holländer J, Genina N, Jukarainen H, Khajeheian M, Rosling A, Mäkilä E (2016) Three-dimensional printed PCL-based implantable prototypes of medical devices for controlled drug delivery. J Pharm Sci 105(9):2665–2676
153. Sandler N, Salmela I, Fallarero A, Rosling A, Khajeheian M, Kolakovic R (2014) Towards fabrication of 3D printed medical devices to prevent biofilm formation. Int J Pharm 459 (1–2):62–64
154. Preis M, Öblom H (2017) 3D-printed drugs for children—are we ready yet? AAPS PharmSciTech 18(2):303–308

Targeting SARS-CoV-2 Novel Corona (COVID-19) Virus Infection Using Medicinal Plants

21

Charles Oluwaseun Adetunji, Muhammad Akram, Olugbemi Tope Olaniyan, Olulope Olufemi Ajayi, Abel Inobeme, Seyi Olaniyan, Leena Hameed, and Juliana Bunmi Adetunji

Abstract

The occurrence of coronavirus disease (COVID-19) pandemic is a global health crisis that has affected several parts of the globe. Therefore, there is an urgent need to search for a natural alternative to several synthetic drugs which have several side effects such as high level of resistance, higher toxicity, and high cost of producing them. Most of the people dwelling in the developing country are also affected with these challenges, most especially people in the rural area who could not afford the high cost of drugs for the management of this COVID-19. The application of medicinal plants has been recognized as a natural bioresource

C. O. Adetunji (✉)
Applied Microbiology, Biotechnology and Nanotechnology Laboratory, Department of Microbiology, Edo State University Uzairue, Iyamho, Edo State, Nigeria;
adetunji.charles@edouniversity.edu.ng

M. Akram
Department of Eastern Medicine, Government College University, Faisalabad, Pakistan

O. T. Olaniyan
Laboratory for Reproductive Biology and Developmental Programming, Department of Physiology, Edo State University Uzairue, Iyamho, Edo State, Nigeria

O. O. Ajayi
Department of Biochemistry, Edo State University Uzairue, Iyamho, Edo State, Nigeria

A. Inobeme
Department of Chemistry, Edo State University Uzairue, Iyamho, Edo State, Nigeria

S. Olaniyan · J. B. Adetunji
Nutrition and toxicology Research Laboratory, Department of Biochemistry Sciences, Osun State University, Osogbo, Nigeria

L. Hameed
Faculty of Eastern Medicine, Hamdard University, Karachi, Pakistan

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_21

that could be applied for the management of COVID-19. Hence, this chapter intends to provide a detailed information on ancient and current literature on the antiviral activity of herbs on coronavirus. This will encourage the practice of using herbs medicines for the prevention and treatment of COVID-19 because at present there is no effective treatment for this infectious and deadly disease. This literature review might provide ideas for further researches on drug discovery and complementary treatment approach.

Relevant information on different types of techniques that could be utilized for targeting the SARS-CoV-2 novel corona (COVID-19) virus as well as specific examples medicinal plants that could be applied for the treatment of (COVID-19) virus were provided. Detailed information on some specific phytochemicals that serve as anti-COVID-19 was also highlighted. Also, adequate information on the application of bioinformatics and computation techniques which could enhance the biological activities of medicinal plants and their modes of action against (COVID-19) virus were provided.

Keywords

Medicinal plants · Phytochemicals · Coronavirus · Bioinformatics · Computation techniques · Antiviral activity

21.1 Introduction

The incidence of coronavirus outbreak in December 2019, called SARS-CoV-2 started in Wuhan, China. In the past this was a lethal endemic virus that resulted to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and middle east respiratory syndrome (MERS) disease [1]. This virus was isolated in January, 2020, from patients with pneumonia [2] and was named Coronavirus disease 2019 (COVID-19) in February, 2020 [3]. Globally, almost ∼31,499,146 cases of COVID-19 have been confirmed as of September 2020, and more than 969,585 deaths, has been documented by the WHO [4].

SARS-CoV-2 is a member of the Nidovirales order of the coronaviridae family. It is a single-stranded RNA that is enveloped [5]. Reports showed that angiotensin-converting enzyme 2 (ACE 2) is an important receptor for SARS-CoV-2 which allows its binding using the spike proteins to host cells [6]. This results in conformational changes of the C-terminal S2 subunit of the spike proteins which ultimately leads to viral entry into the host cell [7, 8] .

Currently, no effective treatment has been approved for this virus [9]. The researchers and clinicians are opting complementary treatment approaches to combat this disease [10]. Since ancient time herbs have been used as a source of healing for different ailments including infectious diseases [11]. Efforts are currently been made to produce vaccines. However, certain drugs are being developed, while some are currently in different phases of clinical trial. The clinical efficacy of these drugs is uncertain [12].

Herbal medicine is currently being explored due to its success in the management of other viral infections. Phytocompounds that target and block ACE 2 receptor not necessarily inhibiting the enzyme activity could help in the management of SARS-CoV-2. This will go a long way in inhibiting viral entry into host cells [6]. Examples of such promising medicinal plants are *Onopordum acanthium, Crataegus laevigata, Quercus infectoria, Berberis integerrima* Bunge, which have been reported to inhibit ACE. This is consequent on the high concentration of phenolic compounds which exhibit antioxidant properties. Viral infection co-occurs with oxidative stress which enhances its replication. Furthermore, plant species of Magnoliaceae, Oleaceae, Labiatae, Lauraceae, Polygonaceae, Nelumbonaceae were also found to hinder the binding of SARS-CoV S protein to ACE. This was ascribed to high concentration of emodin [13].

Emerging information also shows that some phytochemicals target the type 2 transmembrane serine-proteinase serine type 2 RSS2 (TMPRSS2). There are evidences that SAR-CoV-2 also uses TMPRSS2 to gain entry into the host cell [8, 14]. Therefore, it is believed that natural products able to repress the expression of TMPRSS2 indicate effective treatment of SARS-CoV-2 [15]. For instance, Kaempferol significantly inactivated TMPRSS2 expression [16].

Furthermore, a blend of luteolin, quercetin, and kaempferol have been established to portends that capacity to also inhibit TMPRSS 2 in another study [17]. Papain-like proteinase (PLPro) is a protein coded by SARS-CoV-2 genome. It plays an important role in viral replication. Also, it was reported to act against host's innate immunity [6]. It is believed that natural products will be better alternatives to synthetic drugs designed to inhibit PLPro. Examples of these natural compounds include Terrestrimine, N-trans-Caffeoyltyramine, N-trans-Feruloyltyramine, N-trans-Coumaroyltyramine, and Terrestriamide, Cinnamic amides (N-trans-Feruloyloctopamine,) extracted from *Tribulus terrestris* L fruits. Also, *Cullen corylifolium* (L) Medik which is rich in flavonoids has been recounted to impede SARS-CoV-2 while flavonoids obtained from *Paulownia tomentosa* (Thunb) Steud also showed inhibitory effects on SARS-CoV-2.

Some medicinal plants have been found to target chymotrypsin-like protease (3CL PRO). Chymotrypsin-like protease is significant in the replication of SARS-CoV-2, which makes it a probable target for anti-COVID-19 therapeutics. Examples of such natural agents include alkylated chalcones and coumarins obtained from *Angelica keiskei* (Miq) Koidz. Phlorotannins extracted from Ecklonia cava also showed considerable inhibitory effects on SARS-CoV-2 3CL PRO. Additionally flavonoids from different sources are promising in this regard.

In this review, we aim to discuss the pathophysiology and antiviral activity of herbs on SARS-CoV-2. Also, information on bioinformatics and computation techniques could be applied to enhance medicinal activities of medicinal plants and modes of action of medicinal plants against (COVID-19) virus.

21.2 Pathophysiology

It has been discovered that proper insight and adequate understanding about the viral lifecycle will help in recognizing the possible drug targets. SARS-CoV-2 is RNA-enveloped and single stranded [18]. Binding of the viral spike glycoprotein to the host receptor is a crucial step for the entry of coronavirus. Hence, for effective antiviral treatment the entry into the host must be inhibited [19, 20].

Studies have shown that the cells of arteries, heart, intestine, kidney, and lungs in the host have ACE-2 which is available on the surface and is used by coronaviruses for entering the host cell. Boosting the innate and adaptive immune systems is very important against SARS-CoV [21]. Therefore, herbs that improve the immune system can also perform a vital function in the prevention and management of coronavirus symptom.

21.3 Different Types of Techniques That Could Be Utilized for Targeting the SARS-CoV-2 Novel Corona (COVID-19) Virus

Caruana et al. [22] reported that diagnostic tools are a key in the fight against COVID-19 pandemic. It has been suggested that for accurate and rapid diagnosis real time-PCR for RNA viruses is recommended so as to give direction to management procedures, patients care, and epidemiological approaches. The authors suggested that more research are needed to elucidate the relevance of serological diagnosis, prognosis, and response, thus they evaluated the utilization of diagnostic tests for proper guidance. Ramesh et al. [23] showed that coronavirus disease has been declared by the World Health Organization as a global health pandemic. The virus has spread to numerous countries across the world and having the infection will require rapid detection, development of vaccines, and isolation of the infected individuals. There are several methods available for rapid detection and diagnosis of infected individuals, many have different limitations such as speed or accuracy. Thus a swift and accurate diagnostic technique is required to curtail the spread of the coronavirus disease. Recently, there has been a surge in the development of alternative rapid diagnostic platforms or methods for coronavirus disease such as nanosensor based technology, next-generation sequencing, computed tomography scan, loop-mediated isothermal amplification, and point of care testing.

Next-generation sequencing (NGS) is a high-throughput sequencing technology that can be exploited for the evaluation of viral genomic sequence of any length. This technology offers a large scale benefits such as detection of infection, diseases, monitoring of outbreaks, due to high level of traceability and precision in a surveillance routine test. This technique incorporates bioinformatics tools to analyze viral parthenogenesis, phylogenetic, or metagenomics for recombinant or mutated genome. The utilization of this technology for routine laboratory diagnostic procedures is limited due to high cost of equipment. Another technology with high level of sensitivity during diagnostic protocol is the computed tomography scan

recommended by many scientists for the determination of coronavirus disease. Studies have revealed that computed tomography scan results for COVID-19 give bilateral multi-lobar ground-glass opacities in the posterior and peripheral areas, thickened lobular septa, alveolar filling. Studies have shown that computed tomography scan is more reliable, sensitive, and accurate than real time-qPCR at early stage. They also noted that part of the shortcomings is that computed tomography scan is only for indicative and not confirmatory tool, hysteresis of the abnormal computed tomography imaging plus inability to distinguish different virus and non-viral infections.

Loop-mediated isothermal amplification is another powerful tool that could be applied in the diagnostic protocol for coronavirus disease through molecular amplification of viral genomic material with very high accuracy, efficiency, and with a short period of time. Loop-mediated isothermal amplification is easy to operate providing sensitive, specific, and reliable results with single constant temperature during operation as compared to other techniques requiring thermocycler to perform.

Another technique is the advanced point of care testing usually performed at the patient's bedside. The device can detect different diseases with low cost, user-friendly way to operate incorporating biosensors for quick detection and diagnosis. Biosensor is an integrated analytical device made up of transducer, signal detector plus bioreceptor, thus when the analyte gets in contact with the bioreceptor, a signal is generated and transmitted through the transducer, amplified, processed by circuit detector and then displayed. Different approaches are utilized in rapid diagnosis by biosensors like PCR sequences, enzyme-linked immunosorbent assay, gel electrophoresis, radioactive labeling, fluorescent, nanomaterials (nano-sensor) embedded for signal amplification with nanoscale virus analytes. The high specificity, selectivity, and sensitivity for COVID-19 nano-sensor make this technique a powerful approach in detecting and rapid diagnosis of viral infestation. The biosensor can pick nanoscale biomolecules such as membrane protein, toxins, amino acids, immunoglobulins, growth factors, cytokines, coupling agents, intact cells, ionic metals, plus other small molecules for possible amplification.

Roujian et al. [24] reported that viral pneumonia due to novel coronavirus has been revealed to wreck serious havoc across the world resulting into high rate of mortality through human-to-human transmission. The authors analyzed bronchoalveolar lavage fluid from infected patients in Wuhan, China utilizing Sanger next-generation sequencing, rapid amplification of viral cDNA ends was obtained and subsequent phylogenetic evaluation was carried out, thus the findings revealed that the ten viral genome sequences obtained from different patients gave similar results with 99·98% similarity index derived from bat origin bat-SL-CoVZXC21 and bat-SL-CoVZC45. Ahmad et al. [25] revealed that COVID-19 emergence has demanded a rapid diagnostic approach for quick detection, prevention, or treatment strategy due to the active nature. Thus, the authors suggested that in the absence of rapid diagnostic kits such as RT-PCR, computed tomography scan may be used but the clinical impacts of ionizing radiation should be analyzed.

Ali et al. [26, 27] reported that coronavirus disease has caused catastrophic turn on human health all over the world with symptoms like pneumonia, dyspnea,

thrombocytopenia fever, subsequent death, and asthenia. The authors revealed that the virus has wide range of genome of about 26–32 kb in length and thus more rapid and diagnostic technique will be needed to facilitate appropriate control measures. Up till date, there has been no single drug, vaccine, or antibodies proven to be effective against the virus, therefore many molecular biology laboratory tests are being utilized to analyze the pathophysiology of the virus isothermal loop-mediated amplification of coronavirus, real time-PCR, next-generation sequencing, microarray-based assays plus multiplex nucleic acid amplification. They analyzed how these technologies have been utilized to evaluate the basic molecular organization, vaccine design, diagnosis, phylogenetic analysis of SARS-CoV-2.

Beatriz et al. [28] established that epidemiological and clinical presentation together with the history of a patient determines the diagnosis of COVID-19. Therefore, the standard diagnostic protocol is by amplification of the viral nucleic acids using quantitative reverse-transcription polymerase chain reaction. The authors also described other techniques aside quantitative reverse-transcription polymerase chain reaction such as rapid test (immunochromatographic tests), lateral flow immunoassay, and ELISA assays through the utilization of the patient's biological samples like serum, whole blood, or plasma. They exhibited that SARS-CoV-2 protein in these procedures reacts with antibody resulting into antigen–antibody complex formation. The authors concluded that immunochromatographic test is a rapid diagnostic procedure, which is highly specific and sensitive for biological samples. This technique is very suitable for large samples, user-friendly, for easy monitoring and screening of COVID-19.

Arghavan et al. [29] demonstrated that coronavirus is made up of positive single-stranded ss (+) RNA that interact with human angiotensin-converting enzyme II receptor. Thus, identifying important structural protein for viral pathogenesis and route of extension by utilizing molecular biology techniques will help to design vaccines and antiviral drugs against these coronavirus infections. The authors described the use of chest computerized tomography scan as only a complementary method to other molecular test for pulmonary imaging variations analysis as a radiological technique in the coronavirus infection like bronchial wall thickening, centrilobular nodules, vascular enlargement, traction bronchiectasis, architectural distortion, subpleural bands.

Ho et al. [30] reported that early identification and diagnosis of coronavirus through the utilization of molecular tools are very key in control and surveillance system during outbreak. The authors in their study were able to establish a simple procedure to diagnose coronavirus by identifying the conserved regions of the E gene, RdRP gene, AluI, Tsp45I, and restrictive enzymes EcoRI. From their findings, it was observed that 345 bp fragment of the E gene plus 396 bp fragment of the RdRp gene was amplified using the one-step real time-PCR, gel electrophoresis technique, sequencing plus phylogenetic analysis. They concluded that this simple assay using one-step real time-PCR could help in differentiating SARS-CoV and SARS-CoV-2.

Rekha et al. [31] reported that the discovery of coronavirus based on its RNA is premised upon proper design and development of diagnostics methods directed towards many part of coronavirus structure utilizing PCR based diagnostic system,

microarray, and antibody. The authors demonstrated that CRISPR technology is a cheap, reliable, and sensitive technique for testing and evaluating coronavirus infection. They emphasized that testing is a key stratagem in monitoring the scourge of COVID-19 pandemic in public health monitoring. Most of the detection techniques for SARS-CoV-2 utilize nasopharyngeal samples but other novel techniques may require blood and oral samples due to higher reproducibility, reliability, and sensitivity. Loop-mediated isothermal amplification technology requires minimum reagents and resources may be of advantage for testing capacities in laboratories.

Rekha et al. [31] suggested that very soon more advanced technology will emerge that will be able to investigate the physiology of coronavirus with host of biological enzymes and pathways beyond just detection. Artificial intelligence, real time NASBA, rolling circle amplification, smart phones are few of the emerging technologies that can be utilized to optimize and pursue therapeutic development against COVID-19.

Corman et al. [32] reported that the emergence and rapid spread of SARS-CoV-2 has increased the testing capacities of many isolation centers for routine diagnosis. The utilization of PCR based detection, a molecular biology technique has enabled scientists to study viral gene expression through RNA isolation, cDNA synthesis, PCR working mix of the buffer, dNTPs, primers of the target gene, Taq polymerase, cDNA template plus SYBR green dye. The techniques use PCR machine for incubation, fluorescence generated amplification so as to generate cycle threshold values**.** Many scientists have also utilized other techniques such as reverse-transcription loop-mediated isothermal amplification, metagenomic next-generation sequencing, RT-insulated isothermal PCR, CRISPER-based assay plus one-step rRT-PCR assay. These technologies are very unique, sensitive, specific for selective specimen type, or time for the diagnosis of SARS-CoV-2 and other coronavirus subtypes.

Nature [33] reported that antibody-based detection methods which are popularly referred to as immunoglobulins are activated in the immune system by pathogenic viruses. Coronavirus infection is known to generate antibodies which can be utilized for molecular antibody-based tests utilizing lateral flow immunoassays, time-resolved fluorescence immunoassay, electrochemical immunosensor, colloidal gold immunoassay and ELISA novel technologies being developed for antibody tests. These technologies are required to be cost-effectiveness, sophisticated instruments, easy to handle, and rapid detection efficacy. Aptamer-based detection method has been described as single-stranded small-sized artificial nucleotides, which is beginning to attract massive attention as a result of its specific binding through a systematic evolution of ligands by exponential enrichment technique of target analytes. Also aptasensors can be utilized to analyze very minute quantities of samples coupled with a low cost design, rapid detection period for economic benefits in commercial diagnostic procedures.

Lu et al. [34] revealed that CRISPR-based approach has been utilized in many biotechnological procedures mainly for genome editing. The technique has also been adapted for the detection of SARS-CoV-2 utilizing Specific High Sensitivity

Enzymatic Reporter UnLOCKing technique (SHERLOCK). This technique deploys Cas13 and SHERLOCK detection protocol through isothermal amplification of RNA sample, amplified viral RNA, and cleaved reporter production of distinct band for visualization with paper dipstick. This technique is very sensitive, fast, and very efficient for rapid detection of SARS-CoV-2. The authors suggested that CRISPR/Cas13d approach can offer a potential treatment option for COVID-19. Chu et al. [35] reported that molecularly imprinted polymer-based detection for SARS-CoV-2 has been developed with different biosensor and bioassays for high sensitivity, low cost, long-term stability, fast detection method. The authors suggested that this technology is a fascinating sensitive method for small biomolecules for diagnosis of different virus strains. This technology may also incorporate nano-sensor or electrochemical-biosensor based multi-walled carbon nanotubes for human serum samples.

Zhang et al. [36] revealed that gene microarray-based detection can be utilized for diagnosis and detection of SARS-CoV-2 in two steps such as development of specific probe plus generation of targeted cDNA fragments. Oligonucleotide microarray samples may be produced from throat swab or gargling fluid from an infected SARS-CoV-2 patient targeting six single nucleotide polymorphisms. This technology is very useful for large sample size because it can detect higher number of DNA fragments simultaneously. Singh et al. [37] wrote extensively on loop-mediated isothermal amplification-based detection strategies for different viruses including COVID-19. This technique at constant temperature amplifies quickly DNA samples with high simplicity and specificity, hence economically viable.

21.4 Specific Examples of Medicinal Plants Utilized for the Treatment of (COVID-19) Virus

Zhang et al. [38] recounted that Chinese medical herbs have been shown to be very potent against many respiratory infections due to presence of numerous bioactive molecules with strong biological activity, thus the authors suggested that these Chinese medical herbs may be valuable in the management of novel coronavirus. Molecular docking and pharmacological analysis were utilized to evaluate the potency of these herbs against coronavirus like inflammation/ immune response. Sujoy and Alakesh [39] revealed that SARS-CoV-2 has appeared as global pandemic due to high death recorded across the globe. Thus urgent attention is needed to redeem the situation as the virus has developed a capacity to adapt to different environment and rapidly spreading with significant number of individual coming down with the infection needing already collapsed healthcare system. Hence, rapid development of natural therapeutic agents could serve as alternatives approach to synthetic drugs available in the management of infection due to COVID-19.

Paulin et al. [40] revealed that treatment options for the current world pandemic due to novel COVID-19 like dexamethasone and remdesivir are very weak and ineffective, thus the need for drug repurposing for COVID-19 infection continues. The authors demonstrated that herbal medicines from different plant extracts derived

from many low-income countries like Artemisia spp. derivatives are rich in bioactive constituents with strong potent biological activity and thus could be utilized for drug formulations. They emphasized that thorough analysis should be done to establish the toxicity index, pharmacokinetics, safety, and efficacy of these plant extracts. Yang et al. [10] reported that severe acute respiratory syndrome coronavirus 2 is currently ravaging the world causing pneumonia. Currently, there are no specific vaccine or anti-virus drugs for the treatment of the symptoms except for supportive care. The authors noted that in China, many of the patients affected with SARS-CoV-2 are being treated with traditional Chinese medicine, though the mechanisms of action, biological features of the active constituents have not been characterized.

Srivastava et al. [41] revealed that lack of potent antiviral vaccines or drugs against the dreadful COVID-19 has caused serious devastating scenario all over the world. The authors suggested that identification of potent medicinal plant with antiviral and immune boosting constituents would provide therapeutic support for patients infected with the virus. The present synthetic drugs for COVID-19 infections such as hydroxychloroquine and dexamethasone have shown to generate many side effects particularly in patients with low immune system. Again supplementation with allopathic immune booster medicines may be costly, thus medicinal plant and Ayurvedic product will provide the body with rich constituents without any side effects. Mohamed and William [42] demonstrated that there are numerous options for the handling of SARS-CoV-2 such as interferon therapies, small-molecule drugs plus vaccines which may take time to develop, coupled with the development of viral resistance, side effects, viral dormancy, and viral re-emergence against many synthetic drugs currently in use. Thus medicinal plants with phytochemical extracts like essential oils may provide rich source of biomolecules as antiviral agents. The authors essentially focused on the mechanism of action involved in the antiviral of these natural ingredients and the physiological mechanisms against viral entry, assembly, replication, discharge, and virus-specific receptor modulations.

Ilkay and Sezer [43] revealed that SARS-CoV-2 is a member of the β-coronaviridiae family with the biggest RNA genome. Even though the antiviral drugs utilized in the treatment of other respiratory viruses have been used, there is still a wide gap in the treatment outcome. Many of these drugs have shown gross inefficiency with several side effects, therefore a lot of attention is shifting towards finding alternative solutions in medicinal plants and pure biomolecules isolated from them reported to exhibit antiviral properties. Candidate drug development for COVID-19 could be developed from these biomolecules such as polyphenols or flavonoids (luteolin, quercetin, hesperetin, amentoflavone, psoralidin, broussochalcone, terrestrimine, papyriflavonol A), alkaloids (tylophorine, lycorine, 7-methoxycryptopleurine, nummularine B, jubanine H), anthraquinones (emodin, aloe-emodin), saponins (escinidin, glycyrrhizin), terpenes (betulinic acid, curcumin, iguesterin, chrysanthemum in B), coumarins (xanthoangelol E, leptodactylone), diarylheptanoids (hirsutenone), plus lectins (alstotide 1, UDA, APA, HHA), methyl rosmarinate, myricitrin.

Amir et al. [44] showed that at the moment, there are no known antiviral drug effective against COVID-19 infection. Hence, the authors did a review on some traditional medicine with promising effects against COVID-19. Generally, these medicinal plants from India, China, Africa, and Iran have strong inhibitory effect on viral replication, though the mechanisms remain unclear. Therefore, further studies will be needed to be carried out on these medicinal plants to ascertain their toxicity, dosage, biological activity, and concentrations.

Johnson et al. [45] reported that some of the clinical manifestations of COVID-19 infection include fever, cough, fatigue, shortness of breath, plus other complications. Till today, there is no cure for this infection except for supportive or palliative care, hence the need to search for alternative solutions. The authors carefully selected few Nigeria based medicinal plants for possible pharmacological activity against SARS-CoV-2. COVID-19 has been characterized by hyperinflammation, immunosuppression, hyper-cytokinemia, multi-organ failure, increased pulmonary vascular permeability, suppression of angiotensin-converting enzyme 2, damage to the alveoli, activation of c-Jun N-terminal kinase pathway.

Yuxi et al. [46] carried out a review on traditional Chinese herbal medicine against COVID-19 infection and symptoms. They stated that due to the paucity of effectively strong regimes, Chinese herbal medicines may be considered for possible management and clinical trials against COVID-19. Nadeem [47] showed that the pathophysiological conditions associated with COVID-19 cause high mortality rate. The authors revealed that plant bioactive compounds of *Alangium salvifolium* were evaluated for possible potential role as antiviral agents against virus entry into host cell. Molecular docking and simulation was done utilizing bioinformatics tools. From their findings, it was established that the bioactive compound from the plant displayed strong binding affinity with trimeric viral spike glycoprotein thereby showing modulatory inhibitory property against S-participated**.**

Mohammadi and Shaghaghi [48] revealed that plants with protease inhibitors could be utilized as antiviral agents against COVID-19. The authors applied bioinformatics tools to study COVID-19 infection and the possible inhibitory role of medicinal plants Secondary Metabolite. Molecular docking was done, revealing curcumin as a strong protease inhibitor. Kwong et al. [49] demonstrated a method of incorporating orthodox medicine with blend of Traditional Chinese Medicine like San Ju Yin, Xie Bai San, plus Yin Qiao San against coronavirus disease. Shi-you et al. [50] showed that many of the Chinese medicinal herb extracts have been evaluated for possible antiviral activities against COVID-19. Lycoris radiates and its active constituent (lycorine) has been identified as potent antiviral agents.

Benarba and Pandiella [6] demonstrated that presently the synthetic drugs for supportive care for COVID-19 may not give the desired response against the virus, thus traditional herbal medicines have been recommended for possible therapeutic solution to the current pandemic. The authors revealed that these compounds may show inhibitory effects against viral entry or replication. Some of these natural herbal medicines have been reported to block serine protease TMPRRS2, ACE-2 receptor, papain-like or chymotrypsin-like proteases utilized by the virus to invade the cells. Erdan et al. [51] revealed that traditional Chinese medicines have been

reported to play an active role in fighting against coronavirus infections, thus the authors evaluated many of the natural plants such as Qingfei Paidu decoction and their active compounds like quercetin, kaempferol, luteolin, acacetin against COVID-19. Ikpa et al. [52] revealed that the recent pandemic due to coronavirus infecting ravaging the whole world calls for an immediate therapeutic drug development against severe acute respiratory syndrome. The authors suggested that local medicinal plants found across the entire Africa continent may offer possible beneficial approaches towards curbing COVID-19 pandemic. Bioactive constituents from these plants like *Allium sativum, Zingiber officinale, Allium cepa, Echinacea, Garcinia kola, Curcuma longa, Olea europaea, Aloe vera*, *Euphorbia hirta* have been shown to be able to inhibit viral replication thereby revealing potential drug candidate against SARS-CoV-2.

Tanya and Ayush [53] revealed that herbal plants are less expensive and show low level of side effects compared with synthetic drugs. Many of these plants are yet to be elucidated for possible biological activity.

Sagar and Kumar [54] suggested that *Tinospora cordifolia* possesses strong antiviral property against SARS-CoV-2 through inhibition of virus replication and attachment. The authors tested the plants utilizing in silico tools against SARS-CoV-2 receptors, surface glycoprotein, RNA-dependent RNA polymerase, viral protease. They discovered that Berberine, Magnoflorine, Tinocordiside plus Isocolumbin active biomolecules present in the plant showed strong binding capacity, thus validating the plant as a potent candidate for the treatment of COVID-19 infection.

Laksmiani et al. [55] reported acute respiratory syndrome coronavirus 2, thus they carried out a research with the aim to identify different natural active molecules with inhibitory activity against COVID-19 through molecular docking targeting protein in silico autodock 4.2 program. The active compounds such as naringenin, apigenin, brazilein, catechin, brazilin, curcumin, hesperidin, gingerol, andrographolide, luteolin, kaempferol, hesperetin, myricetin, quercetin, asiatic acid were evaluated for target proteins from plants like Caesalpinia sappan L., and Citrus sp. by blocking ACE2, RdRp, TMPRSS2, PLpro and 3CLpro to prevent viral entry, advanced development, and replication.

Eman et al. [56] revealed that no vaccine or particular drug is known for the management of coronavirus disease, thus the utilization of medicinal plants with their constituents cyanidin 3-(600-malonylglucoside), rocymosin B, rutin, verbascoside, caftaric acid, fenugreekine, luteolin 7-rutinoside, caffeic acid was investigated against SARS-CoV-2 by targeting vital enzymes and proteins. The authors carried out molecular docking on different virulent viral factors and enzymes such as 3Clpro, RdRp, and PLpro and the modulatory properties of these constituents. Several other plants like *Glycyrrhiza glabra, Cichorium intybus, Hibiscus sabdariffa, Chrysanthemum coronarium, Anastatica hierochuntica, Nigella sativa, Euphorbia species, Epilobium hirsutum,* and *Psidium guajava* are also investigated and reports showed that they contain potent biomolecules such as isorhamnetin, quercetin, kaempferol, glycerrhizin, apigenin, ursolic acid, and luteolin with multi-targets factors like IL2, PTGS2, IL1b, TNF and VCAM1, other pathways like cytokine–cytokine receptor interaction, TNF signaling pathway,

NOD-like receptor signaling pathway, JAK-STAT3 signaling, NF kappa B signaling pathway, toll-like receptor signaling pathway. Many of these pathways are involved in immune and inflammatory response initiated by the virus on the host cells during SARS-CoV-2 infection, thus these pathways are regulated by these active constituents in mitigating against SARS-CoV-2.

Mani et al. [57, 58] revealed that coronavirus disease-19 has created international attention on ways to curb the spread of the virus through traditional medicinal plants from India. Different varieties of medicinal plants have been evaluated to contain many active biomolecules with potent ability to prevent pathogenic diseases like coronavirus disease-19. The authors suggested that medicinal plants could be incorporated in clinical products such as soaps, masks, and sanitizers which could help to eliminate viral infection and enhance development of sustainable nature-based medicine, expansion of vaccines, and economic growth. The physiological characteristics of many of the Indian medicinal plants need further investigation for possible candidate drug production for the control of COVID-19.

Yang et al. [10] reported that infectious pneumonia triggered by severe acute respiratory syndrome coronavirus 2 may result into lethal and sudden death. At the moment, there is no explicit drug operative for the management except for supportive care to ameliorate the condition. Advancement in Traditional Chinese Medicine practice has opened up various avenues for disease management and treatment through innovative biomolecule development for possible candidate drug formulation against COVID-19 infection. Therefore, experimental studies must be done to elucidate the novel mechanisms of action of many biomolecules with antiviral property in these Traditional Chinese plants.

Huizhen et al. [59] established that the physiological manifestation of COVID-19 is wide, covering asymptomatic infection to severe viral pneumonia and death. They revealed that Chinese medicine performs a significant function in the management of diverse types of diseases, thus evaluation of their efficacy was investigated against COVID-19. From their results, it was observed that Chinese medicinal plants possess huge bioactive constituents with potent antiviral properties against COVID-19.

Mohamad et al. [60] proposed that immune boosters derived from Chinese herbs have offered tremendous benefits for treatment against coronaviruses by inhibiting viral entry and modulating important enzymes. Many of these plants such as Artemisia annua, Lindera aggregate, Lycoris radiate, Licorice root, Isatis indigotica, Houttuynia cordata, Torreya nucifera, Pelargonium sidoides root, dandelion, and many other decoction containing different kinds of herbal plants. The authors suggested that the combination of synthetic medicines and traditional Chinese medicines would produce better results but active constituents should be identified to elucidate the biological mechanism of action and specific drug interactions. Studies have also showed that biomolecules isolated from *Houttuynia cordata, Radix astragali, Radix saposhnikoviae, Glycyrrhizae Radix Et Rhizoma, Pogostemonis Herba, Radix platycodonis, Cyrtomium fortunei J. Sm., Perillae Folium, Glehniae Radix, Rhizoma phragmitis,* and many other in the treatment against COVID-10 are Betulinic acid, Cryptotanshinone, Sugiol, Dihydrotanshinone I, quercetin, Kaempferol,

Coumaroyltyramine, Dihomo-γ-linolenic acid, Lignan, rutin, Tanshinone IIa, N-cis-feruloyltyramine, Betulinic acid, Moupinamide, and auercitrin are very effective against coronavirus infection.

Abidemi et al. [61] revealed that drug repurposing for COVID-19 is on the increase across the globe with many scientists searching for alternative effective therapy or vaccines from the diverse flora of traditional medicine in African to curb the scourge of coronavirus disease infections. Further studies to identify and establish the mechanisms of actions of phytomedicines against COVID-19 need explorations, development, plus chemical evaluation. Some of the suggested mechanisms of actions include inhibition of SARS-CoV-2 fusion with human cells, blockage of cell membrane-derived vesicles for transportation, reduction in endosomes acidity, blockade of proinflammatory cytokines generation. The authors concluded by recommending caution against indiscriminate utilization and consumption of medicinal plants in the guise of managing COVID-19.

Prativa et al. [62] demonstrated that public health tragedies caused by infectious diseases such as coronavirus could result into a major global socio-economic devastation, many approaches have been suggested for vaccines and drug formulations or designs. Traditional herbal medicines are currently being exploited for immuno-modulating and antiviral activity against several infectious diseases such as tuberculosis, influenza, COVID-19, and malaria, due to their high level of accessibility, affordability, plus acceptability. Several countries in the developed countries have been able to combine with their health sector the utilization of traditional medicines to manage many infectious diseases.

Joshi et al. [63] reported that COVID-19 causes illness of the respiratory system and since there are no effective drugs to eliminate the virus, the authors investigated several phytochemicals to identify novel biomolecules with antiviral, antifungal, and antibacterial activity. They were able to evaluate ten constituents through molecular docking techniques and concluded that these molecules can be developed into drug formulation for the management of COVID-19 by acting as inhibitory agents against the virus.

Balachandar et al. [64] showed that viral inhibitory system could be developed through exploring bioactive compounds from traditional based medicinal plants by incorporating the nanofiber-based respiratory masks. Development of fibrous filtration masks consisting of three-layered utilizing biomolecules from potent medicinal plants for viral deactivation was suggested.

Ali et al. [26, 27] discovered some biomolecules from traditional medicinal plants with potent antiviral agents. They reviewed the multidimensional mechanisms involved in their antiviral and immune modulatory activity. Kabidul et al. [65] revealed that in Bangladesh, the COVID-19 surge has caused a lot of economic and health devastation due to high population density with very limited facility to practice social distancing. This is compounded with high level in the cost of treatment, thus people rely of folk medicine as alternative remedies for possible treatment against COVID-19.

Amir et al. [44] highlighted the role of folklore medicine in the management of coronavirus pandemic due to absence of potent vaccine or drug to curb the spread of the virus. The active constituents have potential to inhibit viral replication, interact with key viral enzymes and proteins. The authors concluded by suggesting that further studies should be carried out to identify the biological interaction between the virus and bioactive molecules from plants.

Christian et al. [66] confirmed that there is need to urgently discover potent antiviral molecules against the novel coronavirus disease. Many medicinal plants such as Zingiber officinale, Allium sativum, Allium cepa, echinacea, Garcinia kola, euphorbia hirta, Curcuma longa, olea europaea and Aloe vera possess potent antiviral compounds that can inhibit viral replication. Drug repurposing has been done on various biomolecules to treat and manage the symptoms displayed by individuals infected with SARS-CoV-2. Novel medicinal plants in Nigeria are now being investigated for possible therapeutic value against SARS-COV-2.

Ambrish et al. [67] suggested that one of the most potent pathways for combating COVID-19 is through virus deactivation utilizing natural compounds. Traditional medicines in African, China, and India have been legalized in some part of these areas even though the mechanism of action is yet to be fully established. Molecular biology techniques utilizing herbal remedies like Ginger (*Zingiber officinale*), Garlic (*Allium sativum*), onions (*Allium cepa*), *Garcinia kola*, plus *Aloe vera* will help to elucidate the inhibitory pathways like blockage of viral entry, life cycle, assembly, replication, release, inhibition of viral protease, viral RNA. The bioactive molecules present in these plants such as phenolic compounds, polysaccharides, phenolics, terpenes, lipids, gingerols, shoga, raw fibers, carotenoids, flavonoids, copaenes, minerals, phytoestrogens, diallyl disulfide, terpenoids, anthocyanins, diallyl trisulfide, diterpenoids, flavonoids, triterpenoids, dimeric ellagitannins, myricitrin, gallic acid, aloe-emodin, chrysophanol, emodin, squalene, rutin, afzelin, vitamins, caffeic acid, amino acids, Isorhamnetin, organic acids, allicin, Quercetin, Kaempferol, Myricetin found have the capacity to alter transcription plus translation of viral genome, block viral entry in the host cells thereby preventing SARS-COV-2.

21.5 Herbs with Antiviral Activity Against SARS-CoV-2

Natural resources having antiviral activities are the most important need of our time. The pandemic situation has made the whole globe to realize the benefits of natural bioresources that surrounds mankind. Presently, the whole globe is now searching for alternative drugs that possess antiviral activities most especially from natural compounds derived from medicinal plants. For treating the coronavirus patients in China the health commission has approved the combined usage of traditional medicine and conventional medicine [10].

Many antiviral activities have been documented from natural resources because of various active constituents. Garlic is a medicinal plant that possesses numerous medicinal attributes properties that are rich in sulfur content while the essential oil

portends the potential to inhibit the viral entry into the host and hence prevents the spread of infection [68].

Senna makkai is a rich source of several phytochemicals such as anthraquinones, flavonoids, polysaccharides, sterols, and stilbenoid which is responsible for its medicinal activity. Anthraquinones exhibit a higher level of anti-SARS-related coronavirus activity by damaging the viral envelope and prevent the viral entry into the host [69]. *Citrus sinensis* is a rich source of vitamin C and due to its flavonoid content it possess antiviral activity [70]. Curcumin from turmeric is a naturally occurring phytochemical and possesses promising antiviral effects [71]. It acts as a spike protein inhibitor and prevents the entry of coronavirus into the cell [72].

Glycyrrhizin is an active constituent which has been documented action against SARS-CoV. In vitro studies inhibit the virus life cycle at various levels and prevent the entry, penetration, and viral replication [73]. Black seed is popular for its probable antiviral effects, and its constituents may inhibit coronavirus [74] while the black seed steam has been documented to cure the respiratory disease symptoms. All these findings validate the pharmacological activity of black seeds against COVID-19 [75, 76]. Black seed oil works as an immunity booster and increases the defense level of the body against coronavirus. All these findings suggest the anti-SARS-CoV potential of medicinal herbs [77].

Several medicinal plants that have been evaluated in order to establish their medicinal effect as well as to validate their antiviral effectiveness against coronavirus and to establish their immune-modulating activity are discussed as follows:

21.5.1 *Allium sativum* (Garlic)

Garlic is a common spice used since ancient times as a remedy for common colds, influenza, and various diseases. [78]. The word garlic is derived from Celtic word "all" which means pungent. It is cultivated globally [79]. There are several reports that have established the presence of numerous sulfur compounds which have numerous pharmacological properties and are found abundantly and allicin is an important sulfur content which give garlic its characteristic pungent odor. Garlic also possesses numerous enzymes and contains 17 important amino acids which are beneficial therapeutically [80, 81]. These sulfur containing amino acids and other compounds help in enhancing the immune system activity [82]. Interestingly, the presence of these compounds in the garlic prevents the entry of coronavirus into the host by inhibiting the ACE2 protein which might perform a function of preventing the spread of infection [68].

21.5.2 *Cassia angustifolia* (Senna)

C. angustifolia named as *Cassia Senna* and in Urdu *Senna makkai* is a medicinal 5–8 m tall shrub which belongs to the family Leguminosae. Its origin belongs to

Arab countries like Egypt, Saudi Arabia, and Yemen and it is also widely found in Pakistan hot arid regions. The leaves and pods of *Senna makkai* are used in the form of a decoction to get rid of intestinal worms. The plant has been used since ancient times in disorders like anemia, cholera, laxative, splenomegaly, and typhoid fever [83]. *Burge Sana* (senna leaves) is used to treat constipation and used as an irritant purgative. For skin disorders the powder of senna is mixed with vinegar and applied externally [84]. The main constituents of senna are sennosides which are anthraquinone glycosides which are responsible for antiviral activity. It inhibits the viral adsorption by damaging the viral envelope [69].

21.5.3 *Citrus sinensis* (Sweet Orange)

It is also known as sweet orange. *Citrus sinensis* is a rich source of vitamin C and is consumed during flu seasons in turkey. Its peel extract contains a rich source of flavonoids, limonene, and linalool [85]. *Citrus sinensis* peel extract has antioxidant and antimicrobial action [86]. Flavonoids have been established to have antiviral action [87].

21.5.4 *Curcuma longa* (Turmeric)

Curcuma longa L. known as "*Haldi*" is being cultivated abundantly in Asia [88]. Turmeric is used as a remedy for effective management of several diseases since ancient times [89]. The main chemical constituents of *Curcuma longa* L. are curcuminoids mainly curcumin or diferuloylmethane [90]. *Haldi* possesses various actions such as antioxidant, anti-inflammatory, anti-cancer, and antiviral effects [71]. Its antiviral activity is due to its ability to inhibit the viral spike protein [72].

21.5.5 *Glycyrrhiza glabra* (Liquorice)

Glycyrrhiza glabra named as Liquorice has a specific odor and sweet taste. This word is derived from the Greek meaning sweet root. It is cultivated in Europe and Asia specifically temperate and sub-tropical areas [91, 92].

Since ancient times it is used as a medicinal plant in several part of the globe. It has been used for the management of respiratory tract disorders. Saponins are the main phytochemicals in licorice root. The major constituent is glycyrrhizin and its concentration varies between 1% and 9% [93, 94]. In vitro investigation has documented that glycyrrhizin possesses the potential to inhibit the replication of SARS-CoV [95, 96]. Glycyrrhizin also possesses the ability to prevent viral adsorption and penetration during the early stages of replication. Glycyrrhizin has been

found to be most effective most especially when given during and after the adsorption period. However, the exact mechanism is unknown [73].

21.5.6 *Nigella sativa* (Black Seed)

Nigella sativa L. known as *Habba sawda* or black seed is popular globally for its possible antiviral activity against coronavirus. Most abundant constituents in its seed are volatile oils and alkaloids [97]. A study showed that Nigellidine and α-hederin are the major constituents which are responsible for their antiviral activity [74].

Since ancient times the steam of the black seeds has been used to treat the symptoms of respiratory diseases. These findings validate its therapeutic activity against coronavirus which is also a respiratory disease [75, 76]. Black seed oil was established to enhance immune system response by increasing CDT cells and increased gamma interferon-(INF-) synthesis [98]. It has been documented in a study that black seed oil possesses an antiviral activity against murine cytomegalovirus infection. Also, it could also increase the serum levels of interferon-gamma, T-lymphocytes, and macrophages [99]. The antihistamine activity of black seeds extracts and its constituents such as thymoquinone, nigellone, and thymohydroquinone were observed in an animal study [100]. N. sativa seed oil also possesses antioxidant activity [101]. Another investigation also showed that black seeds extract reduced the replication of coronavirus [70]. Table 21.1 indicates the list of some beneficial plants with higher level of antiviral activity against COVID-19.

Table 21.1 List of herbs used against SARS-related Coronavirus

Name	Family	Major constituent	Mechanism of action	References
Allium sativum (garlic)	Alliaceae	Allyl disulfide and trisulfide	ACE2 receptor inhibitor	Thuy et al. [68]
Cassia angustifolia (Senna)	Leguminosae	Anthraquinones	Disrupt the viral envelope	Sydiskis et al. [69]
Citrus sinensis (sweet orange)	Rutaceae	Limonene	Viral growth inhibitor	Ulasli et al. [70]
Curcuma longa (turmeric)	Zingiberaceae	Curcumin	Inhibitor of 3CLpro	Wen et al. [102]
Glycyrrhiza glabra. (Liquorice)	Fabaceae	Glycyrrhizin	Viral growth inhibitor	Hoever et al. [103]
Nigella sativa (black seed)	Ranunculaceae	Nigellidine and α-hederin	Viral growth inhibitor	Bouchentouf and Missoum [74]

21.6 Phytochemicals with Medicinal Attributes That Could Serve as Anti-COVID Management

Phytochemicals also known as phytonutrients are plant metabolites that have therapeutic potentials which are of immense usefulness to human in disease therapy. They are also available in the form of nutraceuticals in which they show significant health impacts. There are various phytochemicals that have greater potentials to inhibit the life cycle of viruses and these include thiosulfonates, flavonoids, proteins, terpenes, fructans, quinines, saponins, steroids, polyphenols, and proanthocyanidins [104].

Most of these compounds are also described as natural products. Such bioactive compounds such as alkaloids, flavonoids, and peptides have been assessed for their efficacies in treatment of COVID-19. There is however studies still on with respect to their bioavailability and in vivo impacts [105]. Several researchers have documented the effectiveness these phytonutrients in the treatment of various diseases including cancer, bacterial infections, viral disease, and cardiovascular diseases. Few studies have also reported the effectiveness of these bioactive agents in the treatment and management of COVID-19. Previous studies have shown that a wide range of these plants derived chemicals such as tannins, lecithins, coumarins, lignans among others possess efficacies against different groups of coronaviruses including SARS-CoV. The development of a new therapy using these natural products entails different phytochemicals that are available in the herbs which are commonly found in different plant and they could also boost immunity against COVID-19 infection. Ayurveda has been recognized as one of the oldest systems of traditional medicine having several plants with antiviral potentials that could be employed for effective management of COVID-19 diseases [106].

21.7 Mode of Action of Some Phytochemicals Against COVID-19 Infection

It has been discovered that alkaloids possess the potential to inhibit COVID-19 which could block the attachment of the virus thereby inhibiting its growth and bringing about a reduction of the viral load and effect on the lungs. For polysaccharides, they hinder the replication of the virus and prevent their binding to the cell. Flavonoids affect the COVID-19 viruses through the inhibition of the reverse transcriptase thereby preventing the synthesis of RNA. Also, terpenes function by inhibition of the process of replication of the virus while lecithin affects the ability of the virus to penetrate [104].

It has been established that some of the metabolites of some medicinal plants have a greater promising with a higher potential that they could be utilized for the treatment of SARS-CoV-2 by binding to ACE2 to flavonoids. Also, there are other recently documented reports that some groups of phytochemical such as alkaloids and limonoids could also perform same function. Alisha and Tripti [107] documented the presence of a site with a relatively lower binding tendency in limonoid when compared to flavonoid. Limonoids are active groups of

phytochemicals that are found in Meliaceae family most especially within the genera Carapa and Andiroba which is a specie common in the Amazon than is widely known for their anti-inflammatory potentials.

Many natural bioactive compounds found in plants such as polyphenol could be vital in providing a starting point in the search for plant extracts for the treatment and prevention of coronavirus disease. Inhibition of coronavirus enzymes has been reported in antiviral drugs such as the polyphenolic based compounds, since the enzymes are necessary for the replication of the virus. The design of antiviral drugs could be possible using natural products such as luteolin, triterpenoids, gallates, betulinic acids, quercetin, and aloe-emodin. The formulation of new anti-COVID-19 drugs could be possible using the pharmacophore structures that are known. The use of phytochemicals would be remarkable in this dimension since they are safe without side effects [108].

Also herbal medicines that traditionally available as well as the natural products that have been purified would be very vital in the development of antiviral drugs. In a study carried out by Wan et al. [109] it was reported that some of the patients admitted in Chongqing region in China combined traditional herbs and western medicine in their treatment and management of the COVID-19 disease and the results were promising.

Several studies have reported the potentials of various traditional herbs as remarkable source for drug discovery. In their work, Ling [110] collated information on varieties of naturally occurring phytochemicals from different plants that have therapeutic potential. Since the first outbreak of SARS-CoV-1 on 2003, different naturally occurring active compounds have been tested with a view to developing drugs for the treatment. The different bioactive compounds have different mechanisms and pathways in their inhibition of the coronaviruses. Also there are similar features in some of the chemical compositions of these natural metabolites which are in line with some earlier reported works by Jo et al. [111] who proved that the inhibition of SARS-CoV-1 requires a chemical feature that has an aromatic ring that is hydrophobic in nature, moieties of carbohydrates and hydroxyl groups. In some of the bioactive compounds that have potencies against SARS-CoV-1 the aromatic rings are absent however they still poses the an hydrophilic and lipophilic regions in their molecular composition hence capable of initiating hydrogen bonding from several points through the hydroxyl groups.

Lung et al. [112] carried out a study in which they screened about 83 compounds in some herbal medicine from China in assessing their potency against polymerase of SARS-CoV-2. They identified theaflavin which is an antioxidant to be responsible for the activities and potencies against the virus. In a related study, Zhang et al. [38] focused on some other medicine used traditional in China and identified 13 for subsequent studies. The chosen compounds were basically polyphenolic groups such as kaempferol and quercetin which have already been documented for their activity against these diseases.

Nguyen et al. [113] in their study isolated different phytochemicals such as biflavoids and diterpenoids from medicinal plants and investigated their inhibitory potential against SARS-CoV. Various active ingredients such as galusatechin,

epigallocatechin, and quercetin showed remarked inhibitory activity against the viruses through the effect of the hydroxyl groups required for the binding process. The role of quercetin in this process was well identified. Quercetin has polyhydroxyl groups which makes it possible to boost the immune system of the body.

Some other scientists in China have also assessed the potency of selected 26 plant extracts in the treated of SARS-CoV-2 through inhibition process. They reported that the active agents present in the plants interact with the proteins of the virus thus bringing about their antiviral activities. Wen et al. [114] reported that extracts from some traditional known plants from China were useful in the inhibition of SARS-CoV replication. Some of the plants investigated include *S. gentiana, B. dioscorea, C taxillus,* and *T cassia*. They further emphasized that the development of compounds that are capable in inhibiting various respiratory diseases including the coronavirus will be a significant achievement.

Wen et al. [114] carried out an assessment to validate the inhibition potentials of 200 extracts of medicinal herbs from China against coronavirus. They investigated cytopathogenic impact using cellular tests under the in vitro conditions. The extracts from *Loranthi ramus, Gentianae radix* showed potency against the virus. In a related study carried out by Chiow et al. [115], they investigated the antiviral potential of extract of *Houttuynia cordata* using ethyl acetate as solvent. The plant contained quercitrin, quercetin, and cyanserine which were used in the treatment of dengue fever and coronavirus disease in mice.

Lin et al. [116] did a review on some antiviral agents that are naturally occurring and could be used potentially for respiratory diseases including coronavirus diseases. Similarly, Pang et al. [117] outlined few natural remedies that could be useful in the management of COVID-19 diseases; however, they did not work on the mechanisms in which these agents operate nor the bioactive compositions. Lue et al. [118] gave a review with the aim of making inputs on the known extracts and bioactive agents available in natural agents that show potency against the coronavirus disease.

Idrees et al. [119] carried out a review with a view to providing information and knowledge relevant in the treatment of the coronavirus disease through the use of phytochemicals from plants. They emphasized that considering the various bioactive compounds present in plants, they would be useful as alternative therapy in the treatment of COVID-19 since there is no known cure for the disease at the moment. They did an intensive search into all existing literature on use of natural compounds in plants for the treatment of COVID-19 disease. They were able to identify some vital plants that have a range of active ingredients that could be promising in the treatment of COVID-19. Some of the identified plants include *Curcuma longa, Amaranthus tricolor, Hyptis atrorubens, Phyllanthus emblica, Psorothamnus arborescens, Glycyrrhiza radix, Erigeron breviscapus, Rheum palmatum, and Fraxinus sieboldiana.* Table 21.2 indicates the list of some significant phytochemicals with medicinal attributes that could work against COVID-19.

Table 21.2 Phytochemical with medicinal attributes that could work against COVID

S. N	Medical plants	Extract	Mode of action	Phytochemicals present	References
1	*Paulownia tomentosa*	Mimulone	Papain-like protease inhibition	Flavonoid	Cheng et al. [120]
2	*Torreya nucifera*	Luteolin	Inhibition of SARS pseudo-type	Flavonoid and Chalcones	Orhan and Senol-Deniz [121]
3	*Psoralea corylifolia*	Bavachinin	Papain-like protease inhibition	Flavonoid	Boukhatem. and Setzer [74]
4	*Paulownia tomentosa*	Tomentin	Inhibition of papain-like protease	Flavonoid and Chalcones	Islam et al. [75, 76]
5	*Calophyllum blancoi planch*	Pyranojacareubin		Xanthone	
6	*Tripterygium regeli*			Terpenes	Islam et al. [75, 76]
7	*Clivia miniata*	Lycorine	Cell division	Alkaloid	Islam et al. [75, 76]
8	*Forsythia suspensa Vahl.*	Forsythoside A		Polyphenolic	Boukhatem. and Setzer [122]
9	*Glycyrrhiza glabra* roots	Glycyrrhizin	Viral replication inhibition	Saponin	Chowdhury et al. [123]
10	*Cinchona officinalis Back*	Quinine		Alkaloid	Gautreta et al. [124]
11	*Houttuynia cordata thumb*	Rutin	Inhibition of RNA-dependent RNA polymerase (RdRp) and 3C-like protease (3CLpro)	Flavonoid	Chiow et al. [115]
12	*Myrica rubra*	Myricetin	ATPase activity inhibition	Flavonoid	Boukhatem and Setzer [122]
13	*Scutellaria baicalensis*	Scutellarein or Baicalin	ATPase activity inhibition	Flavonoid	Leonova et al. [125]
14	*Asplenium belangeri*		ATPase activity inhibition	Flavones	Islam et al. [75, 76]
15	*Nicotiana benthamiana*	Griffithsin			Barton et al. [126]
16	*Helichrysum odoratissimum* L.	Helichrysetin		Chalcone	Vogel et al. [127]
17	*Psoralea corylifolia*	Psoralidin		Flaovonoid and Chalcons	Islam et al. [75, 76]

(continued)

Table 21.2 (continued)

S. N	Medical plants	Extract	Mode of action	Phytochemicals present	References
18	*Cirsium setidens* Nakai and *Cirsium japonicum* DC.	Pectolinarin			Diniz et al. [128]
19	*Rhodiola rosea L.*	Herbacetin			Zomborszki et al. [129]
20	*Ginkgo biloba* L., *Garcinia brasiliensis* L., and *Nandina domestica* L.	Amentoflavone		Flavonoids and chalcones	Gan et al. [130]
21	*Parkia roxburghii* G.	Epigallocatechin gallate		Flavonoid and Chalcons	Pan et al. [131]
22	*Rubus fruticosus* L. and *Lagerstroemia speciosa* (L.) Pers.	Quercetin	Inhibition of 3CL protease	Flavonoid and Chalcones	Zahoor et al. [132]
23	Psoralea corylifolia	Psoralidin	Inhibition of papain-like protease	Polyphenolics	
24	Cinnamomi cortex	Cinnamtannin and Procyanidin	Inhibition of SARS pseudo-type		Islam et al. [75, 76]
25	*Salvia miltiorrhiza*	Rosmariquinone and Tanshinone	Inhibition of SARS pseudo-type		Islam et al. [75, 76]
26	*Lycoris radiate*		Inhibition or reduction of viral attachment and penetration		Islam et al. [75, 76]
27	*Artemisia annua*		Viral attachment and penetration inhibition	Alkaloids	Boukhatem and Setzer [122]
28	*Lindera aggregata*		Viral attachment and penetration inhibition	Alkaloids	Boukhatem and Setzer [122]
29	*Isatis indigotica fort*	Sinigrin	Inhibition of 3CL protease	Polyphenol	Islam et al. [75, 76]
30	*Boenninghausenia sessilicarpa*	Leptodactylous		Coumarin	Islam et al. [75, 76]
31	*Scrophularia scorodonia*	Saikosaponin		Glycosides	Islam et al. [75, 76]

32	*Rosa nutkana*		Unidentified mechanisms		Boukhatem and Setzer [122]
33	*Torreya nucifera*	Quercetin		Flavonoid	Boukhatem and Setzer [122]
34	*Broussonetia papyrifera*	Broussochalcone B	Inhibition of protease	Flavonoid	Orhan and Deniz [121]
35	*Sambucus formosana*		Inhibition of viral envelopes		Boukhatem and Setzer [122]
36	*Amelanchier alnifolia*		Unidentified mechanisms		Boukhatem and Setzer [122]
37	*Tylophora indica*	Tylophorine	Protease inhibition	Alkaloids	Islam et al. [75, 76]
38	*Hypericum perforatum*		mRNA expression inhibition		Islam et al. [75, 76]
39	*Sambucus nigra*		Inhibition of viral envelopes	Flavonoid	Goud and Prasad [133]
40	*Polygonum multiflorum*		SARS-CoV protein interaction inhibition	Flavonoids, terpenoids	Shen et al. [134], Boukhatem and Setzer [122]

21.8 Bioinformatics and Computation Techniques That Could Be Applied to Enhance Medicinal Activities of Medicinal Plants

There is iota of doubt that medicinal plants have occupied the quote of the therapeutic industry due to its discovery when utilized for the fabrication of drugs that have immersive contribute to the better living of human and that of animal health-wisely [135]. Due to the versatile use of medicinal plants, more innovation has been evaluated to elucidate the potential use of medicinal plants [136]. Over the years, an organoleptic method was first adapted to observe the use of the medicinal plant. This method proceeds to the use of analytical techniques which has brought the use of medicinal plant germane in the pharmaceutical industry [137]. However, time and expenditure factor have been a major challenge to meet the demand of potential use of medicinal plants which calls for the innovation through the use of high-throughput technology such as computational method [138]. Recently, omics techniques based on bioinformatics for development of plant-based drug molecules have been the major view for comparative study of medicinal plants. This technology transcends plants; genomics, transcriptomics, proteomics, and metabolomics which characterize plant metabolic profile [139]. The presence of certain phytochemicals in plants has confirmed their best use in the synthesis of drugs which are derived from medicinal plants. The application of data mining has consequently help in the identification of useful medicinal plants that could be applied for the management of several diseases [140]. Bioinformatics and computational techniques are not only useful in data mining of medicinal plants but also provide detailed livelihood of plant genome [139], which has helped in controlling the therapeutic profiling of medicinal plants extract for treatment of diseases. This data base profiling has been catalogued for specific purpose to elucidate the data mining of potential use of medicinal plant as shown in Table 21.3.

21.9 Conclusion and Recommendation to Future Study

This study has established the potential of different medicinal plants that could be applied for effective management of COVID-19 infection. It has also been established that the different evidence-based studies have supported the implementation of using herbs as potential effective agents and complementary therapy for the treatment of coronavirus. Although a lot of studies are ongoing so as to establish the major mechanism most of these medicinal plants exhibit their antiviral activities against SARS-CoV. There is still a need for proper investigation on the antiviral activity of numerous medicinal plants as well as to perform more research on the structural elucidation, pharmacology and standardization of the biologically active constituents of these medicinal plants most especially those having antiviral activity. Additionally, evidence-based experiment following standard protocols should be performed. The preparation of formulation and the minimum effective dosage need to be investigated and studied extensively. The application of metabolomics could

Table 21.3 Tools and database available for the study of plant-derived compounds most especially those with antiviral activities

S/N	Computational techniques	Uses	link	References
1	The National Center for biotechnology information (NCBI)	Providing access to biomedical and genomic information	Ncbi.nlm.nih.gov	Schoch et al. [141]
2	Kyoto encyclopedia of genes and genomes (KEGG)	Exploring the universe of plant secondary metabolites	http://Genome.jp/keg/genome/plant.html	Kanehisa [142]
3	The international ethnobotany database (ebDB)	Repository for ethno-botanical data supporting multilingual functionality	http://ebdb.org	Skoczen and Bussmann [143]
4	NAPALERT	Ethnomedical information, in vivo and in vitro pharmacology/ biochemical information and secondary metabolites of natural products.	www.napralert.org	Graham and Farnsworth, [144]
5	TCM-ID	Provision of pharmaceutical perspective for herb	http://www.megabionet.org/tcmid	Huang et al. [145]
6	HerbMedPro	Evidence-based catalogue for medicinal herbs	www.herbalgram.org	Abubakar and Haque [146]
7	PubMed	To retrieve plant-derived chemical compounds information	https://pubchem.ncbi.nlm.nih.gov/	
8	Medicinal plant microRNA database	Provide information on regulatory networks and sequences expression of different medicinal plant species	http://mepmirdb.cn/mepmirdb/index.ht.ml	Yu et al. [147], Fei et al. [148]
9	MIPSPlantsDB	Provide information on individual plant species and comparative plant genome	http://mips.gsf.de/projects/plants	Spannagl et al. [149]
10	Plant omics data center (PODC)	Providing modeling information on plants and crop gene networks (GENs)	http://Plantomics.mind.meiji.ac.jp/podc/	Shafi et al. [150]
11	PLEXdb	A unified gene expression resource for plants and plant pathogens	http://www.plexdb.org/	Dash et al. [151]

(continued)

Table 21.3 (continued)

S/N	Computational techniques	Uses	link	References
12	Phytochemical	Provide information on plant-derived molecules such as phytochemicals and medicinal plant	http://faculty.iiitd.ac.in/~bagler/webservers/Phytochemica	Pathania et al. [152]
13	Uttarakhand medicinal plants database (UMPDB)	Provide extensive information on botanical name, common name, taxonomy, genomic taxonomy id, habit, habitat, location in Uttarakhand, part use, medicinal use, genomic information (including number of nucleotides, proteins, ESTs), chemical information, and scientific literature	http://www.frienvis.nic.in/Database/Medicinal-Plant-Uttarakhand_2150.aspx	Kumar et al. [153]
14	IMPPAT	Comprehensive catalogue for natural product extracted from medicinal plants	https://cb.imsc.res/imppat	Mohanraj et al. [154]
15	Cardiovascular disease herbal database (CVDHD)	Natural products isolated from medicinal plant for treatment of cardiovascular disease	http://pkuxxj.pku.cn/CVDHD	Gu et al. [155]
16	KNApSAcK	Comprehensive species-metabolite for plant-derived compounds	http://kanaya.naist.jp/KNApSAck_Family/	Afendi et al. [156]
17		TCM-mesh	Provide information on the phytochemical composition and therapeutic uses of medicinal plants	

also play a crucial role towards the identification of pharmacologically active compounds that could be applied for the synthesis of naturally derived drugs for effective management of COVID-19 infection.

References

1. Kahn JS, Mcintosh K (2005) History and recent advances in coronavirus discovery. Pediatr Infect Dis J 24:S223–S227
2. Gorbalenya AE, Baker SC, Baric R, Groot RJD, Drosten C, Gulyaeva AA, Haagmans BL, Lauber C, Leontovich AM, Neuman BW (2020) Severe acute respiratory syndrome-related coronavirus: the species and its viruses–a statement of the Coronavirus Study Group
3. WHO (2020) Coronavirus disease 2019 (COVID-19): situation report, 73

4. Worldometer (2020) Pakistan coronavirus: 306,886 cases and 6,424 deaths—Worldometer [online]. Accessed Sept 2020
5. Khan S, Liu J, Xue M (2020) Transmission of SARS-CoV-2, required developments in research and associated public health concerns. Front Med 7:310. https://doi.org/10.3389/fmed.2020.00310
6. Benarba B, Pandiella A (2020) Medicinal plants as sources of active molecules against COVID-19. Front Pharmacol 11:1189. https://doi.org/10.3389/fphar.2020.01189
7. Jiang S, Hillyer C, Du L (2020) Neutralizing antibodies against SARSCoV- 2 and other human coronaviruses. Trends Immunol 41(5):355–359. https://doi.org/10.1016/j.it.2020.04.008
8. Rabi F, Al Zoubi MS, Kasasbeh GA, Salameh DM, Al-Nasser AD (2020) SARS-CoV-2CoV-2 and coronavirus disease 2019: what we know so far. Pathogens 9(3):231. https://doi.org/10.3390/pathogens9030231
9. Patel A, Jernigan DB (2020) Initial public health response and interim clinical guidance for the 2019 novel coronavirus outbreak—United States, December 31, 2019–February 4, 2020. Morbidity and mortality weekly report, p 69, 140
10. Yang Y, Md Sahidul I, Jin W, Yuan L, Xin C (2020) Traditional Chinese medicine in the treatment of patients infected with 2019-new coronavirus (SARS-CoV-2): a review and perspective. Int J Biol Sci 16(10):1708–1717. https://doi.org/10.7150/ijbs.45538
11. Petrovska BB (2012) Historical review of medicinal plants' usage. Pharmacogn Rev 6:1
12. Li H, Wang YM, Xu JY, Cao B (2020) Potential antiviral therapeutics for 2019 novel coronavirus. Chin J Tuberc Respir Dis 43(3):170–172. https://doi.org/10.3760/cma.j.issn.1001-0939.2020.03.004
13. Ho TY, Wu SL, Chen JC, Li CC, Hsiang CY (2007) Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. Antiviral Res 74(2):92–101. https://doi.org/10.1016/j.antiviral.2006.04.014
14. Matsuyama S, Nao N, Shirato K, Kawase M, Saito S, Takayama I et al (2020) Enhanced isolation of SARS-CoV-2 by TMPRSS2-expressing cells. Proc Natl Acad Sci U S A 117 (13):7001–7003. https://doi.org/10.1073/pnas.2002589117
15. Schlagenhauf P, Grobusch MP, Maier JD, Gautret P (2020) Repurposing antimalarials and other drugs for COVID-19. Travel Med Infect Dis 34:101658. https://doi.org/10.1016/j.tmaid.2020.101658
16. Da J, Xu M, Wang Y, Li W, Lu M, Wang Z (2019) Kaempferol promotes apoptosis while inhibiting cell proliferation via androgen- dependent pathway and suppressing vasculogenic mimicry and invasion in prostate cancer. Anal Cell Pathol 2019:1907698. https://doi.org/10.1155/2019/1907698
17. Mamouni K, Zhang S, Li X, Chen Y, Yang Y, Kim J et al (2018) A novel flavonoid composition targets androgen receptor signaling and inhibits prostate cancer growth in pre-clinical models. Neoplasia 20(8):789–799. https://doi.org/10.1016/j.neo.2018.06.003
18. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A (2020) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181:271–280
19. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, Mclellan JS (2020) Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 367:1260–1263
20. Hoffmann M, Kleine-Weber H, Krüger N, Mueller MA, Drosten C, Pöhlmann S (2020) The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. BioRxiv
21. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579:270–273
22. Caruana G, Croxatto A, Coste AT, Opota O, Lamoth F, Jaton K, Greub G (2020) Diagnostic strategies for SARS-CoV-2 infection and interpretation of microbiological results. Clin Microbiol Infect 26:1178–1182

23. Ramesh K, Suman N, Samander K, Sanjay M (2020) COVID-19 diagnostic approaches: different roads to the same destination. Virus Dis 31(2):97–105. https://doi.org/10.1007/s13337-020-00599-7
24. Roujian L, Xiang Z, Juan L, Peihua N, Bo Y, Honglong W, Wenling W, Hao S, Baoying H, Na Z, Yuhai B, Xuejun M, Faxian Z, Liang W, Tao H, Hong Z, Zhenhong H, Weimin Z, Li Z, Jing C, Yao M, Ji W, Yang L, Jianying Y, Zhihao X, Jinmin M, William JL, Dayan W, Wenbo X, Edward CH, George FG, Guizhen W, Weijun C, Weifeng S, Wenjie T (2020) Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395:565–574. https://doi.org/10.1016/S0140-6736
25. Ahmad S, Hafeez A, Siddqui SA, Ahmad M, Mishra S (2020) A review of COVID-19 (coronavirus disease-2019) diagnosis, treatments and prevention. EJMO 4(2):116–125. https://doi.org/10.14744/ejmo.2020.90853
26. Ali AA, Al-Shawi, Mustafa FH (2020) Perspective study of exploring some medicinal plants to manage the pandemic COVID-19. European J Med Health Sci 2(4):1–5. https://doi.org/10.24018/ejmed.2020.2.4.374
27. Ali AR, Shamsah HA, Ranjit S, Ruchi T, Mohd IY, Shailesh KP, Mamta P, Yashpal SM, Kuldeep D, Katterine DB, Shafiul H, Alfonso JR (2020) SARS-CoV-2/COVID-19 and advances in developing potential therapeutics and vaccines to counter this emerging pandemic virus – a review. Front Immunol 2:1–46. https://doi.org/10.20944/preprints202004.0075.v1
28. Beatriz AO, Lea C, Ester CS, Thelma SO (2020) SARS-CoV-2 and the COVID-19 disease: a mini review on diagnostic methods. Rev Inst Med Trop São Paulo 62:1–8
29. Arghavan A, Mohsen N, Hamidreza S, Ehsan S, Negin P (2020) The novel insight of SARS-CoV-2 molecular biology and pathogenesis and therapeutic options. DNA Cell Biol 39(10):1–13. https://doi.org/10.1089/dna.2020.5703
30. Ho AS, Dinh TTH, Nghiem DT, Le TBQ, Luong THT, Vu TN, Le BQ, Trinh TH, Nguyen TS, Nguyen TL, Le VN, Nguyen VB, Tran VT, Do Q, Hoang VL, Hoang XS (2020) A simple method for detection of a novel coronavirus (SARS-CoV-2) using one-step RT-PCR followed by restriction fragment length polymorphism. J Med Virol 92(11):2839–2846. https://doi.org/10.1002/jmv.26171
31. Rekha J, Amit KY, Damini V, Nishu D, Minakshi S, Rajeev S, Anil K, Pratima RS (2020) Strategies and perspectives to develop SARS-CoV-2 detection methods and diagnostics. Biomed Pharmacother 129:110446
32. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, Bleicker T, Brünink S, Schneider J, Schmidt ML, Mulders DG, Haagmans BL, van der VB, Brink S, Wijsman L, Goderski G, Romette JL, Ellis J, Zambon M, Peiris M, Goossens H, Reusken C, Koopmans MP, Drosten C (2020) Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Eur Secur 25:2000045. https://doi.org/10.2807/1560-7917.ES.2020.25.3.2000045
33. Nature (2020) Will antibody tests for the coronavirus really change everything? https://media.nature.com/original/magazine-assets/d41586-020-01115-z/d41586-020-01115-z.pdf
34. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W (2020) Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395:565–574. https://doi.org/10.1016/S0140-6736(20)30251-8
35. Chu DKW, Pan Y, Cheng SMS, Hui KPY, Krishnan P, Liu Y, Ng DYM, Wan CKC, Yang P, Wang Q, Peiris M, Poon LLM (2020) Molecular diagnosis of a novel coronavirus (2019-nCoV) causing an outbreak of pneumonia. Clin Chem 66:549–555. https://doi.org/10.1093/clinchem/hvaa029
36. Zhang Z, Zhou Y, Zhang Y, Guo Y, Tao S, Li Z, Zhang Q, Cheng J (2005) Sensitive detection of SARS coronavirus RNA by a novel asymmetric multiplex nested RTPCR amplification coupled with oligonucleotide microarray hybridization. In: Joos TO, Fortina P (eds) Microarrays in clinical diagnostics. Humana Press, Totowa, pp 59–78

37. Singh R, Hong S, Jang J (2017) Label-free detection of influenza viruses using a reduced graphene oxide-based electrochemical immunosensor integrated with a microfluidic platform. Sci Rep 7:42771. https://doi.org/10.1038/srep42771
38. Zhang DH, Wu K, Zhang X et al (2020) In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. J Integr Med 18:152–158. https://doi.org/10.1016/j.joim.2020.02.005
39. Sujoy P, Alakesh M (2020) Traditional indian medicinal plants in the treatment of patients infected with human coronavirus 2019 (SARS-CoV- 2): a review. IOSR J Pharm Biol Sci 15 (2):46–56
40. Paulin MK, Jimmy KK, Micheline K, Françoise VB, Paul MT, Antoine SK, Eric D, Adam Z, Simon T, Fatima S, Leon T, Jean-Jacques MT, Alimuddin Z, Jean BN (2020) Artemisia spp. derivatives for COVID-19 treatment: anecdotal use, political hype, treatment potential, challenges, and road map to randomized clinical trials. Am J Trop Med Hyg 103(3):960–964. https://doi.org/10.4269/ajtmh.20-0820
41. Srivastava AK, Chaurasia JP, Khan R, Dhand C, Verma S (2020) Role of medicinal plants of traditional use in recuperating devastating COVID-19 situation. Med Aromat Plants (Los Angeles) 9:359. https://doi.org/10.35248/2167-0412.20.9.359
42. Mohamed NB, William NS (2020) Aromatic herbs, medicinal plant-derived essential oils, and phytochemical extracts as potential therapies for coronaviruses: future perspectives. Plan Theory 9:800. https://doi.org/10.3390/plants9060800.1-23
43. Ilkay EO, Sezer SFD (2020) Natural products as potential leads against coronaviruses: could they be encouraging structural models against SARS-CoV-2? Nat Prod Bioprospect 10:171–186. https://doi.org/10.1007/s13659-020-00250-4
44. Amir M, Mehrdad H, Farhad SD, Reza R, Hassan N (2020) A narrative literature review on traditional medicine options for treatment of corona virus disease 2019 (COVID-19). Complement Ther Clin Pract 40:101214. https://doi.org/10.1016/j.ctcp.2020.101214
45. Johnson OO, Ebenezer IA, Oyedotun MO, Oluwaseun TO, Boyede DO, Boluwaji MA, Oyewole OI, Adenike TO (2020) A systematic review on COVID-19 pandemic with special emphasis on curative potentials of Nigeria based medicinal plants. Heliyon 6(2020):e04897
46. Yuxi L, Xiaobo L, Liuxue G, Juan L, Dongling Z, Yonggang Z, Mike C, Rongjiang J (2020) Traditional Chinese herbal medicine for treating novel coronavirus (COVID-19) pneumonia: protocol for a systematic review and meta-analysis. Syst Rev 9:75. https://doi.org/10.1186/s13643-020-01343-4
47. Nadeem MK (2020) In-silico study to elucidate corona virus by plant phytoderivatives that hits as a fusion inhibitor targeting HR1 domain in spike protein which conformational changes efficiently inhibit entry COVID-19. Transl Biomed 11(3):1
48. Mohammadi N, Shaghaghi N (2020) Inhibitory effect of eight secondary metabolites from conventional medicinal plants on COVID_19 virus protease by molecular docking analysis. https://doi.org/10.26434/chemrxiv.11987475.v1.
49. Kwong PC, Lin YC, Chen CJ (2020) A strategy of traditional Chinese medicine against COVID-19: linking current basic research and ancient medicine texts. Int J Complement Alt Med 13(2):79–81. https://doi.org/10.15406/ijcam.2020.13.00497
50. Shi-you L, Cong C, Hai-qing Z, Hai-yan G, Hui W, Lin W, Xiang Z, Shi-neng H, Jun Y, Pei-gen X, Rong-song L, Xuehai T (2005) Identification of natural compounds with antiviral activities against SARS-associated coronavirus. Antiviral Res 67:18–23. https://doi.org/10.1016/j.antiviral.2005.02.007
51. Erdan L, Daiyan Z, Hua L, Bowen L, Keming Z, Yonghua Z, Ying B, Yitao W (2020) Treatment efficacy analysis of traditional Chinese medicine for novel coronavirus pneumonia (COVID-19): an empirical study from Wuhan, Hubei Province, China. Chinas Med 15:34. https://doi.org/10.1186/s13020-020-00317-x
52. Ikpa CBC, Maduka TOD, Christian EE, Ikezu UJM (2020) Potential plants for treatment and management of COVID-19 in Nigeria. Acad J Chem 5(6):69–80. https://doi.org/10.32861/ajc.56.69.80

53. Tanya D, Ayush S (2020) Use of herbal medicines on coronavirus. Acta Sci Pharmaceut Sci 4 (4):61–63
54. Sagar V, Kumar AHS (2020) Efficacy of natural compounds from Tinospora cordifolia against SARS-CoV-2 protease, surface glycoprotein and RNA polymerase. BEMS Rep 6(1):6–8
55. Laksmiani NPL, Larasanty LPF, Santika AAGJ, Prayoga PAA, Dewi AAIK, Dewi NPAK (2020) Active compounds activity from the medicinal plants against SARS-CoV-2 using in silico assay. Biomed Pharmacol J 13(2):873
56. Eman S, Ahmed AN, Reham SI (2020) Potential role of medicinal plants and their constituents in the mitigation of SARS-CoV-2: identifying related therapeutic targets using network pharmacology and molecular docking analyses. RSC Adv 10:27961–27983. https://doi.org/10.1039/d0ra05126h
57. Mani D, Sekar V, Jingdi C, Baskaralingam V, Esteban FD (2020) South Indian medicinal plants can combat deadly viruses along with COVID-19?—a review. Microb Pathog 148:104277. https://doi.org/10.1016/j.micpath.2020.104277
58. Mani JS, Johnson JB, Steel JC, Broszczak DA, Neilsen PM, Walsh KB, Naiker M (2020) Natural product-derived phytochemicals as potential agents against coronaviruses: a review. Virus Res 284:197989. https://doi.org/10.1016/j.virusres.2020.197989
59. Huizhen C, Ziyan X, Yuxia Z, Qiu C, Chunguang X (2020) Chinese medicine for COVID-19 a protocol for systematic review and meta-analysis. Medicine 99:25. https://doi.org/10.1097/MD.0000000000020660
60. Mohamad HS, Wenli S, Hong S, Qi C (2020) Chinese herbal medicine for SARS and SARS-CoV-2 treatment and prevention, encouraging using herbal medicine for COVID-19 outbreak. Acta Agricult Scand 70:5. https://doi.org/10.1080/09064710.2020.1763448
61. Abidemi JA, Foluso OA, Margaret OS, Olufunsho A, Abimbola S, Omobolanle A, Moshood OA, Ismail OI, Ifeoma O, Olumuyiwa BS, Ibrahim AO, Olayinka TA, Olukemi O (2020) COVID-19 pandemic: a case for phytomedicines. Nat Prod Commun 15(8):1–9. https://doi.org/10.1177/1934578X20945086
62. Prativa P, Angisha B, Aatish M (2020) Quest for COVID-19 cure: integrating traditional herbal medicines in the modern drug paradigm. Appl Sci Technol Ann 1(1):63–71. https://doi.org/10.3126/asta.v1i1.30275
63. Joshi T, Joshi T, Sharma P, Mathpal S, Pundir H, Bhatt V, Chandra S (2020) In silico screening of natural compounds against COVID-19 by targeting Mpro and ACE2 using molecular docking. Eur Rev Med Pharmacol Sci 24:4529–4536
64. Balachandar V, Mahalaxmi I, Kaavya J, Vivekanandhan G, Ajithkumar S, Arul N, Singaravelu G, Senthil KN, Mohana DS (2020) COVID-19: emerging protective measures. Eur Rev Med Pharmacol Sci 24:3422–3425
65. Kabidul A, Md N, Rahat AM, Anamul H, Rownak J, Mohammed R (2020) Some home remedies used for treatment of COVID-19 in Bangladesh. J Med Plants Stud 8(4):27–32
66. Christian EE et al (2020) Potential plants for treatment and management of COVID-19 in Nigeria. Intl J Med Plant Nat Prod 6(3):1–12. https://doi.org/10.20431/2454-7999.0603001
67. Ambrish KS, Abhishek K, Neeraj M (2020) On the inhibition of COVID-19 protease by Indian herbal plants: an in silico investigation. https://arxiv.org/ftp/arxiv/papers/2004/2004.03411.pdf
68. Thuy BTP, My TTA, Hai NTT, Hieu LT, Hoa TT, Thi PLH, Triet NT, Anh TTV, Quy PT, Tat PV (2020) Investigation into SARS-CoV-2 resistance of compounds in garlic essential oil. ACS Omega 5:8312–8320
69. Sydiskis R, Owen D, Lohr J, Rosler K, Blomster R (1991) Inactivation of enveloped viruses by anthraquinones extracted from plants. Antimicrob Agents Chemother 35:2463–2466
70. Ulasli M, Gurses SA, Bayraktar R, Yumrutas O, Oztuzcu S, Igci M, Igci YZ, Cakmak EA, Arslan A (2014) The effects of Nigella sativa (Ns), Anthemis hyalina (Ah) and Citrus sinensis (Cs) extracts on the replication of coronavirus and the expression of TRP genes family. Mol Biol Rep 41:1703–1711

71. Khor PY, Aluwi MFFM, Rullah K, Lam KW (2019) Insights on the synthesis of asymmetric curcumin derivatives and their biological activities. Eur J Med Chem 183:111704
72. Patel A, Rajendran M, Pakala SB, Shah A, Patel H, Karyala P (2020) Virtual screening of curcumin and its analogs against the spike surface glycoprotein of SARS-CoV-2 and SARS-CoV. J Biomol Struct Dyn 5:1–9
73. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr H (2003) Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet 361:2045–2046
74. Bouchentouf S, Missoum N (2020) Identification of compounds from nigella sativa as new potential inhibitors of 2019 novel coronavirus (Covid-19): molecular docking study. RSC Adv 10:27961
75. Islam MN, Hossain KS, Sarker PP, Ferdous J, Hannan MA, Rahman MM, Chu DT, Uddin MJ (2020) Revisiting pharmacological potentials of Nigella sativa seed: a promising option for COVID-19 prevention and cure. Phytother Res
76. Islam MT, Sarkar C, El-Kersh DM, Jamaddar S, Uddin SJ, Shilpi JA, Mubarak MS (2020) Natural products and their derivatives against coronavirus: a review of the non-clinical and pre-clinical data. Phytother Res 34:2471–2492. https://doi.org/10.1002/ptr.6700
77. Erhirhie E, Ekene NE, Ajaghaku D (2014) Guidelines on dosage calculation and stock solution preparation in experimental animals' studies. J Nat Sci Res 4:100–106
78. Najjaa H, Neffati M, Zouari S, Ammar E (2007) Essential oil composition and antibacterial activity of different extracts of Allium roseum L., a north African endemic species. C R Chim 10:820–826
79. Singh VK, Singh DK (2008) Pharmacological effects of garlic (Allium sativum L.). Ann Rev Biomed Sci 10:6–26
80. Josling P (2005) The heart of garlic Nature's aid to healing the human body. HEC Publishing, Chicago
81. Lawson LD (1998) Garlic: a review of its medicinal effects and indicated active compounds. ACS Publications, New York
82. Lau BH, Lam F, Wang-Cheng R (1987) Effect of an odor-modified garlic preparation on blood lipids. Nutr Res 7:139–149
83. Laghari AQ, Memon S, Nelofar A, Laghari AH (2011) Extraction, identification and antioxidative properties of the flavonoid-rich fractions from leaves and flowers of Cassia angustifolia. Am J Anal Chem 2:871
84. Prakashan N (2009) Pharmacognosy. Prakashan, Nirali
85. Ademosun AO, Oboh G (2014) Anticholinesterase and antioxidative properties of water-extractable phytochemicals from some citrus peels. J Basic Clin Physiol Pharmacol 25:199–204
86. Dhiman A, Nanda A, Ahmad S, Narasimhan B (2011) In vitro antimicrobial activity of methanolic leaf extract of Psidium guajava L. J Pharm Bioallied Sci 3:226
87. Carvalho O, Botelho C, Ferreira C, Ferreira H, Santos M, Diaz M, Oliveira T, Soares-Martins J, Almeida M, Júnior AS (2013) In vitro inhibition of canine distemper virus by flavonoids and phenolic acids: implications of structural differences for antiviral design. Res Vet Sci 95:717–724
88. Eigner D, Scholz D (1999) Ferula asa-foetida and Curcuma longa in traditional medical treatment and diet in Nepal. J Ethnopharmacol 67:1–6
89. Araujo C, Leon L (2001) Biological activities of Curcuma longa L. Mem Inst Oswaldo Cruz 96:723–728
90. Ammon HP, Wahl MA (1991) Pharmacology of Curcuma longa. Planta Med 57:1–7
91. Armanini D, Fiore C, Mattarello M, Bielenberg J, Palermo M (2002) History of the endocrine effects of licorice. Exp Clin Endocrinol Diabetes 110:257–261
92. Fiore C, Eisenhut M, Ragazzi E, Zanchin G, Armanini D (2005) A history of the therapeutic use of liquorice in Europe. J Ethnopharmacol 99:317–324

93. Barnes J, Anderson L, Phillipson J (2002) Herbal medicines 2002. Pharmaceutical Press, Royal Pharmaceutical Society, London
94. Blumenthal M, Goldberg A, Brinckmann J (2000) Herbal medicine: Expanded Commission e-monographs. Integrative Medicine Communications, New York
95. Chen F, Chan K, Jiang Y, Kao R, Lu H, Fan K, Cheng V, Tsui W, Hung I, Lee T (2004) In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol 31:69–75
96. Fujii T, Nakamura T, Iwamoto A (2004) Current concepts in SARS treatment. J Infect Chemother 10:1–7
97. Enomoto S, Asano R, Iwahori Y, Narui T, Okada Y, Singab ANB, Okuyama T (2001) Hematological studies on black cumin oil from the seeds of Nigella sativa L. Biol Pharm Bull 24:307–310
98. Forouzanfar F, Bazzaz BSF, Hosseinzadeh H (2014) Black cumin (Nigella sativa) and its constituent (thymoquinone): a review on antimicrobial effects. Iran J Basic Med Sci 17:929
99. Salem ML, Hossain MS (2000) Protective effect of black seed oil from Nigella sativa against murine cytomegalovirus infection. Int J Immunopharmacol 22:729–740
100. Gilani A, Aziz N, Khurram I, Chaudhary K, Iqbal A (2001) Bronchodilator, spasmolytic and calcium antagonist activities of Nigella sativa seeds (Kalonji): a traditional herbal product with multiple medicinal uses. J Pak Med Assoc 51:115
101. Namazi N, Mahdavi R, Alizadeh M, Farajnia S (2015) Oxidative stress responses to Nigella sativa oil concurrent with a low-calorie diet in obese women: a randomized, double-blind controlled clinical trial. Phytother Res 29:1722–1728
102. Wen CC, Kuo YH, Jan JT, Liang PH, Wang SY, Liu HG, Lee CK, Chang ST, Kuo CJ, Lee SS (2007) Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. J Med Chem 50:4087–4095
103. Hoever G, Baltina L, Michaelis M, Kondratenko R, Baltina L, Tolstikov GA, Doerr HW, Cinatl J (2005) Antiviral activity of glycyrrhizic acid derivatives against SARS− coronavirus. J Med Chem 48:1256–1259
104. Chandel V, Raj S, Rathi B, Kumar D (2020) In silico identification of potent COVID-19 main protease inhibitors from FDA approved antiviral compounds and active phytochemicals through molecular docking: a drug repurposing approach. Chem Biol Lett 7:3. https://doi.org/10.20944/preprints202003.0349
105. da Silva Antonio A, Wiedemann LSM, Veiga-Junior VF (2020) Natural products' role against COVID-19. RSC Adv 10:23379
106. Renjith RD, Sankar M (2020) Scope of phytochemicals in the management of COVID-19. Pharm Res 3(1):26–29
107. Alisha K, Tripti S (2020) ChemRxiv. https://doi.org/10.26434/chemrxiv.12320273.v1
108. Chojnacka K, Witek-Krowiak A, Skrzypczak D, .Mikula K, Młynarz P. 2020 Phytochemicals containing biologically active polyphenols as an effective agent against Covid-19-inducing coronavirus. J Funct Foods 73, 104146
109. Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, Lang C, Huang D, Sun Q, Xiong Y, Huang X, Lv J, Luo Y, Shen L, Yang H, Huang G, Yang R (2020) Clinical features and treatment of COVID-19 patients in Northeast Chongqing. J Med Virol 92:797. https://doi.org/10.1002/jmv.25783
110. Ling CQ (2020) Traditional Chinese medicine is a resource for drug discovery against 2019 novel coronavirus (SARS-CoV-2). J Integr Med 18(2):87–88
111. Jo S, Kim S, Shin DH, Kim MS (2020) J Enzyme Inhib Med Chem 35:145–151
112. Lung J, Lin YS, Yang YH, Chou YL, Shu LH, Cheng YC, Liu HT, Wu CY (2020) The potential chemical structure of anti-SARS-CoV-2 RNA-dependent RNA polymerase. J Med Virol 92(6):693–697
113. Nguyen TTH, Woo HJ, Kang HK, Nguyen VD, Kim YM, Kim DW, Kim D (2012) Flavonoid-mediated inhibition of SARS coronavirus 3C-like protease expressed in Pichia pastoris. Biotechnol Lett 34(5):831–838. https://doi.org/10.1007/s10529-011-0845-8

114. Wen CC, Shyur LF, Jan JT, Liang PH, Kuo CJ, Arulselvan P, Yang NS (2011) Traditional Chinese medicine herbal extracts of Cibotium barometz, Gentiana scabra, Dioscorea batatas, Cassia tora, and Taxillus chinensis inhibit SARS-CoV replication. J Tradit Complement Med 1 (1):41–50. https://doi.org/10.1016/S2225-4110(16)30055-4
115. Chiow KH, Phoon MC, Benny TP, Tan KH, Chow VT (2016) Evaluation of antiviral activities of Houttuynia cordata Thunb. Extract, quercetin, quercetrin and cinanserin on murine coronavirus and dengue virus infection. Asian Pac J Trop Med 9(1):1–7
116. Lin L-T, Hsu W-C, Lin C-C (2014) Antiviral natural products and herbal medicines. J Tradit Complement Med 4(1):24–35
117. Pang J, Wang MX, Ang IYH, Tan SHX, Lewis RF, Chen JI-P, Gutierrez RA, Gwee SXW, Chua PEY, Yang Q (2020) Potential rapid diagnostics, vaccine and therapeutics for 2019 novel coronavirus (2019-ncoV): a systematic review. J Clin Med 9(3):623
118. Luo H, Tang Q-l, Shang Y-x, Liang S-b, Yang M, Robinson N, Liu J-p (2020) Can Chinese medicine be used for prevention of corona virus disease 2019 (COVID-19)? A review of historical classics, research evidence and current prevention programs. Chin J Integr Med 26 (4):243–250
119. Idrees M, Khan S, Memon NH, Zhang Z (2020) Effect of the phytochemical agents against the SARS-CoV and selected some of them for application to COVID-19: a mini-review. Curr Pharm Biotechnol. https://doi.org/10.2174/1389201021666200703201458
120. Cheng C, Jia X, Xiao C et al (2019) Paulownia C-geranylated flavonoids: their structure variety, biological activity and application prospects. Phytochem Rev 18:549–570
121. Orhan IE, Senol-Deniz FS (2020) Natural products as potential leads against coronaviruses: could they be encouraging structural models against SARS-CoV-2? Prod Bioprospect 10:171–2020
122. Boukhatem MN, Setzer WN (2020) Aromatic herbs, medicinal plant-derived essential oils, and phytochemical extracts as potential therapies for coronaviruses: future perspectives. Plan Theory 9:800. https://doi.org/10.3390/plants9060800
123. Chowdhury MA, Shuvho MBA, Shahid MA, Haque AKMM, Kashem MA, Lam SS, Ong HC, Uddin MA, Mofijur M (2020) Prospect of biobased antiviral face mask to limit the coronavirus outbreak. Environ Res 192:110294
124. Gautreta P, Lagiera J-C, Parola P et al (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. J Antimicrob Agents 56:105949. https://doi.org/10.1016/j.ijantimicag.2020.105949
125. Leonova GN, Shutikova AL, Lubova VA et al (2020) Inhibitory activity of Scutellaria baicalensis flavonoids against tick-borne encephalitis virus. Bull Exp Biol Med 168:665–668. https://doi.org/10.1007/s10517-020-04776-y
126. Barton C, Kouokam JC, Hurst H, Palmer KE (2016) Pharmacokinetics of the antiviral lectin griffithsin administered by different routes indicates multiple potential uses. Viruses 8 (12):331. https://doi.org/10.3390/v8120331
127. Vogel S, Ohmayer S, Brunner G, Heilmann J (2008) Natural and non-natural prenylated chalcones: synthesis, cytotoxicity and anti-oxidative activity. Bioorg Med Chem 16(8):4286–4293
128. Diniz LRL, Filho CDB, Fielding BC, de Sousa DP (2020) Natural antioxidants: a review of studies on human and animal coronavirus. Oxid Med Cell Longev 2020:3173281. https://doi.org/10.1155/2020/3173281
129. Zomborszki ZP, Csupor NKD, Peschel W (2019) Rhodiosin and herbacetin in Rhodiola rosea preparations: additional markers for quality control? Pharm Biol 57(1):295–305
130. Gan L, Ma J, You G et al (2020) Glucuronidation and its effect on the bioactivity of amentoflavone, a biflavonoid from *Ginkgo biloba* leaves. J Pharm Pharmacol 49:5602
131. Pan LX, Yi R, Zhao X (2018) Polyphenols in Liubao tea can prevent CCl4-induced hepatic damage in mice through its antioxidant capacities. Nutrients 10(9):1280

132. Zahoor M, Shah AB, Naz S, Ullah R, Bari A, Mahmood HM (2020) Isolation of quercetin from Rubus fruticosus, their concentration through NF/RO membranes, and recovery through carbon nanocomposite. A pilot plant study. Biomed Res Int 2020:7
133. Goud NS, Prasad G (2020) Antioxidant, antimicrobial activity and total phenol and flavonoids analysis of Sambucus nigra (elderberry). Int J Curr Pharm Res 12(1):35–37
134. Shen B, Yang Y, Yasamin S, Liang N, Su W, Chen S, Wang X, Wang W (2019) Analysis of the phytochemistry and bioactive of the genes *polygonum* of polygonaceae. Digital Chin Med 1(1):19–36
135. Zahoor I, Shafi A, Fazili KM, Haq E (2019) Bioinformatics and medicinal plant research: current scenario. In: Hakeem K, Shaik N, Banaganapalli B, Elango R (eds) Essentials of bioinformatics. Springer, Cham. https://doi.org/10.1007/978-3-030-19318-8_8
136. Yi F, Li L, Xu L, Meng H, Dong Y, Liu H, Xiao P (2018) In silico approach in reveal traditional medicine plants pharmacological material basis. Chinas Med 13:33. https://doi.org/10.1186/s13020-018-0190-0
137. Fitzgerald M, Heinrich M, Booker A (2020) Medicinal plant analysis: a historical and regional discussion of emergent complex techniques. Front Pharmacol 10:1480. https://doi.org/10.3389/fphar.201.9.01480
138. Harishchander AA (2017) A review on application of bioinformatics in medicinal plants research. Bioinform Proteome Opn Acc J 1(1):000104
139. Babar MM, Zaidi NS, Pothineni VR, Ali Z, Faisai S, Hakeem KR, Gul A (2017) Application of bioinformatics and system biology in medicinal plants studies. In: Plant Bioinformatics. Springer, New York, pp 376–389. https://doi.org/10.1007/978-3-319-67156-7_15.
140. Romano JD, Tatonetti NP (2019) Informatics and computational methods in natural product drug discovery: a review and perspectives. Front Genet 10:368. https://doi.org/10.3389/fgene.2019.00368
141. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, Leipe D, Mcviegh R, O'Neill K, Robbertse B, Sharma S, Soussov V, Sullivan JP, Sun L, Turner S, Karsch-Mizrachi I (2020) NCBI taxonomy: a comprehensive update on curation, resources and tools. Database 2020:baaa062. https://doi.org/10.1093/database/baaa062
142. Kanehisa M (2016) KEGG bioinformatics resource for plant genomic. Methods Mol Biol 1374:55–70
143. Skoczen S, Bussmann RW (2006) ebDB—filling the gap for an international ethnobotany database. Iyonia a J Ecol Appl 11(2):71–81
144. Graham J, Farnsworth NR (2010) The NAPALERT database as an aid for discovery of novel bioactive compounds. In: Comprehensive natural products II. Elsevier, Boston, pp 81–94
145. Huang L, Xie D, Yu Y, Liu H, Shi T, Wen C (2018) TCMID 2.0: a comprehensive resource for TCM. Nuclei Acids Res 46:D1117–D1120. https://doi.org/10.1093/nar/gkx1028
146. Abubakar AR, Haque M (2019) Medicinal plants with reported anxiolytic and sedative activities in Nigeria: a systematic review. J Faculty Pharm Istanbul Univ 49(2):92
147. Yu D, Lu J, Shao W, Ma X, Xie T, Ito H, Wang T, Xu M, Wang H, Meng Y (2019) MepmiRDB: a medicinal plant microRNA database. Database 2019:baz070. https://doi.org/10.1093/database/baz070
148. Fei Y, shaojun X, Yuwei L, Xin Q, Jingiuan Y (2013) Genome wide characterization of microRNA in foxtail millet (setaria italica). BMC Plant Biol 13:212
149. Spannagl M, Noubibou O, Haase D, Yang L, Gundlach H, Hindemitt T, Klee K, Haberer G, Schoof H, Mayer KF (2007) MIPSPlantsDB—plant database resource for integrative and comparative plant genome research. Nucleic Acids Res 35:834–840
150. Shafi A, Zahoor I, Haq E, fazili KM (2019) Impact of bioinformatics on plant science research and crop improvement. Essential Bioinf 3:29–46
151. Dash S, Hemert JV, Horg L, Wise RP, Dickerson JA (2012) PLEXdb: gene expression resources for plants and plant pathogens. Nucleic Acids Res 40:D1194–D1201. https://doi.org/10.1093/nar/gkr938

152. Pathania S, Ramakrishnan SM, Bagler G (2015) Phytochemical: a platform to explore phytochemicals of medicinal plants. Database 2015:bav075. https://doi.org/10.1093/database/bav075
153. Kumar A, Kumar R, Sharma M, Kumar U, Gajula MNV, Singh KP (2018) Uttarakhand medicinal plants database (UMPDB): a platform for exploring genomic, chemical, and traditional knowledge. Data 3:1. https://doi.org/10.3390/data3010007
154. Mohanraj K, Karthikeyan BS, Vivek-Ananth RP, Chand B, Aparna SR, Mangalapandi P, Samal A (2018) IMPPAT: a curated database of Indian medicinal plants, phytochemistry and therapeutics. Sci Rep 8:4329. https://doi.org/10.1038/s41598-22631-z.
155. Gu J, Gui Y, Chen L, Yuan G, Xu X (2013) CVDHD: a cardiovascular disease herbal database for drug discovery and network pharmacology. J Chem 5(1):51
156. Afendi FM, Okada T, Yamazaki M, Hirai-Morita A, Nakamura Y, Nakamura K, Ikeda S, Takahashi H, Altaf-Ui-Amin M, Darusman LK, Saito K, Kanaya S (2012) KNApSAcK family databases: integrate metabolites-plant species databases for multifaceted plant research. Plant Cell Physiol 53(2):1

Promising Plant-Based Bioactive Natural Products in Combating SARS-CoV2 Novel Corona (COVID-19) Virus Infection

22

Shreya Sikdar Mitra, Samapika Nandy, and Abhijit Dey

Abstract

Known as the obligate intracellular parasites, viruses are the minuscular giants that are associated with heterogeneous effects in living organisms. SARS CoV-2 is one such deadly virus wreaking havoc to the entire globe since February, 2020 and forced the whole world to be shut indoors following certain norms. SARS-CoV-2 bears close resemblance with the previous SARS-CoV and MERS CoV but is unique in mode of causing infection, disease causing ability and fatality rate. Natural plant-based products are in use since time immemorial against diverse types of ailments for the several benefits associated with them. There are numerous reports of phytochemicals with anti-viral characters. Researches are being carried out all over the globe to find out phytochemicals with significant mode of action against the virus. The plant-based chemicals primarily try to target the biomolecules associated with the infection and replication of the virus molecule inside the living cells. Docking studies and analyses are being done on such plant-based extracts and molecules that can efficiently inhibit the binding of the virus with the targets. The binding scores of the phytochemicals are found and compared against standard, conventional drug molecules in use. They are analysed further and several molecules from source plants like *Allium sativum*, *Nigella sativa*, *Eucalyptus* sp., *Camellia sinensis*, *Curcuma longa*, grapefruit and phytochemicals like naringenin, saikosaponins, Eucalyptol, essential oils and many more are found to show promising results in the study. This work tries to make an in-depth study and compilation of all the existing reports and literatures on such phytochemicals that can successfully emerge as alternative treatment approach to combat against the deadly SARS CoV-2 virus.

S. S. Mitra · S. Nandy · A. Dey (✉)
Department of Life Sciences, Presidency University, Kolkata, West Bengal, India
e-mail: abhijit.dbs@presiuniv.ac.in

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_22

Keywords

Coronavirus · COVID · Medicinal plants · Natural products · Drug targets

22.1 Introduction

Respiratory illnesses can be fatal and according to history they are substantial pandemic or epidemic triggering disorder. Various forms of respiratory illnesses are reported all over the world and commonly found they are responsible for affecting a part or the whole of the respiratory pathway. The possible cause can be external like bacterial or viral infections or internal like some physiological or anatomical issues that even may lead to the prolonged or deadly respiratory ailments. In recent times one of such respiratory illness triggered by the SARS CoV-2 viral infection has taken huge toll on mankind. The raging pandemic caused by a microscopic giant forced the whole world to stay indoors.

Viruses are the invisible enemies of the living world that are associated with different sorts of diseases amongst various kingdoms. Documentation exists for the different well-known viral pathogens. But the focus of the entire globe has been on a specific virus named as the Coronavirus of late since December 2019 that has almost brought the entire globe to halt ever since its inception. Having close affinities with the group of SARS and MERS virus yet much more deadlier and bearing much more significant impacts as compared to the former two. The first case of this virus though reported from the Wuhan city of China on December 30, 2019 but it spread in rapid pace from China to different other countries like Japan, Korea and gradually covered the whole globe taking a toll on several human lives. On March 13, 2020 it was declared as a global pandemic by World Health Organization (WHO) (https://covid19.who.int/).

As a result the entire globe awaits for the curative measure against the coronavirus disease 19 (COVID-19) disease. The COVID-19 pandemic is an unparalleled and distinctive of its type that has been posing severe threats for the health care system due to the ever increasing number of the daily infected individuals. The earlier SARS and the MERS epidemic seemed miniature in front of the massive spread and immense effects of the COVID-19 pandemic. The lessons learnt and the experiences gathered from the previous two alike epidemic were scanty and as a result demands for superior strategies and stronger approaches in public health and health care facilities for fighting the disease. Various researches and studies are being held all over the world unanimously towards finding the cure against the deadly miniature.

22.2 Coronavirus

Coronaviruses often abbreviated as the CoV, member of the Coronaviridae family are enveloped viruses containing non-segmented, positive-stranded genomic RNA [1], having a size ranging from 80 to 120 nm in diameter [2]. Studies have found that

the envelope proteins are crucial in the aspect of replication of the virus. CoVs are capable of causing a number of diseases comprising of systemic diseases, bronchitis, gastroenteritis, hepatitis and in the worst cases turn fatal in birds, humans, and other animals [3]. The similar type of CoVs were found to be the causative agents of Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV-2).

A novel coronavirus 2019 (nCoV-19) has been recently identified in humans that is responsible for causing millions of death over this whole year of 2020. The word "corona" literally means crown-like and the virus is found to contain a distinctive crown-like morphology mainly caused due to the transmembrane spike glycoproteins (S proteins) that are found to cause a homotrimeric structure that projects out from the viral surface. Different studies focus on the structural homology between the S proteins of SARS-CoV and SARS-CoV-2 and conservation with respect to the ecto domains. Hence regarding the discovery of molecules for the prevention of the disease may rely on the previously used approaches of disrupting the binding of SARS-CoV or MERS to its host cell receptor and other involved proteins in the whole process.

22.2.1 Structure of the SARS CoV-2

The detection of the SARS-CoV-2 genomic sequence helped to recognize the crucial proteins and the enzymes related to the replication process of the virus. The sequences of the key proteins and the enzymes show 79.5% close proximities with that of the SARS-CoV. The main information obtained through the use of genomic sequences mainly points chief proteins associated with the process of viral replication and inoculation.

These important three are mainly as such-spike protein (TMPRSS2), a papain-like protease (ACE2) and the three chymotrypsin-like protease (3CLpro). Among the three molecules two are host-derived, namely the ACE2 and TMPRSS2. The angiotensin-converting enzyme type 2 (ACE2) is just an analogue of the angiotensin converting enzyme type I (ACE) and part of the renin–angiotensin system that takes part in the process of blood pressure regulation. ACE2, an exopeptidase is found to show its expression on the epithelial cells of the respiratory passage and infects the human cells. TMPRSS2 is the spike protein that has interaction with the virus. Basically it is a serine type 2 transmembrane protease related with the process of viral fusion with the infected cell. Hence these three proteins are the focal ones that are responsible for the process of virus entry and infection within the cell. Though the ACE 2 and the spike protein are mainly the host-derived ones, the 3CL Pro is associated with the virus and can be focussed as the key target in the process of drug development against the virus.

22.2.2 Mechanism of Viral Entry and Infection in the Host Cell

The process of the entry of the virus in the host cell and attacking the host cell is primarily dependent on the three key proteins and enzymes. The whole replication process of the virus completes in the cytoplasm. The process is quite similar to the three groups of related viruses SARS-CoV, MERS and SARS CoV-2. The entire process is described below in the figure below.

22.3 Treatment Approaches Against the Disease

All across the globe different nations are putting their best efforts to develop curative measure against the deadly disease. Efforts are put globally for the development of vaccines, immunotherapeutics, drugs and all other possible anti-viral strategies against the COVID-19 disease. But yet as of now neither directly functioning anti-viral drugs nor vaccines are within the reach for treatment of coronavirus infections. But continual efforts are put by the researchers call across the world in the breakthrough discovery of the vaccine against this virus and the whole world is awaiting for it. But several limitations such as cross protection provided by the vaccines due to vast diversity of sequences of the virus, easy mutability of the virus, etc. are coming to the successful discovery of the vaccine. While some western, traditional or home remedies may provide comfort and alleviate symptoms of mild COVID-19, there are no medicines that have been shown to prevent or cure the disease. WHO does not recommend self-medication with any medicines, including antibiotics, as a prevention or cure for COVID-19. However, there are several ongoing clinical trials of both western and traditional medicines. WHO is coordinating efforts to develop vaccines and medicines to prevent and treat COVID-19 and will continue to provide updated information as soon as research results become available.

22.3.1 Conventional Medications for Treatment

The traditional and established medicines are coming in the light as cure against the current viral threat especially to contribute during the critical care stage. Though the present prophylactic measures are not enough but yet mainly relies on the different suggested opinions. Some protease inhibitors such as Lopinavir/ritonavir, Ribavirin, Chloroquine, Hydroxychloroquine are being used as treatments for the disease. The reputed anti-malarial drugs hydroxychloroquine and chloroquine [4] are also being used as treatment options in many nations as there are proof of the drugs in inhibiting the process of terminal phosphorylation of ACE 2. Both the drugs Chloroquine and hydroxychloroquine are the artificially obtained chemicals from the bark of *Cinchona* plant of Rubiaceae family [5]. But though being used as the anti-viral molecule both of the chemicals are related to different harmful effects primarily on the cardiovascular system. Another drug being used commonly that is an efficient RNA polymerase inhibitor is the Remdesivir. But the safety and efficacy of majority

of the drugs are under trial and are being tested [6]. It has success related to SARS CoV-1 and MERS CoV cases.

Although these drug molecules are being used they are not a permanent and highly efficient cure and overuse of the drugs to control the pandemic scenario and yield opposite results and turn out to be a major concern for public health.

These different types of drug molecules that are in use are not the permanent and very efficient cure measures and overuse of the drugs has its own set of demerits that in this pandemic scenario can result in opposite and negative outcome that can be a vital concern for public health.

22.4 Anti-COVID-19 Natural Remedies

Development of vaccine is probably the only cure for this disease but it is extremely complex and time-taking procedure starting from the discovery up to the market availability. But alongside there are various known natural molecules that have been identified through the application of molecular docking studies as the ligand molecules against the different important protein molecules associated with the disease.

Finding out some natural remedy against this disease is way faster than the development of the vaccine against this deadly virus. But the huge complexities and variations of the natural compounds, their structural and chemical complexities and the exact methods of extraction of the molecules are making the task arduous. Screening of the natural compounds by the help of virtual tools is definitely a handy tool in this area of research and can definitely reduce the time required for the screening process from natural sources directly. This approach mainly relies on the in-silico analysis through molecular docking technique. Using this method several classes of phytochemicals have shown remarkable results that can serve as the natural remedies in COVID treatment. Some of the molecules were found to show identical docking score to the traditional drugs that are being used for the treatment purpose. Classes of molecules such as flavonoids, flavones, alkaloids, quinones, fatty acids, terpenes and steroids are few of them to give promising results in the docking studies.

22.4.1 ACE2 Inhibitors

This is the most studied protein of the CoV associated with the drug discovery programme as well as the one identified by docking studies for the inhibitory activity of phytochemicals. Till date it is considered as the most vital protein and hence has drawn significant importance from the scientific communities to study its mode of action and interaction with different classes of molecules that can ultimately serve to develop treatment strategies against this disease. As per studies there are about 300 plant species that have been reported to possess anti-ACE2 activities. Some of them are known medicinal plant species while other are widely used as food spices.

Few of the listed plants are *Curcuma longa*, pepper (Capsicum spp.), black nightshade (*Solanum nigrum* L.), cinnamon (*Cinnamomum zeylanicum Blume* or *Cinnamomum verum* J. Presl.), olive (*Olea europaea* L.), grapes (*Vitis vinifera* L.), passion fruit (*Passiflora edulis*), *Phaseolus vulgaris*, etc. [7–9]. Mainly the phytochemicals found in this plant species are members of classes of molecules such as alkaloids, flavonoids, terpenes, tannins, xanthones, phenolic compounds and peptides [9].

22.4.2 3CLpro Inhibitors

This is the chief protease involved in the process of replication of the SARS-CoV2 that has received significant attention along with the ACE2 receptor. This is the main virus associated protein that can be used to block the process of viral spread inside the infected cell. Although this is a viral specific protein yet the one of the SARS CoV2 has much structural affinities with that of the SARS CoV1. Khaerunnisa et al. [10] with the help of docking studies showed notable results of inhibiting capacity against the protein by natural molecules such as the naringenin, quercetin, apigenin, luteolin-7-glucoside, kaempferol, curcumin, demethoxycurcumin, catechin, epigallocatechin, etc. These phytochemicals have wide-spread distribution in plant families such as the Leguminosae, Lamiaceae, Apiaceae, Lauraceae, etc. Essential oils are also found to work against this SARS-CoV-2 main protease. da Silva et al. [11] pointed at various flavonoids, volatile terpenoids like linalool, geraniol, etc. which are very easily obtained from aromatic and medicinal plant sources such as basil (*Ocimum basilicum*), lemon balm (*Melissa officinalis*), lavender (*Lavandula angustifolia*), lemongrass (*Cymbopogon citratus*), geranium (*Pelargonium graveolens*), cinnamon (*Cinnamomum zeylanicum*), mandarin (*Citrus reshni*), chamomile (*Matricaria recutita*), copaiba (*Copaifera* sp.) and ginger (*Zingiber officinale*).

22.4.3 TMPRSS2 Inhibitors

Although there are fewer information related to plant compounds activities in relation to inhibition of this replication protein yet there are some evidences and positive results in relation to this too. This protein has been found to have association with diseases such as cancer, spread of disease like influenza and SARS-CoV1. Some of the plants showing activity against this protein are as follows: *Scutellaria* sp., *Oroxylum indicum* [12]. Rahman et al. [12] proposed around 12 metabolites having binding energy with the protein. Geniposide, an iridoid metabolite obtained from the genus *Gardenia* of Rubiaceae family is found to have large amount of inhibition activity. The 12 metabolites listed are found from different natural sources such as marine algae *Sargassum*, *Paxillus* genera of mushrooms, green tea (*Camellia sinensis*), etc.

22.5 Effects of Some Plant-Based Secondary Metabolites on the Virus

22.5.1 Alkaloids

Alkaloids are a diverse group of plant-derived secondary metabolites. These are primarily organic compounds with at least one or more nitrogen atom in their heterocyclic structure. This class of compounds expresses no homogeneity be it in its physical, chemical, biochemical, or physiological characters. No general definitions are enough to define them except that these are the nitrogen containing compounds. Though not very common among the lower plant classes these group of chemicals are abundant in different angiosperm families. This class of nitrogen containing molecules possesses manifold medicinal properties.

Chloroquine and hydroxychloroquine the two widely used and potent drugs serving as the therapeutic measure for this disease are also alkaloids. A variety of alkaloids have been reported to contain anti-viral activities. Williamson and Kerimi [13] listed some of the potent anti-viral alkaloids. Some of the alkaloids noted by them are isoquinoline alkaloids cepharanthine tetrandrine and fangchinoline, palmatine, berberine, coptisine, etc. These molecules mainly function as the DNA intercalators and found to retard the viral functions.

22.5.2 Polyphenols

Phenols are ubiquitously found in the plants and in-fact consist of the largest group of plant secondary metabolite. Polyphenols are the molecules containing more than one phenolic ring in its chemical structure. These chemicals are often related with the taste, odour and flavour of different plants. There are various phenols that are often valued for their pharmacological activities. In respect to SARS CoV2 infection too phenols mainly the polyphenolic compounds are found to possess some significant roles.

A study by Adem et al. [14] showed better efficiency as well as binding scores with Mpro of COVID-19 of flavonoids like rutin and hesperidin than the commonly used traditional drug Nelfinavir. The use of molecular docking binding scores found that on the basis of the affinity scores the potent flavonoids could be ranked as follows hesperidin >rutin>diosmin>apiin>diacetylcurcumin. Various molecules showing significant binding scores are the constituents of daily dietary foods that suggest the compounds to be biologically safe and support its potential to be applied as therapeutic measures against COVID-19. However, more studies have to be carried out for the final authentication of these molecules for the drug discovery process.

22.5.3 Essential Oils

There are varied types of essential oils found to contain medicinal properties that also include anti-viral properties. Primarily molecules such as monoterpenes, phenylpropanoids, sesquiterpenes, etc. are found in the essential oils. Different reports found that point at the anti-viral nature of the essential oils. Some of the noted plants in this respect are lemon grass, thyme, peppermint, *Citrus* sp., tea tree, ginger, eucalyptus and many such aromatic herbs. Sharma and Kaur [15] using the aid of docking studies showed that the phytochemical eucalyptol from the essential oil of eucalyptus plant displayed potent inhibitory action on the coronavirus by blocking the activity of the viral protease Mpro.

22.5.4 Saikosaponin

Saponins are the chemical compounds found to contain polycyclic aglycone moiety with either a steroid or a triterpenoid molecule attached with a carbohydrate unit. This group of molecule is often found from various medicinal plants as the secondary metabolite molecule and is associated with varied biological activities like anti-inflammation, immunomodulation, anti-bacterial, antihepatitis, antinephritis and antihepatoma activities.

Saikosaponins are a group of oleanane derivatives usually found as the glucoside molecule. The study by Cheng et al. [16] focussed on the anti-coronaviral activity of four saikosaponins (A, B_2, C and D). The study pointed that out of the four saikosaponin B2 has highly effective function and its mode of action can stop the early stages of replication of the virus.

22.6 Some of the Plants Showing Notable Action Against the SARS CoV 2 Infection

22.6.1 Garlic (*Allium sativum* L.)

A herb having cosmopolitan distribution, a close relative of onion, shallot, etc. and a member of the Amaryllidaceae family. A common food spice and having various medicinal utilities often used in heart and blood system related ailments. The high amount of organosulphur compounds mainly in the essential oils found in the garlic are anticipated to show powerful interactions with the amino acids of the ACE2 protein. A study conducted by Thuy et al. [17] aimed to prove this along with establishing the inhibition capacity of ligands present in the essential oil of garlic not only to the ACE2 protein but also directly to the main protease of SARS-CoV-2 PDB6LU7 protein.

GC-MS analysis of the garlic essential oil led to the identification of eighteen active substances, including 17 organosulphur compounds. This study at a first attempt used the technique of molecular docking to find out the retarding effects

of the isolated compounds on the host receptor angiotensin-converting enzyme 2 (ACE2) protein in the human body that is one of the primary molecules in developing resistance against the coronavirus. The results hinted at strong interaction of the 17 organosulphur compounds (found in 99.4% contents of the garlic essential oil) with the amino acids of the ACE2 protein and the main protease PDB6LU7 of SARS-CoV-2. The compounds allyl disulphide and allyl trisulphide that are found in the greatest amount in the garlic essential oil exhibit the most powerful anti-coronavirus activity. Docking studies were mainly used for the purpose of the study. This result indicated on anti-viral activities of the essential oils in garlic that can be undoubtedly a valuable natural source in stopping the invasion of the virus in the body as it is a very common food spice ingredient in the Asian households,

22.6.2 *Torreya nucifera* (L.) Siebold and Zucc.

A member of the Taxaceae family mainly found in the snowy areas of Jeju Island in Korea near the sea coasts has a long history of being employed in traditional Asian medicine for its therapeutic role against different conditions such as the stomach ache, haemorrhoids and rheumatoid arthritis. The plant has been reported as a rich source of diverse phytochemicals like flavonoids, terpenoids, bioflavonoids etc. with very promising medicinal values. A study done by Ryu et al. [18] selected this plant as the starting material by virtue of its observed 3CLpro inhibition (62% at 100 lg/mL). The secondary metabolites like quercetin, luteolin and apigenin showed inhibition of 3CLpro activities. Values of binding energy obtained in a molecular docking study compiled the results of enzymatic assays. An apigenin moiety at position C-30 of flavones, as biflavone had an effect on was believed to be responsible for the potential 3CLpro inhibitory activity.

22.6.3 *Houttuynia cordata* R. Br.

It is an annual herb mainly endemic to mountainous areas of eastern Asia and a member of the Saururaceae family. Sometimes it is found as a creeping rhizome spreading over large areas. This herb is reported to own anti-viral properties in vitro against various medically significant viruses like the human immunodeficiency virus-1, herpes simplex virus-1 (HSV-1) and influenza virus. Steam distillate obtained from the plant is remarkably found to immobilize enveloped viruses but not against the non-enveloped viruses. A study undertaken by Chiow et al. [19] attempted at evaluating the in vitro functionalities of the ethyl acetate (EA) fractions of the plant.

The EA fraction of *H. cordata* inhibited viral infectivity up to 6 days. Cinanserin hydrochloride was able to inhibit MHV for only 2 days. The 50% inhibitory concentrations (IC50) of the EA fraction of *H. cordata* added before the viral adsorption stage were 0.98 mg/mL for MHV and 7.50 mg/mL for DENV-2 with

absence of cytotoxicity. The mice fed with the EA fraction up to 2000 mg/kg did not induce any signs of acute toxicity, with normal histological features of major organs. Certain flavonoids exhibited comparatively weaker anti-viral activity, notably quercetin which could inhibit both MHV and DENV-2. This was followed by quercitrin which could inhibit DENV-2 but not MHV, whereas rutin did not exert any inhibitory effect on either virus. When quercetin was combined with quercitrin, enhancement of anti-DENV-2 activity and reduced cytotoxicity were observed.

22.6.4 *Nigella sativa* L.

Commonly known as the black seed or the black cumin or the black caraway or kalonji, this herb is mostly used as spice and also has different medicinal values like anti-viral, anti-cancer, anti-inflammatory and analgesic properties. This annual plant is a member of the Ranunculaceae family, and highly famed as the healing herb in the North African society as well as in Islamic and Christian traditions. The plant has been reported to store different phytochemicals like nigellicine, nigellidine, nigellimine, carvacrol, thymol, thymoquinone, dithymoquinone, α-Hederin, thymohydroquinone etc.

A study performed by Bouchentouf and Missoum [20] using docking analysis pointed at better scores of the compound Nigellidine than the conventional drug Hydroxychloroquine and very close score to that of chloroquine. Alpha-hederin also showed promising results. Hence the main phytochemicals in the herb have potential anti-COVID-19 activities by showing its action on the main protease (Mpro). Obtained results indicated that these molecules present in *Nigella* sp. can show better performance than the drugs under clinical tests.

22.6.5 *Euphorbia neriifolia* L.

A spiny herb is a member of the Euphorbiaceae family and is native of South Asian countries such as India, Sri Lanka and Taiwan [21]. In conventional medicine this plant is reported for its uses as aphrodisiac and diuretic. Euphorbiaceae plant family is a noted one for being the rich source of triterpenoids. Chang et al. [22] conducted a study using the ethanolic leaf extract from the plant *E. neriifolia*. They isolated about 23 compounds out of which there were 22 triterpenoid molecules one flavonoid glycoside. They attempted to test the anti-human coronavirus (HCoV) activity of the isolated triterpenoids molecules. The study demonstrated the structure–activity relationship (SAR) of the various isolates. One of the molecule 3β-Friedelanol was found to show greater potency as the anti-viral agent than the positive control, actinomycin D, which pointed on the further usage of the friedelane skeleton as a potent molecule in the development of the new anti-HCoV drugs.

22.6.6 *Artemisia annua* L.

A native member of the Asteraceae family, the plant is commonly known as the sweet sagewort, sweet wormwood, annual wormwood, etc. It is an annual plant, normally growing in short day length conditions. Common in the cooler climates this plant is often associated with several medicinal properties. This plant is rich source of the sesquiterpene lactone artemisinin. This molecule has been widely used as anti-malarial natural product and several notable studies are there for commercial drug forms too. Other uses like anti-oxidant and anti-viral properties were also reported. A study by Haq et al. [23] focusses on the possible uses of the plant and the compound against SARS-CoV2 as there are different reports of its anti-viral actions against several other viruses.

22.6.7 *Tribulus terrestris* L.

A member of the Zygophyllaceae family is distributed mainly through the warmer regions of India and the southern part of China. It is a rich source of the secondary metabolite saponin. The fruits of *T. terrestris* have varied applications in numerous pharmaceutical formulations as well as different dietary supplements. In a study conducted by Song et al. [24] it was found that the methanolic extract from the fruits of *T. terrestris* fruits showed substantial retardation of the papain-like protease (PLpro) that function as a crucial proteolytic enzyme against wide array of pathogenic virus and bacteria. Successive bioactivity guided fractionation technique resulted in the isolation of six cinnamic amide molecules and one ferulic acid molecule. Efficacy of the compounds against severe acute respiratory syndrome coronavirus (SARS-CoV) was evaluated through measuring the PLpro inhibitory activity to identify the potency and also study the kinetic behaviours.

All the six cinnamic amide compounds exhibited notable inhibitory activity with significant IC50 values in the range 15.8–70.1 μM. The last cinnamic amide displayed maximum inhibitory activity. HPLC chromatogram and liquid chromatography technique confirmed the presence of large amount of these functional PLpro inhibitors in the native fruits.

22.6.8 *Camellia sinensis* (L) Kuntze

A member of the family Theaceae commonly called the tea plant or the tea shrub. This plant is rich source of various types of phytochemicals. Several health benefits have been tagged with regular consumption of any kind of tea. The main secondary metabolite produced is caffeine. Various kinds of polyphenols are found in the plant such as epigallocatechin gallate that function as the anti-oxidants and have several aids for human health. Catechin is a well-known group of polyphenol possessing numerous health advantages such as being anti-oxidant, anti-inflammatory, anti-bacterial, and anti-viral and are abundant in the green tea. A study by Roh et al. [25]

pointed at the anti-viral property of the tea-plant and prospective of being used as anti-SARS-CoV agent. The group found out the novel inhibitory activity of catechin gallate and gallocatechin gallate as anti-SARS molecules.

22.6.9 *Isatis indigotica* Fortune

Preventive effects of the phenolic extracts from different plant parts of the different Chinese herbs were noted during the outbreak of SARS in China, Hong Kong and Taiwan. A member of the Brassicaceae family and a native plant of the China, the roots of *I. indigotica* root (*Radix isatidis*), are found to possess different anti-viral properties. *I. indigotica* root was found effective against influenza, hepatitis A and Japanese encephalitis [26, 27]. *I. indigotica* root contains indigo, indirubin, indican (indoxyl-d-glucoside), sitosterol, sinigrin, etc. [28]. Indigo and indirubin were identified as the primary chymotrypsin inhibitors.

In another study performed by Lin et al. [29], root extracts from the plant *I. indigotica* were used and anti-SARS-CoV effect of the extract containing five major compounds from the plant roots and seven phenolic molecules were tested using cell-free and cell-based cleavage assays for 3CLpro effects. Cleavage assays with the 3CLpro gave positive results with IC50 values were in micromolar ranges.

22.6.10 *Curcuma longa L.*

It is a member of the Zingiberaceae family and commonly called turmeric; mainly an underground, rhizomatous plant. Since long this plant is famous for its uses as spice and integral component of the traditional medicines. This plant is rich source of bioactive phytochemical curcumin mainly responsible for its medicinal properties. A study by Rocha and de Assis [30] highlighted the use of curcumin through the ACE2 receptor inhibition and hence it is effective in the treatment of the COVID-19 disease.

22.6.11 Grapefruit

This is a citrus hybrid and a sub-tropical fruit, also nicknamed as the forbidden fruit. The grapefruit has been documented to contain variety of phytochemicals. Naringenin, a primary flavonoid is found in abundance in the grapefruit. Flavonoids already have reports of having different biological properties against various group of viruses. Naringenin is also an effective anti-viral compound which is also reported for anti-oxidant and anti-inflammatory properties. In a study by Tutunchi et al. [31] various mechanisms of naringenin action were highlighted as potentially applicable against SARS CoV-2 agent.

22.6.12 *Glycyrrhiza glabra* L.

This plant is called liquorice or licorice and this is a member of the Fabaceae family. Liquorice extracts contain glycyrrhizin and glycyrrhizinic acid which are triterpenoid saponin and often used as alternative herbal medicine against conditions like high blood pressure, low blood potassium levels and muscle weakness. Glycyrrhizin is also reported to possess anti-viral properties. Complying with this a study by Luo et al. [32] reported the potential of this molecule as anti-SARS CoV-2 agent by inhibiting the process of viral attachment and viral entry. This phytochemical has been documented to possess the capacity of inducting the production of endogenous interferons that function as the anti-viral compounds and are often associated with the cure of different types of viral diseases.

22.6.13 *Berberis vulgaris* L.

Known as the common barberry, this shrub is a native to the Europe and West Asia. It is the representative member of the family Berberidaceae and this deciduous shrub is a rich source of Vitamin C. This shrub has various uses as culinary item in making of jams and few other native dishes. The quaternary ammonium salt berberine present in the plant can act as anti-diabetic agent; it lowers blood cholesterol and other harmful lipids, reduces blood pressure conditions. A report by Narkhede et al. [33] pointed out the anti-viral activity of this compound and its potential to be used as a natural remedy against COVID-19.

22.6.14 *Zingiber officinale* L.

Common to the globe as the ginger, this flowering plant of the family Zingiberaceae possesses underground stems called the rhizomes that have been for long used as the spice and integral component of the herbal medicine as well. It is a rich store of different types of chemicals such as essential oils, fibres, fatty acids, carbohydrates, proteins, vitamins like B6 and different dietary minerals. Volatile oils such as the zingerone, gingerols, shogaols, etc. are the main active constituents of the plant and are responsible for the aroma of the plant. These phytochemicals have lot of health benefits too. Khaerunnisa et al. [10] mentioned the use of ginger for its essential oils along with other known medicinal herbs as potent inhibitor of the main protease of the SARS CoV-2 virus by the use of docking analysis studies.

22.6.15 *Allium cepa* L.

Common as the onion, a member of the family Amaryllidaceae, this is another widely used food bulb. The underground stem called the bulb has lot of store of various phytochemicals like various types of polyphenols and flavonoids. Fitriani

et al. [34] in their study using molecular docking techniques showed the highest binding energy of the pentacyclic triterpenoid oleanolic acid found in the onions with the SARS-CoV 2 Main protease (Mpro) via hydrogen bonding. Though further works need to be done but this study undoubtedly provides evidence for onion based phytochemicals to be a successful candidate for COVID-19 treatment.

22.6.16 *Psidium guajava* L.

Commonly it called guava and a member of the family Myrtaceae. Widely grown in the tropical and the sub-tropical areas it is an evergreen shrub or tree. The leaves of the plants are rich in different types of flavonoids like morin, quercetin, etc. Often used as traditional medicine, this uses against diabetes, inflammation, hypertension, lung diseases, rheumatic disorders, pain relief, lung ailments, diarrhoea, fever, wounds, ulcer, anti-microbial agent, etc. Fitriani et al. [34] reported that the molecular docking study pointed at the efficacy of one of the phytochemicals present in the fruit, asiatic acid could act as a potent inhibitor of the SARS CoV2 virus.

22.6.17 *Lycoris radiata* Miq.

It is a common bulbous and perennial herb of the family Amaryllidaceae and a native of the country China. This is often called as the red spider lily, hell flower, red magic lily, etc. as it is the source of the reddish alkaloid liquorice. Suryanarayana and Banavath [35] in their study pointed at various plants and their anti-viral functions among which this plant was one. Reports indicated that the phytochemicals isolated from this plant may act as potential anti-viral agents. The plant extracts obtained from this plant have efficacy against the recent virus and can be used as herbal remedies in the future.

22.6.18 *Mentha longifolia* (L.) Huds

It is one of the medicinally important herbs native to Europe that belongs to the family Lamiaceae. *Mentha* sp. is a rich source of various essential oils like menthol, pulegone, etc. and generally used against stomach and throat problems. Khaerunnisa et al. [10] in his study along with various other phytochemicals pointed at the chemical luteolin-7, an essential oil obtained from this plant that showed 3CL pro-inhibition against the SARS CoV2 virus with the help of molecular docking studies.

22.6.19 *Capsicum annuum* L.

A member of the nightshade Solanaceae family, this is used all across the globe for culinary purposes. This plant reportedly has various health benefits. Khaerunnisa et al. [10] pointed at this plant being a potent one for the inhibition of the main protease of the virus due to the presence of the chemical glucosides.

22.6.20 *Hypericum perforatum* L.

Also known as St John's wort this is the flowering plant of the family Hypericaceae used extensively in traditional Chinese medicine as a common treatment against mild to moderate depression and other symptoms that are related to anxiety or insomnia. Yang et al. [36] in their study highlighted on the use of this plant as potent anti-SARS CoV2 agent used widely in the Chinese medicine.

22.6.21 *Eucalyptus* sp.

The plant is commonly known as the gums or eucalypts, a member of the family Myrtaceae. It contains lots of essential oils like eucalyptol which is a high value organic oil (monoterpenoid). Different other volatile compounds like 1,8-cineol, 1,8-cineole, cajeputol, 1,8-epoxy-*p*-menthane, 1,8-oxido-*p*-menthane, eucalyptol, eucalyptol, cineol and cineole were also studied along with this compound. Eucalyptol has multiple uses as fragrances, flavouring agents, insect repellents along with other therapeutic applications. Sharma and Kaur [15], have pointed out in their study the efficacy of eucalyptol as a potent treatment against COVID-19 as it could inhibit the Mpro protein associated with the virus. Molecular docking studies have showed the inhibitory action of the eucalyptol against the main protease associated with the virus.

22.7 Conclusion

The unprecedented impact of one microorganism has crippled the normal pace of life all over the world. The spread of highly infectious and potentially fatal respiratory illness has taken gruesome number of human lives directly and indirectly. All over the world, the collapse of health care system and the pandemic induced gigantic economic loss has critically damaged the well-being of the human race. The search for widely applicable functional vaccine is "heat of this hour" and throughout the globe the researches are going in tremendous speed. However, the rapid mutation in viral genome, climatic condition, region, diet, ethnicity, age and gender wise variability of infection, drug application based complexities, unrealistic pressure on time-bound clinical trials have worsened the whole situation. In general, the researchers are concerned about key enzymes and the protein molecules associated

with the infection mechanism of virus. Like other respiratory illnesses, inhibition of proteins that bind with the cell receptors or prevention of viral DNA replication could be the possible 'cure' and controlled release of non-volatile viral antigens to human body to sensitize natural immune system against COVID-19 may be the most appropriate 'modus operandi' of any future vaccine. Apart from conventional anti-viral drugs, extensive screening is going for both chemically synthesized pharmaceuticals and natural products. Plant-derived natural molecules have played important role against a number of infectious diseases and recently molecular docking studies have revealed potential of large number of phytochemicals against COVID-19. However, availability of certain compounds, their active formulation, mode of application, dosage, toxicity assessment, broad spectrum tolerance, efficacy all are important parameters. Primary screening or in silico assessment can only reveal the potency of particular compound but for clinical trials multi-faceted research is extremely important. At present such researches are going all over the world but the status is still primitive and development of any therapeutic strategy requires extreme precision and significant output so till date many natural products were screened and documented but none has been successfully completed the trial phase. However, the emergence of novel techniques has facilitated the natural product based research and paved a promising avenue for complementary and alternative medicine against COVID-19.

References

1. Li F (2016) Structure, function, and evolution of coronavirus spike proteins. Annu Rev Virol 3:237–261
2. Neuman BW, Kiss G, Kunding AH, Bhella D, Baksh MF, Connelly S, Siddell SG (2011) A structural analysis of M protein in coronavirus assembly and morphology. J Struct Biol 174 (1):11–22
3. Chafekar A, Fielding BC (2018) MERS-CoV: understanding the latest human coronavirus threat. Viruses 10(2):93
4. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, Dupont HT (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 56:105949
5. Thanacoody R (2016) Quinine and chloroquine. Medicine 44(3):197–198
6. Lens S, Miquel M, Mateos-Muñoz B, García-Samaniego J, Forns X (2020) SARS-CoV2 in patients on antiviral HBV and HCV therapy in Spain. J Hepatol 73(5):1262–1263
7. Barbosa-Filho JM, Martins VK, Rabelo LA, Moura MD, Silva MS, Cunha EV et al (2006) Natural products inhibitors of the angiotensin converting enzyme (ACE): a review between 1980-2000. Rev Bras 16(3):421–446
8. Joshi T, Joshi T, Sharma P, Mathpal S, Pundir H, Bhatt V, Chandra S (2020) In silico screening of natural compounds against COVID-19 by targeting Mpro and ACE2 using molecular docking. Eur Rev Med Pharmacol Sci 24:4529–4536
9. Patten GS, Abeywardena MY, Bennett LE (2016) Inhibition of angiotensin converting enzyme, angiotensin II receptor blocking, and blood pressure lowering bioactivity across plant families. Crit Rev Food Sci Nutr 56(2):181–214
10. Khaerunnisa S, Kurniawan H, Awaluddin R, Suhartati S, Soetjipto S (2020) Potential inhibitor of COVID-19 main protease (Mpro) from several medicinal plant compounds by molecular docking study. Scientifica 2020:6307457

11. da Silva JKR, Figueiredo PLB, Byler KG, Setzer WN (2020) Essential oils as antiviral agents, potential of essential oils to treat SARS-CoV-2 infection: an in-silico investigation. Int J Mol Sci 21(10):3426
12. Rahman N, Basharat Z, Yousuf M, Castaldo G, Rastrelli L, Khan H (2020) Virtual screening of natural products against type II transmembrane serine protease (TMPRSS2), the priming agent of coronavirus 2 (SARS-CoV-2). Molecules 25(10):2271
13. Williamson G, Kerimi A (2020) Testing of natural products in clinical trials targeting the SARS-CoV-2 (Covid-19) viral spike protein-angiotensin converting enzyme-2 (ACE2) interaction. Biochem Pharmacol 2020:114123
14. Adem S, Eyupoglu V, Sarfraz I, Rasul A, Ali M (2020) Identification of potent COVID-19 main protease (Mpro) inhibitors from natural polyphenols: An in silico strategy unveils a hope against CORONA
15. Sharma AD, Kaur I (2020) Jensenone from eucalyptus essential oil as a potential inhibitor of COVID 19 corona virus infection. Res Rev Biotechnol Biosci 7(1):59–66
16. Cheng PW, Ng LT, Chiang LC, Lin CC (2006) Antiviral effects of saikosaponins on human coronavirus 229E in vitro. Clin Exp Pharmacol Physiol 33(7):612–616
17. Thuy BTP, My TTA, Hai NTT, Hieu LT, Hoa TT, Thi Phuong Loan H et al (2020) Investigation into SARS-CoV-2 resistance of compounds in garlic essential oil. ACS Omega 5 (14):8312–8320
18. Ryu YB, Jeong HJ, Kim JH, Kim YM, Park JY, Kim D, Rho MC (2010) Biflavonoids from Torreyanucifera displaying SARS-CoV 3CLpro inhibition. Bioorg Med Chem 18(22):7940–7947
19. Chiow KH, Phoon MC, Putti T, Tan BK, Chow VT (2016) Evaluation of antiviral activities of Houttuynia cordataThunb. extract, quercetin, quercetrin and cinanserin on murine coronavirus and dengue virus infection. Asian Pac J Trop Med 9(1):1–7
20. Bouchentouf S, Missoum N (2020) Identification of Compounds from Nigella Sativa as New Potential Inhibitors of 2019 Novel Coronavirus (Covid-19): Molecular Docking Study
21. Bigoniya P, Rana AC (2009) Subacute effect of Euphorbia neriifolia Linn. on hematological, biochemical and antioxidant enzyme parameters of rat. Acad J Plant Sci 2(4):252–259
22. Chang FR, Yen CT, Ei-Shazly M, Lin WH, Yen MH, Lin KH, Wu YC (2012) Anti-human coronavirus (anti-HCoV) triterpenoids from the leaves of Euphorbia neriifolia. Nat Prod Commun 7(11):1934578X1200701103
23. Haq FU, Roman M, Ahmad K, Rahman SU, Shah SMA, Suleman N, Ullah S, Ahmad I, Ullah W (2020) Artemisia annua: trials are needed for COVID-19. Phytother Res 34(10):2423–2424
24. Song YH, Kim DW, Curtis-Long MJ, Yuk HJ, Wang Y, Zhuang N, Park KH (2014) Papain-like protease (PLpro) inhibitory effects of cinnamic amides from Tribulusterrestris fruits. Biol Pharm Bull 37(6):1021–1028
25. Roh C (2012) A facile inhibitor screening of SARS coronavirus N protein using nanoparticle-based RNA oligonucleotide. Int J Nanomed 7:2173
26. Qin GW, Xu RS (1998) Recent advances on bioactive natural products from Chinese medicinal plants. Med Res Rev 18(6):375–382
27. Wu X, Qin G, Cheung KK, Cheng KF (1997) New alkaloids from *Isatis indigotica*. Tetrahedron 53(39):13323–13328
28. Gilbert KG, Maule HG, Rudolph B, Lewis M, Vandenburg H, Sales E, Tozzi S, Cooke DT (2004) Quantitative analysis of indigo and indigo precursors in leaves of *Isatis* spp. and *Polygonum tinctorium*. Biotechnol Prog 20(4):1289–1292
29. Lin CW, Tsai FJ, Tsai CH, Lai CC, Wan L, Ho TY, Chao PDL (2005) Anti-SARS coronavirus 3C-like protease effects of Isatisindigotica root and plant-derived phenolic compounds. Antivir Res 68(1):36–42
30. Rocha FAC, de Assis MR (2020) Curcumin as a potential treatment for COVID-19. Phytother Res. https://doi.org/10.1002/ptr.6745

31. Tutunchi H, Naeini F, Ostadrahimi A, Hosseinzadeh-Attar MJ (2020) Naringenin, a flavanone with antiviral and anti-inflammatory effects: a promising treatment strategy against COVID-19. Phytother Res. https://doi.org/10.1002/ptr.6781
32. Luo P, Liu D, Li J (2020) Pharmacological perspective: glycyrrhizin may be an efficacious therapeutic agent for COVID-19. Int J Antimicrob Agents 55(6):105995
33. Narkhede RR, Pise AV, Cheke RS, Shinde SD (2020) Recognition of natural products as potential inhibitors of COVID-19 main protease (Mpro): insilico evidences. Nat Prod Bioprospect:1–10. https://doi.org/10.1007/s13659-020-00253-1
34. Fitriani IN, Utami W, Zikri AT, Santoso P (2020) In silico approach of potential phytochemical inhibitor from *Moringa oleifera*, *Cocos nucifera*, *Allium cepa*, *Psidium guajava*, and *Eucalyptus globulus* for the treatment of COVID-19 by molecular docking (Preprint). https://doi.org/10.21203/rs.3.rs-42747/v1
35. Suryanarayana L, Banavath D (2020) A review on identification of antiviral potential medicinal plant compounds against with COVID-19. Int J Res Eng Sci Manag 3(3):675–679
36. Yang Y, Islam MS, Wang J, Li Y, Chen X (2020) Traditional Chinese medicine in the treatment of patients infected with 2019-new coronavirus (SARSCoV-2): a review and perspective. Int J Biol Sci 16(10):1708

Phytotherapeutics in Inflammatory Lung Diseases

23

Heba A. S. El-Nashar, Nouran M. Fahmy, Mohamed El-Shazly, and Omayma A. Eldahshan

Abstract

Inflammatory lung diseases such as asthma can be defined as a widely spread chronic inflammatory disease presented with airway hyperresponsiveness, mucus hypersecretion, and remodeling. These diseases may be triggered by genetic predisposition or allergen. Patients are manifested with recurrent episodes of dyspnea, wheezing, shortness of breath, chest tightness, and cough. Conventional therapies used to treat inflammatory lung diseases suffer from limited patient adherence due to their high cost and side effects. Medicinal plants are gaining considerable attention by health care providers due to their favorable therapeutic role, limited side effects, and their potential to be used as adjuvant therapies in the management of inflammatory lung diseases. This book chapter is a summary of pharmacologically studied plant extracts, fractions, and isolated compounds as anti-inflammatory lung diseases agents, especially asthma in different in vitro and in vivo models in the past decade (2010–2020). We also highlighted the medicinal plants, fractions, and isolated compounds with their pharmacological and immunological mechanism of action.

H. A. S. El-Nashar · N. M. Fahmy
Department of Pharmacognosy, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt

M. El-Shazly (✉)
Department of Pharmacognosy, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt

Department of Pharmaceutical Biology, Faculty of Pharmacy and Biotechnology, German University in Cairo, Cairo, Egypt
e-mail: mohamed.elshazly@pharma.asu.edu.eg

O. A. Eldahshan
Department of Pharmacognosy, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt

Center of Drug Discovery Research and Development, Ain Shams University, Cairo, Egypt

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_23

Keywords

Asthma · Cough · Plants · Secondary metabolites · Immunological

23.1 Introduction

Inflammatory lung diseases, especially asthma, are chronic inflammatory airway conditions marked by persistent inflammation, increased mucus secretion, and airway remodeling [1]. Recurrent symptoms of dyspnea, wheezing, shortness of breath, chest tightness, and coughs that intensify at night or early in the morning are the main clinical manifestations [2]. According to The Global Initiative for Asthma (GINA) 2020, over the past three decades asthma prevalence has increased throughout the world affecting more than 300 million individuals [3]. Asthma affects 1–18% of the population in various countries [4]. Asthma is a complex and multifactorial disease that may arise due to genetic predisposition, infections, medications, stress, dust, pollen, allergens, or smoke [2].

The pathogenesis of asthma is attributed to a group of inflammatory cascades that includes stimulation of immune response and over production and expression of T helper (Th2) type lymphocytes. These cascades result in Th2-associated disorder due to the imbalance in TH1/Th2 cytokines release [5]. Th2 mediated cytokines such as IL-4, IL-5, and IL-13, are important clinical indicators that are responsible for the airway inflammation and infiltration, mucus production, and high level of eosinophil and immunoglobulin E (IgE) [4, 6]. Allergens such as dust, pollen, and animal dander cause inflammation and airway remodeling, which is characterized by the deposition of reconditioned collagens and matrix protein damage as a result of the chronic inflammation and damage of the airway epithelium [7]. The release of a variety of inflammatory mediators results from IgE antibody-mediated reaction on the surface of mast cells. Histamine, leukotrienes, prostaglandins, and various chemotactic agents accumulate eosinophils in the respiratory airways and are responsible for the major characteristic manifestations of asthma pathogenesis [6]. Th2 lymphocytes stimulate eosinophils to produce IL-5 and mast cells to produce IL-4 via IgE [8]. As a result, the volume of serum IgE rises, causing mast cells to produce more cytokines, leukotrienes, and chemical mediators like histamine [9]. Bronchoconstriction, increased vascular permeability, and increased mucus production are all caused by histamine. Bronchoconstriction is induced by prostaglandin D2, and leukotrienes increase vascular permeability, mucus secretion, and bronchoconstriction [10].

Current treatment strategies for asthma focus on reducing airway inflammation and decreasing bronchoconstriction. The most popular clinical approach used to treat asthmatic patients is the administration of bronchodilators and anti-inflammatory drugs [6, 11]. Glucocorticoids are one of the most effective treatments for airway inflammation and hyper-responsiveness [12]. Unfortunately, the prolonged use of glucocorticoids may lead to hypertension, hyperglycemia, hoarseness, reduced bone metabolism, adrenal suppression, and increase the possibility of opportunistic

infection with candida. In certain cases, β_2-agonists and leukotriene receptor antagonists may exacerbate asthma and neuropsychiatric symptoms [5, 12]. While traditional drug therapy, such as inhaled corticosteroids in conjunction with long-acting β_2-agonists, is used to control asthma symptoms, it does not reverse all disease-associated symptoms. As a result, modern, affordable, and safe drugs for the management and treatment of asthma patients are urgently needed [13].

Herbal medicine and natural products represent a treasure-trove for the discovery of new therapies and effective treatments for different ailments including asthma. Complementary and alternative medicine (CAM) is still common throughout the world. It is reported that plants are used alone or in combination with synthetic drugs for a better control and management of asthma. A survey of 7685 asthmatic individuals aged 55 or older showed that almost 40% used herbal medicine to relieve their symptoms. [14]. This book chapter reviews the anti-asthmatic herbal medicine used in the last decade, highlights their effects in controlling asthma, their characteristic components, and possible mechanisms of action.

23.2 Medicinal Plants and Inflammatory Lung Diseases (Asthma) Management

The use of medicinal plants in the management of asthma has been practiced in traditional medicine for the last two millennia [15–17]. Literature survey in the past 10 years revealed that 89 medicinal plants were studied as anti-asthmatic herbs. Previous studies focused mainly on the plants, total extracts, fractions, and to a lesser extent on their isolated compounds. Table 23.1 highlights the studied plants as anti-asthmatic, type of extract, active fraction or isolated compound, type of assay, and the mechanism by which these medicinal plants produce their anti-asthmatic activity.

23.3 Conclusion

The extensive need of an effective and safe inflammatory lung diseases (anti-asthmatic) drugs encouraged researchers all over the world to give an attention to nature as a source of new and safe drugs to be used in the management of asthma. Medicinal plants when combined with conventional therapies might be useful in reducing asthma symptoms, dose, and side effects of the therapeutic drug. The structural diversity of plants secondary metabolites and their capability to work through multiple mechanisms of action highlight their potent activity as anti-asthmatic remedies. Reviewing the literature in the past 10 years proofed that the utilization of medicinal plants and their different extracts is beneficial in ameliorating asthma symptoms via their anti-inflammatory and broncho-dilatory effect. Few reports were traced on the compounds responsible for their anti-asthmatic effect. Thus, there is a great need of continuing research on these plants to characterize the bioactive compounds that have anti-asthmatic properties, detect their effective doses, and reduce any toxic effect.

Table 23.1 Medicinal plants in the management of inflammatory lung diseases (asthma)

Plant name (family)	Part used (extract)	Active fraction/compounds	Type of study	Pharmacological and immunological effects	Ref.
Abrus precatorius (Fabaceae)	Leaves (100% ethanol)		Histamine-induced bronchospasm in Guinea pig, histamine-induced contraction of goat tracheal chain, and carrageenan-induced rat paw edema	• The extract significantly delayed the onset time of pre-convulsion dyspnea in Guinea pig, attributing to its bronchodilator effect and inhibition of histamine H1 receptors or stimulation of β2 adrenergic receptors • The extract (150 mg/kg) inhibited about 28.38% of rat paw edema after 1 h	[18]
Agastache mexicana (Lamiaceae)	Aerial parts (essential oil)	Estragole, d-limonene, and linalyl anthranilate	Guinea pig isolated trachea model	• Calcium influx blockage in Guinea pig tracheal smooth muscle	[19]
Alangium lamarckii (Alangiaceae)	Leaves (methanol)		Guinea pig tracheal chain preparation and histamine-induced bronchoconstriction in Guinea pigs.	• Inhibition of the tracheal muscles' contraction induced by histamine • Increase the time for the onset of pre-convulsive dyspnea	[20]
Alstonia scholaris (Apocynaceae)	Leaves (90% ethanol)	Alkaloids including scholaricine (6%), 19-epischolaricine (2%), picrinine (10%), and vallesamine (6%)	OVA-induced allergic inflammatory model	• Reduction of eosinophils, IL-4, IgE, and eotaxin expression • Promotion in IL-10 in BALF • Elevation of SOD activity with decreased lipid	[21]

				peroxidation product (MDA)	
Angelica glauca (Apiaceae)	Leaves (essential oil)	α-Pinene	Histamine-induced bronchoconstriction in Guinea pigs and OVA-sensitization in mice	• Increase of the pre-convulsive dyspnea time in histamine-induced Guinea pigs • Decrease of absolute blood eosinophil count (38.46%), IgE (88.33%), eosinophils' number (8%), and neutrophils (8%) in BALF	[22]
Anthriscus sylvestris (Apiaceae)	Root (70% ethanol)		OVA-induced asthma model and in vitro Th2 polarization model	• Activated cluster of differentiated CD^{4+} T cell population inhibition and GATA-binding protein-3 gene expression in the lung • In vitro inhibition of Th2 cell differentiation and activation • Downregulation of IL-6 and interferon regulatory factor expression • Nitric oxide suppression in asthmatic mice lungs and stimulated RAW cells • Mucus secretion in airway epithelial cells is reduced, inflammatory cell infiltration, eosinophilia, and levels of Th2 cytokines	[23]

(continued)

Table 23.1 (continued)

Plant name (family)	Part used (extract)	Active fraction/compounds	Type of study	Pharmacological and immunological effects	Ref.
Artemisia argyi (Asteraceae)	Whole plant (100% methanol)	Dehydromatricarin A	OVA-induced allergic asthma model	• Inflammatory cell counts, cytokines, inflammatory cell accumulation, ARH, and mucus hypersecretion are all reduced • Inactivation of Erk phosphorylation and downregulation of MMP-9 expression	[24]
Artemisia pallens (Asteraceae)	Whole plant (100% methanol)		OVA-induced airway hyperresponsiveness	• Reduction of lung oxido stress parameters and IgE levels • Upregulation of Nrf2 that protects against oxidative stress • Downregulation of TNF-α, IL-4, IL-6, IL-1β, TGF-β expression • Inhibition of inflammatory influx and fibrosis	[25]
Asparagus cochinchinensis (Asparagaceae)	Roots (aqueous)	Saponin fraction	OVA-induced allergic asthma model	• Reduction in the number of immune cells in the bronchoalveolar lavage fluid, as well as OVA-specific IgE • Suppression of inflammatory cells' infiltration and decrease in	[26]

				bronchial thickness • Decrease of IL-4, IL-13, and COX-2 inflammatory mediators • Airway remodeling with decreased goblet cell hyperplasia, peribronchiolar collagen layer thickness, and VEGF expression	
Bryophyllum pinnatum (Crassulaceae)	Leaves (aqueous)		OVA-sensitized Guinea pigs.	• Inhibition of histamine-induced bronchospasm and increase the time for the onset of pre-convulsive dyspnea • Reduction of mucus viscosity	[27]
Bupleurum chinense (Apiaceae)	Roots (aqueous)		OVA-induced allergic asthma model	• Inhibition of inflammatory cells' accumulation such as BALF eosinophils • Reestablish the balance of Th1, Th2 and Th17-related production • Suppression of GATA3, IL-1β, IL-4, IL-5, IL-6, IgE, IgG1, IgG2a, TNF-α, and RORγt, IL-17A expression in both BALF and lung homogenate • INF--γ expression is upregulated in lung homogenate	[28]

(continued)

Table 23.1 (continued)

Plant name (family)	Part used (extract)	Active fraction/compounds	Type of study	Pharmacological and immunological effects	Ref.
				• Cytoplasmic inactivation of NFκB p65 phosphorylation and IκBα degradation • Induction of native CD^{4+} T cells functional differentiation forward to Th1 and Tr1 through producing INF-γ and IL-10	
Butea monosperma (Fabaceae)	Flowers (methanol, ethyl acetate, and butanol fractions)	Butanol fraction	Lipoxygenase assay Mast cell degranulation assay and lipopolysaccharide (LPS) induced-inflammation in rats	• Butanol fraction showed the highest lipoxygenase inhibitory effect (IC_{50} = 76.5 μg/ml), reduced mast cell degranulation (inhibition % = 60.03 ± 1.28%) • Butanol fraction exhibited a dose dependent inhibition of elevated levels of total cell count, differential leukocyte count, nitrate-nitrate, total protein, and albumin levels in BALF	[29]
Camellia japonica (Theaceae)	Seeds (essential oil)	Oleic acid (52.89%), 6-octadecenoic acid (9.12%), 9,12-octadecadienoic acid (3.32%), mono-	OVA-induced asthma murine model	• Modulation of Th2-related factors in the lung, including GATA-3, IL-4, IL-5, IL-13, and TNF-α • Regulation of	[30]

		oleoylglycerol (2.68%), β-amyrin (2.15%), and octadecanoic acid (2.13%)		inflammatory cells, T-bet, IgE, IL-12 p40, and IL-6	
Carica papaya (Caricaceae)	Leaves (100% ethanol)		OVA-induced allergic asthma model	• Attenuation of inflammatory cells infiltration, alveolar and goblet cell hyperplasia • Suppression of leukocyte counts (total and differential) in both blood and BALF • IL-4, IL-5, TNF-α, NF-κB, and iNOS downregulation	[31]
Cassia occidentalis (Fabaceae)	Aerial parts (acidic aqueous)	Anthraquinones	OVA-induced allergic asthma model	• Promotion ofTh1 cytokine IFN-γ production in BALF • Downregulation of Th1/Th2 cytokine expression in lung tissue • Reduction of inflammatory cell infiltration and production of Th2 cytokines, and OVA-specific IgE • Inhibition of mucus hypersecretion and goblet cell hyperplasia	[32]
Caesalpinia bonducella (Caesalpiniaceae)	Seed kernel (100% ethanol)	2-Methyl-1-hexadecanol	Clonidine and haloperidol-induced catalepsy and milk-induced leukocytosis model	• Antihistaminic activity (at a dose of 50 and 100 mg/kg) • Inhibition of clonidine-induced catalepsy with no	[33]

(continued)

Table 23.1 (continued)

Plant name (family)	Part used (extract)	Active fraction/compounds	Type of study	Pharmacological and immunological effects	Ref.
				effect on haloperidol-induced catalepsy • Reduction of leukocyte and eosinophil count • Inhibition of mast cell degranulation	
Cinnamomum zeylanicum (Lauraceae)	Bark (ethyl acetate)	Type-A procyanidine polyphenols	OVA-induced allergic asthma model	• Decrease the spirometric volume, breathing rate, and PIF, and increased the PEF, FVC and FEV1 • Increase in MCV, MCH, RDW and WBC • Reduced BALF and lung total protein, serum albumin, BALF, and lung albumin • Reduced the elevated levels of BALF • Inhibition of goblet cell hyperplasia and eosinophils infiltration in the peribronchiolar region of lung tissue	[34]
Citrus tachibana (Rutaceae)	Leaves (100% ethanol)		OVA-induced allergic asthma model Compound 48/80-induced anaphylaxis model	• Modulation of Th1/Th2 ratio *via* elevation of Th2 cytokines; TNF-α, IL-4 and -6 and decrease in Th1 cytokines; INF-γ and IL-12	[35]

				• Inhibition of phosphorylation of IκB-α and NF-κB • Blockage of histamine secretion from mast cells • Reduction of airway inflammation, OVA—specific IgE and IgG1 level with an increase of OVA-specific IgG2a level	
Clitoria ternatea (Fabaceae)	Roots (95% ethanol)		Milk-induced leukocytosis and eosinophilia in mice OVA-induced mast cell degranulation and passive cutaneous anaphylaxis in rats	• Reduction of leukocytosis and eosinophilia • Protected degranulation of mast cells	[36, 37]
Codonopsis lanceolata (Campanulaceae)	Roots (70% ethanol)	Lancemaside A	OVA-induced mouse model of asthma	• Reduction of eosinophil infiltration and mucus production • Inhibition of Th2 cells differentiation, as IL-4, IL-5, and IL-13, and chemokines. • Decrease of $GATA^{3+}$ expression • Upregulation of superoxide dismutase (SOD) expression as ROS scavenger, potentiating the immune-suppressive property of macrophages	[38]

(continued)

Table 23.1 (continued)

Plant name (family)	Part used (extract)	Active fraction/compounds	Type of study	Pharmacological and immunological effects	Ref.
Croton zehntneri (Euphorbiaceae)	Leaves (essential oil)		OVA-induced asthma model	• Inflammatory cells in the pulmonary parenchyma are decreased as a consequence of the antioxidant impact	[39]
Daphne pseudomezereum (Thymelaeaceae)	Leaves (100% methanol)	Biflavonoid-rich fraction including neochamaejasmin B, and chamaejasmin D	OVA-induced asthma model and LPS-stimulated RAW264.7 macrophages	• Inhibition of LPS-stimulated nitric oxide, TNF-α and IL-6 • Upregulation of HO-1 in RAW264.7 macrophages • Decrease eosinophil recruitment and IL-5, IL-6, IL-13, IgE, and MCP-1 • Nrf2 activation and HO-1 induction in the lung tissue	[40]
Descurainia sophia (Brassicaceae)	Seeds (100% ethanol)		OVA-induced mouse model of asthma	• Targeting epigenetic inflammatory genes including: *Vegfa, Kit*, Shroom2, Pcmtd1, Zfp568, and 2310035C23Rik	[41]
Dilodendron bipinnatum (Sapindaceae)	Stem bark (70% ethanol)		In vitro enzyme assay and OVA-induced allergic asthma model	• Decrease of IgE, IL-4, IL-5 and IL-13, total leukocytes, neutrophils, eosinophils, mononuclear cells, and inflammatory cytokines • Downregulation of Th2 responses • Decrease of hemorrhagic damage, mucus	[42]

				overproduction, perivascular and peribronchial inflammatory cell infiltrates • Inhibition of mast cell degranulation • Inhibitory effect on 15-LO activity (IC_{50} = 1.0–5.0 μg/mL)	
Dipsacus asperoides (Caprifoliaceae)	Roots (70% ethanol)	Chlorogenic acid (3.20 μg/mg), loganin (1.51 μg/mg), sweroside (7.16 μg/mg), isochlorogenic acid A (3.65 μg/mg), dipsacoside B (8.56 μg/mg), akebia saponin D (166.33 μg/mg), dipsacus saponin C (4.13 μg/mg), dipsacus saponin B (2.78 μg/mg), and akebia saponin PA (11.10 μg/mg)	OVA-induced asthma model	• Downregulation of iNOS and NF-κB phosphorylation • Inhibition of inflammatory cell infiltration, proinflammatory cytokines and IgE • Inflammation of the airway inflammation and mucus hypersecretion reduction	[43]
Dryopteris crassirhizoma (Dryopteridaceae)	Whole plant (95% ethanol)		OVA-induced allergic asthma model	• Th1 cytokines upregulation including IL-10 and IFN-γ • Reduction of Th2 cytokines (IL-4, IL-5, and IL-13), total IgE, OVA-specific IgE, IgG1, and proinflammatory cytokines (IL-6 and TNF-α) • Increase of OVA-specific IgG2a	[44]

(continued)

Table 23.1 (continued)

Plant name (family)	Part used (extract)	Active fraction/compounds	Type of study	Pharmacological and immunological effects	Ref.
				• Inhibition of NF-κB signaling (NF-κB, p-NF-κB, IκB, and p-IκB)	
Echinodorus scaber (Alismataceae)	Leaves (75% ethanol)	Gallic acid, vitexin, and rutin	OVA-induced hypersensitivity model in mice	• Decrease of the total count of leukocyte, eosinophil, and neutrophil • Decrease of Th2 cytokine release (IL-4, IL-5, and IL-13) and IgE level	[45]
Eclipta prostrata (Asteraceae)	Whole plant (100% methanol)	Wedelolactone (1.71%), dimethyl wedelolactone (1.69%) and oroboside (0.02%),	Mouse model of OVA-induced allergic asthma	• Reduction of respiratory resistance, elastance, inflammatory cells and eosinophils in the bronchoalveolar lavage • Decrease of interleukins in lung homogenate	[46]
Elephantopus scaber (Asteraceae)	Leaves (ethanol)		Histamine and acetylcholine-induced bronchospasm, and histamine-induced constriction on isolated Guinea pig trachea	• Increased the pre-convulsive dyspnea time • Protected degranulation of mast cells • Reduction in the histamine-induced tracheal constriction in Guinea pig in a dose-dependent manner	[47]
Epimedium brevicornum (Berberidaceae) and	*Epimedium brevicornum* (leaves)		OVA-induced asthma model	• Reduction of IL-4 and IL-5 cytokines release and IgE levels	[48]

Ligustrum lucidum (Oleaceae)	and *Ligustrum lucidum* (seeds) (100% ethanol)			• Reduction in the number of eosinophils and goblet cell hyperplasia • TGF-1, TGF-2, Smad2 and Smad3 expression are all downregulated, and a significant increase in levels of Smad7 mRNA • Suppression of integral optical density levels of collagen I and III • Synergistic effect with budesonide through the reduction of collagen deposition, smooth muscle thickening of the airway, and BALF lymphocytes	
Eriobotrya japonica (Rosaceae)	Leaves (aqueous)		OVA-induced murine asthma model and human tracheal smooth muscle cell (HTSMC)	• Suppression of NO, EPO, MMPs, IL-4, IL-13, and serum IgE • Reduction of inflammatory cell infiltration and mucus oversecretion • Inhibition of HTSMC proliferation, ERK1/2 overexpression, and translocation of NF-κB in HTSMC • iNOS and COX-2 downregulation in RAW 264.7 cell	[49]

(continued)

Table 23.1 (continued)

Plant name (family)	Part used (extract)	Active fraction/compounds	Type of study	Pharmacological and immunological effects	Ref.
Erythrina mulungu (Fabaceae)	Flowers (100% ethanol)	Alkaloids including erysotrine, erysotrine-*N*-oxide, and hypaphorine	OVA-induced asthma model	• Decrease of IL-4 and IL-5 cytokines • Reduction in cellular inflammatory infiltration in the lung tissue • Increase of IL-13 and INF-γ level • Reduction of bronchial hyperresponsiveness, leukocytes, eosinophils, and lymphocytes in BAL	[50]
Erythronium japonicum (Lilaceae)	Whole plant (80% ethanol)	Chlorogenic acid and caffeic acid	OVA-induced asthma model	• Suppression of white blood cells and IgE level in BALF • Attenuation of mucus secretion, eosinophil infiltration, goblet and epithelial cell hyperplasia • Inhibition of proliferation of T helper cells (CD^{4+}) and B cells (CD^{19+}) in lung tissue • Modulation of the expression of Th2 cell-related factors (GATA-binding protein 3, TNF-α, IL-4, IL-5, IL-6 and IL-13), as well as Th1 cell-related	[51]

				factors (IFN-γ), IL-12p35 and IL-12p40)	
Euphorbia hirta (Euphorbiaceae)	Stem (95% ethanol)	13α-Methyl-27-norolean-14-en-3β-ol	Histamine-induced bronchospasm in Guinea pigs	• Bronchoprotective effect through H1-blocking effect	[52]
Euphorbia thymifolia (Euphorbiaceae)	Aerial parts (100% methanol)		Histamine-induced bronchospasm in Guinea pigs Mast cell stabilizing activity in vitro	• Decrease of IgE, TNF-a, IL-4 and IL-5 in BALF • Inhibition of mesenteric mast cell degranulation • Increase in time of primary ciliary dyskinesia	[53]
Ficus religiosa (Moraceae)	Leaves (aqueous)		Histamine and acetylcholine-induced bronchospasm in Guinea pigs Mast cell stabilizing activity on rat mesentery	• A significant delay in the latency of histamine and acetylcholine-induced pre-convulsive dyspnea development • Protection of mast cells degranulation	[54]
Flacourtia indica (Flacourtiaceae)	Leaves (100% ethanol)		Guinea pig ileum preparation Histamine-induced bronchospasm in Guinea pigs	• Increase in the time for pre-convulsive dyspnea onset • Blockage of histamine and acetylcholine receptors • Inhibition of acetylcholine-induced spasm	[55]
Grifola gargal (Meripilaceae)	Fruiting bodies (aqueous)		Mice model of OVA-sensitization and inhalation	• Reduction of lung eosinophilic infiltration, interleukin (IL)-13 expression, and plasma IgE level	[56]

(continued)

Table 23.1 (continued)

Plant name (family)	Part used (extract)	Active fraction/compounds	Type of study	Pharmacological and immunological effects	Ref.
				• Suppression of cytokine expression in mast cells and eosinophils • Increase of IL-10 • Augmentation of lung regulatory T cells • Lung inflammation and airway hyperresponsiveness (AHR) reduction	
Illicium verum (Schisandraceae)	Fruits (70% ethanol)	(*E*)-Anethole	OVA- induced asthmatic BALB/c mice	• Upregulation of Foxp3-regulatory T cells expression in lungs • Increase IFN-γ production in the splenocyte cultures • Inhibition of eosinophilia and lymphocyte infiltration in lungs	[57]
Involucrum castaneae (Fagaceae)	Whole plant (80% ethanol)	Betulinic acid, oleanolic acid, gallic acid, and emodin	OVA-induced asthmatic Guinea pigs' model	• Reduction of IgE and IL-5 • Downregulation of IL-5 mRNA expression • Upregulation of IFN-γ • Reduced bronchial smooth muscle thickening and inflammatory cell infiltration damage to tissues	[58]
Justicia pectoralis (Acanthaceae)	Aerial parts (20% ethanol)	Coumarin (1.49 mg/ml) and umbelliferone (0.17 mg/ml)	OVA-sensitized rats' model	• Inhibition of the hyperresponsiveness at	[59]

				higher Ca^{2+} concentrations in preparations stimulated by acetylcholine and histamine on isolated trachea • Regulation of gene expression of canonical transient receptor proteins	
Justicia procumbens (Acanthaceae)	Whole plant (100% ethanol)	Justicidin A and justicidin B	OVA-induced mouse model of asthma	• Selective Th2 cell response suppression in concanavalin A (con-A)-activated spleen cell culture and polarized Th2 cells • Immunoglobulin could block T cell immunoreceptor • Modulation of T cell Immunoglobulin and ITIM Domain (TIGIT) expression • Blocking the human adenosine receptor-A3 (A3AR), which is responsible for mast cell-mediated inflammation and bronchoconstriction • Inhibition of human phosphodiesterase 4 (PDE4) that causes bronchoconstriction	[60]
Lagerstroemia indica (Lythraceae)	Whole plant (80% ethanol)		OVA-induced asthmatic BALB/c mice	• Reduction in the levels of IL-2,4,5,13, OVA-specific	[61]

(continued)

Table 23.1 (continued)

Plant name (family)	Part used (extract)	Active fraction/compounds	Type of study	Pharmacological and immunological effects	Ref.
				IgE and TNF-α • Blockage of ROS production in BAL fluid cells • Downregulation of IL-5 expression • Inhibition of leukocytosis, eosinophilia, and mucus secretion by goblet cells	
Lavandula dentata (Lamiaceae)	Flowers and leaves (Tween 80)		OVA-induced asthma in male Guinea pigs	• Reduction of IgE, triglycerides, total cholesterol, glucose levels in serum, and MDA in lungs through increased SOD activity, GSH content in lungs, and GGT activity in serum	[62]
Lignosus rhinocerotis (Polyporaceae)	Sclerotia (aqueous)		OVA-induced inflammation in airway of mouse model	• Suppressing the inflammatory cells CD^{4+} and T cells in lung draining • Reduction of Th2 cytokines and serum IgE • Inhibition of leukocytes infiltration and mucus production in the lungs • Attenuation of lung inflammation	[63]

Lindera obtusiloba (Lauraceae)	Leaves (100% methanol)		OVA-challenged allergic asthma model and TNF-α-stimulated NCI-H292 cell	• Inhibition of inflammatory cell recruitment and reduction of airway hyperresponsiveness • Suppression of Th2 cytokines, mucin 5AC (MUC5AC), activator protein (AP)-1 in BALF and lung tissue • Mitogen-activated protein kinases (MAPKs) and NF-κB phosphorylation inhibition • Downregulation of inflammatory cytokines • Deactivation of NF-κB in TNF-α-stimulated NCI-H292 cells • Translocation of nuclear factor-erythroid 2-related factor (Nrf-2) was activated to nucleus • Activation of HO-1 and NAD (P) H quinine oxidoreductase 1 (NQO1) • Increase of antioxidant enzymes activities • Inhibition of lipid peroxidation in lung tissue and TNF-α-stimulated NCI-H292 cells	[64]

(continued)

Table 23.1 (continued)

Plant name (family)	Part used (extract)	Active fraction/compounds	Type of study	Pharmacological and immunological effects	Ref.
Lippia alnifolia (Verbenaceae)	Leaves (essential oil)	Limonene (6.1%), carvone (6.0%), $^{\Delta}$-cadinene (5.0%), α-copaene (3.8%), followed by germacrene D (3.5%)	Histamine-induced contraction model in isolated Guinea pig trachea	• Multiple signal transduction pathways, such as prostaglandins, NO production, K^+ channels, 2-adrenoceptors, and nicotinic receptors, are activated • Reduction of Ca^{2+} release • Relaxation of histamine-induced contractions	[65]
Mandevilla longiflora (Apocynaceae)	Roots (70% ethanol)	Total flavonoid and phenolics including ellagic acid (11.28%), hesperidin (9.32%), naringin (5.75%), rutin (4.05%), naringenin (3.57%), and luteolin (1.94%)	OVA-induced immediate hypersensitivity model	• Attenuation of leukocyte migration into the airways • Reduction of IL-4, 5& 13, IgE and LTB4 levels	[66]
Menispermum dauricum (Menispermaceae)	Rhizomes (75% ethanol)	Total alkaloids including dauricinoline (7.95%), daurisoline (16.94%), and dauricine (15.40%)	OVA-induced allergic asthma in mouse model	• Decrease of pulmonary inflammation, inflammatory cell counts, IL-4,5, & 13 • Downregulation of TNF-α, total IgE, OVA-specific IgE and eotaxin levels in BALF • Regulation of Th2 response and chemokine level	[67]

Mentha arvensis (Lamiaceae)	Leaves (essential oil)	Menthol (72.6%) as major component, followed by menthone (8.5%), limonene (3.3%) and menthyl acetate (2.4%)	Histamine aerosol-induced bronchoconstriction in Guinea pigs and OVA-sensitized albino mice	• Increase of pre-convulsive dyspnea time in histamine-induced Guinea pigs • Decrease of absolute eosinophil count, IgE and eosinophils, neutrophils in BALF	[68]
Mimosa pudica (Fabaceae)	Whole plant (80% ethanol)		In vitro human mast cell (HMC-1) and OVA-induced-asthma animal model	• HMC-1 cell migration is inhibited by a stem cell factor • In EoL-1 cells, blockage of monocyte chemotactic protein-1 (MCP-1) and IL-6 release • In asthmatic lungs, leukocytosis, eosinophilia, and mucus hypersecretion were suppressed	[69]
Nyctanthes arbor-tristis (Oleaceae)	Pet. ether extract	Pet. ether extract/β-sitosterol	Catalepsy caused by clonidine and haloperidol, as well as milk-induced leukocytosis and eosinophilia in mice	• Antihistaminic, antiallergic, and mast cell stabilization property	[70]
Ocimum basilicum (Lamiaceae)	Leaves (70% ethanol)		OVA-induced allergic asthma model	• Reduction of IL-4, IgE, PLA2, and TP levels • Increase of IFN-γ/IL-4 ratio	[71]
Opuntia humifusa (Cactaceae)	Leaves (80% ethanol)		OVA-sensitized albino mice	• Th1/Th2/Th17-related factors, such as IL-4 and IL-13, were regulated • Goblet cell hyperplasia,	[72]

(continued)

Table 23.1 (continued)

Plant name (family)	Part used (extract)	Active fraction/compounds	Type of study	Pharmacological and immunological effects	Ref.
				inflammatory cell infiltration, mucous hypersecretion, and relative basement membrane thickening were all suppressed	
Petiveria alliacea (Petiveriaceae)	Leaves (100% methanol)		OVA-induced chronic asthma in murine model	• Suppression of airway hyperresponsiveness, eosinophils' infiltration and other inflammatory cells • Decrease of TNF-α, IgE, TGF-β1 and cytokine levels including IL-4,5,13 in the BALF • Inhibition of chemokines' production, eotaxin and ICAM-1 in BALF • Low inflammatory scores in the histopathological studies	[73]
Peucedanum japonicum (Apiaceae)	Roots (70% ethanol)		Asthma murine model and a lipopolysaccharide (LPS)-stimulated Macrophage cell line	• Suppression of inflammatory cell infiltration, eosinophilia and GATA-3 expression in the lung • Reduction of IL-5, 13 levels in BALF • Downregulation of Th2	[74]

				activation • Suppression of iNOS, cyclooxygenase-2, TNF-α, and IL-6 produced by macrophages	
Phyllanthus amarus (Phyllanthaceae)	Aerial parts (100% methanol)	Phyllanthin (68.14%) and hypophyllanthin (31.95%)	OVA-induced experimental airway hyperresponsiveness	• Reduction of total and OVA-specific IgE, as well as oxidative and nitrosative stress (SOD, GSH, MDA and NO) • Inhibition of iNOS, immuneinflammatory makers such as HO-1, TNF-α, IL-1β, and TGF-β1, and Th2 cytokines (IL-4 & 6)	[75]
Phyllostachys nigra (Poaceae)	Stems (aqueous)		OVA-induced asthma mouse model	• decreament of immune cell infiltration and IgE • Upregulation of IFN-γ • Downregulation of IL-4 production from splenocytes • *In vitro* decrease of IL-4 expression in BALF	[76]
Physalis angulate (Solanaceae)	Leaves (methanol)		Guinea pig ileum preparation, Guinea pig trachea and rat fundus strip	• Antagonistic activity on histamine and serotonin receptors	[77]
Physalis peruviana (Solanaceae)	Leaves (100% methanol)		OVA-induced airway inflammation	• Downregulation of nuclear factor-κB/p38 mitogen-activated protein kinase/c-Jun N-terminal kinase,	[78]

(continued)

Table 23.1 (continued)

Plant name (family)	Part used (extract)	Active fraction/compounds	Type of study	Pharmacological and immunological effects	Ref.
				monocyte chemoattractant protein-1 (MCP-1) and T cell marker KEN-5 expression • Inhibition of mucus overproduction in the lung • Upregulation of heme oxgenase-1 (HO-1) in the lung • Concentration dependent decrement of LPS-stimulated MCP-1 • Decrease of eosinophil number and inflammatory cytokine like IL-4, 5, 13 as well as total IgE • Suppressing the inflammatory cells' influx into the lungs	
Piper longum (Piperaceae)	Fruits (pet. ether, ethanol, and aqueous)		Different in vivo models such as histamine-induced bronchospasm in guinea pig, milk-induced leukocytosis, haloperidol-induced catalepsy, and passive paw anaphylaxis in mice	• In guinea pig model, H_1-receptor antagonism was observed via contraction inhibition of isolated ileum • Delay in the latent period of convulsions • Remarked suppression in the number of leucocytes • In a model of haloperidol-induced catalepsy, all	[79]

				extracts were active at all-time intervals • After 2 h of administration in the passive paw anaphylaxis model, all extracts showed significant activity	
Piper nigrum (Piperaceae)	Seeds (100% ethanol)		OVA-induced airway hyperresponsiveness in rats	• Reduction of inflammatory cells such a eosinophils, neutrophils, and mast cells present in lung tissue • Modification of cytokines production including Th1, Th2, Th17 and Treg cells • Inhibition of GATA3, IL-4, 6, 1β, & 17A, RORγt, and TNF-α expression • Overexpression of IL-10 and interferon-γ in BALF and lung tissue • Suppression of total IgE, specific anti-OVA IgE & G1 and histamine release in serum • Inhibition of mast cell degranulation and attenuation of allergic response	[48, 80]
Pistacia atlantica (Anacardiaceae)	Gums (aqueous)	α-Pinene (77.9%), β-pinene (3.66%), and β-Myrcene (6.26%)	OVA-induced asthma	• Eosinophilic cells and anti-IgE, IL-4, 5, 17 cytokines levels were all decreased	[81]

(continued)

Table 23.1 (continued)

Plant name (family)	Part used (extract)	Active fraction/compounds	Type of study	Pharmacological and immunological effects	Ref.
				• IL-10, TGF-β, and INF-γ are among the anti-inflammatory Th1 cytokines that have increased	
Pistacia integerrima (Anacardiaceae)	Galls (100% methanol)		OVA-induced allergic asthma	• Suppression of goblet cell hyperplasia and inflammatory cell infiltration • Down-expression of TNF-α, IL-4 & 5, AQP1 and AQP5 expression levels • Remarked decrement of airway inflammation, lung wet/dry ratio and pulmonary edema	[82]
Pistacia integerrima (Anacardiaceae)	Galls (aqueous)		Histamine-induced bronchospasm in isolated trachea of guinea pig	• Reduced mast cell degranulation, antibody production and antigen-induced histamine release • Delayed the latent period of convulsion • Spasmolytic effect on isolated tracheal chain of guinea pig	[83]
Pistacia weinmannifolia (Anacardiaceae)	Roots (50% ethanol)		OVA and alum-induced inflammation of lungs in murine model	• Decrease of eosinophil number, total and OVA-specific IgE • Reduced Th2 cytokines	[84]

				like IL-4, 5, 13 • The inflammatory cells' influx to the lung was inhibited • Suppression of mucus hypersecretion in the lungs • Inactivation of monocyte chemoattractant protein-1 • Downregulation of mitogen related protein kinases and NF-κB	
Polygonum multiflorum (Polygonaceae)	Roots (100% ethanol)		OVA-induced allergic asthma	• Modulation of Th2 transcription factor GATA-3 expression • Reduction of Th2 cytokines; IL-4, 5, 13, eotaxin, and TNF-α	[85]
Prunus africana (Rosaceae)	Stem bark (aqueous)		OVA-induced allergic asthma	• Reduction of IgE antibody in serum • A decrease in the level of eosinophil in BALF	[86]
Pyrostegia venusta (Bignoniaceae)	Flowers (aqueous)	Verbascoside, isoverbascoside, quinic acid, and chlorogenic acid	OVA-induced allergic asthma	• Decrease bronchial hyperresponsiveness associated with lung inflammation via antioxidant activity	[87]
Ribes nigrum (Grossulariaceae)	Fruits (aqueous)	Nine anthocyanin compounds including delphinidin 3-*O*-glucpyranoside, delphinidin 3-*O*-rutinoside, cyanidin	OVA-induced airway inflammation C57BL/6J mouse model and in vitro CCL11 assay	• Inhibition of CCL11 secretion by 48.55%, chemokine, related to the development of airways	[88]

(continued)

Table 23.1 (continued)

Plant name (family)	Part used (extract)	Active fraction/compounds	Type of study	Pharmacological and immunological effects	Ref.
		3-*O*-glucopranoside, cyanidin 3-*O*-rutinooside, petunidin 3-*O*-glucopyranoside, petunidin 3-*O*-rutinoside, peonidin 3-*O*-rutinoside, delphinidin 3-*O*-coumaroyl glucopyranoside and cyanidin 3-*O*-coumaroyl glucopyranoside		eosinophilia in allergic asthma patients	
Ricinus communis (Euphorbiaceae)	Roots (ethanol)		Milk-induced leukocytosis and eosinophilia, OVA-induced mast cells' degranulation and passive cutaneous anaphylaxis in rats	• Reduction of leukocytosis and eosinophilia • Protected degranulation of mast cells	[89]
Rosa multiflora (Rosaceae)	Fruits (aqueous)		OVA and compound 48/80-induced allergic asthma and mast cell activation	• Eosinophil infilteration, mucus aggregation, goblet cell hyperplasia, and collagen fiber deposits are all reduced • Blockage of histamine release from mast cells and subsequently inhibited degranulation • Decrease of Th2 cytokines like TNF-α, IL-4, 6 levels • Decrease of eosinophils	[90]

				and lymphocytes in the lungs	
Salvia miltiorrhiza (Lamiaceae)	Roots (aqueous)	Salvianic acid A, salvianolic acid B caffeic, rosmarinic acids, and tanshinone IIA	OVA-induced asthmatic mice	• Reduction of E-cadherin, α-SMA and COL1A1 and vimentin levels in TGF-β1-induced BEAS-2B and MRC-5 cells • Reduced the infiltration of airway inflammatory cells, ratio of Th1/Th2 cytokines and goblet cell hyperplasia • Suppressed airway resistance, collagen deposits, and airway wall thickening	[12]
Salvia plebeian (Lamiaceae)	Aerial parts (80% ethanol)		OVA-induced BALB/c mouse model	• Inhibition of proinflammatory mediators including TNF-α and IL-4,6, 8, 13 and NO – Decreased airway eosinophils' number, mucus accumulation, and inflammatory infiltration of LPS-stimulated RAW 264.7 cells.	[91]
Sargassum horneri (Sargassaceae)	Whole plant (70% ethanol)		Mouse asthma model exposed to particulate matter (PM) and OVA	• Inactivation of MAPKs, iNOS, and COX2 phosphorylation • Inhibition of proinflammatory cytokines' expression	[92]

(continued)

Table 23.1 (continued)

Plant name (family)	Part used (extract)	Active fraction/compounds	Type of study	Pharmacological and immunological effects	Ref.
				• Upregulation of antioxidant gene expression	
Schisandra chinensis (Schisandraceae)	Fruits (methanol)		OVA-induced mouse model of asthma	• Reduction of serum IgE level by 40.1% • Reduced airway hyperresponsiveness • Reduced immune cell infiltration	[93]
Scrophularia buergeriana (Scrophulariaceae)	Leaves (70% ethanol)	Aucubin (15.02 μg/mg), harpagide (4.29 μg/mg), 8-acetyl harpagide (0.71 μg/mg), angoroside C (4.85 μg/mg), and harpagoside (2.16 μg/mg)	OVA-induced allergic asthma and LPS-stimulated RAW264.7 cells	• Suppression of inflammatory cell infiltration, IL-5, 6, 13, 17, IgE, and AHR • Reduced airway inflammation and mucus over secretion • Modulation of TNF-α, MMP-9, and NF-κB phosphorylation of LPS-stimulated RAW264.7 cells	[94]
Selaginella uncinata (Selaginellaceae)	Whole plant (70% ethanol)	Total flavonoids including amentoflavone (137.1 mg/g), hinokiflavone (80.3 mg/g) and isocryptomerin (24.0 mg/g)	OVA-induced asthma in rats	• Reduction of IL-4, 5, 13, total IgE and OVA-specific IgE accompanied with increase of IFN-γ level • Upregulation of T2R10 gene expression • Downregulation of eotaxin NFAT1 and c-Myc protein	[95]

				expression-dependent signaling pathway, IP3R1 and Orai1 gene expression	
Siphonochilus aethiopicus (Zingiberaceae)	Roots and rhizomes (aqueous, diethyl ether, and 100% ethanol)	Furanoterpenoid	In vitro assays like glucocorticoid and histamine receptor binding and phosphodiesterase IV enzyme inhibition, accompanied with OVA-induced allergic asthma	• The most promising activity was shown in the diethyl ether plant extract and isolated compound, namely furanoterpenoid (glucocorticoid receptor binding assay; $IC_{50} = 12.9$ and 11.4 μg/ml, respectively), (histamine receptor binding assay; $IC_{50} = 89.0$ and 56.5 μg/ml, respectively), and (phosphodiesterase IV enzyme inhibition; assay $IC_{50} = 26.6$ and 43.6 μg/ml, respectively) • The diethyl ether extract was given intraperitoneally and decreased allergic inflammation, eosinophils, and immune cell infiltration	[96]
Siraitia grosvenorii (Cucurbitaceae)	Fruits (70% ethanol)		OVA-induced allergic asthma	• Suppression of AHR, serum IgE production • Reduction of lymphocytes, CD^{4+}/CD^{69+} T cells' ratio, $CD^{11b+}/Gr\text{-}^{1+}$ granulocytes' ratio, neutrophils, monocytes, and eosinophils in the lung tissue and BAL • Downregulation of Th2	[97]

(continued)

Table 23.1 (continued)

Plant name (family)	Part used (extract)	Active fraction/compounds	Type of study	Pharmacological and immunological effects	Ref.
				cytokines like IL-4, 5, 13, 17), TARC, MUC5AC and TNF-α of the lung, conjugated with upregulation of Th1 cytokine-IFN-γ in the BAL fluid and splenocytes	
Sophora tonkinensis (Fabaceae)	Root and rhizome (50% ethanol)	Maackiain, trifolirhizin, and sophoranon	In vitro enzyme assays, linked with OVA-induced allergic asthma	• Inhibiting the proinflammatory enzymes including 5-lipoxygenase (IC_{50} = 1.61 μg/ml), phosphodiesterase 3 (IC_{50} = 11.8 μg/ml) and phosphodiesterase 4 (IC_{50} = 0.634 μg/ml) and thromboxane synthase (IC_{50} = 5.56 μg/ml) • Total leukocytes, eosinophil infiltration, and IL-5 levels in BAL fluid were reduced, suppressing bronchoconstriction	[98]
Trigonella foenum-graecum (Fabaceae)	Seeds (aqueous)		OVA-induced BALB/c mouse model	• Inhibition of collagen deposition, goblet cells and lung inflammation • Downregulation of Th2 cytokine, accompanied with overexpression of Th1 cytokines • Suppression of	[99]

				inflammatory cells, serum IgE and anti-OVA IgG1	
Uncaria tomentosa (Rubiaceae)	Bark (aqueous)	Mitraphylline, isomitraphylline, isorhyncophylline chlorogenic, quinic acids, and rutin	OVA-induced allergic asthma and in vitro LPS-stimulated macrophage cells (RAW264.7-Luc)	• Suppression of IL-4, 5, 6 and TNF-α, NF-κB transcription, tissue damping, and respiratory elasticity	[100]
Viola tricolor (Violaceae)	Flowers (96% ethanol)		OVA-induced allergic asthma	• Decrease of IL-4 level but on effect on IFN-γ level • Reduction of leukocyte infiltration such as eosinophil and peribronchial inflammation • Increase of IFN-γ level • Inhibition of Th2 cytokine production	[101]
Vitis vinifera (Vitaceae)	Fruits (100% ethanol)	Gallic acid	OVA-induced allergic asthma	• Inhibition of the recruitment of inflammatory cytokines, IgE, nitrites, and eosinophils in blood/serum and BALF	[102]
Warburgia ugandensis (Canellaceae)	Stem bark (aqueous)		OVA-induced mouse model of asthma	• Reduction of IgE antibody in serum • Decrease in the level of eosinophil in BALF	[86]
Woodfordia fruticose (Lythraceae)	Flower (ethyl acetate, acetone, methanol, and 50% ethanol extracts)		Mast cell degranulation assay, membrane stabilization assay, histamine, acetylcholine and	• Stabilizing mast cells • Reducing histamine release • Relaxation against	[103]

(continued)

Table 23.1 (continued)

Plant name (family)	Part used (extract)	Active fraction/compounds	Type of study	Pharmacological and immunological effects	Ref.
			OVA-induced rat model of asthma, guinea pig tracheal chain preparation	acetylcholine and histamine • Induced tracheal chain contraction • Anti-inflammatory and antioxidant activities	
Zanthoxylum bungeanum (Rutaceae)	Seeds (essential oil)		OVA-induced asthma	• Suppression of inflammatory cytokines, chemokines, and adhesion molecules expression • Downregulating the extracellular signal-regulated kinase, conjugated with c-JUN N-terminal kinase activation • Attenuating the lung tissue injury and airway remodeling and leukocytes infiltration into the airway	[104]
Zataria multiflora (Lamiaceae)	Whole plant (50% ethanol)	Thymol, apigenin, luteolin, and 6-hydroxyluteolin	Ovalbumin (OVA)-induced mouse model of asthma	• Attenuation of proinflammatory mediators mainly, IL-4, 17, Th2, Th17, and TGF-β gene expression • Potentiation of Treg cells, Th1 cytokines, and Th1/Th2 ratio • Increase of anti-inflammatory cytokines (IFN-γ and FOXP3) gene expression and IFN-γ/IL-4 ratio in splenocyte	[105]

References

1. Zeng Z, Lin X, Zheng R, Zhang H, Zhang W (2018) Celastrol alleviates airway hyperresponsiveness and inhibits Th17 responses in obese asthmatic mice. Front Pharmacol 9:49
2. Mims JW (2015) Asthma: definitions and pathophysiology. International forum of allergy & rhinology. Wiley, London
3. The Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2006. Available **https://ginasthma.org/wp-content/uploads/2019/01/2006-GINA.pdf** (accessed on 10 November 2020)
4. Jing W, Rong-Guang J, Lu X, Qiu-Juan W, Tian-Hua Y (2014) Anti-asthma effects of synthetic salidroside through regulation of Th1/Th2 balance. Chin J Nat Med 12(7):500–504
5. Gandhi GR, Leão GC, Calisto VK, Vasconcelos AB, Almeida ML, Quintans JS et al (2020) Modulation of interleukin expression by medicinal plants and their secondary metabolites: a systematic review on anti-asthmatic and immunopharmacological mechanisms. Phytomedicine 70:153229
6. Walker R (2011) Clinical pharmacy and therapeutics. Elsevier Health Sciences, Amsterdam
7. Harada T, Yamasaki A, Fukushima T, Hashimoto K, Takata M, Kodani M et al (2015) Causes of death in patients with asthma and asthma-chronic obstructive pulmonary disease overlap syndrome. Int J Chron Obstruct Pulmon Dis 10:595–602
8. Peh HY, Ho WE, Cheng C, Chan TK, Seow AC, Lim AY et al (2015) Vitamin E isoform γ-tocotrienol downregulates house dust mite-induced asthma. J Immunol 195(2):437–444
9. Stevenson DD, Szczeklik A (2006) Clinical and pathologic perspectives on aspirin sensitivity and asthma. J Allergy Clin Immunol 118(4):773–786
10. Hall S, Agrawal DK (2014) Key mediators in the immunopathogenesis of allergic asthma. Int Immunopharmacol 23(1):316–329
11. Reddy AP, Gupta MR (2014) Management of asthma: the current US and European guidelines. Adv Exp Med Biol 795:81–103
12. Luo J, Zhang L, Zhang X, Long Y, Zou F, Yan C et al (2019) Protective effects and active ingredients of Salvia miltiorrhiza Bunge extracts on airway responsiveness, inflammation and remodeling in mice with ovalbumin-induced allergic asthma. Phytomedicine 52:168–177
13. Bush A, Fleming L, Saglani S (2017) Severe asthma in children. Respirology 22(5):886–897
14. Liu F, Xuan N-X, Ying S-M, Li W, Chen Z-H, Shen H-H (2016) Herbal medicines for asthmatic inflammation: from basic researches to clinical applications. Mediat Inflamm 2016:6943135
15. Javadi B, Sahebkar A, Ahmad ES (2017) Medicinal plants for the treatment of asthma: a traditional Persian medicine perspective. Curr Pharm Des 23(11):1623–1632
16. Iwu MM (2014) Handbook of African medicinal plants. CRC Press, Boca Raton
17. Dogra KS, Chauhan S, Jalal JS (2015) Assessment of Indian medicinal plants for the treatment of asthma. J Med Plant Res 9(32):851–862
18. Taur DJ, Patil RN, Patil RY (2017) Antiasthmatic related properties of Abrus precatorius leaves on various models. J Tradit Complement Med 7(4):428–432
19. Navarrete A, Ávila-Rosas N, Majín-León M, Balderas-López JL, Alfaro-Romero A, Tavares-Carvalho JC (2017) Mechanism of action of relaxant effect of Agastache mexicana ssp. mexicana essential oil in Guinea-pig trachea smooth muscle. Pharm Biol 55(1):96–100
20. Chakraborty B, Bhattacharyya UK, Datta R, Boral M, Laha B, Nandy S (2013) Anti-inflammatory and anti-asthmatic activities of Alangium lamarkii (Alangiaceae). J Adv Pharm Educ Res 3:4
21. Zhao YL, Cao J, Shang JH, Liu YP, Khan A, Wang HS et al (2017) Airways antiallergic effect and pharmacokinetics of alkaloids from Alstonia scholaris. Phytomedicine 27:63–72
22. Sharma S, Rasal VP, Patil PA, Joshi RK (2017) Effect of Angelica glauca essential oil on allergic airway changes induced by histamine and ovalbumin in experimental animals. Indian J Pharm 49(1):55–59

23. Kim SB, Lee AY, Chun JM, Lee AR, Kim HS, Seo YS et al (2019) Anthriscus sylvestris root extract reduces allergic lung inflammation by regulating interferon regulatory factor 4-mediated Th2 cell activation. J Ethnopharmacol 232:165–175
24. Shin NR, Ryu HW, Ko JW, Park SH, Yuk HJ, Kim HJ et al (2017) Artemisia argyi attenuates airway inflammation in ovalbumin-induced asthmatic animals. J Ethnopharmacol 209:108–115
25. Mukherjee AA, Kandhare AD, Rojatkar SR, Bodhankar SL (2017) Ameliorative effects of Artemisia pallens in a murine model of ovalbumin-induced allergic asthma via modulation of biochemical perturbations. Biomed Pharmacother 94:880–889
26. Sung JE, Lee HA, Kim JE, Yun WB, An BS, Yang SY et al (2017) Saponin-enriched extract of Asparagus cochinchinensis alleviates airway inflammation and remodeling in ovalbumin-induced asthma model. Int J Mol Med 40(5):1365–1376
27. Salami EO, Ozolua RI, Okpo SO, Eze GI, Uwaya DO (2013) Studies on the anti-asthmatic and antitussive properties of aqueous leaf extract of Bryophyllum pinnatum in rodent species. Asian Pac J Trop Med 6(6):421–425
28. Bui TT, Piao CH, Song CH, Shin HS, Chai OH (2017) Bupleurum chinense extract ameliorates an OVA-induced murine allergic asthma through the reduction of the Th2 and Th17 cytokines production by inactivation of NFκB pathway. Biomed Pharmacother 91:1085–1095
29. Shirole R, Kshatriya A, Sutariya B, Saraf M (2013) Mechanistic evaluation of Butea monosperma using in vitro and in vivo murine models of bronchial asthma. IJRAP 4 (3):322–331
30. Lee SY, Bae CS, Seo NS, Na CS, Yoo HY, Oh DS et al (2019) Camellia japonica oil suppressed asthma occurrence via GATA-3 & IL-4 pathway and its effective and major component is oleic acid. Phytomedicine 57:84–94
31. Inam A, Shahzad M, Shabbir A, Shahid H, Shahid K, Javeed A (2017) Carica papaya ameliorates allergic asthma via down regulation of IL-4, IL-5, eotaxin, TNF-α, NF-κB, and iNOS levels. Phytomedicine 32:1–7
32. Xu W, Hu M, Zhang Q, Yu J, Su W (2018) Effects of anthraquinones from Cassia occidentalis L. on ovalbumin-induced airways inflammation in a mouse model of allergic asthma. J Ethnopharmacol 221:1–9
33. Vikhe S, Nirmal S (2018) Antiallergic and antihistaminic actions of Ceasalpinia bonducella seeds: possible role in treatment of asthma. J Ethnopharmacol 216:251–258
34. Kandhare AD, Bodhankar SL, Singh V, Mohan V, Thakurdesai PA (2013) Anti-asthmatic effects of type-A procyanidine polyphenols from cinnamon bark in ovalbumin-induced airway hyperresponsiveness in laboratory animals. Biomed Aging Pathol 3(1):23–30
35. Bui TT, Piao CH, Kim SM, Song CH, Shin HS, Lee CH et al (2017) Citrus tachibana leaves ethanol extract alleviates airway inflammation by the modulation of Th1/Th2 imbalance via inhibiting NF-κB signaling and histamine secretion in a mouse model of allergic asthma. J Med Food 20(7):676–684
36. Taur DJ, Patil RY (2011) Evaluation of antiasthmatic activity of Clitoria ternatea L. roots. J Ethnopharmacol 136(2):374–376
37. Chauhan N, Rajvaidhya S, Dubey B (2012) Antiasthmatic effect of roots of Clitorea ternatea Linn. Int J Pharm Sci Res 3(4):1076
38. Seo YS, Kim HS, Lee AY (2019) Codonopsis lanceolata attenuates allergic lung inflammation by inhibiting Th2 cell activation and augmenting mitochondrial ROS dismutase (SOD2) expression. Sci Rep 9(1):2312
39. Serra DS, Gomes MDM, Cavalcante F, Leal-Cardoso JH (2019) Essential oil of Croton Zehntneri attenuates lung injury in the OVA-induced asthma model. J Asthma 56(1):1–10
40. Lee JW, Ryu HW, Kim DY, Kwon OK, Jang HJ, Kwon HJ et al (2020) Biflavonoid-rich fraction from Daphne pseudomezereum var. koreana Hamaya exerts anti-inflammatory effect in an experimental animal model of allergic asthma. J Ethnopharmacol 265:113386

41. Baek SJ, Chun JM, Kang TW, Seo YS, Kim SB, Seong B et al (2018) Identification of epigenetic mechanisms involved in the anti-asthmatic effects of descurainia sophia seed extract based on a multi-omics approach. Molecules 23(11):2879
42. de Oliveira RG, Miyajima F, Castilho GRC, Damazo AS, Macho A, Martins DTO (2018) Dilodendron bipinnatum Radlk. ameliorates airway inflammation through multiple targets in a murine model of ovalbumin-induced allergic airway disease. J Ethnopharmacol 226:17–25
43. Shin NR, Lee AY, Park G, Ko JW, Kim JC, Shin IS (2019) Therapeutic effect of dipsacus asperoides C. Ai in ovalbumin-induced murine model of asthma. Int J Mol Sci 20:8
44. Piao CH, Bui TT, Fan YJ, Nguyen TV, Shin DU, Song CH et al (2020) In vivo and in vitro anti-allergic and anti-inflammatory effects of Dryopteris crassirhizoma through the modulation of the NF-κB signaling pathway in an ovalbumin-induced allergic asthma mouse model. Mol Med Rep 22(5):3597–3606
45. Rosa SIG, Rios-Santos F, Balogun SO, de Almeida DAT, Damazo AS, da Cruz TCD et al (2017) Hydroethanolic extract from Echinodorus scaber Rataj leaves inhibits inflammation in ovalbumin-induced allergic asthma. J Ethnopharmacol 203:191–199
46. Morel LJF, Azevedo BC, Carmona F, Contini SHT, Teles AM, Ramalho FS et al (2017) A standardized methanol extract of Eclipta prostrata (L.) L. (Asteraceae) reduces bronchial hyperresponsiveness and production of Th2 cytokines in a murine model of asthma. J Ethnopharmacol 198:226–234
47. Sagar R, Sahoo H (2012) Evaluation of antiasthmatic activity of ethanolic extract of Elephantopus scaber L. leaves. Indian J Pharm 44(3):398
48. Tang X, Nian H, Li X, Yang Y, Wang X, Xu L et al (2017) Effects of the combined extracts of Herba Epimedii and Fructus Ligustrilucidi on airway remodeling in the asthmatic rats with the treatment of budesonide. BMC Complement Altern Med 17(1):380
49. Kim TM, Paudel KR, Kim DW (2020) Eriobotrya japonica leaf extract attenuates airway inflammation in ovalbumin-induced mice model of asthma. J Ethnopharmacol 253:112082
50. Amorim J, Borges MC, Fabro AT, Contini SHT, Valdevite M, Pereira AM et al (2019) The ethanolic extract from Erythrina mulungu Benth. flowers attenuates allergic airway inflammation and hyperresponsiveness in a murine model of asthma. J Ethnopharmacol 242:111467
51. Seo JH, Bang MA, Kim G, Cho SS, Park DH (2016) Erythronium japonicum attenuates histopathological lung abnormalities in a mouse model of ovalbumin-induced asthma. Int J Mol Med 37(5):1221–1228
52. Prachi S, Pradeep T (2014) 13α-methyl-27-norolean-14-en-3β-ol, a Triterpeneisolated from the stem of Euphorbia Hirta (linn) possess an anti-asthmatic properties. Res J Chem Sci 2231:606
53. Parmar G, Pundarikakshudu K, Balaraman R (2019) Anti-anaphylactic and antiasthmatic activity of Euphorbia thymifolia L. on experimental animals. J Tradit Complement Med 9 (1):60–65
54. Kapoor M, Jasani N, Acharya N, Acharya S, Kumar V (2011) Phytopharmacological evaluation and anti–asthmatic activity of Ficus religiosa leaves. Asian Pac J Trop Med 4(8):642–644
55. Tyagi S, Singh M, Singh D, Yadav I, Singh S, Mansoori MH (2011) Anti-asthmatic potential of Flacourtia indica Merr. Afr J Basic Appl Sci 3(5):201–204
56. Harada E, D'Alessandro-Gabazza CN, Toda M, Morizono T, Totoki T, Yasuma T et al (2018) The medicinal mushroom, grifola gargal, ameliorates allergic bronchial asthma. J Med Food 21(2):136–145
57. Sung YY, Kim SH, Kim DS (2017) Illicium verum extract and trans-anethole attenuate ovalbumin-induced airway inflammation via enhancement of Foxp3(+) regulatory T cells and inhibition of Th2 cytokines in mice. Mediat Inflamm 2017:7506808
58. Ye Y, Mo S, Feng W, Ye X, Shu X, Long Y et al (2019) The ethanol extract of Involcucrum castaneae ameliorated ovalbumin-induced airway inflammation and smooth muscle thickening in Guinea pigs. J Ethnopharmacol 230:9–19

59. Moura CTM, Batista-Lima FJ, Brito TS, Silva AAV, Ferreira LC, Roque CR et al (2017) Inhibitory effects of a standardized extract of Justicia pectoralis in an experimental rat model of airway hyper-responsiveness. J Pharm Pharmacol 69(6):722–732
60. Youm J, Lee H, Choi Y, Yoon J (2018) DW2008S and its major constituents from Justicia procumbens exert anti-asthmatic effect via multitargeting activity. J Cell Mol Med 22 (5):2680–2691
61. Yang EJ, Lee JS, Song BB, Yun CY, Kim DH, Kim IS (2011) Anti-inflammatory effects of ethanolic extract from Lagerstroemia indica on airway inflammation in mice. J Ethnopharmacol 136(3):422–427
62. Almohawes ZN, Alruhaimi HS (2020) Effect of Lavandula dentata extract on ovalbumin-induced asthma in male guinea pigs. Braz J Biol 80(1):87–96
63. Muhamad SA, Muhammad NS, Ismail NDA, Mohamud R, Safuan S, Nurul AA (2019) Intranasal administration of Lignosus rhinocerotis (Cooke) Ryvarden (Tiger Milk mushroom) extract attenuates airway inflammation in murine model of allergic asthma. Exp Ther Med 17 (5):3867–3876
64. Lee BW, Ha JH, Shin HG, Jeong SH, Kim JH, Lee J et al (2020) Lindera obtusiloba attenuates oxidative stress and airway inflammation in a murine model of ovalbumin-challenged asthma. Antioxidants 9:7
65. Vilela DAD, Silva BAO, Brito MC, Menezes PMN, Bomfim HF, Duarte-Filho L et al (2020) Lippia alnifolia essential oil induces relaxation on Guinea-pig trachea by multiple pathways. J Ethnopharmacol 246:112162
66. de Almeida DA, Rosa SI, da Cruz TC, Pavan E, Sabino Damazo A, Soares IM et al (2017) Mandevilla longiflora (Desf.) Pichon improves airway inflammation in a murine model of allergic asthma. J Ethnopharmacol 200:51–59
67. Lv L, Yin B, You Y, Sun Z, He J, Cao YJ (2020) Protective effects of total alkaloids from Menispermum dauricum against airway inflammation in asthmatic mice. Planta Med 86 (10):665–673
68. Sharma S, Rasal VP, Patil PA, Joshi RK (2018) Mentha arvensis essential oil suppressed airway changes induced by histamine and ovalbumin in experimental animals. Nat Prod Res 32(4):468–472
69. Yang EJ, Lee JS, Yun CY, Ryang YS, Kim JB, Kim IS (2011) Suppression of ovalbumin-induced airway inflammatory responses in a mouse model of asthma by Mimosa pudica extract. Phytother Res 25(1):59–66
70. Nirmal SA, Pal SC, Mandal SC (2011) Antiasthmatic activity of Nyctanthes arbortristis leaves. Lat Am J Pharm 30:654–660
71. Eftekhar N, Moghimi A, Mohammadian Roshan N, Saadat S, Boskabady MH (2019) Immunomodulatory and anti-inflammatory effects of hydro-ethanolic extract of Ocimum basilicum leaves and its effect on lung pathological changes in an ovalbumin-induced rat model of asthma. BMC Complement Altern Med 19(1):349
72. Lee SY, Bae CS, Choi YH, Seo NS, Na CS, Yoo JC et al (2017) Opuntia humifusa modulates morphological changes characteristic of asthma via IL-4 and IL-13 in an asthma murine model. Food Nutr Res 61(1):1393307
73. Rosa MPG, Jose MMF (2018) Petiveria alliacea suppresses airway inflammation and allergen-specific Th2 responses in ovalbumin-sensitized murine model of asthma. Chin J Integr Med 24 (12):912–919
74. Chun JM, Lee AR, Kim HS, Lee AY, Gu GJ, Moon BC et al (2018) Peucedanum japonicum extract attenuates allergic airway inflammation by inhibiting Th2 cell activation and production of pro-inflammatory mediators. J Ethnopharmacol 211:78–88
75. Wu W, Li Y, Jiao Z, Zhang L, Wang X, Qin R (2019) Phyllanthin and hypophyllanthin from Phyllanthus amarus ameliorates immune-inflammatory response in ovalbumin-induced asthma: role of IgE, Nrf2, iNOs, TNF-α, and IL's. Immunopharmacol Immunotoxicol 41 (1):55–67

76. Ra J, Lee S, Kim HJ, Jang YP, Ahn H, Kim J (2010) Bambusae Caulis in Taeniam extract reduces ovalbumin-induced airway inflammation and T helper 2 responses in mice. J Ethnopharmacol 128(1):241–247
77. Rathore C, Dutt K, Sahu S, Deb L (2011) Antiasthmatic activity of the methanolic extract of Physalis angulata Linn. J Med Plant Res 5(22):5351–5355
78. Park HA, Kwon OK, Ryu HW, Min JH, Park MW, Park MH et al (2019) Physalis peruviana L. inhibits ovalbumin-induced airway inflammation by attenuating the activation of NF-κB and inflammatory molecules. Int J Mol Med 43(4):1830–1838
79. Kaushik D, Rani R, Kaushik P, Sacher D, Yadav J (2012) In vivo and in vitro antiasthmatic studies of plant Piper longum Linn. Int J Pharmacol 8(3):192–197
80. Bui TT, Piao CH, Song CH, Shin HS, Shon DH, Chai OH (2017) Piper nigrum extract ameliorated allergic inflammation through inhibiting Th2/Th17 responses and mast cells activation. Cell Immunol 322:64–73
81. Shakarami Z, Esmaeili Gouvrchin Ghaleh H, Mansouri Motlagh B, Sheikhian A, Jalali Kondori B (2019) Evaluation of the protective and therapeutic effects of Pistacia atlantica gum aqueous extract on cellular and pathological aspects of experimental asthma in Balb/c mice. Avicenna J Phytomed 9(3):248–259
82. Rana S, Shahzad M, Shabbir A (2016) Pistacia integerrima ameliorates airway inflammation by attenuation of TNF-α, IL-4, and IL-5 expression levels, and pulmonary edema by elevation of AQP1 and AQP5 expression levels in mouse model of ovalbumin-induced allergic asthma. Phytomedicine 23(8):838–845
83. Adusumalli S, Ranjit PM, Harish MS (2013) Antiasthmatic activity of aqueous extract of Pistacia integerrima galls. Int J Pharm Pharm Sci 5(2):116–121
84. Lee JW, Min JH, Kim MG, Kim SM, Kwon OK, Oh TK et al (2019) Pistacia weinmannifolia root exerts a protective role in ovalbumin-induced lung inflammation in a mouse allergic asthma model. Int J Mol Med 44(6):2171–2180
85. Lee CC, Lee YL, Wang CN, Tsai HC, Chiu CL, Liu LF et al (2016) Polygonum multiflorum decreases airway allergic symptoms in a murine model of asthma. Am J Chin Med 44 (1):133–147
86. Karani L, Tolo F, Karanja S, Khayeka C (2013) Safety and efficacy of Prunus africana and Warburgia ugandensis against induced asthma in BALB/c mice. Eur J Med Plants 3:345–368
87. Balestra AC, Sandy CM, Ramalho F, Júnior AAJ, Contini SHT, Crevelin EJ et al (2020) Aqueous Pyrostegia venusta (Ker Gawl.) Miers extract attenuates allergen-induced asthma in a mouse model via an antioxidant mechanism. J Asthma 2020:1–11
88. Shaw OM, Nyanhanda T, McGhie TK, Harper JL, Hurst RD (2017) Blackcurrant anthocyanins modulate CCL11 secretion and suppress allergic airway inflammation. Mol Nutr Food Res 61:9
89. Taur DJ, Patil RY (2011) Antiasthmatic activity of Ricinus communis L. roots. Asian Pac J Trop Biomed 1(1):S13–S16
90. Song CH, Bui TT, Piao CH, Shin HS, Shon DH, Han EH et al (2016) Rosae multiflorae fructus hot water extract inhibits a murine allergic asthma via the suppression of Th2 cytokine production and histamine release from mast cells. J Med Food 19(9):853–859
91. Jang HH, Cho SY, Kim MJ, Kim JB, Lee SH, Lee MY et al (2016) Anti-inflammatory effects of Salvia plebeia R. Br extract in vitro and in ovalbumin-induced mouse model. Biol Res 49 (1):41
92. Sanjeewa KKA, Jayawardena TU, Lee HG, Herath K, Jee Y, Jeon YJ (2019) The protective effect of Sargassum horneri against particulate matter-induced inflammation in lung tissues of an in vivo mouse asthma model. Food Funct 10(12):7995–8004
93. Kim H, Ahn Y-T, Kim YS, Cho SI, An WG (2014) Antiasthmatic effects of schizandrae fructus extract in mice with asthma. Pharmacogn Mag 10(Suppl 1):S80
94. Shin NR, Lee AY, Song JH, Yang S, Park I, Lim JO et al (2020) Scrophularia buergeriana attenuates allergic inflammation by reducing NF-κB activation. Phytomedicine 67:153159

95. Yu B, Cai W, Zhang HH, Zhong YS, Fang J, Zhang WY et al (2017) Selaginella uncinata flavonoids ameliorated ovalbumin-induced airway inflammation in a rat model of asthma. J Ethnopharmacol 195:71–80
96. Fouche G, Nieuwenhuizen N, Maharaj V, van Rooyen S, Harding N, Nthambeleni R et al (2011) Investigation of in vitro and in vivo anti-asthmatic properties of Siphonochilus aethiopicus. J Ethnopharmacol 133(2):843–849
97. Sung YY, Kim SH, Yuk HJ, Yang WK, Lee YM, Son E et al (2019) Siraitia grosvenorii residual extract attenuates ovalbumin-induced lung inflammation by down-regulating IL-4, IL-5, IL-13, IL-17, and MUC5AC expression in mice. Phytomedicine 61:152835
98. Yoo H, Kang M, Pyo S, Chae HS, Ryu KH, Kim J et al (2017) SKI3301, a purified herbal extract from Sophora tonkinensis, inhibited airway inflammation and bronchospasm in allergic asthma animal models in vivo. J Ethnopharmacol 206:298–305
99. Piao CH, Bui TT, Song CH, Shin HS, Shon DH, Chai OH (2017) Trigonella foenum-graecum alleviates airway inflammation of allergic asthma in ovalbumin-induced mouse model. Biochem Biophys Res Commun 482(4):1284–1288
100. Azevedo BC, Morel LJF, Carmona F, Cunha TM, Contini SHT, Delprete PG et al (2018) Aqueous extracts from Uncaria tomentosa (Willd. ex Schult.) DC. reduce bronchial hyperresponsiveness and inflammation in a murine model of asthma. J Ethnopharmacol 218:76–89
101. Harati E, Bahrami M, Razavi A, Kamalinejad M, Mohammadian M, Rastegar T et al (2018) Effects of viola tricolor flower hydroethanolic extract on lung inflammation in a mouse model of chronic asthma. Iran J Allergy Asthma Immunol 17(5):409–417
102. Arora P, Ansari SH, Najmi AK, Anjum V, Ahmad S (2016) Investigation of anti-asthmatic potential of dried fruits of Vitis vinifera L. in animal model of bronchial asthma. Allergy Asthma Clin Immunol 12:42
103. Hiralal Ghante M, Bhusari KP, Duragkar NJ, Ghiware NB (2014) Pharmacological evaluation for anti-asthmatic and anti-inflammatory potential of Woodfordia fruticosa flower extracts. Pharm Biol 52(7):804–813
104. Wang JQ, Li XW, Liu M, Wang SC, Cao ZF (2016) Inhibitory effect of Zanthoxylum bungeanum seed oil on ovalbumin-induced lung inflammation in a murine model of asthma. Mol Med Rep 13(5):4289–4302
105. Kianmehr M, Haghmorad D, Nosratabadi R, Rezaei A, Alavinezhad A, Boskabady MH (2017) The effect of Zataria multiflora on Th1/Th2 and Th17/T regulatory in a mouse model of allergic asthma. Front Pharmacol 8:458

Medicinal Plant-Based Advanced Drug Delivery System for the Treatment of Chronic Lung Diseases

24

Nitin Verma, Kamal Dua, and Aparna Sarin

Abstract

Lung disease represents a significant medical problem worldwide. They are usually treated by different synthetic drugs. Yet, incessant high-portion of oral and injectable medications may prompt extreme side effects and at this crossroad, there is a requirement of inhaled formulations that encourage successful medication to the pulmonary routes with no adverse effects. Chemicals isolated form plants, i.e. Common phytoconstituents or phytoalexin (for example, plant antimicrobials) have indicated a remarkable treatment cluster with least adverse effects and incredible ability to treat intrapulmonary and extrapulmonary illnesses contrasted with synthetic medications. In addition, the advancement and integration of various sciences, for example, nanoscience, polymer sciences, material science, and molecule designing along with particles shape and size analysis permits further improvement of the treatment capacity and productivity. This chapter highlights the plant-based advanced drug delivery system for the treatment of chronic lung diseases. Moreover, it also facilitates the scientist with some fundamental foundation data to phytochemical profile, plan prerequisites and medication conveyance frameworks.

N. Verma (✉)
Chitkara School of Pharmacy, Chitkara University, Baddi, Himachal Pradesh, India
e-mail: nitin.verma@chitkarauniversity.edu.in

K. Dua
Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Sydney, NSW, Australia
e-mail: Kamal.Dua@uts.edu.au

A. Sarin
HP Council of Science, Technology and Environment, Shimla, Himachal Pradesh, India

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_24

Keywords

Phytoconstituents · Chronic lung disease · Pulmonary delivery of phytoconstituents · Dry particulate powder inhalers

24.1 Introduction

Chronic pulmonary disorders are one of the main sources of mortality universally, described via constraint in airway, loss of elasticity, pneumothorax or atelectasis, swelling and inflammation in the main passages (bronchial tubes), emphysema, bronchoconstriction chronic bronchitis (CB) and discharge of abnormal fluid from lung [1]. Tobacco smoking, hereditary qualities, air contamination, breath of toxic particles, exposure to chemicals and gases are the main contributors towards the progression of pulmonary diseases. Chronic obstructive pulmonary disease (COPD), asthma occupational lung diseases and pulmonary hypertension are generally prevalent [2]. Globally, more than 500 million people are experiencing different lung illnesses [3]. With the advancement in technology and drug discovery process many new synthetic chemical molecules have been investigated and approved by various drug regulatory bodies available in the market having great restorative worth, yet this treatment causes severe side effects which in turn may be lethal. Conventional drug treatment gives non-targetability in body because of difference in concentration of drug in plasma and a concurrence of drug intake can cause inconvenient for synthetic treatment prime to poor patient consistence. Hence, synthetic medicines have commenced to move on herbal drugs as a prime source to deal with critical health issues, also lead us to look Back to the Mother Nature'. Around 80% of the current total population depends on utilization of natural products for their essential medical services and different needs which indicates the extent of plant-based prescriptions. Besides, herbal drugs having of lots of benefits and are less-poisonous with less unfavourable impacts. As indicated by the World Health Organization (WHO), the utilization of plant-based prescriptions everywhere on the globe surpasses customary medications by a factor a few times [4]. At present, herbal drugs have reclaimed their status for remediation of pulmonary diseases along with their efficacy and safety feature being strongly supported by controlled and randomized clinical trials in patients [5]. Present worldwide research has also presented valuable inputs about specific mechanism of action (MOA) of these herbal remedies [5, 6]. In this chapter, an effort has been made to highlight various aspects related to effectiveness of herbal medicines including their impact on chronic lung disease and other essential physicochemical properties of drug delivery systems are also discussed in detail.

24.2 Phytochemicals from Plant

Plant-based medicines have made irrefutable contributions from ancient cultures and created one of the basics for health care in almost all civilization throughout the world [7]. The use of herbal drugs is an essential part of any traditional system of medicine which is performed in several manners in various beliefs of the civilization [8, 9]. Notwithstanding their broad practice as therapeutic moiety, people's interest in herbal medicines is even increasing with special importance on their medicinal, clinical and financial significance. Herbal drugs themselves are well recognized for their huge range of phytoconstituents which are chemically diversified and pharmacologically active. This makes herbal drugs more interesting as key elements for drug discovery programs and new drug development. Thus, they play an important role and more interest due to their significance in modern medicines such as precursors, pharmaceutical intermediates, chemical entities for synthetic drugs, food supplements and nutraceuticals [8, 10].

Since the start of this century, the development of ground-breaking investigative apparatuses and innovations, sophisticated modern analytical tools, advancement in materials science, bioinformatics tools, computer aided drug designing and molecular biology have obtained fast development in the field of clinical and analytical characterization. These devices and scientific advancements offer new occasions to classify and characterization of these active phytochemicals. Notwithstanding their clinical applications these herbal drugs have been left over and cannot be accepted as an end point.

In its place, active and precise phytochemical are isolated and characterized to chemically synthesized particular drug analogues. These, phytochemicals are responsible for several organoleptic and therapeutic features of plants [11]. More precisely, these chemicals are plant secondary metabolites, for example, alkaloids, glycosides, polyphenolics, lignans, terpenoids, etc. which are biosynthesized in plants through various metabolic pathways. Phytoconstituents and their effects on biological system have been extensively studied and investigated in this century. Their therapeutic benefits are of main attention because of their role in prevention of significant dangerous ailments, for example, cancers, cardiovascular intricacies and respiratory diseases. These ailments are leading causes of death currently which signifies that phytoconstituents will continue to be matter of scientific research community interest. Based on applied health benefits such as free radical scavenging activity, anti-inflammatory and immuno-modulatory, phytochemicals may act as a potential therapeutic agent or as an alternative therapy [8, 10].

24.3 Phytochemical Use in Inhalation Delivery for Lung

Inhalation therapy still is an interesting as a new approach for drug delivery applications, and this particular technique has been recorded all over in a large portion and has strong history [12]. With the growth in the field of medical sciences, material sciences and engineering, nanoscience and molecular biology have

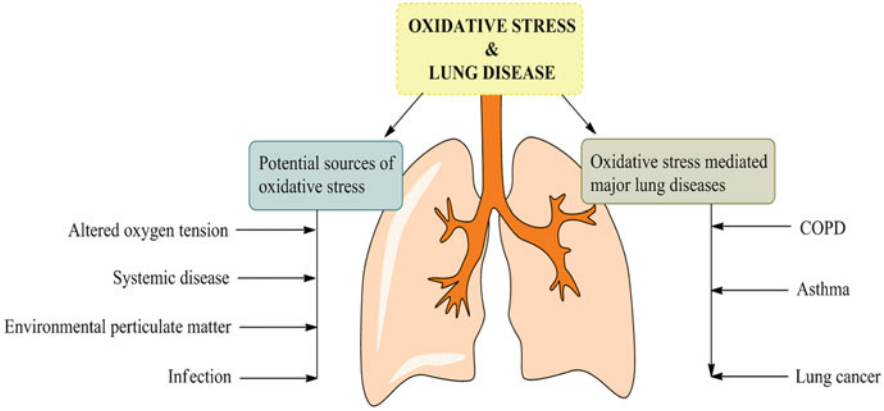


Fig. 24.1 Oxidative stress in pulmonary diseases

assimilated enormous advances in the field of inhalational therapy and drug delivery. Now, we have now raised our hopes higher, attempting to use this non-obtrusive approach to combat multiple extrapulmonary infections in addition [13]. The lung is exposed to an oxygen-rich atmosphere and is subsequently vulnerable to damage caused by oxidative stress (Fig. 24.1). Various cell reinforcement guarantees (antioxidants), as epitomize glutathione, superoxide dismutase (SOD), β-carotene, nutrients C and E, uric corrosive and heme-oxygenase [14–16], are provided to block this harm to lung tissues. However, biological antioxidant defences are often reversed by reactive oxygen or nitrogen species, and an oxidative strain contributes to a variety of lung disorders. The presumption of oxidative damage in cystic fibrosis (CF), asthma, chronic obstructive pulmonary disease and direct to epithelial cell injury by reactive oxygen species has been confirmed in various clinical literature at present [14, 16]. The present medication is used to monitor the excessive discharge of mucus and inflammatory disorders in order to avoid or prevent damage to lung tissue. For lung tissue injury, a few treatment options are available, such as oral / inhaled corticosteroids or high dosages of oral N-acetylcysteine. However, in the face of major side effects, these therapies have insufficient beneficial steps. Hence, improvement of organic cell reinforcement securities through a pharmacological treatment or an eating routine may be a reasonable methodology in treatment of lung diseases. In order to minimize or prevent damage to lung tissue, the present drug is used to control excessive discharge of mucus and inflammatory disorders. There are a few treatment options available for lung tissue damage, such as oral/inhaled corticosteroids or high oral N-acetylcysteine dosages [17]. These treatments, however, have inadequate helpful measures in the face of significant side effects. Since many scientific studies have been conducted on the antioxidant and anti-inflammatory impact of these polyphenolic compounds, however, few scientific publications have discussed the formulation design of these polyphenolic compounds in order to improve bioavailability. Many nanocarriers and microparticles delivered orally have recently been designed and tested. In particular,

several lipid vesicles such as liposomes, microparticles and cochleates are also explored in the drug delivery of phytoconstituents. Oral administration of these drug delivery systems leads to a poor therapeutic response due to the increased first pass metabolism and enzymatic degradation within the gastrointestinal tract (GI) [18]. There is a strong need for elective care to deal with these problems and to make phytoconstituent therapy more successful. An alternative solution may be to obtain a higher local concentration of antioxidants and anti-inflammatory drugs in the tissue of the lung by administering aerosol directly to the airways by means of a nebulizer, soft mist inhaler or dry powder inhaler, pressurized metered dose inhaler [14]. Dry powder inhalers have many advantages compared to other inhalational methods, such as being propellant-free and requiring no reconstitution of powders or cold chain storage and are more convenient, and no need for collaboration between patient inspiration and inhaler operation, more opportunities for carrier engineering and less coastally [12, 19]. Ultimately, phytoconstituent physicochemical and biopharmaceutical properties can be improved by DPIs and a higher drug focus at the desired site can be transmitted (Fig. 24.2).

24.4 Phytoconstituents Based Dry Powder Inhalers (DPI)

The pulmonary drug delivery system (PDDS) is a specific approach to delivery and has become more of an interest in the field of drug delivery research because of its easy transition in development, the potential to treat different pulmonary venous and extra pulmonary diseases, intensified therapeutic potential with minimal antagonism effects. Several new inhaled phytoconstituent drug delivery systems (NDDS) and their main findings are summarized in Table 24.1. These delivery mechanisms will provide better care opportunities that are safe, effective and readily accessible. This section thus highlighted and reviewed the literature available and published in the last decade on inhalable phytochemical agents.

24.4.1 Alkaloid

24.4.1.1 Atropine

Atropine, commonly known as Solanaceous alkaloid, naturally existing tropane alkaloid derived from the different species such as Atropa belladonna, Datura inoxia, Datura stramonium and Datura metel (Solanaceae) family of berries, leaves and roots. The chemical, pharmacological and toxicity profiles have also been extensively investigated and reported [7, 9, 20]. Through use of atropine for the prevention of organophosphate poisoning [21] has also been studied by several researchers. Atropine is widely administered intravenously (i.v.), intramuscularly (i.m.) and orally. If delivered thru i.v., its maximum plasma level is 5 min for injection, while with i.m. the injection or medicament delivers drug within 30 min. A 2 mg i.m.; maximum blood absorption was reported with the dosage 6–8 ng/mL. The peak changes occurred after 2 h after taken orally. An alternative, self-administered and

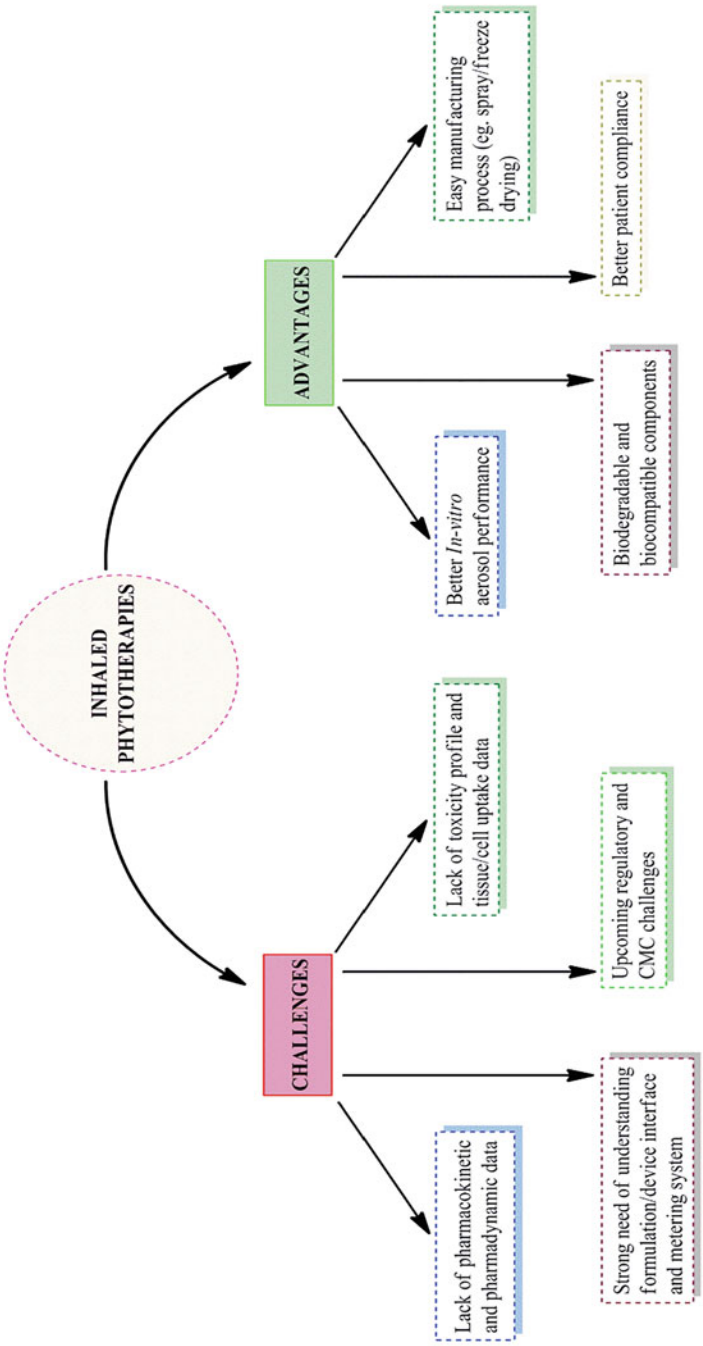
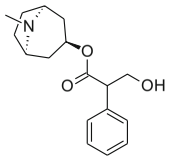
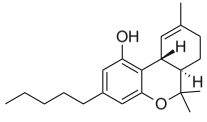
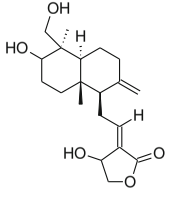


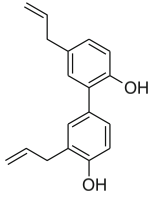
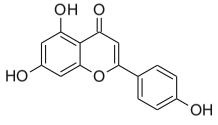
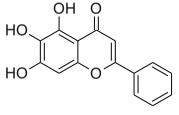
Fig. 24.2 Major challenges and benefits associated with inhalational drug delivery from phytochemicals

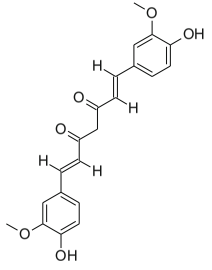
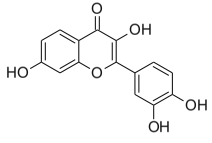
Table 24.1 Phytochemicals for various pulmonary drug delivery system

Chemical class	Phytochemical	Chemical structure	Formulation/conjugate	Methodology	Major outcome	References
Alkaloids	Atropine		Atropine-nanoparticles	Nano-precipitation	1.52-fold improvement in percent respiratory fraction compared to microparticles showed early blood bioavailability in clinical study when delivered using Rotahaler	[22]
			Atropine sulphate micro dose dry powder inhaler	Spray drying	Showed satisfactory pharmacokinetic profile relative bioavailability of 87% when delivered using MicroDose Therapeutx DPI	[21]
Cannabinoid	Dronabinol		Dronabinol solid dispersion	Spray freeze drying	Achieved satisfactory FPF of 50%	[23]
Glycoside	Andrographolide		Andrographolide-loaded scleroglucan microparticles	Spray drying	1.84- and 1.47-fold improvement in ED and % FPF 1.73-fold improvement in bioavailability compared to conventional andrographolide formulation	[26]
			Andrographolide-β-CD inclusion complexes	Freeze drying	1.89-fold improvement in dissolution in SLF better anti-pneumonia compared to andrographolide alone and penicillin	[27]

(continued)

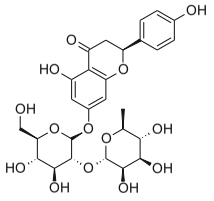
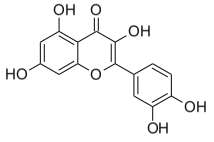
Table 24.1 (continued)

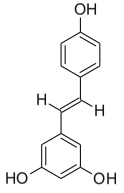
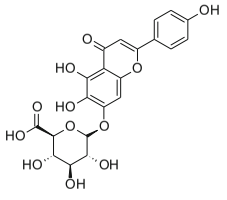
Chemical class	Phytochemical	Chemical structure	Formulation/conjugate	Methodology	Major outcome	References
Lignan	Honokiol		Honokiol-chitosan microparticles	Spray drying	Controlled release up to 96 h with ~90% drug released at end of study	[29]
Polyphenols	Apigenin		Apigenin-loaded bovine serum albumin NPs	Spray drying	Approx. 70 and 95.18% of FPF and emitted dose was observed	[30]
	Baicalein		Baicalein nanocrystal	Anti-solvent recrystallization followed by high pressure homogenization	Approximately 91% bioavailability was achieved after pulmonary administration almost similar to i.v. baicalein at an equivalent dose (10 mg/kg)	[33]
	Curcumin		Curcumin-PLGA-(PEG-Cs) swellable microspheres	Spray drying	Sustained drug release up to 24 h with satisfactory in vitro cytotoxic activity in Raw 264.7 cell lines	[36]
			Curcumin-nanocrystals	Wet milling coupled with Spray drying	3.16- and 7.5-fold improvement in bioavailability and Cmax during in vivo pharmacokinetic study	39

			Curcumin -HP-β-CD-PVP microparticles	Atomized rapid injection solvent extraction system	70-fold improvement in solubility 6.1-fold improvement in %FPF compared untreated curcumin	[38]
			Curcumin-(Ac-Dex)-nanocomposites microparticles	Spray drying	Fast CUR release due to rapid polymer degradation better drug diffusion potential	[41]
			Curcumin-L-lactide-XG-micelles	Direct dissolution coupled with freeze drying	2.20- and 1.77-fold improvement bioavailability and C_{max} after intratracheal administration	[40]
			Curcumin-mannitol nanocomposites	Spray drying with twin jet nozzle system	3.90-fold improvement in dissolution behaviour	[35]
			Curcumin -phytosomes loaded chitosan microspheres	Spray drying	Showed satisfactory FPF of ~60%	[43]
	Fisetin		Fisetin-sulfobutylether-β-CD microparticles	Spray drying	2.3-fold improvement in FPF with satisfactory antioxidant activity	[46]
	Naringin		Naringin microparticles	Spray drying	Achieved satisfactory yield of 60.8% with a FPF of 55.8%	[14]

(continued)

Table 24.1 (continued)

Chemical class	Phytochemical	Chemical structure	Formulation/conjugate	Methodology	Major outcome	References
			Naringin-corrugated microparticles	Spray drying	Achieved satisfactory yield of 60.7% with a FPF of 63.4 % multiple-path model of particle deposition simulation	[15]
	Quercetin		Quercetin-loaded-glyceryl trimyristate SLM	Hot solvent diffusion method	Deliver a high fraction of drug to the deep lungs in	[54]
			Quercetin-glyceryl behenate SLM	Hot emulsion method	1.75-fold improvement in dissolution at end of 24 h with high drug loading capacity	[54]
			Quercetin-loaded tristearin SLM	O/W emulsification via phase inversion technique	SLM showed a linear kinetic across the Calu-3 monolayer (>22% over 4 h)	[55]
			Quercetin-loaded tristearin LM	Melt emulsification followed by sonication and lyophilization	Sustained release profile with 2.3-fold improvement in intracellular delivery	[56]
	Resveratrol		Resveratrol-PCL-microparticles	Spray drying with piezoelectric atomization system	Controlled release up to 12 h (>85%) with FPF of 46.48%	[61]

			Resveratrol-loaded microparticles	Spray drying	Control the level of inflammatory mediators, such as IL-8, TNF-α, LPS and TGF-β1 with antioxidant property equivalent vitamin C	[62]
	Resveratrol and budesonide		Resveratrol and budesonide dual microparticles	Co-spray drying	Exhibit satisfactory antioxidant activity with reduce the levels of TNF-α, TGF-β1 and LPS	[63]
	Scutellarin		Scutellarin-mucoadhesive microparticles	Spray drying	30-fold improvement in bioavailability after intratracheal administration compared to per-oral route	[66]

equally active dosage is desirable during casualty (fatal distressing haemorrhage or serious military or civilian damage) because i.v. practically, is not feasible in the field, while peak concentration by i.m., the dosage may have been inexcusably delayed.

In addition, parenteral pathways need help of paramedical personnel or professionals [22]. The need for reliable, precise release and safe dosage of atropine for the prevention of organophosphate poisoning is present at this juncture. An inhaled atropine formulation (IAF) can therefore be produced or developed to orderly deliver atropine doses in a framework that makes self-administration or dosing without inconvenience for scheduled span of time.

Ali et al has developed, analysed and performed a clinical study on dry powder inhaler nano-atropine sulphate (nano-AS) prepared by nano precipitation technique. The mean particle size was resulted to be 0.3 nm with low water content as well as enhanced flowability was shown by spherical nanoparticles. Utilizing Andersen Cascade Impactor with Rotahaler® system at a flow rate of 60 L/min for 4 s using 3 hard gelatin capsules, aerosol dispersion was analysed. The ACI study indicated substantial ED and respiratory fraction dispersion and deposition of 94.33 and 65.21%, respectively. In addition, relative to atropine microparticles, nanoparticles exhibited a 1.52-fold respiratory fraction increase (42.64%). In addition, bioavailability evidence in a controlled clinical trial of healthy male volunteers showed that approximately ∼3 mg of 6 mg of atropine penetrated through lungs into systemic circulation [22].

Pharmacokinetics profile of atropine sulphate was identified by Corcoran et al in healthy non-smoking human volunteers supplied by AtroPen®, auto-injector (AUTO; 2 mg) via intramuscular route, and delivery through pulmonary route utilizing Micro Dose Therapeutx, Dry Powder Inhaler (DPIA); (1.95 mg [5 dose per 0.4 mg/dose (administered over 12 min)]). DPIA displayed a steady blood profile with an area under curve (AUC) difference coefficient of 0.3 and this concentration rapidly appeared (Tmax-15 min) following drug inhalation. The relative bioavailability was 87% for the DPIA group. In brief, DPIA provides an excellent approach to successful systemic therapy and can be helpful if rapid intervention is required or when the Gastro intestinal pathway is undesirable [21].

24.4.2 Cannabinoid

24.4.2.1 Dronabinol

Dronabinol is a viscous, pale yellow in colour cannabinoid derived from the family Cannabis sativa, Cannabaceae. Chemically, Δ9-tetrahydrocannabinol (THC) is a multifunctional cannabinoid, ranging from analgesic to hypotensive, which has many therapeutic potential. While having many pharmacological operations, it has low water solubility (0.77 mg/mL) [23], first pass metabolism, rapid deterioration in acidic aqueous systems and oxidation in the air have not yet been developed in an acceptable dosage type. It is also a very labile and sticky resin that renders the product formulation and formulation process more complicated. Nevertheless, in

regard to these obstacles, its soft gelatin capsule (Marinol®), sublingual tablet (SLT), pro-drug (THC-hemi-succinate ester salt) indeed has been synthesized to enhance pharmaceutical properties. These formulation advances, however, reveal an unsatisfactory shelf life of the product and demonstrate poor and erratic absorption. Using spray freeze drying to prevent first pass metabolism and other challenges, a respirable solid dispersion powder (SDP) with inulin was synthesized, analysed and reported by Drooge et al. Powders can now be distributed into aerosols of a reasonable particle size acceptable for inhalation purposes [23].

By a spray freeze-drying (SFD) technique, THC conjugated respirable solid dispersion powder (SDP) were developed and recorded through using a stabilizing agent's inulin (oligo fructose). Spherical shape microparticles exhibited rough surface and adequate loading ability for the drug. In addition, it is more suitable for inhalation because of its highly impermeable nature and large specific surface area (90 m^2/g). In conclusion, better structural properties (50%; FPF) and fair physicochemical stability have shown relative to its freeze-dried powder (FDP) [23].

24.4.3 Diterpenoid

24.4.3.1 Andrographolide

Andrographolide is derived from plant Andrographis paniculata of Acanthaceae family. It is a bitter terpenoid also known to be "King of Bitters". Their cultivation is mostly in Southeast Asia and they may offer various therapeutic effects [24]. Andrographolide can reduce blood pressure via smooth muscles relaxation of blood vessels. Despite their therapeutic value they are not commercialized due to their poor water solubility (3.29 mg/mL) and reduced oral bioavailability (2.67%), and they also undergo first pass metabolism [25]. Therefore, a suitable carrier may improve its bioavailability and thus some researchers have reported with effective drug delivery system of andrographolide for lung. Mali et al. developed scleroglucan microparticles loaded with andrographolide with spray drying technique. These spherically shaped microparticles of size 2.32 μm has >98% drug binding capacity. Intratracheal administration of 1.25 mg of andrographolide microparticles demonstrated better antihypertensive action, enhanced plasma drug concentration with no side effects as compared to formulation of conventional andrographolide. In addition, the microparticles demonstrate considerable enhancement in white blood cells (WBC) and lymphocyte count owing to andrographolide immunostimulant activity [26]. The inclusion complexes of andrographolide-β-CD were developed using freeze-drying technique (FDT) and its anti-pneumonia effect was studied in rats by Zhang et al. [27]. These novel microparticles of size 5 Mm displayed highly effective aerosolisation with a FPF and ED of (81.83% and 96.08%) correspondingly. Further, complexes of B-CD exhibited better dissolution of andrographolide in lung fluid by 1.89-fold. Moreover, new inclusion complexes adequately improved andrographolide dissolution locally in tissues of lung and exhibited better anti-pneumonia effect in comparison to penicillin and andrographolide alone [27].

24.4.4 Lignan

24.4.4.1 Honokiol

The traditional system of medicines in Asia uses numerous species of genus Magnolia, such as *M. officinalis*, *M. obovata* and *M. grandiflora* of Magnoliaceae family [28]. They can be found all across globe distribution mostly in east and Southeast Asia. Honokiol is a lignan originated in many species with genus Magnolia that has been reported to possess various therapeutic properties ranging from antibacterial to neuroprotective. They have also gained recognition in the ground of western medicine and have been formulated as oral, systemic and transdermal drug delivery [28]. Also, Honokiol is reported for pulmonary delivery. Honokiol inhalable microparticles are formulated with the help of Chitosan/mannitol (1:8; w/w) followed by spray drying as reported by Li et al. Microparticles size was reported with 8.48 μm and 3% drug loading capacity with ∼50% yield and the microparticles displayed ∼90% drug released at pH 7.4 [29].

24.4.5 Polyphenols

24.4.5.1 Apigenin

Apigenin is the chemical compound found in plants bearing aromatic flower like carrot and celery belonging to the family Apiaceae and the chemical name of apigenin is 4′,5,7-trihydroxyflavone. It is categorized under class II of BCS classification [30]. Majority of beverages, fruits and vegetables also contains Apigenin such as red wine, grapes, apple and chamomile tea [31]. From the past few years Apigenin have been evaluated for therapeutic purpose. The therapeutic efficiency of Apigenin is mainly associated with its antioxidant effects and free radical scavenging (FRS) actions. Besides these, it also possesses therapeutic effects such anti-inflammatory by suppressing mediators of inflammation like cyclooxygenase-2 and cytokines in human and mice lung epithelial cells [30]. Acute lung damage due to inflammation in respiratory tract arises from oxidative stress; the inhalable nanoparticles of apigenin have been reported to manage inflammation of respiratory track by Papay et al. [30]. Papay et al. developed inhalable nanoparticles loaded with apigenin by spray drying method and reported with particle size: 376 nm, encapsulation efficiency: 82.61% and drug loading efficiency: 7.51%. Another formulation is the L-leucine based nanoparticles (NPs) that resulted in improved aerosolisation functioning as compared to lactose-based NPs. But nanoparticles enclosing lactose showed better release of apigenin in altered lung fluid (pH 7.4) whereas L-leucine NPs offered decreased in vitro discharge [30].

24.4.5.2 Baicalein

Baicalein, a 5,6,7-trihydroxyflavone is extorted from the roots of *Scutellaria baicalensis* Georgi belonging to Lamiaceae family is broadly utilized in Traditional Chinese Medicine (TCM) system [32]. Baicalein have been utilized in restoring patient health from diseases like lung cancer, hypertension and inflammatory

diseases. Baicalein is categorized under class II of BCS drug classification as they have low solubility with high permeability and undergo first pass metabolism because of which their use in pharmaceutical industries is limited despite of having varied therapeutic value [33]. Zhang et al. developed inhaled formulation of nanocrystals loaded with Baicalein drug in order to enhance its bioavailability and to circumvent first pass metabolism. The nanocrystals were developed via anti-solvent recrystallization technique (ASRT) after which they were homogenized under high pressure along with a stabilizing agent polysorbate 80 (0.3%) and solvent ethanol. The powder of Baicalein nanocrystals displayed better dissolution report when compared with Baicalein crystal and reported with similar pharmacokinetic profile and significant absorption of Baicalein at consequent 10 mg/kg dose. Thus, particle size reduction with increased surface area has improved Baicalein dissolution property and bioavailability.

24.4.5.3 Curcumin

Curcumin is a hydrophobic polyphenol (diferuloylmethane) with a yellow-orange colour, derived from the *Curcuma longa* rhizome of the Zingibaraceae family. Chemically, it is a β-unsaturated, β-diketone and bis-alpha that shows tautomerism of ketoenol having a stable form of enol in alkali medium and keto in neutral and acidic medium [34]. There are many medicinal properties of curcumin, including anti-inflammatory, anti-carcinogenic and respiratory disorders [34]. The effect of curcumin on the behaviour of both acute and chronic lung disorders has been studied by several researchers [35]. In addition, successful anticancer action against different lung tumour cell lines was also shown; human lung adenocarcinoma cell (A549), human lung adenocarcinoma (Calu-3), lung metastasis cell (B16BL6) [36] and mouse macrophage cell line (RAW 264.7) [37]. Moreover, the performance of many transcription factors and respective signalling pathways were rapidly modified [34]. However, low water solubility of 0.6 μg/mL, high molecular weight of 368.39 g/mol, log P value of 2.5, weak intrinsic dissolution rate, low and unstable bioavailability less than 1% [38], high protein-binding performance, rapid metabolism and rapid excretion from the body are the major problems associated with poor pharmacological responses of this specific polyphenol [35]. Various inhalable formulations of curcumin have been developed and tested to enhance the bioavailability, physical stability and solubility profile of curcumin, including nanocrystals, cyclodextrin complexes [39], nanocrystals formulation [40] polymeric micelles [41], nanocomposites [42] and swelling microspheres [37] in order to solve these problems and to improve its pharmacokinetic profile. In the following section, several research studies on novel inhalable curcumin formulations are discussed.

In a research published by El-Sherbiny et al., dried inhalable curcumin-loaded poly [D, L-lactic-co-glycolic-acid] (PLGA) nanoparticles encapsulated in co-polymer-based swellable microspheres of amphiphilic pegylated-chitosan (PEG-Cs) were formulated to control curcumin aerodynamic parameters and macrophage uptake. Spherical microspheres displayed a smooth surface with a mean particle size of 243.4 nm and a satisfactorily high efficacy of aerosolization was achieved with a fine particle fraction (FPF) of 30.2% and an emitted dose (ED) of

98.1% calculated at 60 l/min through the HandiHaler® system. Microspheres showed over 24 h of accurate curcumin release over time. Due to the strong hydrophilicity of PEG side chains in PEG-g-Cs Co-polymer conjugate, this data was consolidated to improved swelling index (>90% in 20 min) and low moisture content (<1.8%) in phosphate buffer solution having pH 7.4. No local inflammatory effects and toxicity were observed in the findings of the in vitro assay with MTT and TNF-alpha on RAW 264.7 cell lines. In short, these swelling curcumin microspheres were considered to be a competent delivery directly to the pulmonary area for the treatment of many lung disorders [37]. Hu et al. and his team formed curcumin nanocrystals and analyse for in vitro deposition in lung tissues parallel with in vivo pharmacokinetic and tissue distribution studies in rabbits by using the wet milling optimization technique with spray drying (SD) for nanocrystal preparation. The spray-dried curcumin nanocrystals have a spherical shape and a uniform particle size of 1086 nm. In an aqueous solution containing 1% of sodium dodecyl sulphate (SDS), the nanocrystals display an almost complete dissolution rate (98% in 4 h) of curcumin. In addition, with an FPF total of 68.92% and an emitted dose (ED) of 72.1% calculated by an advanced next generation impactor (NGI) method at a flow rate of 60 l/min, an appropriate aerosolisation efficiency was obtained. Pulmonary administration of these nanocrystals subsequently showed a 3.16 and 7.5-fold rise in plasma level and C_{max} (maximum drug concentration) significantly in comparison to oral curcumin delivery at the same curcumin single dose (25 mg/kg). Curcumin recorded the maximum concentration (824.27 μg/g after 6 h) in lung tissues and curcumin content after endotracheal intranasal relative to every other organ in the tissue distribution sample, thereby decreasing cytotoxic effects. The study findings have clearly shown that phytoconstituent nanocrystals are a promising delivery method for pulmonary delivery [40]. Aerosolized microparticles loaded with curcumin were developed by combining hydroxypropyl-beta-cyclodextrin (HP-β-CD) and polyvinyl pyrrolidone (PVP) using the new atomized rapid injection solvent extraction (ARISE) method. This method showed a very good percentage yield, with a smooth surface and elongated behaviour of appropriate particle size. In addition, curcumin microparticles display a 70-fold improvement in curcumin solubility and dissolution profile in the salt solution. In contrast, curcumin-loaded microparticles showed a better FPF (61%), investigated at a velocity of about 28.3 l/min utilizing Andersen Cascade Impactor (ACI). Additionally, comparison to binary systems of (HP-β-CD-Curcumin) and native curcumin, respectively, the produced microparticles exhibited a 1.5 and 6.1-fold increase in FPF [39]. Wang et al. developed and documented curcumin-loaded acetate dextran (Ac-Dex) microparticles (nCm-P) and microparticles (MP) of nanocomposites using a spray drying method. NCm-P showed a puffy surface with a raisin-like morphology and a mean particle size of 200 nm, but MP showed a trembling surface with an average particle size of 1 μm. Better encapsulation efficiency for MP approximately 50% than nCm-P (30%) was integrated into the spray drying process. The in vitro release of the MP and nCm-P systems showed a quicker release of curcumin in acetate buffer (pH 5) relative to phosphate buffer (pH 7.4). In contrast to MP systems, the release patterns revealed that nCm-P systems have a significantly higher curcumin

release profile due to nanometer scale, higher surface area and rapid polymer deterioration with better drug delivery. In addition, aerodynamic parameters with a mass median aerodynamic diameter (MMAD) of 2.5 and geometric standard deviation (GSD) of 2.7 were adequate for both MP and nCm-P systems. In conclusion, the novel acetylated dextran aerosol particle method has shown a great potential for atretic delivery of polyphenolic phytoconstituents into the target portion of the lung tissues [42]. In another study, a novel method, followed by freeze drying (FD), was documented employing L-lactide grafted xyloglucan micelles for pulmonary delivery of curcumin by direct dissolution approach. This curcumin embedded spherical micelles had a mean particle size (102.4 nm) of −18.2 mV negative zeta potential with 96.38% extraction efficiency (EE) and 70% drug loading power (DLC). Sustained release (>50%) of curcumin up to 5 h was verified by novel polymeric micelles and was better suited to an irregular, non-Fickian release kinetic model. Additionally, with an FPF total of 12.16% and an ED of 99.6% calculated using ACI, a substantial aerosolisation effect was observed. At a dosage of 100 mg/kg, the micelles showed a 2.20 and 1.77-fold increase in plasma drug and C_{max} concentrations relative to curcumin suspension following intratracheal administration. Appropriate increase in bioavailability of curcumin after intratracheal administration is eligible for the sustained effect of curcumin in the lungs [41]. In another study, nanocomposite particles embedded with inhalable curcumin were formulated and reported using mannitol as a ligand using a spray dryer configured with a twin jet nozzle. The formulated smooth surface aggregated nanocomposite particles revealed a particle size of less than 3 μm and a 3.90-fold improvement in the curcumin release profile of Tween 80 containing aqueous solution (0.1%). The novel nanocomposite composition showed a substantial FPF of about 20% assessed at a flow rate of 28.3 l/min using the Jethaler® unit. In addition, in several in vitro assays such as "WST assay on A549" lung cancer cell line, "B16BL6" lung metastasis cell line and "Raw 264" macrophages-like cell lines, curcumin-loaded nanocomposites demonstrated dose-dependent cytotoxic effects. Li et al. conducted work on dry powder inhalation (DPI) by spray-drying (SD) technique based on phytosomes-chitosan microspheres and analysed its characterization. Chitosan microspheres filled with curcumin phytosomes were formulated using the SD technique. Good aerodynamic diameter of 3.93 μm was seen in the sphere-shaped including surface microspheres with 12% drug loading power. In addition, curcumin-loaded microspheres display an adequate ED of 98% with an FPF of about 60%. There is a great potential for these formulated microspheres to be used as a DPI for pulmonary delivery applications [43]. In the treatment of different lung disorders, CUR has shown great therapeutic effects. In combination with many biodegradable polymeric materials such as PLGA and dextran, synthetic polysaccharides such as HP-β-CD and strength control compounds such as PVP, it is evident from the above literature that curcumin can be safely incorporated into different microparticulate formulations. Using spray-dried microparticles, the biopharmaceutical properties of curcumin can be easily modified, with a significant dosing necessary for physiological effects. A special capacity for pulmonary transmission is also reported by curcumin-loaded polymeric micelle and novel phyto-phospholipid systems (Phytosome®). In the evaluation of

all delivery systems, the nanocrystals-based curcumin formulation reported significant improvements in blood plasma concentration and in vivo bioavailability. The combination of curcumin with a clearly defined delivery device may therefore be the best solution in clinical practices in terms of patients with lung diseases. The targeted pulmonary delivery of curcumin will be far more optimized through the exponential growth of formulation sciences, coupled with polymers and particle engineering.

24.4.5.4 Fisetin

Fisetin is a diphenylpropane flavone derived from various parts of plants. Chemically, the flavone is 3,3′,4′,7-tetrahydroxy. Because of its various therapeutic activities, for instance, anticancer, anti-inflammatory, antiviral and antioxidant activities, the fisetin has been intriguing for a few days now [44]. In contrast to this, phospholipase-Cβ inhibition, ultimately decreases airway smooth muscle contractions, also exemplifies anti-asthmatic properties [45]. Acceptable water solubility of ~10.45 μg/mL, high lipophilicity, log P 3.2 and low bioavailability profile of 44.1% are the key obstacles associated with its weak therapeutic efficacy [44]. Several new strategies have been developed and tested to enhance its bioavailability, solubility and physicochemical properties by understanding these circumstances, namely nano-emulsions, liposome formulation, nanocochleates and polymer conjugates such as cyclodextrin and cyclosophoroase [46]. The efficacy of lung transmission of the fisetin complex with sulfobutylether-β-cyclodextrin (SBE-β-CD) was recently investigated and reported by Mohtar et al. and co-workers in 2017. The purpose of this study is to enhance the solubility and anticancer activity of fisetin complexes. Fisetin-loaded microspheres were synthesized with a mini spray dryer using synthetic derivative of β-cyclodextrin (SBE-β-CD) and fisetin at a 2:1 ratio. Physicochemical research showed 0.76% crosslinking efficiency, 1.48 μm particle size and concentric patched particle surfaces. It was reported that ethanol derived powder with improved aerodynamic properties by up to 20%, FPF 32.49% and showed a twofold increase in FPF (%) as compared to aqueous system powder. In addition, it was noted that the addition of small amount of (20%) leucine further increased FPF by 2.3-fold. Fisetin microparticles demonstrated an EC50 value equal to fisetin alone with MTT assay on A549 cell line [46].

24.4.5.5 Naringin

Naringin, a chemical constituent of herbal drugs, namely *Drynaria fortune* (Kunze) J. Sm. belonging to the family Polypodiaceae, *Citrus aurantium* L. and *Citrus medica* L. belonging to the family Rutaceae was firstly evidenced by De Vry in 1857 and its chemical conformation first of all was investigated and characterized by Asahina and Inubuse in 1928. Due to the presence of this compound, citrus juices have bitter taste [47]. It has various therapeutic uses such as antioxidant, anti-inflammatory and anticancer owing to its potential impact to regulate numerous signalling processes in several physiological systems [48]. Despite that, its clinical utilization is circumscribed because of its high log P value ~2.4, poor water solubility (1 mg/mL), and low internal dissolution rate and rapid hepatic excretion [47, 49]. By combining phytochemicals with suitable functional excipients the

biopharmaceutical characteristics of poorly absorbed phytoconstituents have been efficiently improved as a result of advancement in synthesis of these functional excipients (suitable functional group attachment) [50]. Various inhalable naringin formulations have been, developed, fabricated and characterized currently by number of researchers.

Inhalable naringin microparticles were prepared by spray drying technique (SD) by employing water: ethanol in ratio of 6:4. It was established that corrugated surface amorphous microparticles were produced by adding 40% ethanol having particle size (9.47 μm) and rational yield (60.8%). Furthermore, improved aerodynamic properties was achieved with a FPF (55.8%) and MMAD (3.29 μm) calculated by means of device Turbospin® at the rate 60 l/min. Concisely, volume of ethyl alcohol ~40% along with concentration of naringin ~3% are significant parameters that influence aerodynamic characteristics of microparticles. The inhalable powders having ethyl alcohol content 50% and proportion of naringin ranging from 4 to5% found to degrade aerodynamic behaviour owing to the formation of conglomerates instead of discrete particles [14]. Corrugated microparticles of naringin with raisin-like surfaces has been prepared having Leucine 5% in a common solvent of ethyl alcohol and water in ratio 3:7 by using the spray drying technique and investigated by the same researchers. It can be concluded that leucine addition (amino acid) has shown 1.13 times increase in FPF % in contrast to preliminarily proclaimed evidence having FPF 55.8%. In addition, naringin incorporated microparticles substantially hinder gene expression of the vital enzymes and cellular multiplication in MTT assay on "CuFi1" and "NuLi1" (derived from human bronchial epithelium of a cystic fibrosis) cell lines [15].

24.4.5.6 Quercetin

Quercetin, ubiquitous polyphenolic flavonoid (3,3′,4′,5,7-penta-hydroxyflvanone) having bright citron yellow colour which is obtained from number of fruits, berries and leafy vegetable. It is one of the vital constituents of the diet and its recommended daily intake is 50–800 mg/day. Essentially, it is a flavonoid that can be used for the emanation of novel and effectual useful foodstuffs as well as therapeutics which exhibits its significance for exceptional range of health impacts, Quercetin have various therapeutic impacts against a large number of disorders as investigated in number of clinical trials [51]. On the other hand, the eminent therapeutic efficacy of quercetin is reduced due to its high lipophilicity, low solubility in the aqueous phase (0.48 μg/ml) and poor oral bioavailability (~2%) [52, 53]. Furthermore, it is having a catechol moiety bearing 3′ and 4′ hydroxyl substitution along with in vivo methylation [51]. Thus, all these reasons may result in high and frequent dosing to achieve optimal valuable impacts which further results in serious unfavourable effects. To figure out aforementioned challenges, solid lipid microparticles (lipid-based drug delivery system) or lipid microparticles of quercetin being developed and analysed.

Silva et al fabricated quercetin-encapsulated solid lipid microparticles (SLM) of soy-lecithin and glyceryl trimyristate using hot solvent diffusion method (GTL) in comparison with microparticles of glyceryl behenate and lecithin by means of hot emulsion method (GBL). Conclusively, fatty acid plays an essential role in particle

shape, dimensions as well as surface of microparticles. GBL has shown to exhibit dissolution 1.75 times higher than that of GTL with equivalent drug (300 mg). In comparison with GBL, GTL have shown better aerodynamic properties in MPPD analysis [54]. Scalia et al., developed and reported quercetin-incorporated SLM having tristearin and phosphatidylcholine by oil/water emulsification method by means of phase inversion method. The developed SLM exhibits particle size 2.90 μm, encapsulation efficacy 71.4% and drug transport of quercetin-SLM intracellularly using Calu-3 cell culturing model was >22% over 4 h. It can be concluded that diffusion of drug across Calu-3 monolayer was improved because of concentration of lipoid/emulsion-based excipients in SLM [55]. The similar Researchers prepared lipoid microparticles (LM) by incorporating tristearin and hydrogenated soybean phosphatidylcholine using melt emulsification accompanied by a ultrasonication and freeze-drying method. The prepared lipid microparticles exhibit 1.32-fold enhancement in %FPF in comparison with formerly reported SLM (20.5%). Following coating, quercetin stability was distinctly ameliorated (16.4%) having no cytotoxicity on A549 cells, foregoing proportion of 0.1–5.0 μM [56]. LM exhibit acceptable in vitro accumulation paradigm and ample amount of quercetin deliver intracellularly particularly connected with antioxidizing impacts of the flavonoid upon A549 cells in vitro in comparison with reported SLM. In brief, developed microparticles signify a propitious delivery alternative for inhalants, because they are produced from pharmacologically biodegradable friendly excipients.

24.4.5.7 Resveratrol

Resveratrol is an eminent polyphenolic phytoalexin (i.e. plantantibiotic), regarded as a stilbenoid which is produced from number of plant species by means of enzyme stilbene synthase. Its chemical name is 3,5,4′-trihydroxy-trans-stilbene which is isolated from roots of Veratrum grandiflorum O. Loes (Melanthiaceae) in 1940 [57]. The significant quantity of resveratrol is present in Japanese knotweed, i.e. Polygonum cuspidatum (Polygonaceae), a plant that is commonly used in the treatment of different disorders in Asian countries [58]. It shows inherent antioxidizing quality via impeding reactive oxygen species (ROS) chiefly through activating activated protein kinase (AMPK) when compared to other phytoconstituents such as kaempferol, naringenin, catechin, myricetin and α-tocopherol that occur naturally, resvratrol exhibit better antiradical activity which signifies its usefulness in a number of diseases. In addition, it is also used for management of a variety of intrapulmonary and extra pulmonary diseases such as pulmonary hypertension, cystic fibrosis, lung carcinoma and musco skeletal disorders in chronic obstructive pulmonary disease [59]. Regardless of innocuous and well acceptable features, high lipophilicity (log P value 3.06), poor water solubility (0.0688 mg/mL), short biological half-life (<15 min) [60], extremely photo-sensitive nature(exposure to light transform 80–90% of trans-resveratrol to cis-resveratrol) [59] and extended liver as well as intestinal metabolism are the foremost drawbacks for the systemic bioavailability of resveratrol [60]. Consequently, various inhalable resveratrol formulations had been addressed as below.

Respirable resveratrol microparticles were produced incorporating trehalose, poly (ε-caprolactone) and sodium deoxycholate through piezo electric atomization together with a nano-spray dryer. A better aerosolization characteristics were attained with a FPF (46.48%) and MMAD (5.22%) measured by means of an Aerolizer® at a flow rate of 28.3 l/min. In addition, developed microparticles of resveratrol exhibit a controlled release(>85% up to 12 h) in a aqueous medium comprising 1% of polysorbate 80 [61]. Trotta et al. prepared resveratrol-encapsulated microparticles by spray drying technique having a high FPF of 40% calculated by means of the RS01 dry powder inhalation device at a flow rate of 60 l/min. Thus Resveratrol-loaded microparticles markedly regulate multiple inflammation arbiters such as tumour necrosis factor alpha (TNF-α), interleukin-8 (IL-8), lipopolysaccharide (LPS) and transforming growth factor beta (TGF-β1) [62]. The similar Researchers fabricated co-spray dried (co-SD) microparticle by using resveratrol and budesonide for management of Chronic Obstructive Pulmonary Disease. Aerosolisation characteristics for co-spray dried (co-SD) microparticles were measured by means of a RS01 dry powder inhaler at flow rate 60 and 90 L/min. They revealed FPF 42.5; 42.5 and 46.7; 46.5% for resveratrol and budesonide correspondingly. As compared to vitamin C they exhibit satisfactory antioxidant activity in DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) assay. Both these formulations were diminishing the concentrations of TNF-α, TGF-β1 and LPS. Additionally, in vitro clinical trials demonstrated that alveolar macrophages might have resveratrol and budesonide amounting from 0.612 to 50 μm [63]. At the end, engineered microparticles of resveratrol obtained by spray drying technique are used to cure extra pulmonary disorders such as hypertension as well as intrapulmonary disorders like COPD and inflammation of lung. Thus, SD is a basic methodology having large scale production and products made by SD exhibit better-quality and less formulation difficulties.

24.4.5.8 Scutellarin

Scutellarin is an essential constituent of breviscapine flavones which is isolated from the *Erigeron breviscapus* (Vant) Hand-Mazz(Compositae). Chemically scutellarin is 4′,5,6-hydroxyl-flavone-7-glucuronide which is frequently employed for management of cerebrovascular and various heart disorders in traditional Chinese medicine for several decades [64]. Recently, it was revealed that scutellarin can also be used to treat repression of high cholesterol level, antihypertrophic impacts, anticoagulant and fibrinolysis as well as endothelium-independent relaxation induction [64]. As it regulates the arachidonic acid metabolism, it shows anti-inflammatory effect. In a current investigation scutellarin shows low oral bioavailability of 10.67% in humans due to its poor solubility in aqueous phase (0.16 mg/mL) and pre-systemic metabolites [65]. Thus, some novel formulation has to be designed to enhance rate of absorption and therapeutic effectiveness of scutellarin. Respirable mucoadhesive microparticles of scutellarin were developed encapsulating poly (vinyl alcohol): poly (vinyl pyrrolidone): hyaluronan: scutellarin in the ratio of 1:1:1:7 through spray drying technique. It was concluded that corrugated surface microparticles with volume mean distribution (2.48 μm) have been produced by incorporating PVA80.

They showed important aerodynamic characteristics like FPF, MMAD and GSD 29.1%, 2.83 μm and 1.58 correspondingly. Scutellarin-loaded mucoadhesive microparticles exhibit no cytotoxic effects in (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) MTT assay upon Calu-3 and A549 cell lineages. Besides, scutellarin is more rapidly and absorbed completely after intratracheal administration (10 mg/kg). Finally, current investigation shows that mucoadhesive microparticles emerged as an innovative and promising strategy for pulmonic delivery of phytoconstituents [66].

24.5 Clinical Trials on Phytoconstituent-Based Dry Powder Inhalers

Inhaled phytoconstituents have numerous advantages for the health of the human beings. It was observed from the preclinical studies the results obtained are not certain they will be safe for humans. Clinical trials are vital for the clinical practice and the basis for proofed drug. Nowadays, some pharmaceutical organizations take efforts on the human clinical trials as reviewed in the successive section.

To treat different pulmonary and extrapulmonary diseases Aerosol Research and Engineering Labs Inc. (ARE Labs) enthusiastically developing a phytoconstituents based DPIs. THC and THC-cannabidiol DPIs using Marinol® (synthetic THC) developed by ARE and mufti-tiered strategies used to extract total pant extract. For the treatment of Alzheimer's and for anorexia in cancer and AIDS ARE Labs specifically developed cannabinoid based DPIs. Currently organization has planned to carry out clinical research on THC inhaler in second half of 2018. Yet there is a need to execute the human clinical trials for inhaled phytoconstituents at broad range.

24.6 Discussion

Recently researchers are attracted towards the phytoconstituents amongst product development researchers for design, development and optimization of novel drug delivery system. However, all the research is still at examination phase. Numerous studies show that analysis of surface, particle size, and aerodynamic performance. Furthermore, various objections were responsible through formulating phytoconstituents for inhalation purposes. Figure 1 represented the advantages and disadvantages of the phytotherapiesare. Phytoconstituents have few biologically related issues such as low water solubility, poor bioavailability and lower permeability. Therefore, it is important to choose appropriate formulation techniques that mainly enhanced the physicochemical and pharmacokinetic profile of phytoconstituents. As the lacking of in vivo studies on toxicity profile and degeneration profile of various "polymeric carriers", the major restriction in development formulations is the source of polymers. Approaches to apply to keep phytoconstituents stability must be governed on a case-by-case basis. In order

various different chemical as well as physical improvements used the phytoconstituents molecule itself to improve its stability. Similarly, to utilized potency of these multifunctional phytoconstituents, more attention should be payed on its toxicological issues, lung clearance rate and pulmokinetics parameters [17, 50]

In addition to this, device and metering system should meet the some needs for the efficient application for pulmonary [66]. Succeeding development of inhaled phytoconstituents, prominently keeps in the three section (1) upcoming new regulatory and CMC requirements, (2) pulmonary pharmacokinetics and toxicity and (3) device development.

24.7 Conclusion

It was summarised from a review of recants literature that inhaled phytoconstituents is significant in treatment of serious pulmonic ailments. However, there is a lacking of research on inhaled phytoconstituents is, yet still in its infantries. But researcher performed investigations to proof the potency of phytochemicals in the treatment of many intrapulmonary and extrapulmonary ailments. They have many advantages for clinicians to enhance the results as well as life period of patients suffered from acute and chronic pulmonary diseases.

References

1. Mehta P, Bothiraja C, Mahadik K, Kadam S, Pawar A (2018) Phytoconstituent based dry powder inhalers as biomedicine for the management of pulmonary diseases. Biomed Pharmacother 108:828–837
2. Tripathi K (2003) Essentials of medical pharmacology, 6th edn. Jaypee, New Delhi
3. Pawar A, Rajalakshmi S, Mehta P, Shaikh K, Bothiraja C (2016) Strategies for formulation development of andrographolide. RSC Adv 6:69282–69300
4. World Health Organization (2018) WHO, chronic respiratory diseases (CRDs): fact sheets. http://www.who.int/respiratory/en/
5. Pawar S, Rajalakshmi P, Mehta K, Shaikh CB (2016) Strategies for formulation development of andrographolide. RSC Adv 6:69282–69300
6. Mali R, Dhake A (2011) A review on herbal antiasthmatics. Orient Pharm Exp Med 11:77–90
7. Mehta P, Shah R, Lohidasan S, Mahadik K (2015) Pharmacokinetic profile of phytoconstituent (s) isolated from medicinal plants-a comprehensive review. J Tradit Complement Med 5 (4):207–227
8. Mehta P, Dhapte V (2016) A comprehensive review on pharmacokinetic profile of some traditional Chinese medicines. New J Sci 2016:1–31
9. Heinrich M, Barnes J, Gibbons S, Williamson E (2012) Fundamentals of pharmacognosy and phytotherapy, 2nd edn. Elsevier Ltd, London
10. Mehta P, Lohidasan S, Mahadik K (2017) Pharmacokinetic behaviour of clinically important TCM prescriptions. Orient Pharm Exp Med 17:171–188
11. Evans W (2009) Pharmacogonasy, 16th edn. Saunders Elsevier, Philadelphia
12. Penton-Arias E, Haines D (2016) Chapter 11-natural products: immuno-rebalancing therapeutic approaches. In: Immune rebalancing, the future of immunosuppression. Elsevier, London, pp 229–249

13. Sanders M (2007) Inhalation therapy: an historical review. Prim Care Respir J 16(2):71–81
14. Sansone F, Aquino R, Del Gaudio P, Colombo P, Russo P (2009) Physical characteristics and aerosol performance of naringin dry powders for pulmonary delivery prepared by spray-drying. Eur J Pharm Biopharm 72(1):206–213
15. Prota L, Santoro A, Bifulco M, Aquino R, Mencherini T, Russo P (2011) Leucine enhances aerosol performance of naringin dry powder and its activity on cystic fibrosis airway epithelial cells. Int J Pharm 412(1-2):8–19
16. Rogers L, Cismowski M (2018) Oxidative stress in the lung- the essential paradox, Curr. Opin Toxicol 7:37–43
17. Khan J, Alexander A, Ajazuddin, Saraf S, Saraf S (2013) Recent advances and future prospects of phyto-phospholipid complexation technique for improving pharmacokinetic profile of plant actives. J Control Release 168(1):50–60
18. Squillaro T, Peluso G, Melone MAB (2017) Nanotechnology-based polyphenol delivery: a novel therapeutic strategy for the treatment of age-related neurodegenerative disorder. Austin Aging Res 1(1):1004
19. Mehta P (2016) Dry powder inhalers: a focus on advancements in novel drug delivery systems. J Drug Deliv 2016:8290963
20. Behcet AL (2014) The source-synthesis- history and use of atropine. Akad Acil Tä Derg 13:2–3
21. Corcoran T, Venkataramanan R, Hoffman R, George M, Petrov A, Richards T, Zhang S, Choi J, Gao Y, Oakum C, Cook R, Donahoe M (2013) Systemic delivery of atropine sulfate by the MicroDose dry-powder inhaler. J Aerosol Med Pulm Drug Deliv 26(1):46–55
22. Ali R, Jain GK, Iqbal Z, Talegaonkar S, Pandit P, Sule S, Malhotra G, Khar RK, Bhatnagar A, Ahmad FJ (2009) Development and clinical trial of nano-atropine sulfate dry powder inhaler as a novel organophosphorous poisoning antidote. Nanomedicine 5(1):55–63
23. van Drooge D, Hinrichs W, Dickhoff B, Elli M, Visser M, Zijlstra G, Frijlink H (2005) Spray freeze drying to produce a stable Δ9-tetrahydrocannabinol containing inulin based solid dispersion powder suitable for inhalation. Eur J Pharm Sci 26(2):231–240
24. Thingale A, Shaikh K, Channekar P, Galgatte U, Chaudhari P, Bothiraja C (2015) Enhanced hepatoprotective activity of andrographolide complexed with a biomaterial. Drug Deliv 22 (1):117–124
25. Bothiraja C, Kumbhar V, Pawar A, Shaikh K, Kamble R (2015) Development of floating in situ gelling system as an efficient anti-ulcer formulation: in vitro and in vivo studies. RSC Adv 5:28848
26. Mali A, Bothiraja C, Purohit RN, Pawar A (2017) In vitro and in vivo performance of novel spray dried andrographolide loaded scleroglucan based formulation for dry powder inhaler. Curr Drug Deliv 14(7):968–980
27. Zhang T, Zhu L, Li M, Hu Y, Zhang E, Jiang Q, Han G, Jin Y (2017) Inhalable andrographolide-β-cyclodextrin inclusion complexes for treatment of Staphylococcus aureus pneumonia by regulating immune responses. Mol Pharm 14(5):1718–1725
28. Woodbury A, Yu S, Wei L, García P (2013) Neuro-modulating effects of honokiol: a review. Front Neurol 4:130
29. Li X, Guo Q, Zheng X, Kong X, Shi S, Chen L, Zhao X, Wei Y, Qian Z (2009) Preparation of honokiol-loaded chitosan microparticles via spray-drying method intended for pulmonary delivery. Drug Deliv 16(3):160–166
30. Pápay Z, Kósa A, Böddi B, Merchant Z, Saleem I, Zariwala M, Klebovich I, Somavarapu S, Antal I (2017) Study on the pulmonary delivery system of apigenin loaded albumin nanocarriers with antioxidant activity. J Aerosol Med Pulm Drug Deliv 30(4):274–288
31. Madunić J, Madunić I, Gajski G, Popić J, Garaj-Vrhovac V (2018) Apigenin: a dietary flavonoid with diverse anticancer properties. Cancer Lett 413:11–22
32. Gao Y, Snyder S, Smith J, Chen Y (2016) Anticancer properties of baicalein: a review. Med Chem Res 25(8):1515–1523
33. Zhang J, Lv H, Jiang K, Gao Y (2011) Enhanced bioavailability after oral and pulmonary administration of baicalein nanocrystal. Int J Pharm 420(1):180–188

34. Naksuriya O, Okonogi S, Schiffelers R, Hennink W (2014) Curcumin nano formulations: a review of pharmaceutical properties and preclinical studies and clinical data related to cancer treatment. Biomaterials 35(10):3365–3383
35. Feng T, Wei Y, Lee R, Zhao L (2017) Liposomal curcumin and its application in cancer. Int J Nanomedicine 12:6027–6044
36. Taki M, Tagami T, Fukushige K, Ozeki T (2016) Fabrication of nanocomposite particles using a two-solution mixing-type spray nozzle for use in an inhaled curcumin formulation. Int J Pharm 511(1):104–110
37. El-Sherbiny I, Smyth H (2012) Controlled release pulmonary administration of curcumin using swellable biocompatible microparticles. J Mol Pharm Org Process Res 9:269–280
38. Yang K, Lin L, Tseng T, Wang S, Tsai T (2007) Oral bioavailability of curcumin in rat and the herbal analysis from Curcuma longa by LC-MS/MS. J Chromatogr B 853:183–189
39. Kurniawansyah F, Mammucari R, Foster N (2015) Inhalable curcumin formulations by supercritical technology. Powder Technol 284:289–298
40. Hu L, Kong D, Hu Q, Gao N, Pang S (2015) Evaluation of high-performance curcumin nanocrystals for pulmonary drug delivery both in vitro and in vivo. Nanoscale Res Lett 10 (1):381
41. Mahajan H, Mahajan P (2016) Development of grafted xyloglucan micelles for pulmonary delivery of curcumin: in vitro and in vivo studies. Int J Biol Macromol 82:621–627
42. Wang Z, Gupta S, Meenach S (2017) Development and physicochemical characterization of acetalated dextran aerosol particle systems for deep lung delivery. Int J Pharm 525(1):264–274
43. Na L, Dan-dan T, Li-wen W, Xiao-yu X, Ji-fen Z (2014) Preparation of dry powder inhalation based on phytosomes-chitosan microspheres by spray-drying method and study on its characterization. Chin Tradit Herb Drug 45(17):2475–2481
44. Bothiraja C, Yojana B, Pawar A, Shaikh K, Thorat U (2014) Fisetin-loaded nanocochleates: formulation, characterisation, in vitro anticancer testing, bioavailability and biodistribution study. Expert Opin Drug Deliv 11(1):17–29
45. Mehta P, Pawar A, Mahadik K, Bothiraja C (2018) Emerging novel drug delivery strategies for bioactive flavonol fisetin in biomedicine. Biomed Pharmacother 106:1282–1291
46. Mohtar N, Taylor K, Sheikh K, Somavarapu S (2017) Design and development of dry powder sulfobutylether-b-cyclodextrin complex for pulmonary delivery of fisetin. Eur J Pharm Biopharm 113:1–10
47. Bharti S, Rani N, Krishnamurthy B, Arya D (2014) Preclinical evidence for the pharmacological actions of naringin: a review. Planta Med 80(6):437–451
48. Chen R, Qi QL, Wang M, Li Q (2016) Therapeutic potential of naringin: an overview. Pharm Biol 54(12):3203–3210
49. Gera S, Talluri S, Rangaraj N, Sampathi S (2017) Formulation and evaluation of naringenin nanosuspensions for bioavailability enhancement. AAPS PharmSciTech 18(8):3151–3162
50. Saraf S, Gupta A, Alexander A, Khan J, Jangde M, Saraf S (2015) Advancements and avenues in nanophytomedicines for better pharmacological responses. J Nanosci Nanotechnol 15 (6):4070–4079
51. de Oliveira M, Nabavi S, Braidy N, Setzer W, Ahmed T, Nabavi S (2016) Quercetin and the mitochondria: a mechanistic view. Biotechnol Adv 34(5):532–549
52. Hatahet T, Morille M, Hommoss A, Devoisselle J, Müller R, Begu S (2016) Quercetin topical application, from conventional dosage forms to nano dosage forms. Eur J Pharm Biopharm 108:41–53
53. D'Andrea G (2015) Quercetin: a flavonol with multifaceted therapeutic applications. Fitoterapia 106:256–271
54. Costa Silva L, Kasten G, de Campos C, Chinelatto A, Lemos-Senna E (2013) Preparation and characterization of quercetin-loaded solid lipid microparticles for pulmonary delivery. Powder Technol 239:183–192
55. Scalia S, Haghi M, Losi V, Trotta V, Young PM, Traini D (2013) Quercetin solid lipid microparticles: a flavonoid for inhalation lung delivery. Eur J Pharm Sci 49(2):278–285

56. Scalia S, Trotta V, Traini D, Young PM, Sticozzi C, Cervellati F, Valacchi G (2013) Incorporation of quercetin in respirable lipid microparticles: effect on stability and cellular uptake on A549 pulmonary alveolar epithelial cells. Colloids Surf B Biointerfaces 112:322–329
57. Pangeni R, Sahni J, Ali J, Sharma S, Baboota S (2014) Resveratrol: review on therapeutic potential and recent advances in drug delivery. Expert Opin Drug Deliv 11(8):1285–1298
58. Carter L, D'Orazio J, Pearson K (2014) Resveratrol and cancer: focus on in vivo evidence. Endocr Relat Cancer 21(3):R209–R225
59. Zhu X, Lei X, Dong W (2017) Resveratrol as a potential therapeutic drug for respiratory system diseases. Drug Des Dev Ther 11:3591–3598
60. Jadhav P, Bothiraja C, Pawar A (2016) Resveratrol-piperine loaded mixed micelles: formulation, characterization, bioavailability, safety and in vitro anticancer study. RSC Adv 6:112795–112805
61. Dimer F, Ortiz M, Pohlmann A, Guterres S (2015) Inhalable resveratrol microparticles produced by vibrational atomization spray drying for treating pulmonary arterial hypertension. J Drug Deliv Sci Technol 29:152–158
62. Trotta V, Lee W, Loo C, Haghi M, Young P, Scalia S, Traini D (2015) In vitro biological activity of resveratrol using a novel inhalable resveratrol spray-dried formulation. Int J Pharm 491(1-2):190–197
63. Trotta V, Lee W, Loo C, Young P, Traini D, Scalia S (2016) Co-spray dried resveratrol and budesonide inhalation formulation for reducing inflammation and oxidative stress in rat alveolar macrophages. Eur J Pharm Sci 86:20–28
64. Xing J, You H, Dong Y, Lu J, Chen S, Zhu H, Dong Q, Wang M, Dong W (2011) Metabolic and pharmacokinetic studies of scutellarin in rat plasma, urine, and feces. Acta Pharmacol Sin 32(5):655–663
65. Qian L, Li N, Tang Y, Zhang L, Tang H, Wang Z, Liu L, Song S, Guo J, Ding A (2011) Synthesis and bio-activity evaluation of Scutellarein as a potent agent for the therapy of ischemic cerebrovascular disease. Int J Mol Sci 12(11):8208–8216
66. Liu X, Ye J, Quan L, Liu C, Deng X, Yang M, Liao Y (2008) Pulmonary delivery of scutellarin solution and mucoadhesive particles in rats. Eur J Pharm Biopharm 70(3):845–852

Medicinal Plant Based Advanced Drug Delivery System for the Treatment of Chronic Lung Diseases

25

Hitesh Malhotra, Anjoo Kamboj, and Rupesh K. Gautam

Abstract

Chronic pulmonary diseases such as bronchial asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, cystic fibrosis, and lung cancers represent the major health issues in both developing and developed countries. Till now various synthetic molecules are used to treat a wide range of pulmonary diseases. But due to some life-threatening side effects of the synthetic molecules, natural phytoconstituents or plant antibiotics are preferred as they have minimal side effects and efficient therapeutic outcomes. Though the drug delivery system used for administering the phytoconstituents so far is out of date, resulting in reduced efficacy of the drugs. So if the novel drug delivery system is used for the administration of herbal medicine, one may get improved results. Further introduction of a novel drug delivery system limits various drawbacks of traditional drug delivery systems. The advanced drug delivery system such as nanotechnology, oligonucleotides based systems, and other novel drug delivery system improves the pharmacokinetics of the drugs. For instance, nano-based systems such as liposomes, polymeric nanoparticles are designed to improve the bioavailability and stability of phytoconstituents used in chronic conditions such as lung cancer. Thus integration of novel drug delivery systems and herbal medicines proves to be an effective measure in combating serious chronic lung diseases.

H. Malhotra · A. Kamboj
Chandigarh College of Pharmacy, Mohali, Punjab, India

R. K. Gautam (✉)
Department of Pharmacology, MM School of Pharmacy, Maharishi Markandeshwar University, Sadopur-Ambala, Haryana, India

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_25

Keywords

Pulmonary disease · Novel drug delivery system · Herbal medicine · Phytoconstituents · Nanoparticles · Microparticles

25.1 Introduction

Respiratory disease, also termed as pulmonary or lung disease is a general term used to describe any conditions that affect the lungs and other parts of the respiratory system [1]. Pulmonary diseases such as bronchial asthma, COPD (chronic obstructive pulmonary disease), occupational lung diseases, and pulmonary hypertension are the major cause of increased mortality around the world [1, 2]. Cystic pulmonary fibrosis, pulmonary tuberculosis, idiopathic pulmonary fibrosis, and lung carcinomas are the major chronic lung diseases and responsible for high mortality rate. Even some of the above conditions are irreversible and life-threatening and till now no effective therapeutic regimen is available for complete restoration of pulmonary functions [3]. As per WHO, approximately two billion people worldwide are exposed directly or indirectly to toxic smoke obtained from burnt fuel and about one billion people are exposed to tobacco smoke which leads to respiratory impairment followed by disability and death. After cardiovascular diseases, respiratory diseases account for the leading cause of death. Around 500 million peoples every year are affected by lung diseases. It is estimated that about 300–500 million people suffer from COPD and bronchial asthma worldwide. Every year around 65 million people are reported to suffer from moderate to severe COPD, out of which approximately three million people die every year. With this COPD ranks as the third most common cause of death globally. Moreover, around nine million cases of pulmonary tuberculosis were reported in 2012, out of which approximately 1.2 million people will die. Further, lung carcinoma is the most common fatal neoplasm with a mortality of 1.6 million people every year [4–8].

The major manifestations are loss of elasticity, airflow obstruction, bronchitis, bronchoconstriction, emphysema, and hypersecretion of mucus. There are diverse predisposing factors that contribute to pulmonary diseases including smoking, air pollutants, occupational chemicals, inhalations of noxious particles, and genetics [2]. The common cause of pulmonary disease includes infection, smoking tobacco, passive tobacco smoking, asbestos, and air pollution. In certain cases, particulate matter contains allergens and endotoxins also predispose to pulmonary problems [9]. Allergens not always cause pulmonary problems, as the size of the inhaled particles and breathe rate are also considered. For instance, an airborne particle with a size of $<$100 nm diameter at a low dose can cross the nose–brain barrier and results in encephalopathy which may cause disorders like Parkinson's and Alzheimer's disease [10].

Currently, a wide array of chemical molecules are discovered and approved by authorities and occupy a major area of a therapeutic regimen for the treatment of fatal lung diseases. For the treatment of chronic lung diseases a variety of chemical drugs,

peptides, antibodies, and genetic molecules have been used. But neither of the categories has been successful to cure chronic lung disease completely. For instance, the drugs that are used in bronchial asthma only produce symptomatic treatment. Similarly, for the treatment of COPD and IPF, steroids and bronchodilators are widely used with no potential therapeutic outcome to cure these types of diseases [11–14].

However, therapy with such drugs is important in chronic lung disease patients, to manage the lifestyle with least sufferings. Nowadays, due to serious adverse effects and therapy failure, researchers start focusing on some alternate therapy. Moreover, conventional therapy fails to produce a targeted effect and the fluctuation in concentration of drug in systemic circulation and recurrent drug administration can cause troublesome due to poor patient compliance [15]. The conventional use of these drugs has some limitations like inappropriate pharmacokinetics and low diffusion of drugs at the site of action which leads to low response to the treatment [16].

Thus, health experts and researchers relocate the therapeutic regimen from allopathic medicines to herbal medicines to handle the crucial health problems. As per World Health Organization (WHO), roughly 75% of the population use plant-based drugs for primary treatment. Furthermore, herbal medicines possess numerous therapeutic properties with fewer adverse effects. As per reports, the use of herbal medicines exceeds allopathic drugs by twice or thrice times in the world. For this reason, presently, herbal medicines have been used for the treatment of acute as well as chronic lung diseases due to their prompt therapeutic outcomes and safety as supported by human studies. Current research has also presented well-proved data about the mode of action of herbal drugs [17].

The aerosol particles inhaled enter and accumulate in the respiratory system by either inertial impaction, gravitational settling, or diffusion. Gravitational settling is preferred in the case where narrow ducts and air spaces in the lungs are the main targets of the drug. The accumulation of nanoparticles with an average diameter of 30–300 nm in the upper respiratory tract or tracheobronchial tree occurs by diffusion phenomena. Lastly, in the case of coarse particles of size >3 μm, the deposition occurs by impaction as the direction of the airflow continuously changes in the mouth and the upper respiratory tract, including the pharynx, larynx, trachea, and bronchial region. Presently, dosage forms like inhalers are widely used in the market for the treatment of acute or chronic pulmonary disease with promising therapeutic outcomes and prominent systemic adverse effects. Therefore, targeted methods of delivery of drugs must be developed to overcome such side effects [18, 19]. For the targeted approach, advanced strategies are recommended to produce promising therapeutic outcomes, for instance, nanoscale carriers for targeted drug delivery systems. Nanoparticles are widely acceptable options as they can improve the pharmacokinetics of the therapeutic agents. Moreover, due to the targeted action of nanoparticles, the adverse effects of the drugs can also be minimized. The development of nanoparticles causes the integration of drug particles in the targeted area and thus minimizes the unwanted effects of the drugs in the body [20, 21]. Another example is the use of a vector system for gene therapy, as it becomes very difficult to deliver genetic molecules at the site of action and

sometimes they degrade in the biological fluids. Thus, to surpass the limitations of the conventional dosage forms, there is an increasing need for such targeted based drug delivery systems [22, 23].

25.2 Rationale of Using Herbs for Chronic Diseases

Plant-based medicines have made an indisputable contribution to the health care system from time immemorial across the globe. For this reason, herbal medicines became an essential part of the medicine system in the ancient world in different forms in various cultures of humanity [24]. The researchers now start exploring the medicines from the past, as the chemists have to synthesize synthetic bullets for all that ailments, and the pharmaceutical companies utilize the entire asset. Since time immemorial, almost all drugs were obtained from the plants and thus the plant being man's only chemist for ages. Herbs are now being reexploited all over the globe and people switch over to herbal therapy to treat chronic conditions. The main reasons for the popularity of herbal medicines are as follows:

a. Toxicological profile of the allopathic medicines
b. Therapy failure
c. Improved therapeutic outcomes of the herbal drugs [25]

Moreover, current therapies act by simply suppressing the symptoms without treating the root cause of the disease pathology. While the natural products focus mainly on eradicating the root cause of the underlying mechanism of the disease and yield superior therapeutic outcomes. Unfortunately, many medical practitioners and patients are not aware of natural alternatives for the treatment of chronic ailments. But still, research in this field is a never-ending process [25].

Regardless of their extensive utilization as drugs, researchers still work on herbal-based drugs mainly on their economic, clinical, and pharmaceutical outcomes.

Herbs contain diverse chemical moieties possessing multiple therapeutic functions and due to this reason, herbal medicines appear as a key element for new drug development as depicted in Fig. 25.1. Moreover, herbal drugs are also utilized in pharmaceutical companies in the form of either excipients, precursors of allopathic drugs, nutraceuticals, or food supplements. Presently due to the availability of advanced analytical tools and technologies, researchers can easily screen out the active chemical moieties present in herbs. Thus, in spite of great efficacy, herbal extracts have been overcome by specific phytoconstituents. Thus phytoconstituents are isolated and categorized to produce drug analogs. These phytoconstituents or chemical moieties present in the herbs are accountable for organoleptic and clinical features of plants. The chemical moieties are nothing but the secondary metabolites such as alkaloids, glycosides, polyphenolic compounds, etc. Phytoconstituents prove to have potential therapeutic outcomes against some major life-threatening diseases such as respiratory infections, cardiovascular complications, and cancer.

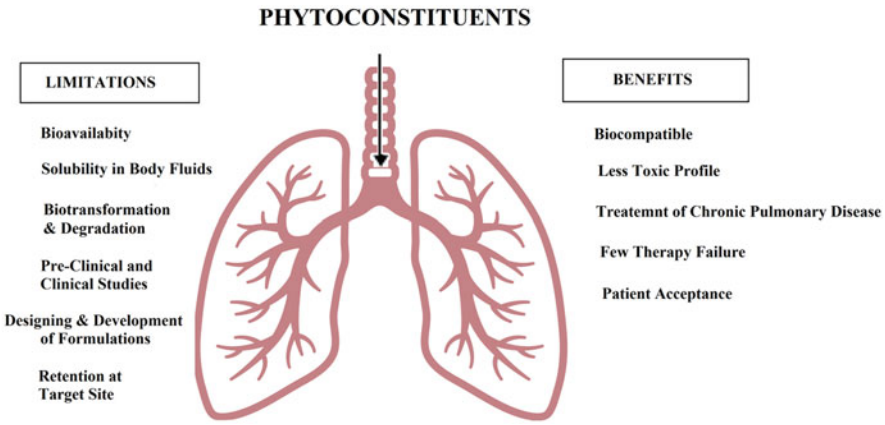


Fig. 25.1 Challenge and advantages of phytoconstituents in pulmonary system

Researchers mainly focus on phytoconstituents which show beneficial effects against these diseases due to the high mortality rate [26–29].

25.3 Novel Drug Delivery System for Herbs

In recent years, the potential of Ayurveda in treating various ailments is being realized. But the use of a conventional drug delivery system for administering the drug to the patient is out of date which reduced the therapeutic outcomes of the medicine. There are many hurdles in producing significant therapeutic outcomes of herbal extracts. For instance, acid labile extracts are destroyed in the fluid present in the stomach. Additionally, pre-systemic metabolism also reduces the concentration of active extract in the systemic concentration as well as at the site of action. Thus, the minimum level of drug concentration, i.e. minimum effective level is not achieved and ultimately there will be no therapeutic effect.

Phytoconstituents are plant-derived chemicals that have minimal side effects and high bioavailability and thus results in better therapeutic outcomes. Currently used medicines are chemical compounds, produce significant adverse effects, and also the chances of rejection are very high as compared to plant-based products. The rejection reaction ranges from mild to life-threatening such as minor headaches, hepatitis, and organ failure that are potentially lethal. Moreover, plant-derived products are purified compounds that can be easily standardized and thus corporate easily in advanced drug delivery systems for overcoming the limitations of natural compounds [30]. Such as lipid-based drug delivery systems, i.e. liposomes and nanoparticles are investigated and implemented for controlled and targeted drug delivery. Another example is the use of pharmacosomes in which a drug is complexed with phospholipids resulting in improved pharmacokinetic properties. Similarly, phytosomes also termed as phytolipid drug delivery systems are designed

for delivering various natural products like *Silybum marianum*, *Ginkgo biloba*, *ginseng* flavonolignans and terpenoids, and so on [31]. The prime advantage of using this delivery system includes high lipophilicity and improved bioavailability and therapeutic outcomes and thus considered for chronic diseases. Phytosomes form a bridge between the conventional delivery system and are of great clinical importance. Thus it is important to incorporate the novel drug delivery system in Indian Ayurvedic medicines to combat serious diseases [32].

Researchers develop various novel drug delivery systems for administering herbs like mouth dissolving tablets, sustained and extended-release formulations, mucoadhesive systems, transdermal dosage forms, microparticles, microcapsules, nanoparticles, implants, etc. The first herb-based mouth dissolving tablet was launched by the name of Res-Q which shows the fast-dissolving capability and thus imparts increased therapeutic efficacy. Res-Q ensures that the drugs reach the blood readily and also bypass the pre-systemic metabolism. In the Ayurvedic system development of Res-Q is the initial step to make herbal drugs more effective in managing chronic ailments like chronic pulmonary problems like asthma. This formulation provides better treatment for respiratory distress syndrome as in the case of Sorbitrate that is used in cardiac disease. Furthermore, a controlled release formulation containing hypericin, hyperforin, and echinacoside is prepared and evaluated [33]. The data obtained exhibits that after oral administration of the formulation, the concentration of active ingredients in the plasma remains steady for around 18 h with the release of 75% of the content. Thus, such herbal-based formulations provide an oral dosage form for maintaining steady-state plasma concentrations of the active compounds and also increase patient compliance [34]. In a similar manner, sustained-release microgranules of *Gingko biloba* were prepared that show better flowability and compressibility properties. But the development of such sustained-release herbal formulation is difficult, as homogeneous mixtures of extracts and excipients are required during the compression process. The granules formed can be manufactured by techniques like extrusion-spheronization, fluid air bed process, or a coating-pan method. The coating-pan method is preferred for the manufacturing of the granules as simple equipment is required and ease of procedure [35].

The development of mucoadhesive tablets containing sage, *Echinacea*, *Lavender*, and *Mastic gum* is another approach to produce sustained-release herbal formulation by using mucoadhesive polymers. Thus, the slow dissolving mucoadhesive tablet developed produces a steady-state concentration of active ingredients for a long time in plasma [36]. Furthermore, transdermal patches containing herbal drug components Boswellic acid (*Boswellia serrata)* and curcumin (*Curcuma longa)* are developed and utilize skin as a site for continuous drug administration into the systemic circulation. By choosing this delivery system, the first-pass metabolism of active components can be avoided and the drug is administered in the body without any pain associated with the parenteral route. Moreover, the development of a transdermal drug delivery system for turmeric to produce local action at the site of administration can also be considered as an advanced version of Ayurvedic turmeric *poultice* or *lepa* [37].

Polyherbal aerosol formulation containing *Flos chrysanthemum indicum*, *Flos lonicerae*, *Herba houttuynia*, *Radix bupleurum*, and menthene has been tested for the treatment of chronic respiratory infections. The researchers conclude that aerosol so formed possesses anti-inflammatory and antiviral activity and thus has good therapeutic outcomes in treating respiratory tract infections [38]. Further, the microparticles of guggulipid (*Commiphora wightii*) have been clinically proven to reduce the levels of harmful lipoproteins in the bloodstream as compared to the conventional dosage form. The result obtained in the case of microparticles is due to improved physicochemical characteristics [39].

The most advanced research in this field is the development of nanoparticles of herbs, for instance, *peach seed*, *safflower*, *angelica root*, *Szechwan lovage rhizome*, *Rehmannia root*, *red peony root*, *leech*, *gadfly*, *earthworm*, and *ground beetle*. Nanoparticles form of these herbs shows better thrombolytic effects as compared to non-nanoparticle form, resulting in quick recovery from pulmonary embolism and thrombi. Also, the herb-based nanoparticles show good oral bioavailability and therapeutic outcomes with prolonged-release effects [40]. In a similar way, sustained-release implants of herb extracts using chitosan are prepared and proved to be very useful in clinical practice. For instance, an extract of danshen (*Radix salvia miltiorrhiza*) is developed using chitosan and gelatine as an implant for healing muscles and tissues at the incision sites. The addition of chitosan and gelatine makes the formulation sustained release and thus prolonged and constant therapeutic effect is maintained [41].

25.4 Concept of Targeted Delivery: Nanoparticles

Nanoparticles are considered to be one of the advanced strategies of drug delivery via the pulmonary route with submicron size particle in diameter. Nanoparticles exhibit distinct physicochemical characteristics due to their submicron size and thus these properties have been utilized for organ/tissue-specific drug delivery as mentioned in Fig. 25.2. For instance, the larger surface area of nanoparticles has a possibility to contact the surrounding tissues and cells and thus enhances the efficiency of drug delivery [42, 43]. When injected systemically, the accumulation of nanoparticles in the pathological area mainly in tumors, hemorrhagic diseases, and inflammatory diseases increases. Thus, cumulatively it will be said that nanoparticles have that properties which make it novel carriers for drug delivery [44].

For administering nanoparticles different routes including parenteral, oral, and inhalational are used. The intravenous route is considered to be the most typical route for administering nanoparticles due to small size and ease of escape from the damaged blood vessels seen in tumors, injury, hemorrhagic diseases, and chronic inflammation [45, 46]. In pathological conditions, due to increased blood flow and endothelial permeability accumulation of nanoparticles occurs which results in more retention in that particular area and thus can be used to treat chronic diseases such as lung carcinomas [47]. But apart from lung cancer, nanoparticles when injected via

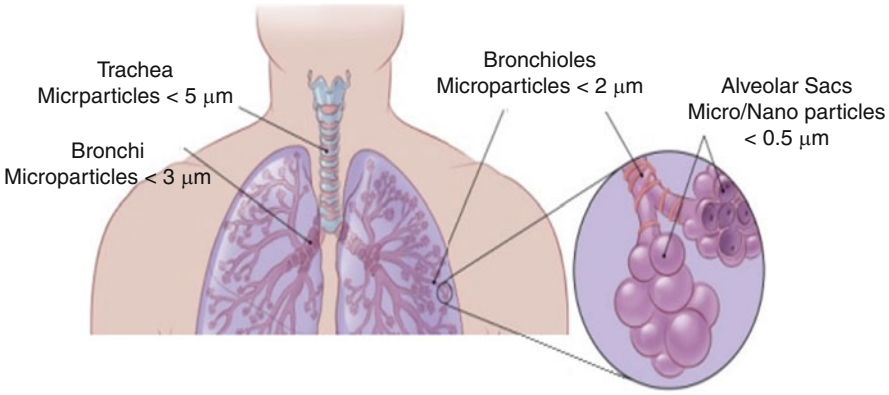


Fig. 25.2 Accumulation of drug particle in pulmonary system

intravenous route are of no clinical importance in the treatment of chronic lung diseases like cystic fibrosis, COPD, and IPF due to the presence of fibrous tissues which may suppress the diffusion of nanoparticles and thus preventing them to reach at the site of action. For instance, indium arsenide- and zinc sulfide-based nanoparticles concentrate well in hepatic cells, nephrons, and the intestinal epithelial cells but their accumulations were extremely less in the lungs. In certain cases, nanoparticles are not appropriate for lung-targeted delivery due to pharmacokinetic limitations [48, 49]. However, studies reveal that nanoparticles might be used for pulmonary delivery by improving the pharmacokinetics of the drugs. Thus, the behaviors of nanoparticles in the biological system may vary and depend upon the type and properties of the nanoparticles [50].

So for pulmonary diseases, the administration of nanoparticles via a pulmonary inhalation route is preferred as this approach enables higher distribution in the lungs [51]. Nanoparticles are administered in the pulmonary area in the form of either dry powder or liquid suspension, using specific devices for efficient aerosolization [52, 53]. Further, nanoparticles and liposomes are also preferred for delivering via the pulmonary route because the chances of size variability and particle aggregation are minimal [54, 55].

25.5 Determinants for the Pulmonary Delivery of Nanoparticles

The therapeutic efficiency of nanoparticles developed for delivering into the pulmonary cavity depends upon the type of formulation, composition, shape, and size of the nanoparticles. Apart from all the above determinants, the aerodynamic diameter of nanoparticles is the principle component to be considered for effective biodistribution of the inhaled nanoparticles [56, 57]. For instance, the particles with a size less than 5–6 μm can easily deliver into the trachea-bronchial region, while particles of 1–2 μm are usually deposited in the bronchioles, and particle size

with <1 μm can be delivered into the alveoli. But by altering the particle size and structure, the pharmacokinetics of the nanoparticles can also be altered [58].

The development of ultra-small-sized nanoparticles, i.e. dendrimers (size <20 nm) using different molecular weights of PEG (polyethylene glycol) polymers, leads to the formation of nanoparticles with a diverse particle size that may alter the biodistribution in the lungs. Thus there was a marked correlation of particle size with retention of the nanoparticles at the target sites [59]. Moreover, the size of the particle also affects the volume of distribution and the availability of the nanoparticles as large aggregates of nanoparticles are released from an aerosol or during the release within the pulmonary systems. Furthermore, the effectiveness of inhalable nanoparticles also depends upon the condition of the patient or technique used for drug delivery, for instance, breathing conditions and aerosolization methods [60]. Studies exhibit that a vibrating mesh nebulizer is efficient to deliver a dosage form in the pulmonary area as compared to a jet nebulizer as less disruption of the nanoparticle formulations appears during nebulization. Thus from this finding, it is concluded that efficient delivery of particles can be affected by the technique adopted for delivering the formulation. Also, biological barriers and phagocytic cells in alveoli also impede the targeted delivery of nanoparticles [61, 62].

25.6 Various Nanoparticles for Chronic Lung Diseases

For preparing the nanoparticles researchers use different raw materials such as metals, proteins, lipids, and polymers. Depending upon the type of material used and structural characteristics, nanoparticles can be classified into dendrimers, polymeric nanoparticles, liposomes, micelles, and inorganic nanoparticles including nanocrystals [63, 64].

1. *Lipid-based nanoparticles/liposomes*: Lipid materials like cholesterol and phosphatidylcholine are used for the fabrication of nanoparticles due to their high biocompatibility. Liposomes offer several benefits as drug carriers as they have the capability to carry large amounts of drug and due to the lipoidal nature of the outer layer cellular uptake is enhanced [65]. For treating chronic lung diseases, liposomes are considered due to their high stability during aerosolization for inhalation. Therefore, liposomes have been a potential carrier system for pulmonary drug delivery of drugs for the treatment of lung carcinomas, chronic infections, and bronchial asthma [66, 67].
2. *Polymer-based nanoparticles*: Polymers either synthetic or natural are macromolecules consisting of repeating units of monomers, have been utilized for drug conjugation and development of polymer-based nanoparticles. The commonly used natural polymers are polysaccharides and proteins, while synthetic polymers used for the manufacturing of nanoparticles are PEG. Natural polymers are highly biocompatible and biodegradable, whereas synthetic polymers offer multiple benefits such as reproducible results, biocompatibility, and biodegradable [68, 69]. Due to the structural variability of polymers, each

type of polymer has characteristic properties and therefore used in the design and development of nanoparticles for gaining a specific therapeutic advantage. For instance, the PEGylation of nanoparticles reduced the aggregation of nanoparticles and improves the penetration into the respiratory mucus due to their muco-biocompatibility [70]. In a similar manner, polyethyleneimine (PEI) polymer-based nanoparticles have been shown to be useful in chronic lung diseases including COPD, pulmonary tuberculosis, and pulmonary hypertension [71].

3. *Dendrimers*: Dendrimers are the branched molecules that show better physico-chemical characteristics as compared to polymers. Dendrimers are highly mono-dispersed nanoparticles whose size and morphological structure affect the final formulation [72]. Dendrimers have the capability to carry a large amount of drugs and also show enhanced pulmonary absorption after inhalation. For this reason, dendrimers have been widely used for drug delivery in lung carcinomas, COPD, pulmonary fibrosis, etc. [73].
4. *Inorganic nanoparticles*: For preparing nanoparticles, inorganic materials like gold, iron oxide, and silica have been used and mainly utilized for diagnostic imaging of diseases in clinical centers. Gold nanoparticles are extensively used for gene delivery due to the fact that cationic metal ions easily bind to anionic DNA and RNA molecules [74]. Apart from such advantages, inorganic nanoparticles are of limited use in the treatment of chronic lung diseases due to a high degree of toxicity. The positively charged gold nanoparticles form a complex with negatively charged body proteins, so to avoid such aggregation PEG coating is a solution. Also, the excretion rate of gold nanoparticles is very low which causes drug accumulation and enhanced toxicity [75].

25.7 Phytoconstituents

25.7.1 Phytoconstituents in Inhalation Delivery

Inhalational therapy has been well evidenced as a novel approach for administering the drugs in the respiratory system, for more than 4000 years. Further with the advancement in technology, for instance, medicinal science, engineering, and molecular biology, a massive improvement is seen in the field of inhalational therapy [76]. Presently, apart from using an inhalational approach in the treatment of pulmonary diseases, researchers utilize it as non-invasive therapy for extra-pulmonary diseases also [77].

Lungs are readily exposed to an air pollutant rich environment and thus prone to injury due to free radicals. So to impede such lung injury, lungs produce various antioxidants like GSH (glutathione), SOD (superoxide dismutase), β-carotene, ascorbic acid, tocopherol, uric acid, and heme-oxygenase. But in rare cases, reactive oxygen or nitrogen species surpass the antioxidant protection and leads to the occurrence of diverse diseases. Studies reveal the role of free radicals in cystic fibrosis, asthma, COPD, and other pulmonary diseases. Therapy widely advised

for pulmonary disease manages altered secretion of mucus and bronchitis so as to delay lung injury. The treatment for pulmonary tissue damage includes oral/inhaled corticosteroids and oral N-acetylcysteine but with limited therapeutic outcomes and potential adverse effects. Thus, the only treatment of pulmonary disorders includes enrichment of biological antioxidant protections [78–80]. While the natural antioxidants such as phytoconstituents such as flavonoids, i.e. polyphenolic compounds are also used as mentioned in Table 25.1. Apart from antioxidant activity, phytoconstituents also possess anti-inflammatory and antibacterial properties due to the presence of polyphenolic compounds. Regardless of health benefits, phytoconstituents have some pharmacokinetics issues like low bioavailability due to which making a formulation is still a big question. Due to poor aqueous solubility, high molecular weight, poor membrane permeability, acid-labile property, and low dissolution rate the phytoconstituents depict poor bioavailability and irregular absorption pattern from the given oral dosage form [101]. For this numerous studies have been documented which includes the formulations containing polyphenolic compound with improved bioavailability. Further, orally delivered nanoparticles and microparticles have been developed and evaluated for the same purpose. Furthermore, lipid vesicles such as liposomes, spherulites, and cochleate are also being tested for the delivery of plant constituents. But in spite of designing various drug delivery systems for phytoconstituents, poor therapeutic outcomes due to the first-pass metabolism within the gastrointestinal tract make the use of natural antioxidants limited [102]. So these obstacles can only be overcome by adopting an alternative approach for administering the phytoconstituents so that maximum concentration can be achieved at the site of injury in the lung and prompt antioxidant and anti-inflammatory activity can be achieved. For instance, aerosol directly delivers the drug to bronchioles using nebulizer, a pressurized metered-dose (pMDI), a soft mist (SMI), and a dry powder inhaler (DPI) are evaluated for this purpose. Out of all the above-mentioned systems, DPIs are preferred as they are free of any propellant, did not require any reconstitution procedure, no need for coordination between patient and practitioner, and are less expensive. Also, DPIs can improve biopharmaceutical and physicochemical characteristics of the phytoconstituents and thus attain higher concentration at the site of injury [76, 103].

25.7.2 Phytoconstituents: Dry Powder Inhalers

The drug delivery system for administering phytoconstituents in the lungs is a unique approach and has been commonly utilized due to the easier manufacturing process, better therapeutic outcomes, and minimal adverse effects. The delivery system can offer safe, precise, and better therapeutic options.

Table 25.1 Phytoconstituents delivered through pulmonary route

S. No.	Phytoconstituents delivery System	Technique	Remarks	References
1.	CR-PEG nanoparticles	Spray dried	Increase retention time, target specific action	Taki et al. [81]
2.	CR nanocrystals	Spray dried	Better dissolution rate and bioavailability	El-Sherbiny and Smyth [82]
3.	CR-PVP microparticles	ARSES	Improved dissolution rate and more miscibility in body fluid	Kurniawansyah et al. [83]
4.	CR-MP and nCmP	Spray dried	Target specific action	Wang et al. [84], Na et al. [85]
5.	RS-caprolactone, trehalose, and sodium deoxycholate microparticles	Spray dried	Controlled release, improved bioavailability, pulmonary targeted action	Dimer et al. [86]
6.	RS-budesonide microparticles	Spray dried	Inhibits the release of inflammatory cytokines in lungs	Trotta et al. [87]
7.	QT-SLM-lecithin and glyceryl trimyristate/lecithin and glyceryl behenate	Hot solvent diffusion/hot emulsion method	Improves the dissolution rate and solubility in body fluids	Scalia et al. [88]
8.	QT-SLM tristearin and phosphatidylcholine microparticles	Emulsification	Enhanced aerosolization efficiency	Scalia et al. [89]
9.	Api-BSA nanoparticles	Spray dried	Enhanced aerosolization efficiency and improved release rate	Madunic et al. [90]
10.	BL-nanocrystals		Improved pharmacokinetic profile	Zhang et al. [91]
11.	FN-SBE-β-CD nanoparticles	Spray dried	Enhanced pulmonary therapeutic efficacy	Mohtar et al. [92]
12.	NG-microparticles	Spray dried	Better aerosolization and therapeutically significant in cystic fibrosis	Chen et al. [93]

(continued)

Table 25.1 (continued)

S. No.	Phytoconstituents delivery System	Technique	Remarks	References
13.	SR-PVA, PVP, HLN microparticles	Spray dried	Improved bioavailability when administered via intratracheal route	Saraf et al. [94]
14.	HK-chitosan/ mannitol microparticles	Spray dried	Better aerosolization and therapeutic efficacy	Li et al. [95]
15.	AR-loaded scleroglucan microparticles	Spray dried	Controlled release pattern and improved therapeutic efficacy	Mali et al. [96]
16.	AR-β-CD microparticles	Freeze-drying	Extended retention in pulmonary tissue with better aersolization efficacy	Zhang et al. [97]
17.	AP sulfate nanoparticles	Nanoprecipitation technique	Improved pharmacokinetics and aerosolization efficacy	Corcoran et al. [98], Ali et al. [99]
18.	DB-inulin microparticles	Freeze-drying	Avoid metabolism, enhanced bioavailability	Van Drooge et al. [100]

25.8 Curcumin (CR)

CR is an unsaturated diketone hydrophobic polyphenol obtained from the rhizome of *Curcuma longa* belonging to the family Zingiberaceae. CR possesses anti-inflammatory, anti-carcinogenic, and anti-microbial activity. Studies also reveal the activity of CR in acute and chronic lung disorders [104]. The promising anti-cancer activity was demonstrated against human lung adenocarcinoma, human lung adenocarcinoma, lung metastasis, and mouse macrophage cell line [81, 82]. Studying the biopharmaceutical and pharmacokinetic properties reveals the poor oral bioavailability of the CR due to low aqueous solubility, high molecular weight, poor dissolution in gastric fluid, first-pass biotransformation, and also rapid removal from the body. So to overcome such limitations different inhalational formulations such as polymeric micelles, cyclodextrin complexes, swellable microspheres, nanocrystals, and nanocomposites have been developed and evaluated for pharmacokinetics characteristics [105]. For instance, spray-dried respirable CR-loaded poly (lactic-co-glycolic-acid) nanoparticles encapsulated in amphiphilic pegylated-chitosan (PEG-Cs) copolymer-based swellable microspheres are designed for controlled CR to release overtime of 20–22 h. Thus, swellable microspheres were

capable to treat pulmonary disorders by maintaining the concentration at the site of tissue damage. Further, CR nanocrystals were developed by milling technique along with spray drying (SD). It was observed that due to uniform particle size and spherical shape, complete dissolution can be achieved in an aqueous medium. The nanocrystals of CR when administered via the pulmonary route showed enhanced drug concentration in plasma as well as at the site of activity. Hence, nanocrystals will be an efficient carrier system for phytoconstituents in the pulmonary area [82]. Similarly, inhalable CR-loaded microparticles were designed using cyclodextrin and PVP (polyvinylpyrrolidone) using an atomized rapid injection solvent extraction system. The product so formed showed a manifold increase in miscibility and dissolution in required media with improved percentage yield [83]. In another study, CR-loaded acetylated dextran nanocomposites microparticles (MP) and microparticles (nCmP) were produced and showed a fast release of CR in buffer media. Thus engineered aerosol particles have a potential for delivery of polyphenols into the desired pulmonary area. Another development includes the L-lactide-xyloglucan-CR complex that exhibits improvement in the concentration of drug in plasma. The improvement in the bioavailability of CR is due to the extended residing of CR within the lungs after pulmonary administration. Similarly, respirable CR nanocomposite particles were prepared using mannitol and researchers observed that drug dissolution was enhanced which ultimately leads to improved bioavailability [84, 85]. Thus, CR has great therapeutic potential in the treatment of lung disorders. CR when incorporated in microparticulate formulations along with biodegradable polymers, synthetic polysaccharides, and force controlling agents (PVP) produced better therapeutic outcomes by improving the pharmacokinetic parameters.

25.9 Resveratrol (RS)

Resveratrol also known as polyphenolic phytoalexin is categorized as a stilbenoid, a derivate of stilbene. Chemically it is a trihydroxy-trans-stilbene and mainly isolated from the roots of *Veratrum grandiflorum* (Melanthiaceae) and aerial parts of *Polygonum cuspidatum* (Polygonaceae) [106]. The phytoconstituent is mainly produced in plants in response to noxious stimuli like infection, physical injury, or UV radiation. RS is a plant-based antioxidant and used to treat reactive oxygen species induced pulmonary injury by combating ROS through the stimulation of activated protein kinase (AMPK). The antioxidant activity of RS is considered to be superior to other phytoconstituents like naringenin, kaempferol, catechin, α-tocopherol, and myricetin. Apart from antioxidant activity, other therapeutic actions include treatment of cancer, viral infections, and pulmonary diseases, for example, cystic fibrosis, hypertension, cancer, and COPD. Apart from non-toxic and well-tolerable properties, poor aqueous miscibility, high lipophilicity, short half-life, light-sensitive nature, and extensive first-pass metabolism are the major disadvantages of RS which leads to poor bioavailability. Thus, currently, inhalable RS formulations have been designed and developed [107–109].

RS microparticles were prepared using caprolactone, trehalose, and sodium deoxycholate delivered through the pulmonary route. The microparticles were developed to depict a controlled release pattern due to the spherical structure of the particle size of RS in an aqueous medium. RS-loaded microparticles achieved high pulmonary retention when delivered by dry powder inhalation device. Besides, microparticles possess potent antioxidant properties as compared to ascorbic acid with minimal cytotoxicity. RS-loaded microparticles are evidently used in pulmonary conditions by inhibiting the release of interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta, and lipopolysaccharide. Further, microparticles using RS and budesonide are developed for the treatment of COPD. This dual combination is evidently used in chronic pulmonary disorders as the combination exhibits antioxidant activity as well as suppresses the levels of TNF-α, TGF-β1, and LPS [86, 87].

25.10 Quercetin (QT)

QT is a polyphenolic yellow color flavonoid (pentahydroxyflavone) obtained from leafy vegetables, fruits, and berries of plants. QT shows a wide range of health benefits and is thus considered to be an essential molecule as an effective functional food for various remedies. Investigations reveal that QT possesses anti-inflammatory, antioxidant, and anti-cancer activity and is also used in the treatment of bronchitis and bronchial asthma [88, 110]. But the clinical potential of QT is hindered due to its low aqueous miscibility, lipophilicity, and poor bioavailability. Additionally, the QT molecule contains hydroxyl substituent with a catechol moiety and undergoes extensive methylation in the body. Thus due to rapid degradation in the body, frequent high dosing is required to attain the therapeutic effect, which leads to intense adverse effects [88].

To overcome such disadvantages, a liposomal drug delivery system such as solid lipid microparticles has been developed. Two novel delivery systems have been developed, i.e. QT-loaded solid lipid microparticles (SLM) using soy-lecithin and glyceryl trimyristate by hot solvent diffusion method and lecithin and glyceryl behenate by hot emulsion method. The addition of a fatty acid molecule shows positive deflection on the morphology of microparticles which improves the dissolution rate. Further, QT-loaded SLM microparticles are prepared using tristearin and phosphatidylcholine. The product so formed has satisfactory aerosolization efficiency and the release of drug as well as the intracellular drug transport also enhances. In addition, lipid microparticle (LM) of QT using hydrogenated soybean phosphatidylcholine and tristearin was prepared, which shows the sustained release of drug QT in a phosphate buffer and additionally stability of quercetin was markedly enhanced, thus prolong the defensive activity against oxidative stress as compared to quercetin alone. In a nutshell, QT microparticles depict a favorable delivery option for the inhalation of QT with improved characteristics [88, 89].

25.11 Apigenin

Apigenin is a trihydroxyflavone generally isolated from the Apium genus in the Apiaceae family. During the past few years, investigations reveal that apigenin possesses numerous therapeutic benefits, for instance, antioxidant activity, free radical scavenging activity, and anti-inflammatory activity. The anti-inflammatory activity is mainly by inhibiting inflammatory mediators, cyclooxygenase, and protein in respiratory epithelial cells and which ultimately leads to acute lung injury or damage. Apigenin (Api) is a BCS class II drug, thus to treat inflammation in the respiratory tract efficiently, the apigenin-loaded nanoparticulate formulation is developed. In a similar manner, bovine serum albumin (BSA)-based apigenin-loaded nanoparticles are designed and developed which shows good aerosolization performance and the release pattern is also enhanced. Furthermore, BSA-Api shows potent antioxidant activity [90, 111].

25.12 Baicalein (BL)

Baicalein is a trihydroxy flavones moiety obtained from the roots of *Scutellaria baicalensis*i (Lamiaceae) and is an important component of the traditional Chinese medicine system. BL is used to treat various conditions like pulmonary hypertension, lung carcinomas, and pulmonary and extra-pulmonary inflammatory diseases. BL is a BSC class II drug with low water solubility and high permeability. Thus, despite a wide range of therapeutic outcomes BL use is still restricted due to poor aqueous solubility and extensive first-pass metabolism. So to overcome such limitations, BL-loaded nanocrystal formulation is designed and developed. The pulmonary nanocrystal formed shows improved bioavailability as compared to BL alone.

Furthermore, the nanocrystal of BL has a better dissolution profile as compared to BL crystal. Thus, BL nanocrystals exhibit improved pharmacokinetic profile due to increased surface area and reduced particle size [91, 112].

25.13 Fisetin (FN)

Fisetin is a tetrahydroxyflavone (diphenyl propane flavone) extracted from vegetables and fruits. FN exhibits multiple therapeutic activities such as anti-cancer, anti-inflammatory, antiviral, and antioxidant activities. Further, FN inhibits phospholipase-Cβ activity in the respiratory tract which results in reduced bronchial muscle contractility and used as a bronchodilator in the treatment of asthma. But, due to low aqueous solubility, high lipophilicity, and low bioavailability, the use of FN in various diseases is still restricted [113, 114]. So to extend the therapeutic efficacy of FN various novel drug delivery systems such as nanoemulsions, liposomes, nanocochleates, cyclodextrin, and cyclosophoroase dimer complexes are designed with improved solubility, stability, and bioavailability. The most

advantageous is the development of pulmonary delivery of FN by sulfobutylether-β-cyclodextrin (SBE-β-CD) complexes with the aim of improved pharmacokinetic profile. Physicochemical analysis reveals that the product so formed showed improvement in particle size and surface morphology of the particle. Moreover, the addition of 20% leucine further enhanced pulmonary performance by twofold as demonstrated by MTT assay [92].

25.14 Naringin (NG)

Naringin was first isolated by De Vry in 1857 and its structure elucidation was done by Asahina and Inubuse in 1928. NG is a bitter molecule mainly isolated from *Drynaria fortunei*, *Citrus aurantium*, and *Citrus medica* [115]. NG regulates cell–cell trans-signaling pathways and possesses a wide range of therapeutic actions such as anti-cancer, anti-inflammatory, and antioxidant activity. In spite of the broad range of activity NG's clinical utility is limited due to poor aqueous solubility, low dissolution rate, and rapid elimination. In a conventional system, phytoconstituents are generally complex with some excipients so as to improve the biopharmaceutical properties. But this will not lead to a fruitful result. Thus NG respirable microparticles are developed that produce a promising result. The microparticle formulation of NG exhibits improved aerosolized property with profound therapeutic efficacy in a pulmonary disorder like cystic fibrosis [93, 94, 116].

25.15 Scutellarin (SR)

Scutellarin is a breviscapine flavone extracted from the *Erigeron breviscapus* belonging to the family Compositae. Chemically, SR is a 4,5,6-hydroxyl-flavone-7-glucuronide and was employed for the treatment of disorders related to the nervous system and cardiovascular system in the traditional Chinese medicinal system. It is investigated that SR possesses anti-hypercholesterolemic, anti-hypertrophic, smooth muscle relaxing, anticoagulant, and fibrinolytic activity. SR shows anti-inflammatory activity by interfering with arachidonic acid metabolism. But the phytoconstituents have limited therapeutic efficacy may be due to poor aqueous solubility and first-pass metabolism. Thus to overcome the therapeutic limitation of SR, respirable mucoadhesive microparticles are prepared using polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), and hyaluronan (HLN). The microparticles so formed have a greater volume of distribution and thus enhanced therapeutic potential with no alteration in toxicity profile [94]. Additionally, intratracheal administration of SR exhibits quick and complete absorption and thus improved bioavailability. Thus, mucoadhesive microparticles have a potential for the delivery of phytoconstituents in the lungs [117].

25.16 Honokiol (HK)

HK is a pleiotropic lignan mainly obtained from the Magnolia genus. The genus is geographically distributed in different parts of Asia mainly but also present in different parts of the world. The most common species of the genus from where HK can be commercially isolated are *Magnolia grandiflora*, *M. obovata*, and *M. officinalis*, belonging to the family Magnoliaceae and also these species were considered to be of great therapeutic importance in the medicines system. In the Chinese medicinal system, the *Magnolia officinalis* plant has long been utilized for its therapeutic value, where it is commonly termed as "houpa." *Magnolia obovata* in Japan has been utilized and is well recognized as "koboku." HK is known to have a wide range of therapeutic index including anti-microbial, neuroprotective, antioxidant, and anti-cancer activity. Due to its increased demand in Western countries, it has been modified and designed for administering through various routes including parenteral, oral, and transdermal [118]. Further, HK is explored to deliver via the pulmonary route to treat various acute and chronic pulmonary disorders. For this, inhalable honokiol microparticles were formulated using chitosan/mannitol. The microparticles formed showed improved aerodynamic properties and release kinetics, thus enhance therapeutic efficiency [95].

25.17 Andrographolide (AR)

AR commonly known as the king of bitters is a diterpenoid lactone mainly obtained from *Andrographis paniculata* (Acanthaceae) [119]. AR is a potent antihypertensive agent act by relaxing the smooth muscles of blood vessels. Apart from this AR also decreases pulmonary hypertension and is used for chronic pulmonary disorders. But due to poor aqueous solubility, low oral bioavailability, peripheral hydrolysis in a weakly basic environment, P-gp excretion in the intestine, biliary excretion and extensive first-pass metabolism the use of AR in clinical practice is limited. Thus for successful clinical outcomes of AR, an appropriate delivery system must be developed that enhances the bioavailability of AR [120]. For this, inhalable AR-loaded scleroglucan microparticles are developed and evaluated. The developed microparticles are spherically shaped with particle size in the range that provides much improvement in therapeutic efficacy and controlled release pattern as compared to conventional AR formulation. The intratracheal delivery of microparticles reveals the prolonged retention of drug in plasma and at the site of action and thus useful in treating pulmonary hypertension. Additionally, AR microparticles act as an immunostimulant by enhancing leukocyte and lymphocyte count in the body [96]. Furthermore, AR-β-CD inclusion complexes are developed using the freeze-drying technique and evaluated for anti-pneumonia activity in rats. AR microparticles inhibit *Staphylococcus aureus* colonization in the lungs and thus able to treat pneumonia. The microparticles formed showed high aerosolization efficiency with a better therapeutic outcome. Also, the β-CD complex formed depicts a better dissolution rate in pleural fluid. Therefore, inclusion

complexes adequately improve the dissolution of AR in pulmonary tissues and exhibit a prominent effect in pneumonia [97].

25.18 Atropine (AP)

Atropine belongs to the class of tropane alkaloids mainly present in the plants of the Solanaceae family, for instance, *Datura innoxia*, *Atropa belladonna*, *Datura stramonium*, and *Datura metel* [121]. Researchers investigated that AP possesses diverse therapeutic potential such as treatment of organophosphate poisoning, bronchodilation, local anesthetic, and so on. Currently, AP is administered through intravenous (i.v.), intramuscular (i.m.), and oral route. But the time required for achieving maximum concentration in plasma after i.v. injection is 5 min, while after i.m. injection it is 30 min and in case of oral dosing, it is 2 h. So, in case of emergency when we need prompt therapeutic effects such as organophosphate poisoning, only intravenous route is used due to the rapid onset of action, while intramuscular and oral routes are not preferred. Conversely, the intravenous route needs a paramedic or some health expert support. Due to this reason, effective, controlled release and safe formulation of AP are required. Thus, an inhaled AP formulation can be developed for précised and accurate dosing that permits self-administration with no discomfort [98, 99].

For this, AP sulfate nanoparticles are developed by nanoprecipitation technique. The nanoparticles so formed are spherical in shape with a particle size that showed better flowability. Moreover, nanoparticles as compared to microparticles show better aerosol dispersion of drugs in the respiratory tract. Further, clinical trial data also reveals an increase in the bioavailability of AP when delivered via the lungs. Also, the pharmacokinetic profile of AP is improved in healthy human volunteers when delivered through the pulmonary route as compared to the i.m. route. Briefly, AP nanoparticles offer a non-parenteral systemic therapy which might be useful for rapid onset [98, 99].

25.19 Dronabinol (DB)

Dronabinol is a pale yellow colored resinous cannabinoid obtained from the *Cannabis sativa*. DB has numerous pharmacological actions such as pain reliever, CNS stimulant, anti-hypertensive, respiratory stimulant, and many more. Unfortunately, in spite of diverse pharmacological action no commercially accepted dosage form is available because of poor aqueous solubility, pre-systemic metabolism, and rapid destruction in acidic media and oxidation. Also, the compound is very sticky which makes it challenging to formulate. So to overcome some of the above limitations dosage forms such as soft gelatine capsule, sublingual tablet, and pro-drug have been made. However, these dosage forms do not produce a sufficient successful rate due to inadequate shelf life and non-uniform bioavailability. Thus, advanced THC loaded respirable solid dispersion powder of DB with inulin is prepared by spray

freeze-drying technique, which avoids metabolism, non-uniform bioavailability, and other disadvantages. Also, THC loaded respirable solid dispersion powder provides a great degree of stability. Furthermore, spherical shape microparticles are prepared which have satisfactory drug-loading capacity with good aersolization and physicochemical stability [100].

25.20 Clinical Status

Phytoconstituents delivered via inhalational route exhibit a wide range of therapeutic advantages. The preclinical data reveals that phytoconstituents have promising therapeutic outcomes, while in human studies there is a doubt related to safety and therapeutic efficacy. Thus researchers are engaged in designing a pulmonary delivery system for phytoconstituents for the treatment of acute and chronic pulmonary disorders. Therefore, a number of clinical trials are to be executed for setting the role of inhaled phytoconstituents in a wide range of pulmonary diseases.

25.21 Discussion

Nowadays, researchers are focusing on the design and development of novel dosage forms for phytoconstituents to treat various diseases. However, such investigation is still a great challenge due to the pharmacokinetic limitation of phytoconstituents. Researchers try to improve these pharmacokinetic properties by altering particle morphology and aerodynamic properties. Still, numerous challenges have to be considered during formulating phytoconstituents for inhalational therapy.

Foremost challenges include some biological oriented problems such as poor aqueous solubility, low bioavailability, and low permeability. To overcome these challenges certain new delivery systems are developed that improve both physicochemical and pharmacokinetic profiles. Apart from the above, the selection of polymeric carrier which exhibits significant drug-loading ratio and good stability for novel formulations development is also an area of concern. Furthermore, the level of biological and physicochemical degradation of phytoconstituents is also studied and strategies must be adopted to maintain phytoconstituents stability. For instance, by modifying the phytoconstituents either chemically or physically the stability can be enhanced (e.g. pegylation). Moreover, utilization of these phytoconstituents for the treatment of pulmonary disorders required significant pulmokinetics, lung clearance rate, and minimal toxicological issues. Till now very few inhaled phytoconstituents are gaining clinical importance due to either pharmacokinetic or therapeutic issues. Also, an effective device and metering system must be developed for the effective pulmonary application. Finally, the development of inhaled phytoconstituents prominently remains in three major segments: pulmonary pharmacokinetics, toxicity, and device development.

25.22 Conclusion

Thus plant-based drugs are used since time immemorial and recognized by practitioners for their better clinical outcomes and lesser toxic effects as compared with synthetic medicines. But by developing modern dosage forms for phytoconstituents researchers enhanced the therapeutic efficacy. Indeed, phytotherapeutics needs a scientific way to deliver the components in an advanced manner to improve patient acceptance and avoid frequent drug administration. This can be done by developing novel drug delivery systems for active constituents obtained from a plant source. Also, by using novel drug delivery systems researchers can increase the therapeutic value by reducing the toxic profile and increasing the bioavailability of the herbal-based constituents. Recently, scientists have started to shift their research to design a drug delivery system for herbal medicines using different scientific approaches.

References

1. Yhee J, Im J, Nho R (2016) Advanced therapeutic strategies for chronic lung disease using nanoparticle-based drug delivery. J Clin Med 5(9):82
2. Tripathi K (2003) Essentials of medical pharmacology, 6th edn. Jaypee, New Delhi
3. World Health Organization (2007) Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach. World Health Organization, Geneva, pp 12–36
4. Burney PG, Patel J, Newson R et al (2015) Global and regional trends in COPD mortality, 1990-2010. Eur Respir J 45(5):1239–1247
5. Halbert RJ, Natoli JL, Gano A et al (2006) Global burden of COPD: systematic review and meta-analysis. Eur Respir J 28:523–532
6. Ley B, Collard HR (2013) Epidemiology of idiopathic pulmonary fibrosis. Clin Epidemiol 5:483–492
7. Masoli M, Fabian D, Holt S et al (2004) Global initiative for Asthma P. The global burden of asthma: executive summary of the GINA dissemination committee report. Allergy 59:469–478
8. Raghu G, Weycker D, Edelsberg J et al (2006) Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 174:810–816
9. Fullerton JN, Gilroy DW (2016) Resolution of inflammation: a new therapeutic frontier. Nat Rev Drug Discov 15(8):551
10. Tian L, Shang Y, Chen R et al (2019) Correlation of regional deposition dosage for inhaled nanoparticles in human and rat olfactory. Part Fibre Toxicol 16(1):6–6
11. Baker KE, Bonvini SJ, Donovan C (2014) Novel drug targets for asthma and COPD: Lessons learned from in vitro and in vivo models. Pulm Pharmacol Ther 29:181–198
12. Durham AL, Caramori G, Chung KF et al (2016) Targeted anti-inflammatory therapeutics in asthma and chronic obstructive lung disease. Transl Res 167:192–203
13. Fujita Y, Takeshita F, Kuwano K (2013) RNAi therapeutic platforms for lung diseases. Pharmaceuticals 6:223–250
14. Meyer KC (2014) Diagnosis and management of interstitial lung disease. Transl Respir Med 2:4
15. Mali R, Dhake A (2011) A review on herbal antiasthmatics. Orient Pharm Exp Med 11:77–90
16. Mehta P, Shah R, Lohidasan S et al (2015) Pharmacokinetic profile of phytoconstituents (s) isolated from medicinal plants-a comprehensive review. J Tradit Complement Med 5 (4):207–227

17. World Health Organization (2018) WHO. In: Chronic respiratory diseases (CRDs): fact sheets. World Health Organization, Geneva
18. Londahl J, Möller W, Pagels JH et al (2014) Measurement techniques for respiratory tract deposition of airborne nanoparticles: a critical review. J Aerosol Med Pulm Drug Deliv 27 (4):229–254
19. Zarogoulidis P, Chatzaki E, Porpodis K et al (2012) Inhaled chemotherapy in lung cancer: future concept of nanomedicine. Int J Nanomedicine 7:1551
20. Burhan E, Ruesen C, Ruslami R et al (2013) Isoniazid, rifampin, and pyrazinamide plasma concentrations in relation to treatment response in Indonesian pulmonary tuberculosis patients. Antimicrob Agents Chemother 57:3614–3619
21. Carvalho TC, Peters JI, Williams RO (2011) Influence of particle size on regional lung deposition—what evidence is there? Int J Pharm 406:1–10
22. Di Gioia S, Trapani A, Castellani S (2015) Nanocomplexes for gene therapy of respiratory diseases: targeting and overcoming the mucus barrier. Pulm Pharmacol Ther 34:8–24
23. Ratemi E, Sultana SA, Al Faraj A et al (2016) Alternative approaches for the treatment of airway diseases: focus on nanoparticle medicine. Clin Exp Allergy 46:1033–1042
24. Mehta P, Dhapte V (2016) A comprehensive review on pharmacokinetic profile of some traditional Chinese medicines. New J Sci 2016:1–31
25. Goldman P (2001) Herbal medicines today and the roots of modern pharmacology. Ann Intern Med 135:594–600
26. Evans W (2009) Pharmacogonasy, 16th edn. Saunders Elsevier, Philadelphia
27. Heinrich M, Barnes J, Gibbons S et al (2012) Fundamentals of pharmacognosy and phytotherapy, 2nd edn. Elsevier Ltd, London
28. Mehta P, Lohidasan S, Mahadik K (2017) Pharmacokinetic behaviour of clinically important TCM prescriptions. Orient Pharm Exp Med 17:171–188
29. Penton-Arias E, Haines D (2011) Natural Products: immuno-rebalancing therapeutic approaches. Immune Rebalancing 2011:229–249
30. Norman GB (2001) Herbal drugs and phytopharmaceuticals. A handbook for practice on a scientific basis, 2nd edn. Medpharm Scientific Publishers, New York, pp 230–248
31. Semalty A, Semalty M, Rawat BS et al (2009) Pharmacosomes: the lipid-based new drug delivery system. Expert Opin Drug Deliv 6:599–612
32. Amit J, Sunil C, Vimal K et al (2008) Phytosomes: a revolution in herbal drugs. The pharma review. Kongposh Publications Pvt. Ltd, New Delhi, pp 24–28
33. Parakh SR, Gothoskar AV (2003) Review of mouth dissolving tablet technologies. Pharmaceutical Technology/Advanstar Communications, Duluth, pp 47–52
34. Blatt Y, Kimmelman E, Cohen D et al (2002) Microencapsulated and controlled-release herbal formulations. United States Patent 6,340,478
35. Marechal D, Yang W, Yuzhang H (2009). Sustained-release microgranules containing gingko biloba extract and the process for manufacturing these. United States Patent 7,569,236
36. Sterer N, Nuas S, Mizrahi B et al (2008) Oral malodor reduction by a palatal mucoadhesive tablet containing herbal formulation. J Dent 36:535–539
37. Verma M, Gupta PK, Varsha BP et al (2007) Development of transdermal drug dosage formulation for the anti-rheumatic Ayurvedic medicinal plants. Anc Sci Life 11:66–69
38. Ma B, Duan X, Wang Z (2000) Clinical and experimental study on Shuanghua aerosol in treating infantile upper respiratory tract infection. Zhongguo Zhong Xi Yi Jie He Za Zhi 20:653–655
39. Tanwar YS, Gupta GD, Ramawa KG (2006) Development and evaluation of microparticles of Gugulipid. The pharma review. Kongposh Publications Pvt. Ltd, New Delhi, pp 124–132
40. Shen YJ, Zhang ZW, Luo XG et al (2008) Nanoparticles of traditional Chinese herbs inhibit thrombosis in vivo. Haematologica 93:1457
41. Zhao HR, Wang K, Zhao Y (2002) Novel sustained release implant of herb extract using chitosan. Biomaterials 23:4459–4462

42. Buzea C, Pacheco II, Robbie K (2007) Nanomaterials and nanoparticles: sources and toxicity. Biointerphases 2:17–71
43. Oberdorster G, Oberdorster E, Oberdorster J (2005) Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect 113:823–839
44. Janib SM, Moses AS, MacKay JA (2010) Imaging and drug delivery using theranostic nanoparticles. Adv Drug Deliv Rev 62:1052–1063
45. Chung CY, Yang JT, Kuo YC (2013) Polybutylcyanoacrylate nanoparticles for delivering hormone response element-conjugated neurotrophin-3 to the brain of intracerebral hemorrhagic rats. Biomaterials 34:9717–9727
46. Matsumura Y, Maeda H (1986) A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer Res 46:6387–6392
47. Ngoune R, Peters A, von Elverfeldt D et al (2016) Accumulating nanoparticles by EPR: A route of no return. J Control Release 238:58–70
48. Gipps EM, Arshady R, Kreuter J et al (1986) Distribution of polyhexyl cyanoacrylate nanoparticles in nude mice bearing human osteosarcoma. J Pharm Sci 75:256–258
49. Rolland A, Collet B, Le Verge R et al (1989) Blood clearance and organ distribution of intravenously administered polymethacrylic nanoparticles in mice. J Pharm Sci 78:481–484
50. Zara GP, Cavalli R, Fundaro A et al (1999) Pharmacokinetics of doxorubicin incorporated in solid lipid nanospheres (SLN). Pharmacol Res 40:281–286
51. Savla R, Minko T (2013) Nanotechnology approaches for inhalation treatment of fibrosis. J Drug Target 21:914–925
52. Kuzmov A, Minko T (2015) Nanotechnology approaches for inhalation treatment of lung diseases. J Control Release 219:500–518
53. Lehofer B, Bloder F, Jain PP et al (2014) Impact of atomization technique on the stability and transport efficiency of nebulized liposomes harbouring different surface characteristics. Eur J Pharm Biopharm 88:1076–1085
54. Allen TM (1998) Liposomal drug formulations. Rationale for development and what we can expect for the future. Drugs 56:747–756
55. Winterhalter M, Frederik PM, Vallner JJ et al (1997) Stealth(R) liposomes: from theory to product. Adv Drug Deliv Rev 24:165–177
56. Muralidharan P, Malapit M, Mallory E et al (2015) Inhalable nanoparticulate powders for respiratory delivery. Nanomedicine 11:1189–1199
57. Van Rijt SH, Bein T, Meiners S (2014) Medical nanoparticles for next generation drug delivery to the lungs. Eur Respir J 44:765–774
58. Kaminskas LM, McLeod VM, Ryan GM et al (2014) Pulmonary administration of a doxorubicin-conjugated dendrimer enhances drug exposure to lung metastases and improves cancer therapy. J Control Release 183:18–26
59. Ryan GM, Kaminskas LM, Kelly BD et al (2013) Pulmonary administration of PEGylated polylysine dendrimers: absorption from the lung versus retention within the lung is highly size-dependent. Mol Pharm 10:2986–2995
60. Paranjpe M, Muller-Goymann CC (2014) Nanoparticle-mediated pulmonary drug delivery: A review. Int J Mol Sci 15:5852–5873
61. Elhissi AMA, Faizi M, Naji WF et al (2007) Physical stability and aerosol properties of liposomes delivered using an air-jet nebulizer and a novel micropump device with large mesh apertures. Int J Pharm 334:62–70
62. Niven RW (1995) Delivery of biotherapeutics by inhalation aerosol. Crit Rev Ther Drug Carr Syst 12:151–231
63. Kim T, Hyeon T (2014) Applications of inorganic nanoparticles as therapeutic agents. Nanotechnology 25:012001
64. Yhee JY, Son S, Kim N et al (2014) Theranostic applications of organic nanoparticles for cancer treatment. MRS Bull 39:239–249

65. Nassimi M, Schleh C, Lauenstein HD et al (2010) A toxicological evaluation of inhaled solid lipid nanoparticles used as a potential drug delivery system for the lung. Eur J Pharm Biopharm 75:107–116
66. Elhissi AMA, Islam MA, Arafat B et al (2010) Development and characterisation of freeze-dried liposomes containing two anti-asthma drugs. Micro Nano Lett 5:184–188
67. Hoesel LM, Flierl MA, Niederbichler AD et al (2008) Ability of antioxidant liposomes to prevent acute and progressive pulmonary injury. Antioxid Redox Signal 10:973–981
68. Jokerst JV, Lobovkina T, Zare RN et al (2011) Nanoparticle PEGylation for imaging and therapy. Nanomedicine 6:715–728
69. Van Vlerken LE, Vyas TK, Amiji MM (2007) Poly(ethylene glycol)-modified nanocarriers for tumor-targeted and intracellular delivery. Pharm Res 24:1405–1414
70. Schuster BS, Suk JS, Woodworth GF (2013) Nanoparticle diffusion in respiratory mucus from humans without lung disease. Biomaterials 34:3439–3446
71. Surti N, Naik S, Bagchi T et al (2008) Intracellular delivery of nanoparticles of an antiasthmatic drug. AAPS Pharm Sci Technol 9:217–223
72. Kesharwani P, Jain K, Jain NK (2014) Dendrimer as nanocarrier for drug delivery. Prog Polym Sci 39:268–307
73. Bharatwaj B, Mohammad AK, Dimovski R et al (2015) Dendrimer nanocarriers for transport modulation across models of the pulmonary epithelium. Mol Pharm 12:826–838
74. Ding Y, Jiang Z, Saha K et al (2014) Gold nanoparticles for nucleic acid delivery. Mol Ther 22:1075–1083
75. Alkilany AM, Murphy CJ (2010) Toxicity and cellular uptake of gold nanoparticles: What we have learned so far? J Nanopart Res 12:2313–2333
76. Mehta P (2018) Imagine the superiority of dry powder inhalers from carrier engineering. J Drug Deliv 2018:5635010
77. Sanders M (2007) Inhalation therapy: an historical review. Prim Care Respir J 16(2):71–81
78. Prota L, Santoro A, Bifulco M et al (2011) Leucine enhances aerosol performance of naringin dry powder and its activity on cystic fibrosis airway epithelial cells. Int J Pharm 412:8–19
79. Rogers L, Cismowski M (2018) Oxidative stress in the lung- the essential paradox, Curr. Opin Toxicol 7:37–43
80. Sansone F, Aquino R, Del Gaudio P et al (2009) Physical characteristics and aerosol performance of naringin dry powders for pulmonary delivery prepared by spray-drying. Eur J Pharm Biopharm 72(1):206–213
81. Taki M, Tagami T, Fukushige K et al (2016) Fabrication of nanocomposite particles using a two-solution mixing-type spray nozzle for use in an inhaled curcumin formulation. Int J Pharm 511(1):104–110
82. El-Sherbiny I, Smyth H (2012) Controlled release pulmonary administration of curcumin using swellable biocompatible microparticles. J Mol Pharm Org Process Res 9:269–280
83. Kurniawansyah F, Mammucari R, Foster N (2015) Inhalable curcumin formulations by supercritical technology. Powder Technol 284:289–298
84. Wang Z, Gupta S, Meenach S (2017) Development and physicochemical characterization of acetalated dextran aerosol particle systems for deep lung delivery. Int J Pharm 525(1):264–274
85. Na L, Dan-dan T, Li-wen W (2014) Preparation of dry powder inhalation based on phytosomes-chitosan microspheres by spray-drying method and study on its characterization, Chin. Tradit Herbal Drugs 45(17):2475–2481
86. Dimer F, Ortiz M, Pohlmann A et al (2015) Inhalable resveratrol microparticles produced by vibrational atomization spray drying for treating pulmonary arterial hypertension. J Drug Deliv Sci Technol 29:152–158
87. Trotta V, Lee W, Loo C (2015) In vitro biological activity of resveratrol using a novel inhalable resveratrol spray-dried formulation. Int J Pharm 491:190–197
88. Scalia S, Haghi M, Losi V et al (2013a) Quercetin solid lipid microparticles: a flavonoid for inhalation lung delivery. Eur J Pharm Sci 49(2):278–285

89. Scalia S, Trotta V, Traini D et al (2013b) Incorporation of quercetin in respirable lipid microparticles: effect on stability and cellular uptake on A549 pulmonary alveolar epithelial cells. Colloids Surf B Biointerfaces 112:322–329
90. Madunic J, Madunic I, Gajski G et al (2018) Apigenin: a dietary flavonoid with diverse anticancer properties. Cancer Lett 413:11–22
91. Zhang J, Lv H, Jiang K et al (2011) Enhanced bioavailability after oral and pulmonary administration of baicalein nanocrystal. Int J Pharm 420(1):180–188
92. Mohtar N, Taylor K, Sheikh K et al (2017) Design and development of dry powder sulfobutylether-b-cyclodextrin complex for pulmonary delivery of fisetin. Eur J Pharm Biopharm 113:1–10
93. Chen R, Qi QL, Wang M et al (2016) Therapeutic potential of naringin: an overview. Pharm Biol 54(12):3203–3210
94. Saraf S, Gupta A, Alexander A et al (2015) Advancements and avenues in Nanophytomedicines for better pharmacological responses. J Nanosci Nanotechnol 15 (6):4070–4079
95. Li X, Guo Q, Zheng X et al (2009) Preparation of honokiol-loaded chitosan microparticles via spray-drying method intended for pulmonary delivery. Drug Deliv 16(3):160–166
96. Mali A, Bothiraja C, Purohit RN et al (2017) In vitro and in vivo performance of novel spray dried andrographolide loaded scleroglucan based formulation for dry powder inhaler. Curr Drug Deliv 14(7):968–980
97. Zhang T, Zhu L, Li M et al (2017) Inhalable Andrographolide-β-cyclodextrin inclusion complexes for treatment of Staphylococcus aureus pneumonia by regulating immune responses. Mol Pharm 14(5):1718–1725
98. Corcoran T, Venkataramanan R, Hoffman R et al (2013) Systemic delivery of atropine sulfate by the MicroDose dry-powder inhaler. J Aerosol Med Pulm Drug Deliv 26(1):46–55
99. Ali R, Jain GK, Iqbal Z et al (2009) Development and clinical trial of nano-atropine sulphate dry powder inhaler as a novel organophosphorus poisoning antidote. Nanomedicine 5 (1):55–63
100. Van Drooge D, Hinrichs W, Dickhoff B et al (2005) Spray freeze drying to produce a stable Δ9-tetrahydrocannabinol containing inulin based solid dispersion powder suitable for inhalation. Eur J Pharm Sci 26(2):231–240
101. Khan J, Ajazuddin AA, Saraf S et al (2013) Recent advances and future prospects of phytophospholipid complexation technique for improving pharmacokinetic profile of plant actives. J Control Release 168(1):50–60
102. Squillaro T, Peluso G, Melone MAB (2017) Nanotechnology-based polyphenol delivery: a novel therapeutic strategy for the treatment of age-related neurodegenerative disorder. Austin Aging Res 1(1):1004
103. Mehta P (2016) Dry powder inhalers: a focus on advancements in novel drug delivery systems. J Drug Deliv 2016:8290963
104. Naksuriya O, Okonogi S, Schiffelers R et al (2014) Curcumin nano formulations: a review of pharmaceutical properties and preclinical studies and clinical data related to cancer treatment. Biomaterials 35(10):3365–3383
105. Feng T, Wei Y, Lee R et al (2017) Liposomal curcumin and its application in cancer. Int J Nanomedicine 12:6027–6044
106. Pangeni R, Sahni J, Ali J et al (2014) Resveratrol: review on therapeutic potential and recent advances in drug delivery. Expert Opin Drug Deliv 11(8):1285–1298
107. Carter L, D'Orazio J, Pearson K (2014) Resveratrol and cancer: focus on in vivo evidence. Endocr Relat Cancer 21(3):209–225
108. Jadhav P, Bothiraja C, Pawar A (2016) Resveratrol-piperine loaded mixed micelles: formulation, characterization, bioavailability, safety and in vitro anticancer study. RSC Adv 6:112795–112805
109. Zhu X, Lei X, Dong W (2017) Resveratrol as a potential therapeutic drug for respiratory system diseases. Drug Des Dev Ther 11:3591–3598

110. de Oliveira M, Nabavi S, Braidy N et al (2016) Quercetin and the mitochondria: a mechanistic view. Biotechnol Adv 34(5):532–549
111. Papay Z, Kosa A, Boddi B et al (2017) Study on the pulmonary delivery system of apigenin loaded albumin nanocarriers with antioxidant activity. J Aerosol Med Pulm Drug Deliv 30 (4):274–288
112. Gao Y, Snyder S, Smith J et al (2016) Anticancer properties of baicalein: a review. Med Chem Res 25(8):1515–1523
113. Bothiraja C, Yojana B, Pawar A et al (2014) Fisetin-loaded nanocochleates: formulation, characterisation, in vitro anticancer testing, bioavailability and biodistribution study. Expert Opin Drug Deliv 11(1):17–29
114. Mehta P, Pawar A, Mahadik K et al (2018) Emerging novel drug delivery strategies for bioactive flavonol fisetin in biomedicine. Biomed Pharmacother 106:1282–1291
115. Bharti S, Rani N, Krishnamurthy B et al (2014) Preclinical evidence for the pharmacological actions of naringin: a review. Planta Med 80(6):437–451
116. Gera S, Talluri S, Rangaraj N (2017) Formulation and evaluation of naringenin nanosuspensions for bioavailability enhancement. AAPS Pharm Sci Technol 18 (8):3151–3162
117. Xing J, You H, Dong Y et al (2011) Metabolic and pharmacokinetic studies of scutellarin in rat plasma, urine, and feces. Acta Pharmacol Sin 32(5):655–663
118. Woodbury A, Yu S, Wei L et al (2013) Neuro-modulating effects of honokiol: a review. Front Neurol 4:130
119. Thingale A, Shaikh K, Channekar P et al (2015) Enhanced hepatoprotective activity of andrographolide complexed with a biomaterial. Drug Deliv 22(1):117–124
120. Bothiraja C, Kumbhar V, Pawar A et al (2015) Development of floating in situ gelling system as an efficient anti-ulcer formulation: in vitro and in vivo studies. RSC Adv 5:28848
121. Behcet AL (2014) The source-synthesis- history and use of atropine. Acad Emerg Med 2014:132–133

Application of Nanodrugs Derived from Active Metabolites of Medicinal Plants for the Treatment of Inflammatory and Lung Diseases: Recent Advances

26

Charles Oluwaseun Adetunji, Abel Inobeme, Olugbemi Tope Olaniyan, Olulope Olufemi Ajayi, Seyi Olaniyan, and Juliana Bunmi Adetunji

Abstract

Pulmonary diseases have been identified as one of the major diseases that are responsible for higher level of mortality globally. The application of nanotechnology has been identified as a sustainable technology that could be utilized for successful delivery of biologically active constitutes available in the newly synthesized nanodrug. Several reports have also established the uses of nanocarriers in drug delivery to the lungs. The use of nanoparticle for drug delivery ensures systematic drug release and enhanced drug bioavailability. This increases drug effectiveness and reduces toxicity. Hence, this chapter intends to provide a comprehensive information on several medicinal plants that could be applied for the management of pulmonary diseases including

C. O. Adetunji (✉)
Applied Microbiology, Biotechnology and Nanotechnology Laboratory, Department of Microbiology, Edo State University Uzairue, Auchi, Edo State, Nigeria;
adetunji.charles@edouniversity.edu.ng

A. Inobeme
Department of Chemistry, Edo State University Uzairue, Iyamho, Edo State, Nigeria

O. T. Olaniyan
Laboratory for Reproductive Biology and Developmental Programming, Department of Physiology, Edo State University Uzairue, Iyamho, Edo State, Nigeria

O. O. Ajayi
Department of Biochemistry, Edo State University Uzairue, Iyamho, Edo State, Nigeria

S. Olaniyan · J. B. Adetunji
Nutrition and toxicology Research Laboratory, Department of Biochemistry Sciences, Osun State University, Osogbo, Nigeria

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_26

chronic obstructive pulmonary disease, lung cancer, and lower respiratory tract infections. Detailed information were also provided on typical examples of nanodrug that could be applied for effective management of pulmonary diseases.

Keywords

Pulmonary diseases · Nanodrugs · Nanotechnology · Drug bioavailability · Drug delivery · Nanoparticle · Nanocarriers

26.1 Introduction

Pulmonary diseases including chronic obstructive pulmonary disease, lung cancer, and lower respiratory tract infections are major causes of mortality, globally. The treatment of lung diseases is via different routes; inhalation, oral, and intravenous. More recently, nanotechnology is being used to enhance drug administration via these routes. The lung has a large surface area, which supports inhalation as the preferred therapy [1].

There are reports on the use of nanocarriers in drug delivery to the lungs. The use of nanoparticle for drug delivery ensures systematic drug release and enhanced drug bioavailability. This increases drug effectiveness and reduces toxicity [2]. Particle size is of essence in this regard. Diffusion is the mechanism of particle deposition of nanodrugs <160 nm diameter, while sedimentation and impaction are mechanisms of nanodrugs >160 nm in diameter [3]. There are evidences that nanoparticles appear to easily get lost during exhalation because of their size and low inertia. Therefore, conjugation of nanoparticle with heavier drugs appears more effective as loss is reduced [4]. Furthermore, nanodrugs for pulmonary diseases are expected to be biodegradable [2].

The treatment/management of lung infections is challenging, because of the drawbacks of delivering adequate quantity of drugs to the site of infection [5]. This led to the preparation of antibiotics for inhalation. Ciprofloxacin prepared into nanoparticles and encapsulated into poly (D,L-lactic-co-glycolic acid (PLGA) proved to deliver the drug to deep parts of the lungs, thereby evading macrophage clearance [5]. Administration of chemotherapy to individuals with lung cancer via inhalation is also being explored. Enclosing paclitaxel into albumin nanoparticles (130-nm) allows swifter drug distribution/permeation and also averts hypersensitivity reactions that are peculiar to Cremophor. Albumin-conjugated paclitaxel is better tolerated and easily absorbed by the cancer cells [6].

Conjugating active metabolites of medicinal plants to nanoparticles seem more promising than the orthodox drugs. This is because a lot of these metabolites possess anti-oxidant and anti-inflammatory properties. Curcumin, 100 mg/kg was found to inhibit the activity of elastase and inflammation caused by cigarette smoke [7].

Moreover, it has been established that several phytochemicals could be utilized for the synthesis of nanodrugs. This might be linked to the facts that these phytochemicals derived from medicinal plants have been validated to show higher

level of biological activities. Reports also showed that curcumin boosted protein kinase C expression, p38 phosphorylation. It also increased the availability of anti-oxidant enzymes [8]. The anti-oxidant and anti-inflammatory properties of resveratrol have been reported. It activates haem oxygenase-1 (HO-1) via Nrf2-anti-oxidant response element (ARE) signaling pathway [9]. Catechin is a flavonoid with anti-oxidant properties. Epigallocatechin-3-gallate inhibited oxidative stress by improving nuclear translocation of Nrf2 and HO-1 gene expression [10].

Moreover, it has been observed that terpenoids also inhibited oxidative stress by activating Nrf2 signaling [11]. CDDO imidazolide reduced oxidative burden in the lungs, it also reduces the destruction of the alveolar due to cigarette smoke [12]. Quercetin is a flavonoid that is present in some fruits and vegetables such as apple, onion, etc. Reports showed that it exerts its anti-oxidant effect by activating Nrf2. Sulforaphane is found in vegetables such as broccoli sprouts, cauliflower, etc. Its anti-oxidant properties are well documented. Its conjugation with nanoparticles is promising in the treatment of lung diseases [11].

Therefore, this chapter intends to provide a detailed information on the application of nanotechnology for the fabrication of Nanodrugs that could be applied for the management of several pulmonary diseases such as chronic obstructive pulmonary disease, lung cancer, and lower respiratory tract infections.

26.2 Specific Examples of Medicinal Plants that Could Be Utilized for Effective Treatment of Inflammatory and Lung Diseases

Snehal and Jignasha [13] reported that several authors have utilized steroids in the treatment of inflammatory diseases. These glucocorticoids are found in plant and animal species and many potential therapeutic isolates can be generated from them with little or no side effects when used for inflammatory treatment. The authors have reported several biologically-active molecules with anti-inflammatory properties from numerous plants which possess similar structural identity with glucocorticoids such as diosgenin, sarsasapogenin, solasodine, boswellic acid, guggulsterones, glycyrrihizin, and withanolides. Many plants have been studied and reported to possess these active constituents, thus can be utilized for anti-inflammatory activity. *Trigonella foenum graecum* L, *Boswellia serrata* Roxb, *Solanum xanthocarpum* L, *Glycyrrhiza glabra* L, *Withania somnifera*, and *Commiphora mukul* are listed by the authors as useful medicinal plant with numerous therapeutic properties. Inflammation in human health has attracted significant attention in the past few years due to intensive research output witnessed in elucidating the pathways involved in the mechanism of inflammatory signaling in the pathogenesis of several diseases such as asthma, rhinitis, rheumatoid arthritis, conjunctivitis, plus multiple sclerosis.

Xia-Wei et al. [14] revealed that Chinese herbal medication has received massive attention as an effective therapeutic agent that could be applied in the management of several pulmonary diseases even though the mechanism of action of most them are yet to be fully elucidated. Thus the authors analyzed the possible mechanisms of

action of Yihuo Huatan Formulation against chronic obstructive pulmonary diseases utilizing pharmacology based approach. It was revealed that about 1267 active constituents are isolated from the Yihuo Huatan Formulation out of which about 180 active ingredients were analyzed for pharmacological activity. The authors revealed that the suggested mode of action of these active molecules include decrease of mucus secretion, alleviation of airway inflammation, maintenance of immune homeostasis through regulation of multiple targets plus pathways.

Rebecca et al. [15] reported that chronic inflammatory respiratory diseases have become prevalent in many parts of the globe and treatment option includes anti-inflammatory therapies that will improve bronchodilation utilizing corticosteroids. The authors demonstrated that phytomedicines are now available and recently considered option in the treatment of chronic inflammatory respiratory diseases as they are plant-based traditional pharmacological practice utilizing various forms of herbs and natural components which are known to be therapeutic towards these conditions. Advancement in the utilization of phytomedicines is hampered by the low level of research activity. Therefore, there is a need to intensify more scientific in harnessing the potentials of plant-based medicines in the treatment of asthma and other chronic obstructive pulmonary diseases. With significant research directed towards this area, many active ingredients can be developed into drugs for the management of asthma and other related diseases with little or no side effects. The authors also suggested that through molecular biology techniques, the possible mechanism of action can be elucidated

Alamgeer et al. [16] revealed that in Pakistan, respiratory diseases are very common due to the environmental condition of the area with little health care centers to cater for the sick people. It is generally known that people rely on traditional method of treatment as an alternative to the orthodox medicine. The authors carried out a study to assess the significance of ethnomedicinal plant which are currently being utilized in Pakistan for the treatment of respiratory disorders. They also analyzed the pharmacokinetics, economic importance, diversity, and preparation approach of these herbs, shrubs, trees and their phytochemicals thus discovered that many of these plants rots plus leaves are used for the treatment of cough, asthma, common cold, bronchitis in the form of concoction.

Ibraheem et al. [17] reported that in many parts of the developing nations, indigenes rely mostly on traditional herbs to treat different kinds of ailments particularly respiratory disorders due to limited accessibility to orthodox medicine and the exorbitant cost of treatment. The authors therefore documented many articles on plant components or species commonly utilized for respiratory disorders across Ede South Local Government Area of Osun State, Nigeria. From their findings, it was revealed that about 87 plant species documented to consume for the treatment of cough and other related respiratory disorders through concoction formulation and administered orally. The authors revealed that many of the plant species are very rich source of active molecules that could be developed into drug for the management of respiratory diseases particularly in Nigeria and Africa.

Fernanda et al. [18] reported that inflammation is the major sign of many respiratory diseases such as asthma, plus chronic obstructive pulmonary disease, acute respiratory syndrome distress, thus many are treated with an anti-inflammatory agent. The authors revealed that many plant-based anti-inflammatory agents such as alkaloids, terpenoids plus flavonoids against respiratory diseases have not been evaluated to properly identify the mechanism of action biologically despite the growing interest in them. Thus, the author's aim is to identify some of the mechanisms of action such as inhibition of NF-κB, modulatory role of natural compounds on pulmonary inflammation, suppression of MAPK pathways, and anti-oxidant promoting effects. It was suggested that clinical trials should be done on these active ingredients to elucidate the safety and efficacy level.

Javad et al. [19] reported that according to World Health Organization, tuberculosis is a very deadly infectious disease classified as global health emergency caused by Mycobacterium tuberculosis. The treatment of this infectious disease consists of intensive plus a continuation phase but unfortunately there seems to be multi-drug-resistant tuberculosis as a result of inefficient healthcare facilities or low compliance to prescribed drugs. Therefore, there is imperative need to improve and discover novel remedies that would quickly suppress the global burden of the disease and other multi-drug-resistant tuberculosis. The authors reported that many active ingredients derived from fungi and marine based organisms are could be utilized for the treatment of tuberculosis together with natural products as adjuvant so as to enhance the efficacy of their anti-tuberculosis activities. They discovered that due to the need to quickly develop novel drug to suppress the global burden of tuberculosis, traditional phytotherapeutic agents are currently being studied to explore possible macromolecules and agents with enhanced biological activities. For the development of novel therapy from natural products, many techniques must be utilized such as isolation, purification, identification, and quantification.

Hyun et al. [20] reported that chronic obstructive pulmonary diseases and acute bronchitis are due to inflammation of the lungs which could be managed by the utilization of plant extract active ingredients such as coumarins, phenolics, flavonoids, iridoids, sirtuins, monoterpenes, triterpenoids, and diterpenes. Jae-Won et al. [21] revealed that *Azadirachta indica* A. Juss popularly called neem leaf has been shown to exert huge anti-inflammatory, anti-oxidant, and antibacterial. Thus the authors investigated the role of the plant extract on pulmonary inflammation. In their report, it was discovered that cell inflammatory infiltration by macrophages, the expression of monocyte chemoattractant protein-1, tumor necrosis factor-α, neutrophil elastase activity, c-Jun N-terminal kinase, activation of extracellular signal-regulated kinase, interleukin, reactive oxygen species, expression of inducible nitric oxide synthase and neutrophils were greatly reduced in the bronchoalveolar lavage fluid. The authors suggested that this plant possess great active ingredient against chronic obstructive pulmonary disease.

Ram et al. [22] revealed that the present treatment for the handling of chronic obstructive pulmonary disease is grossly inadequate thereby resulting into a major global health challenge and several side effects. They showed that alternative therapies are urgently needed, hence medicinal plants like the Ayurveda or Siddha

of India, plus traditional Chinese medicine of China are the emerging area with vast novel biomolecules being deployed by several countries for treatment against obstructive lung diseases like emphysema or bronchitis. The physiological effects found in these plants include relaxant activity, bronchodilatory, antitussive, anti-cholinergic, mucociliary clearance activity plus anti-spasmodic properties. It is generally believed that crude extract may be of beneficial advantage over the isolated constituents in the treatment of respiratory disorders due to the synergistic effects.

Rainer and Ashley [23] reported that globally respiratory infection seems to be a major health challenge particularly as a result of resistance developed against the currently used therapies. The authors showed that traditional medicines can serve as alternatives due to their high level of efficacy. Thus the authors investigated quite a number of medicinal plants for respiratory system herbal remedies in Peru and discovered that many of these plants are regularly utilized for respiratory disorders through oral or topical application. It was suggested by the authors that these plants and their ethnobotanical data can be gathered and developed into drug formulation for different respiratory infections but first the safety and efficacy must be well established before usage.

Amir et al. [24] reported that dyspnea, maximal expiratory flow limitation and inflammation are the major sign of cystic fibrosis, parenchymal inflammation, and chronic obstructive pulmonary disease. The authors revealed that over the years, scientists have rigorously pursued to examine the pathways responsible for the chronic inflammation seen with these respiratory disorders and ways to curb or eliminate it. Thus various molecular targets are currently being investigated for possible novel therapeutic action by natural compounds or molecules. Various natural compounds have been examined for their anti-inflammatory activity particularly lung diseases. The authors suggested that preliminary in vitro and in vivo studies.

Fernanda et al. [18] revealed that pulmonary inflammatory is the major attribute of many chronic obstructive pulmonary diseases and respiratory disorders. The authors showed that traditional medicine and their natural constituents may be alternative therapy for the treatment of respiratory disorder, thus scientific evaluation of these compounds such as alkaloids, flavonoids, terpenoids for biological effects like anti-inflammatory, antiplatelet, antiviral, antitumor, anti-oxidant, antiallergic properties may offer promising role in the management of chronic obstructive pulmonary disease. The authors suggested more clinical trials for pulmonary diseases and the possible mechanisms of action involved in their therapeutic effects.

Okoli et al. [25] reported that the present anti-inflammatory medications have witnessed inherent challenges due to development of multidrug resistance, thus there is continuous search for alternative agent with efficient biological activity from natural sources. Many plants have been list by the authors to be very rich in anti-inflammatory molecules tested through in vivo and in vitro assays such as *Aloe vera*, *Chasmanthera dependens*, *Consolida regalis*, *Culcasia scandens*, *Tanacetum vulgare*, *Crateva religiosa*, *Holmskioldia sanguinea*, *Turnera ulmifolia*, *and Mitracarpus scaber.* The active ingredients present may act in multiple targets or pathways including other physiological properties like antimicrobial, antipyretic,

antiulcer plus analgesic. The authors listed some molecules in these plants that have been identified and characterized by various molecular techniques such as premnazole, lupeol, (+)—usnic acid, zanhasaponins A plus B, (+)—pinitol, parthenolide, sasanquol. Many of these constituents have strong biological effects over the present line of drugs against respiratory disorders thus scientists should be encouraged to analyze how many will be developed into active drug with no side effects.

Mohsen et al. [26] revealed that many Urmian herbalists have been known to cure respiratory ailment utilizing medicinal plants grown around West Azerbaijan Province, thus herbarium samples, data were obtained and analyzed at the Urmia University, Iran. The findings demonstrated that about 20 different medicinal plants of various parts like stem, root, and leaves are routinely utilized for respiratory diseases by boiling. The authors recommended that there is an urgent need to perform further study so as to isolate and characterize the biologically active constituents present in these medicinal plants that so as to develop them into active drug.

Arjun et al. [27] demonstrated that one of the ancient traditional medicines is the Siddha system of medical practice in India for the management of various ailments. The authors showed that respiratory diseases are severe health issues with the present therapies presenting numerous side effects thus the need to search for a more reliable and more effective therapy. The aim objective of the authors is to create awareness around Siddha system of medical practice in India towards the treatment of respiratory diseases with the possibility of further exploring various active constituents for drug formulations. Currently there are limited data available to demonstrate the strength in the Siddha system of medical practice in India, and several potent medicinal plants like *Acalypha indica*, *Adhatoda vasica*, *Solanum xanthocarpum*, *Euphorbia hirta* L., *Solanum nigrum* L., *Caesalpinia bonduc* L., *Borassus flabellifer* L, *Crocus sativus* L, *Solanum trilobatum* L., *Piper longum* L., *Strychnos potatorum* L., *Terminalia bellirica* Roxb, *Celery-keerai*, *Kuppaimeni*, *Apium graveolens* L., *Calotropis gigantea* L., *Piper nigrum* L., *Ocimum sanctum* L., *Tylophora indica* Merrill, *Hibiscus rosa-sinensis*, *Boerhavia diffusa* L., *Adhatoda vasica Nees* for respiratory ailments are not properly documented by these herbalists creating a lack of data. These active constituents include alkaloids, apigenin, choline, shikimic acid, apiin, have been recommended for vasodilatory action, suppressive effects on nitric oxide generation and manifestation of inducible nitric oxide synthase, synthesis of T suppressor cells, spasmolytic, inhibition of mast cell degranulation, inhibition of DNA binding properties of NF-kB plus AP-1 antimicrobial, antifungal, antidiabetic, delayed in hypersensitive response to serum red blood cells, inhibition of inflammatory swellings, immunomodulatory activity on lymphocyte proliferation, removal of histamine, inhibition of nitric oxide or TNF-α production properties.

Rocio et al. [28] reported that respiratory diseases particularly tuberculosis in Mexico are treated with plant-based medicines referred to as Mexican Traditional Medicine like *Aristolochia taliscana*, *Chrysactinia mexicana*, *Saccharomyces cerevisiae*, *Citrus sinensis*, *Persea americana*, *Olea europaea*, *Larrea divaricata*,

Phoradendron robinsoni, *Amphipterygium adstringens* containing active molecules such as Licarin A, 9-methoxytariacuripyrone or 9-amino-9-methoxy-3,4-dihydro-2H-benzo[h]-chromen-2-one. The authors showed that these active compounds could be developed into active drugs against many respiratory diseases without any side effects compared with many current medications utilized.

James et al. [29] revealed that in children, respiratory diseases are responsible for mortality of under 5 years of age in many developing countries compounded by very low efficacy of the current mode of treatment with several underline side effects. Also noted is poor access to modern health facilities in these regions thereby resulting into traditional form of treatment. It has been noticed that despite the richness of many medicinal plant in the management of respiratory diseases, children are still subjected to high risk of complications and other problems due to the lack of adequate knowledge on mode of action, dosage, duration, concentration, and hygiene of the concoction preparation form these medicinal plants. Thus the authors seek to evaluate the ethno-medicinal data of these novel pharmaceutical agents in Kisumu East. The findings revealed that many of the traditional plant species have potent medicinal value and can be blended with the current therapy to reduce the side effects and enhance the effectiveness against respiratory disorders.

Nilima et al. [30] carried out a study to evaluate the importance of traditional medicine against many respiratory diseases. The authors discovered that many people from the developing country rely main on the traditional medicine from potent medicinal plants even though the phytochemical and pharmacological activities are very unclear. They suggested that many possess bronchodilator, anti-oxidant, antimicrobial, expectorant, antifungal, antibacterial, hepatoprotective, anti-inflammatory, antiulcer, antitussive, anti-tubercular, antiviral activities.

26.3 Mode of Action of Some Medicinal Plants in Treating Lung Diseases

The curative potentials of phytochemicals of medicinal plants are well documented. In the management of lung diseases, several phytochemicals have shown efficacy via different mechanisms. Quercetin is known for its anti-oxidant and anti-inflammatory properties. It was also shown to reduce hypersensitivity reactions of the airways [31]. Furthermore, it boosted GSH level while minimizing the production of reactive oxygen species (ROS). Additionally, it enhanced Nrf2 nuclear translocation and Haem oxygenase-1 gene expression [11].

Terpenoids were reported to decrease ROS production, they also boosted Nrf2 nuclear translocation and expression of HO-1 gene [11]. Curcumin enhanced phosphorylation of protein kinase C and p38, while also boosting the activation of HO-1 in monocytes. Resveratrol boosted the production of GSH. It also inhibited the release of cytokines. Resveratrol also boosted the translocation of Nrf2 and expression of HO-1 gene [11].

Sulforaphane suppressed p38MAPK activation and also enhanced Nrf2 translocation. Catechin similarly boosted nuclear translocation of Nrf 2 and HO-1 gene expression [11]. Table 26.1 shows the mechanism of action involved in the

Table 26.1 Modes of action involved in the application of nanodrugs synthesized from different medicinal treatment of inflammatory and lung diseases infection

S/N	Medicinal plant	Family	Compound	Mode of action	phytochemicals	Nano Particles	Reference
1	*Asparagus racemosus*	*Asparagaceae*	Shatavarin		Saponins and flavonoid	Ag	Kerry et al. [32]
	Plumbago zeylanica	Plumbaginaceae	Plumbagin	Degeneration of NF-kappa B signaling pathway	Tannins, flavanoids, and saponins	Au–Ag	Gani and Ganesan [33]
	Artemisia pallens	Asteraceae	Artemisinin	Inhibits MAPKs signaling pathway	Alkaloids, flavonoids	Cu	Shi et al. [34]
	Barleria prionitis	Acanthaceae	Balarenone	Inhibits COX-1 and COX-2 enzyme	Glycosides, saponins, flavonoids, steroids and tannins	Au–Ag	Banerjee et al. [35]
	Limonia acidissima	Rutaceae			Alkaloids, saponins, and flavonoids	Zno	
	Syzygium cumini	Myrtaceae	Rutin	Eosinophil migration inhibition	Flavonoid and Alkaloid	Au–Ag	Bijauliya et al. [36]
	Annona reticulata	Annonaceae	Annonaretin	Lipopolysaccharide inhibition	Tannins, alkaloids, saponins, and flavonoids	Ag	Ngbolua et al. [37]

application of nanodrugs synthesized from different medicinal treatments of inflammatory and lung diseases infection.

26.4 Application of Nanotechnology for the Treatment of Inflammatory and Lung Diseases

Nanotechnology has been recognized as a sustainable biotechnological tool that could deliver numerous prospects to innovate novel solutions that could be applied for effective management of numerous clinical challenges. A typical example includes the application of nanotechnology in the pulmonary field most especially for effective delivery of nucleic acid-based therapeutics and drugs to disease sites. The administration of these drugs through inhalation gives the chance for shortest distribution to the lung epithelium, the coating of the respiratory tract. Therefore, adequate collection of particle size, deep lung delivery could be derived with regulation of phagocytic uptake, the elimination of particles by resident macrophages.

The application of nanotechnology could play a significant role in the pulmonary therapies given through the oral and intravenous via aiming specific cell types and regulation of bioavailability and release kinetics. Moreover, nanotechnology could play a crucial role in providing resistance against multiple drug resistance in leukemia through inhibition of drug efflux from cancer cells, and gives operative delivery of siRNA into lymphocytes so as to prevent apoptosis in sepsis. Regulation of surface features on materials most especially on the devices which entails stents and valves could enhances biocompatibility by blocking of thrombosis, and modification of cell adhesion and stimulation as well as the formation of blood clots. The application of nanoparticle-based thrombolytic agent's portends the capacity to enhance the efficiency of clot elimination. Moreover, the management of blood and lung diseases most especially using nano-scaffold-based techniques for regulation of differentiation and multiplying of stem and progenitor cells has been identified to possess numerous advantages [38].

Kuzmov and Minko [39] provided a comprehensive review on diverse methods involved in the delivering of drugs most especially through inhalation for the management of lung diseases, most especially those that portends the capacity to transport drugs, peptides, and nucleic acids to the site of their action. Also, they could consequently improve the effectiveness of their action by reducing the permeation of nebulized healing agent(s) into the bloodstream and subsequently lessen the antagonistic systemic side influence of the treatment. The application of nanotechnology permits the improvement of the management effectiveness. The authors also provide more information on the application of the modern therapeutic methods of inhaled nanoscale-based pharmaceutics for the recognition and management of numerous lung diseases.

Lung cancer has been identified as one of the leading factors responsible for higher level of mortality globally, most of them are recognized as active tobacco smokers. Non-small cell lung cancer might be attributed for 85% to 90% of this

mortality, while the remaining could be attributed to small cell lung cancer. Life-threatening lethality of lung cancer could be developed as a result of lack of appropriate analytical actions for initial discovery of lung cancer and ineffective unadventurous healing approaches. Therefore, the application of diagnostic system or a multifunctional nanotherapeutic has been identified as a sustainable solution. The expression of physiochemical features of such nanoscale systems is adjusted positively for quick identification of versatile cancer cell targeted diagnostic and therapeutic system. It has been observed that the size of these nanodrugs which are available at nanoscale makes the system to have several merits of passive build up at the site of tumor. In view of the aforementioned, Sukumar et al. [40] gave a general overview on typical examples of three significant subclasses of such nanoscale therapeutic and diagnostic systems which entails bio-nanoparticles-based methods, metal nanoparticles-based methods, polymeric nanoparticles-based procedures. The authors also provide a detailed information on the merits and demerits of each techniques with a forthcoming enhancement in lung cancer therapeutics and diagnostics.

Rout et al. [41] wrote a comprehensive review on nanodrug delivery systems which is also known as nanocarriers. Nano carriers has been identified as nanoengineered biocompatible devices or materials which in conjugation with preferred bioactive compounds performs essential purposeful function in the allied and pharmaceutical sciences. The differentiated capability of this bioengineered colloidal or noncolloidal molecule to rupture the biological barricades in reaching the directed location in the biological system elevates its other multipurpose nature's polydispersity or monodispersity in biodistribution. Additionally, its biodegradability and nontoxicity result in their selection as an exceptional candidate for its application as drug delivery system. It has been observed that numerous conjugations of biological and chemical substances are currently applied for fabrication of biofunctional hybrid nanomaterial through simple methods. The application of these bioconjugated as a nanoparticulated system has been applied in the management of numerous noxious incurable infectious diseases such as disorders and tuberculosis of various forms. Therefore, there authors also gave a general information on various types of nanoparticulated systems as well as their merits as well as their beneficial as well as harmful influences along with the future viewpoint of nanodrug delivery system based on current position.

26.5 Conclusion and Future Recommendation to Knowledge

This chapter has provided a detailed information on the application of nanotechnology for the fabrication of nanodrugs that could be applied for sustainable management of pulmonary diseases. Detailed information on several plants extract, phytochemical derived from medicinal plants were also highlighted [42–47]. The application of informatics, bioinformatics, and metabolomics could also provide a better understanding on the biological activity of the newly synthesized nanodrugs most especially those derived from the biogenic sources. There is need to establish

the modes of action of the active constitutes present in these plants while it is very important to determine the level of toxicity of the newly synthesized nanodrugs when performed at in vitro and in vivo trials.

References

1. Tam JM, McConville JT, Williams RO, Johnston KP (2008) Amorphous cyclosporin nanodispersions for enhanced pulmonary deposition and dissolution. J Pharm Sci 97:4915–4933
2. Sadikot RT, Kolanjiyil AV, Kleinstreuer C, Rubinstein I (2017) Nanomedicine for treatment of acute lung injury and acute respiratory distress syndrome. Biomed Hub 2:477086. https://doi.org/10.1159/000477086
3. Rogueda PG, Traini D (2007) The nanoscale in pulmonary delivery. Part 1: deposition, fate, toxicology and effects. Expert Opin Drug Deliv 4:595–606
4. Heyder J, Gebhart J, Rudolf G, Schiller C, Stahlhofen W (1986) Deposition of particles in the human respiratory tract in the size range 0.005–015 pm. J Aerosol Sci 17:811–825
5. Arnold MM, Gorman EM, Schieber LJ, Munson EJ, Berkland C (2007) NanoCipro encapsulation in monodisperse large porous PLGA microparticles. J Control Release 121:100–109
6. Gradishar WJ (2006) Albumin-bound paclitaxel: a next-generation taxane. Expert Opin Pharmacother 7:1041–1053
7. Suzuki M, Betsuyaku T, Ito Y et al (2009) Curcumin attenuates elastase and cigarette smoke-induced pulmonary emphysema in mice. Am J Physiol Cell Mol Physiol 296:L614–L623. https://doi.org/10.1152/ajplung.90443.2008
8. Kaspar JW, Niture SK, Jaiswal AK (2009) Nrf2:INrf2 (Keap1) signaling in oxidative stress. Free Radic Biol Med 47:1304–1309. https://doi.org/10.1016/j.freeradbiomed.2009.07.035
9. Chen CY, Jang JH, Li MH, Surh YJ (2005) Resveratrol upregulates heme oxygenase-1 expression via activation of NF-E2-related factor 2 in PC12 cells. Biochem Biophys Res Commun 331:993–1000. https://doi.org/10.1016/j.bbrc.2005.03.237
10. Andreadi CK, Howells LM, Atherfold PA, Manson MM (2005) Involvement of Nrf2, p38, B-raf and NF- B, but not PI3K, in induction of hemeoxygenase (HO-1) by dietary polyphenols. Mol Pharmacol 69:1033–1040. https://doi.org/10.1124/mol.105.018374
11. Passi M, Shahid S, Chockalingam S, Sundar IK, Packirisamy GC (2020) Nanotechnology based approaches to combat chronic obstructive pulmonary disease: implications for chronic airway diseases. Int J Nanomed 15:3803–3826. https://doi.org/10.2147/IJN.S242516
12. Sussan TE, Rangasamy T, Blake DJ et al (2009) Targeting Nrf2 with the triterpenoid CDDO-imidazolide attenuates cigarette smoke induced emphysema and cardiac dysfunction in mice. Proc Natl Acad Sci 106:250–255. https://doi.org/10.1073/pnas.0804333106
13. Snehal SP, Jignasha KS (2015) Systematic review of plant steroids as potential antiinflammatory agents: current status and future perspectives. J Phytopharmacol 4(2):121–125
14. Xia-Wei Z, Wei L, Hong-Li J, Bing M (2019) Dissection of pharmacological mechanism of Chinese herbal medicine Yihuo Huatan formula on chronic obstructive pulmonary disease: a systems pharmacology based study. Sci Rep 9:13431. https://doi.org/10.1038/s41598-019-50064-9
15. Rebecca C, Fionnuala TL, Lorcan M (2015) Herbal treatment in asthma and COPD – current evidence. Clin Phytosci 1:4. https://doi.org/10.1186/s40816-015-0005-0
16. Alamgeer WY, Hira A, Amber S, Humayun R, Ishfaq AB, Asaad MA (2018) Traditional medicinal plants used for respiratory disorders in Pakistan: a review of the ethno-medicinal and pharmacological evidence. Chin Med 13:48. https://doi.org/10.1186/s13020-018-0204-y

17. Ibraheem OL, Ikeolu IO, Basirat OR, Adeyemi OA (2020) Ethnobotanical survey of plants used for treating cough associated with respiratory conditions in Ede South Local Government Area of Osun State, Nigeria. Plants 9:647. https://doi.org/10.3390/plants9050647
18. Fernanda PRS, Nathalia MP, Márcia IBM, Renato FR, Mílton AM, João HGL, Lopes S, Iolanda FLCT, Carla MP (2016) Evidences of herbal medicine-derived natural products effects in inflammatory lung diseases. Mediat Inflamm 2016:2348968. https://doi.org/10.1155/2016/2348968
19. Javad S, Bahare S, Zorica ZS, Patrick VTF, Marzieh S, Gail BM, Majid S, Mohammad-Reza M, Temitope OL, Seyed AA, Javid M, Razieh S, William NS, Mehdi S, Farzad K, Atta-ur R, Muhammad IC, Athar A, Marcello I (2017) Medicinal plants used in the treatment of tuberculosis - ethnobotanical and ethnopharmacological approaches. Biotechnol Adv 44:107629. https://doi.org/10.1016/j.biotechadv.2017.07.001
20. Hyun PK, Hyun L, Yong SK (2017) Therapeutic potential of medicinal plants and their constituents on lung inflammatory disorders. Biomol Ther 25(2):91–104
21. Jae-Won L, RyuR HW, So-Yeon P, Hyun AP, Ok-Kyoung K, Heung JY, Krishna KS, Minwoo P, Jung HK, Sangwoo L, Sei-Ryang O, Kyung-Seop A (2017) Protective effects of neem (Azadirachta indica A. Juss.) leaf extract against cigarette smoke- and lipopolysaccharide-induced pulmonary inflammation. Int J Mol Med 40:1932–1940. https://doi.org/10.3892/ijmm.2017.3178
22. Ram A, Selvakumar B, Pavadai V, Vijay PS (2010) Medicinal plants useful for treating chronic obstructive pulmonary disease (COPD): current status and future perspectives. Fitoterapia 82 (2):141–151. https://doi.org/10.1016/j.fitote.2010.09.005
23. Rainer WB, Ashley G (2010) Medicinal plants used in Peru for the treatment of respiratory disorders. Rev Peru Biol 17(2):331–346
24. Amir S, Suryakanta V, Vladimir B, Charlie L, Nicola H (2007) The potential role of natural agents in treatment of airway inflammation. Ther Adv Respir Dis 1(2):105–120. https://doi.org/10.1177/1753465807086096
25. Okoli CO, Akah PA, Nwafor SV (2003) Anti-inflammatory activity of plants. J Nat Remed 3 (1):1–30
26. Mohsen A, Tahereh M, Mahmoud R, Kourosh S, Mahmoud B, Mohammad D (2014) Traditional effects of medicinal plants in the treatment of respiratory diseases and disorders: an ethnobotanical study in the Urmia. Asian Pac J Trop Med 7(Suppl 1):S364–S368. https://doi.org/10.1016/S1995-7645(14)60259-5
27. Arjun R, Duraisamy AJ, Selvakumar B, Vijay PS (2009) Medicinal plants from Siddha system of medicine useful for treating respiratory diseases. Int J Pharm Anal 1(2):20–30
28. Rocio G, Silvia LG, María GC, Clara IE, Ricardo R (2017) Natural compounds from Mexican medicinal plants as potential drug leads for anti-tuberculosis drugs. An Acad Bras Cienc 89 (1):31–43
29. James KM, Joseph MN, James MM, Mitchel OO (2020) Medicinal plants used in managing diseases of the respiratory system among the luo community: an appraisal of Kisumu East Sub-County, Kenya. https://doi.org/10.21203/rs.3.rs-18974/v1
30. Nilima T, Priyanka SA, Tidke S, Sanjay K (2019) Review: herbals as bronchodilator. Indian J Drugs 7(2):43–48
31. Scalia S, Haghi M, Losi V, Trotta V, Young PM, Traini D (2013) Quercetin solid lipid microparticles: a flavonoid for inhalation lung delivery. Eur J Pharm Sci 49(2):278–285. https://doi.org/10.1016/j.ejps.2013.03.009
32. Kerry RG, Gouda S, Sil B, Das G, Shin H, Ghodake G, Patra JK (2018) Mini review; cure of tuberculosis using nanotechnology: an overview. J Microbiol 56(5):287–299. https://doi.org/10.1007/s12275-018-7414-y
33. Gani SB, Ganesan K (2013) Ethnomedical and pharmacological potentials of Plumbago zeylanica L- a review. Am J Phytomed Clin Therap 1(3):313–337
34. Shi C, Li H, Yang Y, Hou L (2015) Anti-inflammatory and immunoregulatory functions of artemisinin and its derivatives. Mediat Inflamm 7:435713. https://doi.org/10.1155/2015/43713

35. Banerjee D, Maji AK, Mahapatra S, Banerji P (2012) Barleria prionitis Linn: a review of its traditional uses, phytochemistry, pharmacology and toxicity. Res J Phytochem 6:31–41. https://doi.org/10.3923/rjphyto.2012.31.41
36. Bijauliya RK, Alok S, Sabharwal M, Chanchal DK (2018) Syzygium cumini (Linn.) - An overview on morphology, cultivation, traditional uses and pharmacology. Int J Pharm Sci Res 9 (9):3608–3620. https://doi.org/10.13040/IJPSR.0975-8232.9(9).3608-20
37. Ngbolua K, Inkoto CL, Bongo GN, Moke LE, Lufuluabo LG, Ashande CM, Tshibangu DST, Tshilanda DD, Mpiana PT (2018) Phytochemistry and bioactivity of Annona reticulata L. (Annonaceae): a mini-review. South Asian Res J Nat Prod 1(1):1–11
38. Buxton DB (2009) Nanomedicine for the management of lung and blood diseases. Nanomedicine 4(3):331–339. https://doi.org/10.2217/nnm.09.8
39. Kuzmov A, Minko T (2015) Nanotechnology approaches for inhalation treatment of lung diseases. J Control Release 219:500–518
40. Sukumar UK, Bhushan B, Dubey P et al (2013) Emerging applications of nanoparticles for lung cancer diagnosis and therapy. Int Nano Lett 3:45. https://doi.org/10.1186/2228-5326-3-45
41. Rout GK, Shin HS, Gouda S, Sahoo S, Das G, Fraceto LF, Patra JK (2018) Current advances in nanocarriers for biomedical research and their applications. Artif Cell Nanomed Biotechnol 46 (sup2):1053–1062. https://doi.org/10.1080/21691401.2018.1478843
42. Adetunji CO, Olaleye OO (2011) Phytochemical screening and antimicrobial activity of the plant extracts of *Vitellaria paradoxa* against selected microbes. J Res Biosci 7(1):64–69
43. Adetunji CO, Olaleye OO, Adetunji JB, Oyebanji AO, Olaleye OO, Olatilewa MO (2011a) Studies on the antimicrobial properties and phytochemical screening of methanolic extracts of *Bambusa vulgaris* leaf. Int J Biochem 3(1):21–26
44. Adetunji CO, Arowora KA, Afolayan SS, Olaleye OO, Olatilewa MO (2011b) Evaluation of antibacterial activity of leaf extract of *Chromolaena odorata*. Sci Focus 16(1):1–6
45. Adetunji CO, Olaleye OO, Umanah JT, Sanu FT, Nwaehujor IU (2011c) In vitro antibacterial properties and preliminary phytochemical of *Kigelia Africana*. J Res Phys Sci 7(1):8–11
46. Adetunji CO, Kolawole OM, Afolayan SS, Olaleye OO, Umanah JT, Anjorin E (2011d) Preliminary phytochemical and antibacterial properties of *Pseudocedrela kotschyi*: a potential medicinal plant. J Res Biosci Afr J Biosci 4(1):47–50
47. Adetunji CO, Olatunji OM, Ogunkunle ATJ, Adetunji JB, Ogundare MO (2014) Antimicrobial Activity of Ethanolic Extract of *Helianthus annuus* Stem. Sikkim Manipal Univ Med J 1(1):79–88

Correction to: COVID-19 Pandemic Panic: Prophylactic as Well as Therapeutic Management with Traditional Ethnic Phytopharmaceuticals with Challenging Nano-spray Inhaler and Advanced Drug Delivery System

Gaurav Gupta, Abhishek Bhattacharjee, Amit Ladha, Adity Sarbajna, Mridul Pokhrel, Partha Palit, and Subhash C. Mandal

Correction to:
Chapter 20 in: K. Dua et al. (eds.),
***Medicinal Plants for Lung Diseases*,**
https://doi.org/10.1007/978-981-33-6850-7_20

This chapter was initially published with incorrect authorship. The fifth author name Mridul Pokhrel was inadvertently omitted. The authorship has now been updated to read as

Gaurav Gupta, Abhishek Bhattacharjee, Amit Ladha, Adity Sarbajna, Mridul Pokhrel, Partha Palit, Subhash C. Mandal

The updated online version of this chapter can be found at
https://doi.org/10.1007/978-981-33-6850-7_20

K. Dua et al. (eds.), *Medicinal Plants for Lung Diseases*,
https://doi.org/10.1007/978-981-33-6850-7_27