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].

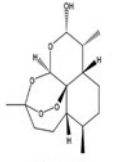
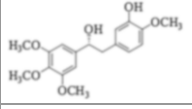
Vitamin C showed the antioxidant activities and found to be protective against lung tissue. Vitamin E is well known for its potent antioxidant property and mainly acts by its membrane repairing, chain breaking, and free radical scavenging activity. The dietary intake of vitamin E is directly correlated 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].

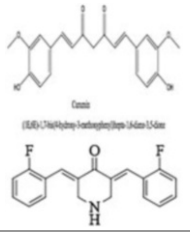
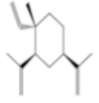
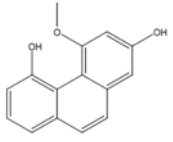
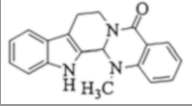
Silibinin is a flavonolignan and found mainly as the chief biological active constituent of silymarin. It is mainly extracted from the dried fruits and seeds of *Silybum marianum*. It plays an important role in the inhibition of initiation and promotion related events in a variety of pre-clinical cancer 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.

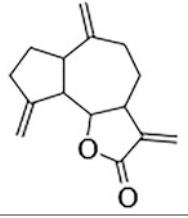
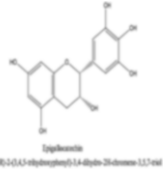
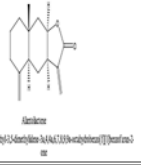
Table 11.2 Some reported medicinal plants useful against lung carcinoma

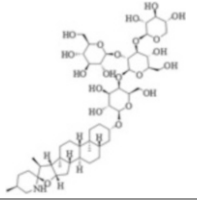
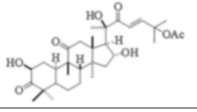
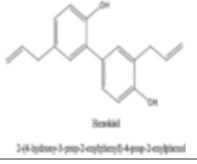
S. No.	Scientific names, common names (family)	Part used	Constituents	Method of preparation (herbal formulation and dosages)	Route of administration	Mechanism	References
1.	Korean angelica, giant angelica, purple parsnip, and dong quai *Angelica gigas* (Apiaceae)	Roots	Decursin (7.3%) 	50 mg/kg/13 days	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)

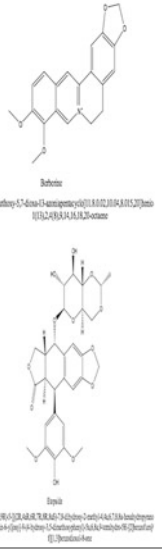
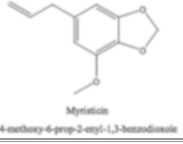
Table 11.2 (continued)

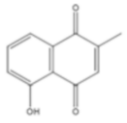
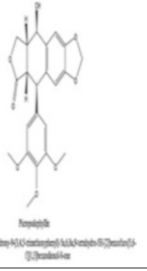
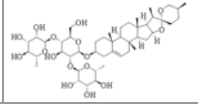
S. No.	Scientific names, common names (family)	Part used	Constituents	Method of preparation (herbal formulation and dosages)	Route of adminis-tration	Mechanism	References
8.	Native cobbler peg *Glossogyne tenuifolia* (Asteraceae)	Woody stem	Glossogin 3,6,9-trimethylenedecahydroazuleno [4,5-b] furan-2(9bH)-one 	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)

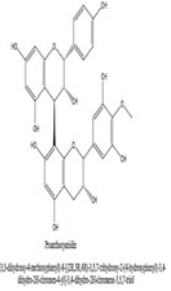
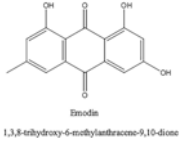
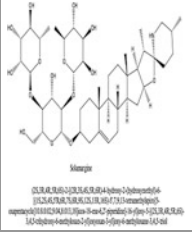
Table 11.2 (continued)

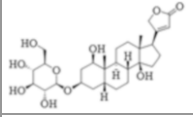
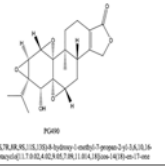
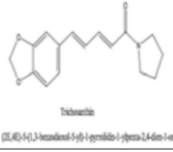
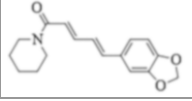
S. No.	Scientific names, common names (family)	Part used	Constituents	Method of preparation (herbal formulation and dosages)	Route of adminis-tration	Mechanism	References
14.	Amur cork tree *Phellodeodendron amurense* (Rutaceae)	Bark	Berberine (33%) Etoposide 	Nanoprecipitation method (1.5 g/kg)	Intraperitoneal	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)

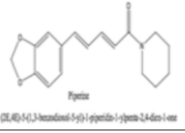
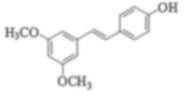
Table 11.2 (continued)

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