Jen-Tsung Chen *Editor*

Ethnopharmacology and Drug Discovery for COVID-19: Anti-SARS-CoV-2 Agents from Herbal Medicines and Natural Products

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Preface

In recent years, the global outbreak of the coronavirus disease 2019 (COVID-19) has caused a severe public health crisis and consequently significant economic losses worldwide. COVID-19 is an RNA virus disease caused by the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which tends to mutate into new strains, therefore posing an ongoing threat to human health. In this scenario, the timely development and subsequent application of drugs and vaccines for managing COVID-19 are extremely challenging. Fortunately, traditional and herbal medicines are well known and are recognized as beneficial and therapeutic agents for various health conditions as well as for the prevention and treatment of coronavirus disease. These medicines have been used for thousands of years across different areas of the world to treat various diseases, and are now evaluated for their roles in managing COVID-19 based on the research system of ethnopharmacology. Bioactive compounds derived from certain traditional or herbal medicines have shown antiviral, anti-inflammatory, and antioxidative properties, suggesting their potential effectiveness against SARS-CoV-2.

This book first presents a complete overview of COVID-19, followed by in-depth analyses of relevant literature and a comprehensive discussion and perspectives on promising anti-SARS-CoV-2 agents based on ethnopharmacology, which covers Chinese medicine, traditional medicines of India and Africa, Turkish folk medicine, essential oils, some well-known medicinal plants, and so on. Additionally, individual chapters extensively explore and refine the roles of black cumin and Gan Cao in combating SARS-CoV-2, focusing on their possible mechanisms of action targeting viral proteins.

In this book, the current status of therapeutic strategies against COVID-19 was summarized and the authors concluded a perspective of potential options for the future. For drug discovery, phytochemicals from medical plants have shown potential as immune enhancers against SARS-CoV-2. Some well-established traditional herbal formulations have exhibited promising antivirus activity, making them potential candidates for managing COVID-19 and its post-illness phase. Nutraceuticals derived from dietary plants, spices, and fruits have been suggested to possess the

ability to inhibit coronavirus activity, potentially preventing future infections or severe illness by emerging variants. Using computer-aided approaches including molecular docking and network pharmacological tools, researchers have gained insights into the possible molecular mechanisms of anti-SARS-CoV-2 activity, and these techniques can predict candidate compounds from medicinal plants that can be explored for their potential in combating COVID-19. In the context of post-illness recovery from COVID-19, bioactive compounds from selected medicinal plants have shown therapeutic potential for neurological disorders. Additionally, ethnopharmacological interventions are proposed to reduce kidney damage and enhance kidney function.

This book provides a summary of the current knowledge in the field of ethnopharmacology for the management of coronavirus diseases. It presents in-depth studies that have proven the anti-SARS-CoV-2 activity of bioactive constituents found in a number of traditional and herbal medicines, including several well-established formulations. All chapters were organized by experts with reliable publications in this field and based on scientific findings from literature and therefore making this book an ideal reference for students, teachers, and researchers in a range of related fields involving life sciences, drug discovery, natural products, bioactive compounds, ethnopharmacology, systems pharmacology, bioinformatics, traditional herbal medicines, and viral diseases. As the editor, I'm grateful to all the contributors for their valuable chapters, and the instruction and help from the editorial office of the publisher are much appreciated.

Kaohsiung, Taiwan Jen-Tsung Chen

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Chapter 1
COVID-19: An Overview of Virology, Mutations, Pathology, Epidemiology, Diagnosis, Preventions, and Treatments

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1.1 Introduction

Coronaviruses (CoVs) relate to a big family of viruses that are known to cause mild to moderate types of respiratory tract infections in human beings (Docea et al. 2020; Rajib et al. 2021). In the twenty-first century, there have been three notable outbreaks of coronaviruses originating from animal sources that raised concerns about global transmission (Udriștoiu et al. 2021a). After the outburst of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the question of its evolution via mutation comes into view. Viral mutation can increase in frequency due to rapid epidemiology, random genetic drift, and natural selection. Because of these forces, it is very difficult to identify if a pandemic changes the result of an infection or the single-point mutation (Grubaugh et al. 2020; Rajib et al. 2021). CoVs belong to four different genera (δ, γ, β, and α) and the major CoVs responsible for infection of the respiratory tract in human beings are human CoV-229E, CoV-OC43 (Palestino et al. 2020). Severe acute respiratory syndrome (SARS), a respiratory disease, initially originated in Foschan, China, in November 2002 with about 8098 cases and thereafter spread to 29 different nations with a mortality rate of 9.6%, whereas Middle East respiratory syndrome (MERS) was recovered from the sample of lung organ of a 60-year-old dead patient in Saudi Arabia in 2012 (Fehr et al. 2017). Both the syndromes are beta coronaviruses that belong to lineages B and C and are considered a spreader of zoonotic diseases. These types of diseases are listed as a top priority by the World Health Organization (WHO) as they are posing harm to the security of the public's well-being on a global scale (Azhar et al. 2019; To et al. 2013).

Later on, in December 2019, some of the local healthcare authorities reported some studies regarding the causes of pneumonia of unknown origin in patients that were epidemiologically linked to a wet animal and seafood wholesale market in Wuhan, China (Hossain et al. 2021; Udriștoiu et al. 2021b).

After the isolation and deep genomic sequencing of the virus from the samples of the lower respiratory tract, it was determined that the virus was a new beta coronavirus whose title was eventually mentioned as SARS-CoV-2 by the International Committee on Taxonomy of Viruses (Yuen et al. 2020). The genomic sequence of the SARS-CoV-2 was submitted to WHO on Jan 12, 2020, and this initiated research in different parts of the sphere to find out a specific means of polymerase chain reaction (PCR) based test for the analysis of SARS-CoV-2 (Amodio et al. 2020). The SARS-CoV-2 belongs to group 2B and has shown about 70% of similarity with the genomic sequence of earlier SARS-CoV (Yang et al. 2020). Many inclusive factors such as smoking, drinking, and the ABO blood group have been found to contribute to the risk of various infectious diseases in a number of studies (Fan et al. 2020). With the help of laboratory tests, in which there is a reduction in the absolute value of lymphocytes, it was determined that SARS-CoV-2 primly acts on T-lymphocyte specifically the same as reported by SARS-CoV (Chen and Guo 2020). The infection of SARS-CoV-2 is found to be milder in comparison to MERS and SARS-CoVs in

terms of transmissibility, mortality rate, and severity which increase the chances of cases remaining undetected (Tsatsakis et al. 2020a). Therefore, WHO recommends that people wash their hands, cover their faces with a mask, avoid consumption of undercooked animals, and people experiencing any symptoms of cough, cold, fever, or problem in breathing, are advised to visit hospitals for their medical assessment. Some vaccines and antiviral agents such as lopinavir/ritonavir and Remdesivir have shown promising effects in the MERS-CoV and SARS-CoV-infected animal models. Therefore, these drugs are being used to treat SARS-CoV-2 (Mahase 2020). This review aims to highlight the important information available for coronaviruses that need to be understood for their control and cure.

1.2 Review Methodology

The literature review is based on the articles and research papers published in English and indexed on different authentic medical and non-medical databases, i.e., Pubmed/MEDLINE, Web of Science, Wiley Online Library, Sciencedirect, Scopus, NCBI, Google Scholar, World Health Organization, Clinical Trials Arena, Worldometers.info, Centre for Health Security.

The next MeSH terms were used for searching: "Antiviral Agents/therapeutic use," "Betacoronavirus,' "COVID-19," "COVID-19 Testing," "COVID-19 Vaccines," "China," "Clinical Laboratory Techniques/methods," "Coronavirus Infections/diagnosis," "Coronavirus Infections/epidemiology," "Coronavirus Infections/physiopathology," "Coronavirus Infections/prevention & control," "Coronavirus Infections/therapy," "Genome, Viral," "Humans," "Pandemics/prevention & control," "Pneumonia, Viral/epidemiology," "Pneumonia, Viral/physiopathology," "Pneumonia, Viral/prevention & control," "Pneumonia, Viral/therapy," "Public Health," "SARS-CoV-2,″ "Viral Vaccines."

Results of the different database searches are reviewed to collect the matter for this article. Finally, 73 out of 252 articles about SARS-CoV, MERS-CoV, and COVID-19 were selected from the aforementioned databases to complete the literature review.

1.3 Emergence and Evolution of SARS-CoV-2

1.3.1 Known Coronaviruses

A total of seven coronaviruses are known to date that is capable to infect a human being. Among them, HKU1, OC43, NL63, and 229E are known for the mildest infection of the upper respiratory tract, others are SARS-CoV and MERS-CoV which are known for typical pneumonia and the seventh one is SARS-CoV-2. Some of these coronaviruses are circulating in the animals such as cats, pigs, bats,

and camels which jump to human beings (known as spillover events) and result in life-threatening ailments (Bassetti et al. 2020).

1.3.2 Origin of Coronavirus

According to the latest studies, bats and snakes are considered the main reservoir of SARS-CoV-2 as shown in Fig. 1.1 but according to WHO, the exact origin of SARS-CoV-2 is still unidentified and according to Wang et al. (2020a) the mortality rate of SARS-CoV-2 is about 2.84% which is lower as compared to and MERS-CoV (34.4%) and SARS-CoV (9.6%) mortality rates (Gralinski and Menachery 2020).

1.3.3 Evolution of SARS-COV-2

Through the phylogenetic analysis of about 103 genomes with the genome of SARS-CoV-2, it was determined that the two main lineages co-occurred are S-type (ancestral type) L-type (obtained after single-nucleotide polymorphism) but the majority of the cases of Wuhan was of L-type, worldwide S-type along with coinfection with both the types (reported in a USA patient) is more notable. There is no latest proof that the immunity in the control of one lineage will come up with protection against another one but this suggested that a patient cured of one lineage can go through the infection with another lineage from a different strain. Therefore, there is an urgent need for the discovery of a vaccine that must focus on the

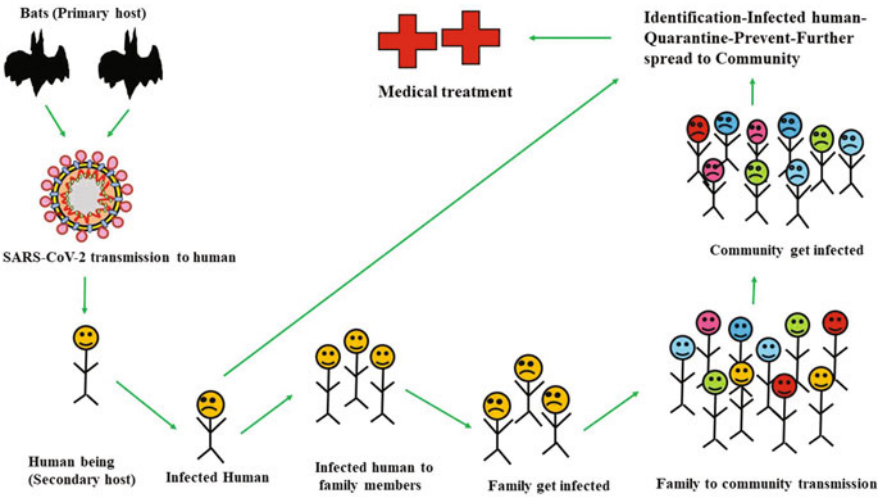

Fig. 1.1 The possible origin and transmission pathways of coronaviruses

conserved region in both types of lineages. Additionally, a discrete vaccine for lineage must also be fabricated (Kakodkar et al. 2020).

1.3.4 Virology and Genome of SARS-CoV-2

Coronaviruses (CoVs) are positive sense, enveloped, single-stranded ribonucleic acid (RNA) viruses of 26.4–31.7 kb of the genome and are greatly diverse (Hui et al. 1920; Verma et al. 2020). In the taxonomy of the virus, CoV is related to the Nidovirales order, Ortho Coronavirinae subfamily, and Coronaviridae family. Based on cryo-electron microscopy and tomography, coronavirus is spherical having ~125 nm diameter. The most notable characteristic of coronavirus is the spikes of club shape, protruding from the exterior of the virion which makes it look like a solar corona, resembling their name coronavirus (Fehr et al. 2015) as shown in Fig. 1.2.

The arrangement of the genome is generally identical in all CoVs. They contain two untranslated regions (UTRs) with coding genes, accessory ORFs, and transcription regulatory motifs (TRFs).

Four types of structural proteins are reported from the coronaviruses: spike (S) protein, nucleocapsid (N), envelope (E), and membrane (M), all of which are encoded by the 3′ end of the virus genome. The S protein encodes for the spikes of CoVs and is cleaved into S1 and S2 domains (Receptor binding and cell membrane fusion domain). The M and E genes are well sustained and code for two small transmembrane proteins in all CoVs. The N protein is a structural protein, that encodes for the packaging of the virus. Like the other CoVs, the SARS-CoV-2 also has many small ORFs (ORF 10, 9, 13, and 14) at the downstream side of N-gene but the functionality of these small ORFs and N-gene of SARS-CoV-2 is not investigated yet (Biswas et al. 2020).

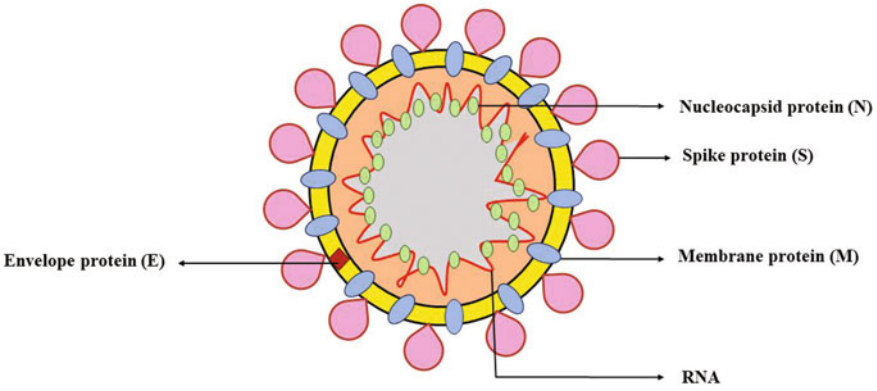

Fig. 1.2 The structure of SARS-CoV-2

1.3.5 Possible Mutations in SARS-CoV-2

Researchers observed various point mutations in the viral genome within different geographic regions when the SARS-CoV-2 is transmitted out of Asia. Three-point mutations in positions 23,403, 14,408, and 3036 were reported in Europe while North America reported having a mutation in positions 18,060, 17,857, and 17,746 but these mutations have not been recognized in Asia. The occurrence and number of point mutations recognized in Asia are raising over time (Zhang et al. 2018).

1. *D614G mutation:* in comparison to human immunodeficiency virus (HIV), SARS-CoV-2 is changing at a very slow rate with its rate of transmission. Korber et al. (Kang et al. 2006) identify a mutation in the samples of many individuals with COVID-19. It is at the 614th position of the spike protein; the aspartate (D) amino acid was replaced by glycine (G). Virologists named this mutation D614G mutation. It was determined that the spread of G614 is more rapid as it is more infectious in comparison to D614. But to fill in the gaps that how D614G affects the pandemic, more in vivo studies are needed (Grubaugh et al. 2020).
2. *NSP6 and ORF10 mutation:* The worldwide analysis of SARS-CoV-2 genomes revealed the presence of two types of mutation, i.e., the NSP6 and the ORF10. Mutation in NSP6 could induce some alterations in the expression of the virus's relationship with its host, specifically autophagic lysosomal machinery. Based on previous studies related to SARS-CoV, it was determined that the deletion of 29 nucleotide segments disrupts the region of ORF9 with ORF10 and 11 as well. No clinical significance related to this deletion is known as these deleted segments co-exist with the non-deleted variant within the same specimen. Alterations in such types of viral regions should be frequently studied as they modify the pathogenicity of SARS-CoV-2 (Benvenuto et al. 2020).

1.4 Life Cycle and Physiopathology of Coronaviruses

Coronaviruses target the host cells through endocytosis. The SARS or SARS-CoV-2 and MERS-CoV protein cohere to the cellular receptor angiotensin-converting enzyme 2 (ACE2) and cellular receptor dipeptidyl-peptidase 4 (DPP4) that induces the release of viral RNA into the cytoplasm of the host cells (Islam et al. 2020; Tsatsakis et al. 2020b). Then the translation of ORF1ab and ORF1a yields pp1ab and pp1a polyproteins, which are split further by proteases enzyme and are encoded by ORF1a to produce 16 non-structural proteins resulting in the formation of RNA replicase-transcriptase complex. This complex directs the fabrication of RNAs of negative sense [(−) RNA] through the replication and transcription process. In the

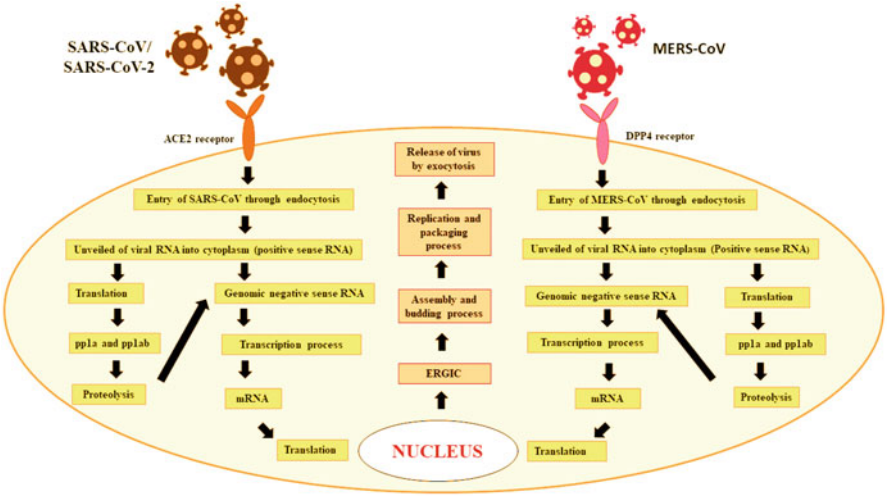

Fig. 1.3 Release of virions through the exocytosis process from the infected host cell

course of replication, negative sense RNA copies are used as templates for the production of full-length positive sense RNA and during the transcription process, a subset of 7–9 sub-genomic RNAs is produced through the transcription of discontinuous type. Although various open reading frames (ORFs) may be present on the different sub-genomic mRNAs only the first ORF (that to the 5′ end) is being translated (Islam et al. 2021). Followed by budding into the lumen of the ERGIC (endoplasmic reticulum (ER)-Golgi intermediate compartment), nucleocapsids of the virus get assembled, and after that virions release through the exocytosis process from the infected host cell (Gathara 2020) as shown in Fig. 1.3.

Recent evidence showed the increased level of IL-1beta in the serum of SARS-CoV-2-infected individuals, which indicates cell pyroptosis. Therefore, this suggests that the activity of cell pyroptosis is somehow related to the SARS-CoV-2 pathogenesis (Yang 2020). In the Caspase-1-dependent classical pathway, when a pathogen enters a cell, a well-conserved molecular structure (pathogen-associated molecular pattern; PAMPs) present on the top of the pathogen will be identified by the NOD-like receptors protein 3 (NLRP3) on the membrane of the cell. This is a tie to the pro-caspase-1 with the help of adaptor protein ASC (Apoptosis-associated speck-like protein containing a caspase recruitment domain) of the cell to devise a multiprotein complex required for the activation of caspase-1. Activated caspase-1 takes part in innate immunity, and switches on the inflammatory cytokines of pro-inflammatory such as pro-IL-18 and pro-IL-1β in various chief inflammatory diseases, supporting the production of IL-18 and IL-1β to set an inflammatory response in cell pyroptosis. In non-classical (caspase-4, 5, 11 dependent) pathway,

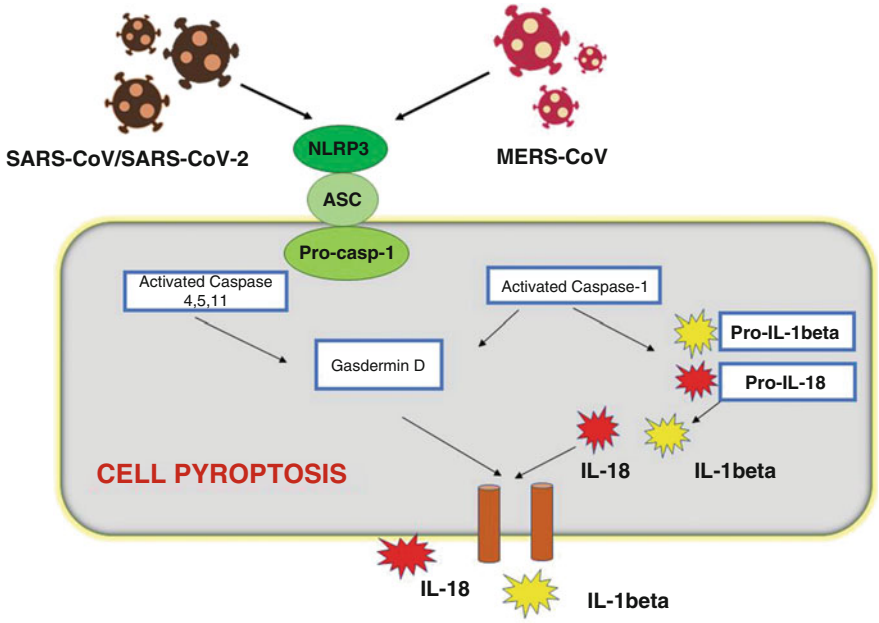

Fig. 1.4 Cell pyroptosis signaling of MERS-CoV/ SARS-CoV/SARS-CoV-2

Pro-caspase-1, NLRP3, and adapter ASC involve together in the formation of the NLRP3 inflammasome, which is needed for the inflammation process. Unlike apoptosis, pyroptosis majorly includes the activation of caspases (4, 5, 11) and inflammation, which incises and polymerizes the members of the Gasdermin family (GSDMD). The cleavage product of the N-terminal of GSDMD could result in the release of cellular content, inflammation, swelling, and lysis to retard the replication of invaded pathogens. Molecules are named the damage-associated molecular patterns (DAMPs), also called alarm factors released by the damaged cells. Similar to the PAMPs, the DAMPs can also be identified by the NLRP3 which results in pro-inflammatory responses and pyroptosis.

Pyroptosis is reported as a quicker process and it is also followed by the production of a great quantity of pro-inflammatory factors in comparison to apoptosis which is a phagocytic, orderly shrinking, and neat process. As a result, pyroptotic cells of both pathways showed the characteristic of decreased viability, cell number, and cell death (Jiang et al. 2020) as shown in Fig. 1.4.

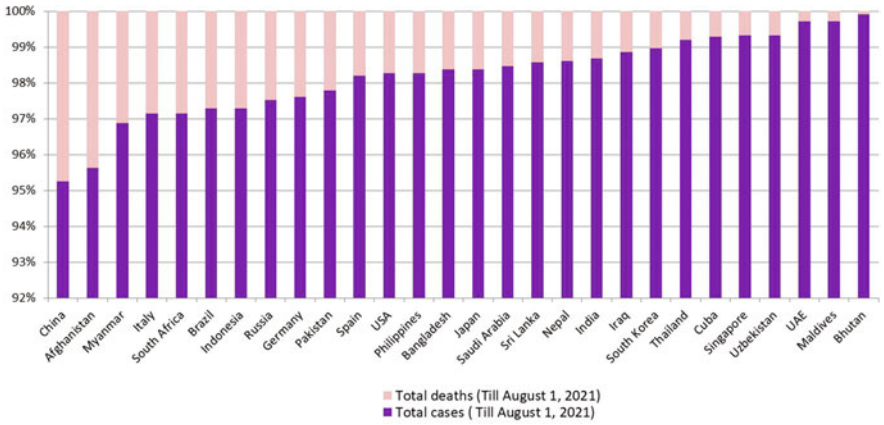

Fig. 1.5 Pink & violet bars together indicating the total number of infected cases and pink bar solely indicating the mortality rate of SARS-CoV-2 worldwide

1.5 COVID-19 Epidemiology, Diagnosis, and Clinical Symptoms

1.5.1 Epidemiology

1.5.1.1 Statistic of COVID-19 Cases with Their Mortality Rate Across the Globe

As of now, the number of coronavirus cases is dropping all over the world, but this number is continuing to peak up along with new mortality cases in some parts of the world (Ashraf et al. 2021) as shown in Fig. 1.5 till the first August 2021.

1.5.1.2 Preventions

Lots of specific treatments and vaccines for SARS-CoV-2 are developed or in the development phase (Hernández et al. 2021; Kostoff et al. 2021). Treatment is concerned and grounded on the clinical state of the patients. As a common safeguard, the public visiting barns, markets, farms, or some other locations where other animals and dromedary camels are available, should follow some general measures of hygiene, which include wearing of mask properly, washing hands regularly before and after touching these animals, keep yourself away from the ill animals and be informed all the time. Products acquired from animals that are properly processed through pasteurization or cooking are considered safe for consumption, but care should also be taken to avoid the chances of cross-contamination with uncooked foods. Immune-compromised individuals should avoid the intake of undercooked meat and the products procured from the camel (World Health Organization 2019;

Ramadan and Shaib 2019). Individuals should put an end to spreading any misconceptions and incorrect details about the SARS-CoV-2 and try to decrease the panic prevalent among the citizens (Goumenou et al. 2020; Singhal 2020).

Another measure/caution which is worth taking care of is that healthcare employees should keep themself down from the probability of exposure while assembling and transferring the specimen of the infected victim to the lab. A goggle is mandatory when health care employees question a sick person at the clinic or execute operations for doubtful patients since the virus may spread by infecting the conjunctiva of the eye through droplets. It would be better if robotics is used for questioning or handling the suspected victim. This will surely decrease the chances of exposure to well-being-related helpers (Wang et al. 2020a).

1.5.1.3 Control Measures by China and Other Countries

On 31 December 2019, the WHO was notified by Chinese Health officials which had induced health officials in Taiwan, Macau, and Hong Kong to increase their border supervision. This also created a sense of fear and concern regarding the emergence of a serious and novel threat to a living being (Hui and Zumla 2019). Bus services for long-distance routes have been banned in China and watch drones have been used across the country to instruct civilians regarding safety measures if they are not taking them (Ayittey et al. 2020). Additionally, China had rapidly created hospitals and assigned them to exclusively handle patients with SARS-CoV-2, closing them off from other disease treatments (Brueck et al. 2020). However, some countries such as Hong Kong, India, Philippines, Malaysia, Papua New Guinea, North Korea, the United Kingdom, Singapore, the USA, and Japan have banned visas policy to the citizen of Hubei or China temporarily to prevent the spread of the virus to their countries (Ayittey et al. 2020). Various countries such as the USA, Australia, Japan, India, Canada, New Zealand, Malaysia, Bangladesh, Egypt, Turkey, South Korea, and some EU countries have evacuated their citizen from China. All these countries kept their citizens in detention for 14 days, which was reported as the incubation phase of SARS-CoV-2 (Ayittey et al. 2020). Across the globe, many nations (Italy, France, UK, USA, Spain, Germany, India, and many more) have enforced limitations on the motion of their citizens having strict lockdowns in their countries with specific guidelines. They have also imposed several fines on persons who avoid the rules. To break the chain of coronavirus, many nations have ramped up their testing process so that they can find out the infected cases at right time and quarantine them as soon as possible to prevent a further rise in the cases.

Table 1.1 Laboratory and clinical tests for SARS-CoV-2

Diagnosis	SARS-CoV-2
Molecular diagnosis	RT-PCR RNA extraction real-time RT-PCR with SARS-CoV-2-specific probes and primers tests were performed in biosafety level III services (Li et al. 2020)
Hematological parameters	(25%) leukopenia (63%) lymphopenia (5%) thrombocytopenia (73%) higher level of lactate dehydrogenase prothrombin IP-10 (interferon gamma-induced protein 10) D-dimer MIP1A (macrophage inflammatory protein alpha), creatinine kinase, C-reactive protein TNF-α (tumor necrosis factor-alpha) MCP1 (monocyte chemotactic protein 1) GCSF (granulocyte colony-stimulating factor) IL-7,10,1 along with deduction in CD8 and CD4 lymphocytes (Bassetti et al. 2020; Hassan et al. 2020; Huang et al. 2020; Rajnik et al. 2021; Wang et al. 2020a; Yuan et al. 2020)
Radiographic features	100% chest abnormalities (bilateral lobular, subsegmental areas of consolidation, and bilateral ground-glass opacity)
Clinical features	For mild cases: Muscle pain, headache, sore throat, mild fever, dry cough, malaise, congestion. For moderate cases: Tachypnea, cough, and breath shortness. For severe cases: Respiratory distress, tachypnea, dyspnea, septic shock, severe pneumonia, acute respiratory sepsis; For critical cases: multiorgan dysfunction, cardiac injury, septic shock, respiratory failure anemia (Bassetti et al. 2020; Cascella et al. 2021; Hassan et al. 2020; Wang et al. 2020a)
Serological tests	The detection of SARS-CoV-2: Various serological assays: Neutralization Protein microarray Chemiluminescence assay (CLIA) Western blot (WB) Enzyme-linked immunosorbent assay (ELISA) Immunofluorescence assay (IFA) (Yan et al. 2020)
P-BEST	A novel pooling-based SARS-CoV-2 testing method is easy to use and increases the capacity of testing, used in diagnostic laboratories (Shental et al. 2020).

1.5.2 Laboratory and Clinical Tests

Diagnosis of COVID-19 involves the combination of one or more techniques that are listed in Table 1.1 and can be done in a biosafety level III facility (Azhar et al. 2019; Bai et al. 2020; Neagu et al. 2021; Richardson et al. 2004).

1.5.3 Clinical Features

1.5.3.1 Risk Factors Related to SARS-COV-2

Smoking

There is some evidence that smokers are more prone to bacterial and viral infections, as compared to non-smokers (Jain et al. 2021). The WHO has reported that the hand-to-mouth action and sharing of tobacco through water pipes are the common factors that raise the chances of smokers getting infected with SARS-CoV-2 (Grundy et al. 2020).

Drinking

Awareness about the use of alcohol-based hand sanitizers to prevent the spread of infection may arise an erroneous rumor on social media sites that consuming alcohol might be a solution against SARS-CoV-2 (Calina et al. 2021). Furthermore, based on meta-analysis and systematic review, Simou et al. (Simou et al. 2018) reported that the consumption of alcohol raises the pneumonic condition in individuals. Therefore, there is a direct correlation between the consumption of alcohol and the amount of ACER2 in the human body (Mallet et al. 2020).

Blood Group

Previous studies have established a correlation between blood group with cancer, cardiovascular, and infectious diseases. The blood group is not correlated with the risk of death and intubation in patients with SARS-CoV-2. According to Latz et al. (2020), blood type O has a low correlation to testing positive, blood types Rh^+, AB, and B are more correlated with positive testing, and blood type A does not correlate with a positive test. Zietz et al. (2020) reported that blood type A sufferers are at more risk of hospitalization, while blood type O has a very low risk, which indicated that the ABO blood type could be utilized as a biomarker to test the severity of novel coronavirus infection.

Clinical Symptoms

Based on the diagnosed cases, the median days from the appearance of the first symptom to the death of the individual were found to be 14 days in SARS-CoV-2 that are similar to the median days of MERS-CoV but in the case of SARS-CoV, it was 3.8 days to 17.4 days. It was found that the progression of the disease was faster in older people with a median day of 5.7 to 11.5 in comparison to younger people. Therefore, more attention should be given to older people who have the possibility of being targeted by a novel coronavirus (Bai et al. 2020).

According to clinical data published in January 2020, SARS-CoV-2 infected patients show many symptoms which include myalgia, fatigue, cough, and fever. All the infected patients reported pneumonia. About 63% of patients were investigated with lymphopenia (63%) as compared to leucopenia which was found only in 25% of the patients (Hui et al. 2020).

On other hand, the level of many inflammatory cytokines such as TNF-alpha, IFN-gamma, MCP-1, IL-10, IL-9, IL-8, IL-7, and IL-1beta was also found to be higher in the plasma of infected individuals as compared to the healthy ones. These characteristics of infection can be associated with pyroptosis of the cell (Yang 2020).

1.6 Potential Treatments

Unlike some recently discovered vaccines, no established therapeutics have been still established (Calina et al. 2020b) Thus, to tackle the pandemic, researchers and other related authorities are focusing on the repurposing of existing drugs. Among repurposed drugs, antiviral drugs: Remdesivir, favipiravir, lopinavir/ritonavir; antiparasitic drugs: hydroxychloroquine, chloroquine, ivermectin; antibiotic drugs: azithromycin, doxycycline, and other drugs such as ACEIs, ARBs, and rivaroxaban are most common which have initially demonstrated anti-COVID-19 actions employing multiple mechanisms of actions (Figs. 1.6, 1.7, 1.8, and 1.9) (Alam et al. 2021; Kostoff et al. 2020).

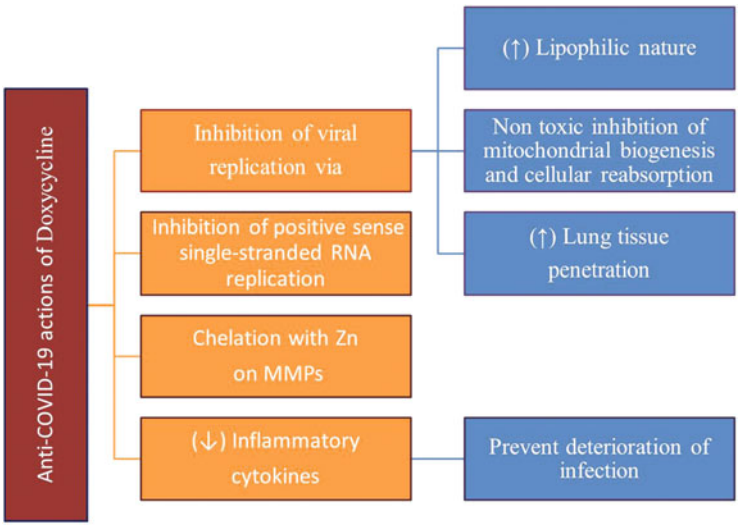

Fig. 1.6 Doxycycline's anti-SARS-CoV-2 activities encompass viral replication suppression and positive sense single-stranded RNA replication inhibition and chelation with Zn on MMPs and down-regulating inflammatory cytokines

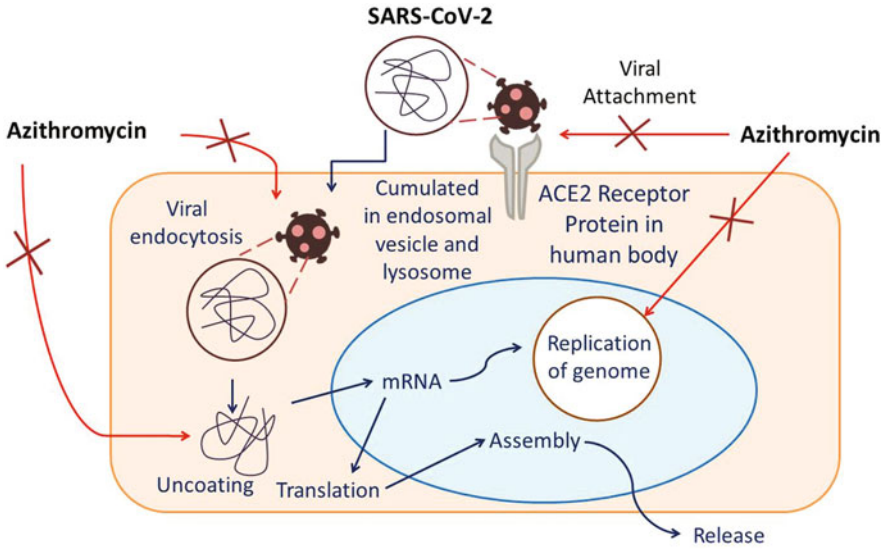

Fig. 1.7 Azithromycin exhibits suppression of SARS-CoV-2's uncoating, modification of the host's antiviral responses mediated by interferon (IFN) pathway, and interference with the binding interaction of SARS-CoV-2 spike protein and host receptor ACE2 protein, all of which lead to a decrement in viral replication and viral endocytosis

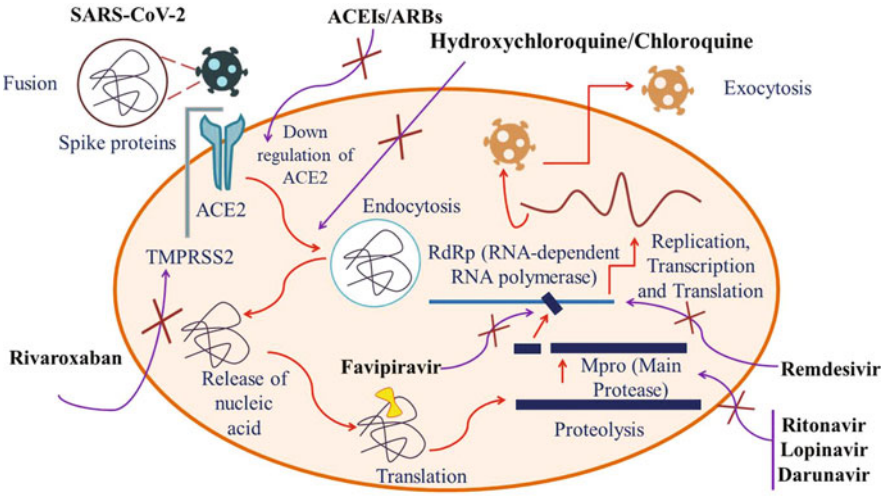

Fig. 1.8 Down-regulation of ACE2 by ACEIs/ARBs. Favipiravir and Lopinavir/Ritonavir, respectively, inhibit the RNA-dependent RNA Polymerase (RdRp) and the main protease (Mpro). By elevating the cell pH using Hydroxychloroquine/Chloroquine, viral fusion onto the cell membrane and endocytosis can be prevented. Rivaroxaban inhibits the transmembrane protease serine 2 (TMPRSS2) enzyme which may prevent SARS-CoV-2 from infecting the host by preventing the fragmentation of spike protein into the S1 and S2 subunits

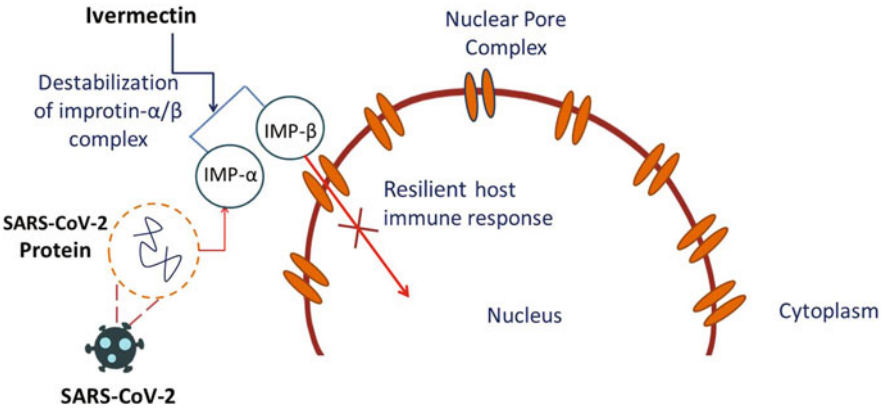

Fig. 1.9 Ivermectin can exert anti-SARS-CoV-2 activity by impeding nuclear transport, which is caused by the instability of the IMP−/α/β complex followed by disruption of RNA viruses

On the contrary, after getting the initial approval few drugs have been deprecated by WHO, i.e., Remdesivir, lopinavir-ritonavir, hydroxychloroquine, and ivermectin, and FDA monotherapy and/or co-therapy of chloroquine and hydroxychloroquine (Sarkar et al. 2020; Torequl Islam et al. 2020). Different research groups in Hong Kong, Australia, Singapore, the USA, Germany, India, Canada, the UK, and China have reinforced the discovery of a particular vaccine for the treatment of novel coronavirus (Calina et al. 2020a, c; Huang et al. 2020). The possible treatments available for the control of the epidemic are listed in Table 1.2.

Table 1.2 Possible treatments for SARS-CoV-2 infection

Possible treatments for SARS-CoV-2	Functions
Support oxygen therapy with high-flow nasal oxygen (HFNO)	Used in case of respiratory failure, decreases the requirement for intubation (Setti et al. 2020)
Allopathic treatments	
Corticosteroid (Dexamethasone)	Decreases the death rate by one-third among SARS-CoV-2 infected patients (Ledford 2020)
Antiviral (Remdesivir GS5734)	Inhibits RNA polymerase in a number of viruses (Gordon et al. 2020)
Antiviral (Arbidol)	Reduces the death rate of SARS-CoV-2 patients (Wang et al. 2020b)
Antiviral drug (Hydroxychloroquine)	Reduces the viral load (Gautret et al. 2020)
Ivermectin	Approved by FDA for the control of SARS-CoV-2 replication in vitro (Kramy 2020)
Anti-flu drug (Oseltamivir)	Used to treat SARS-CoV-2 sufferers (Chen et al. 2020)
Anticoagulant (Enoxaparin)	In case of known thrombosis or thrombophilia, an anticoagulant is required (Kollias et al. 2020)
Inflammation inhibitors (Tocilizumab)	Anti-IL-6 receptor antibody (Berry and Fontana 2020)
Inflammation inhibitors (Sarilumab)	Anti-IL-6 receptor antibody (Berry and Fontana 2020)
Inflammation inhibitors (Anakinra)	Recombinant IL-1 receptor antagonists are utilized in the case of autoinflammatory disorders (Cavalli et al. 2020)
Inflammation inhibitors (Acalabrutinib)	Selective Bruton tyrosine inhibitors regulate the signaling and activation of macrophages (Roschewski et al. 2020)
Traditional treatments	
Qingfeipaidu decoction	Controlled the symptoms of SARS-CoV-2 (Ren et al. 2020)
Lianhuaqingwen	Protect control of SARS-CoV-2 (Runfeng et al. 2020)
Shuanghuanglian oral liquid	Carried out the inhibition of novel coronavirus (Wang et al. 2020b)
Ethnomedicinal plants	Bioactive compounds with antiviral activity (Verma et al. 2021)
The auxiliary blood purification system	
Extracorporeal blood purification technology	Eliminate the storm of cytokine, remove the inflammatory factors, correct the imbalance of electrolytes, and maintain the balance of acid-base to control the capacity load of patients in an effective way (Ke et al. 2020)
Yoga therapy	
Bhastrika pranayama	Free the lungs from unnecessary microbes and air and drains the excessive mucous out from the nasal mucosa (Chaudhary and Janmeda 2020)
AnulomVilom pranayama	Removes congestion, maintains a free flow of energy, boosts up the immune system, and helps to overcome the imbalance of the autonomous nervous system (Chaudhary and Janmeda 2020)
Kapalabhati	Clears respiratory blockages, improves mental function (Chaudhary and Janmeda 2020)

(continued)

Table 1.2 (continued)

Possible treatments for SARS-CoV-2	Functions
Meditation	Maintain a healthy mind, improve immunity, and micro-circulation and reduce the level of stress in the body (Reddy et al. 2021)
Vaccines	
Inactivated vaccine	CoronaVac by Sinovac Biotech, China, and another by Bharat Biotech, India which targets nucleus, envelope, matrix, and spike proteins developed by Sinovac and under phase III trial (Krammer 2020)
Live attenuated vaccine	Developed by the Serum Institute of India and Codagenix; this vaccine was attenuated with the help of codon de-optimization and under the pre-clinical stage (Krammer 2020)
RNA vaccine	RNA vaccines developed by the Chinese Liberation Army and Imperial College London are under phase I; by Arcturus and CureVac under phase I/II trial, by Moderna and Pfizer under phase III (Ewer et al. 2021; Jackson et al. 2020)
Viral vectors vaccine	ChAdOx1nCoV-19 by CanSino and Janssen; another by Gamaleya Research Institute is under phase III and by ReiThera is under phase I (Krammer 2020)

1.7 Conclusions

COVID-19 is one of the most catastrophic pandemics of the last century. As the COVID-19 outbreak spreads across the world, public awareness of the disease has grown, with more information available now than only a few years ago. More investigation is still required especially for public health and clinical assessments to effectively control and cure this viral infection. With an alarming rise in infected sufferers though with a ray of hope, globally many vaccine developments are under trial and some of them are already approved by many nations for use. Mass awareness should be created about the virus since it is highly transmissible. Besides, awareness regarding the usage of repurposing drugs against SARS-CoV-2 should also be raised as it can cause serious drug resistance cases and can cost us a lot in near future. To recapitulate, the future evolution of this disease is still not clear, thus the public should be very cautious in dealing with the virus since it is highly transmissible.

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Author Contributions All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; that is, revising or critically reviewing the article; giving final approval of the version to be published; agreeing on the journal to which the article has been submitted; and confirming to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

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Chapter 2
The Recent Development of Therapeutic Strategies Against COVID-19

Hai-Long Zhang

2.1 Introduction

Coronavirus disease 2019 (COVID-19) is a contagious disease, which is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). COVID-19 can cause death and some symptoms, which usually include fever, dry cough, tiredness, sore throat, etc., were found vary between variants (Williams et al. 2019; Azer 2020). The capacity of infection also differs between variants; for example, the Delta variant has been found to cause more infections due to its faster spread than its previous variants. It had led to a resurgence of COVID-19 in the United States, India, and many other countries. Globally, there have been about 515 million confirmed cases of COVID-19 on 9 May 2022 (World Health Organization n.d.-a). It was reported approximately 81 million confirmed cases of COVID-19 on 9 May 2022 in the United States (World Health Organization n.d.-b).

SARS-CoV-2 has caused severe damage to public health, also reducing international activity and consequently weakening the global economy. Importantly, the virus has a high tendency to develop new variants; therefore, it is significant to develop an effective therapeutic strategy against its fast-changing characteristic. The scientists must ask a question about what kind of therapeutic strategies should be used in combating COVID-19. Indeed, the factors of time, efficacy, and safety are the most important considerations in combating COVID-19. Surely, it is very critical to choose a therapeutic strategy against COVID-19 by considering the coordination of these factors. This chapter provides new insights into a therapeutic strategy against COVID-19 by patent evidence and proposes a novel therapeutic strategy against COVID-19 for the future.

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J.-T. Chen (ed.), *Ethnopharmacology and Drug Discovery for COVID-19: Anti-SARS-CoV-2 Agents from Herbal Medicines and Natural Products*,
https://doi.org/10.1007/978-981-99-3664-9_2

To know about the current therapeutic strategy against COVID-19, a granted patent analysis was conducted, including granted patent documents of China, the United States, Russia, Japan, and Korea. The keywords of TA "COVID-19" or "SARS-CoV-2" were used to search and identify relevant patent documents. All granted patents from December 2019 to May 2022 were retrieved.

2.2 Patent Filing Profile

There are about 163 patent documents in China, 142 patent documents in Russia, and 172 patent documents in the USA, as shown in Fig. 2.1. China, the USA, and Russia play a leading role in the number of patents related to COVID-19 (Figs. 2.1 and 2.2). Japan and Korea has fewer number of patients compared to China, the USA, and Russia. China, the USA, and Russia have lots of granted patents, as shown in Table 2.1, which lists the recently granted patents from the three countries. One reason is that the patents of these three countries have the fastest examination procedure for filing patents. On the other hand, this revealed the three countries may have some better policies or regulations for patents, and research and development when compared to others.

2.3 Patent Distribution

Federalnoe Gosudarstvennoe from Russia had the strongest patent position surrounding COVID-19, which filed 21 granted patents. The Academy of Military Medical Sciences from China and Federalnoe Byudzhetnoe Uchrezhdenie from

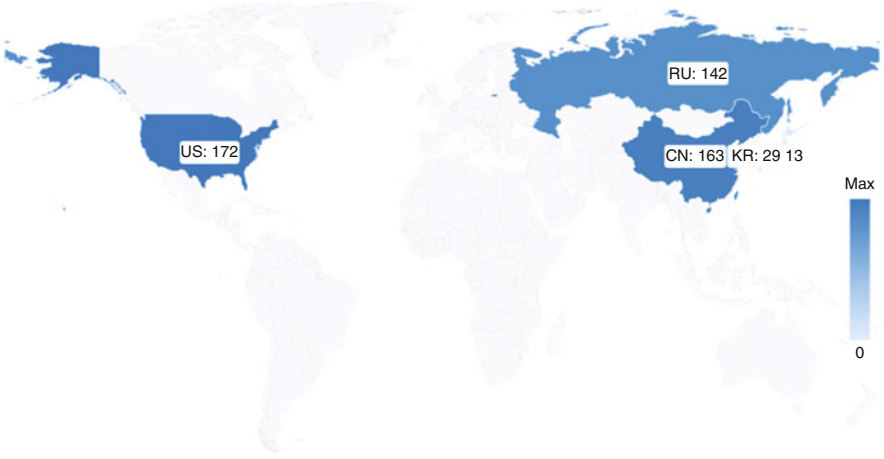

Fig. 2.1 Patent filing profile trend from the five countries

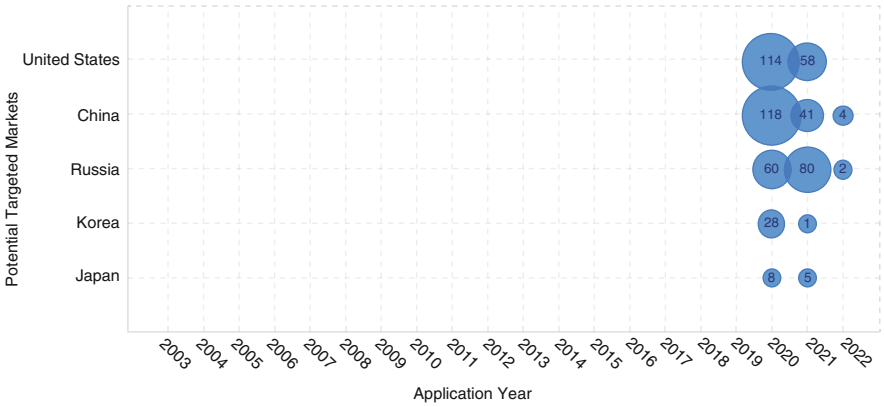

Fig. 2.2 Patent filing profile trends by different years

Table 2.1 Recent granted patents related to COVID-19

Publication number	Application date	Publication date
RU2769220C1	2022-02-10	2022-03-29
CN114150004B	2022-02-09	2022-04-22
CN114150005B	2022-02-09	2022-04-22
CN114107225B	2022-01-25	2022-04-19
CN114085930B	2022-01-21	2022-04-12
RU2766285C1	2022-01-13	2022-03-11
RU2769224C1	2021-12-30	2022-03-29
RU2765729C1	2021-12-29	2022-02-02
CN113981152B	2021-12-28	2022-03-25
RU2769828C1	2021-12-28	2022-04-06
RU2765731C1	2021-12-22	2022-02-02
RU2769223C1	2021-12-22	2022-03-29
CN113913561B	2021-12-15	2022-03-04
CN113913406B	2021-12-14	2022-04-08
RU2767624C1	2021-12-08	2022-03-18
CN113881812B	2021-12-03	2022-02-15
CN113862286B	2021-12-03	2022-03-04
CN113862285B	2021-12-03	2022-03-04
RU2761904C1	2021-11-26	2021-12-13
RU2770357C1	2021-10-28	2022-04-15
RU2764954C1	2021-10-11	2022-01-24
RU2764024C1	2021-09-30	2022-01-12
RU2764015C1	2021-09-30	2022-01-12
RU2764022C1	2021-09-30	2022-01-12
RU2764020C1	2021-09-30	2022-01-12
RU2764023C1	2021-09-30	2022-01-12

Russia were also prolific assignees in patent filing, which filed a total of 22 granted patents. Figure 2.3 shows the number of patents of the top ten applicants who filed over 6 patents. Around 16.6% of the patents were assigned to the top ten applicants, and approximately 33.1%, 31.4%, and 27% of the patents were assigned to the USA, China, and Russia, respectively.

2.4 Technology Areas

As shown in Fig. 2.4, there were five "peaks" in the 3D landscape. Peak 1 represents the patent documents related to traditional Chinese medicines and chemical drugs. Peak 2 and peak 3 represent the patent documents related to vaccines and antibodies. Peak 4 and peak 5 cover the patent documents related to detecting methods, physical protection, and medicinal devices.

There are four therapeutic or prevention strategies against COVID-19, which are based on traditional Chinese medicines, chemical drugs, vaccines, and antibodies. The patents related to traditional Chinese medicines and chemical drugs were clustered in peak 1, as shown in Fig. 2.4.

Peak 1 covered the technologies of traditional Chinese medicines and chemical drugs, e.g., *Centipeda minima* (L.) in preparation application for the treatment of COVID-19 and transmucosal dosage forms of Remdesivir.

Peak 2 focused on the technological area of vaccines for COVID-19, e.g., inactive vaccines and their application, mRNA vaccines and their application, etc. This peak appeared in the 3D landscape a few months after the outbreak of the pandemic.

Peak 3 concerned with the antibodies of COVID-19 and antibody application in the clinic, e.g., antibodies of SARS-CoV-2 and methods thereof. In Fig. 2.4, the 3D landscape shows that the timing of peak 3 (vaccine events) appeared later than peak 2 (antibody events). The number of patents on antibodies was the same as the number of patents on vaccines according to the size of the two peaks.

Peak 4 focused on the technology in assays and detecting methods of SARS-CoV-2, e.g., assays for the detection of SARS-CoV-2. The number of patents related to the detecting method of SARS-CoV-2 was a large proportion of all granted patent documents.

Peak 5 was engaged in physical protection and medicinal devices, e.g., face shield, and the medical devices.

Notably, as shown in Fig. 2.4, peak 3 was slim in the 3D landscape when compared with other peaks, and it indicated that patents related to antibodies showed more similarity. In contrast to peak 3, peak 5 and peak 1 showed broad peaks in the 3D landscape, which indicated less similarity among the patents.

The patents related to traditional Chinese medicines were only filed by applicants from China. Chinese applicants filed patents covering traditional Chinese medicines, chemical drugs, vaccines, and antibodies. The applicants from the USA and Russia filed patents that only cover chemical drugs, vaccines, and antibodies.

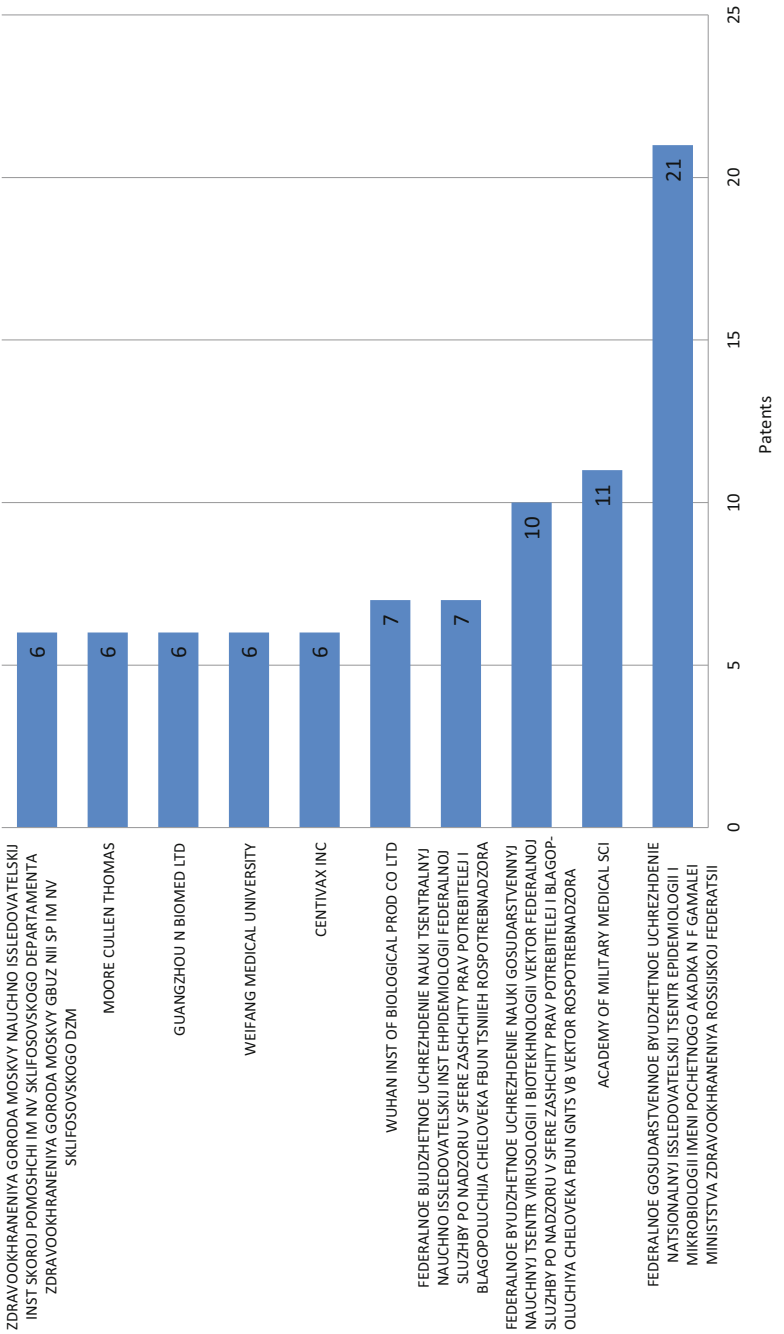

Fig. 2.3 The top ten patent assignees related to COVID-19

Fig. 2.4 The 3D patent landscape related to COVID-19

2.5 Therapeutic Strategy

2.5.1 Traditional Chinese Medicine

In the early stage of the COVID-19 pandemic, traditional Chinese medicines played an important role in disease management since there were no vaccines or chemical drugs available at that time. The prescriptions of Chinese medicines are immediately available as long as having clinical syndromes for patients with COVID-19. Doctors of traditional Chinese medicines can create a prescription by using different Chinese herbs according to the clinical manifestations and syndrome of patients with COVID-19. Also, some traditional Chinese medicines have been used against COVID-19 (Tuta-Quintero et al. 2020; Li and Xu 2021; Wang et al. 2020a, 2021).

According to the theory of Chinese medicines, doctors of traditional Chinese medicines think that the basic pathogenesis of COVID-19 is due to dampness, poison, blood stasis, and closure (Wang et al. 2020b). Based on clinical manifestations and syndrome of patients with COVID-19, the therapeutic method based on traditional Chinese medicines should be concentrated on aspects of dispelling dampness of the body, dispelling heat and damp toxins of the body, and clearing

Table 2.2 Traditional Chinese medicines against COVID-19

Trademark/generic name	Developing company	Approved/EUA date
Qingfei Paidu decoction	NA	NA
Lianhuaqingwen capsule	Yiling pharmaceutical	Mar 2020

dampness in the triple warmer of the body, as well as strengthening essential Qi of the body (Luo 2020).

Based on our knowledge, traditional Chinese medicines have been involved in the management of COVID-19 in China in 2019. One of the typical prescriptions of traditional Chinese medicines is Qingfei Paidu decoction, as shown in Table 2.2.

Qingfei Paidu decoction comprises 21 Chinese herbs, as follows: Ephedrae Herba with 9 g, Glycyrrhizae Radix with 6 g, Armeniacae Semen Amarum with 9 g, Poria with 15 g, Bupleuri Radix with 16 g, Gypsum Raw with 15–30 g, Cinnamomi Ramulus with 9 g, Alismatis Rhizoma with 9 g, Umbellatus Polyporus with 9 g, Atractylodis Macrocephalae Rhizoma with 9 g, Scutellariae Radix with 6 g, Pinelliae Preparata Rhizome with 9 g, Zingiberis Recens Rhizoma with 9 g, Asteris Radix with 9 g, Farfarae Flos with 9 g, Belamcandae Rhizoma with 9 g, Dioscoreae Rhizoma with 12 g, Aurantii Immaturus Fructus with 6 g, and Pogostemonis Herba with 9 g, Citri Reticulatae Pericarpium with 6 g, Asari Herba with 6 g (National Administration of Traditional Chinese Medicine n.d.).

The mechanism study of Qingfei Paidu decoction showed that the composition of this prescription comprised 292 chemical compounds and 214 targets related to these compounds, and the key targets included AKT serine/threonine kinase 1 (AKT1) target, IL6 interleukin 6 (IL6), mitogen-activated protein kinase 8 (MAPK8) target, mitogen-activated protein kinase 1 (MAPK1) target as well as Jun proto-oncogene target (National Administration of Traditional Chinese Medicine n.d.). In general, Chinese herbal medicines play their role in the body through the approach of multi-components delivery, multi-target action, and multi-pathway engagements.

Wu et al. treated 98 cases of COVID-9 by using Qingfei Paidu Decoction in China. With the 3-day treatment of Qingfei Paidu Decoction, the total effect was 84.22%, of which the recovery rate was 21.14%. After 6 days of treatment, the total effect was 90.15%, of which the recovery rate was 31.34%. With 9 days of treatment, the total effect reached 92.09%, meanwhile, the recovery rate was 41.13% (Wang et al. 2020a). Some side effects, including nausea and vomiting, dizziness, and rash, were found, and the total percentage of side effects was about 7%. Specifically, four of them showed nausea and vomiting, two of them showed dizziness, and one of them showed a rash.

Another clinical study showed that 98 cases of COVID-9 were treated by using Qingfei Paidu; the total effect was about 88%. The side effects of Qingfei Paidu treatment were about 5.3%. There were 2 patients with vomiting, 1 patient with nausea, and 1 patient with a rash. However, the side effects were mild and disappeared without other treatment (Hu et al. 2020).

Basically, according to the theory of traditional Chinese medicines, Qingfei Paidu decoction may play a role in anti-SARS-CoV-2 activity by their capacity on

dispelling dampness and eliminating heat and turbidity, as well as nourish the lung and spleen, detoxify, etc.

Notably, the National Health Commission of China proposed to officially use Qingfei Paidu for the treatment of COVID-19. Therefore, the Qingfei Paidu decoction as a general prescription of traditional Chinese Medicines was used for the treatment of COVID-19.

Another popular traditional Chinese medicine, namely Lianhuaqingwen capsule, has been used in the management of COVID-19. Lianhuaqingwen capsule comprises over 13 Chinese herbs, including Honey-Fried Mahuangephedrae Herba, Bitter Apricot, Isatidis Radix, Dryopteridis Crassirhizomatis Rhizoma, Houttuyniae Herba, Pogostemonis Herba, Rhei Radix Et Rhizoma, Rhodiolae Crenulatae Radix Et Rhizoma, Glycyrrhizae Radix Et Rhizoma, Menthol, Forsythiae Fructus, Lonicerae Japonicae Flos, and Gypsum Fibrosum (Yiling Pharmaceutical n.d.).

Lv et al. conducted a clinical study by a collection of 63 patients with COVID-19 who received therapy from Lianhua Qingwen Granules. The clinical results showed that the rate of symptom disappearance in fever was 86.7%, and the rate of symptom disappearance in cough and weakness was 55.6% and 82.5%, respectively. The rate of symptom disappearance in short breath was 68.2%. There are no other side effects in the treatment group (Lv et al. 2020).

Compared with Qingfei Paidu decoction, Lianhuaqingwen has a broader clinical efficacy, which also could be used for the treatment of influenza, and patients with the symptoms of fever, cough, headache, etc. Therefore, Lianhuaqingwen demonstrates lower therapeutic specificity for clinical manifestations and syndrome of COVID-19 compared to Qingfei Paidu decoction. Traditional Chinese medicine treatment could be used for patients with COVID-19, and the earlier treatment is a benefit for patients with COVID-19.

It is a significant feature that traditional Chinese medicines were involved in COVID-19 in China. Traditional Chinese medicines have a unique feature for the therapy of patients with COVID-19 compared to chemical drugs and vaccines, e.g., immediately availability and flexibility. Both chemical drugs and vaccines need time to be developed and studied. Nevertheless, traditional Chinese Medicines do not need to long-time to be developed.

In China, there are two parallel medical systems for combating diseases, which are traditional Chinese medicines and Western medicines. Both these two medical systems have their advantages and disadvantages in the treatment of diseases. In the past years, traditional Chinese medicines have benefited Chinese people in combating COVID-19. A competitive advantage is that the appearance of a therapeutic method of traditional Chinese medicines against COVID-19 is much earlier than chemical drugs, antibody as well as vaccines. Theoretically, it takes about many years to develop a vaccine, which is much later than the clinical use of traditional Chinese medicines.

2.5.2 Chemical Drugs

It appears that chemical drugs are not a very good option for the treatment of COVID-19 at present. The time to develop chemical drugs is longer than that for vaccines, and the time of developing an effective chemical drug is quite difficult to predict. Although there were some patents related to chemical drugs at the early stage of emerging of COVID-19, most of these chemical drugs were developed for a new medical application or repurposed drugs against COVID-19 by using known chemical compounds or drugs. Usually, the efficiency of these chemical drugs is quite low. An example is that Remdesivir is used for the therapy of patients with COVID-19. It is a much more difficult and time-consuming process to develop effective chemical drugs against COVID-19.

Some chemical drugs have been approved by the U.S. Food and Drug Administration (FDA), e.g., Nirmatrelvir and Ritonavir. The U.S. FDA has issued an emergency use authorization for Pfizer's Paxlovid, including Nirmatrelvir and Ritonavir, for the treatment of COVID-19 in adults on Dec 2021 (The U.S. Food and Drug Administration n.d.-a). Nirmatrelvir and Ritonavir could reduce the risk of death or hospitalization by about 89% compared to placebo in patients with COVID-19 (Anon n.d.). However, the safety and effectiveness of Paxlovid for the treatment of COVID-19 need time to be further evaluated.

The U.S. FDA approved an emergency use authorization for remdesivir in the treatment of patients with COVID-19 on October 2020 (The U.S. Food and Drug Administration n.d.-b). Recently, molnupiravir was approved as an emergency use authorization by the U.S. FDA for the treatment of patients with COVID-19 on December 2021 (The U.S. Food and Drug Administration n.d.-c). Molnupiravir is provided by prescription only and should be used for patients with mild to moderate COVID-19, and be initiated as soon as possible after being confirmed as COVID-19. Recently approved or emergency use authorization chemical drugs are listed in Table 2.3.

2.5.3 Vaccines

Vaccines are administered to the body, which stimulates the production of antibodies and provides immunity against specific viruses. The vaccine approach is the most effective therapeutic strategy against COVID-19. About 1 year after the emergence of COVID-19, its vaccines were first available. Several vaccine products are

Table 2.3 Chemical drug against COVID-19

Trademark/generic name	Developing company	Approved/EUA date
Paxlovid	Pfizer	Dec 2021
Remdesivir	Gilead Sciences	Oct 2020
Molnupiravir	Merck	Dec 2021

available and show good safety and effectiveness (Voysey et al. 2021; Dagan et al. 2021; Emary et al. 2021; Al Kaabi et al. 2021; Logunov et al. 2021). Since vaccines are a globally mainstream approach to combating COVID-19, many vaccine products have been approved by the U.S. FDA and the National Medical Products Administration to use against COVID-19, as listed in Table 2.4.

The U.S. FDA announced the first approval of the COVID-19 vaccine (Comirnaty) developed by Pfizer-BioNTech (The U.S. Food and Drug Administration n.d.-d) on August 2021. Comirnaty was developed by using mRNA technology, which is indicated for active immunization to prevent COVID-19.

The FDA approved the second vaccine of COVID-19 called Spikevax on January 2022 (The U.S. Food and Drug Administration n.d.-e). The Spikevax vaccine was developed by Moderna and developed using mRNA technology, which is indicated for active immunization to prevent COVID-19 for people 18 years and older. The FDA announced the third approval of EUA for the COVID-19 vaccine called Janssen COVID-19 on Feb 2021 (The U.S. Food and Drug Administration n.d.-f). The emergency use authorization indicated that the Janssen COVID-19 vaccine was allowed to prevent COVID-19 for patients 18 years and older. The Janssen COVID-19 vaccine is developed by using a specific virus, which is called adenovirus type 26.

Currently, available vaccines against COVID-19 are from several different countries, and different countries may use different technologies to develop vaccines. For example, many companies in China develop COVID-19 vaccine products by using an inactive approach (Al Kaabi et al. 2021). Many companies in the USA develop vaccine products by using the mRNA technology approach (Dagan et al. 2021; The U.S. Food and Drug Administration n.d.-d). However, the inactive vaccines demonstrated more safety than the mRNA vaccines (Al Kaabi et al. 2021). At this stage, the vaccine plays a leading role and is a dominating approach in combating the global COVID-19 pandemic. The recently approved or emergency use authorization vaccines are listed in Table 2.4.

Table 2.4 Vaccine products against COVID-19

Trademark/generic name	Developing company	Approved/EUA date
BBIBP-CorV	Sinopharm	Aug 2021
CoronaVac	Sinovac	Jun 2020
Convidecia	Cansinobio	Feb 2021
Covilo	Wuhan Institute of Biological Products, Sinopharm	Jul 2021
Kconvac	Biokangtai	May 2021
Recombinant COVID-19 vaccine	Anhui Zhifei Longcom biopharmaceutical	Mar 2021
Comirnaty	Pfizer-Biontech	Aug 2021
Spikevax	Moderna	Jan 2022
Janssen COVID-19 vaccine	Janssen Biotech	Feb 2021

2.5.4 Antibodies

Antibodies are also an effective therapeutic approach with high specificity. Currently, antibodies are mainly used in an emergency for patients with mild-to-moderate COVID-19, especially for patients who are at high risk of or severe COVID-19. Clinical use of antibodies against COVID-19 is not as extensive as vaccines. So far, several antibodies have been approved (or an emergency use authorization) by the U.S. FDA, as listed in Table 2.5.

The U.S. FDA approved an emergency use authorization for Bamlanivimab and Etesevimab for patients with COVID-19 on February 2021 (The U.S. Food and Drug Administration n.d.-g). This combination antibody is particularly suitable for patients with high-risk or severe COVID-19 (Food and Drug Administration 2021). Bamlanivimab and Etesevimab should be administered together. The combination use of Bamlanivimab and Etesevimab has revealed good clinical effectiveness in people with moderate COVID-19 (Weinreich et al. 2021; Dougan et al. 2021). The treatment of antibodies should be started as soon as possible, as long as the patients are confirmed as positive for COVID-19, which will be a benefit for people with COVID-19.

Casirivimab and Imdevimab, administered together, were approved as emergency use authorization by the FDA for the treatment of COVID-19 in November 2020 (The U.S. Food and Drug Administration n.d.-h). Casirivimab and Imdevimab were developed by Regeneron Pharmaceutical. Casirivimab and Imdevimab should be administered together by intravenous infusion, which is suitable for the treatment of patients with mild to moderate or high-risk COVID-19.

The FDA approved an emergency use authorization for the monoclonal antibody of Sotrovimab for the treatment of COVID-19 on May 2021 (The U.S. Food and Drug Administration n.d.-i). Sotrovimab was developed by GlaxoSmithKline LLC. Sotrovimab is suitable for the treatment of patients with high-risk or severe COVID-19.

Bebtelovimab was approved as an emergency use authorization by the FDA for the treatment of COVID-19 patients on February 2022 (The U.S. Food and Drug Administration n.d.-j). Bebtelovimab was developed by Eli Lilly and Company. Bebtelovimab is suitable for the treatment of COVID-19 in patients who are at high risk of or severe COVID-19. Particularly, it is suitable for the treatment of patients

Table 2.5 Antibodies against COVID-19

Trademark/generic name	Developing company	Approved/EUA date
Sotrovimab	GlaxoSmithKline	May 2021
Casirivimab	Regeneron pharmaceutical	Nov 2020
Imdevimab	Regeneron pharmaceutical	Nov 2020
Bebtelovimab	Eli Lilly	Feb 2022
Bamlanivimab	Eli Lilly	Feb 2021
Etesevimab	Eli Lilly	Feb 2021

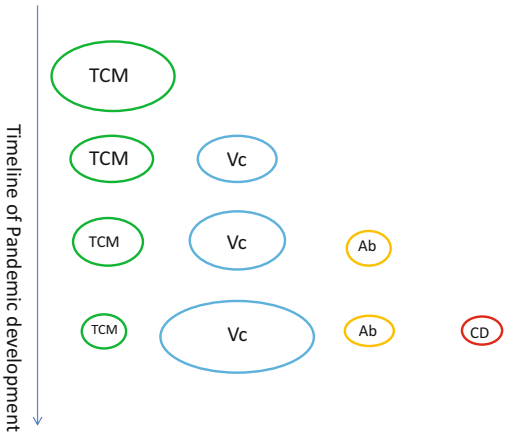

Fig. 2.5 Current option of therapeutic strategy. *TCM* traditional Chinese medicines, *VC* vaccines, *AB* antibodies, *CD* chemical drugs

confirmed as Omicron variants of COVID-19. The recently approved or emergency use authorization antibodies are listed in Table 2.5.

In general, most antibodies were approved for emergency use authorization by the U.S. FDA. The antibodies are suitable for the treatment of mild to moderate patients confirmed as COVID-19, as well as COVID-19 patients who are at high risk or progress to severe. Usually, they should be administered together if two antibodies were used as a package.

In general, there are four therapeutic strategies, including traditional Chinese medicines, chemical drugs, vaccines, and antibodies. Each therapeutic strategy has its advantages and disadvantages in clinical use. Thus, the option of therapeutic strategies according to the progression of COVID-19 is a skillful piece of work. As shown in Fig. 2.5, the author depicts a therapeutic strategy pattern, which shows the option of therapeutic strategies against COVID-19. Each circle indicates therapeutic proportion as the development of the pandemic of COVID-19. The larger circle indicates the larger proportion of use in the whole therapeutic strategy. At the beginning of the emergence of COVID-19, traditional Chinese medicines are the best option for therapeutic strategy against COVID-19 since it is unavailable for vaccines, chemical drugs, or antibodies. About 1 year later, with the development of vaccines, vaccines will be a major trend in therapeutic methods against COVID-19. Antibodies are also available like vaccines, but based on consideration in therapeutic strategy, the clinical use of antibodies is not as extensive as vaccine products. The chemical drug and antibody approaches play a minor role in the whole therapeutic strategies against COVID-19. Hence, at this stage, the overall therapeutic strategy pattern against COVID-19 could be presented as a model as shown in Fig. 2.5.

However, to face potential new variants of coronavirus in the future, the pattern of therapeutic strategies may need some modification. As shown in Fig. 2.6, at the beginning of the emergence of a novel coronavirus, traditional Chinese medicines are suggested to be one of the best options for earlier therapy against future novel coronavirus, since it is immediately available, flexible, safe, and 1000-year practical

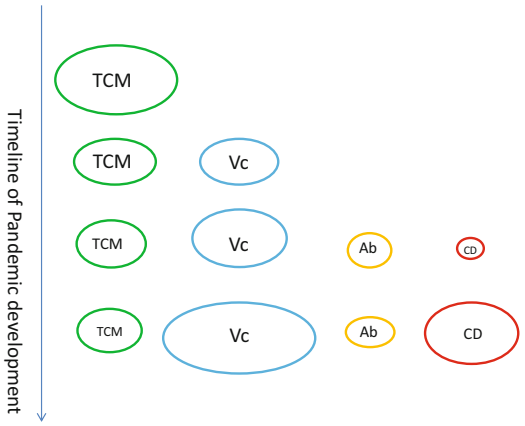

Fig. 2.6 Future option of therapeutic strategy. *TCM* traditional Chinese medicines, *VC* vaccines, *AB* antibodies, *CD* chemical drugs

experience. About 1 year later, vaccines are a major therapeutic method in therapeutic strategies. The difference is that chemical drugs will play a more important role in therapeutic methods against a possible novel coronavirus because new technological development will make it possible to find an effective target, screen the most active compounds, and shorten the time of R&D of chemical drugs. In my opinion, with the rapid development, the potential role of traditional Chinese medicines in the management of COVID-19 variants in the future may become more important. Thus, the overall therapeutic strategy pattern will be presented in a modified model as shown in Fig. 2.6.

The chapter depicts a novel therapeutic strategy pattern against COVID-19. The novel therapeutic strategy pattern will be a benefit against COVID-19. Scientific application and options of the therapeutic method according to therapeutic strategy patterns can save time and improve efficiency and safety in the treatment of patients with COVID-19. The therapeutic strategy pattern will help humans against COVID-19 effectively.

2.6 Conclusion

The chapter provides an opinion on the categories of four therapeutic strategies for the treatment of COVID-19. Each strategy uses a central treatment by traditional Chinese medicines, chemical drugs, vaccines, and antibodies. Traditional Chinese medicines are the fastest available therapeutic approach against COVID-19 and have shown good efficacy and safety in the treatment of patients infected with SARS-CoV-2. The vaccine approach is the most reliable therapeutic approach against COVID-19 and its development and application took about a year after the outbreak of COVID-19. Developing chemical drugs against COVID-19 is a time-consuming approach with a high failure risk. The therapeutic strategy that is based on the use of antibodies has the nature of high specificity. It could be used for the treatment of

mild to moderate COVID-19 patients, or those patients who are at high risk of or severe COVID-19. The development time of antibodies is even longer than vaccines. Overall, this chapter summarizes the current status of therapies against COVID-19 and suggests a potential strategy against new variants.

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Chapter 3
Plant Immunoenhancers: Promising Ethnopharmacological Candidates for Anti-SARS-CoV-2 Activity

Salar Hafez Ghoran, Fatemeh Taktaz, and Seyed Abdulmajid Ayatollahi

Abbreviations

^{18}F-FDG	^{18}F-fluoro-deoxy-D-glucose
^{18}F-FDG-PET	^{18}F-fluoro-deoxy-D-glucose-positron emission tomography
3CL^{pro}	3 chymotrypsin-like protease
5-LOX	5-Lipoxygenase
ACE-2	Angiotensin-converting enzyme-2
ADMET	Adsorption, Desorption, Metabolism, Excretion, and Toxicity
ARDS	Acute respiratory distress syndrome
AREs	Antioxidant-response elements
AS-CDs	Carbon dots derived from *Allium sativum*
BAL	Bronchoalveolar lavage
BRD4	Bromodomain-containing protein 4
CAT	Catalase

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CCL	Chemokine ligand
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
DENV-2	Dengue virus
DPPH	1,1′-diphenyl-2-picrylhydrazyl radical
DTH	Delayed-type hypersensitivity
ECs	Endothelial cells
ED	Endothelial dysfunction
EGCG	Epigallocatechin-3-gallate
ELISA	Enzyme-linked immunosorbent assay
G-CSF	Granulocyte-colony stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GSH-Px	Glutathione-peroxidase
HAV	Hepatitis A virus
HTVS	High throughput screening
IFN-γ	Interferon-γ
iNOS	Inducible nitric oxide synthase
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemoattractant protein 1
MD	Molecular dynamics
MDA	Malondialdehyde
MERS-CoV	Middle East respiratory syndrome coronavirus
MIP-1α	Macrophage inflammatory protein-1α
MPO	Myeloperoxidase
M^{pro}	Main protease
NF-κB	Nuclear factor-κB
NLRP3	NLR family pyrin domain containing 3
NO	Nitric oxide
NQO1	NAD(P)H quinone dehydrogenase 1
PGE2	Prostaglandin E2
PL^{pro}	Papain like protease
PMNs	Polymorphonuclear cells
RBD	Receptor-binding domain
RdRp	RNA-dependent RNA polymerase
ROS	Reactive oxygen species
SARS-CoV-2	Severe acute respiratory syndrome coronavirus type 2
SI	Selectivity Index
SOC	Standard of care
SOD	Superoxide dismutase
SP	Standard precision
SpO_2	Peripheral oxygen saturation
TAOC	Total antioxidant capacity
TCM	Traditional Chines medicine

TLR2	Toll-like receptor 2
TNF-α	Tumor necrosis factor α
UHPLC	Ultra-high-performance liquid chromatography
vWF	von Willebrand factor
WBC	White blood cells

3.1 Introduction

An undesirable outbreak of a kind of infectious respiratory disease, coronavirus disease (COVID) was quickly initiated in Wuhan, China, becoming a worldwide pandemic, which took the lives of millions of lives and caused economic setbacks. Scientists realized that there is a genetic similarity between severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) and the previously emerged coronaviruses, such as SARS-CoV and MERS-CoV (Middle East respiratory syndrome coronavirus) (Hafez Ghoran et al. 2021a). It is well studied that in COVID-19 pathogenesis, various mechanisms, including extensive virus replication, massive necrosis and apoptosis in lung cells, oxidative stress, the high response of inflammation mediators, overexpression of pro-inflammatory factors, cytokine storm, ACE2 downregulation, and the impairment of renin-angiotensin system are involved (Jafarzadeh et al. 2021). Using traditional medicine and looking at previous experiences with viral infections and drug discovery development, certain medicinal plants and herbal preparations have been prescribed to treat SARS-CoV disease. Therefore, increasing daily mortality and morbidity rate during the SARA-CoV-2 pandemic called researchers to pay more attention to nature-derived secondary metabolites, which have proven to be an effective treatment to tackle this devastating pandemic (Hafez Ghoran et al. 2021a). So far, for human SARS-CoV diseases, four types have been characterized: β-HCoV (OC43), α-HCoV (229E), CoV-NL63, and CoV-HKU1. Besides targeting the before-mentioned HCoV viruses, researchers figured that inhibiting a key enzyme in the SARS-CoV-2 host receptor, angiotensin-converting enzyme 2 (ACE2), could be a promising way to stop the virus activity (Zhang et al. 2020a; Geller et al. 2012). From the other point of view, pathological results of SARS-CoV-2 positive individuals displayed a cytokine storm of around 20% in the patient's plasma, which leads to destructive and uncontrolled inflammation. This phenomenon on the molecular scale is because of the overproduction of various cytokines, including interleukins (IL; i.e., IL-6, IL-7, IL-8, IL-9, IL-1β, IL-17), interferon-γ (IFN-γ), tumor necrosis factor-alpha (TNF-α), granulocyte-macrophage colony-stimulating factor (GM-CSF), and granulocyte-colony stimulating factor (G-CSF) as well as chemokine ligands (CCL) viz. CCL2, CCL3, and CCL4. The high concentration of these destroying factors has been recorded in the patient's plasma bearing SARS-CoV-2 and even in the dying stage (Xu et al. 2020). In addition, consideration of anti-inflammation and immune-nanomedicines approaches (Xu et al. 2020; Bonam et al. 2021) leads to feeling better and reduces the time of hospital discharge. From an

ethnopharmacology point of view, finding promising drugs from nature by getting clues from traditional medicine has been well-recognized for reducing infection and viral adhesion. These herbal formulas, including bioactive secondary metabolites, could block the interaction between host cells and viruses by inhibiting receptor-mediated recognition. Finally yet importantly, increasing the general immune system through various types of herbal products, nutraceuticals, and dietary supplements could be the alternative way to stop the mortality caused by SARS-CoV-2 (Bonam et al. 2020; Hensel et al. 2020). Therefore, the main goal is to look for new anti-viral drugs because viral diseases, such as SARS, MERS, and Ebola, are the main threat to humans. The use of medicinal plants is embedded in everyday life because these are easily available, patient-friendly with high curative effects and do not have toxicity and side effects when compared to synthetic drugs. Several researchers have applied plant-derived natural compounds showing great potency to combat this phenomenon. For instance, the anti-viral assessment of some traditional medicinal plants along with their extracts, such as *Allium sativum* L., *Artemisia annua* L., *Anthemis hyaline* DC., *Camellia sinensis* (L.) Kuntze, *Citrus sinensis* L. Osbeck, *Echinacea purpurea* (L.) Moench, *Nigella sativa* L., *Zinziber officinalis*, *Hypericum perforatum* L., *Scutellaria baicalensis* Georgi., *Rheum officinale* Baill., *Juniperus formosana* Hayata., *Euphorbia neriifolia* L., *Glycyrrhiza glabra* L., and *Lycoris radiata* Herb. showed their potency against SARS-CoV in vitro. By the way, for a further pre-clinical and clinical survey, these plants have been recommended (Hafez Ghoran et al. 2021a; Hensel et al. 2020). Overall taken, in this chapter, the author(s) aims to provide current knowledge on some medicinal plants of high ethnopharmacological interests worldwide as potential antiviral and anti-inflammatory sources. These plant species have been prescribed as medicinal plants in folk medicine around the world. Therefore, various plant-derived natural metabolites have salient potential bioactivity for controlling SARA-CoV-2 by enhancing the immune system.

3.2 Reactive Oxygen Species (ROS) and Inflammation Promotion

An important signaling process in the progression of inflammation is oxidative stress caused by reactive oxygen species (ROS). These are oxygen-containing free radicals, such as superoxide anion ($O_2^{-\bullet}$; unstable), hydroxyl radical ($OH^{\bullet}$; unstable), hydrogen peroxide (H_2O_2; stable), and nitric oxide ($NO^{\bullet}$). On this occasion, chronic inflammation can develop by the action of free radicals that damage healthy cells and infections and injuries will have the potency to trigger the immune response. Macrophages, known as immune cells, produce free radicals when they fight off invading microorganisms (Yahfoufi et al. 2018). Normally, a small portion of ROS is produced by cells and is necessary for maintaining homeostasis and function in cells. In this mechanism, physiological imbalances increase the production of

inflammatory factors, cytokines, and chemokines, leading to oxidized proteins, lipids, and DNA and even altering their function (Ansari et al. 2020). The inflammatory response to a viral infection that damages pulmonary cells may also be aggravated by ROS generated by the unchecked flow of inflammatory mediators. Moreover, this condition brings about the desquamation and degradation of alveolar epithelial cells, production of the hyaline membrane, and pulmonary edema (Tian et al. 2020). To more extent, inflammation is induced by ROS through NF-κB activation and elevated transcription of genes encoding cytokines. H_2O_2 can also inhibit NF-κB activation by tyrosine phosphorylation of the nuclear factor-enhancing kappa light chains of activated B cells (IκB) (Pérez-Torres et al. 2021). These physiological events translocate the active NF-κB to the nucleus, where it induces the overexpression of many harmful biomolecules, such as IL-1β, IL-6, and TNF-α, all involved in the inflammatory process (Sul and Ra 2021). The current knowledge manifested that inflammation is an immune response to various infections or damages that can lead to many detrimental and complex diseases. With the growing body of knowledge on inflammatory-related factors, inflammasomes particularly nucleotide-binding oligomerization domain (NOD)-like receptor-containing pyrin domain 3 (NLRP3), have been well studied. Several preclinical studies indicate that antioxidant components can suppress NLPR3 inflammasome activation and scavenge ROS (Sho and Xu 2019). Another important signal molecule for inflammation in the body is NO, produced by acting inducible nitric oxide synthase (iNOS), a carrier of gas-to-cell intracellular information transmission. During an inflammatory response, the iNOS expression will increase, resulting in a high NO release (Wang et al. 2017). However, in oxidative stress conditions, a redox-sensitive transcription factor, nuclear factor erythroid 2-related factor 2 (Nrf2), regulates the oxidant/antioxidant system, besides the regulating antioxidant-related components by cytoprotective genes, phase 2 detoxifying genes (i.e., superoxide dismutase; SOD and NAD(P)H quinone dehydrogenase 1; NQO1), and stress genes (i.e., heme oxygenase 1; HO-1). Indeed, Nrf2 regulates the antioxidant-response elements (AREs). Most importantly, Nrf2/ARE activation acts as a clue to show the protection of body tissues against inflammatory mediators and oxidative stress-associated diseases (Khan et al. 2017). By the way, the progression of diseases happens by inflammation and oxidative stress, two interlocked routes, and jointly interfere with the therapy through multiple signaling pathways (Fig. 3.1).

3.3 Cross-Talk between Inflammation and Viral Infection

Viral infection triggers a reverse immune response referring to a difference in the immune response of individuals to pathogens based on their genetic diversity. Viral infection also promotes ROS production through leukocytes. In addition to ROS overproduction and antioxidant depletion, viral replication is also increased along with viral-associated complications. Lung, kidneys, intestines, and heart, which are rich in ACE2, are primarily affected by an impaired defense system causing massive

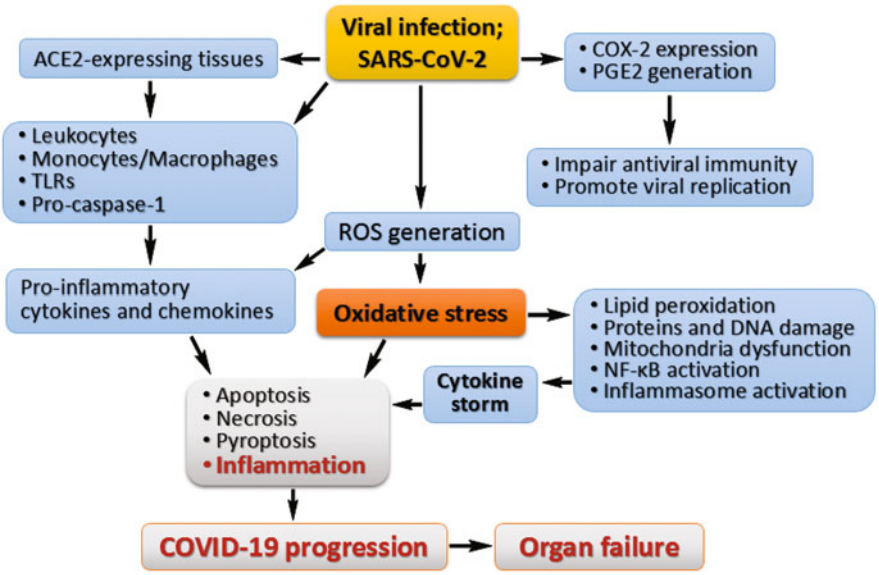


Fig. 3.1 Metabolic pathogenesis of SARS-CoV-2 infection and its consequences on oxidative stress and inflammation

tissue damage. In the lungs, damaged cells bring innate inflammation mediated by pro-inflammatory factors, such as macrophages and granulocytes. However, in severe respiratory dysfunction, an uncontrolled immune response with the corresponding lung inflammation leads to damaged lung tissues, impaired lung function, and reduced lung capacity (Bose et al. 2021). In a viral infection, a well-regulated innate immunity is the first line of defense. However, during severe COVID-19 conditions, hyperinflammation (cytokine storm) results in acute respiratory distress syndrome (ARDS) and represses immunity (Jafarzadeh et al. 2021). Another line of defense includes toll-like-receptor (TLR), which stimulates the NF-κB pathway, leading monocyte cells to produce pro-inflammatory mediators, viz. IL-6, IL-1β, and TNF-α. Furthermore, by recruiting other leukocytes and directly regulating the antiviral pathways, TLR can control viral infection. In the case of COVID-19, the high levels of oxidative stress by inflammatory factors; on the other hand, the reduction of IFN-α and IFN-β makes it worse (Wang et al. 2020). As previously discussed, chronic viral infections can induce inflammation and immunosuppression, resulting in a dysfunctional immune system. In acute viral infections, type I interferons (IFN-Is) produce inflammation; however, IFN-Is also promote chronicity and limit immunity. Noted that chronic inflammation mediated by IFN-I does not promote viral replication alone but results in progressive immune dysfunction and disease (Snell et al. 2017). Most significantly, in order to check the extracellular and intracellular environment for infection signs, the body's innate immune system recruits the pattern recognition receptors. The activation of pattern recognition receptors by virus nucleic acids induces the expression and secretion of

type I interferons (IFN-Is), which are key mediators for antiviral immunity (Stok et al. 2020). In the case of acute COVID-19, the highest concentrations of pro-inflammatory cytokines and chemokines have been observed in the patient's plasma (Mehta et al. 2020). Viral infections frequently trigger severe inflammatory responses that may function protectively or destructively in the innate immune system. Several virus-related diseases, including MERS-CoV, SARS-CoV, and SARS-CoV-2, which deregulate immune and inflammatory responses, bring about organ failure (Li et al. 2021). In general, viral infection not only decreases the antioxidant status but also increases the production of harmful oxidants and ROS, which is related directly to the enhancement of viral replication and viral-related diseases. Concerning SARS-CoV-2 infection, the Nrf2 pathway, which acts as a protective agent against oxidative stress, is suppressed, while NF-κB is activated, increasing inflammation and oxidative damage (Nema et al. 2021). As reported in SARS-CoV patients, both viral infection and viral replication can lead to high levels of virus-associated pyroptosis and vascular leakage in airway epithelial cells. Pyroptosis occurs as part of programmed cell death in cytopathic viruses, which is an intense form of inflammation because of high levels of IL-1β secretion (Chen et al. 2010). During viral infection, NLRP3 inflammasome induces caspase 1, ultimately leading to the cleavage of gasdermin-D (GSDMD), an important cellular membrane protein that leads to cell lysis (Man et al. 2017). Other innate immune cells are neutrophils and leukocytes. In addition to clearing pathogens and debris via phagocytosis, neutrophils are also involved in the inflammatory response (Rosales 2020). There are a lot of attention given to the endothelial dysfunction (ED) disease causing by viral infection like COVID-19. Due to activation and dysfunction of endothelial cells, previously discussed, pro-inflammatory cytokines and chemokines (i.e., monocyte chemoattractant protein-1; MCP-1), von Willebrand factor (vWF) antigen, vWF activity, and factor VIII are increased. As a result, associated with SARS-CoV-2 infection, high concentrations of severe phase reactants, such as C-reactive protein (CRP), IL-6, and D-dimer, have been reported (Zhang et al. 2020b). When tissue is exposed to viral infection, leukocytes influx in excess and activate tissue-resident leukocytes. There are various ways in which clinical inflammation can relieve or aggravate the disease, may not have any effect on the disease, or maybe both alleviate and aggravate the disease at different times, depending on the patient (Janeway 1953). Concerning SARS-CoV-2 and its complicated process, understanding the in-depth process and evaluating antiviral and anti-inflammatory components required more efforts to attenuate acute COVID-19 (Fig. 3.1).

3.4 Immunobooster Ability of Plants through Antioxidant and Anti-inflammatory Activity

In recent years, the role of medicinal plants has been increasingly emphasized and, in addition to their use as either traditional drugs or sources of bioactive compounds, they are "supportive tools" to enhance the immunity system. In this framework, a

combination of classical and modern ethnopharmacology used as health support and alternative strategies has been wieldy encouraged by several types of research due to the benefits these herbal preparations can bring to human health, as well as mitigating health problems. However, the complexity of plant materials and their phytomolecules should be carefully considered, since in some cases, they not only are not immunoenhancer but also toxic agents. In fact, Mother Nature does not provide standardized medicinal plants, and in-depth studies on herbal preparations and their extracts are required in several research areas including, toxicology, pharmacology, clinical biochemistry, etc. (Das 2021). The brilliant examples of plant immunoenhancers belong to the following plant families: Alliaceae (*Allium* sp.), Caryophyllaceae (*Syzygium* sp.), Hypericaceae (*Hypericum* sp.), Lamiaceae (*Salvia* sp. and *Mentha* sp.), Leguminosae (*Curcuma* sp. and *Glycyrrhiza* sp.), Menispermaceae (*Tinospora* sp.), Ranunculaceae (*Nigella* sp.), Rutaceae (*Citrus* sp.), Zingiberaceae (*Zingiber* sp.), etc. The plants have been consumed conventionally in Arabic, Ayurvedic, Chinese, Tibetan, Unani-Tibb, and various folkloric systems of ethnomedicine to establish strong immunity in the human body and avoid viral infection (Hafez Ghoran et al. 2021a). Overall, there are still an array of plants that play as immune boosters and anti-SARS-CoV agents, some of which are mentioned in Table 3.1.

3.4.1 Glycyrrhiza glabra *L.*

Liquorice (*Glycyrrhiza glabra* L.; Leguminosae/Fabaceae) has been used traditionally for thousands of years. Being a perennial plant, it has been used not only as a nutraceutical plant in food products but also for medicinal purposes, including antiallergic and anti-inflammatory properties. In folk medicine, liquorice roots have been widely consumed for asthma, cough, colds, and even chronic obstructive pulmonary disease (COPD) (Bhat et al. 2012). Moreover, some conducted studies in China recommended using liquorice (*Glycyrrhiza* sp.) for deactivating COVID-19 (Wang and Yang 2021). To activate the body's immune system, the liquorice extract can maturate and differentiate the lymphocytes and macrophages (Ng et al. 2021). Liquorice (*Glycyrrhiza* sp.) contains various bioactive metabolites, of which glycyrrhizin (**1**) and glycyrrhetinic acid (Fig. 3.2), belonging to the saponin triterpenoids, are the main active natural products showing potential inhibition of cortisol metabolism because of their steroid-like structures. Flavonoids especially isoflavonoids and chalcones are the other phytochemicals that have been reported from liquorice (Bhat et al. 2012). In terms of antioxidant activity, the liquorice extract, despite scavenging $DPPH^{\bullet}$ radicals (1,1-diphenyl-2-picrylhydrazyl radicals), exhibited significant protective effects towards liposomal membrane lipid peroxidation and liberation of blood ROS. The liquorice's antioxidant activity is because of isoflavonoid derivatives, coumarins, and chalcones (Račková et al. 2007). The plant extract also increases the enzymatic antioxidant status, including catalase (CAT), superoxide dismutase (SOD), glutathione-peroxidase (GSH-Px), and total

Table 3.1 Some traditional medicinal plants for increasing the body's general immunity and anti-coronavirus activity

Plant name	Family	Common name	Part of use	Anti-inflammatory and immunoenhance mechanisms	Anti-SARS-CoV activity	Reference
Alnus japonica (Thunb.) Steud	Betulaceae	Japanese Alder	Bark	Inhibition of the production of lipopolysaccharide (LPS)-induced pro-inflammatory cytokines, including IL-6 and IL-1β in RAW264.7 macrophage cells	Inhibitory activity against SARS-CoV-PL^{pro}	Park et al. (2012), Lee et al. (2017)
Angelica keiskei Ito	Apiaceae	Ashitaba	Roots	Inhibition of endothelin-1 gene expression through the suppression of NF-κB	Dose-dependently, inhibitory activity against SARS-CoV-$3CL^{pro}$ and SARS-CoV-PL^{pro}	Sugii et al. (2005), Mahmud et al. (2021)
Azadiracta indica A. Juss	Meliaceae	Neem	Leaves and flowers	Stimulation of pro-inflammatory cytokines, including IFN-γ, IL-1, and TNF-α	In silico inhibitory activity against SARS-CoV-2 PL^{pro} and SARS-CoV-M^{pro}	Das (2021)
Brassica oleracea L.	Brassicaceae	Broccoli	Aerial parts	Increase of TNF-α production by LPS-stimulated macrophages	Dose-dependently, inhibitory activity against SARS-CoV-2-Wuhan-Hu-1 virus-related cell death in non-human primate Vero C1008 cells and HCoV-OC43	Das (2021), Ordonez et al. (2022)
Bupleurum sp.	Apiaceae	Chai Hu	Roots	Inhibition of NF-κB	Inhibitory activity against HcoV-229E attachment and penetration at concentrations of 0.25–25 μmol/L	Lei et al. (2020), Cheng et al. (2006)
Camellia sinensis	Theaceae	Tea	Leaves and flowers	Inhibition of IL-1β, TNF-α, and NO production in LPS-induced liver inflammation	Inhibitory activity against SARS-CoV-$3CL^{pro}$ activity and suppression of SARS-CoV replication	Chen et al. (2005, 2012)

(continued)

Table 3.1 (continued)

Plant name	Family	Common name	Part of use	Anti-inflammatory and immunoenhance mechanisms	Anti-SARS-CoV activity	Reference
Cibotium barometz L.	Cibotiaceae	Golden chicken fern	Rhizomes	Dose-dependently, suppression of NO production and IL-6 secretion, in IFN-γ/LPS-induced mouse peritoneal macrophage cells	Inhibitory activity against SARS-CoV replication at concentrations of 25 and 200 mg/mL	Wen et al. (2011), Lee et al. (2010)
Cullen corylifolium (L.) Medicus	Fabaceae	Buguzhi	Whole plant	Dose-dependently, suppression of PGE2 and NO production in LPS-induced microglia; Downregulation of COX-2 (protein and mRNA) and iNOS in LPS-induced microglia	Dose-dependently, inhibitory activity against SARS-CoV-PL^{pro}	Kim et al. (2018), Raman et al. (2022)
Curcuma longa L.	Zingiberaceae	Turmeric	Rhizomes	Reduction of NO production in RAW264.7 macrophages along with T helper cell activation.	Inhibitory activity against S protein/SARS-CoV-2 viral entry	Das (2021), Merarchi et al. (2021)
Emblica officinalis Gaertn	Phyllanthaceae	Gooseberry	Fruits	Modulating oxidative stress, inflammatory mediators, and cytokine storm, including IL-6, TNF-α, and COX-2 secretion	Inhibitory activity against SARS-CoV-2 replication	Ratheesh et al. (2022)
Galla chinensis	Anacardiaceae	Chinese gall	Nutgall	Inhibition of secretion of inflammatory cytokines and enhancing the expression of anti-inflammatory factors	Inhibition of binding with SARS-CoV spike protein	Sun et al. (2018), Yi et al. (2004)
Glycyrrhiza glabra L.	Leguminosae	Liquorice	Roots	Increase of NF-κB and IL-10 production	Inhibitory activity against SARS-CoV replication	Das (2021)
Houttuynia cordata Thunb.	Sauruaceae	Chameleon plant	Aerial parts	Inhibition of LPS-induced PGE2 and COX-2 production in mouse peritoneal macrophages	Inhibitory activities against SARS-CoV $3CL^{pro}$ and SARS-CoV RNA-dependent RNA polymerase (RdRp)	Lau et al. (2008), Li et al. (2011)

Isatis indigotica fort.	Brassicaceae	Dyer's woad	Roots	Inhibition of influenza A virus, viral RNA-stimulated pro-inflammatory cytokines, and IFNs via inactivation of p38 MAPK and NF-κB pathways	Inhibitory activity against SARS-CoV $3CL^{pro}$	Liang et al. (2020) Lin et al. (2005)
Moringa oleifera lam.	Moringaceae	Drum stick	Aerial parts	Increase of production of IL-2 and antibody-dependent cellular cytotoxicity (ADCC)	Inhibitory activity against SARS-CoV-2	Das (2021)
Ocimum sanctum L.	Labiatae/ Lamiaceae	Tulsi	Leaves	Stimulation of cytokines, i.e. IL-4, IFN-γ, T helper cells, and increase of the phagocytic activity	Inhibitory activity against SARS-CoV-2 M^{pro} using molecular dynamic stimulation	Das (2021), Saravanan et al. (2022)
Picrorhiza kurroa Royale ex Benth	Scrophulariaceae	Kutki	Seeds	Modulating oxidative stress, inflammatory mediators, and cytokine storm, including IL-6, TNF-α, and COX-2 secretion	Inhibitory activity against SARS-CoV-2 replication	Ratheesh et al. (2022)
Piper nigrum L.	Piperaceae	Black pepper	Seeds	Increase of the phagocytic index and proliferation of macrophage cells	Inhibitory activity against SARS-CoV-2 M^{pro}	Majdalawieh and Carr (2010), Gutierrez-Villagomez et al. (2020)
Scrophularia scorodonia L.	Scrophulariaceae	Figwort	Aerial parts	Dose-dependently, inhibitory activity against LPS-induced TNF-α, PGE2, and NO production	Inhibitory activity against HcoV-229E attachment and penetration at concentrations of 0.25–25 μmol/L	Cheng et al. (2006), Dıaz et al. (2004)
Scutellaria baicalensis Georgi	Labiatae/ Lamiaceae	Chinese skullcap	Aerial parts	Downregulation of NO, iNOs, COX-2, PGE2, NF-κB, and IκBα Downregulation of pro-inflammatory cytokines, including TNF-α, IL-2, IL-6, IL-12, and IL-1β	Inhibitory activity against SARS-CoV-2 replication and SARS-CoV-2 $3CL^{pro}$. Inhibitory activity against SARS-CoV helicase (nsP13)	Liu et al. (2021), Kim et al. (2009), Yu et al. (2012)

(continued)

Table 3.1 (continued)

Plant name	Family	Common name	Part of use	Anti-inflammatory and immunoenhance mechanisms	Anti-SARS-CoV activity	Reference
Tinospora cordifolia (Willd.) Miers	Menispermaceae	Gurjo, Guduchi	Leaves	Modulating oxidative stress, inflammatory mediators, and cytokine storm, including IL-6, TNF-α, and COX-2 secretion	Inhibitory activity against SARS-CoV-2 replication	Ratheesh et al. (2022)
Tribulus terrestris L.	Zygophyllaceae	Bindi	Leaves	Reduction of expression of NO, PGE2, and COX-2 in LPS-induces RAW264.7 macrophage cells Downregulation of inflammatory mediators, including IL-6, IL-10, and TNF-α	Dose-dependently, inhibitory activity against SARS-CoV-PL^{pro}	Song et al. (2014), Ko et al. (2015)
Torreya nucifera (L.) Siebold & Zucc	Taxaceae	Japanese nutmeg-yew	Leaves	Inhibitory activity against NO and PGE2 production; Dose-dependently, blocking the production of iNOS mRNA, COX-2, and TNF-α; Reduction of NF-κB	Inhibitory activity against SARS-CoV $3CL^{pro}$	Kim et al. (2016), Ryu et al. (2010)
Toona sinensis (A. Juss.) Reom	Meliaceae	Cedrela sinensis	Leaves	Inhibitory activities against COX-1 and COX-2	Inhibitory activity against SARS-CoV viral entry and SARS-CoV replication	Chen et al. (2008), Hu et al. (2016)
Withania somnifera (L.) Dunal	Solanaceae	Ashwagandha	Roots	Increase of phagocytic activity of peritoneal macrophages	Inhibitory activity against SARS-CoV-2 RdRp; Inhibitory activity against human trans-membrane serine protease-2 (TMPRSS2) protein binding potency using computational analysis	Das (2021), Prajapati et al. (2022)

Zingiber officinale Roscoe	Zingiberaceae	Ginger	Rhizomes	Increase of production of splenocyte proliferation, and a decrease of inflammatory mediators, including IL-6, IL-1β, and TNF-α in activated macrophages	Inhibitory activity against SARS-CoV-2 $3CL^{pro}$	Das (2021), Zubair et al. (2021)

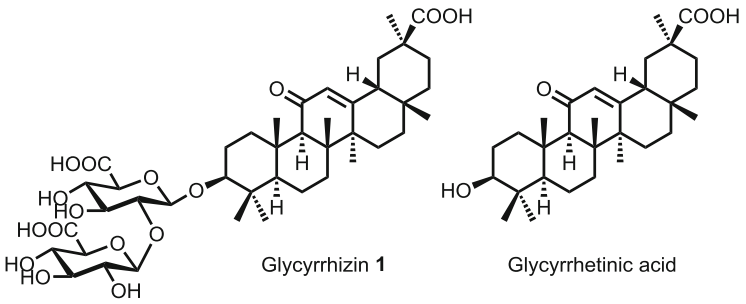


Fig. 3.2 Structures of glycyrrhizin (**1**) and glycyrrhetinic acid reported from *Glycyrrhiza glabra* L.

antioxidant capacity (TAOC), as well as decreases the carbachol-induced concentration in lung tissue (Ng et al. 2021). In in vivo model of asthma induced by ovalbumin (OVA), **1** showed the alleviation of allergic asthma through the increase of IFN-γ levels, a decrease of inflammatory mediators (i.e., IL-4 and IL-5), and the levels of eosinophil in bronchoalveolar lavage (BAL), reduction of OVA-specific IgE, and upregulation of total IgG2a in serum. In addition to alleviation of lung inflammation induced by carrageenan, compound **1** attenuated mucus production in mice models. In the mice model on lung tissue, the liquorice root extract containing flavonoid compounds modulated lipopolysaccharide (LPS)-induced pulmonary inflammation via inhibition of responsible cells (i.e., lymphocytes, macrophages, and neutrophils) and suppression of IL-1β and TNF-α expression (Pastorino et al. 2018). Noted that the liquorice ethanolic extract, besides scavenging the ROS, potentially reduces the levels of inflammatory markers, such as interleukins, TNF-α, NF-κB, IFN-γ, and PI3K, and increases the increment of serum LgA, LgG, and LgM levels together with spleen lymphocytes proliferation (Ng et al. 2021). Interestingly, for compound **1,** a broad spectrum of antiviral activities against various kinds of viruses has been reported (Hafez Ghoran et al. 2021a), so that compound **1** strongly inhibited the replication of SARS-CoV in Vero cells when tested against two coronavirus strains (i.e., FFM-1 and FFM-2) isolated from SARS positive patients, with selectivity index (SI = 67). It is reported that at the beginning of SARS replication, **1** interrupted the adsorption and viral entry (Cinatl et al. 2003). Van de Sand et al. revealed that treatment of **1** potentially inhibited SARS-CoV-2 main protease (M^{pro}), blocking the replication process. Therefore, because of these positive effects of glycyrrhizin, consuming tea prepared from black liquorice roots was recommended for SARS-CoV-2 patients (van de Sand et al. 2021). Taken together, the inhibition of SARS-CoV-2 main proteases (i.e., 3C-like protease; $3CL^{pro}$, papain-like protease; PL^{pro}, and main protease; M^{pro}) and S proteins have been reported for liquorice extract (Ng et al. 2021).

3.4.2 Citrus aurantium *L.*

Citrus species is the most substantial and medicinal fruit of Rutaceae plants, which is freshly consumed in folk medicine or as an additive in food supplements. Some biological activities, including antioxidant, anti-inflammatory, antimicrobial, cancer prevention, and degenerative diseases, have been reported for *Citrus* species, which have a high quantity of bioactive metabolites such as polyphenols, phenolics, flavonoids, essential oils, and vitamins. Using the blooms of *Citrus aurantium* L. (known as bitter orange) are deeply rooted in Iranian traditional medicine because of heart tonic and antidepressant properties (Hafez Ghoran et al. 2020). Besides using a stimulant and appetite suppressant agent, the plant is also consumed in traditional Chinese medicine for treating cardiovascular problems, indigestion, nausea, and cancer (Popoola et al. 2022). Reverse phase-HPLC analyses of *C. aurantium* flowers indicated the presence of phenolics and flavonoids such as gallic acid (**2**), pyrogallol (**3**), syringic acid (**4**), caffeic acid (**5**), quercetin (**6**), naringin (**7**), and rutin (**8**) (Fig. 3.3) as the bioactive compounds. Besides worthwhile contributions in antioxidant activity, *Citrus* polyphenols and crude polysaccharides showed significant anti-inflammatory and immunoenhacment activity on LPS-treated RAW264.7 murine macrophage cells via suppression of mitogen-activated protein kinase (MAPK) and NF-κB processes (Kang et al. 2011), reduction of nitric oxide generation, stimulation of IL-6 and TNF-α secretion, and promotion of IL-6, IL-1β, TNF-α, and iNOS mRNA expression. LC-MS analysis of crude polyphenol extract of *C. aurantium* blossoms represented **7**, **8**, eriocitrin (**9**), neoeriocitrin (**10**), rhoifolin (**11**), hesperidin (**12**), neohesperidin (**13**), veronicastroside (**14**), and hesperetin (**15**) (Fig. 3.3) as the main phytoconstituents (Shen et al. 2017). Local people in China, India, and Africa are consuming the decoction of *C. aurantium* blossoms to treat viral infections, especially COVID-19, and stimulate the body's immunity. The pathways were blocking the entry and replication of SARS-CoV-2 and even suppressing the expression of pro-inflammatory markers leading to an anti-inflammation property (Popoola et al. 2022). Clinically, *C. aurantium* together with two *Citrus* sp. (*C. reticulata* and *C. grandis*) boosts digestive health and relieves the cough in SARS-CoV-2 patients. Compounds **7** and **15**, as the main phenolic compounds in *Citrus* plants, potently prevent the cytokine storm (expression of IL-6, IL-1β, COX-2, and iNOS). Thus, flavonoids in *Citrus* fruits can be anti-SARS-CoV-2 agents and/or can increase the host immunity through anti-inflammatory activities (Liu et al. 2022).

3.4.3 Hypericum perforatum *L.*

St. John's wort (*Hypericum perforatum* L.; Hypericaceae) belongs to Europe, western Asia, and northern Africa, and has therapeutic implications in minor anxiety and depressive episodes. Various bioactive constituents such as hyperforin (**16**; a

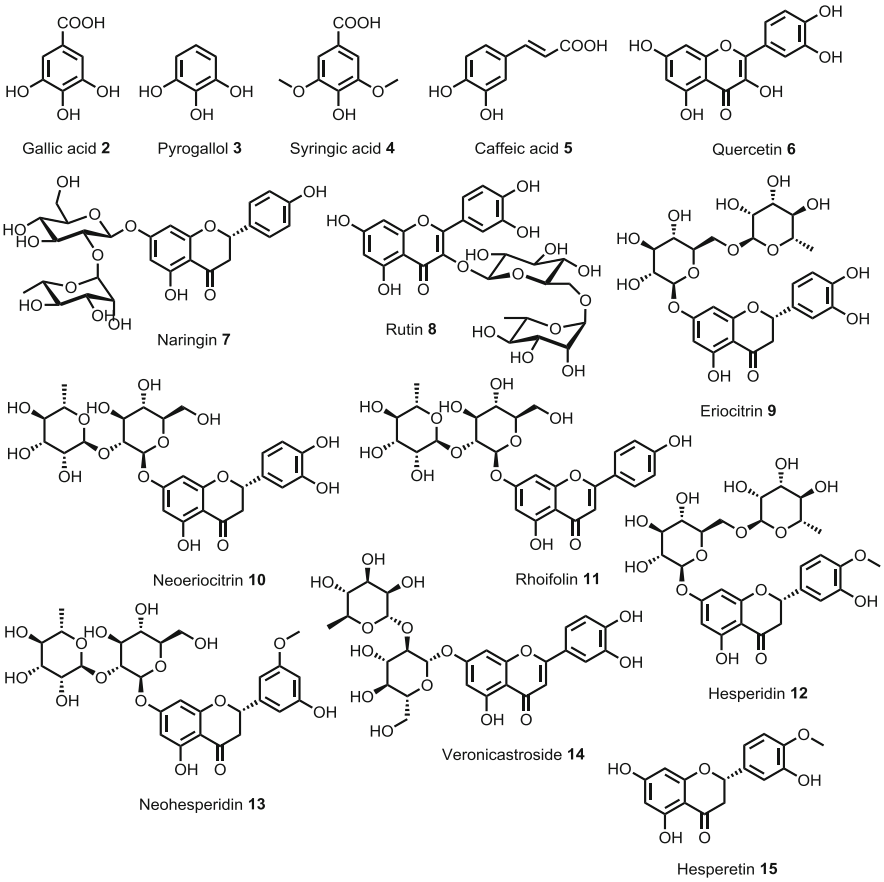


Fig. 3.3 Some bioactive phytochemicals, **2**–**15**, reported from *Citrus aurantium* L.

prenylated phloroglucinol derivative), hypericin (**17**; a naphthodianthrone derivative) (Fig. 3.4), flavonoids, flavonoid glycosides, bioflavonoids, and tannins are responsible for diverse therapeutic effects. Based on the Iranian ethnopharmacological documents, in the northern part of Iran, the flowering branches of the plant are used for relaxing the nervous system, improving the immune system, refreshment of respiratory and uterus systems, astringent, anti-HIV and anticancer activities (Bahmani et al. 2018). Most *H. perforatum* fractions were active against $DPPH^{\bullet}$ and superoxide radicals, nitric oxide production, and lipid peroxidation. These results indicated that caffeoylquinic acids, flavonoids, and phenolic acids, including **6**, **8** (Fig. 3.3), hyperoside (**18**), quercitrin (**19**), 3,8'-biapigenin (**20**), amentoflavone (**21**) (Fig. 3.4) dealt with antioxidant activity, while phloroglucinols and naphtodianthrones did not show significant effects (Orčić et al. 2011). Owing to the presence of these bioactive components, the plant displays high antioxidant activity, which decreases, in a concentration-

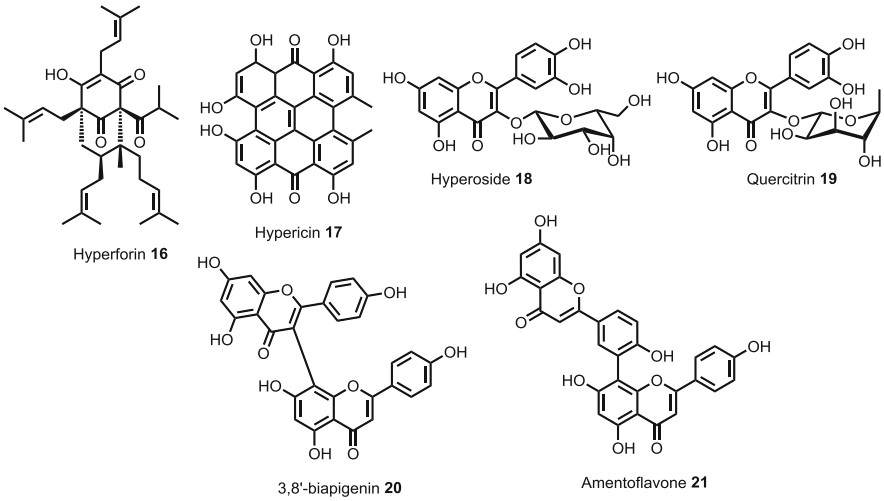


Fig. 3.4 Some bioactive phytochemicals, **16**–**21**, reported from *Hypericum perforatum* L.

dependent manner, the peroxidative and chlorinating activity of human leukocyte myeloperoxidase (MPO). This phenomenon further causes the anti-inflammatory activity of *H. perforatum* (Pabuçcuoğlu et al. 2003). Moreover, having been stimulated with *N*-formyl-methionyl-leucyl-phenylalanine, plant-derived metabolites like hyperguinone and hyperforin strongly reduced oxygen production by polymorphonuclear cells (PMNs) (Heilmann et al. 2003). Not only does *H. perforatum* have immunomodulatory activity but it also has a potent antiviral activity and because of this, the plant is a candidate against COVID-19. The extract of *H. perforatum* and hyperforin (**16**) strongly inhibited the pro-inflammatory mediators and β-cell lines isolated from rat and human pancreatic islets (Novelli et al. 2014). The same authors evaluated the mechanism of action and proposed there is a simultaneous blockage of the multiple phosphorylation steps by *H. perforatum* extract together with compound **16**, which are involved in a cytokine storm, including IL-1β, TNF-α, IFN-γ, NF-κB, MAPK, and JAK/STAT pathways. Furthermore, the plant preparations deactivated the transcription of apoptotic and inflammatory genes, such as COX-2, iNOS, CXCL9, and CXCL10 chemokines, as well as the production of ICAM-1 adhesion molecules. Most significantly, despite the activation of some kinases (i.e., JNK, ERK1/2, IKK, and Akt), *H. perforatum* extract and compound **16** inhibited DNA binding and phosphorylation of NF-κB and STAT-1 (Novelli et al. 2016). Associated with the protective effects of *H. perforatum* on various animal models against chronic inflammation, Menegazzi et al. included that the plant extract is able to attenuate lung inflammation caused by carrageenan in mice through deactivation of NF-κB and STAT-3, inhibition of IL-1β and TNF-α secretion, downregulation of ICAM-1, infiltration of lung neutrophils, and nitration of cellular proteins (Menegazzi et al. 2006). Emerged by the multitasking behavior of *H. perforatum* and its major component, hyperforin (**16**), and showing deserved anti-inflammatory

activity, Masiello et al. proposed the plant as the promising candidate to either inhibit or block the drawbacks of cytokine storm in COVID-19 patients. Administrated the extract of *H. perforatum* and **16**, researchers found compatible results with the selected antiviral drugs, such as chloroquine/hydroxychloroquine, human immunoglobulins, and LMW heparin (Masiello et al. 2020). Interestingly, the *H. perforatum* fractions rich in flavonoid and catechin showed various antiviral activities. Using molecular docking study, the phytoconstituents of *H. perforatum*, for example, hypericin (**17**) and isohypericin, showed effective anti-SARS-CoV-2 activity, where high binding affinity was observed for inhibition of SARS-CoV-2 M^{pro} (Yalçın et al. 2021).

3.4.4 Salvia officinalis *L.*

Sage (*Salvia officinalis* L.; Lamiaceae/Labiatae family) is a multipurpose culinary herb and medicinal plant native to the northern Mediterranean area and widely distributed over the hillsides and shores of southern Europe. Despite variously reported bioactivities such as antimicrobial, antiviral, antioxidant, anti-inflammatory, cytotoxic, hypoglycemic, and astringent, the plant has an effective immunomodulatory activity (Capek and Matulova 2013). The *Salvia* sp. extract contains the most potent antioxidant and immunoenhancer metabolites, including polysaccharides, terpenoids (i.e., carnosol **22**, carnosic acid **23**, and ursolic/oleanolic acid **24/25**), phenylpropanoids (i.e., caffeic acid **5** and rosmarinic acid **26**), flavonoids (i.e., genkwanin **27** and cirsimaritin **28**) (Fig. 3.5), and other phenolic acids. In traditional medicine, the decoction and infusion of the plant and its preparations are used to treat stomach disorders, mouth and throat mucus, diarrhea, periodontitis, gingivitis, and gingival bleeding, as well as abscesses (Hafez Ghoran et al. 2021b, 2022a). Rahman et al. showed that daily supplementation of *S. officinalis* leaves

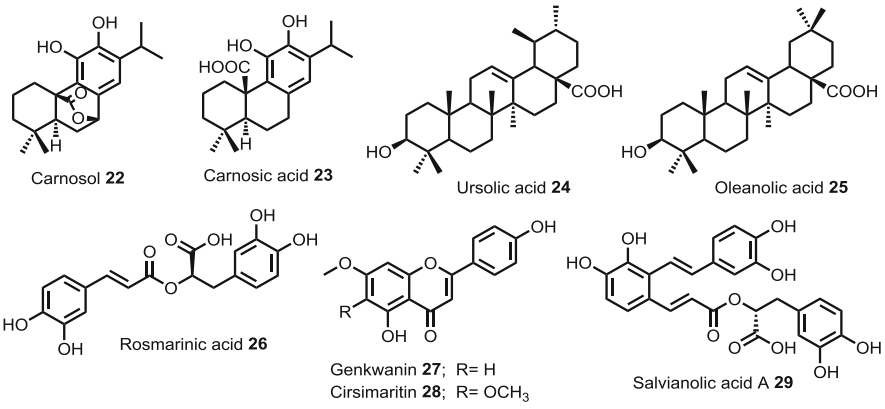


Fig. 3.5 Some bioactive phytochemicals, **22**–**29**, reported from *Salvia officinalis* L.

could efficiently enhance the antioxidant-immune capacity along with resistance against gram-positive bacteria *Aeromonas sobria* infection in *Cyprinus carpio*. At concentrations of 4 and 8 $g.Kg^{-1}$, not only the function of the digestive system was improved by increasing the activity of intestinal enzymes (lipase and amylase), but also the acting of enzymatic antioxidants (SOD and GSH-Px) along with the immunity effects (nitric oxide, anti-protease, and immunoglobulin M) significantly improved. Moreover, both dietary concentrations enhanced the splenic genes expression (*SOD*, *TLR-2*, *IL-6*, *IL-10*, and *IL-1β*), the intestinal genes expression (*Slc26a6*, *PepT1* and/or *Slc15a1*), and muscular genes expression (*SOD* and *IGF-1*) whereas these doses resulted in downregulation of *MSTN* (Rahman et al. 2022). In another research on female Wistar albino rats, *S. officinalis* exhibited anti-inflammation activity in the lung, liver, kidney, and hemolysate versus induced by LPS and oxidative stress via enhancing the enzymatic antioxidant activity of CAT, SOD, and GSH-Px, and regulating molecules in the inflammation pathway. The mechanism of action of *S. officinalis* was detected by the uptake of ^{18}F-fluoro-deoxy-D-glucose (^{18}F-FDG) in hepatic and pulmonary cells and determining the inflammation status using scanning of ^{18}F-fluoro-deoxy-D-glucose positron emission tomography (^{18}FDG-PET). Results indicated that the plant extract attenuates the levels of malondialdehyde (MDA), NO, TNF-α, and NF-κB (Kolac et al. 2017). Moreover, the ethanolic extract of *S. officinalis*, obtained by the soxhlet method, showed better antioxidant activity and decreased the secretion of IL-6 and TNF-α, rather than hydroethanolic and aqueous extracts. The bioactivity probably is because of the presence of compounds **22**, **23**, and **26**. The plant extract had higher to equal anti-inflammatory activity than reference drugs such as diclofenac, salicylic acid, and celecoxib (Vieira et al. 2020). Apart from these activities, the plant extract showed effective antiviral activity against various viral infections. According to Loizzo et al., the essential oil of Lebanon *S. officinalis,* containing the highest 1,8-cineole (43.6%), significantly inhibited SARS-CoV replication (Loizzo et al. 2008). In Unani traditional medicine (or Greek medicine), which is based on natural formulations, it is believed that a combined plant extract with ethanol provides a hand sanitizer that has an appropriate efficiency against COVID-19 (Azad et al. 2020). Using a molecular docking study, salvianolic acid A (**29**) (Fig. 3.5) obtained from *S. officinalis* showed good binding affinity to inhibition of SARS-CoV-2 M^{pro} (Ibrahim et al. 2020).

3.4.5 Mentha x piperita *L.*

Peppermint (*Mentha* × *piperita* L.; Lamiaceae/Labiatae family) is used as a most common herbal tea or tisanes. Despite using the leaves in food flavoring applications, the plant is traditionally consumed for treating throat inflammation, oral mucosa, cold, fever, digestive problems, antimicrobial and antiviral activities, as well as detoxifying the respiratory system. Moreover, peppermint tea/infusion, brewed from plant leaves or essential oils, is prescribed for respiratory-related disorders, including anti-congestive and expectorants. Evidence-based studies

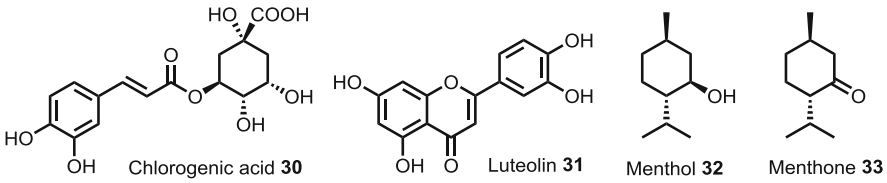


Fig. 3.6 Some bioactive phytochemicals, **30**–**33**, reported from *Mentha* × *piperita* L.

revealed various biological activities such as antioxidant, antiallergenic, antibacterial, anticancer, antidiabetic, antiviral, anti-inflammatory, larvicidal, radioprotective properties, and genotoxicity. The plant leaves are rich in phenolics (i.e. caffeic acid **5**, rosmarinic acid **26**, and chlorogenic acid **30**), flavonoids (i.e., eriocitrin **9**, hesperidin **12**, and luteolin **31**), lignans, and essential oils (i.e. menthol **32** and menthone **33**) (Fig. 3.6) (Mahendran and Rahman 2020). Both products of *M. x piperita* (i.e., essential oil and ethanol extract) represented an effective anti-inflammation in LPS-induced RAW264.7 cells by reducing NO release and suppressing IL-6, TNF-α, and prostaglandin E2 (PGE2) secretion. It is proposed that these processes are linked to virus infection. For instance, respiratory syncytial virus (RSV) brings about the induction of TNF-α secretion. Therefore, the plant could increase innate immunity by interfering with viral entry. Meanwhile, peppermint essential oils decrease the inflammation and lipid peroxidation caused by oxidative stress (Li et al. 2017). In another research, using LPS-stimulated RAW264.7 cells, Cho et al. evaluated the anti-inflammatory properties of the combination of *M.* × *piperita*, *Chrysanthemum zawadskii*, and *Glycyrrhiza glabra* (MCG). MCG mixture reduced the iNOS, IFN-β, and COX-2 expression (inflammatory markers) and IL-6, IL-1β, and TNF-α secretion (pro-inflammatory cytokines). Meanwhile, the MCG mixture suppressed the LPS-stimulated phosphorylation of STAT1, AKT, Iκb, and NF-κB, inhibiting the translocation of NF-κB into the nucleus (Cho et al. 2021). Furthermore, the combination of white tea and *M.* × *piperita* synergistically decreased the above-mentioned pro-inflammatory cytokines. An in-depth study on the mechanism revealed that the herbal preparations inhibited p-IκB-α and MAPK phosphorylation. Therefore, the anti-inflammatory activity was suggested through NF-κB deactivation and MAPK inhibition (Xia et al. 2021). Since there is no data regarding the anti-SARS-CoV-2 activity of *M.* × *piperita* (peppermint), Aldwihi et al. reported that before and during COVID-19, using peppermint-containing preparations like infusion or decoction effectively reduces the period of hospitalization. Based on a clinical study in Saudi Arabia, compared with 22% of hospitalized patients, ~78% of non-hospitalized patients consumed *M.* × *piperita*. Hence, by dietary consumption of peppermint, the time of hospitalization decrease during infection with COVID-19 (Aldwihi et al. 2021). Another adjuvant approach for counteracting SARS-CoV-2 is using aromatherapy and inhalation of essential oils. Based on a randomized clinical trial on peripheral oxygen saturation (SpO_2) in COVID-19 patients, the nebulizer effects of rose oil and peppermint oil were compared. Peppermint oil showed better results and

significantly increased the mean SpO_2 compared to rose oil and the control group. As a consequence, the need for ventilation machines decreased, leading to getting more satisfaction from patients (Ommi et al. 2020).

3.4.6 Allium sativum *L.*

Garlic (*Allium sativum* L.) and onion (*Allium cepa* L.), belonging to the Alliaceae family, are the most researched and best medicinal herbs in traditional medicine for most human health-related diseases. Despite the pungent smell, which is because of organosulphur-containing compounds (i.e. diallyl trisulfide **34**, alliin **35**, and allicin **36**) (Fig. 3.7), *Allium* plants are composed of vitamins (i.e., A, B, C, and E), carbohydrates (i.e., glucose and sucrose), minerals (i.e., phosphor, potassium, and selenium), non-volatile organosulphur-containing compounds (i.e., *S*-allylcystein **37**) (Fig. 3.7), other secondary metabolites, including flavonoids (i.e., quercetin **6**), triterpenoids, steroidal saponins, and nitrogenous compounds, which are in charge of various biological and/or pharmacological activities (Hafez Ghoran et al. 2021c). In traditional medicine of the Far East, *Allium* plants are used because of their preventive properties in cardiovascular diseases, regulation of blood pressure, lowering of blood sugar and cholesterol levels, increase of the immune system, and have antibacterial, antiviral, antifungal, antiparasitic, antitumoral, and antioxidant activities (Ayaz and Alpsoy 2007). Both plants, garlic and onion, have been able to provide better conditions for COVID-19 patients since they possess immunomodulatory, anti-inflammatory, antioxidant, antiviral, antihypertensive, antidiabetic, antimutagenic, and anticarcinogenic activities. According to one in silico study, garlic's metabolites can bond with the amino acids in the active site of SARS-CoV-2 M^{pro} through hydrogen bonds (Aldwihi et al. 2021). Clinical evidence reported that the levels of T helper cells in COVID-19 patients are low, and the inflammation is getting worst. However, *A. sativum* supplementation downregulated IL-6, TNF-α, leptin, leptin receptor, and PPAR-γ levels; on the other hand, it significantly upregulated cytotoxic T cells, T helper cells, and natural killers (NK) (Khubber et al. 2020). In another research, Kalkal et al. suggested that carbon dots derived from *A. sativum* (AS-CDs) could be potential theranostic agents and salient candidates for antiviral and bioimaging purposes. Concerning SARS-CoV-2 patients, AS-CDs through nebulization might downregulate the production of NF-κB and MAPKinase, and detoxify ROS species, which leads to the rejuvenation

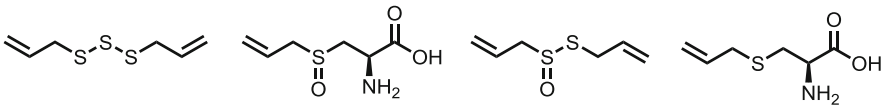


Fig. 3.7 Some bioactive phytochemicals, **34**–**37**, reported from *Allium sativum* L.

of the body's immunity (Kalkal et al. 2021). Keiss et al. reported that the garlic powder extract and diallyldisulfide modulate inflammatory cytokines expression in LPS-stimulated human blood through NF-κB deactivation and a significant decrease of IL-1β and TNF-α production (Keiss et al. 2003). Because of the modulation of cytokine storm, immunoglobulin production, phagocytosis, and activation of macrophages, the *Allium* plants are good candidates to promote the innate immunity system in COVID-19 patients (Donma and Donma 2020). Moreover, *A. sativum* was on the list of Peruvian herbal medicine to treat COVID-19 and respiratory symptoms during the pandemic. It is well documented that the plant inhibited SARS-CoV-2 replication (Villena-Tejada et al. 2021).

3.4.7 Zingiber officinalis *Roscoe*

Ginger (*Zingiber officinale* Roscoe.; Zingiberaceae family) is deeply rooted in ethnopharmacology worldwide. In Iranian, Japanese, Chinese, and Ayurvedic traditional medicine, ginger is consumed for various cancer types, pains, vomiting, cough, and cold symptoms, sore throat, arthritis, indigestion, hypertension, rheumatism, respiratory and infectious diseases. In Malaysia, local people use the plant to treat various immune and infectious diseases (Khodaie and Sadeghpoor 2015). Several studies reported that the ginger extracts with its bioactive constituents, such as vallinoids (i.e. gingerols **38**, shogaols **39**, and paradols **40**) (Fig. 3.8), curcuminoids, flavonoids, and volatile oils, viz. zingerone **41** (Fig. 3.8), zingerol, zingiberene, possess antioxidant, antimicrobial, anti-inflammatory, anticancer, and immunomodulatory activities (Harun and Mohamad 2022). Some animal studies on lung inflammation reported that the *Z. officinale* extract and its bioactive components decline the production of inflammatory markers (i.e., IL-6, IL-1β, and TNF-α) and oxidative stress through decreased MDA and MPO levels, as well as total oxidant content. The plant also prevents lung tissue denaturation and DNA oxidation and

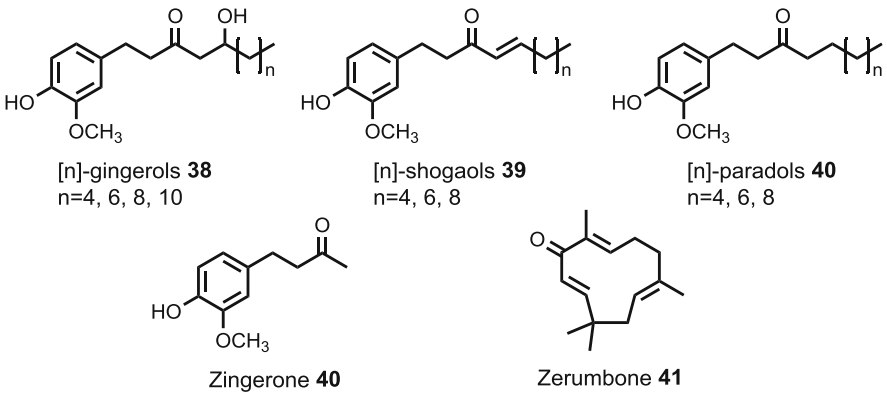


Fig. 3.8 Some bioactive phytochemicals, **38**–**41**, reported from *Zingiber officinale* Roscoe

increases the endogenous antioxidant components (Cifci et al. 2018). 6-Shogaol derived from *Z. officinale* extract plays as an antioxidant component that suppresses ROS, iNOS, and COX-2 production and upregulates the levels of antioxidants (i.e., GSH, Nrf2, quinone-1, and hemeoxygenase-1). In a model of cisplatin-mediated toxicity, zingerone **41**, another ginger metabolite, effectively refines the enzymatic antioxidant (SOD, CAT, and GPx) activities and even enhances GSH production. Meanwhile, compound **41** reduces IL-6, IL-1β, TNF-α, NF-κB, iNOS, and COX-2 expression. Overall, ginger and its secondary metabolites decline the oxidative factors and stimulate the oxidative stress-attenuating proteins. The plant has the capability of managing the health condition of COVID-19 patients (Jafarzadeh et al. 2021). In a study on LPS-induced human colonic epithelial cell lines, *Z. officinale* extract with 6-gingerol and 6-shogaol significantly downregulated IL-6, IL-8, PGE2, and iNOS expression, as well as deactivated NF-κB. Noteworthy to mention that both compounds also avoided the production of COX-2 and PGE2 in vitro in microglia and colonic epithelial cells, which were induced by LPS (Kim et al. 2017). *Z. officinale* extract also downregulated the synthesis of prostaglandins and leukotrienes through enzymatic inactivation, including 5-lipoxygenase (5-LOX), COX-1, and COX-2 (van Breemen et al. 2011) proposing the possibility of reduction of hyper-inflammation in COVID-19 patients. Moreover, in LPS-induced human macrophage cells, zerumbone (**42**) (Fig. 3.8), a sesquiterpenoid compound from *Z. officinale*, suppressed the expression of IL-6, TLR2, TLR4, COX-2, and myeloid differentiation factor 88 (MyD88) as well as NF-κB expression (Kim and Yun 2019). In terms of anti-SARS-CoV-2 activity, computational studies showed that 6-, 8-, and 10-gingerols potently inhibit the SARS-CoV-2 PL^{pro}. Above all, 6-gingerol showed potential binding affinity to the proteins dealing with virus replication, such as SARS-CoV-2 M^{pro}, SARS-CoV-2 $3CL^{pro}$, and cathepsin K (Oso et al. 2022). Another molecular docking study reported that the ginger metabolites (i.e., gingerol, shogaol, geraniol, zingerone, zingiberene, and zingiberenol) not only attach with the SARS-CoV-2 M^{pro} catalytic domain but also destroy the S protein-ACE2 interaction (Ahkam et al. 2020). To more extent, based on a randomized-controlled study in Iran using combination therapy by *Z. officinale* and Echinacea, the clinical symptoms such as breath shortness, coughing, and muscular pain of those none-hospitalized COVID-19 patients were more alleviated than those COVID-19 outpatients used the standard protocol using hydroxychloroquine alone (Mesri et al. 2021). Another randomized-controlled trial was carried out on ARDS patients who were fed for 21 days with an enteral diet containing the rich ginger extract. Compared to the control group, besides decreasing the secretion of IL-1, IL-6, and TNF-α in serum, better oxygenation was observed; however, the time of using electronic ventilation was reduced. Nevertheless, organ failure, barotrauma, and mortality rates happened in patients treated with ginger the same as in the control group. As patients with pulmonary complications have symptoms (i.e., ARDS, fibrosis of lung tissue, sepsis, and pneumonia) similar to COVID-19 signs, ginger and its secondary metabolites play a substantial role in COVID-19 management (Thota et al. 2020).

3.4.8 Syzygium aromaticum *L.*

Clove (*Syzygium aromaticum* L.; family Myrtaceae) is a precious spice composed of dried flower buds, originally from Maluku islands in Indonesia, which is used for food preservation by local people. The worldwide use of clove in folk medicine is due to various bioactive phytochemicals, including hydrocarbons, phenylpropanoids (i.e., eugenol **42** and eugenyl acetate **43**), terpenoids (i.e., β-caryophyllene **44**), steroids (i.e., stigmasterol **45**), flavonoids (i.e., kaempferol **46**), tannins (i.e., bicornin **47**), and phenolic compounds (i.e., ellagic acid **48**) (Fig. 3.9) (El-Saber Batiha et al. 2020). In folk medicine, the essential oil of *S. aromaticum* is used as a painkiller in dental care and in curing tooth infections and toothache. The plant oil consisting of eugenol, eugenol acetate, and thymol shows high antioxidant activity and reduces oxidative stress (Nam and Kim 2013). However, it is also administered for burns and wounds. In Ayurvedic and Chinese traditional medicine, the plant is used not only as a warming and stimulating agent but also for treating respiratory disorders, anti-inflammatory, antiviral, and immunostimulatory activities. Nowadays, *S. aromaticum* with a combination of other medicinal plants, such as *Eucalyptus globulus*, *Cymbopogon citratus*, and *Zingiber officinale* is prescribed by traditional healers to prevent and control SRAS-CoV-2-associated diseases (Vicidomini et al. 2021). Moreover, in the mice model, the essential oil of *S. aromaticum* enhanced the total white blood cells (WBC) and increased the delayed-type hypersensitivity (DTH) response. The plant oil also improved the humor- and cell-mediated immune responses, which is recommended for COVID-19 patients to improve their health (Carrasco et al. 2009). Using enzyme-linked immunosorbent assay (ELISA),

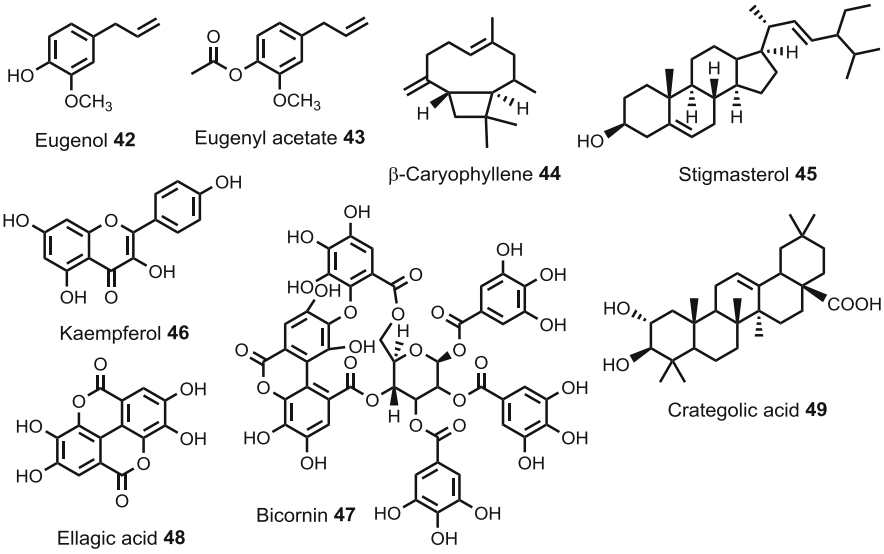
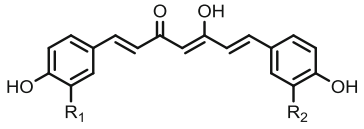


Fig. 3.9 Some bioactive phytochemicals, **42**–**49**, reported from *Syzygium aromaticum* L.

Bachiega et al. concluded that *S. aromaticum* extract and its main compound, eugenol **42**, possess immunomodulatory/anti-inflammatory activity through activation of macrophages to secret the pro-inflammatory cytokines. *S. aromaticum* extract, at 100 μg/mL, significantly reduced IL-6, IL-10, and IL-1β production, while eugenol **42** inhibited the IL-10 and IL-6 production at 50–100 μg/mL (Bachiega et al. 2012). The same behavior was observed by the water-soluble part of the hydroalcoholic extract of *S. aromaticum* and eugenol **42**, which inhibited IL-6 and IL-1β secretion in BALB/mice using the ELISA method (Rodrigues et al. 2009). Regarding anti-COVID-19 activity, the *S. aromaticum* water and ethanol extracts containing 34 identified phenolic compounds, such as flavonoids, flavonoid glycosides, and tannins, repressed the binding of SARS-CoV-2 spike protein to ACE2 and inhibited the ACE2 activity in a dose-dependent manner. Interestingly, besides potent antiradical activity against $DPPH^{\bullet}$ and $ABTS^{\bullet+}$ radicals for water extract, its potency was also better than ethanol extract in ACE2 inhibitory activity. On the other hand, by possessing the highest total phenolic content (TPS), the ethanolic extract of *S. aromaticum* relatively detoxified the unstable $OH^{\bullet}$ radicals. Considering these results, clove (*S. aromaticum*) has a good potency to decrease the infection of SARS-CoV-2 and the development of COVID-19 (Li et al. 2022). A molecular docking study on *S. aromaticum*-derived compounds showed that crategolic acid **49** (Fig. 3.9), an oleanane-type triterpenoid, has the best binding affinity to SARS-CoV-2 M^{pro} through the protein-ligand interaction, which is because of amino acids and hydrogen bonds (Yunus 2021).

3.4.9 Curcuma longa *L.*

Turmeric (*Curcuma longa* L.; Leguminosae/Fabaceae family), native to the south of Asia, is commonly utilized as a spice or dye for culinary purposes with a long history of traditional uses. Various classes of natural products, including essential oils, curcuminoids (i.e., curcumin **50**, demethoxycurcumin **51**, and bisdemethoxycurcumin **52**) (Fig. 3.10), phenylpropanoids, flavonoids, flavonoid glycosides, and phenolic compounds, have been reported from the *C. longa*, however, the yellow color and pharmacological/biological effects of turmeric are largely attributed to the polyphenols like curcuminoid and sesquiterpenoid compounds (Hafez Ghoran et al. 2022b; de Oliveira Filho et al. 2021). In traditional medicine,



Curcumin **50**; $R_1 = R_2 = OCH_3$
Demethoxycurcumin **51**; $R_1 = OCH_3$, $R_2 = H$
Bisdemethoxycurcumin **52**; $R_1 = R_2 = H$

Fig. 3.10 Some bioactive phytochemicals, **50**–**52**, reported from *Curcuma longa* L.

the *C. longa* rhizomes, composed of ~70% of curcumin, are used for jaundice, rheumatism, hepatic disorders, indigestive, carminative, blood purifier, wound healing, stomachic, and alleviation of chronic inflammation. The plant is also used for boosting immune system response and reduction of the pain of inflammation in several diseases (Hamidpour et al. 2015). Memarzia et al., in their review, represented that *C. longa* and its main constituent, curcumin (~70%), can reduce the MDA and NO levels. In contrast, they enhanced the thiol, SOD, and CAT in oxidative stress conditions. Most significantly, both products improved the functionality of immunoglobulin E (IgE), IL-4, IL-17, IFN-γ levels, and T helper cells (Th1 and Th2), as well as transforming growth factor beta (Memarzia et al. 2021). The same authors, furthermore, delineated that *C. longa* and curcumin **50** relieve the tracheal smooth muscle showing their bronchodilatory effects in chronic obstructive pulmonary disorders. In experimental animal models, *C. longa* and compound **50** treatment alleviated most respiratory dysfunctions through antioxidant, anti-inflammatory, and immunomodulatory mechanisms (Memarzia et al. 2022). Looking at the mechanism of action of curcumin against SARS-CoV-2 activity, it is revealed that curcumin interacted with spike protein or ACE2 protein in the COVID-19-stimulated signal transduction pathway. Several transcription factors (i.e., Nrf2, NF-κB, Wnt/β-catenin, STAT-3, and p38/MAPK), which deal with SARS-CoV-2 infection, were also suppressed by treatment of **50**. Moreover, compound **50** decreased virus-associated inflammation by suppressing IL-6, IL-8, IL-10, TNF-α, TNF-β, and COX-2 expression in patients suffering from COVID-19 (Subhan et al. 2020). Thimmulappa et al. concluded that **50** inhibits SARS-CoV-2 activity through the following mechanisms: interacting with membrane proteins of the virus, interference in virus entry, suppression of virus proteases, and stimulation of host immune-boosting reactions. Therefore, compound **50** showed protective behavior on ARDS and lethal patients by NF-κB deactivation and downregulation of IL-6, inflammasome, and HMGB1 pathways, suggesting curcumin (**50**) as an ideal prophylactic therapeutic for COVID-19 (Thimmulappa et al. 2021). It is worth mentioning that a combination of curcumin and bromelain, a cysteine protease obtained from the pineapple stem, showed immunomodulatory effects leading to interference in the vital steps of SARS-CoV-2 pathophysiology. As mentioned before, these nutraceuticals potentially reduced the secretion of pro-inflammatory mediators and inhibited the transcription factors. Based on in silico studies, both bromelain and curcumin prevented SARS-CoV-2 entry into the cells, while curcumin also inhibited viral replication (Kritis et al. 2020).

3.4.10 Nigella sativa *L.*

Black cumin (*Nigella sativa* L.; Ranunculaceae family) is another immunoenhancer herbal medicine traditionally consumed for asthma, cough, bronchitis, chest congestion, acute headache, fever, back pain, dizziness, and inflammation worldwide. Pharmacologically and experimentally, black cumin (the seeds of *N. sativa*) has

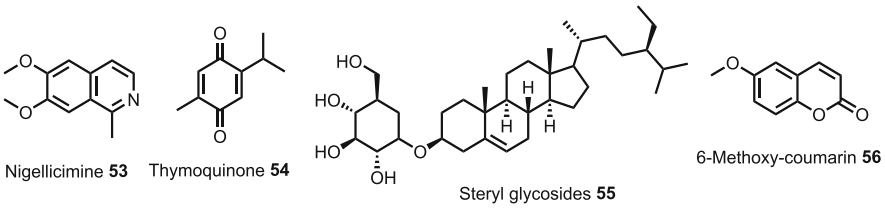


Fig. 3.11 Some bioactive phytochemicals, **53**–**56**, reported from *Nigella sativa* L.

shown various biological properties, such as antibacterial, antioxidant, anti-inflammatory, immunomodulatory, antidiabetic, anti-tumor, hepatoprotective, analgesic, gastroprotective, bronchodilator, and antihypertensive effects. *N. sativa* contains various phytochemicals such as alkaloids (i.e., nigellicimine **53**), terpenoids (i.e., thymoquinone **54**), saponins (i.e., steryl glycosides **55**), coumarins (i.e., 6-methoxy-coumarin **56**) (Fig. 3.11), flavonoids, and phenolic acids (Ahmad et al. 2021). One of the best attitudes of *N. sative* is an immunomodulatory activity through recruiting T helper cells and NK cells. As well as improving the function of NK cells, *N. sative* proteins significantly increased the levels of T cells (i.e., CD4 and CD8) (Haq et al. 1999). According to a clinical trial on 48 healthy young volunteers, the effects of three doses of 0.5, 1.0, and 2.0 g capsule-containing *N. sativa* powder on the body's immunity and general health were in favor of the group who received a 1.0 g dose. The total increase of lymphocyte, CD^{3+}, and CD^{4+} counts was observed in 1.0 g administration showing the plant's immunopotentiation ability by enhancement of T helper cells (Salem et al. 2021). In another research on allergic asthma induced in the murine model, the *N. sativa* fixed oil reduced the production of inflammatory cells (i.e., IL-2, IL-10, and IL-12), IFN-γ, IgG1, and IgG2a (Abbas et al. 2005). Despite the before-mentioned potential properties, *N. sativa* also exhibits antiviral activity and prevents getting ARDS, the principal cause of SARS-CoV-2 mortality. Therefore, *N. sativa* possessing anti-inflammatory and immunomodulatory could be an adjuvant medicinal plant for patients suffering from SARS-CoV-2 infection. (Islam et al. 2021). Considering several clinical trials, inventions, and patent literature, Imran et al. reported that *N. sativa*, *N. sativa* oil, and its phytochemicals have all potency to prevent, manage, and treat COVID-19 infection among high-risk patients (Imran et al. 2022). According to the computational studies, among *N. sativa* secondary metabolites, only α-hederin, nigelledine, hederagenin, thymohydroquinone, and thymoquinone, are potential SARS-CoV-2 inhibitors, which might inhibit SARS-CoV-2 replication (Koshak and Koshak 2020).

3.4.11 Tinospora cordifolia *(Willd.) Miers*

Several Himalayan herbal medicines are showing high anti-COVID-19 activity, for example, *Tinospora cordifolia* (Willd.) Miers (Menispermaceae family). *T. cordifolia* is a native and well-recognized medicinal plant in India and Nepal and is used for hay fever, motility, diabetes, high cholesterol, stomach upset, gout, and itchy skin infections caused by mites (scabies) (Choudhary et al. 2013). The plant contains alkaloids (i.e., tetrahydropalmatine **57**), phenyl propanoide glycosides (i.e., cordifolioside A **58**), terpenoids (i.e., tinocordiside **59**, tinosponone **60**, and cordiofolioside B **61**) (Fig. 3.12), polysaccharides, and steroids, which are responsible for the immunomodulatory activity, thereby demonstrating the diverse biological/pharmacological properties of the plant (Yates et al. 2022). In recent years, the significant immune booster properties of *T. cordifolia* have been well documented through fighting the acute and chronic inflammation and inducing autoimmune-like hepatitis or unmasking an underlying autoimmune chronic liver disease (Nagral et al. 2021). Currently, millions of people in the Himalayan region (Nepal, India, and Bhutan) are using the decoction of *T. cordifolia* for COVID-19 treatment; however, not sufficient scientific reports have been found to support its use (Singh et al. 2021). In a clinical study, an Ayurvedic herbal formulation containing *T. cordifolia* and *Piper longum* was added to the standard of care protocol, and the results were compared with the standard protocol. As a

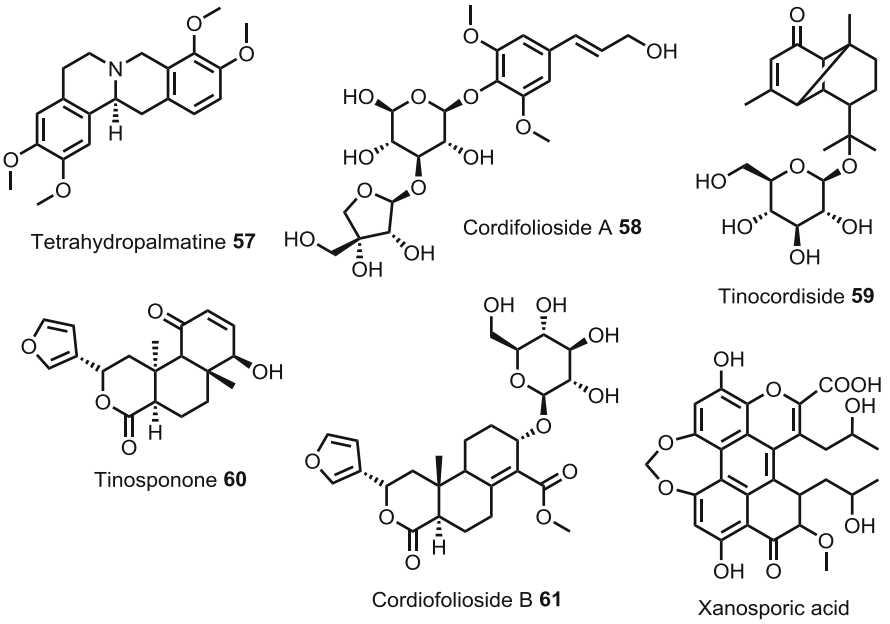


Fig. 3.12 Some bioactive phytochemicals, **57**–**61**, reported from *Tinospora cordifolia* (Willd.) Miers

consequence, the time of recovery and hospital stay decreased. In post-discharge patients, the general feeling was improved by the Ayurveda add-on formulation even 3 months later (Kataria et al. 2022). Using the humanized Zebrafish model, a reliable in vivo system to evaluate viral pathologies, the inhibition of SARS-CoV-2 activity was studied by a tri-herbal medicine, Coronil, composed of *T. cordifolia* (Willd.) Miers, *Withania somnifora* (L.) Dunal, and *Ocimum sanctum* L. Besides inhibition of SARS-CoV-2 spike protein by Coronil, the secretion of pro-inflammatory cytokines (i.e., IL-6, IL-1β, and TNF-α) was attenuated, and the activity of TNF-α stimulated NF-κB/AP-1 transcription was reduced, at human equivalent doses of 12 and 58 μg/kg. Ultra-high-performance liquid chromatography (UHPLC) analysis revealed rosmarinic acid, betulinic acid, ursolic acid, withanoside IV-V, withaferine A, withanone, cordifolioside A, mangoflorine, and palmatine, as the major phytoconstituents in Coronil, which are responsible for immunomodulatory properties (Balkrishna et al. 2020).

There are several computational studies on *T. cordifolia* and its bioactive compounds. According to a molecular docking study, Balkkrishna et al. concluded that tinocordiside (**59**) interrupts the electrostatic bonds between host ACE2 and the virus spike protein receptor-binding domain (RBD). As a consequence, tinocordiside attenuates or blocks the entry of SARS-CoV-2 into the host cells (Balkrishna et al. 2021). Among 11 phytoconstituents of *T. cordifolia*, only tinosponone (**60**), cordiofolioside B (**61**), xanosporic acid (Fig. 3.12), tembetarine, and berberine showed significant docking scores when they studied in silico against SARS-CoV-2 $3CL^{pro}$ complex. Further docking study along with ADMET (Adsorption, Desorption, Metabolism, Excretion, and Toxicity) evaluation revealed that tinosponone (**60**) was the best SARS-CoV-2 $3CL^{pro}$ inhibitor (the highest binding affinity of −7.7 kcal/mol) (Krupanidhi et al. 2021). In another molecular dynamics (MD) simulation study, Shree et al. analyzed the anti-SARS-CoV-2 M^{pro} activity of 28 *T. cordifolia*-derived phytoconstituents. Computational results revealed that tinocordiside has a binding energy of −8.1 Kcal/mol, indicating that it could block the SARS-CoV-2 M^{pro}. (Shree et al. 2022). Furthermore, from 31 phytochemicals reported from *T. cordifolia*, only amritoside recorded good docking scores to SARS-CoV-2 M^{pro}, calculated by three different methods, including high throughput screening, standard precision, and blind docking using Autodock Vina (−5.63, −7.61, and − 7.2 Kcal/mol, respectively). ADMET, Drug-likeness, and prediction of bioactivity score of amritoside validated its ability to be a candidate for COVID-19 M^{pro} inhibitor (Murugesan et al. 2021).

3.5 Phenolic and Polyphenol Compounds against SARS-CoV

3.5.1 Flavonoids and Flavonoid Glycosides

Flavonoids (C_6-C_3-C_6) are placed in the group of phenolic compounds, which are responsible for the yellow color in plants, and are well-known for their antioxidant activity. Indeed, flavonoids are classified into the following subclasses: flavanones, flavonols, flavanols, flavones, isoflavones, chalcones, anthocyanins, and auranes that could be found in high abundance in food resources and fruits. Besides antioxidant activity, these compounds are in charge of efficient anti-inflammatory, immunomodulatory, antibacterial, anti-viral, and anticancer properties. Most significantly, flavonoids can inhibit the SARS-CoV-2 activity by attaching to the spike protein and consequently interfere with the ACE2 receptors and blockage of entry into the host cells. This phenomenon has been approved using several computational studies and bioinformatics surveys indicating quercetin, quercitrin, luteolin, kaempferol, naringenin, fisetin, theaflavin, and epigallocatechin-3-gallate (EGCG) are some potential SARS-CoV-2 inhibitors (Liskova et al. 2021). The importance of natural flavonoids and flavonoid glycosides in to fight against SARS-CoV has been reviewed and discussed in different mechanisms of action. Quercetin (**6**), naringin (**7**), rhoifolin (**11**), hesperidin (**12**), neohesperidin (**13**), hesperetin (**15**) (Fig. 3.3), luteolin (**31**) (Fig. 3.6), kaempferol (**46**) (Fig. 3.9), baicalein (**62**), scutellarin (**63**), myricetin (**64**), scutellarein (**65**), naringenin (**66**), nobiletin (**67**), herbacetin (**68**), morin (**69**), pectolinarin (**70**), and quercetin-3-*O*-β-D-galactoside (**71**) (Fig. 3.13) are some of the potential flavonoids that are appropriate for drug discovery and development of HCoV-229E inhibitors (Hafez Ghoran et al. 2021a). Generally, flavonoids modulate the inflammation caused by COVID-19 and increase immune responses. These compounds bring about overexpression of pro-inflammatory mediators, systematic immune response attenuation, and consequently, reduction of hyper-inflammation in COVID-19 patients (Roshanravan et al. 2020). An animal model on obese mice showed that apigenin (**72**) (Fig. 3.13) significantly ameliorated the plasma levels of IL-6, TNF-α, and IFN-γ (Jung et al. 2016). In addition, flavonoids such as hesperetin (**15**) (Fig. 3.3) and chrysin (**73**) (Fig. 3.13) regulate the function of immune cells not only by increasing the concentrations of T helper lymphocytic cells and NK cells but also by improving macrophage functions through nitric oxide release and modulation of liposomal activity (Sassi et al. 2017). In another research, the beneficial effects of *Citrus* flavonoids like hesperidin (**12**) (Fig. 3.3) were highlighted against SARS-CoV-2 activity because of their antioxidant, anti-inflammatory, and antiviral abilities (Bellavite and Donzelli 2020). In an animal model of mice co-treated with LPS, Compound **12** could also target anti-inflammatory responses leading to IL-33 and TNF-α reduction (Al-Rikabi et al. 2020). As discussed, significant affinity to suppress pro-inflammatory cytokines production during COVID-19 is achieved by flavonoid treatment. In silico studies recorded a high binding score to the helicase, ACE2 protease sites, and the

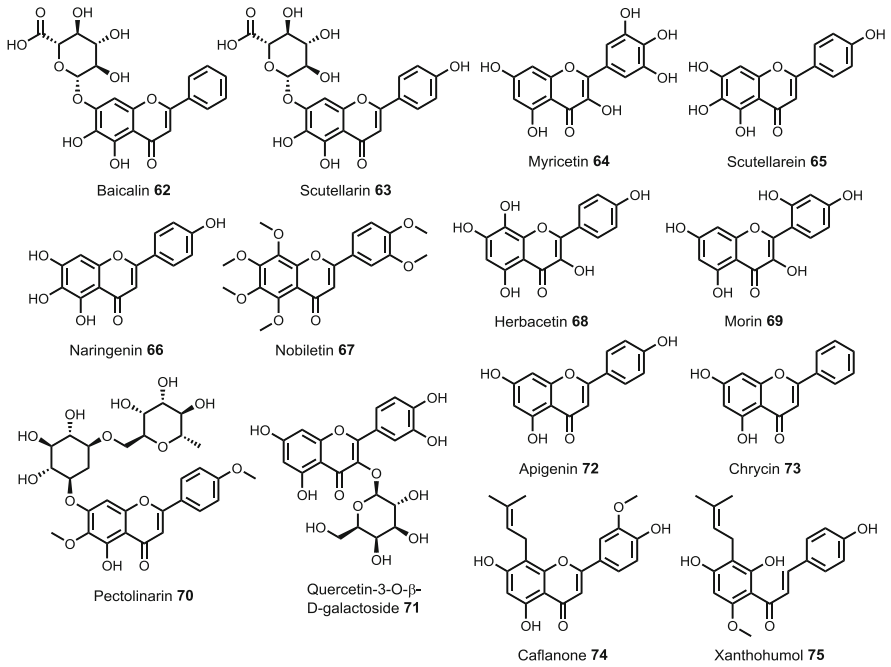


Fig. 3.13 Some bioactive flavonoids and flavonoid glycoside metabolites, **62**–**75**, against SARS-CoV-2 infection

spike protein. In this respect, caflanone (**74**) (Fig. 3.13) effectively repressed the cytokines secretion, including IL-6, IL-8, IL-1β, TNF-α, and macrophage inflammatory protein-1α (MIP-1α) (Ngwa et al. 2020). It is worth mentioning that some active flavonoids approved in traditional Chines medicine (TCM), i.e., naringenin, kaempferol, quercetin, baicalein, luteolin, and wogonin, can manage the COVID-19 process through anti-inflammatory and immunomodulatory properties, regulation of pro-inflammatory markers, blocking viral adsorption, and inhibition of viral replication, resulting in protection of the targeted organs. Using network pharmacology for the characterization of potential phytomolecules and regulate the IL-6, detected at all stages of COVID-19 infection, even the time of dying, this ability does not restrict to quercetin **6**, rutin **8** (Fig. 3.3), and luteolin **31** (Fig. 3.6); however, other flavonoids can prevent and rehabilitate the immune system in COVID-19 patients (Niu et al. 2021). The same behavior was found in those TCM formulas consisting of quercetin, which causes ACE2 downregulation in COVID-19 patients (Niu et al. 2020). Flavonoids potentially target ACE2-associated pathways in COVID-19. Through COVID-19 infection, AngII converts to Ang1–7 resulting in AngII inflammatory function. Pro-inflammatory responses are happened by increasing AngII production and angiotensin II receptor type 1 (AT1R) activation. AngII and AT1R activate NF-κB and MAPK signaling pathways, leading to IL-1, IL-6, IL-1β, and TNF-α overproduction. Indeed, in COVID-19 patients, increased AngII levels in

circulatory and plasma and further lung damage have been detected (Mahmudpour et al. 2020). In one animal model on hypertensive rats, the AngII levels were alleviated by hesperidin treatment (Wunpathe et al. 2018), and in the same way, kaempferol inhibited the inflammation and oxidative stress in cardiac fibroblast cells through the reduction of AngII-stimulated collagen accumulation (Du et al. 2019). In in vivo study on rats, Choucry et al. reported the extract of *Crateva nurvala* Buch. Hamm, which is rich in flavonoids, stimulates Nrf2 and reduces the secretion of pro-inflammatory mediators (i.e., IL-6, TNF-α, and NF-κB) (Choucry et al. 2018). The same behavior was observed by the flavonoid content of *Apios Americana* Medikus, decreasing the secretion of inflammatory cytokines and activating the Nrf2-KEAP1 pathway in LPS-induced macrophage cells (Chu et al. 2019). Interestingly, by in vitro and in vivo models, the effects of xanthohumol (**75**) (Fig. 3.13), belonging to the subgroup of flavonoids, viz. chalcone class, against oxidative stress and inflammatory damage were evaluated. Compound **75** significantly ameliorated LPS-stimulated acute lung injury through AMPK/GSK3β-Nrf2 signaling pathway (Lv et al. 2017). Considering the valuable anti-SARS-CoV-2 points of flavonoids into account, these naturally occurring compounds, i.e., EGCG, luteolin, nobiletin, apigenin, scutellarin, myricetin, and baicalin, could also modulate other SARS-CoV-2-associated pathways, including activation of NLRP3 inflammasome, Nrf2, TLRs, and bromodomain-containing protein 4 (BRD4) (Liskova et al. 2021).

3.5.2 Other Phenolic Compounds

Ma et al. investigated the molecular mechanism of aloin (**76**) (Fig. 3.14), also known as barbaloin; the active anthraquinone glycoside found in *Aloe vera* juice, on LPS-induced inflammatory response. The level of LPS-induced iNOS expression was reduced by aloin treatment, and IL-6, IL-1β, TNF-α, and NO production was decreased dose-dependently. Meanwhile, aloin (**76**) not only suppressed LPS-induced JAL1-ATAT1/3 activation and STAT1/3 nuclear translocation but also inhibited LPS-induced ROS production. Indeed, aloin (**76**) modulated LPS-stimulated inflammation by blocking ROS-mediate activation in the JAK1-ATAT1/3 signaling pathway, thereby blocking the nuclear translocation of STAT1/M (Ma et al. 2018). One oral mouth rinse containing some bioactive compounds, such as aloin isoforms A & B, hexetidine, chlorhexidine, triclosan, methyl salicylate, menthol, eucalyptol, sodium fluoride, and povidone, was in vitro studied to inhibit the main enzymes in SARS-CoV-2 (i.e., PL^{pro} and $3CL^{pro}$). Interestingly, aloin isoforms A & B selectively showed inhibitory activity against PL^{pro} proteolytic activity with IC_{50} values of 13.16 and 16.08 μM, respectively. A molecular docking study represented a hydrogen bond between Tyr268 and aloin isoforms, acting as a curtail factor for their PL^{pro} proteolytic activity. On the other hand, with the aid of molecular dynamic studies, both aloin isoforms were found to inhibit the activity of PL^{pro} deubiquitination (Lewis et al. 2022).

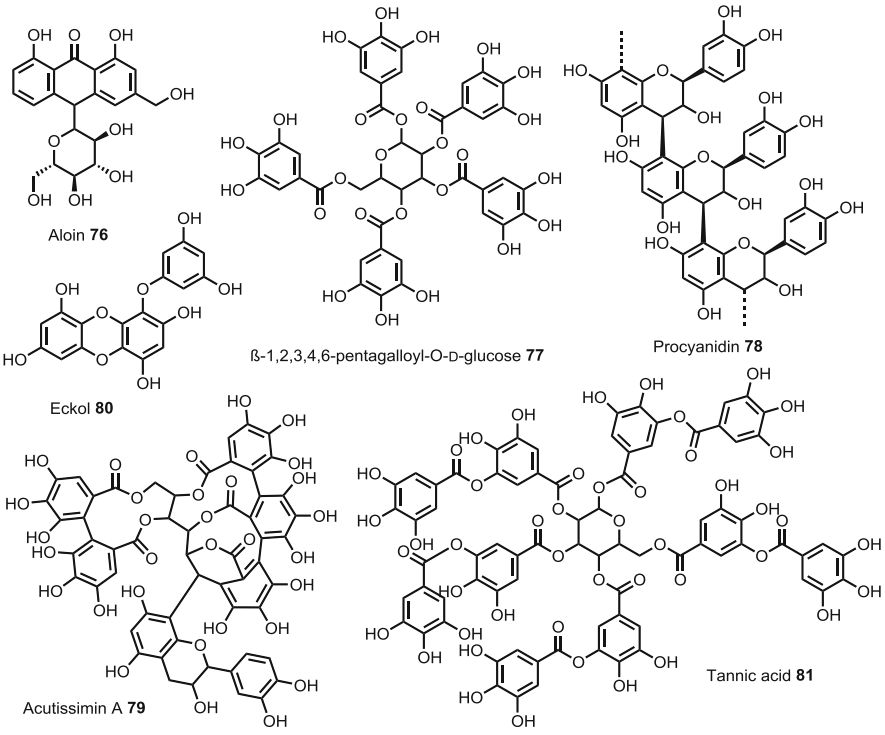


Fig. 3.14 Some bioactive phenolic compounds, **76**–**81**, against SARS-CoV-2 infection

Another group of phenolic compounds is tannins, which are classified into various subclasses, such as hydrolysable tannins (i.e., β-1,2,3,4,6-pentagalloyl-*O*-D-glucose **77**), condensed tannins (i.e., procyanidin **78**), complex tannins (i.e., acutissimin A **79**), and phlorotannins (i.e., eckol **80**) (Fig. 3.14), representing potential antioxidant, antiviral, antimicrobial, anti-inflammatory, and anticancer activities. These compounds are found in fruits, seeds, wood, the bark of trees, various type of wild plants, and even in brown algae. The use of tannins in the leather industry dates back centuries ago, and in traditional medicine, they attenuate infections and diseases. Other applications of high tannin-containing plants in folk medicine refer to anti-diabetic, wound healing, cardiovascular protection, and anti-diarrhea properties (Pizzi 2021). A high abundance of inflammatory mediators and reduction of T helper lymphocytic cells (i.e. CD4+ and CD8+) have been reported in the serum of acute COVID-19 patients (Tang et al. 2020). Interestingly, using tannins along with other polyphenols has been in clinical trials on COVID-19 patients. For example, combined oral tannins derived from chestnut and quebracho with B12 vitamin decreased the TNF-α and MIP-1α levels in hospitalized COVID-19 patients, resulting in diarrhea and pneumonia symptoms reduction (Pisarevsky et al. 2021). In one animal study, the tannins from persimmon (scientific name: *Diospyros virginiana*) were pre-administrated by oral gavage to the Syrian hamsters.

Results showed that the plant extract reduced the severity of infection, SARS-CoV-2 transmission, and pneumonia and decreased the inflammation caused by IL-6, TNF-α, and IFN-γ overproduction (Furukawa et al. 2021). Many scientific studies have reported that tannic acid (**81**) (Fig. 3.14) can potentially inhibit SARS-CoV-2 M^{pro}/$3CL^{pro}$ (IC_{50} range = 1 μM - 13.4 mM) and transmembrane protease serine 2 (TMPRSS2; IC_{50} range = 2.31 μM - 50.0 μM), a vital protease located at cell surface related to the viral entry regulated by its linking to the ACE2. SARS-CoV-2 M^{pro}/$3CL^{pro}$ were also inhibited, besides the combination of tannic acid with polyphenols, with other tannin compounds, such as punicalagin and dimeric proanthocyanidins (Wang et al. 2022). Systematic inflammation in COVID-19 patients is correlated with gut dysbiosis, which is antibiotic-independent. Milano et al., in their randomized placebo-controlled trial on 124 patients, administrated oral tannin to survey the symptoms of COVID-19, cytokine response, and gut dysbiosis. Interestingly, having been treated with an oral tannin-based supplement, the systematic inflammation was decreased; however, the results were not clinically efficient. Moreover, MIP-1α was significantly inhibited with tannin supplementation where it correlated negatively with Bifid bacterium abundance; on the other hand, it positively correlated with IL-1β and TNF-α release (Molino et al. 2022).

3.6 Synergic Activity of Phenolic-Derived Phytochemicals

An array of experimental studies underlines the effectiveness of combination therapy of natural products to represent the synergic ability against the concerned health disorder. According to the study of Zhao et al. on high fat-stimulated inflammation in rats, combined quercetin with resveratrol treatments at doses of 240 and 120 mg/kg/day, respectively, considerably modulate the levels of IL-6 and TNF-α and the circulating inflammatory marker, such as MCP-1, (Zhao et al. 2017).

As discussed in Sect. 3.4.9, curcumin has efficient anti-SARS-CoV-2 activities by inhibiting infection pathways. In terms of enhancement of bioavailability and efficiency, different kinds of curcumin-loaded nanocarriers were developed and investigated. For instance, a curcumin nanosystem (Sinacurcumin®, a soft gel capsule type composed of 40 mg curcuminoids in nanomicelles) was evaluated not for antiviral activity but for suppression of inflammation in COVID-19 patients. Sinacurcumin® potentially attenuates the release of inflammatory markers, resulting in better condition and refreshment in patients with COVID-19 (Valizadeh et al. 2020). To this respect, Dourado et al. suggested two approaches for inhibition of SARS-CoV-2 activity by curcumin, including (**a**) the bioavailability enhancement leads to antiviral activity through delivery by nanoparticles and (**b**) the synergic behavior of curcumin and nanoparticles themselves increase a dual mechanism of action (Dourado et al. 2021). Another interesting phenolic compound is quercetin showing high potency in immunomodulatory, antioxidant, anti-inflammatory, and antiviral activities. Many scientific reports have highlighted the anti-viral properties of quercetin in synergism with zinc, vitamins C, D, and E, as well as other

polyphenol compounds. Therefore, the synergistic behavior of quercetin could validate its efficiency of being an anti-SARS-CoV-2 drug because of well-documented data on prevention, mitigation, and therapy against COVID-19 (Mani et al. 2020). In another study, the *Houttuynia cordata* Thunb. ethyl acetate extract consisting of quercetin, quercitrin, and rutin was in vitro evaluated against dengue virus (DENV-2) and murine coronavirus infection. The plant extract showed anti-coronavirus activity (IC_{50} = 0.98 mg/mL) and inhibited the dengue virus (IC_{50} = 7.50 mg/mL). Quercetin alone inhibited both viruses, while quercetrin only inhibited DENV-2, and rutin did not exhibit any virucidal activities. Interestingly, the combination of quercetin with quercetrin increased the anti-DENV-2 activity. Further in vivo assessment showed that the plant extract had no chronic oral toxicity when the C57BL/6 mice were fed in doses >2000 mg/kg, and histologically, the main organs remained normal (Chiow et al. 2016). As previously discussed, ACE2 and TMPRSS2 are related to the viral entry to the host cells. The higher the TMPRSS2 expression in cells, the more vulnerable to coronavirus. Therefore, by either inhibition or downregulation of TMPRSS2 activity in human cells, it is expected to be a kind of therapeutic approach toward SARS-CoV-2 infection. On this occasion, kaempferol, belonging to flavonol compounds, inactivated the transcription of TMPRSS2 at about 49.14% and 79.48% at concentrations of 5 and 15 mM, respectively. Moreover, expression of TMPRSS2 was significantly reduced when the enzyme was treated with the standardized flavonoids' complex consisting of luteolin, quercetin, and kaempferol showing considerable synergic activity in lower concentrations (Fuzimoto and Isidoro 2020). Most recently, combined resveratrol and pterostilbene showed inhibitory activity toward the replication of the influenza virus and SARS-CoV-2 infection. De Angelis et al. examined A5+ products consisting of polyphenols, other micronutrients, and polydatin, a resveratrol glycoside found in grape juices, against both viral infections. Compared with the polydatin treatment alone, A5+ not only demonstrated a better efficiency in inhibiting both viruses but also considerably reduced the viral proteins expression and virus release showing the possibility of blocking the replication of the virus process. Moreover, in influenza virus-infected cells, A5+ treatment potently decreased the IL-6 production, which is proposed to be a promising anti-inflammatory agent during the infection. Hence, the synergic activity in the A5+ mixture enhances the antiviral activity rather than individual compounds (De Angelis et al. 2021).

3.7 Conclusions

- Ethnopharmacology and medicinal plants can be effective and adjuvant in halting SARS-CoV-2 replication.
- Traditional medicine potentially offers some benefits: reduction of inflammation, enhancement of innate immunity of the body, and improving the health condition of post-hospitalized patients.

- *Glycyrrhiza* sp., *Citrus* sp., *Hypericum* sp., *Salvia* sp., *Mentha* sp., *Allium* sp., *Zingiber* sp., *Syzygium* sp., *Curcuma* sp., *Nigella* sp., and *Tinospora* sp., are some examples of medicinal plants used in folk medicine worldwide to prevent ARDS and treat COVID-19 infection.
- In COVID-19, the increased cytokine storm and circulatory and lung inflammatory markers were observed. Therefore, attenuating these detrimental factors by plant-derived phytochemicals could be promising agents in SARS-CoV-2 therapy.
- In SARS-CoV-2 infection, ethnopharmacology and medicinal plants are recruited to attenuate ROS/oxidative stress and consequently reduce pro-inflammatory cytokines and chemokines.
- Chronic virus infections promote ROS production through leukocytes, monocytes, and macrophages, along with antioxidant depletion and viral replication.
- Phenolic compounds like flavonoids and flavonoid glycosides derived from medicinal plants show anti-inflammatory and immunomodulatory abilities through blocking NF-κB activation and suppression of IL-6, IL-1β, and TNF-α secretion.
- Preclinical studies showed that antioxidants suppress the activation of the NLPR3 inflammasome and scavenge ROS.
- The synergistic activity of phenolic compounds provides promising sights for the treatment of SARS-CoV-2 infection.
- Hypothetically, the effects of natural compounds and plant immunoenhancers on SARS-CoV-2 infection require corroboration in further preclinical, epidemiological, and clinical studies.

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Chapter 4
Herbal Formulations in Fighting Against the SARS-CoV-2 Infection

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Abbreviations

ACE2	Angiotensin-converting enzyme 2
Bp	Base pair
E	Envelope
ER	Endoplasmic reticulum
$HSYF^{pro}$	Hanshiyi Formula
IFN-β	interferon- beta
JGF	Jing Guan Fang
KK	Kabasura kudineer
Kbp	kilo base pair
M^{pro}	Main protease
M	Membrane

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N	Nucleocapsid
PL^{pro}	Papain-like protease
RBD	Receptor binding domain
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
S	Spike
TCM	Traditional Chinese medicine
TMPRSS2	Transmembrane serine protease 2
TXYF	Tongxie Yaofang
WHO	World Health Organization

4.1 Introduction

Herbs are culinary-based plants that are been used to flavor foods and also used as medicines for a long time. These plants are found to have preventative properties against diseases such as diabetes, different heart disorders, and cancer. These plants are rich in antioxidant components. Medicines are derived from these herbs and are used for primary health care in developing countries and are used with the general belief that these drugs are without any side effects, cheap, and easily available (Pal and Shukla 2003; Nargis Begum et al. 2009; Vijayakumar et al. 2015). These are called formulations that are the extracted solution from plants. These formulations are prepared from one or more processed herbs in a particular specific quantity that contains the entire beneficial component for diagnosing and treating the disorders in humans and animals. These herbal formulas can be prepared by extraction, distillation, expression, fractionation, purification, fermentation, and powder formation and are obtained from both fresh and dried plants, fungi, lichens, and algae are involved in forming these formulations (Manikandan and Anand 2016; Vijayakumar et al. 2019; Abubakar and Haque 2020).

These herbal formulations are used as traditional medicines that are used for alleviating various ailments. Traditional medicine is the therapeutic practice of physicians using indigenous medicine. According to World Health Organization (WHO), traditional medicine consists of therapeutic practices that are existing before the development of modern medicines and are still in use to this date (Pal and Shukla 2003; Vijaya Anand et al. 2020). Herbs are been used in traditional medicines for a long time in different regions of the world, their use in the prevention of different diseases and disorders and their treatment, and their valuable pharmaceutical properties have attracted the attention of the world. The WHO has launched a WHO Traditional Medicine Strategy 2014–2023, for corroborating medicinal plant use in management and healthcare services. Using the medicinal plant as an alternative treatment for diseases and maintaining health is an expanding trend (Govindharajan et al. 2020; Teh et al. 2021).

Traditional medicines are been practiced in regions such as China, India, Japan, Korea, and other parts of Asia and also in countries belonging to Africa and Europe.

Indian traditional medicine Ayurveda is the oldest traditional medicinal practice in the world (Arumugam et al. 2020; Saravana Prabha et al. 2020; Anand et al. 2021; Kuchi Bhotla et al. 2021a, b; Chandra Manivannan et al. 2022). It is the ancient Vedic knowledge of healing science that is still been practiced. Ayurveda is known as the "Mother of all healing" and the philosophy behind Ayurveda is preventing unwanted suffering and living a long and healthy life. The history of this traditional medicine can be traced back to the pre-Vedic periods between 4000 BC and 1500 BC. In Ayurveda there are two types of herbal formulation one is purely herbal preparation or Kasthoushadhies and the other is herbiomineral metallic preparation also known as Rasaushadhies. The formulation in Ayurveda is based on two principles using a single drug or using more than one which is also known as polyherbal formulation (Parasuraman et al. 2014).

There are different ways of preparation of herbal formulas and ways of their administration. The herbal formulas are prepared in the form of decoctions, powders, pills, alcohols, and tinctures. A decoction is the dominant form of herbal formula preparation (Dharmananda 1997). It is the common form of administering herbal medicine and is taken orally. It is used for acute conditions; can also be used as a herbal bath for the affected region or the whole body (Yang 2010). It is mainly prepared from the hard parts of the herbs such as roots, bark, and seeds, by heating the required quantity of herbs in water for about 30 minutes (Nagalingam 2017). A dried decoction is another form of herbal preparation, it was first developed in Japan by drying the liquid in the decoction to form a syrup form (Nafiu et al. 2017). Powders and pills are other forms for the preparation of crude herbs, prepared by drying the plants to a sufficient state when they can be crushed to fine particles. This form of herbal formulation can have advantages over liquid formulations.

The powdered herbs are mixed with binder components like honey or malt syrup which is formed into tables or pills which upon ingestion directly can be dissolved to the power form in the stomach (Dharmananda 1997). Tinctures are prepared by soaking different parts of the herbal plants such as leaves, berries, bark, and roots in solvents like alcohol or vinegar. These are concentrated extracts of the herbs. The tinctures can be prepared from fresh plant parts, drying causes a change in their chemistry and may lose their efficiency (Fougère and Wynn 2007). These preparations are an ideal form of use as medicine because of their longer shelf-life and also their mixing is easy (Wynn and Fougère 2007).

4.2 SARS-CoV-2

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was identified by WHO as a pandemic on 11 March 2020. It was first identified in the respiratory tract of a patient with pneumonia in Wuhan, Hubei, China. It is an enveloped positive non-segmented RNA virus that belongs to the genus of β-coronavirus which is the variant of previously identified SARS-CoV and MERS-CoV that caused the pulmonary failure

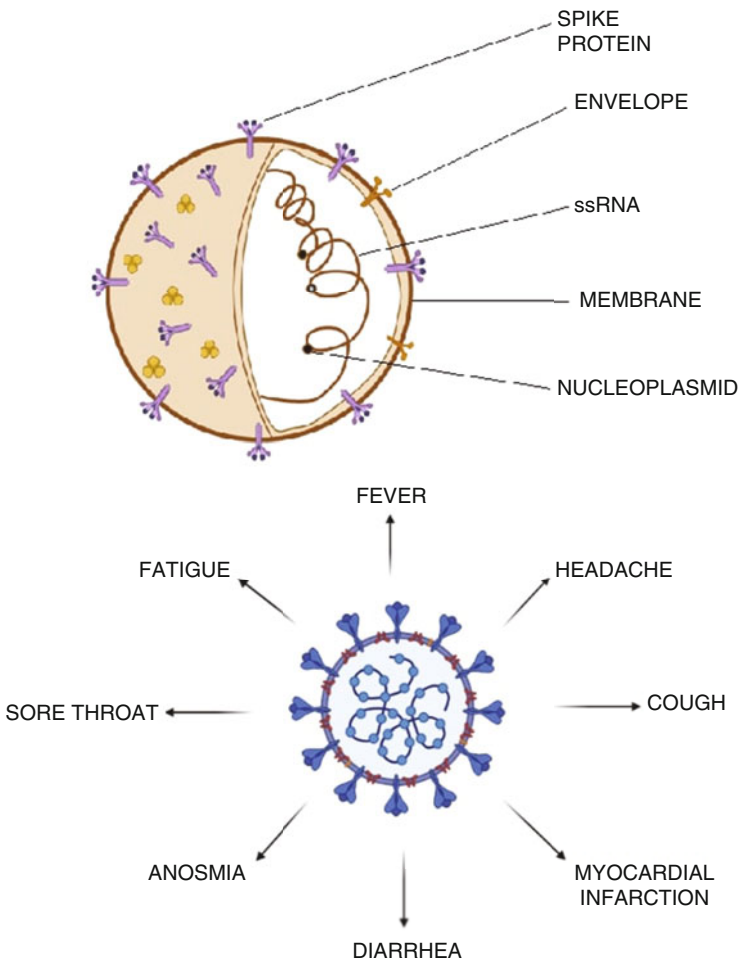

Fig. 4.1 SARS-CoV-2 and different symptoms caused by infection due to COVID-19

and infection in the respiratory tract (Astuti 2020). This virus is a member of the order Nidovariles of the family Coronaviridae.

The total genome content of this virus is 29,891 base pairs (bp) approximately 30 kilobase pairs (kbp) with a GC content of 38%. This virus has four structural proteins spike protein (S), membrane (M), envelope (E), and nucleocapsid (N) (Fig. 4.1) (Dhama et al. 2020). It has 16 nonstructural and 5–8 accessory proteins along with the structural proteins. This virus enters the host cells through the respiratory epithelium where the angiotensin-converting enzyme 2 (ACE2) receptors are expressed. The viral spike protein attaches with the host protein transmembrane serine protease 2 (TMPRSS2) which facilitates the virus entry and also a replication of the viral genome (Cascella et al. 2022). The cause of the severity of these diseases

is divided into three mild, severe, and critical. The manifestation of COVID-19 is fever (Fig. 4.1) and dry cough which are the mild symptoms along with pneumonia which is the common cold symptom (Shanmugam et al. 2020; Kuchi Bhotla et al. 2020; Kuchi Bhotla et al. 2021a, b; Pushparaj et al. 2022; Meyyazhagan et al. 2022).

Other than respiratory complications, other complications such as myocardial injury (Fig. 4.1), arrhythmia, and neurological complications such as myalgia, hypogeusia, hyposmia, and stroke are reported in some cases along with digestive symptoms and liver injury. In critical cases, patients progress to ARDS septic shock and coagulation dysfunction which finally lead to multiple organ failure and death (Wang et al. 2020; Alimohamadi et al. 2021). SARS-CoV-2 attacks the mucus-producing goblet cells and ciliated cells as indicated by the topology of expression of host entry factors by tropism studies in both ex vivo and in vitro, other than this endothelial cells are also found to be susceptible to this virus, the binding of the S protein with the host cells relies on the protease enzymes in the host cells (Pizzato et al. 2022).

4.3 SARS-CoV-2 Proteins

4.3.1 Spike Protein (S)

S protein is one of the important viral proteins, found in different variations in the different variants of the coronavirus mainly in the sequence of the protein and differences in domains of the protein. This protein has two domains S1 and S2, S1 domain binds to the receptors, which are composed of two sub-domain an N-terminal domain and the C-terminal sub-domain or also known as the receptor binding domain (RBD). The S1 domain of the S protein is found to be less preserved between SARS-CoV and SARS-CoV-2, but the S2 fusion domain preserved nearly 90% of the sequence between the two variants (Hatmal et al. 2020). The S protein of SARS-CoV-2 is about 1273 amino acids long but in the SARS-CoV, the protein total length is about 1255, both the domains of this protein fold and are related to having specific functions. This protein is highly glycosylated at the N glycosylation sites, in some sites O- glycosylation is also found in this protein of SARS-CoV-2 (Xia 2021). The S proteins bind to ACE2, a cellular receptor which after the formation of the complex translocated into the cellular endosomes, where this protein is cleaved by cathepsin L also called endosomal acid proteases to activate the activity of fusion of this protein (Du et al. 2009). The SARS-CoV-2, S protein forms a loop that is rich in Arginine residues and is exposed but this loop is not found in SARS-CoV and other related coronavirus variants such as MERS-CoV, OC43, and HKU1 (Hoffmann et al. 2020). Mutation at the N501Y position in the RBD of the S protein exhibited a stronger association rate of the protein with ACE2 receptors also the association was faster but the dissociation compared to the association was slower, which caused a higher rate of transmission of this SARS-CoV-2 variant (Tian et al. 2021).

4.3.2 Membrane Protein (M)

M protein is one of the main structural proteins of SARS-CoV-2. It binds to the other structural protein; binding of this protein will stabilize the binding of the other structural protein to RNA. This M protein incorporates the S proteins which affect the attachment of the host cells with the virus and also its entry (Thomas 2020). The interaction of the M protein with the S protein retains it in the endoplasmic reticulum (ER)-Golgi intermediate compartment, which also stabilizes the structure of the M protein. It has a role in B-cell response and has higher immunogenicity for T-cell response, than other nonstructural proteins (Alharbi and Alrefaei 2021). It is the most abundant structural protein and is a mushroom-shaped dimer, consisting of two transmembrane domain-swapped three-helix bundles and two intravirion domains, it further forms assembles of oligomers and is similar to the ion channel ORF3a in the SARS-CoV-2 (Zhang et al. 2022). M protein can suppress the expression of interferon-beta (IFN-β) and other interferon-stimulated genes that are induced by the genes such as RIG-I, MDA4, IKK ϵ, and TBK1 and also to inhibits the dimerization of TBK1 and phosphorylation of IRF3 (Sui et al. 2021).

4.3.3 Nucleocapsid (N) Protein

The N protein is an important structural protein antigen of SARS-CoV-2. It has roles in the packaging of the RNA molecule and also has a role in releasing the viral particles. It enters along with the viral RNA and facilitates the replication of RNA and the processing of the assembly of the viral particles (Zeng et al. 2020). The viral genome is encapsulated in the N protein and thereby protects the viral genome from the host intracellular environment. It is produced high in the infected cells and also enhances the transcription of RNA and is one of the essential factors for the replication of the viral genome (Savastano et al. 2020).

The N protein of SARS-CoV is homologous to the nucleocapsid of SARS-CoV-2, it was found to spatiotemporally regulate the localization of the protein and also its function, and in further bioinformatic analysis it was found that this protein can regulate the condensation of protein with the RNA or key proteins in the host in vivo (Cascarina and Ross 2020). The C-terminal of this protein is minimally homologous to that of the protein of the human coronavirus and is highly immunogenic (Dobaño et al. 2021). In the HEK293T and Calu-3 cells the N protein is found to interact with 160 cellular proteins, these proteins have roles in ribosome biogenesis, RNA-associated processes, ribonucleoprotein complex biogenesis, ribosomal large and small subunit biogenesis, RNA binding, and catalyze the translation and process of transcription (Zheng et al. 2020).

4.3.4 Envelope (E) Protein

The E protein is one of the less studied proteins among all the structural proteins in SARS-CoV-2. A higher amino acid variation at positions 55, 56, and 69, altered the binding of the E protein with the PALS1 protein which is a tight junction-associated protein that may have a role in the pathogenesis of COVID-19 (Rahman et al. 2021). This protein is an integral membrane protein and has a role in coronavirus maturation, assembly, and virulence it has a PDZ binding motif in its C terminus (Toto et al. 2020). This protein affects the assembly of the virus and budding, it is pentamer viroprotein, which is responsible for the transfer of ion particles in the direction from the lumen to the cytosol. Palmitoylation of this pentamer E protein has a great role in its stability, as the palmitoyl group is lost the porin size is reduced and may collapse too (Sun et al. 2021). The E protein produced by the wild-type SARS-CoV-2 can be translocated inside the cellular organelles like the ER-Golgi intermediate, in which the pH in the organelle increases the expression of this protein (Cabrera-Garcia et al. 2021).

4.3.5 Main Protease (M^{pro})

Main protease (M^{pro}) also known as $3CL^{pro}$ is encoded by the Nsp5 gene and is one of the important proteins in the SARS-CoV-2 variant and is found to have a role in gene expression and replication in coronavirus (Bzówka et al. 2020). The viral replication is carried out by two proteins ppa and ppab. These two proteins are synthesized as an overlapping polyprotein by the replicase gene of the SARS-CoV-2 variant, M^{pro} processes this polyprotein into two functional polypeptides by proteolytically cleaving the overlapping protein (Singh and Mishra 2021). It cleaves the polypeptides after the glutamine residue which is a unique character of a protease as no other proteases in humans has the same cleavage specificity as this protease enzyme. The active site of this protein is composed of four sites S1, S1, S2, and S4 (Qiao et al. 2021). This protein is considered one of the targeted candidates for drug discovery and is one of the best-studied targets. SARS-CoV-2 variant, M^{pro} has some similarities with the betacoronavirus SARS-CoV and MERS-CoV which too caused serious epidemics (Sheik Amamuddy et al. 2020).

4.3.6 Papain-Like Protease (PL^{pro})

Papain-like protease (PL^{pro}) protein is an important coronavirus enzyme that is required for the processing of the polyproteins into a functional complex of replicase and also enables its spread (Shin et al. 2020). This protein is secreted by the gene Nsp3, this protease enzyme cleaves the Nsp1, Nsp2, and Nsp3 (Klemm et al. 2020).

It is basic and is about 315 amino acid residue long polypeptide and has high cysteine residues in its peptide sequence. It is one of a target of SARS-CoV-2 as it plays role in the maturation of different viral proteins and also it induces the assembly of the replicase and the transcriptase enzyme and disrupts the host immune response (Osipiuk et al. 2021). Human coronavirus codes for two PL^{pro} proteins, PLP1 and PLP2 by NL63, OCA4, HKU1, and 229E, whereas the SARS-CoV-2 genome is the same as that of MERS-CoV and SARS-CoV as the codes for a single PL^{pro}, but their enzymatic activity differs. It has a less efficient deubiquitinase enzyme but its deISGylase activity is more efficient (Freitas et al. 2020).

4.4 Herbal Formulation Effects On SARS-CoV-2 Infection

Herbal medicines are been used for curing disease for a long time. Both novel and old formulations effects are been studied for the symptoms in the infections caused by SARS-CoV-2. Hanshiyi Formula (HSYF) (Table 4.1; Fig. 4.2) a Chinese traditional medicinal formula was found to prevent the progression of infection from the mild or moderate to severe form of COVID-19 in the patients. The different plant components in this formulation are found to have antiviral activity and are also able to improve respiratory problems (Tian et al. 2020). Ayurvedic polyherbal formulation Kabasura kudineer (KK) (Fig. 4.2) is found to be effective against symptoms such as fever, cough, sore throat, and shortness of breath which are similar to the symptoms caused by SARS-CoV-2 infection (Table 4.1). This polyherbal formulation is composed of 15 herbs that are *Andrographis paniculata*, *Syzygium aromaticum*, *Zingiber officinale*, *Tragia involuerta*, *Hygrophila auriculata*, *Terminaila chebula*, *Ahatoda vasica*, *Coleus ambonicus*, *Saussurea lappa*, *Clerodendrum serratum*, *Cypreus rotundus*, *Tinospora cordifolia*, *Sida acuta*, *Piper longum*, and *Anacyclus pyrethrum*.

$3CL^{pro}$ or M^{Pro} is one of the target proteins in SARS-CoV-2, 145 components of this formulation were chosen for molecular docking analysis against this targeted protein. The compounds that were found to be effective against the targeted proteins were acetoside, luteolin-7-rutinoside, rutin, chebulagic acid, syrigaresinol, acanthoside, violanthin, andrographidine C, myricetin, gingerenone-A, geraniol, nootkatone, asarianin, and sitosterol which were found to inhibit the M^{pro} protein (Vincent et al. 2020). LCTE or Qing Fei Pai Du Tang a Chinese herbal formulation consisting of 20 herbal ingredients along with one mineral component are found to be effective in treating COVID-19 by alleviating inflammation (Table 4.1). Components present in this soup is found to have inhibiting potential against SARS-CoV-2 and the protein that are responsible for the prevalence of COVID-19 symptoms and also affect the key pathological process (Zhang et al. 2020).

Ayurvedic polyherbal formulations Pathyadi kwath (Table 4.1), Sanjeevani vati, Yastimadhu, Tribhuvan keeratiras, and Septillin are found to be more effective and can be potential treatments as anti-COVID-19 than formulations such as Samshamni vati, AYUSH-64 (Table 4.1; Fig. 4.2), and Trikatu (Table 4.1) in in silico studies

Table 4.1 Composition of herbal formula

Herbal formulation	Plants	Effects	Reference
Amalakyadiganakwatha bhavita churna	*Tinospora cardifolia*, *Zingiber officinale*, *Cyprus rotundus*, *Andrographis paniculata*, *Cissampelos pariera*	Antipyretic effect	Ping et al. (2022)
Ayush kwath	*Ocimum tenuiflorum*, *Cinnamomum verum*, *Zingiber officinale*, *Piper nigrum*	Antiviral	Sulaiman et al. (2020)
AYUSH-64	*Alstonia scholaris*, *Picrorhiza kurroa*, *Swertia chirayita*	Antiviral, anti-asthmatic, immune boosting	Joshi et al. (2022)
Coronil	*Withania somnifera*, *Tinospora cordifolia*, *Ocimum sanctum*	Mitigate the cytokine response in SARS-CoV-2 infection	Balkrishna et al. (2021a, b)
Enterica decoction	*Spondias mombin*, *Persea americana*, *Psidium guajava*, *Trema orientalis*, *Cnestis ferruginea*, *Momordica charantia*, *Vernonia amygdalina*, *Latana carnara*, *Paullinia pinnata*, *Citrus aurantifolia*, *Morinda lucida*, *Bidens pilosa*	Typhoid fever	Kumadoh et al. (2015)
Gojihwadi Kwath	*Onosma bracteatum*, *Glycyrrhiza glabra*, *Anethum sowa*, *Vitis vinifera*, *Ficus hispida*, *Zizyphus jujube*, *Adhatoda vasica*, *Hyssopus officinalis*, *Cordia dichotoma*, *Sisymbrium irio*, *Cymbopogan martini*, *Viola odorata*, *Linum usitatissimum*, *Althaea officinalis*, *Solanum xanthcarpum*, *Piper nigrum*	Antiviral activity	Agrawal et al. (2022)
Hanshiyi formula (HSYF)	*Ephedrae herba*, *Gypsum fibrosum*, *Armeniacae semen*, *Rhizoma et Radix notopterygii*, *Cyrtomii rhizoma*, *Cynanchi paniculati*, *Pogostemonis herba*, *Eupatorii herba*, *Atractylodis rhizoma*, *Atractylodis macrocephalae*, *Crataegi fructus*, *Massa medicate*, *Fructus germinatus*, *Magnoliae officinalis*, *Arecae semen*, *Tsaoko fructus*, *Zingiberis rhizoma*	The antiviral effect improves asthma and respiratory symptoms	Tian et al. (2020)
Honitus	*Ocimum sanctum*, *Glycyrrhiza glabra*, *Viola odorata*,	Management of cough	Gupta et al. (2016)

(continued)

Table 4.1 (continued)

Herbal formulation	Plants	Effects	Reference
	Zingiber officinale, *Adhatoda vasica*, *Piper longum*		
Huangqi Jianzhong tang	*Radix paeoniae*, *Rhizoma zingiberis*, *Saccharum granorum*, *Fructus zizyphi*, *Radix glycyrrhixae*, *Cortex cinnamomi*, *Radix astragali*	Anti-fatigue	Bao et al. (2020)
JACOM	*Justicia adathoda*, *Carica papaya*, *Andrographis paniculata*, *Ocimum tenuiflorum*, *Melia azedarach*	Can be an inhibitor of COVID-19 infection	Kiran et al. (2020)
Jing guan fang (JGF)	*Forsythia suspensa*, *Scutellaria baicalensis*, *Bupleurum Chinese*, *Magnolia officinalis*, *Agastache rugose*	Reduces infection in COVID-19 and also reduces proliferation	Lau et al. (2005)
Kabasura kudineer (KK)	*Andrographis paniculata*, *Syzygium aromaticum*, *Zingiber officinale*, *Tragia involuerta*, *Hygrophila auriculata*, *Terminaila chebula*, *Ahatoda vasica*, *Coleus ambonicus*, *Saussurea lappa*, *Clerodendrum serratum*, *Cypreus rotundus*, *Tinospora cordifolia*, *Sida acuta*, *Piper longum*, and *Anacyclus pyrethrum*	Fever, cough, sore throat, shortness of breath	Vincent et al. (2020)
LCTE or Qing Fei Pai Du Tang	*Rhizoma atractylodis macrocephalae*, *Rhizoma pinelliae*, *Radix bupleuri*, *Pericarpium citri reticulatae*, *Farfarae flos poria*, *Radix glycyrrhizae*, *Cinnamomi ramulus*, *Radix scutellariae*, *Pogostemon cablin* *Herba ephedrae*, *Rhizoma dioscoreae* *Rhizoma belamcandae*, *Rhizoma zingiberis recens*, *Herba asari*, *Semen armeniacae amarum*, *Rhizoma alismatis*, *Fructus aurantii immaturus*, *Polyporus umbellatus*, *Radix asteria*, *Rudis gypsi miscueris*	Anti-inflammatory	Zhang et al. (2020)
LHQW	*Forsythiae fructus*, *Lonicerae japonicae flos*, *Ephedrae herba*, *Armeniacae semen amarum*, *Gypsum fibrosum*,	Antypiretic and anti-toxic effects	Zheng et al. (2020)

(continued)

Table 4.1 (continued)

Herbal formulation	Plants	Effects	Reference
	Isatidis radix, *Dryopteridis crassirhizomatis rhizoma*, *Houttuyniae herba*, *Pogostemonis herba*, *Rhei radix et rhizoma*, *Rhodiolae crenulatae radix*, *menthol*, *Glycyrrhizae radix*		
NRICM101	*Scutellaria baicalensis*, *Houttuynia cordata*, *Morus alba*, *Saposhnikovia divaricata*, *Trichosanthes kirilowii*, *Isatis indigotica*, *Glycyrrhiza glabra*, *Magnolia officinalis*, *Mentha haplocalyx*, *Nepeta tenuifolia*	Antiviral and anti-inflammatory properties	Tsai et al. (2021)
Pathyadi kwath	*Terminalia chebula*, *Terminalia bellirica* *Phyllanthus emblica*, *Azadiracta indica* *Andrographis paniculata*, *Curcuma longa*, *Tinospora cordifolia*	Anti-COVID-19	Joshi et al. (2022)
Qingkailing	*Calculus bovis*, *Cornu bubali*, *Radix scutellariae baicalensis*, *Flos lonicerae*, *Fructus gardeniae*	Reduced fever and also repaired amino acid metabolism	Gao et al. (2013)
Qinghua Zhixie	*Pteris multifida*, *Elsholtzia ciliata*, *Psoralea corylifolia*, *Coptis chinensis*, *Radix Aucklandiae*, *Baked ginger*, *Radix paeoniae alba*, *Radix Saposhnikoviae*, *Rhizoma atractylodis*, *Rhizoma Atractylodis Macrocephalae*, *Agrimonia pilosa*	Alleviate the diarrhea	Ji et al. (2022)
Sang Ju Yin	*Chrysanthemum morifolium*, *Forsythia suspensa*, *Glycyrrhiza uralensis*, *Semen Armeniacae amarum*, *Prunus armeniac*, *Platycodon grandiflorus*, *Phragmites australis*, *Mentha canadensis*	Common cold	Lau et al. (2005)
Sanjeevani vati	*Embelia ribes*, *Zingiber officinale*, *Piper longum*, *Terminalia chebula*, *Terminalia bellirica*, *Emblica officinalis*, *Acorus calamus* *Tinospora cordifolia*,	Anti-COVID-19	Joshi et al. (2022)

(continued)

Table 4.1 (continued)

Herbal formulation	Plants	Effects	Reference
	Semecarpus anacardium, *Aconitum ferox*, Cow's urine		
Samshamni vati	*Tinospora cordifolia*	Anti-inflammatory and antipyretic properties	Joshi et al. (2022)
Shenling Baizhu San	*Panax ginseng*, *Poria cocos*, *Atractylodes macrocephala*, *Glycyrrhiza uralensis*, *Dolichos lablab*, *Dioscorea opposita*, *Nelumbo nucifera*, *Platycodon grandifloras*, *Amomum villosum*, *Coix lacryma-jobi*	Control chronic diarrhea	Wang et al. (2022)
Si Junzi	*Panax ginseng*, *Wolfiporia extensa*, *Atractylodes macrocephala*, *Glycyrrhiza uralensis*	Gastrointestinal problems	Yan et al. (2022)
Tao-Hong-Si-Wu-tang	*Rehmannia glutinosa*, *Paeonia lactiflora*, *Angelica sinensis*, *Ligusticum chuanxiong*, *Prunus persica*, *Carthamus tinctorius*	Anti-fatigue effect	Li et al. (2012)
Tongxie Yaofang (TXYF)	*Atractylodes macrocephala*, *Paeonia lactiflora*, *Citrus aurantium*, *Radix saposhnikoviae*	Irritable Bowel Syndrome-Disease	Liang et al. (2022)
Trikatu	*Piper nigrum*, *Piper longum*, *Zingiber officinale*	Antimicrobial and analgesic properties	Joshi et al. (2022)
Vipro™	*Ocimum basilicum*, *Curcuma longa*, *Citrus lemon*, *Allium sativum*, *Plectranthus amboinicus*, *Momordica charantia*, *Cinnamomum verum*, *Zingiber officinale*, *Piper nigrum*	Alleviates clinical symptoms of COVID-19	Arunkumar et al. (2021)
Vrihatsamaharker churna	*Syzygium aromaticum*, *Myristica fragrans*, *Piper longum*, *Zingiber officinale*, *Piper nigrum*	Treatment for treating nonproductive cough	Vats et al. (2022)
Yu Ping Feng San	*Astragalus mongholicus*, *Atractyloes macrocephala*, *Saposhnikovia divaricata*	Prevents influenza-like symptoms	Lau et al. (2005)

(Joshi et al. 2022). Ayurvedic bhasma preparation is nanoparticles prepared from metals such as gold, silver, copper, zinc, and iron oxide, these compounds can modulate the levels of interleukins, interferons, and TNF-α levels in plasma, also known as swarna bhasma, rajata bhasma, tamra bhasma, and yashada bhasma could

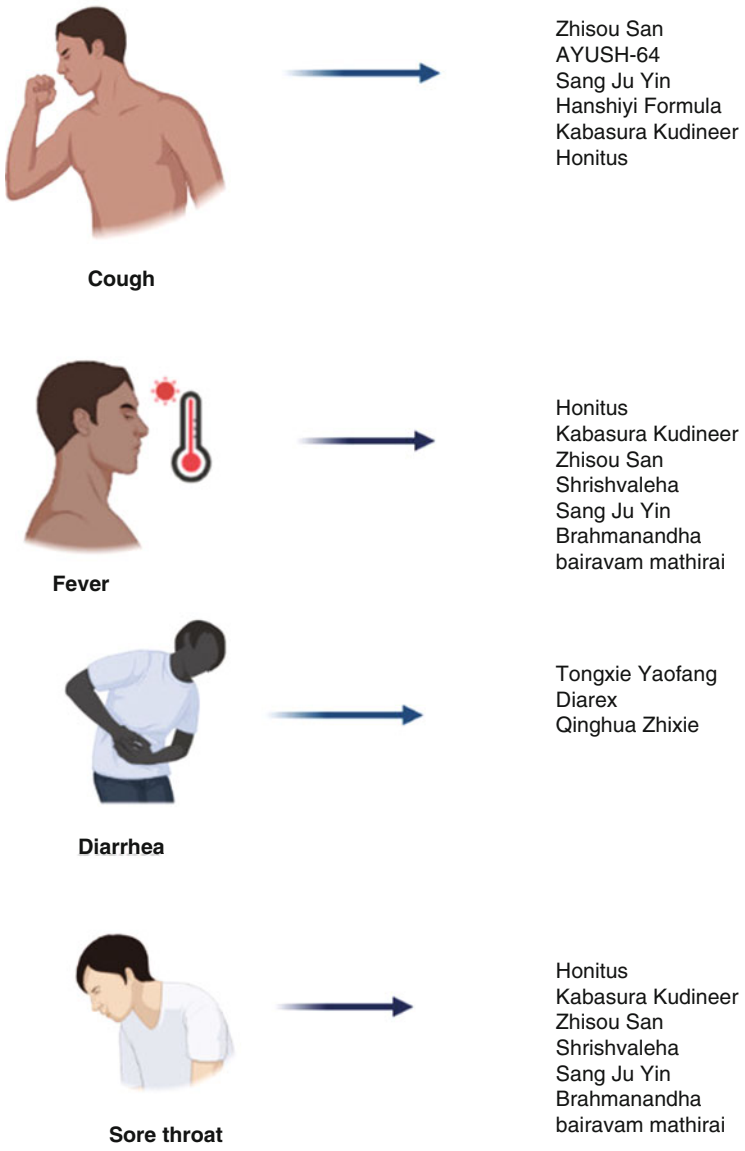

Fig. 4.2 Different herbal formulation effects on COVID-19 symptoms cough, fever, diarrhea, and sore throat

be a possible treatment against infections caused by SARS-CoV-2 due to their activities that include immunomodulatory, anti-inflammatory, antiviral (Sarkar and Das Mukhopadhyay 2021). JGF (Table 4.1) also known as Jing Guan Fang a Chinese herbal formula is found to reduce the symptoms caused by COVID-19, it

mechanistically induces the ACE2 degradation depending on the lysosomal process and suppresses both the mRNA and protein levels of TMPRSS2 in the human lung cell line of WI-38 and MRC-5, in in vivo study in mice this formula found to reduce the levels of both the proteins and also helped in the improvement of the symptoms caused in the disease on inhalation by the mice (Ping et al. 2022).

Withania somnifera a medicinal plant used in many herbal formulas, Withanone is one of the phytochemical compounds of this herb, by docking analysis it was found to bind with the complex of ACE2-RBD and also found to decrease the electrostatic component of binding free energy of the complex, which interrupts the interaction and weakens its infectivity, thus blocking its entry into the host cells (Balkrishna et al. 2021a, b). Persian herbal decoction and capsule treatment in 184 adults patients improved and decreased the clinical symptoms of COVID-19 like dry cough, dyspnea, muscle pain, headache, fatigue, anorexia, chills, runny nose sputum cough (Karimi et al. 2021). *Ayush kwath* (Table 4.1), an Ayurvedic herbal medicine prepared from specified parts of different medicinal plants contains many active components that show immunomodulatory, anti-inflammatory, and antioxidant properties that can be used to manage symptoms of COVID-19 (Sulaiman et al. 2020).

4.5 Herbal Formulation Effects on Different Symptoms of COVID-19

4.5.1 Fever

Fever is the most preserved evolutionary response over 600 years to infections in animals; it is the most common symptom in patients suffering from COVID-19 (Fig. 4.1). A high fever during COVID-19 is an indication of severe infection (Gul et al. 2021). Enterica decoction (Table 4.1) composed of plant materials belonging to 12 tropical plants was found to improve typhoid fever (Kumadoh et al. 2015). Chinese traditional medicine Qingkailing (Table 4.1) herbal formula composed of eight herbs has good antipyretic effects. Rat model-induced pyrexia by yeast treated with qingkailing injection reduced fever and also repaired amino acid metabolism (Gao et al. 2013). Brahmanandha bairavam mathirai (Table 4.1; Fig. 4.2) a Siddha formulation is found to be more effective against viral fever caused by infection of chikungunya virus than the polyherbal formulation Vishnu chakram by in vitro study (Jain et al. 2018). Amalakyadiganakwatha bhavita churna (Table 4.1) is a herbal formulation consisting of *Tinospora cardifolia*, *Zingiber officinale*, *Cyprus rotundus*, *Andrographis paniculata*, and *Cissampelos pariera* an antipyretic formulation can be therapeutically safe for the treatment of fever (Unnikrishnan and Nishteswar 2015). Two herbal formulas Sang Ju Yin (Table 4.1; Fig. 4.2) and Yu Ping Feng Sam (Table 4.1) consisting of traditional Chinese medicine were combined forming a polyherbal decoction, which was found to have good potential in

preventing influenza-like symptoms and also found to effective in preventing the spread of disease caused by SARS (Lau et al. 2005). AYUSH-64 (Table 4.1; Fig. 4.2) a polyherbal formula was used for recovering from influenza-like symptoms, and is safe to use and can be used for different viral infections along with fever. It was practiced since 1980 for inflammation and in 1994 and 1996, this formulation was used in the malaria epidemic, thus it has some anti-malarial characteristics too (Gundeti et al. 2022).

4.5.2 Cough

Cough is a common symptom of SARS-CoV-2 infection (Fig. 4.1) and other respiratory diseases caused by microbes. Ethanolic extract of *Terminalia chebula* fruit, *Mentha piperita* leaves, *Adhatoda vasica* leaves, *Ocimum sanctum* leaves, *Zingiber officinale* rhizome, *Piper longum* fruit, *Glycyrrhiza glabra* roots, and *Withenia somnifera* roots formulated in a form of syrup are found to have an antitussive effect against cough, induced in the guinea pig by citric acid (Meher 2012). A polyherbomineral formulation prepared in the lab was found to be an effective antitussive effect against a sulfur dioxide-induced cough in albino mice, it was found to contain a major piperine active constituent which induces the cough suppressant effect of the components in the formulation (Reena et al. 2014). Traditional Chinese medicine prepared from nine commonly used medicinal plants was found to improve cough scores and also improve dysphonia (Wong et al. 2006). Shrishavaleha (Fig. 4.2) prepared from bark and heartwood of *Albizzia lebbeck* is evaluated for antitussive activity, this formulation was found to alleviate the sulfur dioxide-induced cough in the mice model (Singh et al. 2010). Honitus (Table 4.1; Fig. 4.2) a honey-based cough syrup comprised of herbs such as *Ocimim sanctum*, *Glycyrrhiza glabra*, *Viola odorata*, *Zingiber officinale*, *Adhatoda vasica*, and *Piper longum* are reported to reduce the acute nonproductive cough symptoms and throat irritation (Gupta et al. 2016). Extracts from the seeds of hedge mustard used for herbal cough syrup formulation are found to have an antimicrobial effect against bacterial strains such as *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* spp., *Pseudomonas aeruginosa*, *and Bascillus subtillis* in studies (Sharma et al. 2020). A polyherbal formulation in a syrup base prepared by five namely plants is found to be effective against cough and prevent bronchial tract mucus secretion (Sharma et al. 2022). The herbal formula Zhisou San (Table 4.1; Fig. 4.2) is a potential drug for the treatment of cough variant asthma, the multiple components of this formulation targets inflammation associated with cough variant asthma and Th17/Treg immune balance. It was also found to affect lung function in in vivo studies in mice (Guo et al. 2022). Vrihatsamaharker churna (Table 4.1) is a polyherbal formulation prepared from plant parts like flower buds of *Syzygium aromaticum*, seeds of *Myristica fragrans*, the fruit of *Piper longum*, rhizome of *Zingiber officinale*, and fruit of *Piper nigrum* is used for the treatment for treating nonproductive cough (Vats et al. 2022).

4.5.3 Diarrhea

Diarrhea is one of the preliminary symptoms that develop in COVID-19 infection (Fig. 4.1) along with fever and cough (Fig. 4.1). Along with diarrhea other gastrointestinal symptoms that may appear in COVID-19 infection are nausea, poor appetite, pain in the abdomen, and vomiting. Chinese herbal formula Shenling Baizhu Sanis (Table 4.1) is used for treating chronic diarrhea, and the affected group treated with this formula has recovered (Wang et al. 2022). Diarrhea caused by irritable bowel movements reduces the quality of life of the patient suffering from it. It also affects the mental health of the sufferers and their daily activities are affected too. A Chinese herbal formula Tongxie Yaofang (TXYF) (Table 4.1; Fig. 4.2) consisting of plants *Atractylodes macrocephala*, *Paeonia lactiflora*, *Citrus aurantium*, and *Radix saposhnikoviae* administered to patients suffering from Irritable Bowel Syndrome-Disease, showed safe and effective therapeutic results in people who have another diagnosis like liver depression and spleen deficiency (Liang et al. 2022).

DIAREX a herbomineral Ayurvedic tablet is tested in children and resulted in a decrease in acute diarrhea symptoms (Verma et al. 2022). Chinese herbal decoction Qinghua Zhixie (Table 4.1) is been used for the treatment of diarrhea for a long time, it consists of some active components such as berberine, psoralenoside, quercitin, ehydrocostuslactone, and paeoniflorinv which reduced the 5-hydroxytryptamine and vasoactive intestinal polypeptide and thus alleviate diarrhea. It also balances intestine flora, regulates the brain-gut peptide and also improved intestinal digestion and absorption (Ji et al. 2022). Chinese decoction based on Pulsatilla and Si Junzi (Table 4.1) decoction improved the inflammation caused by diarrhea by inhibiting the signal pathway of PI3K/Akt/NF-κB in a mouse model-induced with diarrhea and the expression of the cytokines IL-1, IL-2, and IL-6 are decreased with increase in anti-inflammatory cytokine the IL-10 (Yan et al. 2022).

4.5.4 Sore Throat

One of the common manifestations of COVID-19 is sore throat (Fig. 4.1), SARS-CoV-2 mainly causes infection in the lower respiratory section but upper respiratory symptoms are also found in a patient infected by this virus (El-Anwar et al. 2020). Sore throats are been improved by plying herbal medicines. Ertong Qingyan Jiere Koufuye, Fufang Shuanghua Koufuye, Yanhouling mixture, and Qinganlan Liyan Hanpian are found to be effective against chronic and acute pharyngitis caused by inflammation due to sore throat (Shi et al. 2007). Lozenges a sweet hard candy containing an active ingredient used for the treatment of sore throat formulated with traditional herbs such as *Adhatoda vasica*, *Althaea officinalis*, *Glycyrrhiza glabra*, and *Trachyspermum ammi* that contain components that has the ability to treat throat infections (Kadirvel et al. 2022). Herbs such as *Adhatoda vasica*, *Adhatoda*

officinalis, *Cordia latifolia*, *Origanum vulgare*, *Thymus vulgaris*, and *Ziziphus jujube* used in the traditional herbal formulation are found to exhibit antimicrobial activity due to their alkaloid and flavonoids content present in these plants (Mehreen et al. 2016). The extract of the roots of *Pelargonium sidoides* EPs 7630 is found to reduce the symptoms of sore throat and hoarseness (Kamin et al. 2022). The novel polyherbal formulation Vipro™ (Table 4.1) developed from traditional medicinal herbs, treatment of the patient COVID-19 suffering from symptoms such as sore throat, throat pain fever, and cough was able to alleviate the symptoms which are as similar to treatment with the standard drugs (Arunkumar et al. 2021).

4.5.5 Effect on Other Symptoms

Many symptoms are found in patients suffering from infections caused by COVID-19. Fever, cough, diarrhea, and sore throat are the primary symptoms other than these, symptoms such as headache, fatigue, anosmia, myocardial injury (Fig. 4.1), and others were also found in certain cases. A Chinese herbal formulation Tao-Hong-Si-Wu-Tang (Table 4.1), administered to 32 male mice were found to have an anti-physical fatigue effect and also decrease the blood lactic acid and blood urea nitrogen (Li et al. 2012). Herbal tea formulations of *Astragalus mongholicus*, *Angelica gigas*, and *Ziziphus jijuba* reduce severe fatigue in adults (Baek et al. 2018). AG formulation prepared from two herbs *Antrodia camphorate* and *Panax ginseng* is a potent formulation with an anti-fatigue effect (Hsiao et al. 2018). Japanese herbal formula, Kampo can be one of the altered medications in treating headaches, but its efficiency of improvement from that of NSAID is not quite different (Katsuki et al. 2022). Mono herbal preparation of *Sambucus nigra* berry can reduce the symptoms in COVID-19 patients such as fever, headache, nasal congestion, and mucus discharge (Harnett et al. 2020). A Chinese herbal formula Huangqi Jianzhong Tang (Table 4.1) can improve the function of the cardiac system in a rat model by regulating the signaling pathway of apoptosis (Bao et al. 2020). Persian herbal formulation in the form of decoction and capsules on treatment in 174 adult patients improved dyspnea along with other symptoms of muscle pain, headache, anorexia, chills, runny nose sputum cough, and vertigo (Karimi et al. 2021).

4.6 Herbal Formulations Targeting SARS-CoV-2 Proteins

4.6.1 Effects on Spike Protein

S protein is one of the important structural proteins of SARS-Cov-2, it binds with the host ACE2 transmembrane protein on infection to enter host cells. It is one of the main drug targets in COVID-19 infection. Coronil, a tri herbal formulation

consisting of herbs *Withania somnifera*, *Tinospora cordifolia*, and *Ocimum sanctum*, is found to effectively inhibit the interaction between ACE2 and wild-type S protein in SARS-CoV-2 induced zebrafish and also inhibited the interaction between the S protein variant S^{D614G} and S^{W436R} which have a higher affinity toward ACE2. A549 cells induced by different variants of S protein, this formulation were able to reduce the levels of IL-6, IL-1β, and TNF-α (Balkrishna et al. 2021a, b). JACOM a novel herbal formulation and the Siddha formulation KK are chosen for in silico computation study against the S glycoprotein.

The phytocomponents chrysoeriol, and luteolin (Table 4.2) of KK (Fig. 4.2) and quercetin (Table 4.2) of JACOM are found to have a high binding affinity with S protein and are found to be free from cytotoxicity and by pharmacokinetic analysis, this compound is found to be absorbable in the gastrointestinal cavity and can be highly allocated to other tissues (Kiran et al. 2020). Atractylenoline III (Table 4.2) from *Atractylodes lancea* used in the traditional medicine of Thai Chinese and Japanese has a strong binding toward the ACE2 with the ASN at 149 positions, it has high inhibitory activity. This compound has anti-inflammatory properties and potential therapeutic properties against respiratory infection and inflammation induced by viral infection (Sun et al. 2020). On pharmacological assay of the Chinese herbal formula NRICM101 (Table 4.1) was found to inhibit the S protein, it was also found to inhibit the activity of M^{pro}, also inhibit the formation of viral plaques and interleukin-6 and TNF-α (Tsai et al. 2021). Epigallocatechin gallate, Curcumin, Apigenin, and Chrysophanol phytochemicals contained in different herbal formulations are found to have a binding affinity with S glycoprotein among them Epigallacatechin has the highest inhibitory effect against this glycoprotein (Subbaiyan et al. 2020).

4.6.2 Effects on the Main Protease

M^{pro} is one of the drug targets in SARS-CoV-2. The components of the Triphala Ayurvedic formulation were investigated in in silico studies against the M^{pro} protein. The components terflavin A, chebulinic acid, and corilagin (Table 4.2) from the formulation are found to inhibit this protein (Rudrapal et al. 2022). Aswagandha (*Withania somnifera*), Giloy (*Tinospora cordifolia*), and Tulsi (*Ocimim sanctum*) are used in the herbal formulation of traditional medicines. Six phytochemicals from these plants are found to be good inhibitors of M^{pro} protein in molecular docking analysis these compounds are derived from Aswagandha, ithanosisde V, and Somniferine (Table 4.2), from Giloy Tinocordiside and Tulsi Vicenin, Isorientin 4′-*O*-glucoside 2″-*O*-p-hydroxybenzoate, and Ursolic acid (Table 4.2) (Shree et al. 2022). Glabridin, Catechin, and Fisetin (Table 4.2) are phytoconstituents and have a tendency to bind with the SARS-CoV-2 protein M^{pro} by hydrophobic and hydrogen bond, this interaction leads to inhibition of this viral protease (Jamali et al. 2022). In autodoc analysis, it was found that Akuammicine N-oxide (Table 4.2), one of a components found in the AYUSH-64 formulation, has a higher affinity toward M^{pro},

Table 4.2 Phytoconstituents in the herbal formula effective against viral and host protein

Phytoconstituents	SARS-CoV-2 proteins	Reference
Chrysoeriol	S protein	Kiran et al. (2020)
Luteolin	S protein	Kiran et al. (2020)
Quercetin	S protein	Kiran et al. (2020)
Atractylenoline III	S protein	Sun et al. (2020)
Epigallacatechin gallate	S protein	Subbaiyan et al. (2020)
Curcumin	S protein	Subbaiyan et al. (2020)
Apigenin	S protein	Subbaiyan et al. (2020)
Chrysophanol	S protein	Subbaiyan et al. (2020)
Terflavin A	M^{pro}	Rudrapal et al. (2022)
Corilagin	M^{pro}	Rudrapal et al. (2022)
Withanosisde V	M^{pro}	Shree et al. (2022)
Somniferine	M^{pro}	Shree et al. (2022)
Tinocordiside	M^{pro}	Shree et al. (2022)
Vicenin	M^{pro}	Shree et al. (2022)
Isorientin 4'-O-glucoside 2"-O-p-hydroxybenzoate	M^{pro}	Shree et al. (2022)
Ursolic acid	M^{pro}	Shree et al. (2022)
Glabridin	M^{pro}	Jamali et al. (2022)
Catechin	M^{pro}	Jamali et al. (2022)
Fisetin	M^{pro}	Jamali et al. (2022)
Akuammicine N-oxide	M^{pro}	Ram et al. (2022)
Amritoside	M^{pro}	Murugesan et al. (2021)
Apigenin-6-C-glucosyl7-O-glucoside	M^{pro}	Murugesan et al. (2021)
Pectolinarin	M^{pro}	Murugesan et al. (2021)
Astragalin	M^{pro}	Murugesan et al. (2021)
Glycyrrhizin	M^{pro}	Choe et al. (2022)
Withaferin A	M^{pro}	Choe et al. (2022)
Curcumin	M^{pro}	Choe et al. (2022)
Nigellidine	M^{pro}	Choe et al. (2022)
Chebulinic acid	M^{pro}	Rudrapal et al. (2022)
Punicalin	M^{pro}	Rakshit et al. (2022)
Cyanidine3-glucoside	M^{pro}	Rakshit et al. (2022)
Quercetin3-O-rhamnoside	M^{pro}	Rakshit et al. (2022)
Pelargonidin3-glucoside	M^{pro}	Rakshit et al. (2022)
Cordifolioside A	M^{pro}	Choe et al. (2022)

(continued)

Table 4.2 (continued)

Phytoconstituents	SARS-CoV-2 proteins	Reference
Apigenin	Nucleocapsid	Husain et al. (2022)
Catechin	Nucleocapsid	Husain et al. (2022)
Apiin	Nucleocapsid	Husain et al. (2022)
Cinnamic acid	Nucleocapsid	Husain et al. (2022)
Fortunellin	Nucleocapsid	Agrawal et al. (2022)
Epicatechin	Membrane protein	Gupta et al. (2022)
Liquiritic acid	Membrane protein	Joshi et al. (2022)
Epicatechin	Papain-like protease	Gupta et al. (2022)
Hesperidin	ACE2	Basu et al. (2020)

it forms H-bonds with the Cysteine residue at 145 positions of the viral protein, Akuammicine N-oxide can be one of a possible candidate for management of the infections in COVID-19 (Ram et al. 2022).

Medicinal plants *Embilica officinalis*, *Phyllanthus niruri*, and *Tinospora cordifolia* are used for forming different herbal formulation, by docking and molecular dynamics study, the bioactive compounds Amritoside, Apigenin-6-C-glucosyl7-*O*-glucoside, Pectolinarin, and Astragalin (Table 4.2) of these plants are found to have better binding affinities with M^{pro} protein and can be promising drug candidate as the inhibitor of this viral protein (Murugesan et al. 2021). Compounds such as Glycyrrhizin, Withaferin A, Curcumin, Nigellidine, and Cordifolioside A (Table 4.2) can inhibit the replication of the coronavirus and have a strong anti-inflammatory effect than the drugs that are been used for curing COVID-19 infections (Choe et al. 2022). Pomegranate peel has various medicinal properties like antimicrobial and anti-malarial and also controls infections in the respiratory system. Compounds contained in the peels such as Pelargonidin3-glucoside, Quercetin3-O-rhamnoside, Cyanidine3-glucoside, and Punicalin (Table 4.2) are found to have a greater affinity to M^{pro} than the Curcumin (Rakshit et al. 2022).

4.6.3 Effects on Nucleocapsid (N), Membrane (M) and Papain-Like Protein (PL^{pro})

N and M proteins are the structural protein of SARS-CoV-2. These two proteins are found to have an important role in the replication of the nuclear material of the virus and also in its assembly and entry into the host cells. Ethanolic extracts prepared from *Cinnamomum zeylanicum*, *Cinnamomum tamala*, *Origanum vulgare*, and *Petroselinum crispum* were tested for their cytotoxic ability by in vitro study. The compounds found in the extracts such as Apigenin, Catechin, Apiin, and Cinnamic acid (Table 4.2) are found to have a stronger binding affinity with the N-terminal C-terminal domain of the N protein than the drug Remdesivir, hence these

compounds can be one of the therapeutic options against COVID-19 infection (Husain et al. 2022). Kadha an Indian Ayurvedic preparation from herbs can control respiratory problems such as cough, flu, and cold. The phytochemicals present in it are found to have anti-inflammatory activities and are found to interact with the RNA binding domain of the N (Maurya and Sharma 2022). Gojihwadi Kwath an Ayurvedic preparation that is used for the treatment of fever, cough, and bronchitis, Fortunellin (Table 4.2) a phytochemical present in this formulation, is shown to have antiviral and immunomodulatory activity in patients of COVID-19. By computational approach, this compound is found to inhibit the virus replication, growth, invasion, and binding of the viral protein with the host cells (Agrawal et al. 2022).

Epicatechin (Table 4.2) is a component extracted from the anupana an Ayurvedic concoction of herbal ingredients. This herbal formula also contains Hesperidin (Table 4.2) and Mangiferin. Epicatechin (Table 4.2) on molecular interaction analysis is found to have better inhibition capability against the membrane protein of SARS-CoV-2 (Gupta et al. 2022). Liquiritic acid (Table 4.2) is one of a component found in herbal formulations, that have an inhibitory effect and by computational method, this compound is found to have a binding affinity of about −15.1 with this structural protein (Joshi et al. 2021). PL^{pro} is an essential coronavirus enzyme required for the processing of the viral polyproteins for their function in replication and other processes Epicatechin (Table 4.2) a secondary metabolite of Anupana formulation is also able to inhibit the PL^{pro}. This component forms an H bond with the Aspartic acid and Asparagine residue at positions 108 and 267 (Gupta et al. 2022).

4.6.4 Effects on TMPRSS2 and ACE2

TMPRSS2 is a cell surface protein in the host cell, VeroE6 and Calu-3 cells induced by SARS-CoV-2 infection resulted in enhancing its expression in infection which causes inefficient entry of the virus into the cells by endocytosis (Iwata-Yoshikawa et al. 2022). On long time treatment with JGF, a Chinese herbal formulation affected the expression of this protein in WI-38 cells and also reduced its mRNA within 24 hrs (Ping et al. 2022). Hesperidin (Table 4.2) is a phytochemical found in both Indian and Chinese traditional medicine. This phytochemical constituent was able to bind noncompetitively with ACE2 and bound the structure of ACE2 and S glycoprotein of SARS-CoV-2. The binding site of Hesperidin (Table 4.2) and S protein on ACE2 is in a different location. Binding of the this phytoconstituent to the ACE2 in a simultaneous bind with the S protein modulates their binding capacity and shows antiviral activity by destabilizing the S glycoprotein that interacts with ACE2 and preventing the interaction (Basu et al. 2020). LHQW a Chinese herbal formulation shows antiviral activities by regulating inflammation, and also repairs injury in the lungs and also improves the ACE2 expression which was cluttered in COVID-19 infection (Zheng et al. 2020).

4.7 Conclusions

Infections caused by SARS-CoV-2 develop serious symptoms in the people infected by the virus. Till now numerous medicines and vaccines are invented for alleviating the complications caused by these virus infections. Herbal medicines prepared from medicinal plants are been used for a long period to find the inhibiting capability of the compounds in these formulations to cure diseases. This chapter is based on herbal formulas and their effect on infections caused by SARS-CoV-2. Different herbal formulas were found to be effective against the infection caused by the SARS-CoV-2 and also found to be effective against the symptoms. In silico analysis was too carried out against the host protein S, M^{pro}, ACE2, etc. with phytochemicals consisting in these formulations. In the future, to conclude the usage of herbal formulas against COVID-19 infection, further clinical studies are needed to be done.

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Chapter 5
Rejuvenation of Traditional Medicine in the Twenty-First Century against SARS-CoV-2

Shristi Modanwal and Nidhi Mishra

5.1 Introduction

SARS-CoV-2 is a positive-sense single-stranded RNA virus that ranges in size from 25 to 32 kb with 29,891 bases that are 96% identical to a bat coronavirus at the whole-genome level and that has 79.6% sequence identity with SARS-CoV (Wu et al. 2020). The structural spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins play a major role in the formation of the viral structure. The viral envelope, which is a lipid bilayer formed from the host cell membrane, contains the S, M, and E proteins, and the N protein interacts with the viral RNA inside the virion core (de Andrade Santos et al. 2020; Mithilesh et al. 2022). In December 2019, the Wuhan coronavirus, also known as the 2019 novel coronavirus, was detected in China. The virus was categorized as SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV) because it shared 79.5% genetic homology with SARS-CoV-1 and was the cause of the 2019 coronavirus disease (COVID-19) pandemic (Ahmad et al. 2021). COVID-19 spread from person to person when an infected individual coughs and sneezes releasing coronavirus droplets into the air. The coronavirus floats in the air or sticks to a surface that your hands touch before touching your eyes, nose, or mouth. The mucous membranes of the respiratory systems are typically infected with coronavirus in this way. The immune system of the body reacts in 2–14 days with symptoms like coughing, breathing issues, fever, chills, muscle discomfort, sore throat, and loss of taste or smell (Lee et al. 2021). These viruses can infect humans and have a wide range of other mammalian hosts, including bats and birds. The coronaviruses get their name

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from the spikey surface proteins that are one of the structural proteins and resemble a crown (Latin corona) (Naserghandi et al. 2020; Nassar et al. 2021). Even though several industries have developed COVID-19 vaccines, community members and researchers are still looking for the most effective treatments, including traditional remedies (Paudyal et al. 2022).

Global demand for various traditional medicines as a potential COVID-19 treatment option is still quite significant due to the lack of appropriate medications. Severe acute respiratory infection (SARI), abnormal immunological response, and thrombosis are all associated with coronaviruses (CoV) in their most serious stages. The research is now concentrated on three approaches: first, testing broad-spectrum antiviral medicines; second, *in silico* screening; and third, drug repurposing (Singh et al. 2021). In addition, the use of herbal medicines and supplements, particularly those with anti-infective and immunomodulatory effects as well as those used as supportive therapies, has grown significantly as an adjunct in economically developed countries. However, this use is frequently not mentioned to medical professionals (Wang et al. 2021). Researchers can use natural remedies to create medical medicines that are secure and simple to use. For instance, plants used in traditional Chinese medicine (TCM), such as *Scutellaria baicalensis*, contain a variety of antiviral substances, such as phytochemicals that may be able to combat SARS-CoV-2 and viral replication inhibitors (Llivisaca-Contreras et al. 2021). A number of medicines have been offered by traditional Indian medical systems, including Siddha, to boost immunity and prevent the spread of COVID-19. Kabasura Kudineer Chooranam, one of the official Siddha formulations, is thought to be an effective remedy with antiviral and immunomodulatory effects (Parthasarathy et al. 2021). It has also been reported for the treatment of COVID-19 in children, TCM has a very high involvement rate (Duan et al. 2022).

Angiotensin converting enzyme 2 (ACE 2), a transmembrane protein in type-2 pneumocytes found in the alveoli, nasal goblet cells, and intestinal epithelial cells, is hypothesized to be the route by which the SARS-CoV-2 virus enters the cell (Gao et al. 2020). Although intestinal epithelial cells may also become infected, it is believed that the virus predominantly affects type-2 pneumocytes in the lungs (Capodice and Chubak 2021). For the treatment of several respiratory diseases, the use of nutritional supplements including herbal medicines is well known. COVID-19 has also attracted attention to the antiviral capabilities of these products. Various researchers have looked into the potential applications of natural products and compounds that are already approved for usage for another purpose (Mahaboob Ali et al. 2022). Combining herbal medicine with modern biomedicine has the potential to alleviate both hypoxemia and chronic obstructive pulmonary disease, as well as to have direct antiviral, immunomodulatory, and anti-inflammatory effects (Luo et al. 2020). Modern medicine has benefited from the introduction of single chemical entities rather than composite natural product sources due to substantial advancements in the field of ethnopharmacology (Yimer et al. 2021). The druggable targets for SARS-CoV-2 are RNA-dependent RNA polymerase, 3-chymotrypsin like protease (also known as M^{pro}) and papain-like protease (PL^{pro}), endoribonuclease Nsp15/NendoU, spike glycoprotein, transmembrane protease

serine 2 (TMPRSS2), angiotensin-converting enzyme-2 (ACE-2), furin, cathepsin L (Faheem et al. 2020; Artese et al. 2020). These proteins/receptors can be targeted to treat COVID-19.

Since ancient times, people all over the world have used plants as medicines, particularly those from Asian countries like India, China, and Japan as well as some African nations. The widespread availability and very inexpensive cost of these plants among indigenous peoples are primarily responsible for their folkloric use. Even now, plants are still incredibly promising medicinal sources for the treatment of several diseases and infectious diseases as well as their effects, such as pain, oxidative stress, cancer, diarrhea, depression, fever, and thrombosis. This increases the possibility of developing medications with anti-COVID-19 properties derived from plant sources through a wide range of mechanisms of action (Alam et al. 2021). The World Health Organization supports the numerous benefits of traditional, complementary, and alternative medicine that is of excellent quality, safe, and potency (Umeta Chali et al. 2021). The patients' immunity is important in COVID-19. Standard drugs that have immunomodulatory effects could therefore be a possibility for COVID-19 patient prevention and treatment (Zhang and Liu 2020). Several studies have found that bioactive compounds derived from plants may have inhibitory effects on the SARS-CoV-2 coronavirus strain.

5.2 COVID-19 Treatment with Indian Traditional Remedies

The Government of India, Ministry of AYUSH (Ayurveda, Unani, Yoga Siddha, Naturopathy, and Homeopathy) organized an interdisciplinary AYUSH research and development special unit and guidance for AYUSH clinical studies in COVID-19 to develop an intervention to prevent or cure COVID-19 using concepts of AYUSH. This was done to promote research and the generation of evidence for various traditional medicines on COVID-19 (Charan et al. 2021). The science of Ayurveda has a system of knowledge in which Tattva (principles) translates to Sastra (theoretical constructs), and Sastra translates to Vyavahara (practical applications). The goal of the entire system is to use knowledge to create beneficial actions for society (Mathpati et al. 2020). Numerous ayurvedic plants have been explored for managing COVID-19 and its symptoms. A few of them are summarized below.

5.2.1 Allium sativum

There are two main categories of T cells: cytotoxic T cells ($CD8^+$ T cells) and helper T cells ($CD4^+$ T cells). Cytotoxic T cells kill tumors and virally infected cells, whereas helper T cells "help" other immune system cells. Both play a crucial role in

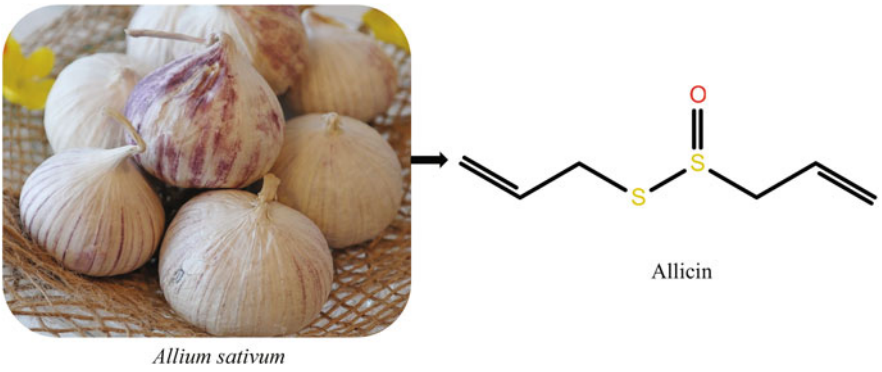

Fig. 5.1 Structure of allicin from plant *Allium sativum*

the immune system. A type of immune cell called natural killer cell can kill tumor and virus-infected cells by cytolysis. These cells were shown to be suppressed in COVID-19-infected patients. They are even significantly lower in extreme cases. A decrease in IFN- γ was also reported. Garlic increases $CD4^+$ and $CD8^+$ cells significantly and induces NK cells (Donma and Donma 2020). Using *in silico* non-covalent and covalent docking screening approaches, recent research suggests that allicin (Fig. 5.1) exhibits dual S-thioallylation of Cys-145 and solvent-exposed Cys-85/Cys-156 residue of SARS-CoV-2 M^{pro}, serving as a strong inhibitor of SARS-CoV-2 M^{pro} (Shekh et al. 2021; Khubber et al. 2020).

5.2.2 Cinnamon

Target cells infected by SARS-CoV-2 express the angiotensin-converting enzyme (ACE2) and type 2 transmembrane serine protease (TMPRSS2) (Amawi et al. 2020). In sheep kidneys, lungs, and testis, *C. zeylanicum* methanolic extract was found to inhibit the angiotensin-converting enzyme. In the kidney, inhibiting ACE activity was as effective as the standard medicine, captopril. Caffeic acid, gallic acid, eugenol, and cinnamic acid (Fig. 5.2) are phenolic compounds, isolated from *Cinnamomum zeylanicum* and have an inhibitory effect on trypsin (a serine protease). The highest potential for inhibiting an enzyme was demonstrated by caffeine (IC50 = 84%) and cinnamic acid (IC50 = 53%) (Yakhchali et al. 2021). As a result of these findings, cinnamon may be recommended as an antiviral drug for SARS-CoV-2 treatment.

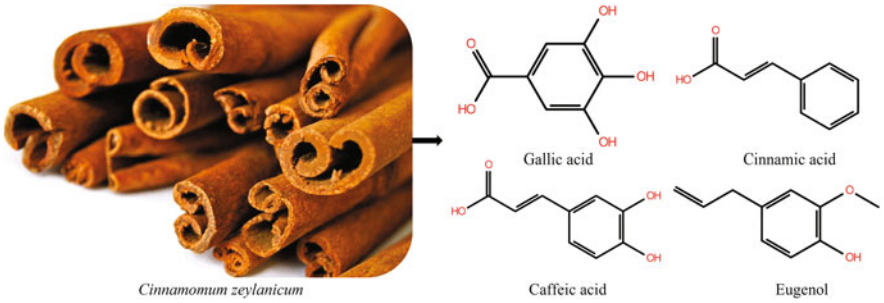

Fig. 5.2 Structure of gallic acid, caffeic acid, eugenol, and cinnamic acid from plant *Cinnamomum zeylanicum*

Fig. 5.3 Structure of curcumin from plant *Curcuma longa*

5.2.3 Curcuma longa

The active component of *C. longa* (turmeric) rhizomes is curcumin, a hydrophobic polyphenol. The pharmacological effects of curcumin include anti-inflammatory, antioxidant, anticancer, anti-bacterial, antiviral, and antidiabetic properties (Babaei et al. 2020). Curcumin (Fig. 5.3) is an effective adjuvant treatment for COVID-19 due to the above and a number of additional benefits. Many in vitro and *in silico* studies suggest the effectiveness of curcumin against COVID-19 (Rattis et al. 2021; Rajagopal et al. 2020). Curcumin has been shown in *in silico*/computational studies to be able to alter SARS-CoV-2 cellular entrance events (spike protein, ACE2, TMPRSS2), their replication (M^{pro}), and the molecular cascade that results in pathologic COVID-19 effects (Rajagopal et al. 2020; Patel et al. 2022; Zahedipour et al. 2020). However, there is no direct experimental evidence to support the advantages of curcumin against SARS-CoV-2.

5.2.4 Linum usitatissimum

The seed of Linum is widely used for medicinal purposes. Herbacetin (Fig. 5.4) is a natural flavonoid from flax seed (*Linum usitatissimum*) (Solnier and Fladerer 2021) and plays a crucial role in inhibiting proteins of SARS-CoV-2. The infection of COVID-19 can be inhibited by *Linum usitatissimum* Secoisolariciresinol diglucoside and herbacetin by targeting ACE and SARS-3CL^{pro}, respectively (Jalali et al. 2021).

5.2.5 Phyllanthus emblica

The biological benefits of *Phyllanthus emblica* (amla) include its immunomodulatory, antioxidant, anticancer, antiviral, anti-inflammatory, antidiabetic, and other biological activities. Amla contains an abundance of vitamin C, which helps to lower oxidative stress and substantially enhance the activity of natural killer cells (Murugesan et al. 2021). The docking analysis revealed the (2S)-eriodictyol 7-O-(6′’-O-galloyl)-D-glucopyranoside from *Phyllanthus emblica*. (The docking analysis revealed the (2S)-eriodictyol 7-O-(6′’-O-galloyl)-D-glucopyranoside from Phyllanthus emblica. (Phyllanthaceae) is a promising lead for the development of anti-SARS-CoV-2 medicines (Orhan and Senol Deniz 2020). In COVID-19 patients, amla tea can reduce the length of time needed for symptom recovery and length of stay in hospitals (Varnasseri et al. 2022). Sixty-six phytoconstituents of *Phyllanthus emblica* were examined in an *in silico* study for potential antiviral effects against the SARS-CoV-2 proteins NSP15 endoribonuclease, main protease, and spike protein receptor binding domain. The promising ability of chlorogenic acid, quercitrin, and myricetin to inhibit the essential viral proteins was validated by docking studies and molecular dynamics simulation. The network pharmacology study showed that specific phytoconstituents were involved in regulating a number of signaling pathways that may be important for immunomodulation, regulating inflammation, and regulating cytokine (Chikhale et al. 2021). In another study, Murugesan S et al. docked 30 amlas bioactive with COVID-19 M^{pro}, of those, 7-ketositosterol (–

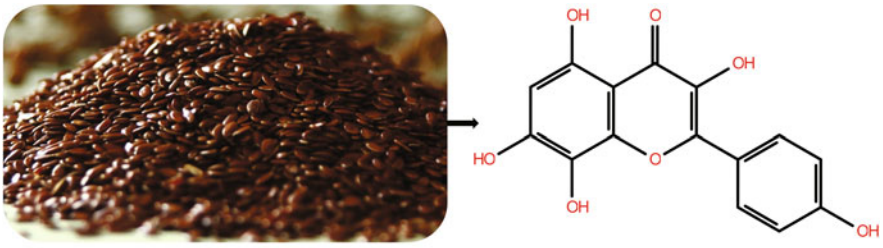

Fig. 5.4 Structure of herbacetin from plant *Linum usitatissimum*

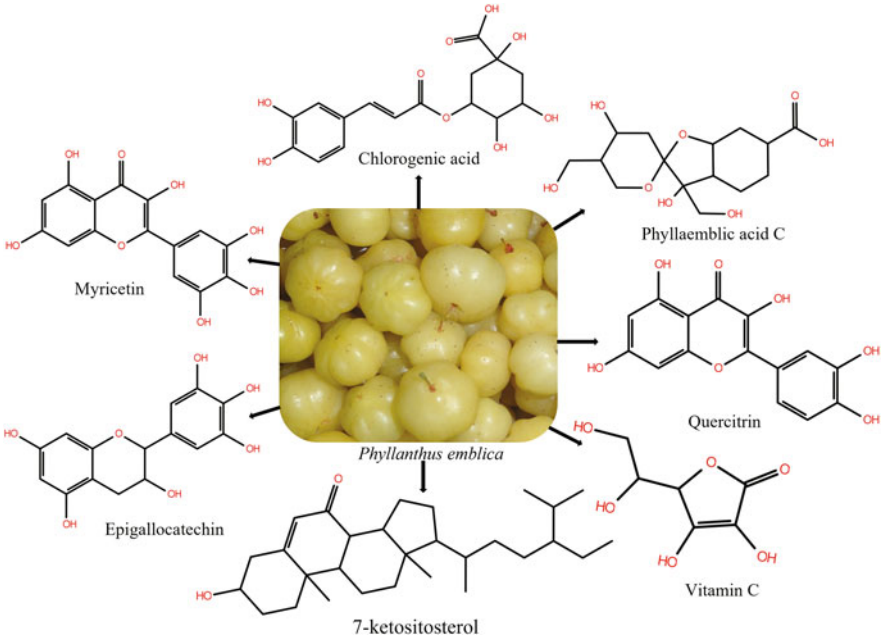

Fig. 5.5 Structure of vitamin C, chlorogenic acid, quercitrin, myricetin, 7-ketositosterol, epigallocatechin, phyllaemblic acid C from plant *Phyllanthus emblica*

46.67 kcal/mol), epigallocatechin (32.69 kcal/mol), phyllaemblic acid C (11.98 kcal/mol), and quercetin (38.77 kcal/mol) were shown to fit the substrate binding cleft of M^{pro} (Murugesan et al. 2021). The structure of some compounds from *Phyllanthus emblica* is shown in Fig. 5.5.

5.2.6 Nigella sativa

A sample of adult patients with mild COVID-19 symptoms who received oral *Nigella sativa* oil dosage supplementation at a dose of 500 mg twice daily for 10 days recovered more frequently than those who received only standard therapy. Low adverse effect profiles were also associated with a quicker return from COVID-19 symptoms and a lower hospitalization rate (Koshak et al. 2021).

5.2.7 Andrographis paniculata

Andrographis paniculata, commonly known as green chiretta, is a perennial herb that is widely distributed in India. According to Enmozhi et al. (2020),

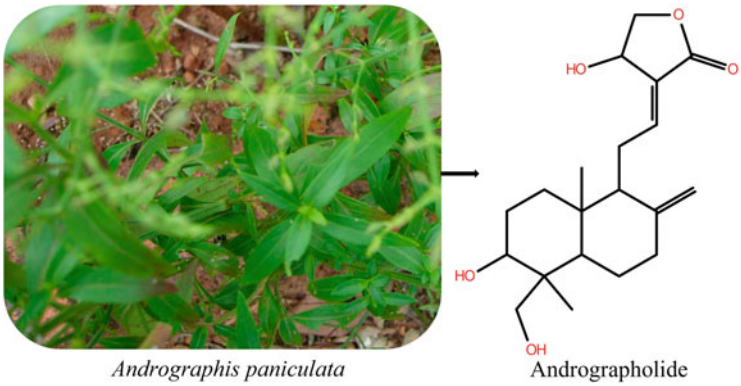

Fig. 5.6 Structure of andrographolide from plant *Andrographis paniculate*

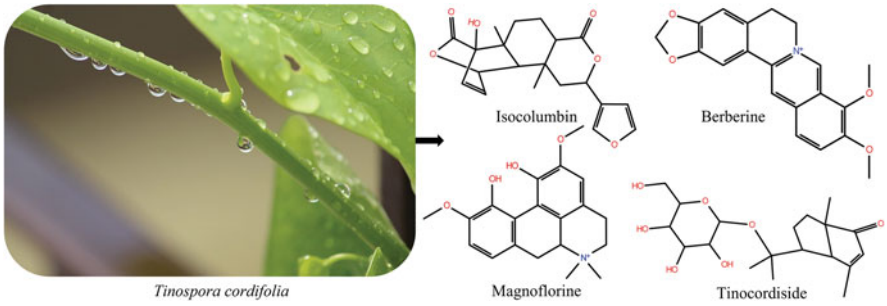

Fig. 5.7 Structure of tinocordiside, berberine, isocolumbin, and magnoflorine from plant *Tinospora cordifolia*

andrographolide (an extract of *Andrographis paniculata*) is bind with the inhibitor site of the main protease (M^{pro}), one of the proteases essential to the SARS-CoV-2 virus. Andrographolide (Fig. 5.6) scored well in the docking study. Compared to synthetic compounds like disulfiram, oseltamivir, tideglusib, and a combination of lopinavir and ritonavir, the docking study was shown to be much higher. Considerable high druggability, permeability, solubility, and target specificity were seen in the andrographolide (Enmozhi et al. 2020).

5.2.8 Tinospora cordifolia

A shrub known as *Tinospora cordifolia*, sometimes known as heart-leaved moonseed, is found primarily at higher altitudes in India. Four compounds of *T. cordifolia*, namely berberine, isocolumbin, magnoflorine, and tinocordiside (Fig. 5.7) were found to have strong binding affinity for four crucial proteins of SARS-CoV-2 involved in the attachment (6VSb, 6M0J) and replication (6M71, 6Y84). The

compounds' efficacy is either equal to or greater than that of some of the most widely used antiviral medications, including favipiravir, lopinavir, and remdesivir (Sagar and Kumar 2020). A study reported that the phytochemical saponarin, which is found in *T. cordifolia*, had a strong binding affinity with the main protease of about 8.75 kcal/mol (Mulpuru and Mishra 2021). In a study, only one molecule, tinocordiside (CID 177384), out of 28 active phytochemicals from *T. cordifolia* (Giloy), showed a maximum binding affinity for SARS-CoV-2 M^{pro} compared to built-in ligand N3 as per YASARA score. Tinocordiside is reported to be a novel, restructured cadinane sesquiterpene glycoside from *T. cordifolia* (Shree et al. 2022). In another study, the components of *T. cordifolia*, such as β-sitosterol (C29H50O), coline (C5H14NO), berberine (C20H18NO4), tetrahydropalmatine (C21H25NO4), and octacosanol (C28H58O) were selected to examine the interactions between drugs and 3CLpro interaction. The *in silico* analysis showed that berberine, out of all the phytochemicals in *T. cordifolia* that were taken into consideration, can regulate the function of the $3CL^{pro}$ protein and can thus limit viral replication (Chowdhury 2021). The IgG antibody response, macrophage activation, induction of cell-regulated immunity, and humoral immunity can also be stimulated by giloy herbs.

5.2.9 Ocimum tenuiflorum

Ocimum tenuiflorum is extensively distributed in India, and Ayurveda in that country mentions its therapeutic uses. *In silico* research concluded that *Ocimum tenuiflorum* extracts may be able to inhibit the SARS-CoV-2 ACE-2 and TRMPSS2 proteins (Jindal and Rani 2022).

5.3 COVID-19 Treatment with Traditional Chinese medicine

Traditional Chinese medicine has historically been used to treat or cure a number of epidemic disorders. More than 3100 TCM medical professionals were sent to the province of Hubei during the COVID-19 treatment phase, and TCM procedures were incorporated into the COVID-19 diagnosis and therapy guidelines. Approximately 60,107 confirmed cases have been successfully treated by TCM (Ren et al. 2020). The World Health Organization recognizes the history of traditional medicine as an inherited legacy of knowledge, skills, and practices that are local to a community. The effectiveness of TCM against COVID-19 has been reported in a number of studies (Devpura et al. 2021). Chlorogenic acid, hyperoside, acaciin, p-hydroxyacetophenone, scopoletin, rutin, quercetin, (3R,4R,6S)- 3,6-dihydroxy-1-menthene, scoparone, luteolin, apigenin, quercetin, acacetin, aristolactam, and

apigenin-7,4/-dimethyl ether are some of the phytocomponents from Chinese herbal extract and are employed in the treatment and prevention of SARS (Zhang and Chen 2008). The anti-SARS properties were also seen in the extracts of *Artemisia annua*, *Lindera aggregate*, *Isatis indigotica*, *Lycoris radiate*, *Torreya nucifera*, and *Houttuynia cordata*. Other TCM herbs that have been recommended for use in treating and preventing coronavirus include *Radix astragali* (Huangqi), *Radix saposhnikoviae* (Fangfeng), *Rhizoma Atractylodis Macrocephalae* (Baizhu), *Radix glycyrrhizae* (Ganacao), *Fructus forsythia* (Lianqiao) (Shahrajabian et al. 2020). It has been proved that TCM was extremely effective in treating COVID-19. There are currently several TCM medications available; however, only a few are covered in this chapter.

5.3.1 *Qingfei Touxie Fuzheng Recipe*

For the treatment of COVID-19, recent studies suggested using this mixture with Western therapy. The upregulation of antiviral components and the downregulation of pro-inflammatory mediators might be one strategic approach (Al-kuraishy et al. 2022). When taken by COVID-19 patients, the Qingfei Touxie Fuzheng recipe reduced IL-6 levels and improved lung inflammation or lesion absorption. Interestingly, in addition to their potent anti-SARS-CoV-2 activity, artemisinin and its derivatives controlled several immune cells, including macrophage, monocyte, dendritic cell, and T cell, to prevent the release of pro-inflammatory cytokines and the outbreak of cytokine storms, which protect tissues from damage (Lyu et al. 2021).

5.3.2 *Shufeng Jiedu*

Traditional Chinese medication called Shufeng Jiedu capsule (SFJDC) contains eight different medicinal herbs and is frequently used to treat influenza infection and other viral infections of the respiratory tract. It is now recommended for the management of COVID-19. When combined with arbidol, SFJDC shows promising results in the treatment of COVID-19 patients with no complications (Chen et al. 2020, 2021). In a study, Xia L et al. found that as compared to the model group, SFJDC significantly decreased the infection rate in the lung of HCoV-229E mice, reduced the levels of the inflammatory cytokines IL-6, IL-10, TNF-α, and IFN-γ, and enhanced the number of $CD4^+$ and $CD8^+$ cells in the blood. Network analysis showed that SFJDC inhibits NFκB activity across a number of signaling pathways. It has been clinically shown that adding SFJDC to conventional antiviral therapy (AVD) considerably sped up clinical recovery for COVID-19, as well as decreased fatigue and coughing when compared to AVD alone (Xia et al. 2021).

5.3.3 Jinhua Qinggan

Jinhua Qinggan was developed during the 2009 H1N1 pandemic. JH is composed of 12 herbs, including *Gypsum Fibrosum* (Shigao), *Ephedra sinica Stapf* (Mahuang), *Lonicera japonica Thunb.* (Jinyinhua), *Prunus armeniaca L.* (Kuxingren), *Forsythia suspensa* (Thunb.) Vahl (Lianqiao), *Fritillaria thunbergii Miq.* (Zhebeimu), *Scutellaria baicalensis Georgi* (Huangqin), *Anemarrhena asphodeloides Bunge* (Zhimu), *Artemisia annua L.* (Qinghao), *Mentha canadensis L.* (Bohe), *Glycyrrhiza inflata Batalin* (Gancao), and *Arctium lappa L.* (Niubangzi). In a molecular docking study, the constituents of JH, formononetin, stigmasterol, β-sitosterol, and anhydroicaritin were found to have a certain affinity for the SARS-CoV-2 3CL hydrolase and ACE2 enzymes (Chu et al. 2021). Jinhua Qinggan granules might stop SARS-CoV-2 by controlling cytokines through the metabolic pathway of arachidonic acid. Jinhua Qinggan granules played a role in apoptosis regulation via PI3K-Akt, MAPK, and Ras pathways (Huang et al. 2020).

5.3.4 Huoxiang Zhengqi (HXZQ)

The HXZQ components include *Agastache rugosus*, Perilla leaf, *Angelica dahurica*, and licorice, as well as six other TCM constituents. Due to its antiviral, anti-inflammatory, and immunomodulatory properties as well as its capacity to relieve gastrointestinal pain, HXZQ was suggested for the prevention of SARS-CoV-2. Additionally, clinical and pharmacological analyses have shown that HXZQ has therapeutic potential on fever, nausea or vomiting, stomach discomfort, and diarrhea linked to viral infection, indicating that HXZQ may potentially reduce COVID-19-related symptoms (Al-Romaima et al. 2020). For COVID-19 patients, using Huoxiang Zhengqi dropping tablets and Lianhua Qingwen granules in addition to western therapy may have therapeutic benefits. The inflammatory cytokine release induced by lipopolysaccharides was decreased by Huoxiang Zhengqi capsules. *Radix isatidis*, one of the key ingredients in Huoxiang Zhengqi, contains anti-inflammatory, antiviral, antipyretic, and immunity-boosting properties (Xiao et al. 2020).

5.3.5 Lianhua Qingwen

Traditional Chinese medicine known as Lianhua Qingwen (LHQW) is available in a number of dosage forms, such as capsules, granules, and decoction. LHQW is composed of 13 components. It has a wide range of antiviral properties, because of its immunomodulatory and as well as its inhibitory activity of pro-inflammatory cytokines and virus reproduction. The therapeutic properties of LHQW on

COVID-19 are predicated on its potent ability to bind to the SARS-CoV-2 therapeutic targets ACE2 and M^{pro}. As a result, it has proven to be beneficial for COVID-19 as a supplement and synergistic therapy strategy (Runfeng et al. 2020; Fan et al. 2022; Zhuang et al. 2021). The inhibitory effects and anti-inflammatory ability of Lianhua Qingwen against SARS-CoV-2 were analyzed by Runfeng et al. Lianhua Qingwen has traditionally been used to cure some ailments, including fever, cough, fatigue, influenza, bronchitis, pneumonia, and the early stages of measles. The Chinese National Health Commission recommended using this herbal preparation to treat or control COVID-19 (Runfeng et al. 2020; Ding et al. 2017; Yang et al. 2020). The herbal mixture had an IC50 of 411.2 g/ml and suppressed SARS-CoV-2 replication in a dose-dependent manner. A dose-dependent inhibition of the release of pro-inflammatory cytokines (TNFα, IL-6, CCL-2/MCP-1, and CXCL-10/IP-10) was also obtained by the mixture (Benarba and Pandiella 2020). Song et al. reported that the *Scutellaria baicalensis* extracts have baicalin, which is one of the main TCM herbal components, and hesperetin, an active compound found in tangerine peels. The COVID-19 symptoms have been treated with both bioactive compounds. The use of Xuebijing injection, a TCM medication has been widely accepted as a way to both reduce the time needed for patient ventilation in extreme situations and perhaps lower the risks of pneumonia spreading within the community (Song et al. 2019). According to a study, Lianhua Qingwen components such as 18β-glycyrrhetinic acid, indigo, β-sitosterol, naringenin, stigmasterol, luteolin, and quercetin may target ACE2 and protect the target organs of COVID-19 via the renin–angiotensin system (Huang et al. 2020).

5.3.6 Herbal Chinese Medicine Components Which Are Active Against SARS-Cov-2

Chinese herbal medicine is comprised of a huge group of secondary metabolites (such as flavonoids) that show wide structural diversity and a plethora of compounds (such as flavones, flavonols, flavanonols, and isoflavones) that mediate a large number of useful bioactivities, including anti-browning, anti-tuberculosis, antimicrobial, anticancer, and antioxidant effects. An essential natural compound called scutellarein, a flavone monomer, could be extracted from the plant *Erigeron karvinskianus* and utilized as a traditional natural supplement. Scutellarein has IC50 values for SARS-CoV and HIV of 0.86 M and 2.50 M, respectively (Wang and Yang 2021). Scutellarein, dihydromyricetin, and quercetagetin (Fig. 5.8) are three natural flavonoids that have been reported by Liu et al. to efficiently suppress SARS-CoV-2 3CLpro activity in vitro and strongly reduce the replication of SARS-CoV-2 in vero cells, with IC50 values of 5.80 M, 1.27 M, and 1.20 M, respectively (Liu et al. 2020).

In addition to being immunomodulatory and adaptogenic substances, natural polysaccharides and terpenoids are also known for their antiviral,

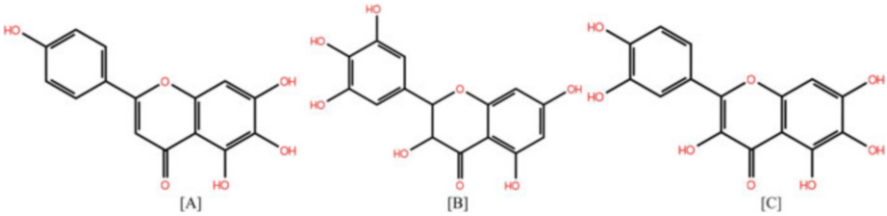

Fig. 5.8 Structure of scutellarein (**a**), dihydromyricetin (**b**), and quercetagetin (**c**)

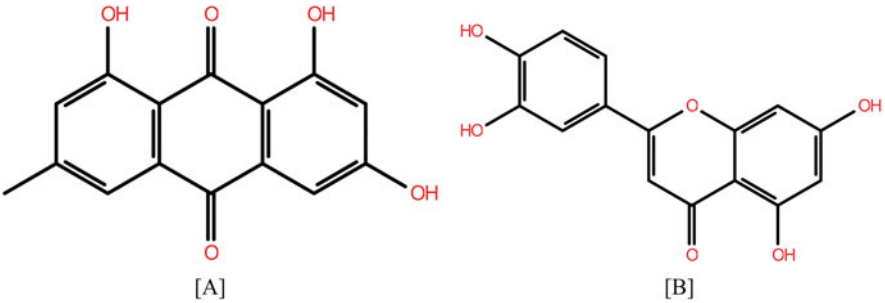

Fig. 5.9 Structure of emodin (**a**) and luteolin (**b**)

immunomodulatory, anticancer, and anticoagulant bioactivities. Additionally, a number of plant triterpenes, including dammarenediol-II, hydroxyhopanone, ursonic acid, shoic acid, eichlerianic acid, and hydroxyoleanonic lactone, are crucial in the regulation of cellular metabolism (Llivisaca-Contreras et al. 2021). The *in silico* study showed that the 6-desacetyl nimbinene, isomeldenin, nimocinol, beta-sitosterol, quercetin, components of *Azadirachta indica* inhibit the Spike protein of SARS CoV-2 by generating proper pose inside the active site (Navabshan et al. 2021).

5.4 COVID-19 Treatment with Indonesian Medicinal Plants

The compounds emodin and luteolin (Fig. 5.9), which are present in a number of edible plants across Indonesia, may be able to protect against or lessen viral infection. The interactions between ACE-2 receptors and the S-protein in SARS-CoV can be blocked by these compounds. *Aloe vera* (L.) *Burm. F.*, *Rheum officinale Baill.*, Cassia plants such as *Cassia alata L.* and *Senna obtusifolia* (*L.*) are among the edible Indonesian plants that are rich sources of emodin and are utilized in folk medicine, mainly in tropical areas of the world. The plants, *Apium graveolens L.*, *Elephantopus scaber L.*, *Allium cepa L.*, and *Brassica oleracea L.* are high in

luteolin. Many investigations have reported the presence of emodin or luteolin in various mangrove plants (Illian et al. 2021).

Potential antiviral Indonesian herbal candidates for SARS-CoV-2 include hesperidin, kaempferol-3,4′-di-O-methyl ether (Ermanin); myricetin-3-glucoside, peonidin 3-(4′-arabinosylglucoside); quercetin 3-(2G-rhamnosylrutinoside); and rhamnetin 3-mannosyl-(1–2)-alloside. The plants for COVID-19 prevention that include those constituents are *Moringa oleifera* and *Psidium guajava (*Erlina et al. 2022*)*. In a study, the Indonesian plants' compounds were screened and found 3-O-caffeoylquinic acid, justicidin D, 10-methoxycamptothecin, and inoxanthone as the potential SARS-CoV-2 RdRp inhibitors, emetine and carbine as potential SARS-CoV-2 spike protein inhibitors, and quercetin, quercetin 3-O-methyl ether, and dihydroquercetin as 3CLpro SARS-CoV-2 inhibitors. In vitro tests show that lycorine exhibits antiviral activity against SARS-CoV-2 with an EC50 of 0.31 μM (Alharthi et al. 2021).

5.5 COVID-19 Treatment with Ayurvedic Metal Nanoparticles

By preventing viral binding and entry into the cell, reducing viral replication, and directly killing viruses, nanoparticle (NP) based medications can fight against viral infections. For the treatment of COVID-19, various metal NPs, polylactic acid, etc. are frequently applied (Yasamineh et al. 2022). In modern science, green synthesized nanoparticles can be compared to the bhasmas mentioned in Ayurveda. Plant extracts are used to develop bhasma, which has high therapeutic value and is biocompatible, eco-friendly, stable, safe, and effective (Sreelakshmi et al. 2021). The significant antiviral potential is shown by various metal nanoparticles against a wide range of viral infections. Coronavirus can be successfully combatted with iron, gold, silver, copper, zinc, and other metal oxide nanoparticles. Disrupting the coronavirus's outer layers is one potential method of action for the metal nanoparticles to combat it. For COVID-19 treatment, Swarna Bhasma, Rajata Bhasma, Tamra Bhasma, and Yashada Bhasma are suggested due to their capacity to lower plasma interleukins, interferons, and TNFα (Sarkar and Das Mukhopadhyay 2021). Auranofin, a gold compound may be able to reduce SARS-CoV-2 infection and related lung damage because of its antiviral, anti-inflammatory, and anti-ROS activity. Auranofin may have a major impact on SARS-CoV-2 protein synthesis by inhibiting redox enzymes like thioredoxin reductase and induction of ER stress (Rothan et al. 2020). Thioredoxin reductase inhibition restricts NFκB DNA binding and NFκB-dependent gene expression. Additionally, auranofin inhibits the number of steps in the NFκB-IL-6-STAT3 signaling pathway, homodimerization of TLR4 (toll-like receptor), and viral replication and significantly lowers the expression of inflammatory response proteins like IL-6 (Sonzogni-Desautels and Ndao 2021).

5.6 Plants Studied for COVID-19 Treatments

Some researchers have turned to plant-based treatment modalities due to the absence of precise effective medicines against SARS-CoV-2. This is because many medications are made from plant materials or the bioactive components of herbs. Since plant-based treatments showed intriguing efficacy against a variety of viruses by boosting immunity, there is a significant interest in the discovery of potential anti-COVID-19 herbal medications (Al-kuraishy et al. 2022). The Chinese medicinal plants being studied include the *Radix astragali* (*Astragalus propinquus* Schischkin), *Radix glycyrrhizae* (*Glycyrrhiza uralensis* Fisch. ex DC.), *Radix saposhnikoviae* (*Saposhnikovia divaricata* (Turcz.) Schischk.), *Rhizoma atractylodis Macrocephala* (Chikowe et al. 2021). *Teucrium viscidum*, *Artemisia vulgaris*, *Verbena officinalis*, *Aster indicus*, *Pseudelephantopus spicatus*, *Hedyotis acutangula*, *Cyclea barbata*, *Alpinia malaccensis*, *Pothos scandens*, *Mimosa pigra*, *Plantago major*, *Artemisia verlotiorum*, *Tadehagi triquetrum*, *Blumea balsamifera*, *Zingiber ottensii*, *Ricinus communis*, *Tacca chantrieri*, *Zingiber officinale*, *Elephantopus scaber*, *Biancaea sappan*, *Scoparia dulcis*, *Cyclea barbata*, *Tinospora crispa*, *Celtis tetrandra*, and *Centella asiatica* are medicinal plants used for treatment of symptoms of COVID-19 among Hmong and Karen (Phumthum et al. 2021). Plants such as *Eucalyptus globulus Labill, Piper aduncum, Matricaria recutita*, and *Erythroxylum coca* were used to treat COVID-19-related respiratory problems (Villena-Tejada et al. 2021). *Thymus vulgaris*, *Achyranthes bidentata*, *Cinnamomum cassia*, *Cydonia oblonga*, *Embelin ribes*, *Justicia adhatoda*, *Momordica charantia*, *Withania somnifera*, *Althea officinalis*, and *ginseng* were used for a severe infection of COVID-19.

Azadirachta indica (Neem), the acetone–water extract of neem should be able to eliminate SARS-CoV-2 from vascular endothelium. If this procedure is successful, COVID-19 may not be circumvented by the formation of endothelial dysfunction or implied uncontrolled inflammation (Eze et al. 2022). *Gymnanthemum amygdalinum* increases the number of $CD4^+$ as well as white blood cells. Ethanolic extracts of *Nigella sativa* seeds, through the downregulation of the gene expression of various leukocyte transient receptor proteins (TRP) like TRPA1, TRPC4, TRPM6, TRPM7, TRPM8, and TRPV4 genes, in mice studies have confirmed anti-corona virus species of MHVA59 (mouse hepatitis virus-A59). *Eurycoma longifolia* (has NFκB inhibitory activity), *Mentha piperita Allium cepa*, *Malva sylvestris*, *Isatis indigotica*, *Psoralea corylifolia*, *Glycyrrhiza glabra* (Demeke et al. 2021) are medicinal plants which were studied or used against SARS CoV-2.

5.7 Phytoconstituents Being Studied for COVID-19 Treatment

The list of phytochemicals, targets, and references is given in Table 5.1.

Table 5.1 Studied phytoconstituents against COVID-19

Targets	Phytoconstituents	Study	References
Spike (S) proteins	Resveratrol	*In silico*	Islam et al. (2021), Wahedi et al. (2020)
	Saikosaponins U and V	*In silico*	Sinha et al. (2020)
	Luteolin-7-glucoside-3′-glucuronide	*In silico*	Prasanth et al. (2021)
	Melitric acid A	*In silico*	Prasanth et al. (2021)
Main protease (Mpro)	Withaferin A	*In silico*	Sudeep et al. (2020)
	Rutin	*In silico*	Johnson et al. (2021)
	Luteolin-7-glucoside-3′-glucuronide	*In silico*	Prasanth et al. (2021)
	Melitric acid A	In silico	Prasanth et al. (2021)
	Pycnanthuquinone C	*In silico*	Chtita et al. (2022)
	Pycnanthuquinone A	*In silico*	Chtita et al. (2022)
	Berberine	*In silico*	Chowdhury (2021)
RNA-dependent RNA polymerase	Theaflavin	*In silico*	Lung et al. (2020)

5.8 Risks Associated with the Incorrect Use of Natural Products

Although several plant species have the ability to lessen or decrease COVID-19 symptoms, clinical investigations are still required to confirm their potential health benefits and uncover any negative effects. For example, despite the purported health benefits of ginkgo (*Ginkgo biloba*), at large doses can impact those who have peptic ulcers and clotting issues and increase cerebral blood flow (Llivisaca-Contreras et al. 2021). TCM for COVID-19 has the traits of many components and multiple targets, which were involved in various parts of the disease and had significant therapeutic value. TCM, however, also has certain drawbacks. For instance, it was challenging to detail the process behind TCM formulae because they included numerous components and targets yet were not targeted while exerting their therapeutic effect (Kang et al. 2022).

5.9 Conclusions

Research on the antiviral potential of herbal products has increased in the aftermath of the emergence of SARS-CoV-2 and the ongoing COVID-19 global pandemic. This is mainly due to the current shortage of efficient, secure, widely accessible antiviral medications, as well as the fact that herbal remedies are generally affordable and simple to transport without the need for special storage conditions. Furthermore, the widespread use of Ayurvedic remedies in India provided a chance to test these therapies in carefully managed and controlled clinical studies. Several possible traditional Indian medicinal plants and clinical studies of traditional Indian medicinal plants are now listed in several clinical trial databases for the development of pharmacological treatments against COVID-19. *Ocimum tenuiflorum* and *Tinospora cordifolia* are the two most promising traditional medicinal plants used in India for the treatment of COVID-19 because they showed strong immunomodulatory, thrombolytic, and binding affinity. Acute respiratory infections are known to be caused by a variety of viruses and several plants, including *Achyranthes bidentata*, *Cinnamomum cassia*, *Cydonia oblonga*, *Embelin ribes*, *Justicia adhatoda*, *Momordica charantia*, *Withania somnifera*, and *Zingiber officinale*, have strong antiviral properties. These herbs also have significant thrombolytic and immunomodulatory properties. Several *in silico* studies revealed that a traditional herb reported to bind with the crucial SARS-CoV-2 protease may show potential for the treatment of COVID-19. Although for the treatment of mild, severe, or critical COVID-19, some traditional medicinal plants cannot be recommended, more supportive studies are required for the recommendation. But these herbal remedies might be added with other treatments. Prospective cohort studies are urgently required to better understand the potential of herbal remedies. Since the population sample for COVID-19 is available, a series of prospective studies with well-designed research should soon begin yielding reliable evidence for this herbal treatment of COVID-19 or related respiratory infectious disorders. To ensure the safety and effectiveness of traditional medicine, in vitro and in vivo tests are required.

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Chapter 6
Traditional Herbal Medicines and Their Active Constituents in Combating SARS-CoV-2 Infection

Shivangani, N. Jaya Lakshmi, Lemnaro Jamir, and P. Hariprasad

6.1 Introduction

Since its initial appearance in December 2019, a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) has rapidly become a medical emergency and a global crisis (Dhama et al. 2020). Viruses have caused the majority of epidemic diseases over the last century. In 1918, an H1N1 (influenza) virus carrying avian genes caused a similar pandemic in humans. There were more than 500 million cases of viral infection, and 50 million deaths, ushering in the twentieth century. It is widely regarded as the deadliest pandemic in human history. New H_2N_2 influenza also known as "Asian Flu" emerged in 1957–1958 that caused a pandemic and claimed 1.1 million lives globally (Piret and Boivin 2021). Numerous cases of an unusual viral respiratory infection were recorded in Wuhan, China, in December 2019. A new coronavirus linked to betacoronaviruses was discovered in clinical specimens in January 2020 (Hu et al. 2022). The novel coronavirus and illness were known by the designations SARS-CoV-2 and COVID-19. Additionally, on March 11, 2020, the World Health Organization (WHO) classified COVID-19 as a pandemic (Cucinotta and Vanelli 2020).

According to WHO figures, more than 6.6 million deaths and over 649 million confirmed cases have been reported (as of 18 December 2022). Almost every country and territory on the planet has been affected by the disease. As of June 2022, the USA had reported the most deaths (1,002,946), followed by Brazil (668,693), India (524,873), the Russian Federation (380,517), and Mexico

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(325,271). Individuals, families, food security, healthcare systems, industries, and economies in a number of countries are all feeling the strain. The effect of COVID-19 has been catastrophic, turning the lives of many people on their heads and leading to tragedy for some (Saxena 2020). The destructive nature of SARS-CoV-2 stems from its ability to spread among hosts. The primary means of transmission is by respiratory droplets generated by sneezing and coughing. These droplets may enter the nose or mouths of those nearby, or they may be inhaled into the lungs. Additionally, the infection can be spread through fomites and their infectious secretions (Boone and Gerba 2007).

6.2 Pathogenicity and Life Cycle of SARS-CoV-2

SARS-CoV-2 is a spherical, single-stranded positive-sense RNA (+ssRNA) betacoronavirus with approximately 30 kb of genomic length (Klein et al. 2020; Lu et al. 2020). It consists of four structural proteins (envelope (E), nucleocapsid (N), membrane (M), and spike (S)) and sixteen non-structural ones. At the 5′ end, the RNA replication enzyme is encoded. The proofreading function of non-structural protein 14 (nsp14) keeps the mutation rate low. Viral multiplication and amplification occur in the host cell's endoplasmic reticulum and Golgi apparatus, as does virion assembly. Exocytosis is the final stage of virus release from the cell, allowing the infection to spread further (Cascella et al. 2022; Klein et al. 2020).

The life cycle of SARS-CoV-2 in the host cell is classified into various phases. To begin with, the viral Spike-Fc binds to the bronchial epithelial ACE2 receptor to initiate the infection cycle. This process also causes ACE2 expression to decrease, resulting in severe acute respiratory failure (Kuba et al. 2005). Small intestinal epithelial cells, like lung epithelial cells, have the ACE2 receptor protein on their surface and may act as a second site for SARS-CoV pathogenesis. Endocytosis is triggered when the S protein binds to the ACE2 receptor, which allows the virus to enter the host cell. Transmembrane serine protease 2 (TMPRSS2) then cleaves the S2′ site of the SARS-CoV-2 S protein, enabling the virus to fuse with the host membrane and infect the airways (Bestle et al. 2020; Fraser et al. 2022). When the virus's membrane merges with the membrane of the host cell, the virus can inject its genetic material into the host. The RNA of the virus must be translated by the host's machinery to produce replication and structural proteins. RNA-dependent RNA polymerase (RdRp) is one of the non-structural proteins that result from disassembling the replication enzyme. By sending signals to the host's ribosomal machinery, viral RNA is translated into a functional RNA polymerase protein. The plus ssRNA is replicated by the viral RNA polymerase into the dsRNA. The N, S, M, and E proteins are transcribed from RNA that is located outside of the genome. N is processed in cytoplasmic protein, while S, M, and E are modified in the rough endoplasmic reticulum after translation. Viruses assemble their nucleocapsid (N) and structural proteins E, M, and S inside their envelopes (McBride et al. 2014).

The Golgi vesicle is responsible for the final stages of virion development, where the lipid envelope is added to the assembled viral components. Exocytosis is the process by which viruses mature enough to infect other cells are released from their host (Shereen et al. 2020; Iqbal et al. 2020).

6.3 Covid Associated Conditions

It may take weeks to months to recover from coronavirus disease; however, infection and symptoms may persist in a few people even after the initial infection. Although years have passed since the first occurrence of COVID-19, people still have long-term difficulties. According to Kamal et al. (2021), only 10.8 % of all individuals have no manifestation following disease healing, despite the majority of subjects having many symptoms and illnesses. Possible risks include heart failure, lung illness, and neurological conditions like stroke. Brain fog and exhaustion may be brought on by cytokines that impact the brain and pass the blood–brain barrier (BBB). These symptoms may indicate a postviral syndrome caused by COVID-19 and should be taken seriously.

Furthermore, the most commonly reported symptoms are reading difficulties, dry skin, insomnia, nonspecific myalgia, and elevated anxiety (Moldofsky and Patcai 2011). Interferon-gamma and interleukin-7 are produced when lymphatic drainage is disrupted. Proinflammatory cytokines can cross the BBB in circumventricular structures such as the hypothalamus, causing autonomic dysfunction that begins as a fever and progresses to chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) (Hives et al. 2017). CFS/ME is characterised by abnormal sleep-wake cycles, cognitive dysfunction, and extreme, ongoing exhaustion. The "post-COVID-19 syndrome," which is characterised by long-term chronic fatigue and post-exercise neuroimmune discomfort, was also observed by several COVID patients (Perrin et al. 2020). Persistent neurological symptoms, olfactory dysfunctions, and lung symptoms and dysfunctions are also common in COVID patients (Salamanna et al. 2021). A more severe and potentially fatal link exists between ENT and coronavirus: invasive fungal sinusitis caused by mucormycosis (DeShazo et al. 1997).

6.4 Variants of Concerns SARS-CoV-2 (VOCs)

Since the initial revelation of COVID-19 in December 2019, a number of SARS-CoV-2 variants have been discovered. However, due to their global impact on public health, WHO designated a small number of mutant strains as variants of concern (VOCs) (Table 6.1). The great majority of these alterations were expressed by the spike glycoprotein. This category also calls for increased sequence surveillance, laboratory characterisation, and epidemiological research to determine disease transmission rate, clinical manifestation, reinfectivity threat, and immunity to existing

Table 6.1 Brief description of existing SARS-CoV-2 variants of concern declared by WHO

VOC	Strain designation	Reported country	Mutations	Key features	Reference
Alpha	B.1.1.7	United Kingdom Dec 2020	Δ69-70 del, Δ144 del, N501Y, T716I, P681H, D1118H, A570D, and S982A	Amplified affinity to host hACE2 receptor due to spike mutations; 43% to 82% more transmissible and associated with high mortality	Galloway et al. (2021), Davies et al. (2021)
Beta	B.1.351	South Africa Dec 2020	D80A, L18F, D215G, K417N, R246I, E484K, D614G, N501Y, and A701V	The danger of spreading GOT increased and the efficacy of plasma therapy in neutralising it has reduced	Tegally et al. (2021), Wang et al. (2021)
Gamma	P.1	Brazil Jan 2021	L18F, T20N, P26S, D138Y, R190S, H655Y, T1027I V1176, K417T, E484K, and N501Y	Reduced neutralisation effects by monoclonal antibody treatment	Faria et al. (2021)
Delta	B.1.617.2	India Dec 2020	T19R,156del, 157del, L452R, R158G, P681R, T478K, D614G and D950N	Increased risk of mortality owing to 2nd wave of COVID-19	Singanayagam et al. (2022), Twohig et al. (2022)
Omicron	B.1.1.529	South Africa Nov 2021	V70del, E31del, R32del, S33del, N211del/L212I, H69del, Y143del, Y144del, Y145del, G204R, D3G, A63T G142D, Q19E, T95I, P13L, R203K, A67V, Y505H, Q493R, N501Y, Q498R, G496S, E484A, N440K, T478K, S477N, G446S, K417N, S375F, S373P, S371L, G339D	Mutations in Spike protein led to vaccine breakthroughs; many subvariants such as BA.1-5 were also identified	Vaughan (2021)

vaccines (Vasireddy et al. 2021; Meites et al. 2022). Given the recent global spread of heavily mutated Omicron VOC and the expected increase in viral diversity, the WHO has created a new category titled "omicron subvariants under monitoring" to alert global public health authorities to which VOC lineages may require additional attention and surveillance. These include the BF.7 and XBB omicron subvariants, which currently dominate the epidemiological scene of SARS-CoV-2 infection due to their increased transmissibility, high resistance to antibody neutralisation, and fractional resistance to COVID-19 vaccine-induced immunity (Torjesen 2021; Velavan et al. 2023). In the long run, mutational variations may result in vaccine-resistant viral strains. Such strains outperform, particularly in immunocompromised patients with long transmission cycles. These elements lengthen the time it takes for natural selection to operate on this novel variant and increase the frequency of new mutations (Cascella et al. 2022).

6.5 Druggable Molecular Targets of SARS-CoV-2

Agents used to treat SARS-CoV-2 infection can prevent the virus entry into host cells by interfering with the host recognition system, inhibition of structural proteins to prevent viral self-assembly, acting on the RNA synthesis through viral RNA, and blocking vital viral enzymes involved in the replication. This section briefly discusses the various molecular targets involved in SARS-CoV-2 pathogenesis.

Spike Protein The interaction of SARS-CoV-2's type I transmembrane glycoprotein (spike protein, approx. 200 kDa) facilitates host cell recognition and entry. Initially synthesised as a monomer, this protein undergoes homotrimerization after post-translational glycosylation in the endoplasmic reticulum (Tang et al. 2020; Ou et al. 2020). The SARS-CoV-2 spike proteins are approximately 1273 AA long and comprise an N-terminal S1 domain that binds to host cell receptors and a C-terminal S2 domain that is involved in host cell membrane fusion (Wrapp et al. 2020). The S1 subunit has a receptor-binding domain (RBD) and an N-terminal domain (14-305 amino acids) (Liu et al. 2020; Xia et al. 2020). The RBD is made up of subdomains that generate the trimer and interact with the receptor (Lu et al. 2013; Li et al. 2005). The S2 subdomain is made up of two heptad repeat domains: a fusion peptide domain and a transmembrane domain. After the S1 domain of spike protein interacts with the host cell's receptor, the S2 domain goes through conformational changes. The heptad domains are important targets for fusion inhibitors because they work together to form a helical bundle core, which improves the tight contact between the cellular and viral membranes during fusion. Figure 6.1a depicts all of the structural components of spike glycoprotein. Small compounds that block Spike-ACE2 interaction via RBD (shown in Fig. 6.1b) are being investigated to prevent and inhibit viral attachment in host cells.

Non-Structural Protein (NSP) SARS-CoV-2 has 16 highly conserved NSPs that share structural similarities with other coronaviruses. While any NSP in principle

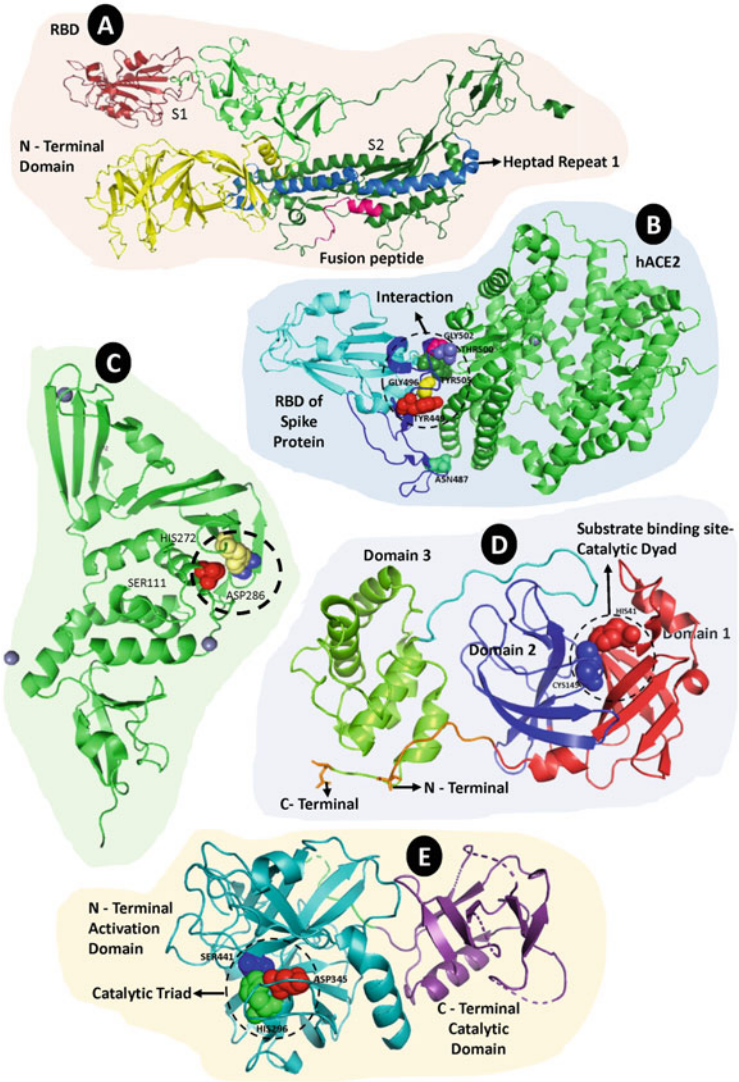

Fig. 6.1 Cartoon structure of different SARS-CoV-2 and human proteins identified as potential drug targets along with their key/catalytic amino acid residues. (**a**) Spike glycoprotein (PDB ID: 7TGW). (**b**) Interactions between receptor-binding domain of spike-ACE2 (PDB ID: 6M0J). (**c**) PL^{pro} (PDB ID:7CJM). (**d**) M^{pro} (PDB ID:6LU7). (**e**) Interactions between receptor-binding domain of spike-transmembrane protease serine 2 (PDB ID: 7MEQ)

could be used as a drug target, the reported ligand, 3D crystal structure, and function in viral infection are particularly promising indicators of future success. Only the three chymotrypsin proteases ($3CL^{pro}$, nsp5), papain-like protease (PL^{pro}, nsp3),

RdRp (nsp12), and the methyltransferase-stimulating factor complex (NSP10 and NSP16) have crystal structures. RdRp, helicase, and two intracellular proteases, M^{pro} and PL^{pro}, have all been extensively studied as potential therapeutic targets based on this logic.

Papain-Like Protease (PL^{pro}) PLpro is typically found in two copies, PL1pro and PL2pro, and has a total of 1945 amino acid residues (212 kDa) as part of NSP3, a large multidomain protein that is important to the RTC (Lei et al. 2018; Woo et al. 2010). PLpro's three-dimensional structure is shown in Figure 6.1c. The enzyme activity is found in NSP3 between a nucleic acid-binding domain and a SARS-specific domain (SUD/HVR). By cleaving peptide links, this cysteine protease releases NSP1, NSP2, and NSP3. Proteases Pp1a and Pp1b, whose substrate locations are located near the LXGG motif, are essential for PLpro proteolytic activity (Harcourt et al. 2004). NSP1 is a protein with 180 amino acid residues that constrains host translation by interacting with the 80S ribosome (Schubert et al. 2020; Thoms et al. 2020). NSP2 is a protein with 638 amino acid residues that may have an effect on host cell survival (Zhao et al. 2020). It is hypothesised that SARS-COV-2 PLpro has a deubiquitinating function because PLpro is highly conserved and present in all coronaviruses (Ratia et al. 2014). For its essential function in RTC assembly, viral polypeptide chain cleavage and maturation, and host immunity suppression, PLpro is an attractive therapeutic target (Osipiuk et al. 2021).

Main Protease (M^{pro}) The M^{pro} responsible for the multiplication of SARS-CoV-2 is a cysteine protease with 306 residues and three domains. It is found in a dimer form, with both the N- and C-terminal catalytic sites present in each monomer (Lee et al. 2005). It is clear from the 3D structures of other CoVs that the 15-residue loop connecting domains II and III contains a Cys-His catalytic dyad and a Mpro substrate binding region located in the pocket between domains I and II (Fig. 6.1d) (Jin et al. 2020). The M^{pro} or $3CL^{pro}$ first cleaves the polypeptide chain to generate mature enzymes, forming an RTC. In addition, it splits NSP4 and NSP16 off of the downstream end of peptide chain 1ab at 11 NSP sites. The maturation of NSPs is dependent on 3CLpro and is vital for the viral life cycle (Yang et al. 2005). Several molecules, peptides, and peptidomimetics with $3CL^{pro}$ inhibitory activity have been reported, with small molecules of plant origin discussed later in the manuscript.

RNA-Dependent RNA Polymerase (RdRp) RdRp, or nuclear envelope protein 12 (NSP12), is a component of the viral replication and transcription complex. Its a must-have for the transcription of viral RNA replication. While NSP12 has negligible catalytic activity on its own, when combined with cofactors NSP7 and NSP8, it becomes a powerful polymerase (Subissi et al. 2014; Kirchdoerfer and Ward 2019). Therefore, the NSP12-NSP7-NSP8 complex has been postulated to play a crucial function in viral propagation. The RdRp complex of SARS-CoV-2 includes a dimeric NSP8 subunit, a heterodimer complex, and a core catalytic NSP12 subunit. In addition, SARS-CoV-2 RdRp is structurally identical to SARS-CoV RdRp. A recently discovered RdRp mutation in Europe, 14408C > T, that occurred via an unknown route has been linked to higher mutation rates than viral genomes from

Asia (Pachetti et al. 2020). Ribavirin, remdesivir, favipiravir, and hydroxychloroquine are four antiviral drugs that target RdRp and have been approved by the Food and Drug Administration (FDA) for use against HIV and other viruses; they can be used as rescue treatments for COVID-19. Repurposing current RdRp-based antiviral medicines for this purpose is likewise the subject of intensive study (Ko et al. 2020; Gangadharan et al. 2022; Xie et al. 2021).

Human Angiotensin-Converting Enzyme-2 (hACE-2) Spike proteins of SARS-CoV-2 are associated with hACE-2 for host cell recognition and entry, making hACE-2 a potential target in managing COVID-19 (Hoffmann et al. 2020; Zhou et al. 2020). Homeostasis of vascular processes is controlled by hACE2, a membrane protein, through its catalytic activity in the renin–angiotensin system (RAS) (Tikellis and Thomas 2012). Angiotensin II is the primary vasoactive protein produced by the RAS system. It produces angiotensin 1e7, an inhibitor of angiotensin II activity, and acts as a potent vasoconstrictor through its angiotensin II type I receptor (AT1R) (Clarke and Turner 2012). Increased ACE-2 cellular expression has been observed during long-term treatment with an angiotensin receptor blocker. Following virus attachment and membrane fusion, researchers found a decrease in ACE-2 levels. Since AT1R causes increased angiotensin expression due to increased ACE-1 action and inhibited ACE-2 action, it leads to significant pathophysiological changes in the lungs (Gurwitz 2020). Despite the mystery, it appears that treating COVID-19 with ARBs might be beneficial rather than harmful to lung function.

Transmembrane Protease Serine 2 (TMPRSS2) Proteases are enzymes that specifically and rapidly degrade proteins and peptides, thereby activating and regulating a wide range of fundamental physiological processes. As can be seen in Fig. 6.1e and 6.4, TMPRSS2 is primarily localised in the epithelial cell membrane of the lungs, where it plays a role in priming spike proteins. This mechanism induces the union of viral membrane with cellular membranes and their interactions. According to previous studies, SARS-CoV spike proteins need to be primed by TMPRSS2 before they can enter host cells (Matsuyama et al. 2010; Glowacka et al. 2011). One study indicates that camostat is an approved therapeutic TMRSS2 inhibitor that blocks TMPRSS2's priming activity (Hoffmann et al. 2020). Because of this, TMPRSS2-based small molecule therapies could be effective against COVID-19.

Furin The trans-Golgi network is home to the proprotein convertase furin (Feliciangeli et al. 2006). Furin is a proteinase that, when activated by an acidic pH, breaks specific precursor proteins with defined motifs, resulting in biologically active mature proteins that have been linked to a wide range of cardiovascular diseases, cancers, and COVID-19 infections. The viral spike glycoprotein must be proteolyzed at the S1/S2 and S2 cleavage regions before the virus can enter host cells (Wu et al. 2020). The proprotein convertase furin eases membrane fusion and viral replication by cleaving the S1/S2 site (PRRAR). Inhibition of furin reduced viral replication in Calu-3 cells, suggesting it may be a target (Bestle et al. 2020).

6.6 Conventional Management and Treatment Measures for COVID-19

Several nations have taken precautions against the virus by including social distancing and self-isolation, which is contact between people. The best ways to prevent the spread of disease are still the old standbys: washing one's hands often and wearing protective gear like a surgical mask (Chu et al. 2020; Sardar et al. 2020). National closures of public places were enacted in many countries as a means by which governments hoped to limit the spread of the disease by reducing people's opportunities for interpersonal contact (Balachandar et al. 2020). However, long-term physical distancing is difficult where some countries reported infection waves after relaxing the lockdown rules. Prolonged lockdowns also cause income loss and poverty, especially in developing nations (UNDP 2020; Bonaccorsi et al. 2020).

Because of the striking resemblance between their genomic sequences and that of SARSCoV-2, antiviral drugs originally developed to treat SARS and MERS are now routinely prescribed to treat SARS-CoV-2 infection. Extensive scientific studies on COVID-19 patients are currently being conducted with antiviral drugs like remdesivir, lopinavir, hydroxychloroquine, and dexamethasone (Adhikari et al. 2021; Lamontagne et al. 2020; Balkhair 2020). Due to their promising results, the WHO has recommended these medications (Adhikari et al. 2021; Lamontagne et al. 2020; Balkhair 2020). While hydroxychloroquine is frequently prescribed for asymptomatic patients, especially those caring for suspected or confirmed COVID-19 cases, dexamethasone is usually reserved for patients who are critically ill (Lamontagne et al. 2020). The majority of antiviral medications that are currently on the market also cause virus resistance, side effects, recurrence, and delayed response. This scenario dissatisfies numerous public health institutions, researchers, and healthcare practitioners who continue to seek a cure for COVID-19. Many research studies are focussed on medications and vaccines evaluated at the experimental and field levels around the world to combat the SARS-CoV-2 pandemic (Lamontagne et al. 2020; Alam et al. 2021). Antiviral medications used for treating SARS and MERS are today routinely prescribed to treat COVID-19 due to the significant similarity between their genomic sequence and SARSCoV-2. Dexamethasone is typically prescribed for severely ill patients, whereas hydroxychloroquine is commonly prescribed for asymptomatic conditions, particularly for those involved in the care of suspected or confirmed SARS-CoV-2 infection (Lamontagne et al. 2020). The majority of antiviral medications that are currently available also cause virus resistance, side effects, recurrence, and delayed response. Numerous public health organisations, academics, and medical professionals who are still working to find a cure for COVID-19 are unhappy with this situation. Numerous studies focusing on drugs and vaccines tested at the experimental and field levels worldwide are being carried out during the SARS-CoV-2 pandemic (Lamontagne et al. 2020; Alam et al. 2021).

6.7 Vaccines for COVID-19

Since the beginning of the current pandemic, there has been an increase in the international effort to develop vaccines to prevent SARS-CoV-2 infection. People of all ages receive vaccinations to build up their humoral and cell-mediated immunity to prevent illness. Currently, 13 vaccines have been developed and authorised/approved, while 58 vaccines are through various rounds of testing. The covid vaccines most widely administered are discussed below,

mRNA-1273 (Moderna TX, Inc) (Moderna TX, Inc) A synthetic liposome-encapsulated mRNA that encodes for the full-length stabilised spike glycoprotein of the SARS-CoV-2 virus makes up this vaccine. It is capable of inducing a focused antiviral response against a spike protein. Since it lacks living or inactive pathogen subunits, it is also regarded as being relatively safe (Tu et al. 2020). In the USA, this mRNA vaccine is now widely used after receiving expedited FDA approval for phase II studies (Kaur and Gupta 2020).

BNT162b1 (BioNTech-Fosun Pharma-Pfizer) A crucial target of the virus-neutralising antibody, the trimerized SARS-CoV-2 RBD is encoded for by the codon-optimised mRNA vaccine known as BNT162b1. The RBD antigen is more immunogenic than other vaccines because it includes a trimerization domain. The mRNA is effectively transported because it is encased in ionizable cationic lipid nanoparticles with a diameter of 80 nm. According to phase 1/2 clinical trials, the concentration of IgG antibodies specific to RBD ranges from 8 to 46.3 times that of convalescent serum. This vaccine was assessed to have a geometric mean titre of SARS-CoV-2 neutralising antibodies between 1.8 and 2.8 times higher than that of convalescent serum (Mulligan et al. 2020).

ChAdOx1 (University of Oxford) AstraZeneca The recombinant adenovirus vaccine ChAdOx1 was created using a codon-improved S glycoprotein that has a leader sequence at the 5′ end that codes for tissue plasminogen activator. The tPA leader and the SARS-CoV-2 amino acid coding sequence (2–1273) were propagated in the shuttle plasmid. Between the Gateway recombination cloning site and the human cytomegalovirus promoter region, tetracycline-acting sites, and a polyadenylation signal from bovine growth hormone are all encoded on this transport plasmid (Falsey et al. 2021).

6.8 Role of Medicinal Plants and Their Secondary Metabolites in Managing COVID-19

The Earth is home to more than 500,000 species of plants, among which 10–15% are used as sources of pharmaceuticals and 10% as food (Borris 1996). A significant portion of the global population relies on plant-based medications and

phytochemicals for primary healthcare (Farnsworth 2007). Throughout human history, separating and characterising biologically active compounds and molecules from nature have resulted in the development of new remedies, propelling the health care and pharmaceutical sectors forward (Pye et al. 2017). In China, India, Japan, Africa, and several other countries, ethnomedicine has been the primary therapeutic approach since antiquity (Chang and But 2014; Dev 1999; Schultes and Raffauf 1990).

In traditional medicine and folk remedies, secondary plant metabolites play a crucial part in treating a variety of ailments. Usually, primary metabolites are converted into secondary metabolites in small quantities during a firm growth phase and for a definite function. They give plants resistance to biotic and abiotic stress. Thus, defence mechanisms used by plants vary depending on their unique requirements and are influenced by climatic variations, physiological traits, and environmental factors (Ballhorn et al. 2009). They provided the active pharmaceutical ingredients for drugs used to treat conditions as diverse as migraine, malaria, nervous disorders, and cancer. Several of these chemicals have been utilised as whole plants or plant extracts for human consumption or medicinal purposes. The scientific rationale for using plant substances in traditional medicine from diverse ancient civilizations can be traced back to the finding that secondary metabolites have various biological effects. They can prevent plant diseases and have antibacterial, antifungal, anti-inflammatory, anti-allergic, and antiviral activities. The chemical structures of secondary plant metabolites are used to categorise them into distinct classes. The major classes of plant secondary metabolites consist of alkaloids, terpenes, phenolics, and saponins. Potent pharmacological activities of this class of secondary metabolites are frequently reported (Hussein and El-Anssary 2019).

Plants' ability to create a wide variety of secondary metabolites stifled protein and enzyme function and reduced viral propagation in several ways. For a long time, people have turned to medicinal plants for relief from and protection against many sorts of ailments, including respiratory virus infections (Kiran et al. 2020; Park et al. 2016; ul Qamar et al. 2020). It is advantageous to use these herbs to treat viral infections because they stop viral replication and, through their effects on the immune system and inflammation regulation, indirectly enhance the health of the host. While there have been numerous studies on the efficacy of medicinal plants against SARS-CoV and MERS-CoV, the same cannot be said for COVID-19 illness, for which the available research is mostly limited to in silico experiments with phytometabolites (Mohammadi and Shaghaghi 2020). Figure 6.2 shows the various classes of plant secondary metabolites that target the host and viral elements involved in SARS-CoV-2 pathogenesis.

In this chapter, a review of the relevant literature was done using several sources, including PubMed, Science Direct, Web of Science, Google Scholar, and Scopus, to determine the role of medicinal floras and secondary metabolites in combating SARS-CoV-2. Different combinations of keywords related to "antiviral plants", "plants used against COVID", "plants used against SARS-CoV-2", and "plant molecule inhibitors targeting SARS-CoV-2" were used to retrieve the relevant

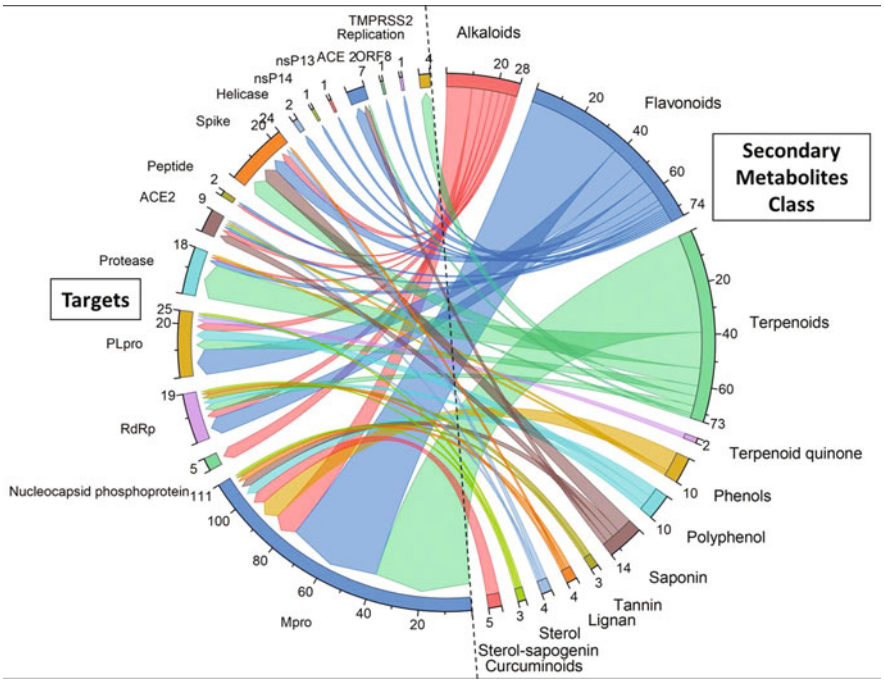

Fig. 6.2 The chord graph indicates the class of secondary metabolites and their SARS-CoV-2 targets

publications. A total of 64 papers were referred, further divided into two parts "pre-covid" before 2019 and "post-covid" from 2019 to 2022 (depicted schematically in Fig. 6.3). Based on this survey, the highest reports of antiviral plants against COVID-19 were identified from India owing to its rich diversity in medicinal plants, followed by Korea and China, respectively. Plants from the Fabaceae family are found to be the key inhibitors for SARS-CoV-2, following the family Lamiaceae, Asteraceae, and Zingiberaceae, respectively.

6.8.1 Use of Phyto-Crudes in Treating COVID-19 and Their Mode of Action

Many medicinal plants' crude extracts have shown antiviral efficacy against SARS-CoV, MERS-CoV, and SARS-CoV-2, which have the characters to advance drug development and is useful in treating COVID-19 (depicted in Fig. 6.4).

Wen et al. (2011) tested nearly 200 crude preparations of Chinese medicinal herbs in an in vitro study using Vero E6 cells to study the SARS-induced cytopathogenic effect (CPE). At dosages ranging from 25 to 200 g/ml, six herbal extracts from the

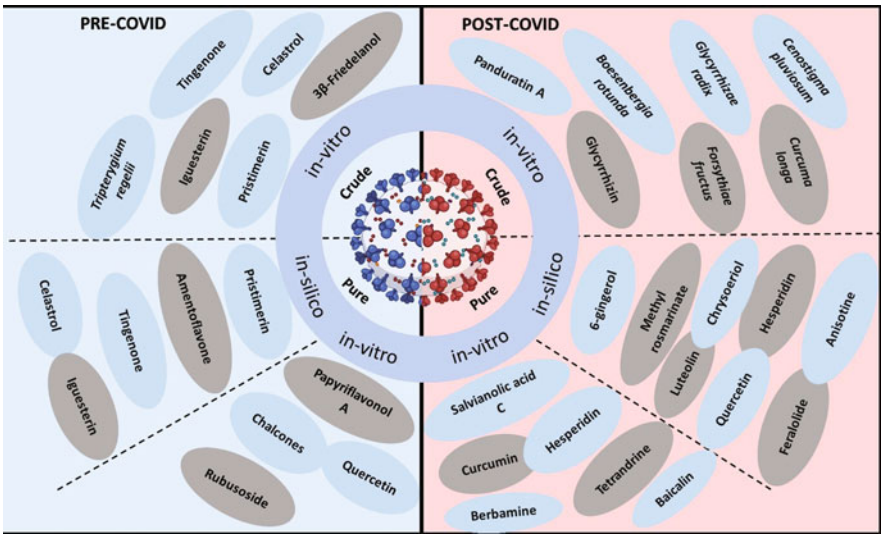

Fig. 6.3 Pre- and post-COVID studies involving plants, extracts, and purified metabolites targeting many structural and non-structural proteins of the SARS/MERS virus

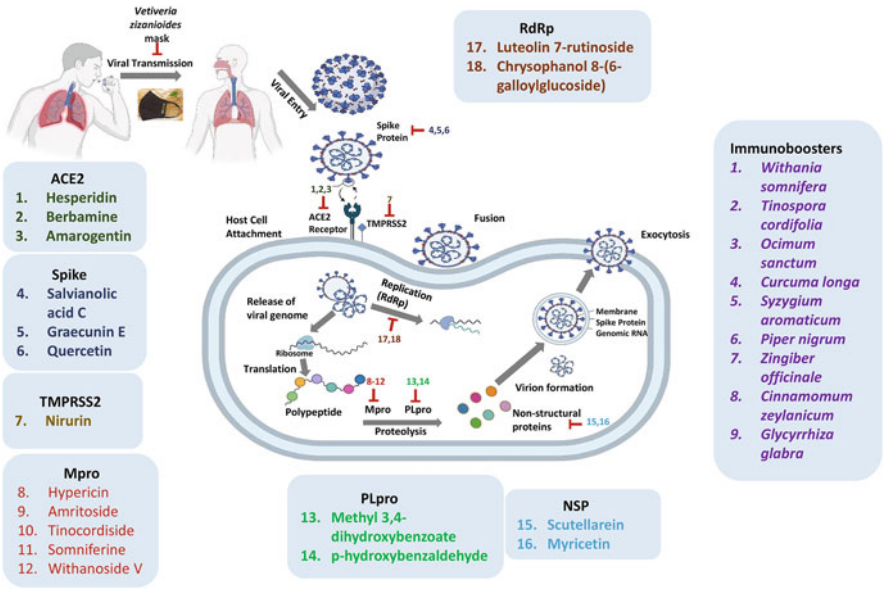

Fig. 6.4 Different well-established drug targets of SARS-CoV-2 and potential plant secondary metabolites were reported against those targets

Gentiana scabra (rhizome), *Taxillus chinensis* (leaf), *Cibotium barometz* (rhizome), *Cassia tora* (seed), and *Dioscorea batata* (tuber) were reported to be powerful SARS-CoV inhibitors. It was determined what dosages of six extracts were necessary to hinder viral multiplication by 50% (EC_{50}) and Vero E6 cell proliferation by 50% (CC_{50}). With IC_{50} values of 39 g/ml and 44 g/ml, respectively, *Cibotium barometz* and *Dioscorea batata* ethanol and methanol extracts also suppressed SARS-CoV 3CL protease activity, which is thought to be the primary mode of action. In an associated study, the terpene 3-friedelanol, from *Euphorbia neriifolia* leaves (ethanolic extract), outperformed the positive antiviral drug against human Coronavirus (Chang et al. 2012).

According to Ryu et al. (2010b)'s studies, methanol extracts from the bark of *Tripterygium regelii*, a plant in the Celastraceae family, can significantly reduce the expression of 3CLpro action of SARS-CoV-2, with a concentration of 30 g/mL inhibiting it by more than 70%. Four quinone-methide triterpenoid derivatives were isolated and identified as pristimerin, celastrol, iguesterin, and tingenone by their spectroscopic studies following bioactivity-directed fractionation of chloroform extracts. Celastrol was found to have an IC_{50} value of 10.3 M and binding energy of −9.58 kcal/mol in additional in vitro and in silico studies with 3CLpro. Similar to this, pristimerin has a binding energy of −9.87 kcal/mol and an IC_{50} value of 5.5 M, whereas tingenone and iguesterin had IC_{50} values of 9.9 and 2.6 M and binding energies of −9.75 and −9.18 kcal/mol, respectively.

Several phyto-crudes were reported for their antiviral activity following the SARS-CoV-2 outbreak in 2020. The anti-SARS-CoV-2 activity of Lianhua Qingwen, a patented traditional Chinese medicine, was demonstrated by Runfeng et al. (2020). On Vero E6 cells, cytopathic effect and plaque reduction assays were used to gauge Lianhua Qingwen's antiviral effectiveness against SARS-CoV-2. Plants like *Forsythia fructus*, *Lonicera japonica*, *Ephedra sinica*, *Gypsum fibrosum*, and *Rhodiola crenulate*, among others, are included in the composition of Lianhua Qingwen. In support of this, Hu et al. (2022) studies found that Lianhua Qingwen significantly reduced the mRNA synthesis of proinflammatory cytokines (IL-6, CCL-2/MCP-1, TNF-α, and CXCL-10/IP-10) and successfully prevented SARS-CoV-2 replication in Vero E6 cells. Furthermore, Lianhua Qingwen significantly decreases SARS-COV-2 multiplication, modifies virus shape, and exhibits anti-inflammatory effects in vitro.

Seventeen plant products used in both contemporary and traditional cuisines were identified in a strategic approach study as potential SARS-CoV-2 3CLPro inhibitors. Plant methanolic extracts were examined for their capacity to inhibit SARS-CoV-2 3CLpro activity in vitro using a fluorescence resonance energy transfer (FRET) evaluation. At 500 μg/mL, extracts of rhizomes of *Curcuma longa* (turmeric), seeds of *Brassica nigra* (mustard), and *Diplotaxis erucoides* (wall rocket) significantly inhibited $3CL^{pro}$ activity, with residual enzyme activities of 0%, 9.4%, and 14.9%, respectively. Among all the plant extracts, turmeric exhibited a 15.74 μg/mL of IC_{50} value, indicating the potential role of turmeric metabolites in reducing $3CL^{pro}$ activity (Guijarro-Real et al. 2021). Kanjanasirirat et al. (2020) examined 122 Thai natural plant products using fluorescence-based SARS-CoV-2 nucleoprotein

detection in Vero E6 cells in conjunction with a plaque reduction assay. With IC_{50} values of 3.62 g/mL and 0.08 M, respectively, treatment of Vero E6 cells with extracts of *Boesenbergia rotunda* and its metabolite panduratin A significantly reduced SARS-CoV-2 infectivity after viral infection. The pre-entry phase of SARS-CoV-2 spread was also prevented by panduratin A treatment with an IC_{50} of 5.30 M. This study showed that panduratin A can treat and prevent SARS-CoV-2 infection. Furthermore, panduratin A's antiviral activity was confirmed by the discovery that it prevented viral replication in human airway epithelial cells.

The bioactive saponin glycyrrhizin from *Glycyrrhiza glabra* was found to have potent antiviral activity against SARS-CoV-2. Glycyrrhizin prevents viral replication by blocking viral Mpro. At concentrations as low as 0.024 mg/mL (30 M), glycyrrhizin completely inhibited Mpro activity. At 1 mg/mL (post-entry) or 0.5 mg/mL (combined pre- and post-entry), glycyrrhizin completely inhibited SARS-CoV-2 proliferation (van de Sand et al. 2021). Pattaro-Júnior et al. (2022) used computational studies with Mpro as the target to evaluate the antiviral efficacy of a crude extract of Cenostigma pluviosum var. peltophoroides stem bark against SARS-CoV-2. Further, a recombinant Mpro was used to evaluate the inhibitory potential of proteolytic activity, and antiviral efficacy was analysed with infected Vero cells as experimental proof. In proteolytic kinetics experiments, pentagalloylglucose generated the best results, reducing the activity of recombinant M^{pro} by around 60%.

Nilavembu Kudineer (NVK) is a polyherbal Siddha decoction used as an effective antiviral therapy against chikungunya and dengue in India (Jain et al. 2020). It has been verified that this traditional treatment is safe, effective, and widely accepted. It is composed of *Andrographis paniculata*, *Trichosanthes cucumerina*, *Plectranthus vettiveroides*, *Hedyotis corymbose*, *Cyperus rotundus*, *Piper nigrum*, *Zingiber officinale*, *Santalum album*, and *Vetiveria zizanioides*. In their study, Srivastava et al. (2021) examined the relative effectiveness of Nilavembu Kudineer and placebo in treating mild to moderate SARS-CoV-2 illness. Patients treated with Nilavembu Kudineer demonstrated a significant decrease in SARS-CoV-2 load, length of hospitalisation time, and time needed to become asymptomatic as compared to placebo-treated patients.

6.8.2 *Use of Purified Plant Secondary Metabolites in Treating COVID-19 and Their Mode of Action*

As shown in Fig. 6.4, several purified PSMs are evaluated for their potential to inhibit the replication of SARS-CoV, MERS-CoV, and SARS-CoV-2 by inhibiting the viral proteins such as main protease (Mpro), papain-like protease (PLpro), RNA-dependent RNA polymerase (RdRp), spike proteins, and angiotensin-converting enzyme (ACE2).

6.8.3 Main Protease (M^{pro})

Biflavonoids are broadly diversified metabolites in bryophytes, gymnosperms, and angiosperms. Dimers of flavones, flavonones, and flavone-flavonones make up biflavonoids. The scientific community has started paying more attention to biflavonoids in recent years because of the pharmacological activities they exhibit, such as their ability to fight cancer, bacteria, viruses, inflammation, etc. (He et al. 2021). *Torreya nucifera* is a traditional Asian medicine that has been used for centuries. Eight diterpenoids and four biflavonoids were extracted from the plant and tested for their ability to inhibit SARS-CoV 3CLpro using FRET. Inhibitory activity against 3CLpro was most prominent for the biflavone amentoflavone (IC_{50} = 8.3 M). Three other purified flavones (luteolin, quercetin, and apigenin) were studied to determine the underlying structure–activity relationship of biflavones. The IC_{50} values for inhibiting 3CLpro activity were 280.8, 20.2, and 23.8 M for apigenin, luteolin, and quercetin, respectively. Results from enzymatic experiments were confirmed by binding energy values predicted by a molecular docking analysis (Ryu et al. 2010a).

Alkaloids are naturally occurring phytochemicals with established biological properties, a number of which have been competently investigated for their wide-ranging antiviral actions against diverse RNA and DNA viruses (Abookleesh et al. 2022). Abdallah et al. (2022) investigated the potential to inhibit SARS-CoV-2 Mpro under in vitro conditions by testing 33 plants from 17 different Saudi Arabian plant groups that were rich in alkaloids and phenols. To determine how effective the bioactive extracts were at inhibiting this enzyme, their key components were isolated. Additional computational analyses were performed, and their antiviral activity against the Egyptian SARS-CoV-2 variant was assessed. SARS-CoV-2 Mpro was inhibited by a high percentage in tests with extracts from *Nigella sativa*, *Aframomum melegueta*, and *Psiadia punctulata*. High percentages of inhibition (73.80%, 65.2%, 71.8%, and 63.21%) were found for gardenins A and B (*Psiadia punctulata*), 6-gingerol and 6-paradol (*Aframomum melegueta*), and thymoquinone (*Nigella sativa*), respectively. Anisotine, a naturally occurring alkaloid isolated from *Justicia adhatoda* leaves, has been shown to inhibit the Mpro of SARS-CoV-2 in a computational study. As shown by a binding energy of −7.9 kcal/mol, anisotine has a strong interaction with the catalytic residues of Mpro (His41 and Cys145) (Ghosh et al. 2021). In addition, *Justicia adhatoda*, also known as Vasaka, synthesises several alkaloids (vasicoline, anisotine, vasicinone, adhatodine, vasicine, and vasicolinone). These alkaloids are widely recognised for antiviral action against herpes simplex viruses and influenza (Chavan and Chowdhary 2014).

Flavonoids represent one of the most diverse classes of secondary metabolites, with over 9000 structurally distinct forms. Vegetables, tea, seeds, nuts, wine, and fruits are common sources of flavonoids. They are small, 15-carbon-backbone molecules with a variety of health benefits. Anti-inflammatory, antioxidant, antibacterial, antiviral, anticancer, and neuroprotective effects are just some of the many biological effects of flavonoids that have been discovered since their discovery in 1938 (Cazarolli et al. 2008; Kumar and Pandey 2013). Kandeil et al. (2021)

reported that the antioxidant compounds curcumin, quercetin, and hesperidin exhibited anti-SARS-CoV-2 activity. These phytochemicals inhibited virus replication in Vero E6 cells significantly. Their efficacy was also confirmed by molecular docking methods. The compounds are said to inhibit Mpro and to act directly on the virion to trigger inactivation. SARS-CoV-2 was tested against a Chinese herbal remedy for respiratory infections called "Shuanghuanglian" (Su et al. 2020). Shuanghuanglian's bioactive components inhibited 3CLpro and SARS-CoV-2 replication in a Vero E6 cell model in a dose-dependent manner. Bioactive components of Shuanghuanglian identified as baicalin and baicalein have been found to have potential anti-SARS-CoV-2 activity.

Andrographolide is a flavonoid discovered in the Acanthaceae plant, Andrographis paniculata. The antiviral properties of andrographolide have been reported in studies on several different viruses, including dengue, herpes simplex virus type 1, and Chikungunya (Gupta et al. 2017). In a study that relied on computational methods like molecular docking, target analysis, toxicity prediction, and ADME prediction, andrographolide's potential to inhibit SARS-major COV-2's protease (Mpro) was evaluated. When docked against the catalytic site of Mpro using computational docking tools, Andrographolide scored a much lower −3.09 Kcal/mol than synthetic compounds like disulfiram (−46.16 Kcal/mol), tideglusib (−61.79 Kcal/mol), and shikonin (−17.35 Kcal/mol) (Enmozhi et al. 2021; Jin et al. 2020).

In another study, alkaloids, flavonoids, and terpenoids from ayurvedic medicinal herbs Amla (*Emblica officinalis*), Bhumi Amla (*Phyllanthus niruri*), and Giloy (*Tinospora cordifolia*) were docked, and a simulation study was performed targeting M^{pro} of SARS-CoV-2. A total of 96 bioactive molecules, docked with Mpro of SARS-COV-2 and selected molecules were recognised and further confirmation was made through a molecular dynamics investigation. The least binding energy of −10.32 kcal/mol was recorded by withanoside V, followed by somniferine (−9.62 kcal/mol), tinocordiside (−9.10 kcal/mol), vicenin (−8.97 kcal/mol), isorientin 4′-*O*-glucoside 2″-*O*-p-hydroxybenzoate (−8.55 kcal/mol), and ursolic acid (−8.52 kcal/mol), respectively. The most promising drug candidates were analysed by the DruLiTo, pkCSM, and Molinspiration servers for their drug-likeness, ADEMT, and bioactivity score prediction (Murugesan et al. 2021). The Mpro inhibitory potential of Moroccan medicinal plants against SARS-CoV-2 was evaluated by computational investigations conducted by Aanouz et al. (2021). A total of 67 compounds of plant origin were docked, among which Crocin, Digitoxigenin, and β-Eudesmol recorded the least binding energy which is equal to −8.2 kcal/mol, −7.2 kcal/mol, and −7.1 kcal/mol, respectively, as compared to the chloroquine.

6.8.4 Papain-Like Protease (PL^{pro})

Alnus japonica, a member of the family Betulaceae, is an endemic Alnus species in Korea, North China, and Japan that have well-reported antiviral activity (Tung et al. 2010). In a scientific investigation made by Park et al. (2012a), secondary

metabolites isolated from *Alnus japonica* were screened for their antiviral activity against the PL^{pro}, which regulates the replication of SARS coronavirus. Among the isolated hirsutenone, diarylheptanoids recorded the most promising suppression of PLpro activity which was evident by lower IC_{50} (4.1 M). When the structure–activity link was examined, it became clear that the compound's catechol and unsaturated carbonyl moiety were crucial for inhibiting the SARS-CoV protease. Another perennial herb with antiviral properties against the zika virus is *Angelica keiskei* (Umbelliferae), which has traditional uses as a mild cathartic, diuretic, and antiviral (Kil et al. 2017; Mottin et al. 2022). Four coumarins and nine alkylated chalcones from *Angelica keiskei* (leaf) were found to inhibit $3CL^{pro}$ and PL^{pro} of SARS-CoV. Cell-free trans-cleavage inhibition assays and deubiquitination activity assays were used to determine the degree of inhibition. The perhydroxyl group on chalcone 6 was the most effective inhibitor of 3CLpro and PLpro, with IC_{50} values of 11.4 M and 1.2 M, respectively (Park et al. 2016).

Flavonoids isolated from *Psoralea corylifolia* seeds were investigated to inhibit the SARS-CoV's PL^{pro}. The crude ethanol extract showed promising results, having 15 μg/ml as an IC_{50} value. Six aromatic molecules named bavachinin, isobavachalcone, neobavaisoflavone, 4′-*O*-methylbavachalcone, psoralidin, and corylifol A were identified by bioactivity-guided fractionation of ethanolic extracts. With IC_{50} concentrations ranging between 4.2 and 38.4 μM, all flavonoids recorded dose-dependent PL^{pro} inhibition. Isobavachalcone ($IC_{50,}$7.3 μM) and psoralidin ($IC_{50,}$ 4.2 μM) were identified as the two most promising inhibitors of PL^{pro} (Kim et al. 2014).

Natural phenolic acids and their derivatives inhibited the replication of several human viruses. These viruses included hepatitis C virus, hepatitis B virus, influenza virus, herpes simplex virus, human immunodeficiency virus, and respiratory syncytial virus (Wu et al. 2017). In a scientific investigation conducted by Srinivasan et al. (2022), several phenolic secondary metabolites were analysed for their antiviral property against PL^{pro} of SARS-CoV-2. They identified three phenolic chemicals, viz. 4-(2-hydroxyethyl) phenol (YRL), 4-hydroxybenzaldehyde (HBA), and methyl 3, 4-dihydroxybenzoate (HE9), that bind to PL^{pro} catalytic site, thereby inhibiting the enzyme activity. The molecules that were found through X-ray screening and then functionalized were able to inhibit PLpro in a deISGylation activity experiment. Further, the antiviral potential of these compounds is confirmed with Vero cell line experiments.

6.8.5 RNA-Dependent RNA Polymerase (RdRp)

Our review of the available literature suggests that there are few in vitro and in vivo studies looking for RdRp inhibitory plant secondary metabolites. The drugs from Chinese traditional medicinal with documented anti-SARS-CoV properties and structurally comparable chemicals were screened by computational studies targeting SARS-CoV-2's RdRp. Similarly, the most common phenolic compound, theaflavin

in *Camellia sinensis* (family, Theaceae) was proposed as a potential inhibitor of SARS-CoV-2's RdRp. In comparison to other flavonoids, theaflavin recorded the least idock score of −9.11 kcal/mol when interacting with RdRp's catalytic pocket of SARS-CoV-2. However, theaflavin recorded −8.03 kcal/mol and −8.26 kcal/mol of idock score with RdRp's of SARS-CoV and MERS-CoV, respectively. Further investigation showed that hydrophobic interactions were the primary contributors to binding, and the interaction was stabilised by multiple hydrogen bonds between theaflavin and AAs of RdRp's catalytic site (Lung et al. 2020). In a similar attempt, Hesperidin, a flavonoid isolated from fruits of *Citrus sinensis*, a member of the family Rutaceae, was reported as a potential anti-SARS-CoV-2 via inhibiting RdRp (Goyal et al. 2020). Koulgi et al. (2021) performed computational studies to find potential RdRp inhibitory plant secondary metabolites. They found four potential metabolites swertiapuniside, cordifolide A, sitoindoside IX, and amarogentin, commonly found *Swertia chirayita*, *Tinospora cordifolia,* and *Withania somnifera* as inhibitors of RdRp through MD simulation studies. The glycosidic residue of these phytochemicals was found to form favourable interactions with RdRp's seven conserved motifs containing polar and charged amino acids.

In a different attempt, Ahmad et al. (2020) screened drugs approved by FDA following computational methods against RdRp, aiming to repurpose these drugs to manage COVID-19. Here, Ornipressin, Lypressin, Examorelin, Polymyxin B1, Nacortocin, Cistinexine, and Cisatracurium were reported as potential inhibitors of RdRp.

6.8.6 Spike Protein

Risener et al. (2023) screened 1867 extracts primarily derived from 632 plants, 27 fungi, and one chromista and 18 pure compounds to inhibit the attachment/entry of a pseudotyped lentivirus model expressing SARS-COV-2 spike into human HEK-293T-hACE2 cells. After initial screening and eliminating the extracts with cytotoxicity and containing cardiac glycosidase, two extracts from the *Solidago altissima* flower and *Pteridium aquilinum* rhizome were found to have significant potential to inhibit the entry of four pseudotyped variants and infectious SARS-CoV-2 with $EC_{50} < 5$ μg/mL. In a similar attempt, Yang et al. (2020) studied the efficacy of a flavonoid compound Salvianolic acid C in a cell line assay using a pseudovirus model system containing the S protein of SARS-CoV-2. When the experiment was carried out utilising HEK293T cells expressing hACE2, Salvianolic acid C was found to inhibit the viral entry into the host cell with IC_{50} of 3.85 μM. Further, the researchers validated the results with SARS-CoV-2 and Vero-E6 cells, where they found similar results with EC_{50} of 3.41 μM.

Extracts from seven medicinal plants grown in high-altitude from Nepal were tested for their capabilities to block interactions following enzyme-linked immunosorbent assay (Basnet et al. 2022). *Tinospora cordifolia* recorded a 50% reduction in SARS-CoV-2 S protein–hACE2 interactions at 1.25 mg/mL, followed by extracts of

Heracleum nepalense and *Pogostemon benghalensis*. Meanwhile, positive control molnupiravir required 50 μM concentration to inhibit the interaction by 25%. Further computational studies with secondary metabolites of *Tinospora cardifolia* highlighted cordifolioside-A as a potential metabolite which interferes with host recognition by SARS-COV-2 by blocking critical amino acids of S1-RBD.

For colds, coughs, and fever, Kabasura Kudineer Chooranam (KKC), a Siddha remedy, is extensively prescribed in Southern India. 32 plant secondary metabolites of herbs found in KKC and 5 from JACOM herbal formulation were molecular docked against the S protein of SARS-CoV-2. Chrysoeriol, Luteolin, and Scutellarein belong to the flavonoids class of secondary metabolites, and these are some of the main phytochemicals present in Chooranam and exhibit a good binding affinity for the S protein of SARS-CoV-2. It has been discovered that all these compounds exhibit hydrogen bond interactions with at least four amino acid residues in S protein, indicating their stronger affinity for S protein (Kiran et al. 2020).

Another study tested the antiviral properties of seselin extracted from *Aegle marmelos* leaf extracts. In silico evaluation of the efficiency of seselin against multiple SARS-COV-2 targets, including S protein's S2 and M^{pro}were performed. Having binding energies of −6.3 kcal/mol, −6.9 kcal/mol, and −6.7 kcal/mol, respectively, seselin demonstrated the highest interaction with receptors, spike protein S2, and SARS-CoV-2 M^{pro}. Docking studies involving three unique receptors showed that all the protein–ligand complexes with the minimum energy were stabilised by hydrogen bonds and stacking interactions. According to the findings of the pharmacokinetic study, this secondary metabolite exhibited desirable druggability characteristics. These observations demonstrated the potential of seselin to inhibit many targets of SARS-COV-2 and a potential candidate to be a feasible therapeutic treatment for COVID-19 (Nivetha et al. 2021).

6.8.7 Angiotensin-Converting Enzyme (ACE2)

Organosulfur are signature compounds present in Allium plants, including onions (*Allium cepa*) and garlic (*Allium sativum*). Organosulfur compounds from *Allium sativum*, allyl disulfide and trisulfide, were studied in silico and demonstrated considerable binding potential with human ACE2 (−9.07 kcal/mol). Results indicate that the 17 major organosulfur compounds from the essential oil of garlic recorded an energetically favourable interaction with ACE2 protein, thereby reducing the capabilities of SARS-CoV-2 to recognise the host cell and subsequent entry into host cells (Thuy et al. 2020). A similar computational study has reported that hesperidin, a flavonoid present in *Citrus sinensis* inhibits ACE2, RdRp, and open reading frame 8 (ORF8) of SARS-CoV-2 (Goyal et al. 2020). Hesperidin bounds tightly at the active position of ACE2 with the binding energy of −9.5 kcal/mol and also bounds tightly in the active position of RdRp with a docking score of −10.01. Similarly, it is bound tightly to an active site of ORF8 with a binding energy of −14.45 kcal/mol. Huang et al. (2021) demonstrated the SARS-CoV-2 suppressive nature of berbamine

alkaloid by interfering with the endolysosomal trafficking of ACE2. They evaluated the anti-SARS-CoV-2 action of berbamine using Vero-E6 cells and discovered that berbamine considerably suppressed viral load having EC_{50} 2.4 μM. Some reported plant extracts and their secondary metabolites targeting SARS-CoV-2, SARS-CoV, and MERS-CoV are listed in Table 6.2.

6.9 Herbal Formulations Used for COVID-19 Management

Medicinal plants have been widely utilised to improve health by enhancing the host's resistance to certain diseases. At the start of the epidemic, the nature of the coronavirus was poorly understood, and the type of medications to be consumed was inaccessible due to the lockdown. Much of the world resorted to home remedies that could alleviate the symptoms (cold, cough, headache, and fatigue) of COVID 19 which was regarded as a pneumonia-like disease. This section discusses community-based medicine, which includes various herbal formulations used worldwide to manage COVID-19. Ethnobotanical studies reveal that different medicinal plants were used for their antioxidant, anti-inflammatory, and immunity-boosting characters based on geographical location.

A literature survey of medicinal plants consumed in Morocco fez city reported 49 plant species representing 28 families were suggested to explore further for COVID-19 management. Among them, the most representative families were Lamiaceae (12.5 %), containing many aromatic plants such as *Mentha pulegium, Origanum majorana, Rosmarinus officinalis, Salvia officinalis,* and *Thymus vulgaris* used as essential oils prepared from aerial parts. Followed by Asteraceae (11%), a family of plants *Artemisia vulgaris, Artemisia absinthium, Chamaemelum nobile,* and *Saussurea costus* were orally consumed (Benkhaira et al. 2021). Another research from Morocco found that oral ingestion of infusion or decoction of aerial components from Lamiaceae and Asteraceae species, seeds from Apiaceae species, rhizomes from *Zingiber officinale* and *Alpinia officinarum*, and dried powder from young Cupressaceae leaves. The fruits of *Phoenix dactylifera*, the seeds of *Lepidium sativum* and *Nigella sativa*, the rhizome powder of *Curcuma xanthorrhiza*, the oil of *Olea europaea*, and the bulbs of the Liliaceae family are also consumed directly. For inhalation, a hot infusion of Eucalyptus globulus is utilised (Alamri et al. 2020). The Ethiopian medicinal plants such as *Azadirachta indica, Moringa borziana, Acacia abyssinica, Acanthus polystachyus, Acacia etbaica, Acacia nigra,* and *Osyris quadripartite* used to treat viral infections were reported to be rich in flavonoids, terpenoids, and polyphenols (Tegen et al. 2021).

It is no exaggeration to say that the traditional medicine system of Indian is one of the world's ancient medical disciplines and has been instrumental in the development of healthcare worldwide ever since it was first practised thousands of years ago. Indigenously recognised traditional medicinal systems of India are Ayurveda, Yoga, Unani, Siddha, and Homoeopathy (AYUSH), which takes a holistic approach to treat a variety of diseases. The pharmacological modalities of AYUSH rely on

Table 6.2 Compilation of medicinal plants, class of compounds, and secondary metabolites reported to be anti-SARS-CoV and anti-SARS-CoV-2

S. No	Plant	Family	Plant part	Nature of study	Relevant SM	SM class	Target/mode of action	Reference
1	*Torreya nucifera*	Taxaceae	Leaves	A	Ferruginol, amentoflavone	Terpenoids, flavonoids	SARS-CoV Mpro	Ryu et al. (2010a)
2	*Tripterygium regelii*	Celastraceae	Bark	B	Celastrol	Terpenoids	SARS-CoV Mpro	Ryu et al. (2010b)
					Pristimerin			
					Tingenone			
					Iguesterin			
3	*Alnus japonica*	Betulaceae	Bark	A	Hirsutenone	Diarylheptanoids	SARS-CoV PLpro	Park et al. (2012b)
4	*Scutellaria baicalensis*	Lamiaceae	Whole plant	A	Scutellarein	Flavone	SARS-CoV helicase, nsP13	Yu et al. (2012)
	Aglaia perviridis	Meliaceae	Whole plant	C	Myricetin	Flavonoids	SARS-CoV helicase, nsP14	
5	*Psoralea corylifolia*	Fabaceae	Seeds	A	Isobavachalcone	Flavonoids	SARS-CoV PLpro	Kim et al. (2014)
					Psoralidin			
					4′-*O*-methylbavachalcone			
6	*Paulownia tomentosa*	Paulowniaceae	Fruits	A	Tomentin E	Flavonoids	SARS-CoV PLpro	Cho et al. (2013)
					Tomentin A			
					Tomentin B			
					3′-*O*-methyldiplacol			
					4′-*O*-methyldiplacol			
7	*Tribulus terrestris*	Zygophyllaceae	Fruits	A	Terrestriamide	Phenylpropanoids	SARS-CoV PLpro	Song et al. (2014)
					N-trans-feruloyloctopamine			

8	*Cibotium barometz*	Dicksoniaceae	Rhizome	D	NA	NA	SARS-CoV Mpro	Wen et al. (2011)
	Dioscorea batatas		Tuber					
9	*Salvia miltiorrhiza*	Lamiaceae	Roots	A	Cryptotanshinone	Terpenoid quinone	SARS-CoV—PLpro	Park et al. (2012b)
					Tanshinone IIA			
10	*Euphorbia neriifolia*	Euphorbiaceae	Leaves	D	3β-Friedelanol	Terpenoids	Antiviral activity against SARS-CoV	Chang et al. (2012)
11	*Angelica keiskei*	Apiaceae	Leaf	A	Chalcones	Flavonoids	SARS-CoV Mpro and PL pro	Park et al. (2016)
12	*Broussonetia papyrifera*	Moraceae	Roots	A	Papyriflavonol A	Flavonoids	SARS-CoV—PLpro	Park et al. (2017)
13	*Echinacea purpurea*	Asteraceae	Roots	A	NA	NA	MERS-CoV	Engler et al. (2017)
14	NA	NA	NA	C	Rubusoside	Terpenoids	SARS-CoV Mpro	Nguyen et al. (2015)
					Quercetin	Flavonoids		
					Rubusoside+Quercetin			
15	*Zingiber officinale*	Zingiberaceae	Rhizome	E	6-gingerol	Phenolic	SARS-CoV 5R7Y protease	Rathinavel et al. (2020)
16	*Plectranthus amboinicus*	Lamiaceae	NA	E	Chrysoeriol	Flavonoids	Spike (S) protein of SARS-CoV-2	Kiran et al. (2020)
	Costus speciosus	Costaceae			Luteolin			
	Carica Papaya	Caricaceae			Quercetin			
17	*Citrus sinensis*	Rutaceae	Fruit	E	Hesperidin	Flavonoids	SARS-CoV-2 ACE2	Goyal et al. (2020)
							SARS-CoV-2 RdRp	
							SARS-CoV-2 ORF8	

(continued)

Table 6.2 (continued)

S. No	Plant	Family	Plant part	Nature of study	Relevant SM	SM class	Target/mode of action	Reference
18	*Justicia adhatoda*	Acanthaceae	Leaf	E	Anisotine	Alkaloids	Mpro of SARS-CoV-2	Ghosh et al. (2021)
19	*Aloe vera*	Asphodelaceae	Leaf	E	Feralolide	curcuminoids	SARS-CoV-2 Mpro	Mpiana et al. (2020)
20	*Psorothamnus arborescens*	Fabaceae	NA	E	5, 7, 30, 40-Tetrahydroxy-2′-(3,3-dimethylallyl) isoflavon	Flavonoids	SARS-CoV-2 Mpro	ul Qamar et al. (2020)
	Myrica cerifera	Myricaceae	NA	NA	Myricitrin			
	Hyptis atrorubens	Lamiaceae	NA	NA	Methyl rosmarinate	Phenolic		
21	*Forsythiae Fructus*	Oleaceae	NA	D	NA	NA	SARS-CoV-2 replication	Runfeng et al. (2020)
22	NA	NA	NA	E	Herbacetin	Flavonoids	SARS-CoV-2 Mpro	Jo et al. (2020)
					Pectolinarin			
					Rhoifolin			
23	NA	NA	NA	E	Naringenin	Flavonoids	SARS-CoV-2 Mpro	Khaerunnisa et al. (2020)
					Kaempferol	Polyphenols		
					Quercetin	Flavonoids		
					Allicin	Thiosulfonates		
					Catechin	Flavonoids		
					Gingerol	Phenolic		
					Zingerol	Phenolic		
					Epicatechin-gallate	Flavonoids		
					Curcumin	Curcuminoids		
					Oleuropein	Phenolic		
					Apigenin-7-glucoside	Flavonoids		
					Demethoxycurcumin	Curcuminoids		
					Luteolin-7-glucoside	Flavonoids		

24	*Andrographis paniculata*	Acanthaceae	NA	E	Andrographolide	Flavonoids	SARS-CoV-2 Mpro	Enmozhi et al. (2021)
25	NA	NA	NA	E	Gallic acid	Polyphenol	SARS-CoV-2 Mpro	Alrasheid et al. (2021)
					Quercetin	Flavonoids		
					Naringin	Flavonoids		
					Capsaicin	Alkaloids		
					Psychotrine			
26	*Crocus Sativus*	Iridaceae	NA	E	Crocin	NA	SARS-CoV-2 Mpro	Aanouz et al. (2021)
	Nerium Oleander	Apocynaceae			Digitoxigenin	Cardenolide glycoside		
	Laurus Nobilis	Lauraceae			β-Eudesmol	Sesquiterpenoid	SARS-CoV-2 Mpro	
27	*Camellia sinensis*	Theaceae	NA	E	Theaflavin	Phenolic	SARS-CoV-2 RdRp	Lung et al. (2020)
28	*Aegle marmelos*	Rutaceae	NA	E	Seselin	Curcuminoids	SARS-CoV-2 Mpro, spike protein S2	Nivetha et al. (2021)
29	*Curcuma longa*	Zingiberaceae	Rhizomes	D	NA	NA	SARS-CoV-2 Mpro	Guijarro-Real et al. (2021)
31	NA	NA	NA	NA	Quercetin	Flavonoids	SARS-CoV-2 Mpro	Bahun et al. (2022)
					Ellagic acid	Polyphenol		
					Curcumin	Curcuminoids		
					Epigallocatechin gallate	Polyphenol		
32	*Echinacea purpurea*	Asteraceae	Herb and roots	C	Echinaforce®		Antiviral activity against MERS-CoV	Signer et al. (2020)
33	*Withania somnifera*	Solanaceae	NA	E	Withanoside V	Alkaloids	SARS-CoV-2 Mpro	Shree et al. (2022)
					Somniferine			
	Tinospora cordifolia	Menispermaceae			Tinocordiside	Sesquiterpenoid		
	Ocimum sanctum	Lamiaceae			Vicenin	Flavonoids		
					Isorientin 4′-*O*-glucoside 2″-*O*-p-hydroxybenzoate			
					Ursolic acid	Terpenoids		

(continued)

Table 6.2 (continued)

S. No	Plant	Family	Plant part	Nature of study	Relevant SM	SM class	Target/mode of action	Reference
34	NA	NA	NA	NA	Methyl 3,4-dihydroxybenzoate	Polyphenol	SARS-CoV-2 PLpro	Srinivasan et al. (2022)
					p-hydroxybenzaldehyde			
					4-(2-hydroxyethyl) phenol			
35	*Picrorhiza kurroa*	Plantaginaceae	NA	E	Acetovanillone	Phenylketones	SARS-CoV-2 PLpro, RdRp	Khuntia et al. (2021)
	Azadirachta indica	Meliaceae			Myrtenol	Terpenoids		
	Cyperus rotundus	Cyperaceae			Nimbochalcin	NA		
36	NA	NA	NA	E	10-Hydroxyusambarensine	Alkaloids	SARS-CoV-2 Mpro	Gyebi et al. (2021)
					Cryptoquindoline			
					6-Oxoisoiguesterin	Terpenoids		
					22-Hydroxyhopan-3-one			
37	*Tinospora cordifolia*	Menispermaceae	NA	E	Amritoside	Tannin	SARS-CoV-2 Mpro	Murugesan et al. (2021)
					Apigenin-6-*C*-glucosyl7-*O*-glucosid	Flavonoids		
	Emblica officinalis	Phyllanthaceae	NA		Pectolinarin			
					Astragalin			

38	*Calotropis gigantean*	Apocynaceae	NA	E	Juniper camphor	Terpenoids	SARS-CoV-2 Mpro	Dutta et al. (2021)
					Ethyl 4-fluoro-1-methyl-1H-imidazole-5-carboxylate			
					Bicyclo[4.3.0]nonane, 1 isopropenyl-4,5-dimethyl-5-phenylsulfonylmethyl			
					Stearic acid			
39	*Rheum emodi*	Polygonaceae	NA	E	Emodin	Alkaloids	N-terminal domain (NTD) of nucleo-capsid phosphoprotein	Rolta et al. (2021)
					Aloe-emodin			
					Anthrarufin			
					Alizarine			
					Dantron			
40	*Marrubium vulgare*	Lamiaceae	NA	E	Luteolin 7-rutinoside	Flavonoids	SARS-CoV-2 RdRp	El Alami et al. (2020)
	Rumex dentatus	Polygonaceae			Chrysophanol 8-(6-galloylglucoside)	Alkaloids		
	Acacia	Fabaceae			Kaempferol 7-(600-galloylglucoside)	Flavonoids		
	Rumex dentatus	Polygonaceae			Chrysophanol 8-(6-galloylglucoside)	Alkaloids		
	Guiera senegalensis	Combretaceae			3,4,5-tri-*O*-galloylquinic acid	Tannin		
	Chenopodium ambrosioides	Amaranthaceae			Mulberrofuran G	Flavonoids		
	Datura innoxia	Solanaceae			Withanolide A	Alkaloids		
	Capparis decidua	Capparaceae			Isocodonocarpine	Alkaloids		
	Senna obtusifolia	Fabaceae			Calonysterone	Sterol		

(continued)

Table 6.2 (continued)

S. No	Plant	Family	Plant part	Nature of study	Relevant SM	SM class	Target/mode of action	Reference
41	*Nyctanthes Arbor-tristis*	Oleaceae	NA	E	Astragalin	Flavonoids	SARS-CoV-2 protease	Srivastava et al. (2021)
					Lupeol	Terpenoids		
	Aloe barbadensis	Asphodelaceae			Aloenin	Glycoside		
					Aloesin			
	Tinospora cordifolia	Menispermaceae			Berberine	Alkaloids		
					Sitosterol	Sterol		
	Curcuma longa	Zingiberaceae			Curcumin	Curcuminoids		
	Azadirachta indica	Meliaceae			Nimbin	Terpenoids		
	Withania somnifera	Solanaceae			Withanolide	Alkaloids		
					Withaferin A	Saponin		
	Zingiber officinale	Zingiberaceae			Gingerol	Phenolic		
					Shogaol	Phenolic		
	Allium cepa	Amaryllidaceae			Quercetin	Flavonoids		
	Ocimum tenuiflorum	Lamiaceae			Ursolic acid	Terpenoids		
					Apigenin	Flavonoids		
	Cannabis sativa	Cannabaceae			Cannabidiol	Cannabinoids		
	Piper nigrum	Piperaceae			Piperine	Alkaloids		
42	*Boesenbergia rotunda*	Zingiberaceae	Rhizome	F	Panduratin A	Flavonoids	SARS-CoV-2 infectivity in Vero E6 cells	Kanjanasirirat et al. (2020)

43	*Trigonella foenum-graecum*	Fabaceae	NA	E	Graecunin E	Saponins	SARS-CoV-2 spike protein	Puttaswamy et al. (2020)
					Trigofoenoside E1	Saponins		
					Uttronin B	Saponins		
					Stigmasteryl glucoside	Steroid		
					Yuccagenin	Terpenoids		
	Veratrum album	Liliaceae			Pseudojervine	Saponins		
	Mallotus philippensis	Euphorbiaceae			Kamalachalcone C	Flavonoids		
	Phyllanthus niruri	Phyllanthaceae			Nirurin	Flavonoids	SARS-CoV-2 TMPRSS2	
	Foeniculum vulgare	Apiaceae			Cis-Miyabenol C	Flavonoids		
	Plumbago zeylanica	Plumbaginaceae			Plumbagin	Alkaloids		
	Punica granatum	Punicaceae			Granatin B	Tannins		
	Hypericum perforatum	Hypericaceae			Hypericin	Alkaloids	SARS-CoV-2 Mpro	
	Ginkgo biloba	Ginkgoaceae			Amentoflavone	Flavonoids		
					Ginkgetin	Flavonoids		
					Isoginkgetin	Flavonoids		
					Agathisflavone	Flavonoids		
	Terminalia chebula	Combretaceae			Terflavin B	Flavonoids		
	Paeonia delavayi	Paeoniaceae			Mudanpioside J	Terpenoids		
	Justicia purpurea	Acanthaceae			Justalakonin	Lignans		

(continued)

Table 6.2 (continued)

S. No	Plant	Family	Plant part	Nature of study	Relevant SM	SM class	Target/mode of action	Reference
	Chrysobalanus icaco	Chrysobalanaceae			Myricetin 3-rutinoside	Flavonoids	SARS-CoV-2 RdRp	
	Citrus limon	Rutaceae			Eriodictyol-7-*O*-rutinoside	Flavonoids		
	Bupleurum rotundifolium	Apiaceae			Rotundioside B	Terpenoids		
	Emblica officinalis	Phyllanthaceae			Phyllanemblinin C	Tannins		
					Emblicanin A	Tannins		
	Hippomane mancinella	Euphorbiaceae			Hippomanin A	Flavonoids glycoside		
44	NA	NA	NA	C	Salvianolic acid C	Flavonoids	SARS-CoV-2 spike protein	Yang et al. (2020)
45	*Scutellaria Baicalensis*	Lamiaceae	NA	C	Baicalin	Flavonoids	SARS-CoV-2 Mpro	Huang et al. (2020)
46	NA	NA	NA	C	Berbamine	Alkaloids	SARS-CoV-2 ACE2	Huang et al. (2021)
47	*Andrographis paniculata*	Acanthaceae	NA	E	Neoandrographolide	Terpenoids	Mpro, PLpro, RdRp, Spike-ACE2	Murugan et al. (2021)
48	*Ocimum sanctum*	Lamiaceae	NA	E	Chlorogenic acid	Phenolic	SARS-CoV-2 Mpro	Mohapatra et al. (2020)
					Luteolin-7-*O*-glucuronide	Flavonoids		
49	*Allium sativum*	Amaryllidaceae	NA	E			SARS-CoV-2 ACE2	Thuy et al. (2020)
50	*Moringa oleifera*	Moringaceae	NA	E	Kaempferol	Flavonoids	SARS-CoV-2 peptide	Hamza et al. (2021)
					Anthraquinone	Alkaloids		

51	NA	NA	NA	E	Luteolin	Flavonoids	SARS-CoV-2 Mpro	Ansari et al. (2020)
52	*Citri reticulatae*	Rutaceae	NA	E	Hesperidin	Flavonoids	Mpro, ACE 2 receptor	Yang et al. (2020)
	Bupleuri radix	Apiaceae			Saikosaponin A	Saponin		
	Mori folium	Asteraceae			Rutin	Flavonoids		
	Eriobotryae folium	Rosaceae			Corosolic acid	Terpenoids		
	Rehmanniae radix	Orobanchaceae			Verbascoside	Polyphenol		
	Scutellariae radix	Lamiaceae			Baicalin	Flavonoids		
	Glycyrrhizae radix	Fabaceae			Glycyrrhizin	Saponin		
	Mori ramulus	Moraceae			Mulberroside A	Stilbenoid		
	Lonicerae flos	Caprifoliaceae			Cynaroside	Flavonoids		
53	*Citrus Sp.*	Rutaceae	NA	E	Hesperidin	Flavonoids	SARS-CoV-2 Mpro	Adem et al. (2020)
					Rutin			
					Diosmin			
					Apiin			
					Diacetylcurcumin	Curcuminoids		
54	NA	NA	NA	E	Glabridin	Flavonoids	SARS-CoV-2 Mpro	Jamali et al. (2021)
					Catechin			
					Fisetin			
55	*Acacia seyal*	Fabaceae	NA	E	Rutin	Flavonoids	Mpro, SARS-CoV-2 receptor binding domain	Ahmed et al. (2020)
	Cymbopogon commutatus	Poaceae			Catechin			
	Indigofera caerulea	Fabaceae			Kaempferol			

(continued)

Table 6.2 (continued)

S. No	Plant	Family	Plant part	Nature of study	Relevant SM	SM class	Target/mode of action	Reference
56	*Swertia chirata*	Gentianaceae	NA	E	Amarogentin	Phenolic	Spike glycoprotein, ACE2 receptor	Maurya et al. (2022)
	Artemisia vulgaris	Asteraceae			Eufoliatorin	Saponin		
	Alstonia scholaris	Apocynaceae			α-amyrin	Terpenoids		
	Caesalpinia crista	Fabaceae			Caesalpinins	Saponin		
	Picrorhiza kurroa	Plantaginaceae			Kutkin	Saponin		
	Alstonia scholaris	Apocynaceae			β-sitosterol	Sterol		
	Atropa belladonna	Solanaceae			Belladonnine	Alkaloids		
57	*Justicia procumbens*	Acanthaceae		E	Justicidin D	Lignan	RdRp, Mpro, and spike	Gani et al. (2021)
	Camptotheca acuminata	Nyssaceae			10-methoxycamptothecin	Alkaloids		
	Calophyllum inophyllum	Clusiaceae			Inoxanthone	Flavonoids		
	Hymenocallis arenicola	Amaryllidaceae			Caribine	Alkaloids		
58	*Eurycoma harmandiana*	Simaroubaceae	NA	E	Canthin-6-one 9-*O*-beta-glucopyranoside	Alkaloids	Mpro, Mpro, Plpro	Verma et al. (2021)

59	*Glycyrrhiza glabra*	Fabaceae	NA	E	Rocymosin B	Polyphenol	Mpro, Mpro, Plpro	Shawky et al. (2020)
	Cichorium intybus	Asteraceae			Verbascoside			
	Anastatica hierochuntica	Brassicaceae			Rutin	Flavonoids		
	Trigonella foenum-graecum	Fabaceae			Fenugreekine	Sterol-sapogenin		
60	*Nigella sativa*	Ranunculaceae	NA	A	Thymoquinone	Alkaloids	SARS-CoV-2 Mpro	Abdallah et al. (2022)
	Aframomum melegueta	Zingiberaceae			6-gingerol	Phenolic		
					6-paradol	Alkaloids		
	Psiadia punctulata	Asteraceae			Gardenin A	Flavonoids		
61	*Glycyrrhiza glabra*	Fabaceae	NA	D	Glycyrrhizin	Saponin	SARS-CoV-2 Mpro	van de Sand et al. (2021)
62	*Cenostigma pluviosum*	Fabaceae	Stem bark	D			SARS-CoV-2 Mpro	Pattaro-Júnior et al. (2022)
63	NA	NA	NA	C	Curcumin	Curcuminoids	SARS-CoV-2 Mpro	Kandeil et al. (2021)
					Hesperidin	Flavonoids		
64	*Apium graveolens*	NA	NA	E	Apigenin	NA	SARS-CoV-2 Mpro	Sampangi-Ramaiah et al. (2020)
	Coriandrum sativum				Coriandrin			
	Salvia officinalis				Safficinolide			

natural compounds of plant and animal or mineral base (Adhikari and Paul 2018). Post trials, Ayush has approved Zingi-Vir and Virulina as antiviral agents, Astha 15 as an immunity booster and Kabasura Kudineer, Arogya Kashayam, Tulsi drops, and Ayudh as health supplements (Ahmad et al. 2021). Amongst Chinese formulations such as Qing-Fei-Pai-Du-Tang (QFPDT), Lianhua Qingwen capsule (LHC), Taiwan Chingguan Yihau (NRICM101), and Jing Si herbal drink (JSHD) are approved for COVID-19 (Su et al. 2022). NLC-001, a 3CL protease inhibitory product of plant origin was approved by US FDA. Currently, clinical trials as oral dietary supplements of NLC-001 are being conducted in Israel, targeting SARS-CoV-2 infection. Meanwhile, Todos Medical Ltd. evaluates potential global commercialization opportunities (Golodetz et al. 2020).

In Table 6.3 a list of herbal remedies is compiled that can be used for the treatment and management of COVID-19.

6.10 Employing Computational Tools to Discover PSM Aiming COVID-19 Management

COVID-19 vaccine and drug candidates were developed through well-planned scientific investigations (Liu et al. 2021; Dong et al. 2020). Nevertheless, full immunisation treatment and therapeutic efficiency assessment under actual conditions (in vivo and clinical trials) remain challenges, necessitating the continuing research and development of the best management strategies for SARS-CoV-2 infection.

The exponential growth of bioinformatics in recent years suggests that this type of progress may be hastened by the discipline's ability to tackle problems on previously insurmountable scales. The relatively new field of computational and structural biology can "decode" pathogens and hosts based on genomic sequences, allowing researchers to predict and accelerate the mechanism of pathogen insights and investigate ways to stop the spread of pathogens. The rapid development of computational technology, especially in the fields of artificial intelligence (AI) and machine learning (ML), has increased the scope of this technology's use in the fields of biology, medicine, and public health and prompted a rethinking of the best ways to treat various diseases. The use of this assay has been widespread during the current COVID-19 pandemic for the purposes of drug screening, vaccine/drug design, and disease prediction (Liu et al. 2022). Computational drug discovery methods such as molecular docking, dynamic simulations, and various analyses such as ADMET are extensively used to find the potential of synthetic or natural compounds that can target structural and function proteins of SARS-CoV-2.

Through computation approaches, terpenes (NPACT01552, NPACT01557, and NPACT00631) bind specifically to SARS-CoV-2 S RBD, Mpro inhibitors such as tinosponone, montelukast, ChEMBL275592, ChEMBL288347, biflavone amentoflavone, quercetin-3-*O*-rhamnoside, and RdRp inhibitory compound

Table 6.3 Compilation of herbal remedies available as a product in the global market to manage COVID-19 disease

Ref.	Categories	Product name	Ingredients	Mode of action	Target
1	A	Herbal Strategi	*Cymbopogon citratus*; *Azadirachta indica*; *Citrus limon*; *Ocimum tenuiflorum*	Defensive mechanism against COVID-19	Removes the virus from hands
2	A	ARAR Neem care sanitizer	0.20% (v/v) *Azadirachta indica*, 0.20% (v/v) *Citrus medica* mixed with 80% v/v ethanol, 0.125% (v/v) of H_2O_2 and 1.45% (v/v) of glycerol.	Defensive mechanism against COVID-19	NA
3	A	Himalaya pure hands	*Aloe barbadensis*	Defensive mechanism against COVID-19	NA
4	A	Mangalam CamPure Camphor Hand Sanitizer	*Cinnamomum camphora*	Defensive mechanism against COVID-19	NA
5	B	Jing-Si-Herbal-Tea	*Anisomeles indica*; *Artemisia argyi folium*; *Chrysanthemi Flos*; *Glycyrrhizae radix*; *Perillae folium*; *Houttuyniae herba cum radice*; *Ophiopogonis radix*; *Platycodonis Radix*; microcrystalline cellulose and maltodextrin	Disease management for COVID-19	NA
6	B	Ayush Kwath -Dabur	*Zingiber officinale*; *Ocimum sanctum*; *Piper nigrum*; *Cinnamomum zeylanicum*	Immunity against COVID-19	NA
7	B	Coronil tablet	*Withania somnifera*; *Ocimum sanctum*; *Tinospora cordifolia*	Disruption of S Protein-ACE-2 Interaction	Recognition and entry of the virus into the host cell
8	B	Guduchi Ghanavati (Supplement)-Himalaya	*Tinospora cordifolia*	Defensive mechanism against COVID-19	

(continued)

Table 6.3 (continued)

Ref.	Categories	Product name	Ingredients	Mode of action	Target
9	B	Golden Milk Turmeric Latte—CARE	Haldi (turmeric; *Curcuma longa*) powder in milk	Defensive mechanism against COVID-19	NA
10	C	Azadvir	*Ocimum sanctum*; *Cedrus deodara*; *Boswellia serrate*; *Azadirachta indica*; *Mentha piperita*; *Thymus vulgaris*; *Cinnamomum camphora*	Management of COVID-19	NA
11	C	Ayush Kadha -YOGAFY	*Ocimum sanctum*; *Curcuma longa*; *Syzygium aromaticum*; *Elettaria cardamomum*; *Citrus limon*; *Withania somnifera*; *Tinospora cordifolia*; *Piper nigrum*; *Zingiber officinale*	Prevention and management of the novel Coronavirus (SARS-CoV-2)	NA
12	C	Taiwan Chingguan Yihau (NRICM101) decoction	*Scutellaria baicalensis*; *Houttuynia cordata*; *Morus alba*; *Saposhnikovia divaricate*; *Trichosanthes kirilowii*; *Isatis indigotica*; *Glycyrrhiza glabra*; *Magnolia officinalis*; *Mentha haplocalyx*; *Nepeta tenuifolia*	Management of COVID-19	Target S protein/ACE2 interaction, $3CL^{pro}$ activity, viral plaque formation, and cytokines interleukin (IL)-6 and tumour necrosis factor (TNF)-α
13	C	Ayush Kwath	*Ocimum sanctum*; *Cinnamomum zeylanicum*; *Piper nigrum*	Defensive mechanism against COVID-19	NA
14	C	Chyawanprash	*Phyllanthus emblica*; *Piper longum*; *Tribulus terrestris*; *Pistacia integerrima*; *Phyllanthus Amarus*; *Vitis vinifera*; *Inula racemose*; *Terminalia Chebula*; *Tinospora Cordifolia*	Defensive mechanism against COVID-19	NA

15	C	Huo-Xiang-Zheng-Qi	*Atractylodis Rhizoma*; *Citri Reticulatae Pericarpium*; *Magnoliae Officinalis*; *Angelicae dahuricae radix*; *Arecae Pericarpium*; *Pinelliae rhizoma*; *Glycyrrhizae radix*; *Pogostemonis herba*; *Perillae Folium*	Management of COVID-19	PTGS2, HSP90AB1, mPGES-1, LTA4H, NOS2, PTGS2
16	D	ShuFeng JieDu capsule	*Polygonum cuspidatum*; *Forsythia suspense*; *Isatis indigotica*; *Bupleurum chinense*; *Patrinia scabiosifolia*; *Verbena officinalis*; *Phragmites communis*; *Glycyrrhiza uralensis*	SFJDC treats COVID-19 by multi-compounds and multi-pathways	RELA, MAPK1, MAPK14, CASP3, CASP8, and IL6 were the key target genes
17	D	DivyaSwasari-Vati (DSV) (Patanjali)	*Glycyrrhiza glabra*; *Pistacia integerrima*; *Cressa cretica*; *Zingiber officinale*; *Piper longum*; *Piper nigrum*; *Cinnamomum zylancium*; *Anacyclus pyrethrum*; *Syzygium aromaticum*; Salt crease, Gall plant	Disease management for COVID-19 Suppressed the proinflammatory cytokines, IL-6 and TNF-α	Target spike protein of SARS-CoV-2
18	D	Qingfei Paidu Tang (QFPDT)	*Ephedra sinica*; *Bupleurum chinense*; *Pogostemon cablin*; *Cinnamomum cassia*; *Scutellaria baicalensis*	Treatment of coronavirus (COVID-19)	Cytokine storm prevention and angiotensin-converting enzyme 2 (ACE2) receptor-binding regulation
19	D	Nilavembu Kudineer Chooranam	*Andrographis paniculate*; *Vetiveria zizanioides*; *Plectranthus vettiveroides*; *Santalum album*; *Trichosanthes dioica*; *Zingeber officinale*; *Piper nigrum*; *Mollugo cerviana*	Disease management for COVID-19	spike glycoprotein, protease, and angiotensin-converting enzyme 2 (ACE2) receptor,
20	D	Divya Swasari Ras (Patanjali)	*Glycyrrhiza glabra*; *Syzygium aromaticum*; *Cinnamomum zeylanicum*; *Pistacia integerrima*; *Cressa cretica*; *Zingiber officinale*; *Piper nigrum*; *Piper longum*; *Anacyclus pyrethrum*	Treatment against COVID-19	SARS-CoV-2 S protein and human ACE 2

(continued)

Table 6.3 (continued)

Ref.	Categories	Product name	Ingredients	Mode of action	Target
			Herbally processed calcined mica ash, Herbally processed calcined shell of Pearl oyster ash, Herbally processed calcium rich gypsum ash, Herbally processed calcined cowry shell ash of *Cypraea moneta*		
21	D	Kaba Sura Kudineer	*Zingiber officinale*; *Piper longum*; *Syzygium aromaticum*; *Tragia involucrate*; *Anacyclus pyrethrum*; *Andrographis paniculata*; *Hygrophilla auriculata*; *Terminalia chebula*; *Justicia adhatoda*; *Plectranthus amboinicus*; *Costus speciosus*; *Tinospora cordifolia*; *Clerodendrum serratum*; *Sida acuta*; *Cypreus rotundus*	Disease management for COVID-20	SARS-CoV-2 S protein
22	D	Lianhuaqingwen capstule	*Forsythia suspense*; *Ephedra sinica*; *Lonicera japonica*; *Mentha haplocalyx*; *Dryopteris crassirhizoma*; *Rhodiola rosea*; *Gypsum fibrosum*; *Pogostemon cablin*; *Rheum palmatum*; *Houttuynia cordata*; *Glycyrrhiza uralensis*; *Armeniaca sibirica*	Treatment against COVID-19	Target pro-inflammatory cytokines (TNF-α, IL-6, CCL-2/MCP-1 and CXCL-10/IP-10)
23	D	Marshmallow root's syrup	*Althaea officinalis*	Treatment against COVID-19	NA
24	D	Divya Anu Taila-Patanjali	*Aegle marmelos*; *Nymphaea stellate*; *Solanum indicum*; *Solanum virginianum*; *Pluchea lanceolate*; *Desmodium gangeticum*; *Uraria*	Treatment against COVID-19	Ameliorate proinflammatory cytokines such as IL-1β,TNF-α, IFN-γ, IP-10, MCP-1, IL-4, and IL-8

			picta; *Embelia ribes*; *Cinnamomum tamala*; *Amomum aromaticum*; *Vitex negundo*; *Mallotus philippensis* Goat milk and Sesame oil		
25	D	Saliravira	*Echinacea purpurea*; *Glycyrrhiza glabra*; *Rheum palmatum*; *Hyssopus officinalis*; *Rosmarinus officinalis*; *Panax ginseng*	Antiviral, anti-inflammatory, and immune-enhancing agent	NA
26	D	Koflet syrup-Himalaya	*Glycyrrhiza glabra*	Immunomodulatory, anti-inflammatory	Viral fusion protein
27	D	Fah talai jone capstule	*Andrographis paniculata*	Treatment against COVID-19	NA
28	D	Phela	*Clerodendrum glabrum*; *Gladiolus dalenii*; *Rotheca myricoides*; *Senna occidentalis*	Treatment against COVID-19	Inhibits >90% of SARS-CoV-2 and SARS-CoV infection
29	D	Su He Xiang Pill (SHXP)	*Liquidambar orientalis*; *Styrax tonkinensis*; *Cyperus rotundus*; *Aucklandia lappa*; *Cyperus rotundus*; *Eugenia caryophyllata*; *Aquilaria sinensis*; *Santalum album*; *Boswellia carterii*	Treatment against COVID-20	NA
30	D	Tanreqing Capsule	*Scutellariae radix*; *Lonicerae japonicae*; *Forsythiae fructus* bear bile powder and goat horn	Treatment against COVID-20	COX-2, sEH, IL6, CCL2, CASP3, IL4, MAPK1, RELA, FOS, NOS2, IL1B, CXCL10, MAPK14, EGFR

A: COVID-19 Preventive products, B: Immunity booster, C: Prevention and treatment of COVID-19, D: Treatment against COVID-20, NA: Information not available

Reference: (1) https://www.amazon.in/, (2–4) Malabadi et al. (2021), (5) Liu et al. (2021), (6) https://www.amazon.in/DABUR-Kaadha-Ayurvedic-Immunity-Boosting/dp/B08C5T9FSL, (7) Balkrishna et al. (2021), (8) Thakar et al. (2022), (9) https://www.amazon.in/Golden-Turmeric-Latte-Saffron-Herbs/dp/B08B7WNTMD?th=1, (10) https://www.ijbcp.com/index.php/ijbcp/article/view/4574/3151, (11) Maurya and Sharma (2022), (12) Tsai et al. (2021), (13) Gautam et al. (2022), (14) Godatwar et al. (2021), (15) Li et al. (2022), (16) Chen et al. (2020), (17) Balkrishna et al. (2020), (18) Zhong et al. (2020), (19) Srivastava et al. (2021), (20) Balkrishna et al. (2022); Balkrishna et al. (2021), (21) Srivastava et al. (2021), (22) Srivastava et al. (2021), (23-24) Balkrishna et al. (2021), (25) Khorshiddoust et al. (2022), (26) Gomaa and Abdel-Wadood (2021), (27) Yearsley (2021), (28) Matsabisa et al. (2022), (29) Li et al. (2021), (30) Zhang et al. (2021)

galidesivir, have been identified from various studies (Muhseen et al. 2020; Krupanidhi et al. 2021; Abu-Saleh et al. 2020; Liu et al. 2022; Ryu et al. 2010a; Aftab et al. 2020).

According to the results of an investigation conducted by Puttaswamy et al. (2020), several different classes of PSM, anthocyanidins, flavonoids, glycosides, biflavonoids, ellagitannins, and triterpenes, have the potential to inhibit TMPRSS2, S protein of SARS-CoV-2, Mpro, and RdRp. The triterpenoid saponin glycyrrhizic acid, also known as glycyrrhizin, has demonstrated antiviral activity against both the SARS-CoV and SARS-CoV-2 viruses. Clinical trials are currently being conducted (Murck 2020). Molecular docking and machine learning tools in a study have been used to screen over 2000 natural compounds for 3CLpro inhibitor, where the compound rutin exhibited the highest AUC score and binding affinity, suggesting rutin as a potential drug candidate against COVID-19 (Xu et al. 2020).

Computational analysis can also design viral protein-targeting small molecules or peptides. In vitro inhibition assays, molecular docking, and X-ray crystallography were utilised by Zhang et al. (2020) to enhance ketoamide class M^{pro} inhibitors with numerous functional groups. This was done to identify the most promising potential candidates. Specific inhibitors of Mpro's backbone were developed as part of the research conducted by Dai et al. (2020). Several peptidyl inhibitors targeting viral proteins have also been studied, in addition to small molecules. A common strategy was using the structure of the hACE2 and SARS-CoV-2 S RBD complex as a basis for designing peptide inhibitors that encompass essential ACE2 residues and bind to the RBD to avoid the RBD from interacting with host cells. These peptide inhibitors are intended to stop the RBD from interacting with the host cells (Han and Král 2020; Pomplun et al. 2020).

6.11 Conclusion and Future Scope

In the past two decades, SARS-CoV-2 casual agent of COVID-19 is the 3rd coronavirus to cause a worldwide epidemic in consort with MERS and SARS. Almost every nation and region on the planet has been impacted severely by the disease. Physical isolation, hygiene, medication, and vaccination were all used to reduce the spread of disease. Vaccination is the most successful preventive measure for this disease, but as new COVID variants evolved, the protection provided by the original vaccines did not. Scientists want to develop broadly protective vaccines that can target future variants and even related coronaviruses before they arise. Moreover, SARS-CoV-2 and its emerging variants are the outcome of evolving nature of the virus, posing a challenge to researchers. Therefore, in this chapter, herbal drugs, remedies, and practices for treatment and management of SARS-CoV-2 have been focused upon. Plants of the family Fabaceae and Lamiaceae are testified to have potent antiviral properties against SARS-CoV-2, along with plants of the family Asteraceae, Zingiberaceae, and Rutaceae. Plant secondary metabolites classes like alkaloids, flavonoids, and terpenoids majorly affect several targets of SARS-CoV-2,

which includes M^{pro}, PL^{pro}, RdRp, spike, helicase, nucleocapsid, peptide, ACE 2, and TMPRSS. Looking into the plant diversity and huge amount of antiviral molecules they possess, there is a lack of in vivo studies and clinical trials. Computational studies are more in number as compared to in vitro studies. So, in future, more focus should be shifted to in vitro and in vivo studies for proper utilisation of antiviral plant molecules.

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Chapter 7
Antiviral Phytocompounds Against Animal-to-Human Transmittable SARS-CoV-2

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7.1 Background

COVID-19 which causes disease in the human respiratory system is brought on by coronavirus-2, which culminates in SARS-CoV-2. Since COVID-19's debut in Wuhan, China, in December 2019, almost 230 nations have joined (Chauhan 2020). Because of its genetic resemblance to SARS-CoV-1, the disastrous near-pandemic virus that hit in 2002–2003, SARS-CoV-2, the COVID-19 agent, was given this moniker (Ksiazek et al. 2003). The genetic sequences of SARS-CoV-2 and viruses from either humans or animals have never been detected before 2019. Both the SARS and MERS coronavirus (MERS-CoV; 70% similarity) are beta coronaviruses (Cov) with the same genetic makeup and viral structure (SARS-CoV; 349 fatalities in China between 2002 and 2003) (Biswas et al. 2021a; Zilani et al. 2021). Several healthcare facilities in Wuhan, China, reported a large number of patients with pneumonia whose origin was unknown in the latter part of December 2019. These people had signs of viral pneumonia with those who had SARS and MERS, such as coughing, fever, and also feeling mild to acute pain in the chest, as well as more severe symptoms such as dyspnea and bilateral lung infiltration (Zhu et al. 2020; Gralinski and Menachery 2020). Recent research studies reported that the SARS-CoV-2 spike (S) mutant protein D614G exhibited lesser infection to the upper respiratory tract compared to the B.1.1.7 (now known as the alpha variation, the first epidemic in the UK) (Plante et al. 2021).

The lack of licensed medications for the treatment of virulent diseases has come to light consequently for COVID-19. Numerous natural phytochemicals (NPs) possess bioactive characteristics that have antiviral (AV) and anti-inflammatory effects. Several vascular NPs, comprising alkaloids, polyphenols, tannins, and flavonoids, have been demonstrated to be effective as AVs, particularly for the treatment purpose of COVID-19 (Español et al. 2021). Inflammation is one of the primary COVID-19 indications and symptoms. The anti-inflammatory properties of several NPs offer a workable solution for accelerating the recovery from anosmia and ageusia brought on by COVID-19. Even without considering the essential oils' chemical composition, scent training has already been shown to speed anosmia recovery (Koyama et al. 2021). NPs utilized in olfactory training are among those found in essential oils (lemon, rose, eucalyptus, and clove) (Koyama and Heinbockel 2020; Paul et al. 2022).

Recent research has placed a strong emphasis on the AV effects of diverse NPs generated from different resources, such as vegetables, fruits, plants, and cereals, as possible sources of various bioactive components. In addition, a lot of natural substances have polypharmacology or many mechanisms of action. Due to their polypharmacology, natural products may be more successful than traditional single-target pharmaceuticals (Tomas et al. 2022). The AV activity of those components may also be impacted by the additive or synergistic actions of many components; for instance, griffithsin and carrageenan together were successful in preventing COVID infections, along with the most recent SARS-CoV-2 mutations (Alsaidi et al. 2021; Khan et al. 2021a; Ahmed et al. 2022).

Before considering using the medicine, one should be aware of any possible adverse effects, such as hyperglycemia, ulceration, hepatic liver failure, angioedema, stomach irritation, hemolytic anemia, and immune system problems (Shakoor et al. 2021). Natural medications with high absorption and low cytotoxicity are the best options. During the initial phase of COVID-19 infection, these NPs can effectively halt the connection of the virus and its penetration in the cell by blocking enzymes ACE2, papain-like protease (PLpro), and 3CLpro (Dey et al. 2022a; Munshi et al. 2022; Sohel et al. 2022). The synergistic action of several NPs is opening the door for the design and recognition of novel SARS-CoV-2 AV treatment drugs. Combining azithromycin and hydroxychloroquine is reported to be somewhat more efficient in diminishing the viral efficiency in cases of COVID-19 (Gautret et al. 2020). The plants *Scutettaria baicalensis* and *Asplenium belangeri* contain the flavonoids myricetin and scutellarein respectively, which halt the action of ATPase of the nsP13 which is the helicase of SARS-CoV-2 (Yu et al. 2012). The Government of India has suggested a composition comprised of 15 different plants, including *Hygrophilla auriculata*, Zingiber *officinale*, *Tragia involucrata*, *Plectranthus amboinicus*, *Saussurea costus*, *Adhatoda vasica*, *Syzygium aromaticum*, *Terminalia chebula*, *Anacyclus pyrethrum*, *Piper longum*, and *Tinospora cordifolia* (Arefin et al. 2021; Paul et al. 2021; Rahman et al. 2021; Hossain et al. 2022).

7.2 Structural Composition of SARS-CoV-2

Bioinformatic research about the structure composition of SARS-CoV-2 has revealed that it has characteristics in common with the family of coronavirus. It is a member of the 2B lineage of beta-CoVs (Lai et al. 2020). Five SARS-CoV-2 infected individuals had their full genomes sequenced at the beginning of the Wuhan pneumococcal outbreak. The study found 79.5 percent of the information in these genome sequences and the sequencing of SARS-CoV is identical though these are different viruses. It is believed that the virus is a novel human betacoronavirus (Zhou et al. 2020). According to a study, the strain of bat coronavirus BatCov RaTG13 and SARS-CoV-2 is 96% identical. These findings imply that SARS-CoV-2 arose spontaneously, a major source of infections was bats Cov RaTG13 and may have come from a bat (Zhou et al. 2020; Zhang et al. 2020; Wang et al. 2020a).

There is a widespread consensus that CoVs, a diverse collection of single-stranded RNA viruses that can infect both people and animals, can cause respiratory, gastrointestinal, hepatic, and neurological problems (Weiss and Leibowitz 2011). CoVs are classified into four genera: alpha, beta, gamma, and delta CoVs. The six human coronaviruses (HCoVs) that have been identified so far are the HCoVs-OC43, beta-CoVs, SARS-CoV, HCoVs-HKU1 (Hossain et al. 2022; Lai et al. 2020), and MERS-CoV (Yang and Leibowitz 2015). Alpha-CoVs include HCoVs-229E, HCoVs-NL63, and HCoVs-OC (Drosten et al. 2003).

7.2.1 *Spike (S) Proteins*

The transmembrane (TM) region embedded in the viral envelope, an extracellular N-terminus, and a brief intracellular C-terminal stretch comprise the structural S protein (180 to 200 k daltons) (Liu et al. 2014). When the virus encounters the host cell, the S protein undergoes substantial structural changes, allowing the virus to cling to the host cell's membrane. The S protein often has a metastable, prefusion structure. Polysaccharide molecules are used to stop the immune system from identifying the spikes as soon as they enter (Bosch et al. 2003; Watanabe et al. 2020).

The SARS-CoV-2 S is composed of the S1 and S2 subunits, which contain a total of 1273 amino acids. However, unlike the S1 subunit, which has 14–685 amino acid residues, the S2 subunit contains 686–1273 amino acid residues (Fig. 7.1). The other two do this task by binding to receptors and fusing membranes. In contrast to the S1 subunit, which contains the receptor-binding domain (RBD, 319–541 amino acid residues), the S2 subunit contains the fusion peptide (FP), the heptapeptide repeat

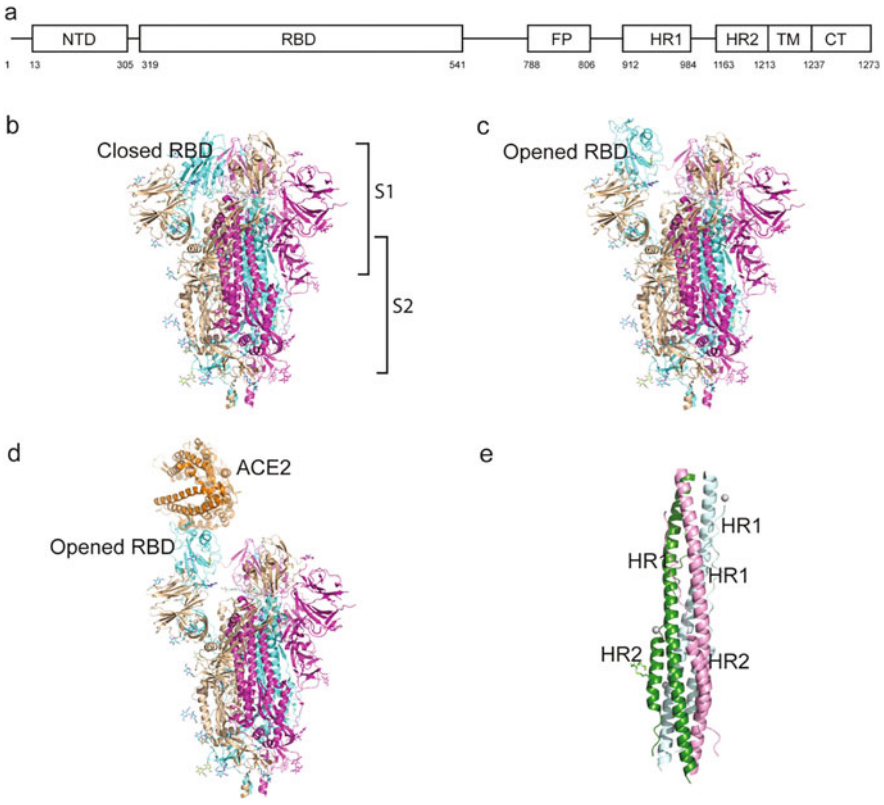

Fig. 7.1 (**a**) Schematic representation of the SARS-CoV-2 spike. (**b**–**c**) open and close—S protein's RBD, (**d**) the opened RBD [S1 subunit] of S protein allows it to connect to ACE2. (**e**). The S2 subunits HR1 and HR2 work together to generate a six-helix structure

sequence 1 (HR1), HR2 (1163–1213 amino acid residues), the TM domain (1213–1237 amino acid residues), and the cytoplasm domain (12 amino acid residues) (Xia et al. 2020; Biswas et al. 2022a; Dey et al. 2022b). Around the virus particle, the S protein trimers create an interesting halo that resembles a bulbous crown. Using the structure of coronavirus S protein monomers as a guide, we can see that the S1 and S2 subunits create the virus' characteristic bulbous head and stalk region (Tang et al. 2020; Huang et al. 2020a). When it first makes an appearance, the CoV S protein is an inactive progenitor. To activate the membrane fusion domain, the S protein must be cleaved into the S1 and S2 subunits by proteases in the target cells (Bertram et al. 2013). As cellular proteases cleave the S protein into the S1 and S2 subunits, SARS-CoV-2 employs the serine protease TMPRSS2 as a protein primer. Although the location of the SARS-cleavage CoV is unknown, the location of the SARS-CoV-2 S is known to exist (Hoffmann et al. 2020; Du et al. 2007).

7.2.2 Membrane Protein (M)

The M protein is 223 amino acids long and is divided into three primary domains: the TMH1, TMH2, and TMH3 transmembrane helices, the long C-terminal endodomain found on the cytoplasmic face of virions (Zhang et al. 2022). There isn't much research on M protein homodimers and the ones that do only partly explain how M-M interactions lead to homodimer formation. The juxtamembrane hinge region, N-terminal three transmembrane helices, and the inward-facing C-terminal sheet sandwich domain (BD), which is made up of an outer sheet (residues 1, 2, and 6), an inner sheet (residues 1, 2, and 6), make up the three structural segments that make up the M protein (residues 3, 4, and 5). When the long form is transformed into the shortened form, the two bundles spin in opposite directions: toward one another on the extraversion side, and against one another on the introversion side. As a result, the two bundles shift their interface, drawing closer together in the extraversion lobe and further apart in the introversion lobe. Because of this, the axis of dimerization is strongly twisted in the opposite direction of the linker that connects TM1 and TM2 (Zhang et al. 2022; Dey et al. 2022c; Hasan et al. 2022a).

Because they regulate how the helical bundles and BDs are arrayed in relation to one another, the hinge region and the TM1-TM2 loop are expected to be significant in the structural change between the two types. The hollow that forms at the top of the bundle is deeper and inserted into the hinge area. Every other structural protein is capable of interacting with the M protein. By ensuring that the N protein-RNA complex remains contained within the internal virion, the binding of M protein contributes to the stabilization of N proteins and encourages the completion of viral assembly. Because the M protein cooperates with the S protein to establish a connection with and enter the host cell, mutations in either protein could have an impact on viral attachment and entry. Glycosylation of the virus's S protein may aid in its ability to evade the immune system (Thomas 2020; Hasan et al. 2022b; Morshed et al. 2022; Rahman et al. 2022). However, the mechanism of glycosylation

of the structural protein (S) and the physiological function of the membrane protein (M) protein is still unknown.

7.2.3 Nonstructural Protein

In contrast to the genes for structural proteins, the 5′ region of the viral RNA genome also includes the genes for various other types of proteins (Yadav et al. 2021). The SCoV nsp1 protein, which is the gene 1 polyprotein's most N-terminal product and is present in both infected and expressing cells, works to silence the expression of host genes. Nsp1 obstructs the hosts' AV signaling pathways, preventing infected cells from producing type I interferon. The nsp1 protein of the nearly similar mouse hepatitis virus functions as a virulence factor, and the type I interferon system is also disrupted. Additionally, host gene expression is also suppressed. When Nsp1 attaches to 40S ribosomes, host protein synthesis is inhibited. Capped mRNA is further modified by ribosome-bound nsp1, which prevents translation (Huang et al. 2011). The interaction of the NSp2 protein with internal host communication during SARS-CoV infections is demonstrated by the link between the host proteins PHB2 and prohibitin 1 (PHB1) (Cornillez-Ty et al. 2009).

Nsp3 is the largest predicted protein from the coronavirus genome, with a molecular weight of around 200 kD. The replication/transcription complex must contain Nsp3. It is composed of multiple domains, the organization of which varies between CoV genera due to domain duplication or absence. There are eight different Nsp3 domains, and all known CoVs contain the same four: Ubl1, PL2pro, Nsp3 ectodomain (3Ecto), and Glu-rich acidic domain (also known as the "hypervariable region"). Furthermore, all CoVs have the TM1 and TM2 transmembrane domains (Lei et al. 2018; Dey et al. 2021; Bibi et al. 2022; Biswas et al. 2022b).

Numerous Nsp6, Nsp4, and Nsp3 trans-membranes exist. Nsp3, Nsp4, and Nsp6 are only found in the ER of certain cells following transfection with expression plasmids, despite being expressed in the RTC during infection. Studies involving immunoprecipitation have shown that there is a connection between nsp4 and the C-terminal third of nsp3, which is responsible for MHV (nsp3C). After being co-transfected with expression plasmids, these proteins showed a similar pattern of colocalization in the perinuclear foci as they did in infected cells. Researchers found that when Nsp3 and Nsp4 are expressed together, a membrane remodeling process takes place that results in the formation of cytoplasmic and dynein-myosin vesicles (CMs and DMVs), respectively. The replication complex, the creation of DMVs, and the virus-caused membrane rearrangement all depend on the glycosylated MHV nsp4 protein. Studies using electron and confocal microscopy show that SARS-CoV nsp3, nsp4, and nsp6 expression promotes the development of DMVs in the transfected cells. However, it is uncertain how the SARS-nsp3 CoVs and nsp4 interact as well as how they might prevent viral replication by changing membrane structure (Sakai et al. 2017; Baral et al. 2022; Singh et al. 2023).

The smallest RNA-polymerase complex consists of nsp7 and nsp8 cofactor proteins, the C-terminal region of nsp12 encoding the RNA-dependent RNA-polymerase (RdRp) catalytic domain, and other proteins. Cryo-electron microscopy (cryo-EM), which was used to obtain the structures, showed that the stoichiometry of the nsp12:nsp7:nsp8 complex is 1:1:2. Studies done in vitro have demonstrated that at least nsp7 and nsp8 must be bound for nsp12 to function as a polymerase. Studies on the nsp7 and nsp8 complexes without nsp12 have received minimal attention in terms of their structure and biology (Courouble et al. 2021). In contrast to SARS-CoV nsp12's conventional RdRp, which efficiently replicates a very large RNA genome in vivo, RNA processing is subpar in vitro. SARS-CoV nsp7 and nsp8 initiate the RNA-synthesizing activity of nsp12 and increase the severity of SARS-CoV pathogenesis. Biochemical and reverse genetic analyses were used to determine the importance of conserved nsp7 and nsp8 residues. When two nsp8 residues (P183 and R190) required for interaction with nsp12 and a third (K58) required for the polymerase complex's interface with RNA were replaced, the virus perished, whereas numerous nsp7 mutations had little effect on virus replication. The nsp7/nsp8/nsp12 complex can interact with nsp14, a dual-function enzyme that has 3′-5′ exoribonuclease activity as well as RNA cap N7-guanine methyltransferase activity. This enzyme is associated with replication fidelity as well as 5′-RNA capping. This connection can be made without compromising efficiency. The discovery of this tripartite polymerase complex, which associates with the nsp14 proofreading enzyme, reveals new information regarding how coronaviruses construct RNA-synthesizing machinery to replicate the largest known RNA genomes. This protein complex provides remarkable examples of the integration of RNA polymerase, capping, and proofreading functions (Subissi et al. 2014; Al Azad et al. 2022; Sarker et al. 2022).

7.3 Limitations of Present Antiviral Solution Against SARS-CoV-2

There are several COVID-19 vaccinations available, but the effectiveness of COVID-19 immunizations across a range of populations and their potential for persistent protection is still in doubt. As a result, developing SARS-CoV-2 AV drugs is crucial. However, the effectiveness of AVs has not yet been shown beyond a reasonable doubt. The AV may function by blocking viral enzyme activity, preventing viral entrance, concentrating on a specific host need to restrict the creation of viral particles, or by viral replication. Some AV drugs work by obstructing the entry, suppressing the protease, and through many additional methods. AV drugs are employed to treat diseases caused by viral infections. To ensure that the medications used to treat COVID-19 or other viruses function properly and according to label instructions, more research and testing are required.

Future effective treatment of similar viruses may be possible with these drugs (Biswas et al. 2021a, 2023; Rahman et al. 2020a).

Favipiravir, an AV drug, is used to treat people in Japan who have contracted the flu. Favipiravir is a purine nucleoside derivative that inhibits viral RNA-dependent RNA polymerase, thereby preventing viral genome replication and transcription (Furuta et al. 2017). However, due to the lack of a control group and its open-label design, it is unable to demonstrate the statistical effectiveness of favipiravir. The study only covered hospitalized patients due to a lack of funding and conflicting methodologies, and a sizable portion of follow-up SARS-CoV-2 (RT-PCR) assays was not acquired. The trial's early completion could have made it more difficult to share further information about clinical results. Additionally, patients in the SoC group underwent extra AV therapy (Bosaeed et al. 2021; Rahman et al. 2020b; Islam et al. 2022).

Remdesivir, a nucleoside monophosphoramidate prodrug for coronavirus infection, was approved by the FDA in 2019. There are concerns about the treatment effectiveness of remdesivir for COVID-19 since no trials have discovered substantial differences in mortality or the time it takes for a clinical improvement between control groups and redeliver-treated groups. Remdesivir was unable to outperform other experimental medications in terms of therapeutic benefit in COVID patients, in contrast to the significant, therapeutic preclinical data reached in rhesus macaque models. The dramatic contrast between the promising preclinical results for COVID-19 and the poor clinical effectiveness of remdesivir has baffled many (Yan and Muller 2021; Huang et al. 2021).

Due to the limited quality and confidence of the available data as well as the high heterogeneity, it is now challenging to make a solid determination regarding the advantages of umifenovir for SARS-CoV-2. Hospital length of stay (LOS), nucleus acid negative conversion time, or the chance of developing a disease could not be significantly reduced. In conclusion, there is no proof that umifenovir can improve patients' vital outcomes in COVID-19 patients (Huang et al. 2021). A retrospective analysis of real data from hospitalized patients with mild to severe COVID infection found that the clinical and virological outcomes were the same for lopinavir/ritonavir, hydroxychloroquine, lopinavir/ritonavir + hydroxychloroquine, and standard of care (Gagliardini et al. 2021). Thus, for COVID-19, finding new, powerful AV medications is crucial.

7.4 Plant-Based Bioactive Compounds and Synergistic Effects Thereof

Traditional plant-based medications were used effectively to treat patients afflicted with SARS-CoV in Guangdong Province, China, from the latter half of 2002 until the middle of 2003 (Brovelli et al. 2004; Peng et al. 2004). Secondary metabolites received a lot of attention because they have bioactive properties, even though there

isn't much known about the nature and composition of these plants or how they work (Gourinat et al. 2015). For instance, the use of the alkaloid quinine, extracted from the Cinchona officinalis tree bark, in the treatment of malaria dates back to the 1960s (Achan et al. 2011). Similar in form to quinine is the drugs chloroquine (Cq) and hydroxychloroquine (Huq). The viral load of SARS-CoV-2 is reduced more effectively when Huq is combined with azithromycin (Prasad et al. 2020). Equally promising against SARS-CoV is glycyrrhizin, a saponin derived from the roots of the Glycyrrhiza glabra plant (Gavrilov 1975). Because SARS-CoV and SARS-CoV-2 have the same structures and ways of spreading, glycyrrhizin could also be used to treat the current pandemic. The 3CLpro and RdRp proteins that are present in SARS-CoV are inhibited from functioning by the water extract of *Houttuynia cordata*. Flavonoids myricetin (from *Myrica ruba*) and scutellarein (from *Scutettaria baicalensis* and *Asplenium belangeri*) are known to inhibit ATPase production by the SARS-CoV helicase nsP13, making the water extract active against the virus (Huang et al. 2020b). It has also been demonstrated that flavones from *Torreya nucifera* inhibit 3CLpro function. These flavones include amentoflavone, quercetin, luteolin, and apigenin (Ryu et al. 2010a). Lycorine is an alkaloid that is derived from *Lycoris radiata*. It has antiviral (AV) activity against the poliovirus and herpes simplex virus, and it has shown efficacy against SARS-CoV (Li et al. 1912). Emodin, sinigrin, and hesperetin, which were found in *Isatis indigotica*, also showed that they stopped 3CLpro from working (Lin et al. 2005a). In addition, the lectins that are found in plants can impede the activity of viruses. In a study, the antiviral (AV) properties of 33 lectins derived from different plant species were evaluated for their potential efficacy against SARS-CoV and feline coronavirus (FCoV). By targeting mannose, they discovered that mannose-binding lectin possessed potent anti-coronaviral activity by inhibiting both the entry and release of virus particles (Keyaerts et al. 2007; Ferdausi et al. 2022; Al Saber et al. 2022). Synthetic drug nelfinavir and agglutinin extracted from *Galanthus nivalis* both proved effective against FCov when administered in combination (Browning et al. 2010). This shows how important it is to study how NPs and man-made molecules work together to get around the viral load in the host system. But not much was done in this direction to study how biomolecules and drugs work together to fight viruses. Recently, a natural stilbene derivative called resveratrol (trans-3, 5, 4′-trihydroxystilbene) that is found in high amounts in *Vitis vinifera*, *Polygonum cuspidatum*, and *Vaccinium macrocarpon* was shown to stop MERS-Cov infection (Lin et al. 2017). Ayurvedic, Siddha, and Unani (nonnative) medicines are the three branches of traditional Indian medicine, and each of these schools prescribes NPs to their patients. Ayurveda is the oldest school of traditional Indian medicine (Thileepan and Prasad 2018). The Indian Government's Ministry of AYUSH (Ayurvedic medicine, Yoga and Homeopathy, Unani, Siddha, and Naturopathy) has recommended a formulation containing 15 plants to treat SARS-CoV-2. These plants are *Zingiber officinale*, *Piper longum*, *Syzygium aromaticum*, *Tragia involucrata*, *Anacyclus pyrethrum*, *Hygrophilla auriculata*, and *Terminalia* (Parada et al. 2020). Although Sivaraman, Pradeep, and Vellingiri have emphasized the benefits of this plant-based cocktail that reduces infection levels, no exhaustive research has been conducted to determine the

chemical composition or mode of action of these plants (Sivaraman and Pradeep 2020; Vellingiri et al. 2020). Artemisinin derivatives isolated from *Artemisia annua* are being studied for their effect on SARS-CoV-2 at the Max Planck Institute for Colloids and Interfaces in Germany, in collaboration with ArtemiLife Inc. in the United States (Prasad et al. 2020).

7.5 Insight into the Molecular Mechanisms of Natural Bioactive Compounds Targeting SARS-CoV-2

7.5.1 In Vitro Studies

7.5.1.1 Curcuma Longa

Antiviral medications that target numerous viral subtypes, Curcumin's strength lies in initiating cellular signaling pathways associated with lung disease, metabolic disease, liver disease, and inflammation (Marx et al. 2020). Curcumin interacts directly with over thirty proteins, including DNA polymerase, thioredoxin reductase, focal adhesion kinase, protein kinase (PK), tubulin, and lipoxygenase (LOX), according to previous research. Other examples of these interactions include LOX. In addition, curcumin influences crucial intercellular signaling cascades, such as the inhibition of NF-B and PI3K/Akt signaling, which are both essential for efficient viral replication. Curcumin also has anti-inflammatory properties. As a result of influencing viral replication-related processes as well as cellular post-transcriptional and post-translational modifications, viral multiplication is stifled. This includes the replication of the viral genome and the attachment of the virus (Pourhajibagher et al. 2021). It has also been demonstrated that curcumin therapy modifies the shape of the S protein in viruses, preventing their entry into cells. Docking studies revealed that curcumin binds to RBD-S, PD-ACE2, and SARS-CoV-2 protease (Grosshans and Cerf 2004; Soni et al. 2021; Hosseini et al. 2021).

7.5.1.2 *Saponin* Derivatives

Human fetal lung fibroblasts were tested for their susceptibility to SARS-CoV-2 replication inhibition using saikosaponins A, B2, C, and D. At concentrations up to 25 mol/L, saikosaponins A, B2, C, and D showed no cytotoxicity. At this concentration, however, all of the NPs showed significant SARS-CoV-2 inhibition. One of the most efficient blockers was found to be saikosaponin B2, which produced a result of 100 0.2% inhibition at a concentration of 25 mol/L. The half-maximal effective concentrations (EC50) of saikosaponins A, B2, C, and D were calculated to be 8.6, 0.3 (SI = 26.6), 1.7, 19.9, and 13.2. Further research was performed, and the results showed that saikosaponin B2 was the most effective virus-host adhesion and penetration blocker (Bray et al. 2006).

7.5.2 *Propolis*

Honeybees produce propolis, a resinous NP used in herbal medicine that is typically employed as a medical aid and defensive enhancer. Propolis has been demonstrated to have significant anti-inflammatory and pain-relieving effects by modulating a variety of metabolic pathways. Several recent studies demonstrate that propolis extract and some of its constituents act against several important SARS-CoV-2 targets, including reducing TMPRSS2 expression and reducing ACE2 anchorage, as well as immuno-modulating monocytes/macrophages (reducing production and removing IL-1 beta and IL-6), minimizing the signaling molecules NF-KB and JAK2/STAT3, and blocking PAK1, which determine inflammatory actions and fibrosis caused by SARS-CoV-2 (Diurno et al. 2020; Mehari et al. 2012; Piñero et al. 2020).

7.5.3 *Algae-Derived Bioactive Metabolites*

Carrageenan, nostoflan, microvirin, galactans, and cyanovirin are some of the bioactive metabolites derived from algae that have been proposed as potential treatments for SARS-CoV-2. They prevent viral infection by attaching themselves to the SARS-CoV-2 S protein and preventing the S protein from attaching itself to the heparin sulfate co-receptor in host tissues. This is how they function as diversions (Pradhan et al. 2022). Nagle et al. demonstrated that exopolysaccharides composed of carrageenan and sulfated polysaccharides derived from Porphyridium inhibit virus attachment to the host cell. Modified chitosan is highly effective against four different types of human coronavirus: HCoV-OC43, HCoV-NL63, HCoV-229E, and HCoV-HKU1 (Pereira and Critchley 2020). In an in vitro cell-based study, rhamnan sulfate from the green seaweed *Monostroma nitidum* was more effective than heparin at stopping S protein RBD or pseudoviral particles from attaching to immobilized heparin. It also showed strong AV activity against both the wild-type and delta form of SARS-CoV-2 (Song et al. 2021). Furthermore, fucoidan and rhamnan sulfate inhibit the expression of genes involved in the epidermal growth factor receptor pathway, which aids in the fight against coronavirus (Cai et al. 2020). Griffinsin, which was isolated from red algae, was very effective against SARS-CoV-2 by preventing viral entry, integrating viral DNA into RNA, inhibiting viral protease activity, and inhibiting viral reverse transcriptase activity (Ahan et al. 2022). Folic acid, phycoerythrobilins, and phycocyanobilins, which were found in Arthrospira, showed that they might be effective against SARS-CoV-2 (Petit et al. 2021). Ulvansare, a polysaccharide isolated from a green alga, is also being studied as a possible therapeutic agent against SARS-CoV-2 (Pereira and Critchley 2020). It is anticipated that the high-mannose-binding lectin griffithsin, which originates from red algae, will prevent SARS-CoV from entering the cell by

binding to S glycoprotein. What's more, griffithsin did not harm the host cell even when present in extremely high concentrations (Zumla et al. 2016; Biswas et al. 2021b).

Algae of the red variety *Porphyridium* sp.-derived sulfated polysaccharides are promising AV NPs that can be used to coat sanitary products for SARS-CoV-2 prophylaxis (Alam et al. 2021). A phaeophyte called *Ecklonia cava* produces a product called dieckol, which has been shown to prevent the trans−/cis-cleavage of the SARS-CoV-2 3CLpro (chymotrypsin-like cysteine protease) (Zaporozhets and Besednova 2020). Moreover, the *Ecklonia kurome*-derived NPs dieckol targets 3CLpro and prevents SARS-CoV-2 from replicating. Several in silico investigations on the AV effects of metabolites generated from *Arthrospira* and other marine algae including *Grateloupia filicina*, *Gracilaria corticate*, *and Laurencia papillosa* on several target proteins of SARS-CoV-2 were carried out by various researchers (Kalasariya et al. 2022). Reactive oxygen species (ROS) are released because of SARS-CoV-2 infection, making neighboring cells much more susceptible to virus infection. Strong antioxidant capabilities have been documented for some bioactive substances produced from marine algae. The carotenoid fucoxanthin, which was obtained from *Sargassum siliquastrum*, prevented H_2O_2-induced DNA damage by boosting GSH synthesis and SOD gene expression (Pangestuti et al. 2013; Singh et al. 2021). In RAW264.7 cells stimulated with tert-butyl hydroperoxide (t-BHP), fucosterol extracted from *Ecklonia cava* has been shown to effectively reduce ROS generation (Jung et al. 2013). The powders of *Sargassum* spp., of which *C. vulgaris* and *A. maxima* as well as the fucoidan Alquimar were purified, are powerful inhibitors of SARS-CoV-2 in vitro. The findings of this research suggest that these algae might be useful in the treatment of SARS-CoV-2 infections; however, additional comprehensive preclinical and clinical research is still necessary to verify this finding (Garcia-Ruiz et al. 2022).

Recent studies have shown that SARS-CoV-2 and SARS-CoV share a staggering 83% similarity in the sequence of their PLpro gene in addition to a staggering 96% similarity in the sequence of their 3CLpro and RdRp genes (Morse et al. 2020; Li and De Clercq 2020). Therefore, the current SARS-CoV inhibitors may be effective against SARS-CoV-2 (Thiel et al. 2003, 2001). Table 7.1 and Fig. 7.2 represent the potential natural bioactive NPs for SARS-CoV-2.

7.5.4 In Vivo Studies

7.5.4.1 Artemisia Annua

It has been demonstrated that in people with SARS-CoV-2 infection, interleukin-1 (IL-I) induction after virus binding to TLR promotes cellular damage. Fever and fibrosis are both mediated by IL-I, making it a highly inflammatory pleiotropic cytokine. In pulmonary fibrosis, the growth factor transforming growth factor beta

Table 7.1 Natural bioactive compounds targeting SARS-CoV viral proteins

Compound	Viral strain	IC_{50}/EC_{50}	Target	Reference
Hesperetin	SARS-CoV	60.00 μM	3CLpro	Lin et al. (2005b)
Quercetin-3-β-galactoside	SARS-CoV	42.79 μM	3CLpro	Chen et al. (2006)
18-Hydroxyferruginol	SARS-CoV	45.80 μM	3CLpro	Ryu et al. (2010b)
Kayadiol	SARS-CoV	75.20 μM	3CLpro	Ryu et al. (2010b)
Amentoflavone	SARS-CoV	8.30 μM	3CLpro	Ryu et al. (2010b))
Scutellarein	COVID-19	3.02 μM	3CLpro	Su et al. 2020)
Quercetin	SARS-CoV	73.00 μM	3CLpro	Nguyen et al. (2012))
Quercetin	SARS-CoV	23.80 μM	3CLpro	Ryu et al. (2010b)
Quercetin	COVID-19	$K_i = 7.00$ μM	3CLpro	Abian et al. (2020)
Isoforsythiaside	COVID-19	5.85 μM	3CLpro	Su et al. (2020)
Curcumin	SARS-CoV	23.50 μM	3CLpro	Ryu et al. (2010c)
Tingenone	SARS-CoV	9.90 μM	3CLpro	Ryu et al. (2010c)
Pectolinarin	SARS-CoV	37.78 μM	3CLpro	Jo et al. (2020)
Andrographolide	SARS-CoV	15.05 μM	3CLpro	Shi et al. (2020)
Kaempferol	COVID-19	34.46 μM (antiviral activity)	3CLpro	Khan et al. (2021b)
Broussochalcone A	SARS-CoV	9.20 μM	PLpro	Park et al. (2017)
Anacardic acid	COVID-19	17.08 μM	PLpro	Chen et al. (2021)
Ginkgolic acid	COVID-19	16.30 μM	PLpro	Chen et al. (2021)
Kobophenol A	COVID-19	1.81 μM	S protein	Gangadevi et al. (2021)
Rhamnan sulfate	COVID-19	1.6 ng/mL	S protein	Song et al. (2021)
Tannic acid	COVID-19	13.4 μM	Mpro	Wang et al. (2020b)
Daidzein	COVID-19	56 μM	Mpro	Ghosh et al. (2022)
Puerarin	COVID-19	42 ± 2 μM	Mpro	Hu et al. (2020)
Ampelopsin	COVID-19	128 ± 5 μM	Mpro	Nguyen et al. (2021)
Silymarin	COVID-19	46.88 μM	Mpro	Saravanan et al. (2022)
Ursolic acid	COVID-19	12.6 μM	Mpro	Tripathi et al. (2021)
Chlorogenic acid	COVID-19	39.48 ± 5.51 μM	Mpro	Su et al. (2020)
Ellagic acid	COVID-19	11.8 ± 5.7 μM	Mpro	Bahun et al. (2022)
Curcumin	COVID-19	11.9 μM	Mpro	Antonopoulou et al. (2022)
Herbacetin	COVID-19	33.1 μM	Mpro	Tallei et al. (2020)
Rhoifolin	COVID-19	27.4 μM	Mpro	Choudhry et al. (2020)

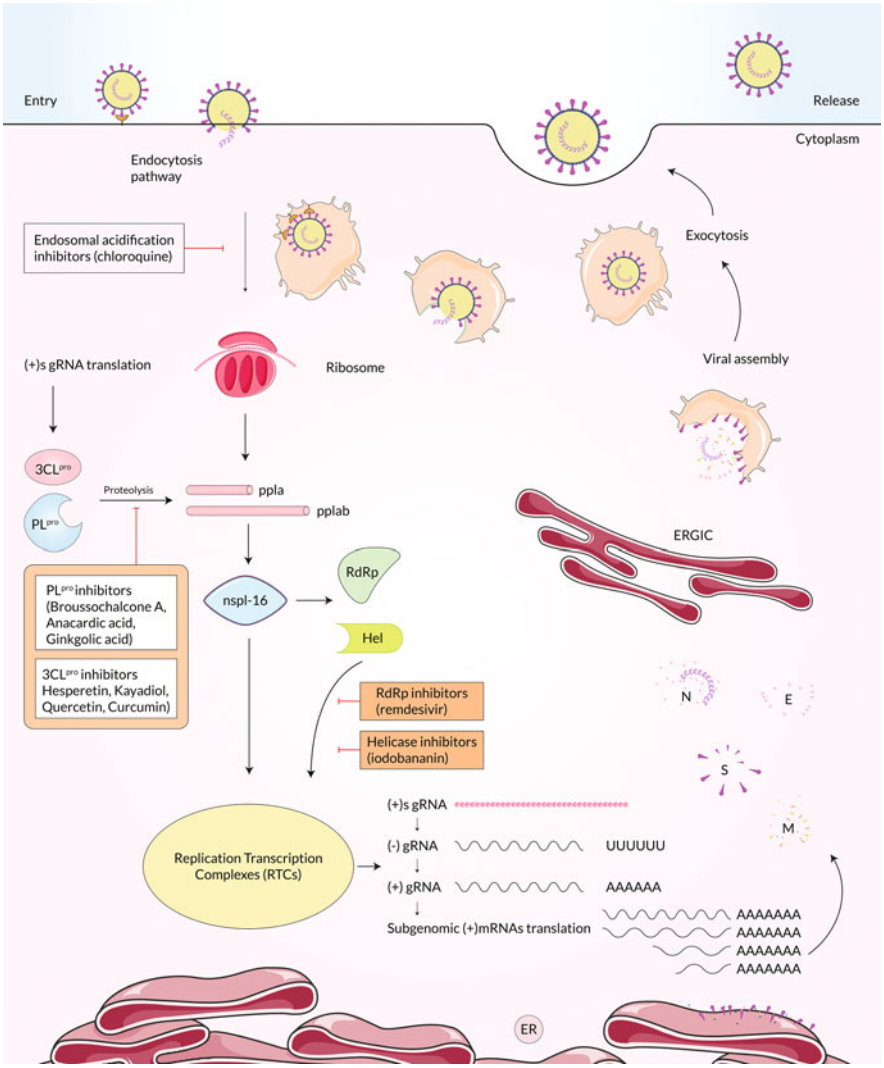

Fig. 7.2 Molecular mechanisms of natural bioactive compounds targeting SARS-CoV-2

1 (TGF-1) and its downstream components Smad3 and SMA are over-expressed. Additionally, the heat shock protein HSP47 is associated with an increase in collagen deposition. *Artemisia annua*, a possible SARS-CoV-2 treatment, has been shown in rats to inhibit the production of pulmonary fibrosis by blocking the aforementioned molecules and their relevant pathways (Fig. 7.3) (Peeri et al. 2020).

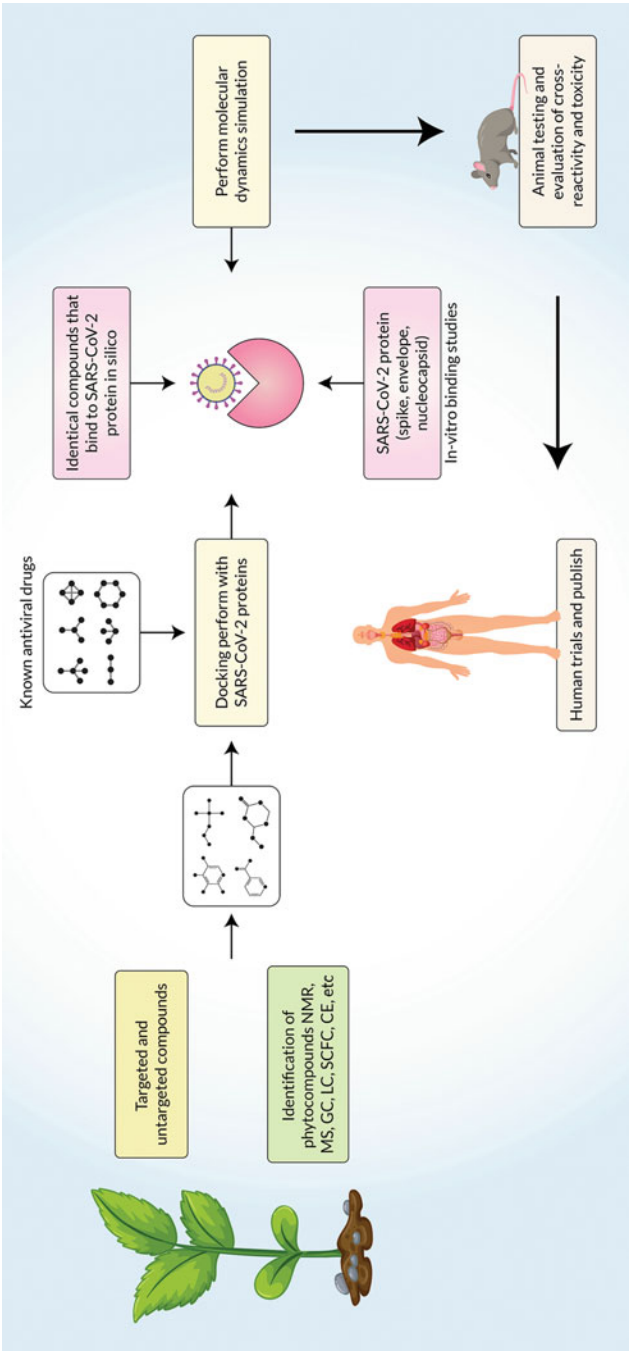

Fig. 7.3 Isolation of phytocompounds from different plant routes using NMR, GC, LC, MS, etc. Molecular Docking studies can be done on the targeted compound to see how it interacts with a specific part of the SARS-CoV-2 proteins. If it is given the potential binding affinity and strong interaction, then will perform MD simulations to check the binding behavior and drug-protein mechanism. These can be used in animal models to test the efficacy of anti-SARS-CoV-2 action, with results confirmed by clinical trials. *NMR* nuclear magnetic resonance, *MS* mass spectrometry, *GC* gas chromatography, *LC* liquid chromatography, *MD* molecular dynamics

7.5.4.2 Tripterygium Wilfordii

Lung and upper airway epithelial cells contain TMPRSS2. Epitheliasin, an airway protease, has been associated with the emergence of respiratory viruses such as influenza and coronaviruses (Bugge et al. 2009; Kim et al. 2006). The inflammatory response is activated via the NF-kB pathway in the TMPRSS2 deletion mouse model with MERS-Cov and SARS-CoV infection, suggesting a link between TMPRSS2 and the NF-kB system (Iwata-Yoshikawa et al. 2019). Suppressing TMPRSS2 may have two effects on SARS-CoV-2: it may prevent the virus from entering cells and reduce the amount of S protein that is cut during ACE2-mediated viral entry (Hoffmann et al. 2020). Both the proinflammatory response and the degree of lung pathology caused by SARS and MERS-Cov may be affected by celastrol, although in different ways. This may be due to celastrol's possible interference with the NF-kappaB pathway. In rats with lipopolysaccharide (LPS)-induced acute respiratory distress syndrome (ARDS), celastrol reduced the expression of proinflammatory cytokines (TNF-, IL-1, IL-6, and IL-8) and NF-B, resulting in a decrease in inflammation-mediated damage (Sahebnasagh et al. 2020). In addition, celastrol's anti-inflammatory effects have shown promise in reducing chronic obstructive pulmonary disease in mice. These mechanisms include a decrease in inflammatory cytokines, such as IL-8, TNF-, and monocyte chemoattractant protein-1, and an increase in antioxidant defenses, such as superoxide dismutase and catalase. These results indicate that celastrol may be an effective treatment for COPD (Zeng et al. 2018). Patients with asthma or improved airway hyper-responsiveness showed a positive outcome in vivo after receiving oral celastrol, and this effect was accompanied by a reduction in disease severity and a dampening of Th17 proinflammatory cells. However, celastrol has been shown to alleviate the severity of ventilator-induced lung injury in mice (Wei et al. 2018; Ren et al. 2018).

7.5.4.3 Pudilan Xiaoyan Oral Liquid

Compared to the model control group, the lung viral RNA copy number was significantly reduced in SARS-CoV-2-infected hACE2 transgenic mice treated with PDL (4 ml/kg) administered intragastrically beginning 1-hour post-virus inoculation and continuing once daily for 5 days. On day five after infection, hACE2 mice with SARS-CoV-2 developed controlled pneumonia with interstitial hyperplasia in their lung tissues. There was an increase in the thickness of the alveolar interstitium due to the presence of inflammatory cells, and there was also an increase in the thickness of the interstitium and infiltration of inflammatory cells around the blood vessels. Alveolar interstitium enlargement was also observed in PDL-treated animals, but moderate interstitial pneumonia and few inflammatory cell infiltrates were found in lung tissue (Li et al. 2020).

7.6 Bio-farming: To Develop Plant-Based Vaccines and Active Metabolites

Recombinant molecule technology and its expression in plants using bio-farming are well established, and numerous studies have already demonstrated the efficacy of plant-based vaccinations (Prasad et al. 2020). Cloning and protein expression in plants are now commonplace tasks in labs all over the world due to the rapid advancement of plant biotechnology. This facilitates the bio-farming process used to generate recombinant biomolecules such as antibodies, vaccines, hormones, and enzymes in plant systems (Rosales-Mendoza 2020). To exploit plants as bioreactors for practical vaccine production, it is necessary to (a) achieve a high level of expression of recombinant genes, (b) can quickly and efficiently design and generate new antigens in response to novel pathogen subtypes, (c) detect the genes to be transfected, and (d) make sure the safety of produced proteins to be used in people or animals (Takeyama et al. 2015). In the past 30 years, techniques for genetically altering plants have been created to enable the production of heterologous proteins in plant cells. Initially, nuclear transformation mediated by Agrobacterium and later chloroplast via the biolistic approach were used to genetically modify plants. These core techniques laid the groundwork for a variety of transformation techniques that are currently used to manufacture various vaccine designs in plants (whole organisms, particular tissues, and cell culture), as well as microalgae (Gelvin 2003; Monreal-Escalante et al. 2022). Employing the plant system solves the post-translational modification issue when using bacteria as a host (Takeyama et al. 2015). By using plants as a host instead of bacteria, the issue of post-translational changes is also resolved (Shoseyov et al. 2014). There is a lot of variation among plant species or within a single plant for the generation of commercial recombinant proteins. Recombinant proteins have been created by a variety of plants, including the hepatitis B vaccine made in lettuce, as well as others like potato, maize, rice, and soybean (Kapusta et al. 1999). To generate a rabies vaccine, tomatoes have undergone genetic modification, making them a unique crop for the production of vaccines (Twyman et al. 2003). Clinical trials are being conducted on a number of plant-produced vaccines against viruses like the influenza viruses (H1N1, H5N1, and H7N9), hepatitis B virus, norovirus, and rabies virus (Takeyama et al. 2015). Additionally, vaccinations based on plant biotechnology are being developed to prevent the propagation of tuberculosis. Seven oral plant-bioengineering-based TB vaccines have so far undergone comprehensive testing in experimental, preclinical, and phase I clinical studies (Zenteno-Cuevas 2017).

Plant biotechnology enables the expression of foreign proteins in plants, suggesting a rapid development of a possible SARS-CoV-2 vaccine candidate. To what extent this antigen is expressed depends on the type of antigen being attacked. For the next section, we will discuss the possibility of developing the SARS-CoV-2 vaccine by using the plant biotechnology-based platform shown in Fig. 7.4.

Even though there are already a number of COVID-19 vaccines available, various companies are working on plant-based vaccines, some of which are currently

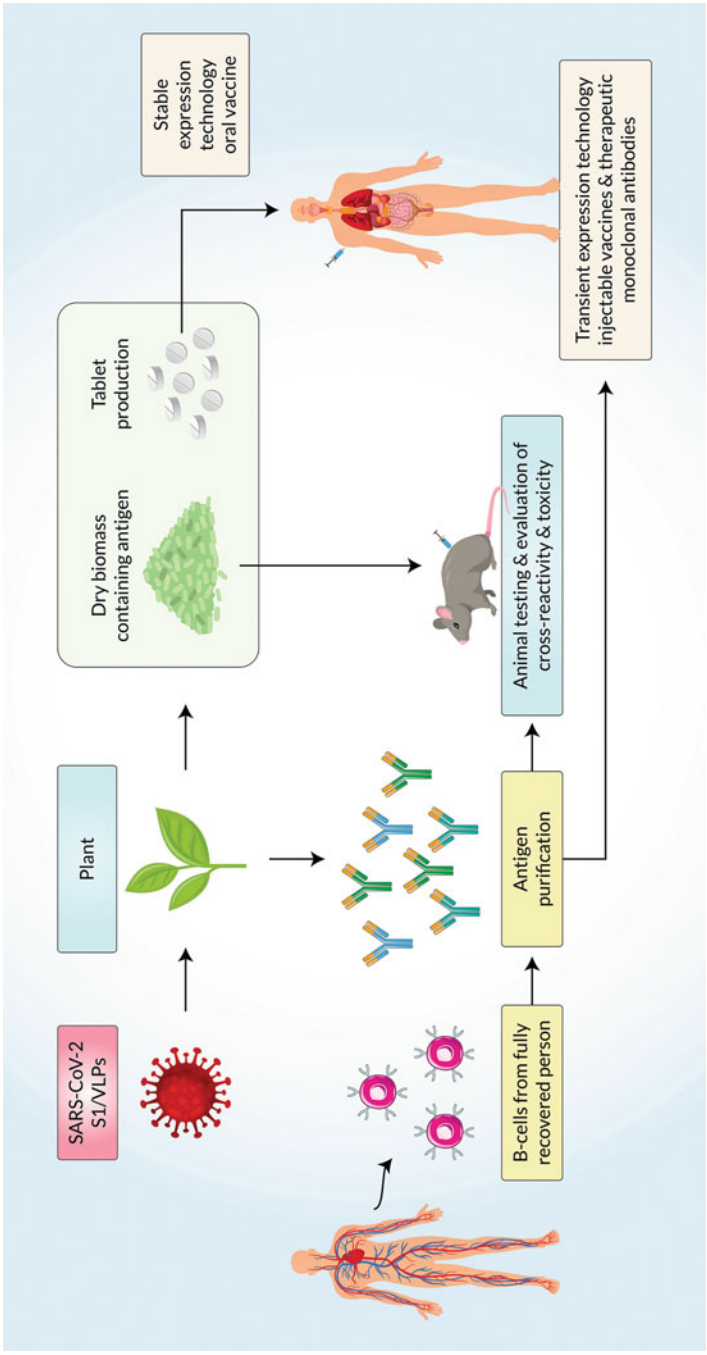

Fig. 7.4 Applications of plant-based biotechnology toward the development of SARS-CoV-2 vaccine candidates and diagnostic tools

undergoing clinical trials (Monreal-Escalante et al. 2022; Maharjan and Choe 2021). Researchers have succeeded to get mice to produce virus-specific Immunoglobin-A (IgA) by transforming *Solanum lycopersicum* fruit with S glycoprotein of SARS-CoV (Pogrebnyak et al. 2005). Another study examined the SARS-CoV N recombinant protein's immunogenicity when it was transiently generated in *Nicotiana benthamiana*. A significant humoral immune response was induced after the third parental injection with tobacco-produced recombinant N protein (Shanmugaraj et al. 2021). Recently, Medicago (Quebec, Canada), a biopharmaceutical company, announced that they had developed a plant-derived CoVLP (Coronavirus Like Particle) vaccine targeting COVID-19 that was approved by the Food and Drug Administration when administered alone or in combination with AS03 or CpG1018 adjuvants from the GSK Company (Brentford, Middlesex, UK). In this pilot study, we aimed to measure the immunogenicity of CoVLP formulations using a neutralizing antibody (NAb) and cellular responses, as well as the short-term safety of these products (Ward et al. 2021). Antigenic differentiation between circulating VOI and VOC has contributed to a decline in vaccine efficacy, at least in part because immune responses mounted against the ancestral S protein present in all administered vaccines are less likely to cross-react with the superior SARS-CoV-2 variants (Cai et al. 2021; Fiolet et al. 2022). Understanding CoVLP+AS03's place in the changing viral landscape requires research into its ability to produce NAbs to VOI/VOC. In the efficacy part of the Phase 3 trial, efficacies of 75.3% (Delta), 88.6% (Gamma), and 100% (Alpha) were seen, even though the number of participants was small. This fits well with the strong and long-lasting cross-reactivity to the Alpha, Delta, and Gamma variants that were seen (Charland et al. 2022). The most advanced clinical trials have been conducted by Medicago and Kentucky BioProcessing Inc. (Owensboro, KY, USA) (Uthaya Kumar et al. 2021). Since the expression of hemagglutinin protein in plants has resulted in virus-like particles (VLPs), scientists believe that S protein expression may be necessary for the production of SARS-CoV-2 VLPs. In this situation, if the nucleus makes a protein that targets the trans-Golgi secretion route, it may make a protein that can be used to make VLPs for SARS-CoV-2 through the processes of secretion and glycosylation (Satija and Lal 2007). Geminiviruses, like the Bean yellow dwarf virus, have been selectively bred to rapidly increase plant production of medicinal proteins. In addition, a novel synthetic COVID-19 antibody derived from a phage display library is currently being evaluated using geminivirus vector technology (Rattanapisit et al. 2020; Mahmood et al. 2020).

Some health risks, such as the possibility of mutation and recombination (in the case of attenuated viruses), have been linked to the use of viral vectors in human vaccines (in the case of viral vectors). Due to potential side effects, the production of monoclonal antibodies against SARS-CoV-2 may not be a viable long-term treatment. Thus, a vaccine based on SARS-CoV-2 VLPs expressed in plants has a chance of succeeding in the future. In conclusion, metabolite engineering has great potential for the creation of antiviral drugs against SARS-CoV-2 and other infections in plants and other heterologous species.

7.7 Antiviral Bioactive-Based Nanocarrier Approaches

The plant provides us with multiple NPs, which fulfill synergistic effects for human beings (Goyal et al. 2022). Most of the drug products that are inhaled are delivered with a size <5 μm. It can be effective by applying nanoparticle formulation with a size <1 μm and used as a carrier to enhance the bioavailability, and delayed metabolism as well as improve therapeutic activity (Goyal et al. 2022; Varahachalam et al. 2021). For instance, catechin contains chitosan nanoparticles resulting in an increased level of intestinal absorption (Dube et al. 2010). Natural flavonoids such as myricetin load a nanoparticle carrier, which noticeably raises its solubility line (Sindhu et al. 2022). The incorporation of flavonoids into erythrocytes can boost bioavailability and antiviral activity. The flavonoids have shown positive results to protect the red blood cell membrane from oxidative damage (Table 7.2) (Sims Jr et al. 2020). In the bloodstream, chitosan flavonoids keep antioxidant action and combat free radicals (Fiorani et al. 2003). Polylactic acid-4 is used as a nanoparticle to encapsulate quercetin, which allows the slow release of quercetin (Zhang et al. 2016). Some studies have shown that methanolic extract from ginger (*Zingiber officinale*) is used for silver nanoparticle synthesis to observe the inhibitory strength of SARS-CoV-2 (Kurniawan and Ikhsanudin 2020).

One of the problematic issues is flavonoids, which have low water solubility and play a function in less bioavailability. Nanotechnology has shown a revolution to solve this problem. Fisetin, a typical plant flavonoid from polyphenol present in numerous plant-like fruits and vegetables (in strawberries, pineapples, onions, and persimmons), possesses less aqueous solubility as well as resultant little bioavailability. Despite this condition, it is effective to improve health and show potent therapeutic results against SARS-CoV-2 (Antika and Dewi 2021; Pandey et al. 2021). Therefore it is significant to improve its bioavailability. Some nanotechnology approaches have proposed that based on fisetin's lipophilic nature, it can be utilized in multifarious techniques including liposomes (a short artificial vesicle in a

Table 7.2 List of antiviral phytoconstituents and their formulation

Active phytocompounds	Formulation	Applications	References
Oxymatrine	Phytosome	Increases the bioavailability	Jiang et al. (2014)
Artemisia arborescens	Liposomal	Improve the ability to suppress the viral infection	Yue et al. (2010)
Hypocrellins	Nanoparticles	Improve the level of hydrophilicity	Sinico et al. (2005)
Mayrine	Emulsion	Improves the sustainability	Wang et al. (2010)
Quercetin	Microsphere	Enhances the bioavailability	Sun and Yeh (2005)
Honokiol	Cyclodextrin inclusion complexes	Enhances the solubility and bioavailability	Casettari et al. (2012)

spherical shape), nanoemulsion (nano-form emulsions) for enhancing the release of active pharmaceutical ingredients (API) (Mignet et al. 2012; Ragelle et al. 2012; Feng et al. 2019).

Gold nanoparticles (AuNP) have antiviral activity and are widely used for COVID-19 treatment and stabilize with a particular biocompatible polymer (Kerry et al. 2019). Carbon-based nanoparticles are potentially used in these fields to deliver various nanomedicines against different types of diseases for their diverse structure, high drug-loading efficiency, low immunogenicity, enhanced bioavailability, and optical and physiological properties (Debnath and Srivastava 2021). Carbon nanomaterials (CBNs) are effective against almost 13 single-stranded RNA viruses, like SARS-CoV-2 (Serrano-Aroca et al. 2021). Carbon is a necessary element for our human body, covering the maximum surface, and could assist to associate with various types of polymers to improve efficacy. When SARS-CoV-2 attacks a specific organ in our body, it exhibits a potent physiological disbalance of the most biochemical cell cycles and metabolism in our body. CBNs help the generation of angiogenic features that induce signaling pathways by the propagation of endothelial and mesenchymal stem cells. SARS-CoV-2 cannot infect those cells (Mallakpour et al. 2021).

Albumin is a vital protein in the blood and reflects multiple physical properties. Albumin nanoparticles are nontoxic and nonimmunogenic. The residue of albumin protein has several pharmacophore entities significant in the binding of drugs. When Covid-19 infects our body, the cytokine level is increased, and diminishes the albumin level. Drugs loaded with albumin nanoparticles can be effective for this purpose. Polyethylene glycol (PGE) coating the surface of albumin nanoparticle bound was developed to enhance the bioactivity of natural steroid ginsenoside saponins found in plants (Park et al. 2021; Debnath and Srivastava 2022). The different categories of nanomaterials (NMs) and nanoparticles (NPs) have been used for vaccine development against SARS-CoV-2 as in Fig. 7.5.

7.8 Challenges and Limitations

SARS-CoV-2 infections can be a dangerous threat, and diagnoses have been challenging when faced with a lack of proper management systems and selective therapies. Hence, the identification of disease is essential for the management of COVID-19 (Yang et al. 2020). Although some report ribavirin, promazine, and inosine-5-monophosphate (IMP) dehydrogenase were used to inhibit viral replication, these were later proven invalid (Barnard et al. 2006a, b; Morrey et al. 2008). Real-time polymerase chain reaction (RT-PCR) and other potentially high-accuracy techniques can be used to detect SARS-CoV-2 viral genetic materials, but this is a costly method that requires a time-consuming protocol and diagnostic kits that are not available in all countries. In contrast, less expensive tests can be used for detection, but their accuracy level is limited (Mattioli et al. 2020). Many countries, especially with poorer settings, have failed to implement COVID-19 testing and

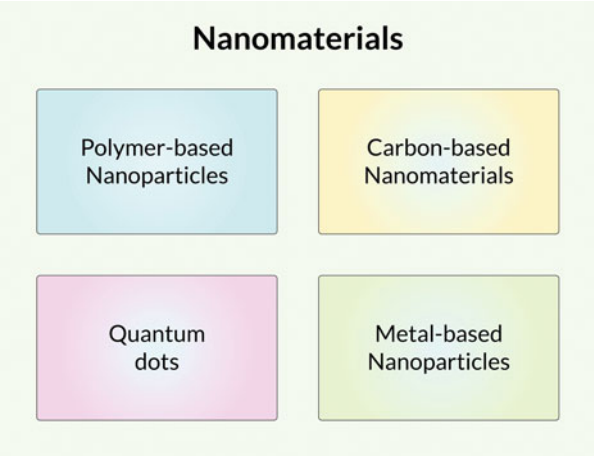

Fig. 7.5 The different types of nanoparticles used for the treatment of SARS-CoV-2. Carbon-based nanomaterials have excellent characteristics for the detection of a pathogen like SARS-CoV-2. For example, graphene and graphene oxide and carbon nanotubes. They demonstrate various potential applications such as biosensor diagnosis, airborne virus filtration, antiviral coating, and delivery of different drugs (Ferrari et al. 2015). Quantum dots such as carbon quantum dots and zirconium quantum dots can inhibit viral RNA replication (Mullard 2020). Metal-based nanoparticles, including gold nanoparticles (AuNPs), copper nanoparticles, silver nanoparticles, and zinc nanoparticles are widely used against SARS-CoV-2 (Weng and Neethirajan 2018; Warnes et al. 2015). Polymer-based nanoparticles include synthetics polymer, nitrocellulose, chitosan nanoparticles, and lipid nanoparticles used for empowering antiviral vaccine design (Sivasankarapillai et al. 2020)

highlighted the demand for extra efforts as well as to diagnose the disease technical development is needed. First-generation vaccines have high activity against SARS-CoV-2, but the long-term effect of vaccines is changeable (Grady 2020). Several research studies have reported that the flavonol glycosides have been used as a drug but had a few adverse effects. The sugar moieties of flavonoids aglycone raise bioavailability. Flavonols with glucose are fast absorbed which is the limitation of bioavailability (Xiao 2017). Various research institutes and multinational companies have been performing the synthesis of clinical trial drugs to rapidly combat SARS-CoV-2 (Rudra et al. 2017). At present, antiviral drug development is the first challenge that successfully can shut down viral replication when a virus admits into the human body. The main target for drug development is receptor protein where the virus binds and helps uncoating, as well as loosening the salvation of its contents (Schaechter 2009). Angiotensin-converting enzyme 2 (ACE2) interacts with SARS-CoV-2, which is linked to the highest rates of mortality worldwide. ACE2 is not only expressed in the lung, kidneys, and heart but also present in the nasal mucosa, thymus, liver, and brain. The renin-angiotensin system (RAS) controls the mechanism of ACE2 (Patel et al. 2016). It is a critical challenge to regulate the harmful effect of ACE2. The antiviral drug can prevent the mortality rate if the

virus has not replicated and infected the number of cells in the human body (Goyal et al. 2020).

7.9 Conclusion and Future Prospective

The SARS-CoV-2 infection has been challenging for all countries. The pathogenesis and transmission rates are more rapid than SARS-CoV-1, causing high mortality on the planet. Some precautions are needed to control virus expansion, for example, changing lifestyle, maintaining social distance, and movement limitations. SARS-CoV-2 can cause diverse mutations over time and show high infection volume. After a long time, at the end of 2020, many scientific laboratories and passionate researchers have succeeded in publishing the first approved vaccine against COVID-19. Many populous countries like the USA, China, and India have contributed to the discovery of the vaccine and that has already been approved. Best therapeutics must be promoted to regulate the present manifestation. Considering this occurrence, a huge number of natural bioactive NPs are developed against SARS-CoV-2, which are capable of suppressing the virus replication process and metastasis as well as evaluating their activity and side effects. This on-going pandemic situation shows adverse effects on the economy, so we require a minimum-cost vaccine that can show large-scale immunity. NPs are suitable for discovering AV vaccines for this purpose and recently, some are engaged in clinical trials. Multiple natural products such as essential oils and NPs are extracted from the plant, observing the activity of these NPs against viral infection. Cooperation between scientific laboratories and the government is necessary for the synthesis of plant-based AV vaccines. The synergistic effects should be tested for determination of effectiveness based on the future. It is possible to develop potential therapeutics against the SARS-CoV-2 infection through NPs targeted delivery of the therapeutics after evaluating its effectiveness in vivo clinical trial. In addition, phytopharmaceuticals also will play a vital role in contributing to the production of safe and effective drugs.

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Chapter 8
Plant-Derived Bioactive Compounds as Potential ACE-2 Inhibitors Against SARS-CoV-2 Infection

Muhammad Adil, Pragya Tiwari, Jen-Tsung Chen, and Shamsa Kanwal

8.1 Introduction

SARS-COV-2 is the causative agent of the COVID-19 pandemic that resulted in extensive morbidity, mortality and economic losses throughout the world (Kanmodi and Kanmodi 2020). Moreover, the remarkable evolutional capacity of etiological agents caused the emergence of different variant strains (such as omicron and delta) and sequential waves of disease across the diverse parts of the world (Dhawan et al. 2022). This single-stranded RNA virus possesses a nucleocapsid with a characteristic helical configuration (Khan et al. 2020). Apart from its several non-structural proteins, the SARS-COV-2 also exhibits four distinct structural proteins that are referred to as envelope (E), nucleocapsid (N), membrane (M), and spike (S) proteins (Rakib et al. 2020). Spike protein comprising of S_1 and S_2 subunits is used by SARS-COV-2 for binding with the ACE-2 receptors of human cells. The S_1 subunit binds with the ACE-2 receptor of host cells, whereas, the viral cell membrane is fused with the host cell through the S_2 subunit (de Matos et al. 2022).

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Despite the development of effective vaccines, the global COVID-19 control status highly varies on account of uneven distribution attributed to technological, socioeconomic, political and geographical factors (Ma et al. 2021). Therapeutic management of COVID-19 infection was primarily anticipated using either traditional medicines or different antiviral and anti-inflammatory agents leading to variable success rates. Besides, the technique of drug repurposing was also employed to find the prospective therapeutic utility of typical drugs against COVID-19 infection. However, despite the extensive research and considerable advancement in the development of therapeutic modalities, highly effective and FDA-approved therapies against COVID-19 infection are still lacking (Raman et al. 2022). Therefore, the discovery and development of more effective and safe therapeutic agents are also inevitable along with strengthening the vaccine-based preventive strategies.

The relatively lower burden of SARS-COV-2 infection in Asian and African regions has been correlated with the widespread use of ethnomedicinal natural products (Abubakar et al. 2021). Plant-based natural compounds constitute the oldest and most significant source of pharmaceutical products and contribute to almost 60% of drugs presently available in the market (Beutler 2009). Currently, plant-derived bioactive compounds have gained substantial attention for the therapeutic management of SARS-COV-2 infection on account of their relatively lower side effects and equivalent efficacy in comparison with typical drugs (Malviya et al. 2022). Various plant-derived bioactive products including alkaloids, phenolic compounds and terpenoids have revealed promising efficiency against SARS-COV-2 infection through their anti-inflammatory, antioxidant and antimicrobial activities (Raman et al. 2022). Keeping in view the rapidly changing genomic pattern of SARS-COV-2, uneven availability of effective vaccines and lack of disease-specific, FDA-approved drugs, plant-derived bioactive products with promising ACE-2 inhibitory activity may provide new lead compounds for the development of more efficient and safe therapeutic agents against the devastating SARS-COV-2 infection.

8.2 Therapeutic Rationale for ACE-2 Blockage in the Context of SARS-CoV-2 Infection

The pivotal role of renin angiotensin aldosterone system (RAAS) in the maintenance of fluid homeostasis and regulation of blood pressure is well-established for decades. Apart from the classical pathway of RAAS comprising of angiotensin-II and aldosterone, the angiotensin 1–7-associated new cascade has also been described in cardiovascular, renal and central nervous systems (Simões e Silva and Teixeira 2016). ACE-2 converts angiotensin-II into angiotensin 1–7 which exerts anti-inflammatory, antifibrotic and vasodilatory effects upon receptor occupancy (de Matos et al. 2022). Additionally, it also inhibits the vasodilation and enhancement of vascular permeability by altering the pulmonary metabolism of bradykinin

(Tikellis and Thomas 2012; Sanchis-Gomar et al. 2020). Previously, the antagonism of RAAS for the treatment of cardiovascular diseases was primarily achieved through the blockage of aldosterone, renin or angiotensin type 1 (AT_1) receptors (Bernardi et al. 2016; Ferrario and Mullick 2017). However, the occurrence of COVID-19 outbreak shifted the future research on RAAS toward ACE-2 as a potential target for disrupting the viral interaction with human cells (Junior et al. 2021).

Organs characterized by higher ACE-2 expression are more frequently affected by SARS-COV-2 infection (Letko et al. 2020). Besides principally targeting the respiratory tract, SARS-COV-2 also invades the cardiovascular, renal, digestive and central nervous systems (To et al. 2004). It predominantly targets the type II alveolar cells due to higher ACE-2 expression (Verdecchia et al. 2020). The presence of ACE-2 in the pancreas and small intestine, and its implication in the manifestation of digestive signs (such as vomiting and diarrhea) during the early stage of COVID-19 infection has been described (Gheblawi et al. 2020; Yan et al. 2020). ACE-2 regulates the homeostasis of antimicrobial peptides, intestinal microflora and amino acid concentrations in the gastrointestinal tract (Abubakar et al. 2021). The critical role of ACE-2 in the intracellular movement of SARS-COV-2 was corroborated in 2003 (Kuhn et al. 2004). Owing to its strong affinity for ACE-2, the viral S protein undergoes activation by the transmembrane protease serine 2 and the viral membrane is fused with the host cell membrane for subsequent release of viral RNA into the host cells via a receptor-based endocytosis process (Hoffmann et al. 2020). Strong intermolecular interaction between the lysine 31 fraction of host ACE-2 enzyme and 394-glutamine fragment associated with the receptor binding motif of SARS-COV-2 S protein occurs through significant Van der Waal forces (Zhou et al. 2020).

ACE-2 consists of two distinct isoforms termed as sACE-2 and mACE-2. Its soluble type, called sACE-2 is found in trace quantities in the bloodstream and is devoid of any membrane anchor (Wysocki et al. 2010). Conversely, the mACE-2 exhibits distinguishable extracellular and transmembrane domains and lies adjacent to the cell membrane (Ma et al. 2021). The extracellular domain of mACE-2 is used by SARS-COV-2 as a binding site for its intracellular transport (Lu et al. 2020). Whereas, sACE-2 is known to antagonize the binding of SARS-COV-2 with mACE-2 (Batlle et al. 2020). Moreover, the interaction of sACE-2 with viral S protein and resultant endocytosis via AT_1 receptors also reflect its significant role in the pathophysiological pathway of COVID-19 infection (Yeung et al. 2021). The vasoconstrictor, angiotensin-II is typically hydrolyzed by ACE-2 into angiotensin-(1–7), a vasodilator that exerts a hypotensive effect (Verdecchia et al. 2020). Contrarily, the ACE-2 dysfunction occurring during the SARS-COV-2 infection results in hypertension and inflammatory changes in the affected organs (Letko et al. 2020). Therefore, ACE-2 has been established as the principal target of therapeutic intervention for blocking the intracellular transport of SARS-COV-2.

8.3 Screening of Natural Products for Potential ACE2 Inhibition against SARS-CoV-2

A wide range of assays is presently available for the screening of natural products in terms of ACE-2 inhibitory activity. Moreover, continuous advancement in the fields of computational drug designing, medicinal chemistry and analytical techniques is expected to contribute appreciably toward the addition of more superior, economical and convenient testing methods.

8.3.1 Biochromatography

Biochromatography has been developed in 1980s and widely applied for determining the bioactive constituents and mechanisms of action of potential drugs (Zhao and Jiang 2010). In this method, bioactive materials (living cells, active macromolecules) attached to chromatographic carriers are employed to induce interference between biological macromolecules and the respective drug, and further screened for in vivo drug expression during pathological and physiological conditions (Chen et al. 2013). The activity of drug is influenced by its retention in a bio-chromatographic column and bioactivity is demonstrated when the drug binds to cells or biological macromolecules (Beigi and Lundahl 1999; Lagerquist et al. 2001). This technique can be classified into biomembrane chromatography, molecular-biology chromatography and cell membrane chromatography.

8.3.1.1 Cell Membrane Chromatography

Cell membrane chromatography includes the selective interaction between the ligands and membrane receptors. Specific receptors are present on the cell membrane and the powerful adhesion of silicon hydroxyl on SiO_2 and self-fusion of phospholipids comprise the stationary phase (He et al. 2001). Moreover, the binding parameters between ligands and membrane receptors are effective in determining the desired constituents of complex samples (Chen et al. 2013). Current advances in bioengineering and molecular biology have improved the screening of bioactive components in complex samples, further facilitating the biomimetic studies on in vitro drug interaction (Hou et al. 2009). A recent study discussed the collection, of ACE-2^h cells, cell membrane separation, mixing with SiO_2 and loading into an ACE-2/cell membrane chromatography column (Lv et al. 2021). The bioactive components, methylephedrine, ephedrine and pseudoephedrine were screened through ACE-2/cell membrane chromatography, bioaffinity chromatography and HPLC-IT-TOF-MS system (Gao et al. 2021).

8.3.1.2 Molecular-Biology Chromatography

This technology is widely applied to screen and identify bioactive constituents in a complex sample. In this method, the interaction of drugs in the body with biological molecules, namely enzymes, receptors and antibodies is taken into account. It employs receptors, transporters, enzymes and other biomolecules (with key functions) as stationary phases for the separation and purification of bioactive constituents and determination of the biochemical parameters, respectively (Wang et al. 2000; Yoo et al. 2009). When coupled with nuclear magnetic resonance, mass spectroscopy and other methods, the molecular-biology chromatography forms an integrated system that can provide better identification and structural assessment of bioactive components.

8.3.2 Computational Screening Methods

8.3.2.1 Virtual Screening

Virtual screening represents a frequently used method to identify the active compounds having high binding affinity for target proteins. The databases including multiple molecules are screened for determining the best lead molecules in drug development (Haga and Ichikawa 2016). It is classified into structure-based virtual screening and ligand-based virtual screening. The ligand-based virtual screening is mainly used when structural information and properties of bioactive compounds are available, forming a basis for the selection of new potential compounds (Wang et al. 2020), while, structure-based virtual screening is conducted to predict the stable molecular complexes (Lionta et al. 2014).

8.3.2.2 Molecular Docking Strategies

Molecular docking comprises a virtual drug-designing approach, based upon the interaction between the drug molecule and it's receptor. This method defines a feasible strategy for screening natural products as ACE-2 inhibitors against various diseases (Hirayama 2017), including SARS-CoV-2 infection. In this technique, the scoring functions are utilized to ascertain the ligand binding site and conformational state between the ligand and the target, and subsequently predict the binding energies (Li et al. 2013). The binding affinities of the bioactive ligands and the receptor sites are properly identified and further subjected to clinical validation. Moreover, the potential compounds which show a certain bioavailability and are absorbed, metabolized and excreted by the body, show key prospects in drug development. In addition, the absorption, distribution, metabolism and excretion (ADME) attributes of the compounds are virtually determined using a mathematical algorithm (Gimeno et al. 2019). A useful study was conducted to screen the potential

ACE-2 inhibitors as therapeutic targets of SARS-CoV-2, applying molecular docking, drug-likeness, and ADME predictions of each compound (Vardhan and Sahoo 2020). The study showed that ursolic acid, obacunone, glycyrrhizic acid and maslinic acid showed good binding affinities at the ACE-2 catalytic site.

8.3.2.3 Molecular Dynamics Simulations

The molecular docking method has limitations in dealing with flexible molecules like proteins, that restrict it's wider applications (Okimoto et al. 2009). Several methods including local optimization of the side chains and flexible butting were explored but these methods do not allow rearrangement and extension of protein structures and conformational changes (Friesner et al. 2004; Huang and Zou 2010; De Vivo et al. 2016). Although a key challenge accounts for receptors' flexibility, molecular dynamics work based on interatomic interactions demonstrate variations with time. Moreover, the molecular dynamics method provides information on structural dynamics and energy information about protein–ligand interactions (Ma et al. 2021).

8.3.3 Surface Plasmon Resonance

Surface plasmon resonance is gaining momentum to study various biomolecule interactions and is based on biosensor technology. It is widely employed in screening drugs and is a highly sensitive and label-free method (Patching 2014). This method involves the linking of protein to the chip (as a receptor) surface and the flowing of the analyte solution through it. The binding of compounds (regarded as ligands) with receptors leads to an increase in sensor mass and change in refractive index. Moreover, this is converted into resonance and signal graphs over time. By the assessment of signal graphs, the kinetic properties and the binding affinity of protein and ligand molecules can be known and compounds having good affinities can be identified (Prabowo et al. 2018). Moreover, the detection of compounds is based on the change in refractive index and labeling of small molecules is not required.

8.3.4 Gene Chip Technology

The technique, also referred to as DNA microarray, is a method in which DNA fragments are linked to glass, silicon or other phases in a particular arrangement. In this method, fluorescent or isotope is used to label DNA fragments and a number of gene expressions are detected via base hybridization (Zhu 2003; Huo et al. 2007). This assay has gained widespread recognition and is used to understand the

pathogenesis of diseases, gene function and high-throughput drug screening, among others (Ma et al. 2021). In this technology, a comparison between normal human cells and diseased cells can be made by analyzing differential gene expression (Wang et al. 2008). Furthermore, the method can be directly employed to study the changes in gene expression in different tissues before and after taking medication and identify new lead compounds for drug development (Scherf et al. 2000).

8.4 Major Bioactive Natural Products as ACE-2 Inhibitors against SARS-CoV-2

Natural products characterized by low molecular weight that partially or completely inhibit the enzyme functions, are gaining recognition as ACE-2 inhibitors/modulators. In the present time, natural products with ACE-2 modulatory activity are being discovered and studied for their prospects in drug discovery. Bioactive natural products screened through in vitro, in silico, and in vivo assays and associated with promising ACE-2 inhibitory potential have been summarized in Tables 8.1, 8.2, and 8.3, respectively.

8.4.1 Alkaloids

Alkaloids are classified as nitrogen-containing organic compounds with different structures and constitute a prospective source of antiviral drugs (Ma et al. 2021). Alkaloids obtained from African plants were evaluated through molecular dynamics and docking techniques, for the inhibition of ACE-2 and the association between SARS-CoV-2 and target human cells (Gyebi et al. 2022). The results of this study indicated a high affinity of cryptoquindoline and cryptospirolepine for ACE-2, TMPRSS2, and SARS-CoV-2 S protein. Several other alkaloids, namely uncarine F, bicuculline, speciophylline and anisodamine bind to the S protein and ACE-2. In addition, bis-benzylisoquinoline alkaloids effectively blocked the S protein-ACE-2-associated cell membrane fusion through their effect on the host cell calcium channels. These compounds hindered the calcium channels, Ca2þ--mediated fusion and entry of viruses into the cell (Ma et al. 2021).

8.4.2 Flavonoids

Flavonoids are commonly found in a number of fruits and vegetables, including the citrus varieties (Tutunchi et al. 2020). This class of compounds represents the largest group of ACE-2 inhibitors showing potent activity. The flavonoids, namely

Table 8.1 List of bioactive natural products screened through in vitro assays and associated with promising ACE-2 inhibitory potential

Bioactive natural product(s)	Reference
Anthocyanins	Ojeda et al. (2010)
Berberine	Kang et al. (2002)
Chlorogenic acid	Chiou et al. (2017)
Echinatin	Ke et al. (2017)
Epigallocatechin-3-gallate	
Licochalcone A	
Apigenin	Al Shukor et al. (2013)
Benzoic acid	
Catechol	
Chlorogenic acid	
Ellagic acid	
Epicatechin	
Gallic acid	
Kaempferol	
p-coumaric acid	
Phloretin	
p-hydroxybenzoic acid	
Protocatechuic acid	
Pyrogallol	
Resveratrol	
Rutin	
Syringic acid	
Tannic acid	
Resveratrol	Moran et al. (2017), Kim et al. (2018), Tiao et al. (2018)
Oenothein B	Kiss et al. (2004)
Acteoside	Geng et al. (2010)
Isoacteoside	
Plantainoside D	
Plantamajoside	
Oleanolic acid	Gutiérrez-Román et al. (2021)
Ursolic acid	
Quercetin	Guerrero et al. (2012)

hesperidin, naringin, quercetin, kaempferol, and naringenin showed ACE-2 binding affinities for the S protein of SARS-CoV-2 (Chen and Du 2020). Besides, hypertensive rats treated with apigenin showed significant upregulation of ACE-2 gene expression (Sui et al. 2010). Likewise, a natural flavone, baicalin, modulated the ACE-2 expression and diminished angiotensin-II-induced endothelial dysfunction (Wei et al. 2015). Thus the anti-inflammatory phytochemical constituent, baicalin also disrupts the entry of SARS-COV-2 into the host cells (Goyal and Goyal 2020). Another flavanone found in grapefruit, called naringenin downregulated the ACE-2

Table 8.2 List of bioactive natural products screened through in silico assays and associated with promising ACE-2 inhibitory potential

Bioactive natural product(s)	Reference(s)
Baicalin	Islam et al. (2021)
Caffeic acid	Elfiky (2021)
Chlorogenic acid	
p-coumaric acid	
Curcumin	Utomo et al. (2020)
Hesperidin	Wu et al. (2020)
Andrographolide	Maurya et al. (2020)
Berberine	
Gallic acid	
Luteolin	
Mangiferin	
Nimbin	
Piperine	
Thebaine	
Withaferin A	
Zingiberene	
Oleanolic acid	Kumar et al. (2021)
Catechol	Al Shukor et al. (2013)
Epicatechin	
Protocatechuic acid	
Pyrogallol	
Resveratrol	
Rutin	
Syringic acid	
Quercetin	Muhammad and Fatima (2015), Smith and Smith (2020)
Ursolic acid	Kumar et al. (2021)

expression and reduced nephron-vascular impairment in an animal model of hypertension (Wang et al. 2019). Myricitrin produced by *Myrica rubra* blocked the entry of SARS-COV-2 into the host cells through the induction of conformational modification in the ACE-2 enzyme (Ngwa et al. 2020). Moreover, several reports emphasize the potential of flavonoids in modulating the ACE-2 functions to counteract the SARS-CoV-2 infection. Rutin, isolated from viola, tobacco, hydrangea and buckwheat provokes the endocytosis of SARS-COV-2 following the proteolytic breakdown of ACE-2 at the junction of S_1 and S_2 subunits (Balmeh et al. 2020).

Table 8.3 List of bioactive natural products screened through in vivo assays and associated with promising ACE-2 inhibitory potential

Bioactive natural product(s)	Reference
Baicalin	Deng et al. (2012)
Caffeic acid	Chiou et al. (2017), Agunloye et al. (2019)
Curcumin	Abd Allah and Gomaa (2015)
Esculetin	Kadakol et al. (2015)
Gallic acid	Lee et al. (2015)
H-Ginsenoside Rb1	Zheng et al. (2017)
Hesperidin	Wunpathe et al. (2018)
Magnolol	Chang et al. (2018)
Naringenin	Gao et al. (2018)
Nicotine	Oakes et al. (2018)
Oxymatrine	Huang and Chen (2013)
Quercetin	Luo et al. (2017), Adefegha et al. (2018)
Resveratrol	Kim et al. (2018)
Rosmarinic acid	Liu et al. (2016)
Tanshinone IIA	Wu et al. (2014)
Trigonelline	Hamden et al. (2013)

8.4.3 Phenols

Phenols constitute a category of metabolites, widely found in nature and used in the medicine and food sector, owing to their antitumor, antioxidant, and other functions (Dai and Mumper 2010). The phenolic carboxylic acids, salvianolic acid C, salvianolic acid B and salvianolic acid A were studied for their toxicity in ACE-2 cells (found to be low) and their binding affinities with ACE-2 and RBD were evaluated by molecular docking studies (Hu et al. 2021). Another study employed a 2D ACE-2 column/C18 column/TOFMS system and screened active binding components to ACE-2, further validated by surface plasmon resonance. Moreover, the in vitro inhibitory capacity of the constituents and binding affinities of the active components were determined by the ACE-2 inhibitor screening kit and molecular docking studies, respectively (Chen et al. 2021).

8.4.4 Steroids and Steroid Glycosides

Ginsenosides, the triterpene saponins, are commonly present in the rhizome of ginseng. Ginsenoside Rg3 was shown to suppress the Ang II-induced renal damage through the induction of ACE-2 level (Liu et al. 2019). Moreover, azukisaponin I, ginsenoside Rg6 and arundoin also modulated the ACE-2 functions (Zi et al. 2020). These bioactive constituents showed low inhibition when analysed through ACE-2

kinase inhibition assay. Glycyrrhizin, isolated from *Glycyrrhiza glabra*, prevented the intracellular viral entry after binding to ACE-2 (Chen and Du 2020).

8.4.5 Terpenoids

Terpenoids are volatile substances and include diterpenes, monoterpenes, triterpenes and sesquiterpenes. This class of metabolites shows multiple pharmacological functions including antiviral, antitumor, anti-inflammatory and antibacterial effects, among others (Jaeger and Cuny 2016). Other studies on triterpenoids, namely maslinic acid, ursolic acid and astragaloside IV showed significance as S protein-ACE-2 inhibitors. Moreover, other diterpenoids like limonene and citronellol, present in lemon and geranium, downregulated ACE-2 expression in epithelial cells and showed cytotoxicity on Ht-29 cells, suggesting antiviral properties. The anti-SARS-COV-2 activity of terpenoids such as glycyrrhizic acid and its analogs is gaining considerable attention. This is supported by virtual screening methods, namely docking, molecular dynamics and network pharmacology that showed glycyrrhizic acid as an inhibitor of S protein-ACE-2 (Vardhan and Sahoo 2020).

8.5 Conclusions and Future Perspectives

Regardless of the striking structural resemblance between ACE-I and ACE-2, the conventional ACE inhibitors are ineffective for ACE-2 blockage (Tikellis and Thomas 2012). Unlike the cardioselective ACE-2 typical blockers, natural products with potential ACE-2 inhibitory activity are known for their unique multitarget pharmacological effects. The pleiotropic pharmacological actions and resultant anti-inflammatory, antimicrobial and bronchodilatory effects of bioactive compounds can be translated into clinically useful drugs against SARS-COV-2 infection (Junior et al. 2021). Consequently, plant-derived scaffolds can be efficiently employed for designing novel ACE-2 inhibitors against COVID-19 infection (Muchtaridi et al. 2020). Additionally, the association of human ACE-2 with the S protein of other genetically identical coronaviruses has also been postulated (Kai and Kai 2020). Therefore, the ACE-2-inhibitory natural products may also exhibit therapeutic utility against other coronaviruses (Ma et al. 2021).

Currently, natural products are primarily evaluated for ACE-2 inhibitory potential using virtual screening, molecular dynamics simulation and molecular docking techniques. Regardless of its improved and rapid assessment capacity, virtual screening can sometimes lead to false positive results on account of variability in receptor conformation and flexibility of the binding sites located on protein molecules (Ma et al. 2021). Accordingly, the combination of virtual screening with bioassays is recommended for enhancing its efficacy and avoidance of false positive

results. A combination strategy involving the co-application of two different techniques such as molecular dynamics simulation with molecular docking, and virtual screening with surface plasmon resonance can help to overcome the constraints in effectiveness and accuracy caused by a single method (Ma et al. 2021). In addition to the aforementioned techniques, fluorescence polarization assay and affinity mass spectrometry can also be employed to screen the natural products for potential ACE-2 blocking capacity.

So far, the affinity of several compounds including alkaloids, phenolics and terpenoids with ACE-2 has been demonstrated by means of in silico studies. Curcumin, quercetin, limonin, dithymoquinone, isothymol, and anabsinthin represent the plant-derived secondary metabolites that have been extensively screened for their ability to inhibit ACE-2 in the context of COVID-19 treatment. Despite the currently available numerous in vitro and in silico reports on ACE-2 inhibition attributed to natural products, confirmatory evidence from clinical studies is still insufficient (Junior et al. 2021). Accordingly, such promising substances should be further subjected to preclinical and clinical investigations for subsequent development as future drugs.

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Chapter 9
Insights into In Silico Methods to Explore Plant Bioactive Substances in Combating SARS-CoV-2

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9.1 Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and can range from acute respiratory failure to a mildly attacking state with cough and fever, or it can be completely symptomless. Early on, the disease manifests as interstitial pneumonia and acute respiratory distress syndrome (ARDS) in approximately 10–20% of all patients, generally with co-morbidities (Huang et al. 2020; Paules et al. 2020). On March 11, 2020, the World Health Organization (WHO) declared the coronavirus outbreak a pandemic; a series of deaths and illnesses have been diagnosed. After 2 years, the virus seemed to have subsided but ended incorrectly. Since then, a few vaccines have been developed, but none can eradicate the virus; thus, a particular motive for drug development has been needed during this crisis (Mukerjee et al. 2022). Nonetheless, Chang et al. 2020 have suggested that FDA-approved antiviral medications against the same types of viruses may produce positive outcomes (Chang et al. 2020). Other researchers have observed that hydroxychloroquine is effective against COVID-19, and in silico approaches revealed Remdesivir and Ivermectin to be potential drugs too.

Especially in India, where Ayurveda has been practiced for so long, it is very likely to search for plant-derived biomolecules as drugs against the virus. Also, even at higher concentrations, plant-derived biomolecules do not cause cellular toxicity, making them a good candidate for an antiviral drug (Singh et al. 2021; Maitra et al. 2022). The virus genome is a 29.7 kB long positive-sense single-stranded RNA that

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consists of around 12 open reading frames (ORFs), which produce two polyproteins that are further processed by protease enzymes 3CLpro and PLpro to yield 16 non-structural proteins. Apart from the non-structural proteins, four structural proteins are also produced for the virion, namely the S, E, M, and N proteins, which are discussed in detail in this chapter (Boopathi et al. 2021). Thus, after extensive research and testing, several biochemical compounds were discovered to be suitable as antivirals, and several points in the virus were identified to be targeted. Focusing on drug targets has aided in understanding and improving potential antiviral drug design methods. Synthetic and semi-synthetic drug development, as well as drug repurposing of potential molecules, is a very time-consuming process, which is shifting the focus to computational methods such as virtual molecular docking apart from molecular dynamic simulation, which can be used more effectively (Singh and Florez 2020; Debnath et al. 2022). Thus, with a solid knowledge of the molecular-structural characteristics of the drug and the potential drug targets, the drug design can be assessed in no time. The following chapter discusses the different molecular characteristics and potential drug targets of the coronavirus and the plant bioactive compounds to be used as potential drugs with the help of in silico drug design methods.

9.2 Coronavirus: Introduction and Molecular Basics

The COVID virus that has recently caused problems is SARS-CoV-2, which belongs to the order Nidovirales, family Coronaviridae, and genus coronavirus. Coronaviruses (CoVs) consist of a positive-sense single-stranded RNA (ssRNA) ranging between 26.2 and 31.7 kb as genetic material, which is further enclosed inside a protein envelope (Yang et al. 2006). Coronavirus is known to infect various hosts, including birds—avian coronavirus; pigs—porcine epidemic diarrhea virus; mice—mouse hepatitis virus and most importantly, human—human coronavirus, which includes severe acute respiratory syndrome coronavirus (SARS-CoV), SARSCoV-2, Middle East Respiratory Syndrome-CoV (MERS-CoV), HCoV-OC43, HCoV-NL63, and HCoV-229E.

The coronavirus genome is considered one of the most significant viruses with RNA as its genome (Belouzard et al. 2012). The genome of SARS-CoV-2 has approximately 13–15 ORFs, which are limited on two sides by 5′ and 3′ untranslated regions (UTRs) (Lu et al. 2020). The genome translates into two types of proteins, structural and non-structural proteins (NSPs), of which there are 27 distinct ones for SARS-CoV-2 (Liu et al. 2020). The first ORF, ORF 1 a/b, consumes 2/3 of the genome and translates into 7096 residues of the long polypeptide (PP). PP1a and PP1b are encoded by ORF1a and ORF1b, respectively, resulting in 16 NSPs after further processing (Wu et al. 2020). These NSPs are involved in a range of viral processes, including the construction of the replicase transcriptase complex, which is one of those processes. The portion of the virus' genome that has not yet been replicated encodes the messenger RNA (mRNA) that develops the structural

Table 9.1. Different functionalities of NSP of SARS-CoV-2

Sl. No.	Protein	Function	Reference
1.	NSP1	Specific function not known, but is assumed to be involved in mRNA degradation and characteristic immune response antagonism	Almeida et al. (2007), Lei et al. (2020)
2.	NSP2	Replicase products which involved in host cell variation in signaling pathway as a result of interaction with PHB and PHB2	Harcourt et al. (2004)
3.	NSP3	Plays part in the processing of polyproteins by attaching to nucleocapsids, viral genome, and other proteins	Lei et al. (2018)
4.	NSP4	Viral membrane rearrangement and replication in association with NSP3	Lei et al. (2018)
5.	NSP5	Named as main protease or 3C-like protease which cleaves viral protein	Shamsi et al. (2021)
6.	NSP6	Has part in preliminary initiation of autophagosome from host endoplasmic reticulum as a potential transmembrane scaffold protein	Shamsi et al. (2021)
7.	NSP7	RNA-dependent RNA polymerase (RdRp) binds to ssRNA forming a hexadecameric compound in attachment with NSP8 acting as a clamp for polymerase and NSP12	Yin et al. (2020)
8.	NSP8	Forms a hexadecameric complex in association with NSP7 and cofactor of NSP12. NSP12-NSP7-NSP8 complex performs RNA polymerization activity on the poly U tail with the addition of ATP	Yin et al. (2020)
9.	NSP9	Single-stranded binding protein to facilitate virulence and replication	Zhang et al. (2020a, b)
10.	NSP10	Acts as a cofactor of NSP16 and NSP14 to form a heterodimer to perform MTase activity and has a role in mRNA cap methylation, ExoN for proofreading of viral genome and 2-*O*-methyltransferase	Joseph et al. (2006)
11.	NSP11	Not known	Gupta et al. (2020)
12.	NSP12	RdRp and nucleotidyltransferase	Kirchdoerfer and Ward (2019)
13.	NSP13	RNA helicase and 5′ triphosphatase activity	Gupta et al. (2020)
14.	NSP14	3′ to 5′ exonuclease activity, ExoN activity, N7 methyltransferase (addition of 5′ caps to the viral genome)	von Grotthuss et al. (2003)
15.	NSP15	Mn^{2+} assisted endoribonuclease activity	Guarino et al. (2005)
16.	NSP16	Protein 5 recognition and 2′-*O*-ribose methyltransferase activity by defending viral genome from melanoma differentiation	Chen et al. (2011)

proteins. These structural proteins include the spike, envelope, membrane, and nucleocapsid. Other auxiliary proteins are also generated (McBride et al. 2014). The details of 16 non-structural proteins are given in Table 9.1..

Pp1a and Pp1b take over the host ribosome and form the replication–translation complex for the virus's good (Te Velthuis et al. 2012; Stobart et al. 2013). 16 NSPs are produced after proteases break down PP. NSP1 and NSP2 decrease the expression of host genes, NSP3 forms a multidomain complex, NSP5 is an M protease that aids in replication, NSP4 and NSP6 are transmembrane (TM) proteins, NSP7 and NSP8 operate as primases, and other NSPs have unique roles (Te Velthuis et al. 2012). NSP9 is an RNA-binding protein that is essential for viral infection in its dimeric form. CoV infection can be avoided by disrupting NSP9 dimerization (Egloff et al. 2004; Hu et al. 2017). NSP10 functions as a cofactor for the replicative enzyme's activation (Bouvet et al. 2014). The NSPs NSP12, NSP13, NSP14, NSP15, and NSP16 all exhibit RNA-dependent RNA polymerase activity, helicase activity, exoribonuclease activity, endoribonuclease activity, and methyltransferase activity. All NSPs play a significant role in transcription and replication (Wang et al. 2016). Spike surface glycoprotein (S), a small envelope protein (E), membrane (M), and nucleocapsid (N) proteins are the four primary structural proteins that are also synthesized. CoV genetic material is frequently subject to recombination, which can result in the emergence of new strains with altered virulence (Hilgenfeld 2014).

Angiotensin-converting enzyme 2 (ACE2), a monocarboxypeptidase found on the cell membranes of various organs such as the heart, lungs, arteries, intestine, kidney, gastrointestinal tract, esophagus, colon, and small intestine, but absent from the stomach and testes, eventually functions as a cell receptor for SARS-CoV (Oudit et al. 2009, Rehman et al. This enzyme allows the SARS-CoV to enter; thereafter, its genome is translated into PPs, which in turn encode for NSPs. The major protease (Mpro) and papain-like protease (PLpro) mediate the processing of PP, chopping it into smaller pieces to facilitate replication and aid in the formation of new virions (Zhang et al. 2020a, b). ORF1a and ORF1b in SARS-CoV-2 are of 486 kDa and 790 kDa, respectively, and are processed by proteases at three sites, ending up with NSP1, NSP2, and NSP3. The other NSPs are processed by 3-chymotrypsin-like cysteine protease (3CLpro). The nucleocapsid packages of the genome are made up of the soluble structural protein N. The M protein, which is the most common protein in the virion envelope (Masters 2006; Hogue and Machamer 2007), interacts with the tiny E protein, which is just 79–109 amino acids in length. The CoV enters the host cell by endocytosis when the S protein binds to the ACE2 enzyme. It is a three-region type I-TM protein with a clove shape (Belouzard et al. 2012). The ectodomain (ED) region, the TM region, and the intracellular domain, which make up the intracellular short tail section, are collectively formed by the receptor-binding S1 domain (tri-headed) and membrane fusion component S2 (trimeric stalk) on the C-terminal. Even before the genetic code is translated into NSPs such as RNA-dependent RNA polymerase (RdRp), 3CLpro, and PLpro, followed by other structural proteins (N, M, E, and S) of the virus, the S1 domain binds to the host receptor, and the S2 segment aids in the merging of host and viral membranes for the transport of the RNA genome. The spike protein, which gives the virus its moniker of "crown virus," seems to be in the trimeric form on the exterior of the virion.

9.3 Plant Bioactive Compounds as Therapeutics

Natural substances have been a significant source of possible pharmacological hits and lead throughout the last few decades (Petrovska 2012; Ivanova et al. 2018; Gantait et al. 2014). Potential drugs for various epidemics, endemics, and sporadic diseases around the world are highly concentrated, specifically targeted, and have a number of side effects. This is where plant-derived bioactive natural compounds come into play. A specific amount within the host body is not reactive to the established immune system and thus does not attempt to demolish the host's already achieved health. Plant-derived biochemicals have been in use since ancient times, far before chemically synthesized drugs were available in markets, and they have been successful in keeping the human lineage alive from the Stone Age till now. India, specifically, being so rich in its biodiversity, is believed to hold numerous medicinal plants that ensure the cure of many diseases, the practice of which in ancient India has been called "Ayurveda."

According to the World Health Organization (WHO), traditional plants are used by 65–80% of the population in underdeveloped countries to treat medical conditions (Robinson and Zhang 2011; Ghosh et al. 2022; Maniruzzaman et al. 2022). According to Mukhtar et al. (2008), approximately 25% of commonly used medications, including those used to treat malaria, illnesses such as human immunodeficiency virus (HIV), tuberculosis, cancer, cardiovascular disease, diabetes, inflammatory diseases, and so on, have all been developed from naturally occurring substances.

In nature or produced at the time of processing food or medicinal plants, bioactive compounds are necessary or nonessential substances that have the ability to modulate a variety of biological processes for the betterment of human health (Biesalski et al. 2009). While nonessential chemicals are neither necessary for any biological activity nor is their absence harmful to the host body, essential compounds meet essential biological functions in the host body, and their absence results in sickness (Biesalski et al. 2013). Vitamins, such as vitamins A, B, C, D, and E, have emerged as being among the most researched and important components. According to Chambial et al. (2013), they have shown promise in the treatment of conditions including allergies, bone development, wound repair, conservation of connective tissue, and many others (Chambial et al. 2013; Das et al. 2022). The vast majority of bioactive substances that are nonessential are phytochemicals. According to their chemical composition, they are classified as polyphenols, terpenoids, phytosterols, alkaloids, and other substances (Somani et al. 2015). There are more categories for phytochemicals that take into consideration factors like the number of rings and carbons, among other things (Tsao 2010). Vegetables, fruits, algae, cereal grains, and medicinal plants are rich sources of this group of compounds since they are generated in the secondary metabolism of plant cells (Zhang et al. 2015). The vegetables with the highest levels of phytochemicals are broccoli, spinach, broccoli, red peppers, and other foods with high levels of polyphenols and antioxidant capacity (Liu 2013). Purple rice, red rice, and black rice are three grains that are

regarded as having a high phytochemical content. Many different plants and flowers contain phytochemicals that may have positive impacts on health, including medicinal plants like *Camellia sinensis*, *Ephedra sinica,* and *Dioscorea bulbifera* (Zhang et al. 2015).

The effectiveness of certain plant-derived compounds used in both ayurveda and the west against a number of viral infections, including dengue, chikungunya, hepatitis, Ebola, and others, has been documented (Bhuiyan et al. 2020; Boukhatem and Setzer 2020). Four Ayurvedic herbs were used in COVID-19 clinical studies by the Ministry of Ayush (India): ashwagandha (*Withania somnifera* L.) Dunal; guduchi (*Tinospora cordifolia* (Willd.) Miers); yashtimadhu (*Glycyrrhiza glabra* L.); and pipli (*Piper longum* L.) (Kotecha 2021). Glycyrrhetinic acid (Huang et al. 2016), guggulsterone (Shah et al. 2012), boswellic acid (Darshan and Doreswamy 2004), withaferin A (Bale et al. 2018), and diosgenin (Haratake et al. 2017) are examples of such plant-derived anti-inflammatory steroids (Gyebi et al. 2021). Table 9.2. shows many plant extracts that have been examined and shown to be effective against SARS-CoV.

9.4 In Silico Drug Designing: Structure-Based Molecular Docking

Drug repurposing of prospective compounds is a time-consuming process in creating synthetic and semi-synthetic drugs. As a result, computing virtual molecular docking and molecular dynamic simulation are examples of in *silico* technologies that could be put to good use. Then, to start the medication development process, promising pharmaceutical compounds can be later verified by an in vitro or in vivo study. In that regard, molecular docking has grown significantly as a method for developing new pharmaceutical drugs.

Numerous potentially useful therapeutic targets for various disorders have been discovered since the human genome project was completed. Furthermore, advances in nuclear magnetic resonance spectroscopy, high-throughput protein purification, and crystallography have contributed to the definition and improvement of protein and protein–ligand interaction and structural elements. Because of these changes, in silico techniques can continue and progress in drug discovery.

In addition to being more effective, direct, and rational in finding approaches with lower costs than the conventional high-throughput screening (HTS) methods, virtual screening (VS) techniques have been used for hit identification and lead optimization (Moitessier et al. 2008). Ligand-based and structure-based strategies are available for VS. Quantitative structure–activity relationship (QSAR) or pharmacophore modeling are two ligand-based methods that may be utilized when there is a collection of active ligand molecules accessible despite limited or no structural knowledge about the targets. Since the 1980s, molecular docking has been the most popular and

Table 9.2. A few phytochemicals with antiviral properties against CoV

Sl. No.	Phytochemicals	Mode/target of inhibition	The scientific name of the source plants	Reference
1.	Abietane	$3CL^{pro}$	*Lycopus europaeus* L.	Wen et al. (2007)
2.	Cepharanthine	3CLpro	*Catharanthus roseus* (L.) G. Don	Zhang et al. (2005)
3.	Tomentin B	3CLpro	*Paulownia tomentosa* Steud.	Chen et al. (2005)
4.	Apigenin	3CLpro	*Torreya nucifera* (L.) Siebold & Zucc.	Ryu et al. (2010)
5.	Tomentin C	3CLpro	*Paulownia tomentosa* Steud.	Chen et al. (2005)
6.	β-sitosterol	3CLpro	*Isatis tinctoria* L. (Brassicaceae)	Lin et al. (2005)
7.	Betulonic acid	3CLpro	*Juniperus formosana* Hayata	Wen et al. (2007)
8.	Rhein	Restrict viral entry	*Houttuynia cordata* Thunb	Ho et al. (2007)
9.	Broussochalcone B	3CLpro and PLpro	*Broussonetia papyrifera* (L.) L'Her. ExVent.	Park et al. (2017)
10.	Tomentin D	3CLpro	*Paulownia tomentosa* Steud.	Chen et al. (2005)
11.	Catechin gallate	Viral replication	*Camellia sinensis* (L.) Kuntze	Roh (2012)
12.	Aloe emodin	3CLpro	*Isatis tinctoria* L.	Lin et al. (2005)
13.	Cinnamtannin B	Pseudovirus infection	*Cinnamomum verum* J. Presl	Zhuang et al. (2009)
14.	Chrysin	Restrict viral entry	*Scutellaria baicalensis* Georgi	Ho et al. (2007)
15.	Corylifol A	PLpro	*Cullen corylifolium* (L.) Medik.	Kim et al. (2014)
16.	Tomentin E	3CLpro	*Paulownia tomentosa* Steud.	Chen et al. (2005)
17.	Diplacone	PLpro	*Paulownia tomentosa* Steud.	Cho et al. (2013)
18.	Emodin	Restrict viral entry	*Rheum officinale* Baill.	Ho et al. (2007)
19.	Ferruginol	CoV-replication	*Chamaecyparis obtuse* var. *formosana* Hayata	Wen et al. (2007)
20.	Gallocatechin gallate	Viral replication	*Camellia sinensis* (L.) Kuntze	Roh (2012)
21.	Hesperetin	3CLpro	*Isatis tinctoria* L.	Lin et al. (2005)
22.	Hinokinin	3CLpro	*Phyllanthus amarus* Schumach. &Thonn.	Wen et al. (2007)

(continued)

Table 9.2. (continued)

Sl. No.	Phytochemicals	Mode/target of inhibition	The scientific name of the source plants	Reference
23.	4-Hydroxy-isolonchocarpin	PLpro	*Broussonetia papyrifera* (L.) L'Her. ExVent.	Park et al. (2017)
24.	Indigo	3CLpro	*Isatis tinctoria* L.	Lin et al. (2005)
25.	Isobavachalcone	PLpro	*Cullen corylifolium* (L.) Medik.	Kim et al. (2014)
26.	Juglanin	Blocks the 3a channel	*Taxus caespitosa* Nakai	Schwarz et al. (2014)
27.	Psoralidin	PLpro	*Cullen corylifolium* (L.) Medik.	Kim et al. (2014)
28.	Neobavaisoflavone	PLpro	*Cullen corylifolium* (L.) Medik.	Kim et al. (2014)
29.	Myricetin	3CLpro	*Isatis tinctoria* L.	Yu et al. (2012)
30.	Rosmariquinone	CoV-replication	*Salvia miltiorrhiza* Bunge	Park et al. (2012)
31.	Savinin	3CLpro	*Chamaecyparis obtusa* var. formosana	Wen et al. (2007)
32.	Broussochalcone A	3CLpro and PLpro	*Broussonetia papyrifera* (L.) L'Her. Ex vent.	Park et al. (2017)
33.	Scutellarein	3CLpro	*Scutellaria baicalensis* Georgi	Yu et al. (2012)
34.	Silvestrol	Cap-mRNA Translation	*Aglaia foveolata* Pannell	Müller et al. (2018)
35.	Tanshinone I	PLpro	*Salvia miltiorrhiza* Bunge	Park et al. (2012)
36.	Tetra-*O*-galloyl-b-D-glucose	Restrict viral entry	*Phyllanthus emblica* L.	Yi et al. (2004)
37.	Sinigrin	3CLpro	*Isatis tinctoria* L.	Lin et al. (2005)
38.	Tylophorine	3CLpro	*Tylophora indica* (Burm. f.) Merr.	Yang et al. (2010)
39.	3′-*O*-methyl diplacone	PLpro	*Paulownia tomentosa* Steud.	Cho et al. (2013)
40.	4′-*O*-methyl diplacone	PLpro	*Paulownia tomentosa* Steud.	Cho et al. (2013)
41.	3′-*O*-methyl diplacol	PLpro	*Paulownia tomentosa* Steud.	Cho et al. (2013)
42.	4′-*O*-methyl diplacol	PLpro	*Paulownia tomentosa* Steud.	Cho et al. (2013)
43.	7-Methoxy-cryptopleurine	3CLpro	*Tylophora indica* (Burm. f.) Merr.	Yang et al. (2010)
44.	6-geranyl-40,5,7-trihy-droxy-	PLpro	*Paulownia tomentosa* Steud.	Cho et al. (2013)

(continued)

Table 9.2. (continued)

Sl. No.	Phytochemicals	Mode/target of inhibition	The scientific name of the source plants	Reference
	30,50-di-methoxy flavanone			
45.	8b-hydroxy abieta-9 (11),13-dien-12-one	CoV-replication	*Chamaecyparis obtusa* var. *formosana*	Chang et al. (2012)
46.	Tomentin A	3CLpro	*Paulownia tomentosa* Steud.	Swain et al. (2021)
47.	Amentoflavone	3CLpro	*Torreya nucifera* (L.) Siebold &Zucc.	Ryu et al. (2010)
48.	Bavachinin	PLpro	*Cullen corylifolium* (L.) Medik.	Kim et al. (2014)
49.	Broussoflavan A	3CLpro and PLpro	*Broussonetia papyrifera* (L.) L'Her. ExVent.	Park et al. (2017)
50.	Curcumin	3CLpro	*Curcuma longa* L.	Wen et al. (2007)

widely acknowledged approach compared to methods that use structures (Kuntz et al. 1982).

Docking approaches are used to model the molecular-level interaction between molecules and proteins in order to understand the behavior of molecule and protein binding at the binding site as well as the underlying biochemical process. In general, the docking procedure is divided into two steps: first, determining the pose, which includes the ligand's conformation, location, and orientation; and second, determining the binding affinity, which is connected to the sampling technique and scoring schemes, respectively. If the location of the binding site is known, docking efficiency can be increased. This can be done by comparing proteins from related families, those with similar activities, or those that have crystallized along with other ligands. GRID (Goodford 1985; Kastenholz et al. 2000), POCKET (Levitt and Banaszak 1992), SurfNet (Laskowski 1995; Glaser et al. 2006), PASS (Brady and Stouten 2000), and MMC (Mezei 2003), among others, can be used to discover active sites within proteins when no information about binding sites is available. Blind docking is the term used when docking is performed without knowledge of the binding location.

Fischer's lock-and-key hypothesis (Fischer 1894), according to which ligands fit into receptors like a lock and key, was the basis for docking in the past. Then, when Koshland's induced fit theory was developed, it replaced the lock-and-key hypothesis by arguing that the protein's active sites are constantly changing due to interactions with ligands. In the end, this hypothesis gave a more accurate description of what happens during docking when ligands and receptors are seen as flexible instead of rigid.

Utilizing computational methods, molecular docking is used to predict the complex ligand–protein structure, and it has two parts: sampling algorithms and scoring functions. The first step in sampling is matching the protein and ligand

conformations, after which the conformations are rated using the scoring function. It should be ranked among all the created conformations by the testing functions, and the sampling methods should ideally be the same as the experimental binding conditions.

Concerning the six degrees of translational, rotational, and conformational freedom of the proteins and ligands, it is possible to come up with countless numbers of modes of binding among the two, which, if done, can be extremely expensive to generate computationally. Thus, various sampling algorithms are produced to determine the most suitable. The MA process relies on the shape features and chemical information of the ligand molecule's shape map in the active site of a protein. Protein and ligand are accepted as pharmacophores, and each distance between the two is calculated for a match, which results in new ligand conformations with the help of the distance matrix between pharmacophores and matching ligands. Few characteristics are taken into account while samplings, such as the chemical properties of hydrogen donors or acceptors. The matching algorithms, if documented, save a lot of time and labor, thus enriching the active compound libraries, i.e. database enrichment (Brint and Willett 1987; Fischer et al. 1993; Norel et al. 1994). Incremental construction, or IC (Des Jarlais et al. 1986; Leach and Kuntz 1992; Rarey et al. 1996), is a fragmental approach that matches the ligand in a fragmented and incremental manner. The ligands are broken into several fragments using the rotatable bonds, which are used to dock at the active site. One fragment, being the largest, is interacted with first based on its significant functional role, and other fragments are added on an incremental basis. In terms of ligand flexibility, different ligand orientations are taken into account. MCSS or multiple copy sequential search (Miranker and Karplus 1991; Eisen et al. 1994) and LUDI (Böhm 1992a) are fragment-based methods for de novo design well and for modification of known ligands to improve binding to the active site of the protein. In the case of MCSS, the ligand is fragmented into 1000–5000 copies of the functional group. It is placed randomly on the binding site, for which instantaneous minimization of energy or suppressed molecular dynamics are targeted. In that sense, a series of energetically suitable binding sites and orientations are identified based on the energy of interactions, and new molecules are designed to link up those functional groups. In LUDI, small molecules are put into the active sites of protein molecules in a way that lets hydrogen bonds form, and hydrophobic groups are put into the pockets that are left over. First, the interaction points that can form H-bonds or be filled by groups that do not like water are counted. So, the interaction sites are filled with parts that fit well, and then the parts that fit well are joined by bridge fragments to make a single molecule (Böhm 1992b). Monte Carlo (MC) and genetic algorithm (GA) are types of random methods that look for conformational space by changing the orientation or number of ligands in a population. MC creates different conformations of ligands by rigid body translation or bond rotations, and poses generated by this are assessed by energy-based selection. Conformations are not completed unless a predetermined level of quality is obtained. MC enables the ligand to cross the energy barriers on the potential energy surface by generating a large amount of change. Conversely, GA is known to have derived the concept of evolution from Darwin's ideas. The degree of

Table 9.3 Various software using different sampling algorithms

Sl. No.	Algorithm	Software	Reference
1.	Matching algorithms (MA)	DOCK	Kuntz et al. (1982)
		FLOG	Miller et al. (1994)
		LibDock	Diller and Merz Jr (2001)
		SANDOCK	Burkhard et al. (1998)
2.	Incremental construction (IC)	DOCK 4.0	Ewing et al. (2001)
		FlexX	Rarey et al. (1996)
		Hammerhead	Welch et al. (1996)
		SLIDE	Schnecke and Kuhn (2000)
		eHiTS	Zsoldos et al. (2006)
3.	LUDI	–	Böhm (1992a)
4.	Monte Carlo (MC)	AutoDock	Goodsell and Olson (1990)
		ICM	Abagyan et al. (1994)
		QXP	Mcmartin and Bohacek (1997)
		Affinity	–
5.	Genetic algorithms (GA)	AutoDock	Morris et al. (1998)
		GOLD	Verdonk et al. (2003)
		DIVALI	Clark (1995)
		DARWIN	Taylor and Burnett (2000)

freedom of the ligand is represented by genes, which collectively form the ligand's conformation, represented by a chromosome. Mutation occurs when random changes are made to the genes, and crossing over is the exchange of genes between chromosomes, both of which are genetic operations on the genetic algorithm, which in turn operates on the structure of the ligand. Scoring functions evaluate brand-new structures, and the ones that exceed the threshold are used for the next generation. Molecular dynamics (MD) are used to move each atom independently among the other atoms, which indicates the flexibility of both the ligand and protein. Because MD is associated with difficulties in overcoming high energy and conformational barriers, which lead to short sampling, it is operated for local optimization. Thus, MD is performed to identify subtle orientations after the random identification conformation of ligands. Table 9.3 enlists different software using different sampling methods.

Scoring is accomplished by guessing rather than calculating, employing assumptions and simplifications of protein and ligand binding selectivity to distinguish correct from incorrect conformations and binders from incorrect locations to an active site in a reasonable amount of time. There are three methods for scoring: force-field, knowledge-based, and empirical. The traditional scoring method, force-field-based scoring, evaluates the binding energy through non-bonded interactions like electrostatics and van der Waals interactions and contributions from hydrogen bonds, solvation, and entropy. While empirical scoring is straightforward to assess, its applicability for ligand–protein complexes outside of the training set is only partially evident. In the knowledge-based scoring of ligand and protein complexes,

statistical analysis is carried out to determine the contact frequencies between atoms or the distance between the ligand and the protein. It assumes that the more favorable a contact is, the more likely it will occur. For each atom in the ligand and protein, the score is computed by counting the number of favorable connections and penalizing the number of repulsive interactions below a threshold. The distribution of frequencies is converted into paired atom-type potentials. Due to their computational simplicity, knowledge-based functions have the benefit of being able to scan enormous compound datasets. By integrating multiple distinct scores to evaluate the docking confirmation, consensus scoring has been established to reduce enrichment in virtual screening drastically.

Aside from the complexity of receptor flexibility, particularly the flexibility of the backbone and the movement of several essential secondary elements of the receptor that involve ligand binding and the catalyst, real-world applications show how computational methods can be used to find hits in an extensive database and create new molecules. For computational studies and figuring out how the structure of a protein interacts with ligands, the structure of the protein can be obtained from experiments or databases like the Protein Data Bank (PDB).

9.5 Potential Drug Targets of SARS-CoV-2

SARS-CoV-2 seemed to have a spherical form and certain pleomorphic traits when studied under an electron microscope. When the virus was seen in the epithelial regions of the human airway, it manifested as inclusion bodies and membrane-bound vesicles in the cytoplasm. As determined earlier by genome sequencing (Hall Jr and Ji 2020), SARS-CoV-2 shares more than 85% of its genetic makeup with the bat SARS-like CoV (bat-SL-CoVZC45, MG772933.1) genome. Scientists have found that SARS-CoV-2 attacks the lower airways by binding to the ACE2 enzyme and causing the pulmonary system to make more inflammatory cytokines and chemokines, which can cause flu-like symptoms within 2 weeks of infection (Jiang et al. 2020).

The first area to prevent CoV infection is where it attaches to the host cells, which is the best spot to stop the infection. The viral nucleoprotein is released in the host cells once the virions are bound to cell membranes, and the protein covering has been removed. As the primary contributor to the systemic occurrence of the events, the structural protein S is one of the crucial targets of inhibition by creating possible drugs while retaining the S protein as a prospective pharmacological target. Its many components' structures and molecular uniqueness have already been addressed. The N-terminal domain (NTD) and the C-terminal domain (CTD) are the critical components of the S1 domain, which functions as the principal antigen on the surface of viruses with the receptor-binding domain (RBD) (Du et al. 2009). The R453 residue of RBD and K341 of ACE2 both play a crucial role in the ACE2 enzyme's interaction with the S protein's RBD, which has 18 residues and 14 amino acids (Prabakaran et al. 2004). Two heptad repeat sections (HR 1 and 2) and a

hydrophobic fusion peptide (Du et al. 2009) are present in the S2 subunit. Ultimately, the RBD has been the primary therapeutic target for S proteins. In a study involving the sequence similarity of a peptide to the RBD of the S protein, SARS-CoV entry into Vero cells was successfully inhibited (IC50 of about 40 mM) (Du et al. 2009). Han et al. (2006) discovered that chloroquine inhibits SERS-CoV by raising endosomal pH, which changes the terminal glycosylation of ACE-2 and eventually prevents the virus from attaching to its receptor (Vincent et al. 2005).

The structural protein E is the minor transmembrane structural protein of CoV and consists of two domains: a hydrophobic domain and a charged cytoplasmic tail (8.4–12 KDa). It appears to have a significant role in viral morphogenesis during the entry and exiting of the host cell. Additionally, protein E inhibition has been demonstrated in lower viral tiers and immature and ineffective progeny (Kuo et al. 2007; Schoeman and Fielding 2019). Since protein E forms a pentamer that functions as an ion channel, giving it the name E channel or viroporin, it can be a potential therapeutic target (Verdiá-Báguena et al. 2012; Nieto-Torres et al. 2014). This function is critical for the interaction between viruses and their hosts and is advantageous to the pathogenicity of the virus. Additionally, it has been discovered that protein E participates in the regulation and trafficking of intercellular proteins, which increases its potential as a significant therapeutic target.

By interacting with other CoV proteins, integrating the Golgi complex into new virions, and stabilizing the nucleocapsid protein, the membrane protein, also known as the M protein, preserves the form of the viral envelope (Schoeman and Fielding 2019; Arndt et al. 2010). It has three transmembrane domains with long C- and short N-termini on the inside and outside, respectively (Hogue and Machamer 2007). This protein also plays a significant role in cellular homeostasis, which is controlled by the interactions of other proteins. M and S protein contact is necessary for the S protein to interact with the ERGIC complex. M and N protein interactions control viral uptake and release and dictate the virus's form (Schoeman and Fielding 2019). M protein aids in the humoral response to certain viruses and can produce potent neutralizing antibodies in SARS patients (Pang et al. 2004).

The structural protein N is composed of three intrinsically disordered regions (IDRs): the N-terminal RNA-binding domain (NTD), a central linker region rich in Ser/Arg (SR), and a C-terminal dimerization domain (CTD). But these proteins aid in packaging the viral genome into the viral nucleocapsid through their roles in RNA-binding, dimerization, N-M protein interactions, and nucleocapsid protein oligomerization (Chang et al. 2014). The ribonucleoprotein complex that governs viral genome replication and transcription, cytoskeleton remodeling, and host cell death is maintained and formed by the N protein, which increases the protein's suitability as a therapeutic target. These N proteins facilitate viral genome release into the endoplasmic reticulum-Golgi intermediate compartment network (ERGIC). The N protein uses a region of its structure that contains around 140 amino acids to bind to the viral RNA. To treat COVID-19, it may be feasible to target the RNA-binding protein.

In addition to producing structural proteins, the virus also generates 16 different types of non-structural proteins. These 16 NSPs are composed of two polyproteins

encoded by two ORFs: ORF 1a and ORF 1b, which together create the PP1a and PP1b polyproteins. The 16 NSPs are produced when two cysteine proteases break down the polyproteins. NSP1-NSP3 are cleaved by a papain-like protease, or PLpro, whereas NSP4-NSP16 are cleaved by chymotrypsin-like cysteine protease, 3CLpro, or Main protease (Mpro) (Lindner et al. 2005; Zhang et al. 2020a, b). Since 3CLpro could create 12 major non-structural proteins (NSP 4 to NSP 16), including the viral RdRp (NSP 12) and helicase (NSP 13), it has been the subject of far more research than PLpro. The homodimer form of 3CLpro has a Cys-His dyad on the active site, which displays protease. The protease is crucial for RNA replication, transcription, and subsequent viral proliferation, making 3CLpro one of the most crucial targets for therapeutic research. The 306 amino acid residues are divided into domains (I and II) in the N-terminal region: domain I has amino acid residues 8–101, and domain II has 102–184. Domain III is in the C-terminal part and has residues 201–303. The active dimer structure of the protease is provided by a 15-residue long loop (residues 185–200), which connects domains II and III and is composed of a globular cluster of five helices. Studies have revealed that nucleoside analogs, terpenes, peptides, flavonoids, and quinolines have considerable anti-SARS-CoV-2 action. More surprisingly, because humans lack a homolog of 3CLpro, it has been continually investigated as a crucial target for therapeutic research (Zhang et al. 2020a, b). Like other CoVs, SARS-CoV-2 has a substrate-binding site for 3CLpro in the gap between domains I and II, which breaks down polyproteins to produce NSPs and creates a complex called a replicase transcriptase (RTC). Less than 11 Leu-Gl (Ser, Ala, and Gly) cleavage sites of polyprotein replicase 1ab are recognized by 3CLpro. Targeting conserved enzyme residues in 3CLpro can create safe and effective SARS-CoV-2 treatments.

Several polymerase inhibitors, including Remdesivir, have been developed to treat various viral illnesses because RNA-dependent RNA polymerase (RdRp) has been recognized as one of the most crucial enzymes for transcription and replication. Its central part is the multi-subunit replication and transcription complex of RdRp's NSP12. For NSP12 to operate correctly, NSP7 and NSP8 are needed (Kirchdoerfer and Ward 2019).

The endosomal cysteine proteases cathepsin B and L (CatB/L) and the serine protease TMPRSS2 (Simmons et al. 2005; Glowacka et al. 2011), which are known to play a role in the priming of S protein, have been reported to be involved in the binding of the virions in addition to the viral proteases 3CLpro and PLpro. Since it was found to be necessary for the virus to cause disease and spread, TMPRSS2 has become a possible therapeutic target.

A class of polypeptide-signaling molecules known as cytokines interacting with cell surface receptors controls a wide range of biological activities (Ratia et al. 2006). A condition known as "cytokine storm" is characterized by elevated immune system activation and is connected to several viral infections (Yuen and Wong 2005). It has been clear that one of the processes causing acute respiratory distress syndrome and multiple organ failure in COVID-19 is due to excessive cytokine production in response to viral infection (Tay et al. 2020). According to studies, individuals with COVID-19 have higher levels of inflammatory cytokines than healthy people do,

including interleukin (IL)-1, IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, IL-18, tumor necrosis factor (TNF), granulocyte-macrophage colony-stimulating factor (G-CSF), and macrophages (Huang et al. 2020). In any case, the interaction between glucocorticoid receptors (GR) and their ligands, glucocorticoids (GCs), influences the production of cytokines in both acute and chronic inflammatory diseases (Chow and Simons Jr 2018). The activated GR complex has the potential to bind to promotor-responsive elements, which would result in the inactivation of important pro-inflammatory transcription factors (such as AP-1 and NF-kappa B). Alternatively, the activated GR complex could either upregulate the expression of cytokine inhibitory proteins, such as I kappa B, which inactivates the transcription factor NF-kappa B, thereby suppressing the secondary expression of many cytokines (Brattsand and Linden 1996). Unfortunately, adverse side effects include osteoporosis, glucose and lipid metabolism abnormalities, and hypertension, which limit the usage of GCs (Sannarangappa and Jalleh 2014). As a result, developing medicines targeting the active areas of human glucocorticoid receptors (hGRs) has significant potential.

9.6 Conclusion

From December 2019 onward, instances of quickly spreading viral pneumonia were identified in Wuhan, China, which were eventually identified as a novel strain of coronavirus dubbed SARS-CoV-2 because of its 82% resemblance to the previously known SARS coronavirus (SARS-CoV). The virus resulted in a terrible epidemic that affected the whole world and appears to have faded but not ceased entirely. There are currently no effective antiviral drugs or vaccines, which opens the door to alternate solutions. Medications derived from plants have been employed by ancient civilizations to control early epidemics for a considerable amount of time and are even promising in our contemporary emergency. Several biomolecules produced by plants are efficient against the coronavirus in vivo and in vitro investigations; thus, the creation of specialized antiviral drugs is essential. In the current context of the urgent need for COVID virus medications, the computational in silico technique is both time- and resource-efficient. This chapter briefly describes the molecular docking technique as a possible weapon in a drug design system employing bioactive chemicals originating from plants. This study is anticipated to be completed rapidly with the use of in silico approaches such as molecular docking and plant bioactive compounds that can be introduced into the human body in large quantities without adverse side effects.

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Chapter 10
Dietary Plants, Spices, and Fruits in Curbing SARS-CoV-2 Virulence

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Abbreviations

$3CL^{Pro}$	3C like protease
ACE-2	Angiotensin-converting enzyme 2
AgNPs	Silver nanoparticles
AIDS	Acquired immune deficiency syndrome

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APG	Acylphloroglucinol
C-domain	C-terminal domain
CHIKV	Chikungunya virus
CLR	C-type lectin receptors
CoVs	Corona viruses
CVB1	Coxsackievirus B1 virus
DENV-2	Dengue 2 virus
DPP4	Dipeptidyl peptidase 4
EB	Ebselen
EBV	Epstein-Barr virus
ER	Endoplasmic reticulum
FDA	Food and Drug Administration
FP	Fluorescence polarization
HA	Hemagglutination
HAT	Human airway trypsin-like protease
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR1	Heptad repeat 1
HSV-1	Herpes simplex type I virus
mAbs	Monoclonal antibodies
MF	Meliae Fructus
M^{Pro}	Main proteases
NAs	Nucleotide analogs
NSPs	Non-structural proteins
NTD	N-terminal domain
PAV	Pavetannin C1
PIV	Parainfluenza virus
PL^{Pro}	Papain-like proteases
PRRSV	Porcine reproductive and respiratory syndrome virus
PRV	Pseudorabies virus
PV	Poliovirus
RBD	Receptor binding domain
RLV	Rauscher murine leukemia virus
RSV	Respiratory syncytial virus
RT	Reverse transcriptase
RV	Rhinoviruses
SFN	Sulforaphane
TEN	Tenuifolin
TMPRSS-2	Transmembrane serine protease 2
TRV	Tobacco rattle virus

10.1 Introduction

The recently emerged SARS-CoV-2 virus reported during the year 2019 in December has created a global pandemic and has become a global concern in this present era. It globally affected human health and economic activities (Shanmugam et al. 2020; Kuchi Bhotla et al. 2020; Kuchi Bhotla et al. 2021a, b; Pushparaj et al. 2022; Meyyazhagan et al. 2022). To date, there are no known therapeutic agents to treat this virus except a few Food and Drug Administration (FDA) recommended medications and vaccination (Cannalire et al. 2020). Many reports suggest that good nutritive healthier food will help overcome the infection of SARS-CoV-2 and its prolonged pathological conditions. The phytotherapy (herbalism) is generally defined as the incorporation of plants or herbs in the daily diet that is expected to enhance or modulate the individual's immune system for preventing disease, this phytomedicine therapeutic approach is found to be an affordable and safer alternative which may also minimize the occurrence of drug resistance and will typically improve the effort of the world to fight against deadly SARS-CoV-2 which is illustrated in Fig. 10.1 (Goyal and Goyal 2020). It has been well confirmed in peer research that natural phytochemicals have the potentials to combat COVID-19 and its pathogenicity without any side effects. During this period of global fretfulness, it is pertinent to implement enduring measures to battle these awful viruses. A better understanding of the basic structural targets on the virus surface facilitates the invention of the drug, which is a novel safe and effective targeted therapeutic

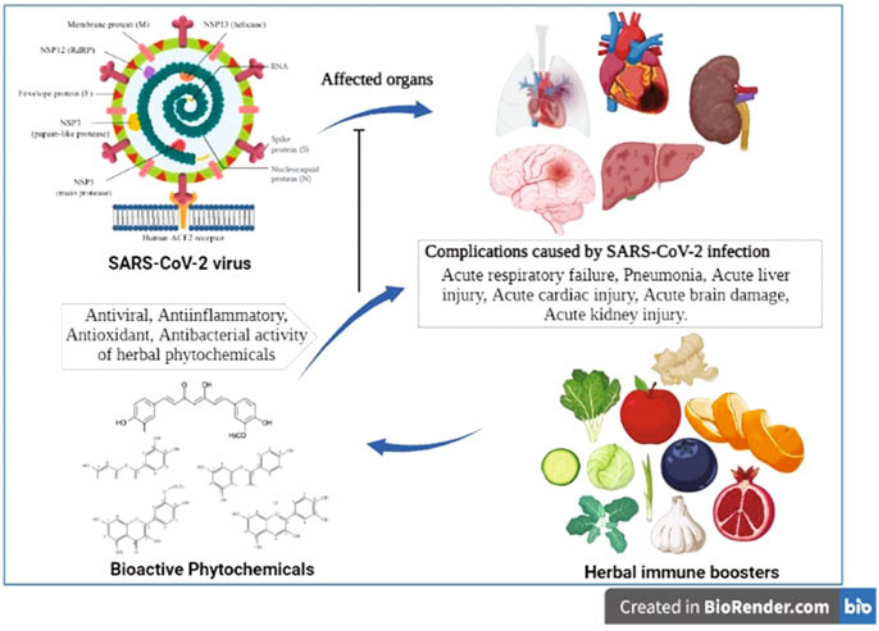

Fig. 10.1 The dietary plants, spices, and fruits in curbing SARS-CoV-2 virulence

approach. Hence, this current chapter aims to summarize the herbal immune boosters, fruits, culinary spices, and their nutritive compounds facilitating the immune defensive mechanism for counteracting infection of SARS-CoV-2 and this chapter will elaborate on the basic structural targets of SARS-CoV-2 virus (Ou et al. 2020).

10.2 Major Structural Targets of the SARS-CoV-2 Virus

The viral protease enzymes are the vital targets effectively render over SARS-CoV-2 focus on the main protease enzyme (M^{Pro}) enzyme, RNA-dependent RNA polymerase (RdRp), spike glycoprotein, 3 chymotrypsin-like proteases ($3CL^{Pro}$), and papain-like protease (PL^{Pro}) which comes up with the high degree of conservation across corona viruses emerging for the identification of the broad spectrum of inhibitors (Cannalire et al. 2020). The two crucial proteases, M^{Pro} and PL^{Pro} are notable for viral replication (Goyal and Goyal 2020). M^{Pro} enzyme is recognized as a $3CL^{Pro}$ and contains a high level of structural and sequential resemblance to SARS-CoV M^{Pro} (Zhang et al. 2020). $3CL^{Pro}$ plays a significant role in the enzymatic action of replicase polyproteins to inhibit SARS-CoV (Peele et al. 2020). PL^{Pro} a viral protease enzyme that are essential for viral polypeptide (Thiel et al. 2003) processing and conduct the antiviral reactions ubiquitin enzyme in the host defense mechanisms (Keng et al. 2011). The spike (S) glycoprotein vital role mediates the entry of the virus to the host cell target for immune responses and neutralizing antibodies of the Coronaviridae family (Tang et al. 2020). The viral spike protein requires a protease cleavage for its activation to proceed to fusion with the receptor (Ou et al. 2016). The $3CL^{Pro}$ cleavage functions as the proteolytic cleavage of functional maturation of pro-activity antiserum cross-reactive against SARS-CoV virus $3CL^{pro}$ (Froggatt et al. 2020; Chen et al. 2021). RdRp represents itself as a catalytic subunit to cofactors required for efficient boosting which lowers the thermostability with the polymerase complex of SARS-CoV-2 (Peng et al. 2020; Wang et al. 2020).

10.2.1 Spike Glycoprotein

The spike glycoprotein (S) of corona viruses is one of the most crucial targets for the creation of SARS vaccines and treatments because of efficient receptor recognition and facilitates membrane fusion and viral entry and also a primary target for neutralizing antibodies and also a key factor in coronavirus tropism (Du et al. 2009; Ou et al. 2020). Trimeric S protein monomers are roughly 180 kDa in size and comprise the S1 and S2 subunits, which mediate membrane fusion and attachment, respectively. Both C and N terminal sections in the S1 fold are two distinguished structures. The receptor-binding domain of a virus can either be the N-terminal domain (NTD) or the C-domain (receptor binding domain). In case of

activation of the spike protein for SARS-CoV-2 and Middle East respiratory syndrome coronavirus (MERS-CoV) the protease cleavage is involved in a sequential manner where there exists initial cleavage between S1 and S2 and next is the cleavage that activates the S2' site.

The cleavage process takes place utilizing the host protein-cleaving enzymes like trypsin, furin, transmembrane serine protease 2 (TMPRSS-2), cathepsins, TMPRSS-4, or human airway trypsin-like (HAT) protease, based on viral strains and cell types (Ou et al. 2020). The ability of the SARS-CoV-2 to migrate the species barrier is also significantly influenced by spike protein since the adaptive evolution of S protein can end up transmitting the SARS-CoV from animals to humans. The S protein, similar to other proteins seen in various other viral strains, is produced and placed in an inactive state in viral particles. During viral infection, a host protease cleaves the S1 and S2 subunits, stimulating them and permitting membrane attachment including a viral entry in the formed precursor that is not yet activated and present inside the envelope of the virus. A cellular protease cleaves the S protein at the time of infection of the cell, releasing it. The S1 subunit is an essential factor in host cell identification and adhesion and the most plausible target for neutralizing antibodies and creating medicines due to its host the receptor binding domain (RBD) which is essential for angiotensin-converting enzyme 2 (ACE-2) binding. The S2 subunit is involved in viral entrance and membrane fusion.

It has three important regions to establish this function: fusion peptide (FP, 788–806 residues), heptapeptide repeated sequence 1 (HR1) (912–984 residues), and heptapeptide repeated sequence 2 (HR2) (1163–1213) (Souza et al. 2022). SARS-CoV-2 S protein attaches the virus to the host cellular receptor, ACE-2. This contact is directed by a designated RBD on S. The crystal structure of the RBD associated with the human ACE-2 is said to be a protease domain at 2.9-angstrom resolution revealing that the RBD has a mild concave-like surface that carries the peptidase's N-terminal lobe. The atomic features at the two proteins interface highlight the significance of residue modifications that allow for effective cross-species associated infection and same species transmission (Li et al. 2005a, b). Modification of the spike can modify cell and tissue tropism and, in rare situations, can change virus pathogenicity when combined with other viral and host variables (Belouzard et al. 2012). The S protein is the key determinant of CoV tropism. The trimeric structure of the S glycoproteins on the viral surface allows for the attachment to a cell surface receptor and membrane fusion (Hulswit et al. 2016; Du et al. 2017). The viruses belong to the category of intracellular parasites, where they interact with the host receptors to establish their infection, the SARS-CoV-2 also initiates its entry by employing interaction with the ACE-2 receptor of host ACE-2.

ACE-2 has also been discovered as a SARS-CoV and human coronavirus NL63 functional receptor. The RBD of the S1 subunit attaches to the ACE-2 and this is a reason for S1 to be primed at the S1/S2 junction through host proteases which include furin or endosomal proteases, revealing a secondary site (S2′) is cut by the TMPRSS2. The cleavage irreversibly changes the shape of the removed protein S, allowing the subunit of S2 to enter into the host membrane and direct the fusing of the virus and host membranes (Bakhiet and Taurin 2021). The S protein is notable

for its extensive N-linked glycosylation, which covers a high part of the protein's surface area and exhibits conformation-dependent dynamic alterations. Aside from shielding, N-glycans, particularly at the N165 and N234 locations, are implicated in the modification of RBD confirmation, which might be utilized as a therapeutic target. Furthermore, it has a disulfide-bonded external N-terminus, a transmembrane domain, and a palmitoylated short intracellular C-terminus. Since it is a key determinant of the host immune response and is involved in the pathogenesis process through the virus through the activation of the endoplasmic reticulum (ER) stress response, any alterations due to mutations may result in altered pathogenesis (Yadav et al. 2021a, b). The activation of cathepsin L inside the endocytic vesicle results in the priming of the spike proteins, which results in the release of the viral RNA genome into the cytoplasm (endocytic pathway).

The TMPRSS2however, is crucial in priming the spike proteins at the cell surface, allowing the viral DNA to enter (non-endocytic pathway). Once inside the cytoplasm, the viral RNA ORF1ab portion is converted to the replicase polyprotein PP1ab, which is reacted at by enzymes secreted by the virus such as PL^{pro} and $3CL^{Pro}$ (M^{Pro}) to create nsps 1–16, including RdRp and helicase, which are essential for virus replication. Protein S binds to ACE-2 and assaults target cells including bronchial cells, nasal epithelial cells, and pneumocytes. The RBM-ACE-2 link activates the S protein, revealing the fusion peptide and causing it to assume a more favorable shape with epistatic areas, permitting the entry of the virus to the host cell. The TMPRSS2 protein is a protease enzyme that works similarly to the ACE-2 receptor in binding to the spike protein of SARS-CoV-2. The furin site is present in the usual coronavirus which contains a unique sequence of amino acids between S1 and S2 in SAR-CoV-2, consisting of Pro-Arg-Arg-Ala-Arg (Pro: proline; Arg: Arginine; Ala: Alanine). This sequence separation is critical for the effective absorption of lung cells. Without the furin site, the virus appears less infectious (Candido et al. 2022).

The interaction of the RBD in the S protein of the SARS-CoV-2 ACE-2 host receptor, as well as subsequent replication in the coronavirus S protein, leads the virus to invade the host cell. Locus E (LY6E) of the human lymphocyte antigen 6 complex restricts CoV entrance inside the host membrane receptor by interaction with the gene of humans and promoting S protein-directed membrane attachment. It has also been demonstrated that some natural formulations block the S protein from attaching to the human receptor present in the cell (Nandi et al. 2021). SARS-CoV-2 S protein may bind to various innate immunological receptors, including C-type lectin receptors (CLRs). Through a Ca^{2+}-dependent interaction, CLRs bind to particular glycans. Several receptors, including L-SIGN/CD209L/CLEC4M, DC-SIGN/CD209, mannose receptor/MR/MRC1/CD206, Dectin-2/CLEC6A, and MGL/CLEC10A/CD301 are found to have a maximum expression in the including monocytes, dendritic cells, immune system, and macrophages of the humans and act as the first line of defense against invading pathogens. CLRs such as DC-SIGN can influence toll-like receptor-induced activation and so direct glycan-specific reactions of host immune systems against infections (Shajahan et al. 2021).

10.2.2 Main Protease Enzyme (M^{Pro}) Enzymes

SARS-CoV-2 M^{Pro} is an important protease of CoV-2 which has been essential for mediating the replication of the virus and its transcription. It has also served as a potent target for the designing and development of antiviral agents against SARS-CoV-2 (Sabbah et al. 2021). The inhibition of the main protease helps prevent the multiplications of viruses and so can be used in the discovery of targeted drugs (Rudrapal et al. 2022). Pfizer's newly approved nirmatrelvir serves as a potent inhibitor of viral main protease functioning in the therapeutic front as well as the context of prophylaxis against infection (Mótyán et al. 2022). The mimetic of the peptide and inhibitor of the covalent coronavirus protease has the ability the inhibition of active sites. The drug invention for inhibiting the potential protease possesses various strategies including the observation of minimum molecular weight compounds for the inhibition of protease, good fragments from peptidomimetic compounds, including the optimal fragments for the lead monitorization and final selection and improvisation of hybrid molecules for the required pharmacokinetic and pharmacodynamics properties. The good inhibitors of the main protease of SARS-CoV-2 are derived with the help of in silico fragment-based drug design (Teli et al. 2022). It is strongly inhibited by nine ebselen derivatives (EBs) with IC_{50} 0.07–0.38 μM.

Among this EB2–7 a greater inhibition of the replication of virus SARS-CoV-2 of HPAepiC cells with an IC_{50} value of 4.08 μM. Thus, it is concluded that EBs may end up in the discovery of drugs for COVID-19 and SARS-CoV-2 infections (Qiao et al. 2021). Three phytochemical components, namely with M^{Pro} binding site licoleafol, epi-catechin gallate, and silibinin are said to be effective against CoVID-19 resulting in higher binding affinity. Thus, they can be used as an effective anti-CoVID-19 drug (Mukherjee et al. 2022). His41, Cys145, and Glu166 are the three compounds identified and subjected to in-depth augmentation deep reinforcement learning, docking for covalency, and imitations of molecular dynamics through which they are tested for their potential ability of inhibition against SARS-CoV-2 by forming high-frequency contacts with key amino acids (Zhang et al. 2022). Four cyclic peptides were scrutinized utilizing virtual screening, of which MN-2 exhibited a greater affinity to M^{Pro}. Thus, a cyclic peptide that is not covalent MN-2 serves as a specific factor to inhibit omicron (Yin et al. 2022).

10.2.3 Papain-Like Protease (PL^{Pro})

PL^{pro} is the coronavirus proteins that are considered specific agents against the virus as they are needed for the replication of the virus. Thus, targeting of PL^{pro} with various antiviral drugs prevents the replication of viruses including the inhibition of their regulation of the signaling cascades of the cells which may lead to lethality as a result of infection (Baez-Santos et al. 2015). It also targets the immune response

including posttranslational ubiquitin and ISG15 modifications. The replication cycle takes place in the virus and the responses of the host immune in association with PL^{pro} lie as a specific chance in the drug delivery (Ullrich and Nitsche 2022). It also plays a significant activity in the cleaving and the maturation of viral proteins, the arrangement of the replicase-transcriptase complex along with the destruction of host responses (Osipiuk et al. 2021). Furthermore, it provides a virulence trait among members of the same species of SARS-CoV (Niemeyer et al. 2018). The proteolytic processing of SARS-CoV-2 is carried out by the PL^{pro} and is composed of one of the main targets examined for the pharmacological intervention of in silico methodologies (Rieder et al. 2022). It can be reversibly inactivated by various covalent inhibitors such as VIR251 ligand through the development of covalent bonds with remnants of catalytic site (Cys111) employing Michael addition reaction.

The mechanism of inhibition undergoes four stages including entry of the ligand inside the pocket for protease pocket, Cys111 removal of protons from the thiol group through Brønsted-Lowry base, the addition of Cys111-S-at the ligand and exchange of proton from the protonated base to the covalently bound ligand (Hognon et al. 2022). Three phenolic compounds bound with PL^{pro} were found an increase of PL^{pro} mutation resulting in the evolution of recent variants of SARS-CoV-2 preventing the preliminary molecular communications to ISG15 by evaluating a natural compound library which was scrutinized by X-ray screening and complexed to PL^{pro} revealed best inhibitor PL^{pro} in an observation by deISGylation activity assay. Increased mutation of PL^{pro} results in generation of novel variants of SARS-CoV-2 in spite of some natural compounds found to restore the immune response against the virus of the host cell in COVID-19 infections (Srinivasan et al. 2022).

A zinc finger domain is present in PL^{pro} which is essential for the attachment of the substrate and maintaining the stability of the structure. Zinc had a greater curbing potential on PL^{pro}, followed by calcium, manganese, iron, and magnesium that had minimal or null effects on the activity of PL^{pro} which was confirmed by the attachment of zinc and manganese with PL^{pro} through tryptophan intrinsic fluorescence analysis (Shetler et al. 2022). The invention of inhibitors of PL^{pro} is carried out by vigorous and simple sandwich-like fluorescence polarization (FP) screening assay and anacardic acid was found to be an effective inhibitor against PL^{pro} in vitro (Yan et al. 2022). The molecular rules the PL^{pro} substrate specificity and provides an outline for the development of inhibitors with an effective therapeutic value of drug designing (Rut et al. 2020).

10.2.4 RNA-Dependent RNA Polymerase

RdRp role in transcription and replication of the genetic material of the virus is identified as an appealing target for developing innovative antiviral methods. Though the genetic resemblance of SARS-CoV-2 to SARS-CoV (79%) and MERS-CoV (50%) is less, the RdRps of these three variants is largely conserved,

indicating this protein is a promising broad-spectrum antiviral target for corona viruses (Wang et al. 2021a, 2021b). RdRp, also known as nsp12, catalyzes the synthesis of viral RNA and hence plays a critical role in both replication and transcription of SARS-CoV-2 genetic material, perhaps with the help of cofactors nsp7 and nsp8. As a result, nsp12 is regarded as a prime target for nucleotide analog antiviral agents (Gao et al. 2020). The smallest core component for viral RNA replication is specified as nsp12-nsp7-nsp8. The SARS-CoV-2 RdRp complex is made up of core catalytic unit nsp12, a heterodimer of nsp7-nsp8 (nsp8–1), and an extra subunit nsp8 (nsp8–2). A b-hairpin (residues V31 to K50) and a domain of nidovirus-specific extension are found at the N-terminus of nsp12 (NiRAN, residues S115 to A250). RdRp core, palm subdomain, and NiRAN sandwich the b-hairpin.

The C-terminal catalytic domain (residues L366 to F920) of nsp12 communicates with the interface subdomain of NiRAN (residues L251 to R365). The RdRp active site in SARS-CoV-2 is constituted by seven conserved A to G catalytic motifs. The RdRp, palm subdomain has five of these A-E motifs, whereas the remaining two F and G motifs are contained in the finger subdomain (Jiang et al. 2021). Most of the viral polymerases, notably Hepatitis C virus (HCV) NS5B (residue D220) and poliovirus (PV) polymerase include the typical residue of divalent-cation-binding D618, which is found to be conserved in motif A (residue D233). From 759 to 761 catalytic residues of RdRp protein is necessary for viral transcription and are mostly conserved in motif C of viral RdRps, which binds to 3 prime ends of RNA (from 317 to 319 in HCV and from 327 to 329 in PV) (Vicenti et al. 2021). When the virus infects the host cell, it contributes to the creation of the replication machinery of the viral genome by interacting with different components.

RdRP controls the elongation of the RNA strand, which involves the insertion of nucleotides of hundreds to thousands. Once incorporated into the freshly produced RNA strand, nucleotide analogs (NAs) can block the RNA elongation mediated by RdRP. Transcription of RNA by RdRP from the 3′ ends of RNA as a template can be primer-dependent or primer-independent. Primer-independent RNA synthesis by RdRP may start synthesizing with nucleotides without primer. Primer-dependent, RNA synthesis by RdRP however, makes use of primers that are short oligonucleotide or a protein that covalently attaches to nucleotides as a primer; the primer anneals with the template RNA to give a starting point for RNA synthesis (Zhu et al. 2020). RdRp inhibitors are classified into two types based on their structures and mechanisms of action nucleoside analog inhibitors that act at the substrate site and non-nucleoside inhibitors that engage with allosteric binding sites (Xu et al. 2022). RdRp incorporates NAs into nascent viral RNA, which subsequently either terminates or slows down RNA production, exerting antiviral effects.

Many inhibitors of NA are investigated against SARS-CoV-2 causing COVID-19 from the beginning of the outbreak. After entering the host cell, antiviral nucleoside prodrugs targeting the viral protein RdRp must convert into 5′-triphosphates, which compete with nucleotide triphosphates that are endogenous in origin as viral RdRp substrates (Zhao et al. 2021). Between its fingers and thumb subdomains, the first turn of the RNA is bound to the nsp12 subunit. The active site of the palm subdomain of RdRp is made up of five conserved motif components of nsp12,

A-E. The 3′ ends of the RNA are attached to motif C which contains the RNA synthesis residues D760 and D76110, 14. The extra motifs F and G found in the fingers subdomain of nsp12 are responsible for RNA template positioning. The interactions of nsp12 with newly transcribed RNA strands suggest that short RNA is retained throughout the early stages of RNA production (Hillen et al. 2020).

10.2.5 3-Chymotrypsin-like Protease ($3CL^{Pro}$)

$3CL^{Pro}$ also called M^{Pro} is a structurally conserved protease among CoVs responsible for the SARS-CoV-2 genome replication (Anand et al. 2003; Mody et al. 2021; Nascimento Junior et al. 2020). Two replicative polyproteins (PP1a and PP 1 ab) are cleaved by $3CL^{Pro}$, this protein is encoded by the viral replicase gene along with PL^{pro} to generate non-structural proteins (NSPs) that are pivotal for viral replication (Anand et al. 2002; Mody et al. 2021). NSP4 to NSP16 are generated via the activity of $3CL^{Pro}$ (Deng et al. 2014). The functional replication complex is produced by the activity of the proteinases (Anand et al. 2002). It is an attractive target for therapeutic approaches against the SARS coronavirus (Anand et al. 2003). The use of $3CL^{Pro}$ proteinase inhibitors is the most common treatment and several covalent and non-covalent inhibitors have been found (Ghosh et al. 2008; Nascimento Junior et al. 2020). They can successfully prevent viral replication and many such protease inhibitors have been created and found to be effective in CoV cell cultures (Deng et al. 2014).

Peptoids and non-peptidomimetics are the two types of $3CL^{Pro}$ inhibitors (Liu et al. 2020). The peptidomimetic $3CL^{Pro}$ inhibitors bind covalently to Cys-145 residue in the active site of $3CL^{Pro}$ by utilizing electrophilic warhead groups (Ghosh et al. 2008; Liu et al. 2020). Both aldehyde compounds 11 and 12 and a-ketoamide compounds 25–27 are some peptidomimetic inhibitors with anti-SARS-CoV-2 effects, while compounds 29a-d (decahydroisoquinoline and octahydroisochromene derivatives), compounds 39, 40a, 40b (inhibitor with 3-pyridyl or triazole moiety) are some of the nonpeptidic $3CL^{Pro}$ inhibitors (Liu et al. 2020). Antiviral activity against SARS-CoV is exhibited by a 3-chloropyridyl ester-based $3CL^{Pro}$ inhibitor developed by Ghosh et al. in cell culture assays (Ghosh et al. 2008). PF-07321332 also called nirmatrelvir is a derivative of PF-00835231 (a hydroxymethyl ketone derivative) with the activity of anti-COVID-19 in 89% of patients (Reina and Iglesias 2022). Some of the drugs that target the $3CL^{Pro}$ enzyme with high specificity include boceprevir, ombitasvir, paritaprevir, tipranavir, ivermectin, and micafungin which can be used either alone or in combination with other drugs (Mody et al. 2021). But corona viruses that encode double-mutant $3CL^{Pros}$ are found to be resistant to these $3CL^{Pro}$ inhibitors as they exhibit delayed processing of the replicative polyproteins along with reduced sensitivity to the viral inhibitors and their mechanism of pathogenicity has been demonstrated in the study by Deng and their colleagues (Deng et al. 2014).

10.3 The Plausible Role of Plants and Herbs in Counteracting the Risk and Improving the Treatment of COVID-19 by Targeting SARS-CoV-2

It has been a timeworn practice of utilizing herbal compounds in developing drugs. Medicinal plants that biologically yield active compounds have great interest among scientists, as they are being significant in preventing the human epidemic as illustrated in Table 10.1 (Umesh et al. 2021). In the entire world, the medicinal plants, herbs, and spices that belong to South Asian countries especially India have greater therapeutic usefulness and hence are contemplated as a generous pivot of ingredients (Halder et al. 2022; Natesh et al. 2021). The bioactive compound from plants has exhibited antiviral, anti-inflammatory, and antibacterial activities against various viruses, including the Zika virus, chikungunya virus, hepatitis, dengue virus, influenza viruses, and SARS-CoV. In vitro studies have reported that those compounds obstruct the replication of SARS-CoV. Recently, the data generated using computational approaches gave very encouraging results that the potential bioactive compounds from the herbal sources function as opposed to the targets of SARS-CoV-2 (Natesh et al. 2021; Halder et al. 2022). The discovery of a new drug is time-intensive and normally takes a definite number of years for clinical approval. In this deadly illness, such medicinal plants are particularly attractive in such cases where there is no known possible substitute medications or vaccination (Nargis Begum et al. 2009; Vijayakumar et al. 2015, 2019; Manikandan and Anand 2016; Govindharajan et al. 2020; Vijaya Anand et al. 2020; Halder et al. 2022). The current study tries to explore, whether Indian spices can be used as novel agents for controlling this pandemic (Umesh et al. 2021). It has been proclaimed that target protein inhibition may cause attenuation of viral replication or minimize the virus infectivity. Further it requires confirmation on the effect of bioactive spices on minimizing the virus infectivity from in vivo and in vitro studies (Arumugam et al. 2020; Saravana Prabha et al. 2020; Anand et al. 2021; Kuchi Bhotla et al. 2021a, b; Chandra Manivannan et al. 2022a, b; Halder et al. 2022).

10.3.1 Glycyrrhiza glabra

Glycyrrhiza glabra is a blooming plant that belongs to the bean family called Fabaceae, which is denoted by the common names of Liquorice, Licorice, or Black Sugar. In India, *Glycyrrhiza glabra* is known as Athimaduram. The native liquorice plant is in the Western part of Asia, North part of Africa, and the Southern European parts. The root of liquorice contains glycyrrhizin, a substance that is 50–170 times sweeter than sucrose. *Glycyrrhiza glabra* root is used in the form of powder to treat SARS-COVID (Lim 2015). It is reported that the *Glycyrrhiza glabra* has an in vitro anti-SARS effect against SARS-COVID and the natural compounds

Table 10.1 Herbal immune boosters, active compounds, and their mechanism of action against viruses

Botanical name	Common name	Major chemical constituent	Edible parts	Virus type	Mechanism of action	Reference
Glycyrrhiza glabra	Liquorice, mulethi	Glycyrrhizin	Leaves, roots	SARS-CoV	Inhibits viral adsorption, penetration, and replication	Patel et al. (2021), Cinatl et al. (2003), Malabadi et al. (2021)
Areca catechu	Areca nut	Arecoline, arecaidine, guvacine, guvacoline	Dried ripe seed	SARS-CoV-2	Inhibits viral RNA levels and infectious titers	Khan et al. (2021)
Armeniaca sibirica	Apricot	Sibiriaester A, sibiriaester B	Leaves, seed	SARS-CoV-2	PGE2 gets suppressed and produces NO	Wu et al. (2018), Khan et al. (2021), Mukherjee et al. (2022)
Rauvolfia serpentine	Indian snakeroot	Reserpine	Dried root	SARS-CoV-2	Inhibits the SARS-CoV-2 replication	Khan et al. (2021), Malabadi et al. (2021)
Curcuma spp.	Turmeric	Curcumin, eugenol	Rhizome	SARS-CoV-2	Inhibits $3CL^{Pro}$ of SARS-CoV-2; has good binding affinity with M^{Pro} and S protein	Malabadi et al. (2021)
Allium cepa	Onion	Flavonols: Quercetin, quercetin glycosides, kaempferol	Bulb	SARS-CoV-2	Interfere with entry and replication cycles such as PL^{pro}, $3CL^{Pro}$, and NTPase/helicase	Bondhon et al. (2021)
Brassica oleracea	Broccoli	Glucosinolate type sinigrin, sulforaphane	Flower	SARS-CoV-2	Blocks the cleavage process of $3CL^{Pro}$	Gasparello et al. (2021)
Psidium guajava	Guava	Eugenol	Leaves, fruits	SARS-CoV-2	Binds with M^{Pro} and S protein to interfere with virus	Malabadi et al. (2021)
Cinnamomum verum	Cinnamon	Butanol, procyanidins	Dried bark	SARS-CoV-2	Blocks the entry of virus cells through endocytosis	Malabadi et al. (2021)
Salvia officinalis	Sage	b-ocimene, 1,8-cineole, a-pinene, b-pinene	Essential oils	SARS-CoV-2	Obstructs the interaction of virus and host receptor and also attachment of cellular membrane and the viral envelope	Babaeekhou et al. (2021)

Artemisia annua	Annual wormwood	Artemisinin, deoxyartemisinin, artemisinic acid, arteannuin-B, stigmasterol, friedelin, friedelan-3-β-ol, artemetin, quercetagetin, 6,7,3′,4′--tetramethyl ether	Whole plant	SARS-CoV-2	Inhibits the $3CL^{Pro}$ tease of the virus and blocks the viral RdRp activity	Lin et al. (2014), Khan et al. (2021) Malabadi et al. (2021)
Lycoris radiate	Red spider lily	Lycorine, glycyrrhizin	Stem	SARS-CoV-2	Against viral strains BJ-001 and BJ-006 activity	Li et al. (2005a, 2005b), Khan et al. (2021), Malabadi et al. (2021)
Glycyrrhiza uralensis Fisch.	Licorice	Echinatin	Root	SARS-CoV-2 Human respiratory syncytial virus (HRS)	Disrupts the viral uptake into the host cells and the interaction between RBD of SARS-CoV2 and ACE-2	Khan et al. (2021)
Rosmarinus officinalis	Rosemary	Oleanolic acid	Leaves	SARS-CoV-2, herpes viruses, HIV, influenza	Inhibit the proliferation of SARS-CoV-2	Nolkemper et al. (2006), Khan et al. (2021)
Zingiber officinale	Adrak, ginger rhizome	Arcurcumene, β-sesquiphellandrene, α-zingiberene and β-bisabolene, flavan, and 4, 6-dichloroflavan [6]-gingerol	Rhizome	SARS-CoV-2 *Rhinovirus* IB	Blocks TMPRSS2 receptor	Khan et al. (2021), Malabadi et al. (2021)
Origanum vulgare	Oregano	Carvacrol	Essential oil	SARS-CoV-2, HRS virus	Inhibits SARS-CoV-2 spike RBD crystal structure	Gilling et al. (2014), Khan et al. (2021), Fallah et al. (2021)
Hyoscyamus niger	Nightshade; ajwain kharasani	Acyclovir	Flower	SARS-CoV-2 Influenza A	Acts as a bronchodilator and has inhibitory effects on the Ca^{2+} channel.	Khan et al. (2021), Kosari et al. (2021)

(continued)

Table 10.1 (continued)

Botanical name	Common name	Major chemical constituent	Edible parts	Virus type	Mechanism of action	Reference
Allium sativum	Garlic	Allicin, alliin, diallyl sulfide, diallyl disulfide	Root, leaves	SARS-CoV-2, HIV, HSV-1, influenza A and B,	Formation of hydrogen bonds between viruses and bioactive compound	Bayan et al. (2014), Khan et al. (2021), Khubber et al. (2020)
Solanum nigrum	Black nightshade	Solanine, solamargine	Leaves	HCV	Inhibits NS3 protease	Patel et al. (2021)
Moringa oleifera	Drumstick tree	Quercetin, linolenic acid	Leaves, seeds, tubers, flowers, pods	HIV type 1	Inhibits viral replication	Patel et al. (2021), Malabadi et al. (2021)
Justicia adhatoda	Bansa, malabar nut, adhatoda	Phenols, tannins, alkaloids, anthraquinone, saponins, flavonoids,	Leaves	Influenza virus, herpes simplex virus-2 (HSV 2)	Inhibit the cleavage activity of the virus	Chavan and Chowdhary (2014), Khan et al. (2021), Malabadi et al. (2021)

present in *Glycyrrhiza glabra* will hinder the host fusion steps of the virus through the viral envelope. Glycyrrhizin acts on the cellular signaling pathways like protein kinase C; casein kinase II; and with the activator protein I and nuclear factor κB (Cinatl et al. 2003). Antiviral compounds of *Glycyrrhiza glabra* can inhibit or block the viral replication cycle during the virus attachment to the cells, also interfere with the viral enzymes, or suspend the replication of the viral genome (Malabadi et al. 2021).

10.3.2 Areca catechu

Areca catechu is a palm species that belongs to the family called Arecaceae. It grows in the region of the Pacific, Asia, and east Africa. The common names of areca are areca palm, betel nut palm, supari, Indian nut, Pinang palm, and catechu. This palm, in English, is known as the betel tree as its fruit, the areca nut is frequently used with the betel leaf. The seeds of *Areca catechu* (areca nut) have been in use for clinical practice in China and India. Raw areca and charred-type areca nuts are very commonly used (Peng et al. 2015). It is a widespread traditional medicine that is chewed to separate the fluid collected in the alimentary canal and to kill the worms (Ansari et al. 2021). It inhibits the levels of viral RNA and infectious titers of SARS-CoV-2 (Ngwe Tun et al. 2022). Kaempferol, a compound of areca, showed the best binding affinity to the 7BQY and 6Y2FB enzymes (Emon et al. 2021).

10.3.3 Armeniaca sibirica

Armeniaca sibirica belongs to the Rosaceae family. It is being cultivated as a medicinal edible plant, which is well known as "apricot." It is domestic to the climates of temperate, continental, and mountainous which includes the regions of Northeast China, Southeast Mongolia, and the East part of Siberia. The dried leaves are used for medicinal purposes (Wu et al. 2018). Wild apricot *Armeniaca sibirica* is the kind of bitter apricot. Leaves of *Armeniaca sibirica* were taken up as a natural tea, as it is rich in antioxidants, also it is rich in dietary fiber, which has health-promoting properties (Zhang et al. 2018). *Armeniaca sibirica* is said to be a SARS-CoV-2 protease inhibitor, an in silico approach called AutoDock Vina, had revealed that *Armeniaca sibirica*, has the highest binding affinity with SARS-CoV-2 spike (S) protein and may help to prevent COVID-19. It has antiviral properties and can prevent SARS-CoV-2 from infiltrating host cells (Yunus 2021). It inhibits the replication of SARS-CoV-2 and induces apoptosis in infected cells (Qin et al. 2019).

10.3.4 Rauvolfia serpentine

Rauvolfia serpentine belongs to the family Apocynaceae. This family contains 50 species that are found worldwide in the Himalayas, Indian peninsula, Burma, Indonesia, and Sri Lanka and are indigenous to India, Bangladesh, and Asia. This plant is generally known as Sarpagandha, Chandrabagha, Snakeroot plant, Chotachand, Chandrika, and Harkaya (Kumari et al. 2013). *Rauvolfia serpentine*, its dried root can be used as green tea and is a common plant that can be used by COVID-19 infected patients and not serious patients during the isolation period. Reserpine, an alkaloid isolated from the roots of *Rauvolfia serpentina* (Indian snakeroot) inhibits the activity of the $3CL^{Pro}$ enzyme, inside the viral cells (Khan et al. 2021). The molecules of *Rauvolfia serpentina* showed anti-CoV activity via multiple mechanisms such as suppression of PL^{pro}, the relation between ACE-2 and SARS-CoV (S) protein, viral polymerase, virus replication/cell division, viral attachment, and penetration stages. Besides, the compounds were found to be active in blocking the virus binding to the host cell, 3a channel, and the viral entry to host cells (Semwal et al. 2020).

10.3.5 Curcuma *spp.*

Curcuma belongs to the family called Zingiberaceae, which comprises perennial and rhizomatous species, and is naturally found in tropical and subtropical regions. Turmeric is an evergreen plant that grows mostly in India, China, Thailand, Malaysia, Indonesia, and Northern Australia (Ayati et al. 2019). Curcumin, a compound found in *Curcuma* is shown to have an antiviral activity; it is an effective inhibitor of Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV). It has anti-SARS-CoV 2 components and the strong binding affinity of those active components to the COVID-19 6 LU7 and 6Y2E proteases was expressed (Manzano-Santana et al. 2021). The mechanism of actions as anti-SARS-CoV-2 of the molecules of *Curcuma* causes the inhibition action in viral transcription and replication by binding to the N protein; prevents the invasion of the virus into the host cell by inhibiting the binding of S protein to ACE-2 receptors; inhibits the viral transcription and maturation by inhibiting the function of $3CL^{Pro}$; and binds directly to ACE-2 receptor (Hendrayana et al. 2021). The docking studies states that the compounds of *Curcuma* (curcumin, quinine, and demothoxycurcumin) exhibit strong binding affinity toward RdRp with the binding energy of −7.80, −7.80, and −7.64 kcal/mol, respectively, *Curcuma* has potential to develop to be the future anti-SARS-CoV-2 (El-Aziz et al. 2022).

10.3.6 Allium cepa

Allium cepa comes from the family of Amaryllidaceae. This plant is generally referred to as the onion bulb or common onion. It is exclusively cultivated in Central Asia and Iran. The phytochemical compounds of this plant exhibit viral inhibition of non-enveloped viruses by prohibiting the process of absorption or penetration. The primary mechanism is the blockage of cellular receptor sites, thus inhibiting the virus invasion. The secondary mechanism is the exhibition of neutralizing effects caused by the inhibitors that interact with the viruses (Harazem et al. 2019). Quercetin and kaempferol show crucial antiviral activity against herpes simplex type I virus (HSV-1), rabies virus, PV, mengo virus, pseudorabies virus (PRV), sindbis virus, parainfluenza type 3virus. The in vitro study data reveals that flavonol quercetin obstructs pulmonary viral replication by minimizing the viral titer (Pareek et al. 2017). Amarogentin represents the greater affinity toward the spike glycoprotein of coronavirus with almost 9 hydrogen bonds together with amino acid residues, namely Thr739, Thr768, Gln314, Val736, Cys738, Ser735 and Arg765 also it exhibited the greater MolDock score of 149.76 kcal/mole (Hendrayana et al. 2021).

10.3.7 Brassica oleracea

Brassica oleracea belongs to the Brassicaceae family, which is previously called the Cruciferae. It is native to the Mediterranean region and Southwestern Europe, Northward to Southern England, growing on Seaside cliffs (Ferreres et al. 2005). It is a biennial life cycle type of plant (Rodríguez et al. 2015) Astragalin and coumaroylquinic acids and the compounds from *Brassica oleracea* consist of prospective inhibitory ability averse to (S) protein. The compounds of *Brassica oleracea* exhibit a remarkable affinity toward the S2 domain of spike protein (Jose et al. 2022; Illian et al. 2021). Sulforaphane (SFN), a naturally occurring nutritional supplement found in abundant quantities in cruciferous vegetables was said to have antiviral activity. The in vitro studies reveal that SFN administration is a propitious therapeutic approach as it obstructs the viral replication of four strains of SARS-CoV-2 and the seasonal coronavirus HCoV-OC43. On earlier intranasal infection of the SARS-CoV-2 virus, the prophylactic SFN supplementation to mice remarkably reduced the viral titer in the pulmonary tract and also minimized the pulmonary pathology and injury (Ordonez et al. 2021).

10.3.8 Psidium guajava

Psidium guajava belongs to the family called Myrtaceae. The common names of guava are yellow guava, lemon guava, or apple guava, which is a small evergreen

shrub or tree indigenous to the Caribbean, Central America, and South America. The fruits and leaves are part of the plant that has antiviral properties. The vital compound of this plant was Asiatic acid which has a binding energy score of – 8.31 kcal/mol (Fitriani et al. 2020). It has been established that the major bioactive compounds from this plant may inhibit viral replication which includes pheophytin a, pheophytin b, β-caryophyllene, and Jejuguajavone A which were examined using animal models. The combined therapeutic approach with the combination of pheophytins with β-caryophyllene or Jejuguajavone A expressed essential interdependent antiviral effects which results in the conservation of affected animals even from variants of SARS-CoV-2 including omicron (Kim et al. 2022). The potent inhibitor luteolin obstructs the furin protein which is induced by the cleavage of the S protein (Wardani 2022).

10.3.9 Cinnamomum verum

Cinnamomum verum belongs to a family called Lauraceae. The inner side bark of *Cinnamomum verum* has been considered the true Cinnamon. It is indigenous to Sri Lanka and Southern India and is further extensively grown in Southeast Asia, China, Burma, Indonesia, Madagascar, the Caribbean, Australia, and Africa. The extract of this plant remarkably inhibits the pepsin enzyme which leads to significant HIV protease inhibition which exhibited a remarkable IC_{50} value that revealed the anti-HIV potential of this plant (Singh et al. 2021a, 2021b). The computative enumeration has established that kaempferol 3-O-rutinoside, baicalin, and hesperidin may debilitate cellular viral absorption and prevent SARS-CoV-2 infection. At the level of RNA, the bioactive compounds such as procyanidins and butanol from this plant extract exhibited antiviral activity. The tea prepared using the bark of Cinnamomum improves immunity in COVID-19 patients. Furthermore, the phenolic compounds of this plant displayed potent trypsin enzyme inhibition ability which includes majorly caffeic acid and cinnamic acid additionally includes gallic acid and eugenol these findings have led to recommending Cinnamon as a herbal medicine to act against SARS-CoV-2 infection and also to other complementary viral infections (Yakhchali et al. 2021).

10.3.10 Justicia adhatoda

Justicia adhatoda belongs to the family called Acanthaceae. It is a perennial, evergreen, and highly branched shrub, widely distributed throughout the tropical regions of Southeast Asia and in India, Sri Lanka, Malaysia, and Burma (Sobia et al. 2018). It is extensively referred to as Vasaka or Malabar nut. It is a beneficial Ayurvedic plant employed to treat colds, asthma, cough, and tuberculosis. The importance of the Vasaka plant for treating pulmonary ailments is followed since

the ancient Indian saying, "As long as the Vasaka plant exists there will be no human suffering from phthisis" (Pa and Mathew 2012). It indicates that about 51.5% of herbal bioactive compounds from this plant are effective to treat COVID-19. It has been reported that phytocompounds such as quercetin, xanthoxylol, chinensinaphthol methyl ether, podophyllotoxin, and apigenin may function against multiple target proteins of SARS-CoV-2 (Suryanarayana et al. 2021). The crude extracts of *Justicia adhatoda* reported the antiviral effect against the influenza virus by hemagglutination (HA) reduction. The studies suggest that *Justicia adhatoda* has a strong anti-influenza virus activity (Jamwal et al. 2022).

Salvia officinalis generally named sage belongs to the family called Lamiaceae. It is an evergreen perennial subshrub, with hard stems, grayish leaves, and blue to purplish flowers, it is indigenous to the Mediterranean region (Miraj and Kiani 2016). The phytocompounds from *Salvia officinalis* extract exhibit greater binding energy for kaempferol 3-O-rutinoside and neodiosmin with CoV-2-SP (Babaeekhou et al. 2021). The notable flavonoid Rutin creates indestructible hydrogen bond interactions with crucial M^{Pro} residues. Molecular docking studies have revealed that flavonoids of this plant extract possess anti-coronavirus ability (Moezzi 2022). It was reported that the methanol extract and ethanolic extract and essential oils of *Salvia* sp. consist of antiviral potential against various deadly viruses. It can minimize the period and critical symptoms in patients with pulmonary ailments (Abou Baker et al. 2021).

10.3.11 Artemisia annua

Artemisia annua belongs to the family of Asteraceae, which is considered to be an annual herb with tremendous woody unistem consisting of aromatic leaves, native to Asia, but naturalized in many countries including North America. Otherwise referred to as annual mugwort, annual and sweet wormwood, sweet Annie, and sweet sagewort (Ferreira and Janick 1996). The ethanolic extract of *Artemisia annua*, in vivo test, states that it contains antiviral properties counter to SARS-CoV-2 (Li et al. 2005a, b). As the extract exhibits high phenolic content they are associated with pulmonary diseases and effective over lung fibrosis with the highest formulates toward the antiviral activity of respiratory problems. It is the first report that shows the boiled or hot water *Artemisia annua* extracts exhibited antiviral activity toward SARS-CoV-2 and its variants B1.1.7 and B1.351 which were performed in humans. The upcoming fortunate clinical trials may hold the hope that *Artemisia annua* can be prospectively used as a prudent therapeutic approach that can be practiced globally at an accessible cost which may be a substitute for vaccines (Nair et al. 2021).

10.3.12 Lycoris radiate

Lycoris radiate belongs to the family called Amaryllidaceae. *Lycoris radiate* Herbert (Amaryllidaceae, L'Her) is extensively found in China, Japan, and Korea (Liu et al. 2012). The lycorine was purified from *Lycoris* spp. and was identified as an auspicious bioactive compound opposing the antiviral activity of SARS-CoV with an EC_{50} value of 34.5 ± 2.6 μg/mL. Herbal medicines of *Lycoris radiate* have been second-hand in coronavirus outbreaks like SARS-CoV and MERS-CoV. *Lycoris radiate extract* showed anti-SARS effects with a 50% effective concentration (Lawan et al. 2020).

10.3.13 Rosmarinus officinalis

Rosmarinus officinalis is an aromatic plant allied to the family called Lamiaceae in which the leaves are needle-shaped. It is cultivated throughout the world. Southeast Spain is one of the major producers and importers of rosemary. Rosemary is a unique spice and an economically available antioxidant that has antiviral properties and is popularly utilized as a therapeutic dosage, in the USA and Europe (Nieto et al. 2018). Some flavonoids like hesperidin, genkwanin, isoscutellarein 7-*O*-glucoside, hispidulin 7-*O*-glucoside, eriocitrin, luteolin 3'-*O*- *β*-D-glucuronide, and diosmin have been identified in *Rosmarinus officinalis*. In molecular docking studies, bioactive compounds such as ursolic acid, rosmarinic acid, and oleanolic acid are determined to possess antiviral activity countering SARS-CoV-2. The binding affinity of active molecules toward the COVID-19 6LU7 and 6Y2E proteases was found to be greater (Manzano-Santana et al. 2021). The phenolic compounds such as carnosol and carnosic acid along with two abietane-type diterpenoids have been analyzed to found as the greater amount in Rosemary extracts, which exhibit antiviral activity by inhibiting the viral reverse transcriptase. It exhibits the functions such as inhibition of viral RNA replication and synthesis either before the binding of the virus to the host cell or after the viral entry into the host cell (Zrig 2022).

10.3.14 Zingiber officinale

Zingiber officinale comes under the family called Zingiberaceae. The tea prepared using the *Zingiber officinale* improves immunity in COVID-19 patients. It has been greatly recognized for its medicinal value since more than a thousand years cultivated as a spice. It is used extensively in Traditional Chinese Medicine to treat headaches, nausea, and colds (Jiang et al. 2006). SARS-CoV entry inhibitors should be encoded with the molecules that attach with the surface target receptors such as ACE-2 and TMPRSS2 that obstruct the membrane fusion and interaction with the

cell receptors. The molecule called gingerol from *Zingiber officinale* prevents the progression of the coronavirus by obstructing the cell's TMPRSS2 receptor. The phytochemical cyanin exhibits extensive inhibitory activity against the M^{Pro} of corona viruses and their variants (Manzano-Santana et al. 2021).

10.3.15 Origanum vulgare

Origanum vulgare belongs to the family called Lamiaceae and it is indigenous to the Mediterranean region and western Eurasia (Pezzani et al. 2017). *Origanum vulgare* was established as the prospective substitute for constraining of SARS-CoV-2 delta variant (Torres Neto et al. 2022). Some studies exhibited that phenolic compounds of *Origanum vulgare* have the inhibitory activity to counter the replication of the respiratory syncytial virus (RSV). The compounds such as carvacrol, a monoterpenoid phenol found in *Origanum vulgare*, can consort with SARS-CoV-2 M^{Pro} and endeavor its resistance process (Belmouhoub and Aberkane 2021). The gamma-terpineol was referred to as a lead compound of *Origanum vulgare* and was said to have the best binding affinity and pharmacological properties. The findings suggest that the identified compound may serve the inhibiting property. Hence, *Origanum vulgare* was recommended as a potential inhibitor of $3CL^{Pro}$ of COVID-19 (Saif 2022).

10.3.16 Hyoscyamus niger

Hyoscyamus niger also referred to as a traditional hallucinogen belongs to the family called the family Solanaceae (Al-Snafi 2018). *Hyoscyamus niger* was indigenous to Europe, North Asia, and North and west Africa. It was later cultivated in East Asia, Australia, and North America (Hu et al. 2022). The utilization of herbs in Indian traditional therapeutics has been suggested to cure COVID-19. It showed antiviral properties against bronchitis and was used as a novel therapeutic agent against SARS-CoV-2 (Alburae 2020). Herbal extracts of *Hyoscyamus niger* were demonstrated to minimize the inflammatory cascade induced by SARS-CoV, in respiratory distress. *Hyoscyamus niger* extract was adopted to target the Ca^{2+} channels which are inferred to induce downstream pathways associated with viral infections. The studies suggest that the methanolic extract of *Hyoscyamus niger* may represent an affordable naturally obtained therapeutic approach (Kosari et al. 2021).

10.3.17 Allium sativum

Allium sativum comes under the family called Amaryllidaceae. The plant was cultivated as a common vegetable and spice to develop an immune system. It functions opposing by inhibiting the penetration or absorption of non-enveloped viruses which acts on the cell surface and obstructs the receptor site which is necessary for numerous viral invasions whereas various other inhibitors produce a neutralizing effect on reacting with the virus (Harazem et al. 2019). The tea made of leaves and roots of *Allium sativum* are used to improve the immunity in COVID-19 patients. The bioactive components of garlic such as S-cysteine, L-cysteine, S-propyl, S-ally-mercapto-cysteine, and alliin exhibit the inhibitory effect against M^{Pro} of SARS-CoV-2 by hindering the hydrogen bonds. Molecular docking studies have revealed that the alliin bioactive component itself or in interaction with a major therapeutic drug could exhibit a stronger antiviral potential to eradicate SARS-CoV spread with minimum toxicity and side effects (Khubber et al. 2020). Garlic supplementation leads to the prominent provoke of CD4+ and CD8+ cells and also induces the production of NK cells (Donma and Donma 2020).

10.3.18 Solanum nigrum

A therapeutic plant *Solanum nigrum* belongs to the family of Solanaceae. *Solanum nigrum* often referred to as Makoi or black nightshade, generally breeds as a weed in wetland habitats. The favorable soil conditions of this plant include stony, deep soils, dry or shallow, and also can be propagated in tropical and subtropical regions (Jain et al. 2011). Spirostan-3-ol, Solasodine, Diosgenin, N-methylsolasodine, and Solanocapsine are the phytochemicals found in this weed that was effective in inhibiting the surface targets of SARS-CoV-2 such as NSP16-NSP10, NSP9, and M^{Pro} (Manzano-Santana et al. 2021). At the non-toxic concentration, the methanol and chloroform extracts of this weed provided approximately 37% and greater than 50% inhibition of HCV, respectively. The peer research results revealed that the chloroform extract of seeds of this weed exhibits the antiviral effect to counter the expression and activity of HCV NS3 protease by mediating the transfer of HCV NS3 protease plasmid into the liver cells (Javed et al. 2011). Moreover, the extracts of this weed are expected to exhibit an inhibitory effect on significant enzymes which includes protease and α-glucosidase and reverse transcriptase (RT) and obstruct HIV-1 viral replication (Yu 2004).

10.3.19 Moringa oleifera

Moringa oleifera comes under the family called Moringaceae. It is generally referred to as Drumstick. Its plant is rarely found in marginal land and is widely cultivated for its leaves and fruits and used as a superfood due to its antioxidant and antiviral properties. Earlier reports have established that several bioactive components are present in *Moringa oleifera* which exhibits effective binding with the receptors of SARS-CoV-2 which includes M^{Pro} and Spike protein (Sen et al. 2021). Since the bioactive compounds of this plant associate with M^{Pro} and inhibit viral multiplication, the inhibition of M^{Pro} is anticipated to sarcastically minimize the viral concentration in the patients infected with coronavirus (Kharisma et al. 2021; Nair and James 2020).

10.3.20 Justicia adhatoda

Justicia adhatoda belongs to the family called Acanthaceae. It is a perennial, evergreen, and highly branched shrub, widely distributed throughout the tropical regions of Southeast Asia and in India, Sri Lanka, Malaysia, and Burma (Sobia et al. 2018). It is extensively referred to as Vasaka or Malabar nut. It is a beneficial Ayurvedic plant employed to treat colds, asthma, cough, and tuberculosis. The importance of the Vasaka plant for treating pulmonary ailments is followed since the ancient Indian saying, "As long as the Vasaka plant exists there will be no human suffering from phthisis" (Pa and Mathew 2012). It indicates that about 51.5% of herbal bioactive compounds from this plant are effective to treat COVID-19. It has been reported that phytocompounds such as quercetin, xanthoxylol, chinensinaphthol methyl ether, podophyllotoxin, and apigenin may function against multiple target proteins of SARS-CoV-2 (Suryanarayana et al. 2021). The crude extracts of *Justicia adhatoda* reported the antiviral effect against the influenza virus by HA reduction. The studies suggest that *Justicia adhatoda* has a strong anti-influenza virus activity (Jamwal et al. 2022).

10.4 Fruits Against the Vulnerability of SARS-CoV-2 Infection

As the world returns to immune-boosting traditional treatments, there is renewed interest in the Indian medical system, which is endowed with a plethora of herbal drugs and therapies. Citrus fruits and liquids with potential health benefits are among the most abundant sources of chemicals that were illustrated in Table 10.2. Flavanones (such as hesperetin, isosakuranetin, naringenin, eriodictyol, and their related glycosides), which occur in levels ranging from 180 to 740 mg/L (depending on

Table 10.2 Fruits, their chemical compounds, and their potential health benefits

Scientific name	Common name	Major chemical constituent	Virus type	Mechanistic property	Reference
Phyllanthus emblica	Amla	Amritoside, pectolinarin, astragalin, quercetin	SARS-CoV-2	Immunity booster, natural cure for respiratory disorders	Zannella et al. (2021), Ben-Othman et al. (2021)
Vitis vinifera	Grapes	Luteolin, kaempferol, apigenin, isorhamnetin, myricetin, chrysoeriol, biochanin, isookanin, scutellarein, resveratrol	HSV-1, SARS-CoV-2	Inhibits viral replication in the early stages of infection by directly blocking the proteins enriched on the viral surface, anti-inflammatory and anticarcinogenic properties	Zannella et al. (2021), Orallo (2006)
Malus domestica	Apple	Phloretin, procyanidin, quercetin	Influenza virus, SARS-CoV-2	Antioxidant properties, antiviral properties	Shimamura et al. (2017), Papadakis (2022), Ben-Othman et al. (2021)
Citrus sinensis	Oranges	Hesperidin	SARS-CoV-2, HIV-1	The inhibitory effect of methylglyoxal is higher in the late stage of HIV-1 infection	Elghani et al. (2022), Behbahani (2014)
Capsicum annuum	Red bell pepper	Dichloromethane (DCM), butanol (BUT)	Tobacco rattle virus (TRV)	Anti-inflammatory in vivo effects	Allemand et al. (2016), Tian et al. (2014)
Citrus limon	Lemon	Limonene, limonin, naringenin	SARS-CoV-2, DEN virus	Secondary metabolites exhibit a wide range of biological properties, including anticancer, antibacterial, antifungal, anti-malarial, and antiviral activities	Tundis et al. (2014), Frabasile et al. (2017)
Citrus limetta	Mosambi	Nano-Ag and Fe	CHIKV	Antiviral property	Choudhary et al. (2020)
Carica papaya	Papaya	Quercetin, protocatechuic acid, p-coumaric acid, caffeic acid, chlorogenic acid, kaempferol, 5,7-dimethoxycoumarin, nelfinavir, amprenavir, lopinavir-ritonavir	DENV 2, SARS-CoV-2, HIV, HCV	Inhibitory activity on NS2B-NS3 protease is very essential for viral assembly	Senthilvel et al. (2013), Hariyono et al. (2021)
Fragaria ananassa	Strawberries	Acylphloroglucinol (APG) glucosides, anthocyanin, phytomelatonin	SARS-CoV-2	Antiviral and antioxidant activity	Song et al. (2016), Okeke et al. (2022)

citrus species and cultivar) play a variety of biological roles. These compounds strengthen the body's defenses against oxidative stress and help to prevent cardiovascular disease, atherosclerosis, and cancer. They also have anti-inflammatory, antiviral, and antibacterial properties (Barreca et al. 2017). Apigenin is a flavonoid present in many plants, including the majority of vegetables and fruits. Apigenin has been proven in studies to have anti-inflammatory, antioxidative, antibacterial, antiviral, antitumor, and cardiovascular protective activities (Xu et al. 2021).

Betulinic acid, which is found in a variety of medicinal plants and fruits, has a variety of biological effects, including its exceptional anti-HIV activity, which has piqued the interest of many pharmacists. Some betulinic acid derivatives displayed inhibitory effects at nanomolar concentrations and have started phase II clinical trials (Huang et al. 2018). *Meliae fructus* is the dried ripe fruit of the Meliaceae family. *Meliae fructus* has antibacterial, antioxidant, anticancer, anti-inflammatory, and analgesic effects, and it is commonly used in traditional medicine to treat inflammation and helminthic infection (Basu et al. 2018). Quercetin may be found in a variety of fruits and vegetables, including apples and citrus, as well as onion, broccoli, kale, and tomato. Papaya leaves, green and black tea leaves, buckwheat, seeds, and grains all contain quercetin. It was discovered that quercetin inhibited viral reverse transcriptases in the Rauscher murine leukemia virus (RLV) and HIV.

Quercetin also suppresses the replication of negative and positive-strand RNA as well as the translation of capsid proteins in Rhinoviruses that cause colds (RV). SARS-CoV-3CLp can be inhibited by the same quercetin that inhibits SARS-CoV-$3CL^{Pro}$ (Saakre et al. 2021). The lentil lectin from *Lens culinaris*, which binds to oligomannose-type glycans and GlcNAc at the non-reducing end terminus, was found to have the most potent and broad antiviral activity against a panel of mutant strains and variants, which include artificial mutants at the N-/O-linked glycosylation site, naturally occurring amino acid mutants, as well as epidemic variants B.1.1.7, B.1.351, and P. Lentil lectin has also been demonstrated to have antiviral properties against SARS-CoV and MERS-CoV (Wang et al. 2021a, b). Researchers have recently focused on hesperidin, a flavonoid that interacts with the major proteins of the SARS-CoV-2.

Several computational methodologies utilized by different investigations independently demonstrated that hesperidin has a low binding energy with the coronavirus "spike" protein as well as the primary protease that transforms the virus's early proteins (pp1a and pp1b) into the complex responsible for viral replication. The binding energy of hesperidin to these important components is lower than that of lopinavir, ritonavir, and indinavir, indicating that it may have an antiviral effect. Furthermore, both hesperidin and ascorbic acid protect cells against the oxidative stress generated by a viral infection and inflammation (Bellavite and Donzelli 2020).

10.4.1 Phyllanthus emblica

Phyllanthus emblica is a tree native to Southeast Asia's tropical climatic regions (Zhao et al. 2015). It is popularly known as "Aonla," "Amla," or "Indian gooseberry" and is a popular fruit tree that belongs to the order Geraniales and family Euphorbiaceae. According to ancient Indian mythology, it was the very first tree to originate on Earth. Scientific data supports the antiviral effectiveness of amla in the treatment of hepatitis B virus (HBV), HIV, Coxsackie VB3, and HSV. The fruits of *Emblica officinalis* are used extensively in Rasayana to cure a variety of infectious and non-infectious disorders. Docking studies and MDS verified quercitrin, chlorogenic acid, and Myricetin's promising ability to inhibit the n-CoV-2 major viral proteins (Chikhale et al. 2021). Some Phyllanthus species are inhibitory to HBV, HCV, HIV, and HSV, while *Phyllanthus emblica* is inhibitory to respiratory syndrome virus (PRRSV). Pedunculagin, azadirachtin, chebulagic acid, and nimbolide may be ACE-2 receptor and M^{Pro} inhibitors for SARS-CoV-2. Seselin inhibited multiple SARS-CoV-2 targets, including M^{Pro} and spike protein. However, there is no evidence that these medications can be used to treat COVID-19. As a consequence, the efficacy of these drugs to inhibit SARS-CoV-2 RdRp was tested (Pandey et al. 2021).

10.4.2 Vitis vinifera

Vitis vinifera (grape) is a fleshy non-climacteric fruit (Alem et al. 2021). The grapevine is native to Western Asia and Southern Europe. Grape seed and skin include flavonoids, proanthocyanidins, polyphenols, anthocyanins, procyanidins, and the stilbene derivative resveratrol. Grape seed extract, in particular, has been demonstrated to offer several pharmacological and therapeutic effects, including antioxidative, anti-inflammatory, and antibacterial capabilities, as well as cardioprotective, hepatoprotective, and neuroprotective qualities (Nassiri-Asl and Hosseinzadeh 2016). The fractioned component produced from chloroform extract inhibited the Parainfluenza virus more effectively (PIV) and HSV-1. Leaf extracts at pH 7.00 and 13.00 suppressed the early stages of HSV-1 infection as well as the pandemic and currently ubiquitous SARS-CoV-2.

The leaf extract significantly outperformed the Greco extract applied as a positive control against HSV-1 and SARS-CoV-2 (Zannella et al. 2021). The chemicals 3-galloylcatechin, proanthocyanidin B1, and luteolin 7-galactoside discovered in African flora grapes have been identified as hit compounds against various SARS-CoV-2. These chemicals might be potential leads and nutraceuticals used for the prevention or treatment of COVID-19. These compounds' scaffolds can be optimized to overcome minor flaws in their metabolism and toxicity (Iheagwam and Rotimi 2020).

10.4.3 Malus domestica

In temperate climates, the apple (*Malus domestica*) is one of the most extensively produced and commercially significant fruits (Chen et al. 2021). The apple, like other important temperate fruit tree species, is a member of the Rosaceae family (Cornille et al. 2014). Chinese quince had the most phenolics, which were mostly polymeric procyanidins. Quince included significant levels of hydroxycinnamic derivatives, including 5-caffeoylquinic acid, polymeric procyanidins, and 3-caffeoylquinic acid. The apple had the fewest phenolics, primarily monomeric and oligomeric procyanidins, and 5-caffeoylquinic acid (Hamauzu et al. 2005). According to a recent review paper, screening of conserved plant miRNAs against the HBV and HCV revealed six HCV gene sequences that are most likely to be targeted by miR-156, miR-157, miR-166, miR-172, and miR-390. While five conserved plant miRNAs have been demonstrated to be especially likely to align and interact with the six HBV gene sequences: miR-166, miR-169, miR-172, miR-390, and miR-399 (Mangukia et al. 2022).

10.4.4 Citrus sinensis

Citrus sinensis is one of the most significant citrus cultivar groups, accounting for more than 70% of total annual Citrus species output. It is native to Asia, but it has spread to the Pacific and other tropical places throughout the world. It is an evergreen flowering tree (Favela-Hernández et al. 2016*). Citrus sinensis* is a member of the Rutaceae family, and its juice and pulp portions have been demonstrated to have hypolipidemic effects in rats with diet-induced hypercholesterolemia (Mallick and Khan 2016). Researchers have recently focused on hesperidin, a flavonoid that interacts with the major proteins of the SARS-CoV-2. Several computational methodologies utilized by different investigations independently demonstrated that hesperidin has a low binding energy with the coronavirus "spike" protein as well as the primary protease that transforms the virus's early proteins (pp1a and pp1b) into the complex responsible for viral replication. The binding energy of hesperidin to these important components is lower than that of lopinavir, ritonavir, and indinavir, indicating that it may have an antiviral effect. Furthermore, both hesperidin and ascorbic acid protect cells against the oxidative stress generated by a viral infection and inflammation (Bellavite and Donzelli 2020). *Citrus sinensis* monofloral honey exhibited substantial anti-HIV-1 activity, with EC_{50} values of 70 g/ml (Behbahani 2014).

10.4.5 Capsicum annum

Capsicum annuum (Solanaceae) was domesticated in Mexico, where wild and cultivated (chile pepper populations (>60 landraces)) coexist, and wild-like individuals develop spontaneously in human situations (Pérez-Martínez et al. 2022). *Capsicum annuum*, a tropical and subtropical fruit plant, has a variety of vital nutrients and bioactive chemicals that have been shown to have a variety of bioactivities such as free radical scavenging (antioxidant), anti-inflammatory, antibacterial, antiviral, and anticancer properties (Khan et al. 2014). Several edible plants found across Indonesia contain emodin and luteolin compounds, which can prevent or reduce viral infection. In SARS-CoV, luteolin inhibits connections between S protein and ACE-2 receptors (Illian et al. 2021).

10.4.6 Citrus limon

Citrus limon is a Rutaceae tree with evergreen foliage and yellow edible fruits. The diverse chemical makeup of *Citrus limon* determines its medicinal potential. Flavonoids are the most abundant secondary metabolites in the fruit, although there are also coumarins, phenolic acids, carboxylic acids, amino acids, and vitamins. Monoterpenoids, particularly D-limonene, are the primary constituents of essential oils (Klimek-Szczykutowicz et al. 2020). When compared to the typical antiviral medication, diosmetin had the best docking values against the M^{Pro} of SARS-CoV-2. The order associated with biochemical reactivity in DFT calculations is as follows: eriodictyol > quercetin > spinacetin > apigenin > diosmetin > luteolin, whereas the regions of oxygen and hydrogen atoms from the selected isolated compounds are suitable for electrophilic and nucleophilic attacks, respectively.

Furthermore, the HOMO-LUMO and global descriptor values of these compounds indicated a good outcome (Khan et al. 2021). Because the ACE-2 receptor, a host cell receptor, has been found to play a vital role in virus cell entry, ACE-2 blockers may be a viable antiviral intervention target. Geranium and lemon oils strongly reduced ACE-2 in epithelial cells. Furthermore, immunoblotting and qPCR analysis revealed that geranium and lemon oils had potent ACE-2 inhibitory properties. Geranium and lemon essential oils, as well as their derivative compounds, are key natural antiviral medicines that may aid in the prevention of COVID-19 in humans (Senthil Kumar et al. 2020). Citrus essential oils (Family Rutaceae) are extremely effective against the dengue mosquito *Aedes albopictus*. Under experimental circumstances, *Citrus limon* oils showed high action against *Aedes albopictus.* These oils include secondary metabolites that are extremely beneficial to plants in terms of insect pest deterrence. Many researchers have discovered limonoids in citrus oils to be particularly active against mosquitoes (Khan et al. 2014).

10.4.7 Citrus limetta

Citrus limetta (Rutaceae) is a commercial citrus fruit crop that is utilized in the juice processing industry. *Citrus limetta* peels are a perishable waste item, posing a significant difficulty in the juice processing industry. The ethanol extract (ClPs) exhibits promising anti-inflammatory action and is high in hesperidin concentration, according to the preliminary pharmaco-chemical profile of peel extracts (Babu et al. 2021). In a study, several nanometals (Ag, Zn, and Fe) were infused into raw *Citrus limetta* peels. The plaque assay, real-time PCR, and immunofluorescence assays all demonstrated that the three nano-biomaterials reduced the Chikungunya virus (CHIKV) viral titer and viral RNA levels significantly. The findings indicated that silver and iron nano-biomaterials have more antiviral activity against CHIKV than zinc (Choudhary et al. 2020).

10.4.8 Carica papaya

Papaya (*Carica papaya*) is commonly grown in tropical and subtropical regions. While ripe fruit is widely consumed across the world, unripe fruit is only consumed in a few Asian nations (Hiraga et al. 2021). *Carica papaya* belongs to the Caricaceae family. According to one study, quercetin is a good candidate for the development of effective anti-dengue medicines. *Carica papaya* flavonoid quercetin may have antiviral activity by interfering with the viral assembly process of the Dengue virus (DENV2) virus (Senthilvel et al. 2013). The presence of several secondary metabolites, including flavonoids, alkaloids, sterols, triterpenoids, isothiocyanates, tannins, and other phenolic chemicals, explains the broad range of activity. Recently, it was shown that papaya fruit pulp possesses antiviral properties against Zika and DEN virus. Betulinic acid, a pentacyclic triterpene, has antiviral action against HIV and HSV. The n-hexane fraction not only had the highest selectivity index, but it also had the strongest anti-SARS-CoV-2 activity (Adel et al. 2022).

10.4.9 Fragaria ananassa

Wild Fragaria (Rosaceae) species are found across the northern hemisphere and in southern South America. *Fragaria ananassa*, the contemporary cultivated strawberry, arose in the eighteenth century in Europe as a result of hybridization between two species brought from North and South America (Liston et al. 2014). Strawberry methanolic extracts were used to make silver nanoparticles (AgNPs) to test their SARS-CoV-2 inhibitory activity. The strawberry methanolic extract was the most effective against SARS-CoV-2. The extraction of secondary metabolites from strawberry crude methanolic extracts resulted in the identification of several compounds,

including phenolic, flavonoids, fatty acids, sesquiterpenes, triterpenes, sterols, and others. The docking study suggested different patterns of interaction between strawberry compounds and seven SARS-CoV-2 protein targets, including five viral proteins (M^{Pro}, ADP ribose phosphatase, NSP14, NSP16, and PL^{pro}) and two human proteins (AAK1, Cathepsin L). The study of molecular docking and dynamics modeling demonstrated that neo hesperidin can bind to both human AAK1 and SARS-CoV-2 NSP16 proteins (Al-Sanea et al. 2021).

10.4.10 Citrus paradisi

Citrus (Rutaceae) is an old, widely traded and widely consumed crop. Grapefruit essential oil is known as the "dieter's buddy" because of its anti-obesity properties. At 80 ppm, grapefruit EO is also a strong larvicide against *Anopheles stephensi* (Dosoky and Setzer 2018). Citrus essential oils include 85–99% volatile components such as sesquiterpenes, monoterpene (limonene), and hydrocarbons; aldehydes (citral), alcohols (linalool), ketones, acids, and esters. The most effective essential oil for decreasing viral titer on berries was rosemary cineole, followed by grapefruit EO. One of the most common chemicals found in citrus trees is limonene (LMN). LMN has been shown to affect many signaling pathways as well as suppress inflammatory mediators such as cytokines, adhesion molecules, prostanoids, chemokines, and eicosanoids. Given the etiology of COVID-19, which includes infection, inflammation, and immunity, we hypothesized that LMN, with its anti-inflammatory, immunomodulatory, and antiviral properties, might reduce the severity and progression of the condition. The use of LMN in COVID-19 treatment looks speculative, but considering its good physiochemical and druggable properties, it cannot be disregarded (Adel et al. 2022).

10.5 Spices Involved in Traditional Indian Cooking to Step Ahead the Battle of COVID-19 Infection

The Indian style of cooking involves the usage of ingredients that adds not only taste but also medicinal properties. The spices pose a strong source of therapeutic in traditional ailments which are also involved in regular diets by incorporating them in cooking. Turmeric and pepper are two major ingredients used in Indian cuisine and they possess medicinal values like anti-inflammatory, anticancer, and antiviral properties (Rattis et al. 2021; Priya and Kumari 2017) that are the needs of the current social scenario. This section deals with a brief elaboration of the medicinal values of different spices used in Indian cuisine and their activity against SARS-CoV-2 depicted in Table 10.3. Spices (the seed, leaf, flower, fruit, bud, root, and rhizome of several plants used to give taste and flavor to food) are particularly

Table 10.3 Spices used in Indian cuisine and their activity against SARS-CoV-2

Spices	Scientific name	Major chemical constituent	Virus type	Medicinal properties	Reference
Turmeric	*Curcuma longa*	Curcumin	Influenza A virus, DEN virus, SARS-CoV-2	Antibacterial, antiviral, antitumor, and hepatoprotective activity	Rattis et al. (2021)
Ginger	*Zingiber officinale*	Zingiberol, paradol, shogoals, and gingerol	HSV, HRSV, SARS-CoV-2	Colds, nausea, arthritis, migraines, and hypertension	Bode and Dong (2011)
Coriander seeds	*Coriandrum sativum*	Linalool, rutin, lopinavir, quercetin	SARS-CoV-2	Anti-diabetic, anticancer, antifungal, antiulcer, hepatoprotective, antimutagenic sedative-hypnotic, anticonvulsant, and anti-fungal properties	Nair et al. (2012)
Cumin seeds	*Cuminum cyminum*	Cumin aldehyde, γ-terpinene, p-cymene, β-pinene, and estragole	HSV, SARS-CoV-2	Fertility, respiratory and gastrointestinal disorders, toothache, diarrhea, and epilepsy	Saab et al. (2021)
Black pepper	*Piper nigrum*	Piperidine	SARS-CoV-2	Acute respiratory infection, asthma, chronic indigestion, and flu	Priya and Kumari (2017)
Cloves	*Syzygium aromaticum*	Eugenol, eugenol acetate, and gallic acid	SARS-CoV-2	Anti-inflammatory, antiviral, insect repellent, antimicrobial and antiparasitic	Xu et al. (2016)
Mustard	*Brassica juncea*	Curcumenol, N-desmethylselegiline, phentermine, and sphingolipid	Peritonitis, neuralgia, and SARS-CoV-2	Anti-inflammatory, antibacterial, and antiviral	Tian and Deng (2020)
Fenugreek	*Trigonella foenum-graecum*	Trigoneoside	Malaria, SARS-CoV-2	In the treatment of diabetes, cancer, hypercholesterolemia, myocardial infarction, skin irritation, indigestion and flatulence, inflammation, anemia, immune deficiency, and kidney diseases	Priya and Kumari (2017)

(continued)

Table 10.3 (continued)

Spices	Scientific name	Major chemical constituent	Virus type	Medicinal properties	Reference
Cinnamon	*Cinnamomum verum*	Cinnamaldehyde, eugenol, caryophyllene, cinnamyl acetate, and cinnamic acid	H1N1, HSV, SARS-CoV-2	Upregulation of inhibitory receptors	Connell et al. (2016)
Fennel	*Foeniculum vulgare*	Trans-anethole, LMN, pinene, trans-ocimene, fenchyl acetate, and fenchone	HAV and HCV, HSV	Antiviral activity	Suleiman and Helal (2022)

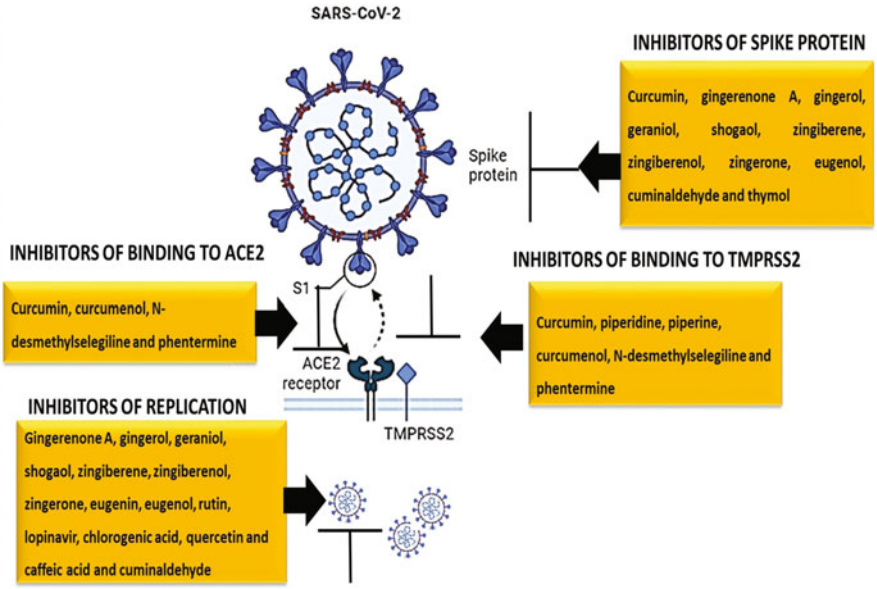

Fig. 10.2 Compounds identified in dietary spices and their role in SARS-CoV-2 Inhibition

medicinal. A profusion of trials involving clinical and preclinical research have documented the efficacy of numerous spices with a variety of diseases. Spices are a recent interest of phytoresearch including immune-boosting home treatments in the period of uncertain times due to their possible immune-boosting capabilities and great safety profiles illustrated in Fig. 10.2 (Devan et al. 2022; Natesh et al. 2021).

10.5.1 Turmeric

Turmeric (*Curcuma longa*) is from the Zingiberaceae family and is one of the native plants of India. Turmeric is one of the main ingredients used often in all types of Indian cuisine. Even though it is one of the primary ingredients, it is used only in small amounts. Curcumin is a polyphenol mainly found in turmeric and it is recommended that about 12 g/day of curcumin can be safe without any side effects (Gupta et al. 2013). The main bioactive constituents identified in the rhizomes of turmeric are sesquiterpenes, steroids, curcuminoids, and polyphenols (Omosa et al. 2017). Turmeric is identified to have various therapeutic properties like antioxidant, anti-inflammatory, antibacterial, antiviral, antitumor, and hepatoprotective activity for which it is being used in traditional medicine (Rattis et al. 2021).

Curcumin is enhanced with antiviral properties and it has been explored against a wide range of viruses like influenza A virus (Chen et al. 2010; Ou et al. 2013), DEN virus, Zika (Balasubramanian et al. 2019), CHIKV (Mounce et al. 2017), HCV

(Chen et al. 2012), RSV (Obata et al. 2013; Yang et al. 2016), Japanese encephalitis virus (Dutta et al. 2009), EBV (Hergenhahn et al. 2002), human cytomegalovirus (Lv et al. 2014a,b), and HIV (Gupta et al. 2011). Curcumin in Vero-E6 cells was observed to stop the replication of SARS CoV at a 3–10 μM concentration (Wen et al. 2007). Curcumin stops the infection of SARS-CoV-2 in cardiac myocytes by acting with protein S and ACE 2 receptors because of its higher affinity and ability to control endothelial cell activation (Rattis et al. 2021). In the work done by Marín-Palma et al. (2021) the D614G and Delta variation of SARS-CoV-2 was used for the evaluation of curcumin as therapeutic, it was found that the curcumin at lesser to cytotoxic levels inhibited the replicative cycle and also minimized the release of pro-inflammatory cytokines like IL-8, IL-6, and IL-1β (Marín-Palma et al. 2021). It has also been identified that curcumin displayed higher binding affinity toward the SARS-CoV-2 S protein and also can control the expression of TMPRSS, Cat B and L which are some of the key molecules in the viral entry and viral decay (Jena et al. 2021; Hoffmann et al. 2020; Padmanabhan et al. 2020).

10.5.2 Ginger

Ginger is an ingredient used in Indian cuisine to enhance the flavor of food. Apart from the culinary uses, it is also employed in medicines practiced traditionally for the ailment of various diseases like colds, nausea, arthritis, migraines, and hypertension (Bode and Dong 2011). The ginger (*Zingiber officinale)* belongs to the family Zingiberaceae similar to turmeric. Ginger is enriched with the phytochemicals like phenols, steroids, and alkaloids. The rhizome possesses the aromatic compound zingiberol which has analogs such as zingerone, paradol, and shogoals along with the sub-bioactive compounds like 6-gingerol, 4-gingerol, 10-gingerols, 8-gingerol, 6-shogaols, and 14-shogaols (Singh et al. 2021a, b; Ali et al. 2008). Ginger is found to have activity against viruses like HRSV, HSV, CHIKV, and influenza virus (Dorra et al. 2019). The ginger is also observed to possess an inhibitory effect for SARS-CoV-2 in a docking study, where its compounds like geraniol, gingerenone A, shogaol, zingiberene, gingerol, zingerone, and zingiberenol had interaction with both M^{Pro} and Spike protein (Ahkam et al. 2020). The inhibition of M^{Pro} is crucial as it is involved in the viral replication process by mediating polyproteins pp1a and pp1ab (Hilgenfeld 2014).

10.5.3 Coriander Seeds

Coriander (*Coriandrum sativum*) leaves and dried seeds are used in Indian cooking (Baliga et al. 2015). The coriander belongs to the family Apiaceae. The coriander seeds have been used to treat disorders of the digestive, urinary, and respiratory systems (Momin et al. 2012). The properties that enhance the seeds are diuretic,

carminative, stimulant, and diaphoretic effects along with antioxidant, anti-diabetic, anticancer, antifungal, antiulcer, hepatoprotective, antimutagenic sedative-hypnotic, anticonvulsant, and antifungal properties (Nair et al. 2012). Linalool is one of the volatile compounds as well as a plant-specific compound found in different parts of coriander including its seeds, and it is observed to stimulate the immune system through inhalation or by the use of essential oil obtained from coriander (Dissanayake et al. 2020). Coriandrum was found to inhibit the nucleocapsid phosphoprotein which is a conserved structure of coronavirus by the interaction of phytoligands such as (+)−germacrene A, alpha-thujene, and geranyl acetate (Muthumanickam et al. 2021). The compounds like rutin, lopinavir, chlorogenic acid, quercetin, and caffeic acid, identified in the coriander seeds were observed to possess maximum binding affinity toward the M^{Pro} enzyme of SARS-CoV-2 (Kumar et al. 2021).

10.5.4 Cumin Seeds

Cumin seeds (*Cuminum cyminum*) belong to the family Apiaceae and are one of the most common ingredients in Indian and Pakistani dishes. Cumin seeds are used in traditional medicine as an ailment for fertility, respiratory, and gastrointestinal disorders and also to treat toothache, diarrhea, and epilepsy (Saab et al. 2021). Plant-specific compounds like cumin aldehyde, γ-terpinene, p-cymene, β-pinene, and estragole are identified in the cumin seeds, which are found to have antiviral activity (Bonesi et al. 2020). The cumin seeds' activity inhibited the infections of viruses like HSV1 and HSV2 as they inhibited the plaque developed by viral infection (El-Serehy et al. 2016). The cumin aldehyde present in the essential oils of cumin seeds was identified to be one of the potent compounds in inhibiting SARS-CoV-2 infection (Saab et al. 2021). The steaming of cumin seeds with other plants like eucalyptus, etc., could help in the inhibition of infectivity of SARS-CoV-2, as the volatile compounds like cumin aldehyde, thymol, and terpenes in association with various other compounds can interact with the amine group of the surface protein of SARS-CoV-2 and heal the lungs and throat (Marwah and Marwah 2020). The cumin aldehyde had also shown the minimum binding energy against the M^{Pro} of SARS-CoV-2 in the in silico analyses (Rout et al. 2022).

10.5.5 Black Pepper

The black pepper (*Piper nigrum*) is a spice that is primarily used in most Indian dishes and it comes under the Piperaceae family. Pepper is used in the ailment of digestive and respiratory diseases due to the infection of viruses that cause pathogenesis such as acute respiratory infection, chronic indigestion, asthma, and flu (Priya and Kumari 2017). The piperidine present in the pepper helps in rising the

curcumin and catechin levels in the plasma and curbs the entry of 2019 n-CoV into the cell (Joshi et al. 2018). Pepper in combination with other dietary spices like turmeric and ginger can prevent the SARS-CoV-2 pathogenesis and this action is directed by the inhibition of TMPRSS2 of the host cell which is the underlying reason for SARS-CoV-2 entry (Yadav et al. 2022). The compounds like piperidine and piperine observed in the black pepper have been found to have the potential to inhibit SARS-CoV-2 by in silico analysis (Rajagopal et al. 2020).

10.5.6 Cloves

The cloves (*Syzygium aromaticum)* are the flowers that are obtained from the tree belonging to the Myrtaceae family (Chandra Manivannan et al. 2022a, b). Cloves are one of the ingredients used in Indian cooking. The cloves are enriched with bio-activities like anti-inflammatory, antioxidant antiviral, antimicrobial, insect repellent, and antiparasitic properties (Xu et al. 2016). The cloves are abundant in phenolic content with the presence of phenolic contents like eugenol, eugenol acetate, hydroxybenzoic acids, hydroxycinnamic acids, hydroxyphenylpropene, and gallic acid. The aspects of cloves like strong, pungent, and spicy order make it to be used in commercial applications like perfumes, cleaning agents, and also to anesthetize certain fishes (Taylor and Roberts 1999). Eugenol is one of the abundant phenol present in cloves and its excess amount can lead to cytotoxicity. The eugenol in a computational study against SARS-CoV-2 was found to inhibit the spike protein (Kiran et al. 2020). Eugeniin and eugenol found in the cloves were observed to exhibit a better binding effect on M^{Pro} of SARS-CoV-2 (Chandra Manivannan et al. 2022a, b).

10.5.7 Mustard

The mustard (*Brassica juncea*) belongs to the family Brassicaceae which is an often used spice in Indian cuisine. The mustard seeds are enriched with various minerals like iron, magnesium, calcium, zinc, and phosphorous which are essential for healthy living (Divakaran and Babu 2016). The phytochemicals like vitamins, dietary fibers, chlorophylls, and glucosinolates along with their degradation products make mustard seeds good in antioxidant, anti-inflammatory, antibacterial, and antiviral activity (Tian and Deng 2020). In traditional folk, medicine mustard has been used as a stimulant, diuretic as well as purgative to manage diseases like peritonitis and neuralgia, etc. (Chan et al. 2014). The compounds identified in mustard like curcumenol, N-desmethylselegiline, phentermine, and sphingolipid derivatives were effective in the ACE-2 and TMPRSS2 receptor modifications for the prevention of the SARS-CoV-2 infection in computational analysis (Dave et al. 2020).

10.5.8 Fenugreek

The fenugreek (*Trigonella foenum-graecum*) has also got its application in the Indian style of cooking. It belongs to the family Fabaceae (Flammang et al. 2004). The fiber, phospholipids, glycolipids, linolenic acid, oleic acid, choline, nicotinic acid, vitamin A, B1, B2, C, and niacin add to the potential aspects of fenugreek (Chatterjee et al. 2010; Leela and Shafeekh 2008). The pharmacological properties of fenugreek seeds help in the treatment of cancer, diabetes, myocardial infarction, hypercholesterolemia, skin irritation, indigestion and flatulence, anemia, inflammation, immune deficiency, kidney diseases, aging, etc. Fenugreek seeds have been used to treat malaria (Priya et al. 2011). The compounds identified in the fenugreek seeds are observed to have inhibitory properties against M^{Pro} of SARS-CoV-2 (Sen et al. 2022). The trigoneoside found in fenugreek was identified to be an efficient candidate against the active sites of SARS-CoV-2 in an in silico analysis (Pandey et al. 2022).

10.5.9 Fennel

Common *Foeniculum vulgare* sometimes known as fennel is an ancient medicine utilized to treat various illnesses affecting distinguished organs. It is a medicinal plant of the Umbelliferae (Apiaceae) family that has been recognized and utilized by humans since antiquity because of its taste. It was grown in practically every nation (Badgujar et al. 2014). The research found 67 volatile components containing phenylpropenes and monoterpenes as main ingredients, including trans-anethole, limonene, pinene, trans-ocimene, fenchyl acetate, and fenchone. In fennel hydrodistilled oils, phenylpropenes predominated, while monoterpenes predominated in the majority of the headspace scent. The unsupervised multivariate data analysis techniques PCA and HCA were used to analyze infraspecific variability. The plaque reduction test, HAV 3C proteinase, and HCV NS5B polymerase inhibitory assays were used to study the antiviral activity of samples against HAV and HCV, with percentage inhibition ranging from 66% to 85% and IC_{50} values ranging from 1.8 to 26.7 g mL-1. In silico molecular docking scores in later enzyme binding pockets indicated critical allosteric interactions with trans-ocimene and fenchyl acetate, which had the lowest Gibb's free energy (Ibrahim and Moussa 2021). *Foeniculum vulgare* was shown to have a high percentage of inhibition value at the maximal noncytotoxic dose, with 83 percent inhibition against the influenza virus. The essential oil from the fruit of this spice in combination with 12 distinct Turkish therapeutic plants exhibited antiviral activity against HSV-1 and CoxB4 viruses at 21.95% and 13.14%, respectively (Suleiman and Helal 2022).

10.5.10 Cinnamon

Cinnamomum verum has been used as a spice for both medicinal and culinary purposes since ancient times. It is indigenous to Sri Lanka and southern India, although it is also found in several Asian, Caribbean, Australian, and African nations. It is also used to treat asthma, bronchitis, diarrhea, headaches, inflammation, and heart problems. The main chemicals identified in its essential oil are cinnamaldehyde, eugenol, caryophyllene, cinnamyl acetate, and cinnamic acid (Singh et al. 2021a). Various researches have demonstrated *Cinnamomum verum's* anti-HIV efficacy in the treatment of acquired immune deficiency syndrome (AIDS) (Semenya et al. 2012). In a study using a customized cinnamon combination, effectiveness against H1N1 and HSV was demonstrated. It has anti-HSV1 action by directly inactivating free virus particles and may interfere with virion envelope structures essential for host cell entrance (Brochot et al. 2017). Cinnamon bark extract and its nanoparticles were evaluated in Vero cells against the H7N3 influenza A virus, and cell viability was estimated using the tetrazolium dye (MTT) assay. The silver nanoparticle obtained from the extract of this plant exhibited potent antiviral activity (Fatima et al. 2016). Tenuifolin (TEN) and Pavetannin C1 (PAV) have been found as hit drugs against the COVID-19 primary protease enzyme (Prasanth et al. 2021; Connell et al. 2016). IND02, a cinnamon-derived type A procyanidin polyphenol with trimeric and pentameric forms, has anti-HIV-1 action averse to CXCR4 and CCR5 viruses, with a 1–7 M ED50 for the trimer (Connell et al. 2016).

10.6 Conclusions

The SARS-CoV-2 infection has caused a global decline in population and economic status. The management of SARS-CoV-2 infection had been a challenge during the time of the pandemic and different modes of medication were practiced at different places. The allopathic treatment was used as a curative, but the preventive measure was provided by the practice of traditional medicine. The traditional medicine in India and other countries is incorporated with their traditional cooking style. The plants, fruits, and spices of medicinal importance used in various traditional dishes are briefly elaborated on in this chapter along with their phytoconstituents and their mode of action. The plants, fruits, and spices used on a culinary basis are identified to possess great potential as a preventive and curative measure for SARS-CoV-2 infection and virulence. The plants, fruits, and spices elucidated in this chapter further need investigation in proper clinical trials.

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Chapter 11
Therapeutic Potential of Selected Medicinal Plants for Neurological Disorders after the Infection of COVID-19

Ravindra Verma, Prakash S. Bisen, and Mònica Bulló

11.1 Introduction

World Health Organization statistics indicate that 14% of the global disease burden is caused by neurological disorders, and 85% of global deaths are caused by cerebrovascular diseases. Lower-middle-income countries have a higher death rate (16.8%) than high-income countries (13.2%) (https://www.who.int/mental_health/neurology/neurological_disorders_report_web.pdf). WHO also stated that COVID-19-related mental health system upheavals are mostly affecting preexisting mental health issues (Lancet 2020). According to a United Nations study, COVID-19 affects more than one in five people mentally and is associated with a number of neurological disorders (Brief 2020). The mechanism behind the evolution of SARS-CoV-2, which causes the severe acute respiratory syndrome, is unclear. Several of the claims are based on research conducted at Wuhan University, and others are based on ecological evidence (Boni et al. 2020; Xiao et al. 2020; Lam et al. 2020; Latinne et al. 2020). Several neurological disorders have been reported in patients infected with the SARS-CoV-2 virus, including heart, liver, and brain infections (Karuppan et al. 2021). Blood clotting and cytokine storms in the peripheral and

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central nervous systems are responsible for a number of these neurological disorders (Fotuhi et al. 2020). SARS-CoV-2 may cause neuroinvasive respiratory disease in COVID-19 patients who exhibit respiratory failure (Sellner et al. 2020). In the nasal mucosa, lamina cribrosa, and olfactory bulb, as well as retrogressive axonal movement, ACE-2 receptors enable SARS-CoV-2 entry into the central nervous system (Hartung and Aktas 2020). The high levels of angiotensin II observed in COVID-19-infected patients are associated with several disorders, including vasoconstriction, kidney failure, heart disease, apoptosis, and oxidative stress, all of which accelerate aging and lead to cognitive decline (Vidrio et al. 2022; Elrayess et al. 2022; Amezcua-Guerra et al. 2022). There are a number of biomarkers associated with COVID-19, including interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-7 (IL-7), granulocyte colony-stimulating factor (GCSF), and tumor necrosis factor-alpha (TNF-alpha) (Azizi Jalilian et al. 2022; Chaumont et al. 2020). The exact mechanisms responsible for coronavirus entry into the nervous system are unknown (Susilawathi et al. 2021).

Several patients have reported blood clots in their brains and multiple organs as a result of COVID-19 infection. This protocol does not specifically treat neurological disorders associated with COVID-19 infection (Tang et al. 2021). In this study, herbs were examined for their potential to aid the early recovery of COVID-19 patients from neurological disorders. The discovery of new drugs for infectious diseases, such as cancer, kidney and heart disease, and neurological disorders, can be attributed to nature and its derivatives. Plant derivatives are thought to contribute to early recovery. It is critical to identify potential drugs from traditional medicines without harming nature's database. Scientists must rethink and rearrange nature's database compassionately. More than 50 million people are suffering from dementia, a neurological disease associated with aging (https://www.alz.co.uk/research/WorldAlzheimerReport2019.pdf). In addition to ensuring that the elderly and corona warriors maintain social distance, it is also critical to provide mental health and psychosocial support (Wang et al. 2020). According to COVID-19 data in Wuhan, fatigue (63%), sleep disorder (26%), and anxiety/depression (13%) were the most commonly reported disorders (Nalbandian et al. 2021).

11.2 Methodology

In this study, we reviewed the available literature related to the clinical and neuropathological findings of COVID-19 patients. This study examined specific herbs associated with neurological complications observed in patients with SARS-CoV-2 infection and afterward. PubMed, MEDLINE, Scopus, EMBASE, Google Scholar, EBSCO, Web of Science, Cochrane Library, WHO database, and ClinicalTrials.gov were searched for the neuroprotective potential of herbs for post-COVID-19 patients. For Boolean search, the terms are herbs and neuroprotective potential, post-COVID-19 symptoms, etc. Assessing the pathobiological mechanisms

involved in neurological complications associated with COVID-19 using biomarkers that indicate an immune response to SARS-CoV-2.

11.3 Discussion

Studies have been done on COVID-19 and post-COVID-infected patients (Leach et al. 2021). Unfortunately, there is no scientific evidence proving the effectiveness of herbs in treating neurological disorders in COVID-19 patients. However, there are widely recognized literature about the use of herbal drugs in many neurodegenerative disorders and cerebrovascular accidents (Ding and He 1986; Akhondzadeh 2007; Wu et al. 2010; Makkar et al. 2020). The most common drug for treating Parkinson's disease is Leva-dopa, which is found in the seeds of the *Mucuna pruriens* plant (Katzenschlager et al. 2004). It is expected that the findings of this study will have a significant impact on the management of COVID-19 patients and post-COVID patients. Some neurological disorders like migraine headaches, loss of smell, etc., might be cured by the use of herbal remedies (Sen 2020).

11.3.1 Neurological Disturbances in COVID-19 Patients

The majority of people with COVID-19 infections experience neurological symptoms such as muscle pain, headaches, confusion, dizziness, and loss of taste and smell (Koralnik and Tyler 2020; Acharya et al. 2020; Liguori et al. 2020). In a study of 236,379 patients with COVID-19 disease, 14 neurological and psychiatric disorders were observed in six months, including intracranial hemorrhage (0.56%), ischemic stroke (2.10%), parkinsonism (0.11%), Guillain-Barré syndrome (0.08%), nerve, nerve root, and plexus disorders (2.85%), myoneural junction and muscle disease (0.45%), encephalitis (0.10%), dementia (0.67%), mood disorder (13.66%), anxiety disorder (17.39%), psychotic disorders (1.40%), substance use disorder (6.58%), and insomnia (5.42%) (Taquet et al. 2021). The neurological symptoms of patients who have a higher risk of neurological disorders due to COVID-19 are described in Table 11.1 and Fig. 11.1.

11.4 Immune Response and Brain

An inherent immune response exists in the central nervous system (CNS). A CNS response to infection or disease involves an innate immune reaction. Several types of injuries to the CNS system are observed, including acute injuries (mechanical trauma, strokes, etc.), chronic neurodegenerative diseases (multiple sclerosis, Alzheimer's, etc.), brain tumors (gliomas), and infections (HIV, E. coli, etc.)

Table 11.1 Neurological patients at higher risk due to COVID-19

S. No.	Name of disease	COVID-19 effects	Reference
1	Alzheimer's disease and related dementias (ADRD)	Mental hygiene, trauma, and stigma	Brown et al. (2020)
2	Parkinson's disease (PD)	Mitochondrial dysfunction, proteostasis, lipid metabolism, and stress responses	Gonzalez-Latapi et al. (2021)
3	Motor neuron disease (pwMND)	Proximal muscle weakness of acute or subacute onset and high creatine kinase levels	Barp et al. (2021)
4	CNS disorder with reduced mobility or immobility	Movement disorders, frontal syndrome, brainstem impairment	Lambrecq et al. (2021)
5	Neuromuscular disorder with reduced mobility and compromised respiratory function	Exacerbation, ventilatory muscle weakness, or cardiomyopathy	Tseng and Chen (2021)
6	Autoimmune condition (a) Multiple sclerosis (b) Neuromyelitis optica spectrum disorder (c) Myasthenia gravis (d) Guillain-Barre syndrome (e) Chronic dysimmune neuropathies	(a) Comorbidities, obesity, and black/African ancestry (b) Vomiting and hiccoughs (area postrema syndrome) (c) Diaphragmatic task failure (d) Presence of *Campylobacter jejuni* (e) –	Reder et al. (2021), Ghosh et al. (2021), Galassi and Marchioni (2021), Vogrig et al. (2021), Younger (2021)

(Lampron et al. 2013). During the course of SARS-CoV-2 infection, the endothelium is able to detect circulating IFN type 1 signaling and thus limit the entry of SARS-CoV-2 into the central nervous system (Iadecola et al. 2020). In terms of stress and neurological disorders, nuclear factor erythroid 2-related factor 2 (Nrf2) is a dominant biomarker (Johnson and Johnson 2015). Study results suggest that deregulation of the NF-κB pathway may modulate T cell activation, which may lead to autoimmune and inflammatory responses. It is the activation of $CD4^+$ T-helper cells that is the main feature of inflammation (Guisado-Vasco et al. 2020). In pathogenic diseases, immune response promotes the development of macrophages, dendritic cells, and proinflammatory cytokines (IL-1, IL-6, IL-12, and tumor necrosis factor-α) (Zhang et al. 2017a). Parkinson's disease (PD) is related to immune responses in the central nervous system (Su and Federoff 2014). The presence of $CD4^+$ and $CD8^+$ T cells is a strong immune response biomarker associated with PD. Researchers have observed that regulatory T cells (Tregs) in PD patients are less effective in suppressing effectors T cells (Saunders et al. 2012).

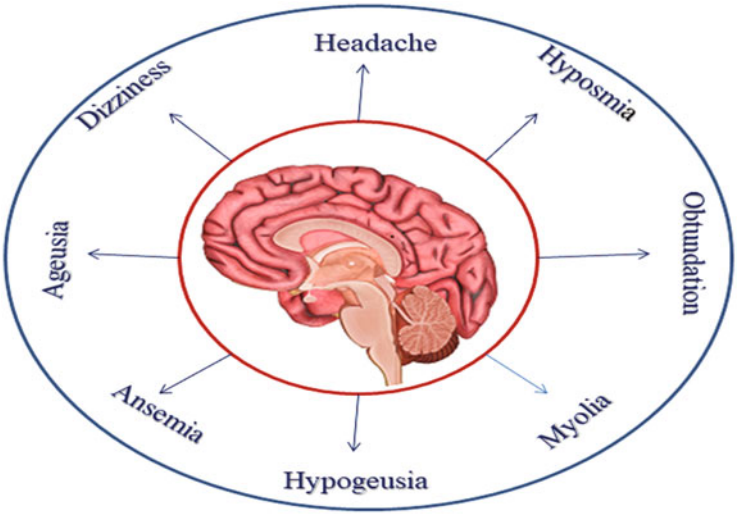

Fig. 11.1 Neurological symptoms in COVID-19 patients

Amyloid-β directly activates microglia in Alzheimer's disease (AD) through the NALP3 inflammasome pathway and production of IL-1β. In Alzheimer's disease, amyloid-β directly activates microglia through the NALP3 inflammasome pathway and production of IL-1β. This may intensify neurodegeneration (Fuhrmann et al. 2010; Masters and O'Neill 2011). Pathologic inflammation in the CNS is integral to diseases like multiple sclerosis (MS), AD, PD, stroke, and traumatic brain injury (Ransohoff and Brown 2012).

11.4.1 Evidence of Clinical Trials for Neurological Disorders in COVID-19 Patients

The clinical trial of patients with neurological symptoms concluded that altered mental status (42%), headache (42%), central (21%), and peripheral weakness (32%). For mild to critical COVID-19 patients, increases in NfL protein, total tau, and GFAp levels were observed in 63%, 37%, and 16% of patients, respectively (Virhammar et al. 2021). A study that examined the neurological manifestations of 901 patients found encephalopathy, Guillain-Barré syndrome, and stroke to be the most prevalent disorders among COVID-19 patients (Ellul et al. 2020). Figures 11.2 and 11.3 show the effects of cytokine strokes on the brain and neurological disorders associated with COVID-19.

A study found some COVID-19 neurological patients exhibit SARS-CoV-2 in the central nervous system, while others do not (Mitra et al. 2022). The eight drugs (hydroxychloroquine, baricitinib, ruxolitinib, remdesivir, tocilizumab, lopinavir/

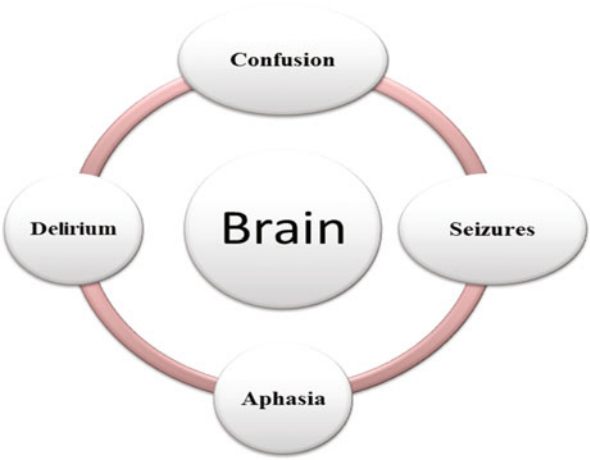

Fig. 11.2 Cytokine storm effects on the brain

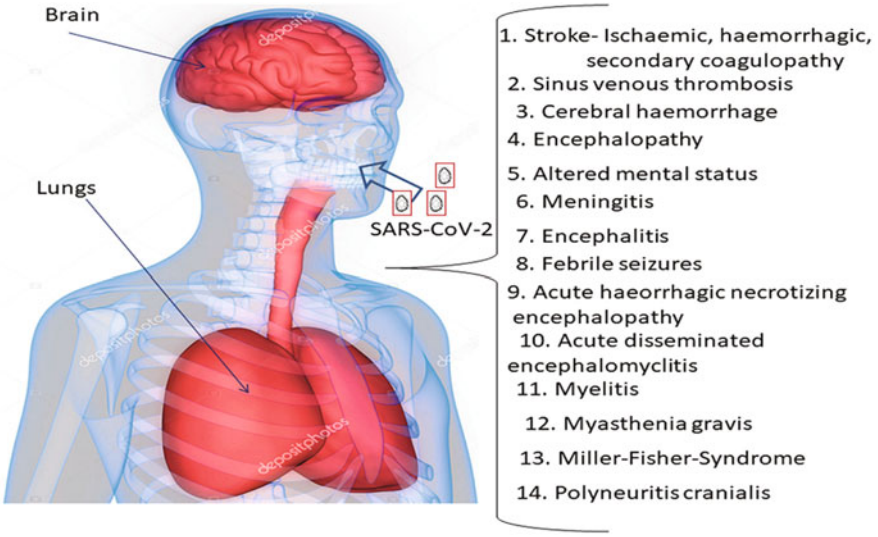

Fig. 11.3 Neurological disorders reported occurring with COVID-19

ritonavir, favipiravir, and azithromycin) were tested for penetrating capacity in a well-tolerated brain, and hydroxychloroquine and baricitinib were found to be most likely to penetrate the brain (Richardson et al. 2020). COVID-19-infected patients' MRI studies confirm abnormalities in the cerebral parenchyma (Nuzzo et al. 2021).

11.4.2 Herbs for Neurological Disorders

Traditionally, *Bacopa monnieri* Linn. is used as a biomedicine for treating neurological disorders and psychiatric disorders (Russo and Borrelli 2005). No clinical studies have been conducted on the effects of *Bacopa monnieri* on the improvement of memory in healthy adults and older adults with age-related memory problems. *Bacopa monnieri* and its bioactive components have shown neuroprotective properties in reducing ROS, neuroinflammation, aggregation, inhibiting amyloid-β and improving cognitive abilities (Dubey and Chinnathambi 2019; Abdul Manap et al. 2019). The treatment of Alzheimer's disease has been reported in a few studies, but no studies have examined *Bacopa monnieri* alone in patients with depression (Brimson et al. 2021). Scientists have supported *Mucuna pruriens* as a treatment for PD, but the most common Parkinson's drug is Leva-dopa, which is abundant in *Mucuna pruriens* (Fothergill-Misbah et al. 2020; Cassani et al. 2016; Cilia et al. 2018; Khazdair et al. 2021). *Mucuna pruriens* treated Parkinson's patients show positive effects (https://clinicaltrials.gov/ct2/show/NCT02680977).

Withania somnifera is a neuroprotective herb. Withanone extracted from *Withania somnifera* inhibits amyloid β-42 and modulates proinflammatory cytokines (Pandey et al. 2018; Dar et al. 2017; Kuboyama et al. 2014; Lopresti and Smith 2021). The main phytocompounds in *Withania somnifera* are sitoindoside VII–X, withaferin A, withanosides IV, withanols, withanolide A, withanolide B, anaferine, beta-sitosterol, and withanolide D. These compounds are effective in treating anxiety disorders, Alzheimer's, Parkinson's, schizophrenia, Huntington's disease, dyslexia, depression, autism, addiction, amyotrophic lateral sclerosis, attention deficit hyperactivity disorder, and bipolar disorders (Zahiruddin et al. 2020). Table 11.2 shows the herbs commonly used in neurological disorders with their biomarkers for immune response to diseases.

A recent survey shows that 61.9% of herbal treatments and 25.3% of herbal-drug combinations are used by COVID-19 patients with mental illness or psychiatric issues (Alonso-Castro et al. 2021). Study outcomes have not been published for herbal treatments for neurological disorders in COVID-19 patients. An ongoing clinical trial on "Functional Assessment of Ashwagandha Root Extract during Weight Loss" evaluates the effect of Ashwagandha root extract capsule on nervous system disease (ClinicalTrials.gov identifier, NCT03112824) (https://www.clinicaltrials.gov/ct2/show/NCT03112824). Nuclear factor erythroid 2-related factor 2 (Nrf2) is a dominant biomarker for stress and associated neurological disorders. The combination of drugs (carnosol, withaferin A, and luteolin), rosemary, ashwagandha, and sophora japonica is undergoing a clinical trial (https://clinicaltrials.gov/ct2/show/NCT04638387). The study reported neuroprotective effects of ethanolic extract of *Acorus calamus* (Shukla et al. 2002). In Ayurveda, roots and rhizomes of the plant are used for the treatment of epilepsy, neurosis, insomnia, and other diseases (Vohora et al. 1990; Martis et al. 1991). An *Acorus calamus* leaf extract modulates the characteristics of interleukin-8 (IL-8), (IL-6), RNA protein level, and interferon regulatory factor 3 (IRF3), as well as nuclear

Table 11.2 Herbs used in neurological disorder and their biomarker for the immune response against diseases

S. No.	Herbs	Important phytochemicals	Biomarkers related to immune response	Neurological effects
1	*Acorus calamus* (Bach)	Galloylquinic acid, Bacopaside III and Bacopaside, α-asarone and β-asarone (trans and cis forms, respectively, of 2,4,5-trimethoxy1- propenyl benzene) acorenone, iso-acorone, (Z)-sesquilavandulol and dehydroxy isocalamendiol acofuran, a sesquiterpenoid, coumarine, saponin, asamyl alcohol, methyl eugenol, calamenol, α- pinene, acorine, acoretine, lucenin, acoradin (Yende et al. 2008)	Nitric oxide, interleukin-2 (IL-2), and tumor necrosis factor-a (TNF-a) (Mehrotra et al. 2003)	CNS depressant, anticonvulsant, anti-spasmodic, hypolipidemic, immuno-suppressive, anti-inflammatory, cryoprotective, and antioxidant (Rajput et al. 2014)
2	*Asparagus racemosus* (Shatavari)	Shatavarins, sarsasapogenin, quercetin, rutin (quercetin 3-O-rutinoside) and hyperoside (quercetin 3-O-galactoside), quercetin 3-glucuronide, ferulic, caffeic, and chlorogenic acids (Srivastava et al. 2018)	Significant increase of CD^{3+} and CD^{4}/CD^{8+}, percentages effect on T cell activation. Significant upregulation of Th1 (IL-2, IFN-g) and Th2 (IL-4) cytokines suggesting its mixed Th1/Th2 adjuvant activity (Gautam et al. 2009)	Antidepressant activity (Meena et al. 2011)
3	*Bacopa monnieri* (Brahmi)	Dammarane-type triterpenoid saponins with jujubogenin and pseudojujubogenin as the aglycones including bacosides A1-A3, bacopa saponins A-G and bacopasides I–V (Shahid et al. 2017)	TNF-α and IL-6 from activated N9 microglial cells, caspase 1 and 3, matrix metalloproteinase-3 (Nemetchek et al. 2017)	Alzheimer's and Spinocerebellar ataxia (SCA) (Jeyasri et al. 2020)
4	*Blumea balsamifera* (Ngai camphor)	l-borneol, 10-epi-γ-eudesmol, γ-eudesmol, β-eudesmol, α-eudesmol, limonene, l-camphor, palmitic acid, and d-camphor (Pang et al. 2014)	LPS-induced RAW264.7 cells by decreasing activity of TLR4-NF-κB signaling pathway and inhibiting NLRP3 inflammasome activation (Liao et al. 2021)	Improve drugs delivery to the blood–brain barrier in the central nervous system (Zhang et al. 2017b)

5	*Cannabis* (Bhang)	$\triangle^9$-tetrahydrocannabinol, $\triangle^8$-tetrahydrocannabinol, cannabinol, and cannabidiol (Ashton 2001)	IFN-γ producing CD8+ T cells, glycogen synthase kinase 3β (GSK-3β) hyperphosphorylation caused by Aβ (Nichols et al. 2021; Li et al. 2020)	Epilepsy and Alzheimer's disease (Hosami et al. 2021)
6	*Centella asiatica* (Mandookparni or Gotu kola)	triterpenoid saponins, asiaticoside, asiatic acid, madecassic acid, aglycones, saponins-asiaticoside B, brahminoside, centelloside, indcentelloside, thankuni side, isothankuniside, brahamic acid, betulic acid and alkaloid hydrocotyline, madecassic acid, glucose, rhamnose, sitosterol, Stigmasterol (Samy and Chow 2011)	Reduces amyloid-β pathology and activates NRF2-regulated antioxidant response pathway (Zweig et al. 2021)	Memory enhancement, Alzheimer's (Boondam et al. 2019)
7	*Convolvulus prostratus* (Shankha pushpi)	Microphyllic acid, kaempferol, kaempferol-3-glucoside, 3,4 dihydroxycinnamic acid, scopoletin, convolamine, convolidine, sitosterols, 2-butanone, pentanoic acid, cinnamic acid, silane, decanoic acid, 2-pentanol, ascorbic acid, 10-bromodecanoic acid, tridecane, phthalic acid, eicosane, octatriacontyl pentafluoropropionate, 1-octadecene sulphonyl chloride, squalene, pyrimidine, heneicosane, 1,2-benzenedicarboxylic acid, cyclononasiloxane, octadecamethyl, nonacosane, sulfurous acid pentadecyl 2-propyl ester, straight chain hydrocarbons (C22–C33), fatty acids (C14–C28), fatty alcohols (C24– C32), vitamin E, and cyclononasiloxane (Salehi et al. 2020)	Regulate the neuronal factor and proteins by inhibiting acetyl-cholinesterase and regulate the neuronal cascades, cytokine- IL-6, MCP-1, ICAM-1 (Balkrishna et al. 2020)	Enhance memory or as a brain and nerve tonic, Alzheimer's disease (Semwal et al. 2021)

(continued)

Table 11.2 (continued)

S. No.	Herbs	Important phytochemicals	Biomarkers related to immune response	Neurological effects
8	*Curcuma longa* (Turmeric)	Demethoxycurcumin (2, DMC), bisdemethoxycurcumin (3, BDMC) and cyclocurcumin (4, CYC), tetrahydrocurcumin (5, THC) (Randino et al. 2016)	PI3K/Akt, NF-κB, TNF-α, modulating tau oligomers (Mathew and Hsu 2018; Panaro et al. 2020)	Alzheimer agents (Cascio et al. 2019)
9	*Mucuna pruriens* (Velvet beans)	1–3,4-dihydroxyphenylalanine, pentadecanoic acid, 14-methyl-, methyl ester, dodecanoic acid, 9, 12-octadecadienoic acid (Z, Z)-methyl ester, 9,12-octadecadienoic acid, and 2-myristynoyl-glycinamide (Saikarthik et al. 2017; Lampariello et al. 2012)	(TNF-α), (IL-1β), IL-6, and enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and cyclooxygenase-2 (COX-2) (Rai et al. 2017)	Parkinson's disease (Cilia et al. 2017)
10	*Nyctanthes-arbor tristis Linn.* (Har Singar or Parijat)	4-hydroxy hexahydro benzofuran-7-one, 6β-hydroxyloganin, and arbortristoside, diterpenoids, nyctanthin, nyctanthoside, rengyolone, astragalin, flavonoids, anthocyanins, d-mannitol, essential oils, glycosides, carotenoids (Parekh and Soni 2020; Bharshiv et al. 2016)	Splenocytes proliferation and increased production of cytokines, especially IL-2 and IL-6 (Bharshiv et al. 2016)	Anti-epileptic and anxiolytic (Srikalyani and Ilango 2009)
11	*Ocimum tenuiflorum* (Tulsi)	Oleanolic acid, ursolic acid, rosmarinic acid, eugenol, carvacrol, linalool, B-caryophyllene (Singh and Chaudhuri 2018)	Increased Natural Killer (NK) and T-helper cells (Jamshidi and Cohen 2017)	Anti-stress, loss of memory, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD). Oxidative stress and mitochondrial dysfunction (Singh and Chaudhuri 2018; Jamshidi and Cohen 2017)

12	*Phyllanthus emblica* (Ambla)	Ascorbic acid (vitamin C), gallic acids, amlaic acid, arginine, aspartic acid, astragallin, β-carotene, β-sitosterol, chebulagic acid, chebulic acid, chebulaginic acid, chebulinic acid, corilagic acid, corilagin, cysteine, ellagic acid, emblicol, gibberellins, glutamic acid, glycine, histidine, isoleucine, kaempferol, leucodelphinidin, methionine, phenylalanine, phyllantidine, phyllemblic acid, quercetin, riboflavin, rutin, thiamin, threonine, tryptophan, tyrosine, valine, zeatin (Habib-ur-Rehman et al. 2007)	Epithelial barriers, phagocytes (neutrophils, macrophages), B- and T-lymphocytes, modulate cytokine production, decrease histamine levels, reduced proinflammatory cytokine, (TNF-α) and (IL-1β) levels, and appreciably upregulate the anti-inflammatory cytokine (IL-10) concentration (Chatterjee et al. 2010)	Memory deficit, Alzheimer's disease (Ashwlayan and Singh 2011; Biswas et al. 2015)
13	*Swertia chirata* (Chirayita)	Secoiridoid bitters, triterpenoids, xanthones, and alkaloids. Swertiamarin, gentiopicroside, amarogentin, and amaroswerin, amarogentin (Karan et al. 1999)	Inflammatory mediators by blocking the expression of COX-2 and phosphorylation of Akt, IKK-β, MAPK, and NF-κB, activation in LPS-stimulated macrophages (Hu et al. 2019)	Antidepressant properties, CNS stimulant, Parkinson's disease (Shikha et al. 2010)
14	*Vitex negundo* (Nirgundi)	Benzoic acid 3-hydroxy, Ledol, 9,12,15-octadecatrienoic acid, and Vitamin E, 4HPyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl caryophyllene, and n-hexadecanoic acid (Kumar et al. 2010)	Suppressed expressions of inflammatory Th1/Th2 cytokines, chemokines, endopeptidases (MMPs)s, oxidative effector enzyme (iNOS), adhesion molecules, IL-4/IFN-γ release with simultaneous enhancement in levels of IL-10, IFN-γ, MUC3, and enhanced phosphorylation of NF-κB, PI3K, Akt and p38MAPKs and downregulated AMPK (Tirpude et al. 2021)	Anti-stress (Tirpude et al. 2021)

(continued)

Table 11.2 (continued)

S. No.	Herbs	Important phytochemicals	Biomarkers related to immune response	Neurological effects
15	*Withania somnifera* (Ashwagandha)	Withanolides, withaferin A, alkaloids, steroidal lactones, tropine, cuscohygrine, rutin, hyperoside, quercitrin, myricetin, quercetin, kaempferol, rhamnetin, gallic acid, caffeic acid, chlorogenic acid, ferulic acid, p-coumaric acid, p-hydroxybenzoic acids, caffeine, theobromine, theophylline, harmine, harmane, yohimbine, berberine, noscapine, and papaverine (Tripathi et al. 2020; Tiwari et al. 2015)	TNF-α-induced increases in CCL5 while attenuating the increase in CCL2 expression and NF-κB activation increase in dendrite growth markers, KLK8, and MAP2 (Grunz-Borgmann et al. 2015; Konar et al. 2019)	Alzheimer's disease (Konar et al. 2019)

factor κB (NF-κB) activation (Kim et al. 2009; Sharma et al. 2020). Vitamin E and C intake are inversely associated with the risk of PD (Hantikainen et al. 2021). *Phyllanthus emblica* is an excellent source of vitamin C. Research indicates that *Phyllanthus emblica* reduces kainic acid-induced elevations of TNF-α in the brain, improving cognitive function levels in the brain and improving the cognitive deficit (Gaire and Subedi 2014). In neurodegenerative disorders, *Phyllanthus emblica* has proved to be beneficial due to its antioxidant, cholesterol-lowering, and anti-inflammatory properties (Husain et al. 2019; Uddin et al. 2016).

Borneol is a natural compound found in *Blumea balsamifera* that acts as blood–brain barrier permeability in the central nervous system. Borneol is an effective agent that can improve drug delivery to the brain: neurological function scores (NFS) and the cerebral infarction area (Kulkarni et al. 2021; Chen et al. 2019). Thus, *Blumea balsamifera* has the potential to provide neuroprotection for a variety of neurological disorders.

Asparagus racemosus ethanolic extract has been shown to enhance brain-derived neurotrophic factor (BDNF), as well as estrogen receptors (ERs) (Lalert et al. 2018). In molecular docking study involving *Asparagus racemosus (Wild.),* SARS-CoV-2, the NSP15 Endoribonuclease and Spike Receptor-binding domain was identified. In terms of their effectiveness against the spike receptor-binding domain and NSP15 endoribonuclease, asparoside-C, asparoside-D, and asparoside-F are the most effective (Chikhale et al. 2020). *Asparagus racemosus* phytocompounds exhibit adaptogenic, neuroprotective, antioxidant, anti-inflammatory, and nootropic properties without causing side effects. It may be a possible treatment for neurological disorders such as stress, anxiety, depression, and epilepsy (Majumdar et al. 2021).

Cannabis sativa L is a medicinal herb used in treating a variety of diseases and neurological disorders (Mechoulam 2019). The main neuroprotective ingredients found in cannabis are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The neuroprotective properties of cannabinoids have led to them being referred to as the "Aspirin of the 21st century" (Baker et al. 2003). A hypothesis study on cannabidiol against SARS-CoV-2 proposed that it exerts immunomodulatory and anti-inflammatory effects, as well as decreasing uncontrolled cytokine production responsible for acute lung injury (Esposito et al. 2020). Cannabidiol has been suggested as a support drug against the COVID-19 pandemic with precaution (Paland et al. 2021; Anil et al. 2021).

Convolvulus prostratus is commonly known for its neuro-modulating properties. A number of phytocompounds from *Convolvulus prostratus*, including 4′-methoxy kaempferol, 7-methoxy quercetin, convolamine, scopoletin, and hydroxy-cinnamic acid, are responsible for neuroprotective effects in the brain (Alshoushan et al. 2021). An extract of *Convolvulus prostratus* modulates IL-1b, IL-6, TNF-a, alanine transaminase, and aspartate transaminase. Ayurveda shows that *Convolvulus prostratus* improves anxiety, irritability, inability to relax, lack of concentration, disturbed sleep, loss of memory, palpitations, headaches, dry mouth, upset stomach, and restlessness (Belwal et al. 2020).

Swertia chirata has traditionally been used in India to boost appetite and as a febrifuge (Liu et al. 2017). The herb's methanol extract is reported to have anti-

diabetic activity because it contains mangiferin, amarogentin, amaroswerin, sweroside, and swertiamarin as active constituents (Suryawanshi et al. 2009). Chirata sweat is known to be effective in the treatment of hepatitis, liver disorders, inflammation, chronic fever, malaria, anemia, GIT disorders, hypertension, mental disorders, and diabetes (Kumar and Van Staden 2016). The therapeutic potential of bellidifolin from *Swertia chirayita* has been explored for the treatment of inflammatory-mediated immune deficiency (Hu et al. 2019).

Traditional Indian medicine uses *Vitex negundo Linn.,* for treating respiratory and inflammatory disorders. Vitegnoside extracted from *Vitex negundo* inhibited p38 MAPK/MK2, JNK/c-Jun, and downstream NF-κB inflammatory transduction. In a study on the effect of vitegnoside from *Vitex negundo* on Alzheimer's disease, it was found that vitegnoside promoted neuroprotection by enhancing cell viability, maintaining cytomembrane integrity, and maintaining nuclear homogeneity (Wang et al. 2019).

Physiochemical analyses have demonstrated that crude extracts from *Nyctanthes arbor-tristis* have potential anti-inflammatory, anti-malarial, anti-viral, and immunostimulatory properties (Agrawal and Pal 2013). Researchers note that aqueous leaf extracts from *Nyctanthes arbor-tristis* are the most potent immunomodulators (Bhatia and Kaur 2001).

The herb *Centella asiatica* is well-known for its use in treating mental disorders in India and China. It is believed that triterpene derivatives like asiatic acid, madecassic acid, asiaticoside, madecassoside, and Brahmic acid provide positive effects on the aging brain (Samy and Chow 2011; Orhan 2012). Ethanolic extracts have been found to increase neural development (nerve growth factor (NGF) in human SH-SY5Y cell lines) (Soumyanath et al. 2005). This herb was traditionally used in memory enhancers and for treating Alzheimer's disease (Orhan et al. 2013).

Curcuma longa has been studied for its antidepressant properties. *Curcuma longa* contains curcumin, which has been found to be effective against neurological disorders such as Alzheimer's and multiple sclerosis (Witkin and Li 2013; Witkin et al. 2013). There is evidence that curcumin can effectively treat fearful or traumatic memories when used alone or in combination with existing medications (Monsey et al. 2015). The curcumin compound interacts directly and indirectly with various transcription factors such as nuclear factor kappa B (NF-κB), activator protein 1 (AP-1), β-catenin, and signal transducer and activator of transcription (STAT) proteins (Witkin et al. 2013; Liu et al. 2014; Shishodia et al. 2007). Additionally, it can act as a partial agonist of peroxisome proliferator-activated receptor-γ (PPAR-γ), a ligand-activated transcription factor involved in neurological disorders and anti-inflammatory signaling pathways. The nuclear receptor PPAR-γ affects metabolism, reproduction, and immune response (Bernardo et al. 2021). In addition to curcumin, other compounds in turmeric include digalloyl-hexoside, caffeic acid, hexoside, curdione, coumaric acid, caffeic acid, sinapic acid, quercetin-3-D-galactoside, casuarinin, bisdemethoxycurcumin, curcuminol, demethoxycurcumin, isorhamnetin, valoneic acid, and curcumin. Their therapeutic value varies according to the disease (Sabir et al. 2021; Maithili KarpagaSelvi et al. 2020). Furthermore, there is scientific evidence that curcumin may have a bioactive role against SARS-

CoV-2 infection as well (Babaei et al. 2020; Zahedipour et al. 2020; Rattis et al. 2021).

Ocimum tenuiflorum is a traditional herb used to prevent and treat the common cold, cough, headache, fever, influenza, sore throat, bronchitis, malarial fever, and migraine headaches (Joshi et al. 2017; Iqbal Chowdhury et al. 2020). *Ocimum tenuiflorum* oil contains 50.4% eugenol, ursolic acid, caryophyllene, linalool, and 1,8-cineole (Bhavya et al. 2018). Ocimumoside A and B are used for treating neurological disorders (Singh and Chaudhuri 2018). There is strong evidence that the daily administration of 10 g of an aqueous extract of fresh tulsi leaves for 2 weeks results in symptomatic improvement in patients with acute hepatitis viral infection (Jamshidi and Cohen 2017).

11.5 Conclusions

During the COVID-19 pandemic, the demand for medicinal plants was found to increase significantly. Among them, herbs such as *Curcuma longa, Ocimum tenuiflorum,* and *Withania somnifera* are gaining popularity as immune boosters against COVID-19 infection. Theoretically, SARS-CoV-2 causes inflammation in the body, which is controlled primarily by adaptive immune responses. The SARS-CoV-2 enters the cell through the ACE-2 receptor and is recognized by the toll-like receptor 7 (TLR-R) present in the endosome (Poulas et al. 2020). As a result, alpha interferon, TNF-alpha, as well as IL-12 and IL-6, are produced, and $CD8^+$ cytotoxic T cells are formed, and through $CD4^+$ helper T cells, antigen-specific B cells and antibodies are produced (Ahmadpoor and Rostaing 2020). Antibodies against unknown or known pathogens are produced by B cell receptors (BCRs), which recognize the pathogenic attack, counter-invading pathogens, and provide long-term protection against them (Nielsen and Boyd 2018). The immune system serves as the body's complete defense against pathogens. It is now clear that inborn medicinal herbs promote the immune system through various pathways against infection and inflammation. Many studies support the study objective, but there are still some gaps. Medicinal plants have the potential to treat neurological disorders at an affordable price in COVID-19 or post-COVID-19 patients. It is essential for a clear understanding of comprehensibility to conduct clinical trials on herbs and their secondary metabolisms, as well as their effects on various neurological disorders. Biomarkers, neuroradiological findings, and pathobiological mechanisms need to be re-examined to find the most suitable drugs. The interaction between humans and herbs, and the mechanism of action, should also be re-examined. The therapeutic potential of herbs for neurological disorders requires further mechanistic studies using modern scientific techniques and approaches. It is imperative to conduct further animal studies and clinical trials to explore how these herbs may help alleviate neurological disorders in COVID-19 patients.

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Chapter 12
Glycyrrhizae Radix et Rhizoma (Gan Cao) for the Management of COVID-19

Lin Ang, Eunhye Song, Hye Won Lee, and Myeong Soo Lee

12.1 Background

12.1.1 General Description

Glycyrrhizae Radix et Rhizoma is considered one of the most widely used medicinal plants for its health benefits. The Glycyrrhiza genus under the Fabaceae family has about 20 species that are mostly found in Asia, Europe, North America, and South America continents, and among them, 8 species are found in China (Li et al. 2020). The dry root and rhizome of the three recognized Glycyrrhiza species—*Glycyrrhiza uralensis* Fisch, *Glycyrrhiza glabra* L., and *Glycyrrhiza inflata* Batal—is referred to as Glycyrrhizae Radix et Rhizoma (glycyrrhiza), commonly known as licorice or liquorice, and also called *Gan Cao* in China. Traditional medicine uses glycyrrhiza widely to relieve coughs or to treat diverse illnesses such as hepatitis, influenza, and gastric ulcer (Guo et al. 2014; Pastorino et al. 2018). Glycyrrhiza has great economic potential, and its extract has been used widely as an ingredient in food, cosmetics, or tobacco (flavor) (Pastorino et al. 2018; Güçlü-Ustündağ and Mazza 2007; Isbrucker and Burdock 2006).

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12.1.2 History of Pharmacological Use of Glycyrrhiza

From the earliest days of recorded history, glycyrrhiza (primarily the species *Glycyrrhiza glabra* L., Leguminosae) has been used as a remedy. Historical records from various geographical regions and periods noted its extensive use (Armanini et al. 2002). The earliest reported use of glycyrrhiza for medicinal purposes dates back to ancient Assyrian, Egyptian, Chinese, and Indian cultures (Chopra and Chopra 1994; Thompson 1930). In addition, Greek sources indicate that glycyrrhiza was first used as a drug in Europe (Table 12.1) (Fiore et al. 2005). The plant's name is derived from two Greek words: *glukus* (sweet) and *rhiza* (root).

12.1.3 Comparison with Traditions of Glycyrrhiza Use outside Europe

Ayurveda of the Indian subcontinent and the traditional medicine of China are the two major sources of traditional herbal medicinal knowledge outside of Europe. Glycyrrhiza is a common ingredient added to most herbal formulas in China. The oldest Chinese herbal classic, *Shennong Bencao Jing (The Divine Farmer's Classic of Materia Medica)*, which dates back to 200 BC, mentions the usage of glycyrrhiza. This work, according to mythology, is grounded on sources that date back to Emperor Shennong (around 2700 BC). Some of the described symptoms were widespread in Europe, including coughing, palpitations, pharyngitis, gastric pain, digestive tract ulcers, and sores. Additionally, the use of glycyrrhiza for drug and food poisoning intoxication is documented in the book (Fiore et al. 2005).

Ayurveda makes significant use of the latter glycyrrhiza recommendation. This medical knowledge includes phytotherapy, which was first formalized in India around 450 BC, although the oldest existing Sanskrit manuscript is from roughly 500 AD (Wujastyk 2003). In addition to its use in antidote mixes for diverse acute and chronic poisonings, *Glycyrrhiza glabra* has other uses that have been documented in Sanskrit, including voice improvement, viral respiratory tract infections, wound infections, surgical ear wounds, hemorrhaging wounds caused by bloodletting, and acute and chronic liver diseases such as hepatitis (Thyagarajan et al. 2002).

Antiviral effects are discussed in European, Indian, and Chinese documentations in the context of virally caused voice alterations in the larynx, viral infection-related coughs and pharyngitis, viral skin illnesses including condyloma and ulcers, and viral hepatitis.

Table 12.1 History of use regarding glycyrrhiza

Date	Country	Author	Documented information
4th–3rd century BC	Greece	Theophrastus (Philosopher, botanist/4th–3rd century BC)	Suggested that the Greeks gained knowledge of the pharmacological applications of glycyrrhiza from the Scythians and called it "Scythian root"
1st century AD	Italy	Pedanius Dioscorides (Greek physician and pharmacognosist in the Roman army/ca. 40–90 AD)	Listed glycyrrhiza among the 650 medicinal plants included in Medical Matters and categorized plants based on their medicinal therapeutic attributes
1st century AD	Italy	Pliny the elder (23–79 AD)	Provided comprehensive information on glycyrrhiza in Natural History and recommended licorice for treating asthma, sore throat, mouth ulcer, and sterility
1st century AD	Italy	Aulus Cornelius Celsus (around 25 BC–50 AD)	Reported the beneficial effects of glycyrrhiza
1st century AD	Italy	Scribonius Largus (2–52 AD),	Reported the beneficial effects of glycyrrhiza
2nd century AD	Italy	Claudius Galen (129–211 AD),	Reported the beneficial effects of glycyrrhiza
5th century AD	Italy	Marcellus Empiricus (4th/5th century AD)	Reported the beneficial effects of glycyrrhiza
5th century AD	Italy	Cassius Felix (5th century AD)	Reported the beneficial effects of glycyrrhiza
6th–7th century AD	Spain	Saint Isidor (560–636 AD)	Addressed the origin of the term Glycyrrhiza in *Etymologies or Origins*
8th–9th century AD	Italy	School of Salerno (8th–9th century AD)	Examined glycyrrhiza and its pharmacological properties in their work *Rule of Health* (*Regimen sanitatis)*
10th–11th century AD	Iran	Ibn Sina/"Avicenna" (980–1037 AD)	Included glycyrrhiza in *The Canon of Avicenna*, which was considered an important recapitulation of medical knowledge and influenced Europe
12th century AD	Germany	Hildegard von Bingen (1098–1179)	Compilation of a medical treatise, *Cause et cure*, integrated herbal knowledge including glycyrrhiza
13th century AD	Syria	Abu Mohammed Abdallah ibn Ahmed al-Malaqi/"Ibn Al Baytar" (around 1197–1248)	Covered more than 1400 substances of plant, food, and drugs in his encyclopedia, *The Book of Medicinal and Nutritional Terms*
14th century AD	Italy	*Jacobus Philippus* (1390–1400)	Documented the use of glycyrrhiza in *El Libro Agreg'a de Serapiom*

(continued)

Table 12.1 (continued)

Date	Country	Author	Documented information
15th–16th century AD	Germany	Leonhart Fuchs (1505–1566)	Created a botanical nomenclature and described glycyrrhiza
16th century AD	Italy	Castore Durante (1529–1590)	Covered more than 900 herbal species in his work, *Herbario Nuovo (New Herbarium)*, ordered alphabetically according to common names, explained the applications and uses of herbs, which included glycyrrhiza
17th century AD	United Kingdom	Nicholas Culpeper (1616–1654)	Documented medical uses of glycyrrhiza in *Complete Herbal*
18th century AD	Italy	Guiseppe Donzelli	Described glycyrrhiza and explained its etymology as sweet root
18th century AD	Sweden	Carl von Linne (1707–1778)	Classified plants into genera and species and discovered three distinct species among the genus Glycyrrhiza: *Glycyrrhiza glabra, Glycyrrhiza echinata*, and *Glycyrrhiza hirsute*

12.2 Active Components of Glycyrrhizae Radix et Rhizoma

The triterpenoid saponin glycyrrhizin, which is also referred to as glycyrrhizic acid or glycyrrhizinic acid, is the primary active component in glycyrrhiza and is typically present in concentrations ranging from 6% and 10% (Li et al. 2020; Murray 2020). Flavonoids, such as isoliquiritigenin, liquiritigenin, isoliquiritin, glabrol, kumatakenin, and licochalcone A, B, and E, are also regarded as the glycyrrhiza's primary component. Glycyrrhiza has a broad range of pharmacological actions for its effects on the immune system, central nervous system, endocrine and cardiovascular systems, functions of the liver and kidneys, (Zhao et al. 2018; Rauchensteiner et al. 2005; Lin et al. 2005) as well as anti-inflammatory, anticancer, anti-virus, antibacterial, and so forth (Shon et al. 2004; Kim et al. 2004).

Glycyrrhiza has a significant amount of triterpenoid saponins (Table 12.2). In the study of active components of glycyrrhiza, 77 triterpene saponins were isolated. Various types of triterpenoid saponins can be found in each species of glycyrrhiza. The species *G. uralensis* isolated 50 oleanane-type pentacyclic triterpene saponins, *G. glabra* isolated 38, and *G. inflate* isolated only 13 saponins.

Table 12.2 Types of triterpenoid saponins found in Glycyrrhizae Radix et Rhizoma

Glycyrrhiza species	Components found
G. uralensis	Glycyrrhizin, Licoricesaponin G2, Araboglycyrrhizin, Uralsaponin B, Licoricesaponin B2, Licoricesaponin C2, Licoricesaponin H2, Licoricesaponin J2, Licoricesaponin K2, 18*β*-glycyrrhizic acid, Licoricesaponin M3 (uralsaponin T), Licoricesaponin N4, Uralsaponin V, 3*β*-*O*-*β*-D-glucuronopyranosyl-glycyrrhetinic acid, Licoricesaponin A3, Licoricesaponin E2, 22*β*-acetoxylglycyrrhizin, Uralsaponin D, 22*β*-acetoxyl-glycyrrhaldehyde, Licoricesaponin D3, Licoricesaponin F3, Licoricesaponin L3, 3*β*-*O*-[*β*-D-glucuronopyranosyl-(1 → 2)-*β*-D-glucuronopyranosyl]-glycyrretol, 3*β*-*O*-[*β*-D-glucuronopyranosyl-(1 → 2)-*β*-D-glucuronopyranosyl]-olean-9,12-diene-30-oic acid, Uralsaponin C, Uralsaponin E, Uralsaponin F, 3*β*-*O*-[*β*-D-glucuronopyranosyl-(1 → 2)-*β*-D-glucuronopyranosyl]-glycyrrhetic acid, Uralsaponin M, Uralsaponin N, Uralsaponin O, Uralsaponin P, Uralsaponin Q, Uralsaponin R, Uralsaponin S, Uralsaponin U, Uralsaponin W, Uralsaponin X, Uralsaponin Y, 3*β*-*O*-[*β*-D-glucuronopyranosyl-(1 → 2)-*β*-D-glucuronopyranosyl] -24-hydroxyglabrolide, Macedonoside E, 22*β*-acetyl-uralsaponin C, Glyuralsaponin A, Glyuralsaponin B, Glyuralsaponin C, Glyuralsaponin D, Glyuralsaponin E, Glyuralsaponin F, Glyuralsaponin G, Glyuralsaponin H
G. glabra	Glycyrrhizin, Licoricesaponin G2, Araboglycyrrhizin, Uralsaponin B, Licoricesaponin B2, Licoricesaponin C2, Licoricesaponin H2, Licoricesaponin J2, Licoricesaponin K2, 18*β*-glycyrrhizic acid, Licoricesaponin M3 (uralsaponin T), Licoricesaponin N4, Uralsaponin V, 3*β*-*O*-*β*-D-glucuronopyranosyl-glycyrrhetinic acid, Apioglycyrrhizin, Macedonoside A, Licoricesaponin O4, Licoricesaponin M1, Licoricesaponin M2, Licoricesaponin M3, Licoricesaponin M4, 30-hydroxyglycyrrhizin, Glycyrrhizin-20-methanoate, 24-hydroxyglucoglycyrrhizin, Rhaoglycyrrhizin, 11-deoxorhaoglycyrrhizin, Rhaoglucoglycyrrhizin, Rhaogalactoglycyrrhizin, 11-deoxo-20α-glycyrrhizin, 20α-galacturonoylglycyrrhizin, 20-α-rhaoglycyrrhizin, Glabasaponin A, Glabasaponin B, Glabasaponin C, Glabasaponin D, Glabasaponin E, Glabasaponin F, Glabasaponin G
G. inflate	Glycyrrhizin, Licoricesaponin G2, Araboglycyrrhizin, Licoricesaponin A3, Licoricesaponin E2, 22*β*-acetoxylglycyrrhizin, Uralsaponin D, 22*β*-acetoxyl-glycyrrhaldehyde, Apioglycyrrhizin, Macedonoside A, Licoricesaponin P2, licoricesaponin Q2, 24-hydroxy-licoricesaponin E2

12.3 Biological Activities

Glycyrrhiza has been found in a number of studies to have pharmacological benefits against cancer, viral infection, oxidative stress, inflammation, and immunoregulation (Li et al. 2019). Bioactive properties such as hepatoprotective, anti-inflammatory, antibacterial, antiviral, and anticancer effects are highly correlated to the herb's active components. Although most pharmacology research focused on glycyrrhizin and glycyrrhetinic acid, glycyrrhiza also contains a large number of flavonoids with substantial pharmacological effects on their own.

12.3.1 Anti-Inflammatory Properties

Glycyrrhiza possesses notable anti-inflammatory and anti-allergic properties (Kuroyanagi and Saito 1966; Cyong and Otsuka 1982) As glycyrrhizin or glycyrrhetinic acid attaches to glucocorticoid receptors, the majority of glycyrrhiza's anti-inflammatory effects have been related to cortisol effects. Despite so, many of the herb's activities inhibit or suppress cortisol (Kumagai et al. 1967a). Tryptophan oxygenase activation, hepatic cholesterol synthesis stimulation, hepatic glycogen synthesis stimulation, thymus atrophy inhibition, etc. are some of the antagonistic actions of cortisol. Glycyrrhizin, nevertheless, supports cortisol's regulation of the production of antibodies, the stress response, and inflammation. The glycyrrhiza's primary impact on glucocorticoid metabolism is probably brought about by the reduction of 5-β-reductase activity, which lengthens cortisol's half-life. Additionally, glycyrrhiza can enhance cortisol to convert it into cortisone (van Uum et al. 2002).

According to an animal study by Wang et al., it was found that glycyrrhizin reduced the inflammatory response caused by lipopolysaccharide (LPS) in mouse endometrial epithelial cells by blocking the TLR4 signaling pathway (Wang et al. 2017). In Akamatsu et al. in vitro study (Akamatsu et al. 1991), it was reported that glycyrrhizin prevented neutrophils from generating reactive oxygen species, a type of inflammatory mediator. In addition, glycyrrhizin may block the expression of high-mobility group protein B1 and the consequent generation of inflammatory cytokines in Sprague-Dawley rats after subarachnoid hemorrhage, as reported by Li et al. (2017). In Pang et al. study, inhibiting HMGB1 with glycyrrhizin reduced brain damage following diffuse axonal injury (DAI) in SD rats by acting as an anti-inflammatory (Pang et al. 2016). According to research by Li et al. using lipopolysaccharide (LPS)-induced inflammation mouse model, total saponins of glycyrrhiza may have an anti-inflammatory mechanism that involves inhibiting primary enzymes in the arachidonic acid metabolism pathway and reducing the release of inflammatory factors (Li et al. 2010).

12.3.2 Antiviral and Antimicrobial Properties

Studies have shown that glycyrrhizin and glycyrrhetinic acid induce interferon (Abe et al. 1982). Interferons attach to the surface of cells, where they trigger the production of intracellular proteins that stop viral DNA from being transcripted, resulting in antiviral effects.

Glycyrrhizin has a wide spectrum of antiviral activities and could be used as a natural antiviral agent (Moghimipour et al. 2015). It has been demonstrated to inhibit the growth of multiple DNA and RNA viruses in cell cultures, including severe acute respiratory syndrome coronavirus (SARS-CoV), human immunodeficiency virus (HIV), vaccinia, herpes simplex virus (HSV), Newcastle disease, Epstein-Barr,

and vesicular stomatitis viruses, and to irreversibly inactivate HSV-1 (Cinatl et al. 2003; Sasaki et al. 2002; Lin 2003; Pompei et al. 1980). As it reduces the activity of the virus while simultaneously increasing the activity of the host cell, glycyrrhizin is an effective antiviral component against HIV, hepatitis B, coxsackievirus B3, enterovirus 71, HSV, and avian influenza A-H5N1 (Wang et al. 2015).

Upon administration of glycyrrhizin, the survival rate of mice with herpetic encephalitis increased approximately 2.5-fold, while HSV-1 replication was reduced in the control group (Sekizawa et al. 2001). Other glycyrrhiza components also exhibited immunomodulatory properties (Barfod et al. 2002). It has been demonstrated that glycyrrhizin blocks the replication of the SARS-CoV and varicella zoster virus in vitro (Baba and Shigeta 1987; Hoever et al. 2005). Wolkerstorfer et al. discovered that glycyrrhizin prevented the uptake of the influenza A virus into the cell (Wolkerstorfer et al. 2009). Glycyrrhizin also has a direct impact on anti-hepatitis B by influencing the extracellular secretion of hepatitis B surface antigen, reducing liver impairment in people with chronic hepatitis B, and eventually enhancing immunity. Additionally, HIV can be considerably slowed down in its growth by glycyrrhizin via activating the immune system (Sun et al. 2019).

Alcohol extracts from glycyrrhiza demonstrated in vitro antibacterial activity against *Streptococcus mutans*, *Haemophilus influenzae*, *Candida albicans, Bacillus subtilis, Staphylococcus aureus, Mycobacterium smegmatis*, *Moraxella catarrhalis*, and *Streptococcus pyogenes* (Fukai et al. 2002a, b; Tsukiyama et al. 2002; Mitscher et al. 1980). In general, the saponins have less antibacterial activity than the isoflavonoid components, which account for the majority of the antimicrobial activities.

12.3.3 Anticancer Properties

The anticancer effects of glycyrrhiza components are extremely diverse with flavonoids and coumarins being the most active components (Wang and Nixon 2001). In an animal study (Takahashi et al. 2004), isoliquiritigenin has been found to reduce colon cancer in mice. It has been demonstrated that isoliquiritigenin dramatically reduces the growth of breast and prostate cancer cell lines (Kanazawa et al. 2003; Maggiolini et al. 2002). In addition, isoliquiritigenin inhibited leukopenia brought on by 5-fluorouracil treatment and greatly decreased pulmonary metastasis (Yamazaki et al. 2002). Licocoumarone, a coumarin compound in glycyrrhiza, was also found to cause cell apoptosis (Watanabe et al. 2002).

As demonstrated by Deng et al., glycyrrhizin significantly decreased the expression of thromboxane synthase (TxA2) and proliferating cell nuclear antigen, reversed liver and kidney damage in tumor-bearing mice, and may have this impact through inhibiting the TxA2 pathway (Deng et al. 2017). Additionally, dipotassium glycyrrhizinate also had anticancer effects on the glioblastoma cell lines by enhancing apoptosis and decreasing proliferation. The antitumor action of dipotassium glycyrrhizinate is correlated to NF-B suppression, where miR16 and miR146a are, respectively, mediated by IRAK2 and TRAF6 (Bonafé et al. 2019). The cytotoxic

assay revealed no cytotoxic effect for glycyrrhizin, whereas their equivalent aglycones had shown cytotoxic activities against human cervical cancer cells and human breast adenocarcinoma cells (Zheng et al. 2010).

12.3.4 Hepatoprotective Properties

There have been numerous in vitro and in vivo studies reporting on the potential mechanisms by which glycyrrhiza saponins present hepatoprotective actions. Through multitargeting therapeutic mechanisms such as anti-inflammation, anticancer, antioxidative stress, antisteatosis, antifibrosis, immunoregulation, and drug–drug interactions, glycyrrhizin has been shown to prevent liver disease and reduce drug-induced liver damage (Li et al. 2019).

In a study conducted using BALB/c mice, Tsuruoka et al. (Fukai et al. 2002a) demonstrated that glycyrrhizin could prevent the increase in alanine aminotransaminase and aspartate aminotransaminase while decreasing hepatocyte degeneration and inhibiting inducible nitric oxide synthase mRNA expression in the mice liver (Tsuruoka et al. 2009). Lee et al. observed that glycyrrhizin mitigated carbon tetrachloride (CCl_4)-induced liver damage in mice, most likely via downregulating proinflammatory mediators and inducing heme oxygenase-1 (Lee et al. 2007). According to Nakamura et al., glycyrrhizin inhibited soluble enzyme release from CCl_4-induced rat hepatocytes (Nakamura et al. 1985). Sato et al. discovered that glycyrrhizin could alter the expression of hepatitis B virus-related antigens on hepatocytes (Sato et al. 1996). Moreover, Lin et al. discovered that a three-day pretreatment with glycyrrhizin protected Sprague-Dawley rats from retrorsine-induced liver injury (Lin et al. 1999). Wistar rats are somewhat protected from ischemia-reperfusion-induced liver injury by glycyrrhizin (Nagai et al. 1992). Orazizadeh et al. also showed that glycyrrhizin successfully protects Wistar rats from $NTiO_2$-induced hepatotoxicity (Orazizadeh et al. 2014).

Other triterpenoid saponins found in glycyrrhiza also demonstrated hepatoprotective properties. Glyuralsaponins B and H exhibited antioxidant effects against cysteine-assisted Fe^{2+}-induced liver microsomal lipid peroxidation (Liu et al. 2019). In addition, galactosamine and carbon tetrachloride-induced liver damage could be prevented by glycyrrhetinic acid. The enzymatic action of nicotine adenine disphosphonucleotide also resulted in the inhibition of nonenzymatic lipid peroxidation and the formation of free radicals (Kiso et al. 1984).

12.3.5 Others

Glycyrrhiza saponin monomers have a variety of additional pharmacological and physiological functions. Glycyrrhizin was found to have immunomodulatory, neuroprotective, and antioxidant properties (Ojha et al. 2016; Ming and Yin 2013;

Akman et al. 2015). Furthermore, glycyrrhizin may treat allergic rhinitis, by partly altering the Th1/Th2 balance by inhibiting the OX40 receptor and by boosting the activation of regulatory T cells (Fouladi et al. 2018).

Glycyrrhizin also has a different effect on estrogen metabolism by inhibiting estrogen action when the levels are too high and potentiating estrogen action when the levels are too low (Kumagai et al. 1967b). It has been demonstrated that glycyrrhetinic acid counteracts many of the estrogen's effects, especially exogenous estrogens (Kraus and Kaminskis 1969). Such estrogenic action is due to its isoflavonoid component which appears to have more estrogenic activity than the estrogen antagonism of glycyrrhetinic acid (Tamir et al. 2001). Notably, these same substances also slow down breast cancer cell growth (Maggiolini et al. 2002).

12.4 Clinical Applications of Glycyrrhizae Radix et Rhizoma

Glycyrrhiza is included frequently in traditional Eastern medicine, and it has been a staple of Western herbal medicine for decades. The most common clinical applications of glycyrrhiza containing glycyrrhizin are in the treatment of viral diseases (Murray 2020). Due to the diversity of the pharmacological effects, glycyrrhiza has also been used in many other diseases.

12.4.1 Obesity and Metabolic Syndrome

Medications containing glycyrrhetinic acid may be useful in treating a variety of metabolic syndrome-related symptoms. In a pilot investigation (Armanini et al. 2003), normal-weight participants consuming glycyrrhetinic acid-containing commercial preparations reported a reduction in body fat mass. In another study (Fuhrman et al. 2002), moderately hypercholesterolemic patients supplemented with glycyrrhiza extract for 1 month decreased plasma susceptibility to oxidation, decreased systolic blood pressure, and increased resistance of plasma low-density lipoprotein.

In double-blind clinical research (Tominaga et al. 2009), overweight participants were randomly assigned to one of the four groups: low-dose licorice flavonoid oil (LFO), middle-dose LFO, high-dose LFO, and placebo. The participants in all LFO groups, except the placebo group, had considerably reduced body fat masses than at baseline, while the high-dose LFO group showed significant declines in body mass index and body weight.

Another study on LFO investigated its ability to improve the muscle mass of older people undergoing knee osteoarthritis rehabilitation and found that trunk muscular mass increased considerably more in the LFO group compared to those in the

placebo group. Moreover, the percentage of body trunk fat and body fat in the LFO group was also lowered (Kinoshita et al. 2017).

12.4.2 Gastric and Duodenal Ulcers

Numerous clinical trials have demonstrated that deglycyrrhizinated licorice (DGL) is an effective antiulcer agent over the years. It has been demonstrated that DGL is a highly effective treatment for stomach ulcers (Turpie et al. 1969; Rees et al. 1979; Kassir 1985). In a clinical trial (Turpie et al. 1969), patients with stomach ulcers were given DGL or a placebo, and those receiving DGL experienced a considerably higher decrease in ulcer size with 44% of complete healing. DGL has also been proven to be more effective in comparison to cimetidine, ranitidine, and antacids in both the short-term treatment and maintenance of patients with peptic ulcers in several studies (Kassir 1985; Morgan et al. 1982, 1985). DGL is recommended to prevent gastric ulcers in patients requiring long-term treatment as it has been demonstrated in clinical studies to reduce the gastrointestinal bleeding caused by ulcerogenic medicines (Rees et al. 1979).

Duodenal ulcers can benefit from DGL as well. In previous research (Tewari and Wilson 1973), individuals with severe duodenal ulcers who received DGL treatment significantly improved, and no patients needed surgery after one year follow-up period. In another study (Kassir 1985), patients with verified chronic duodenal ulcers had their therapeutic effects of DGL compared to those of antacids or cimetidine. The healing rates were similar between the groups, although the DGL group saw fewer relapses than those who took cimetidine or antacids. These findings imply that DGL is a superior duodenal ulcer treatment, in addition to its protective properties and extremely low toxicity.

12.4.3 Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome

Preparations containing glycyrrhizin are promising in the treatment of acquired immunodeficiency syndrome (AIDS) and other human immunodeficiency virus (HIV)-related diseases. In double-blind clinical research on hemophiliac patients with HIV (Ikegami et al. 1993), none of the patients who received the glycyrrhizin progressed to immunological abnormalities or developed AIDS. The group without glycyrrhetinic acid, in contrast, saw a decrease in helper and total T-cell counts as well as antibody levels, and some patients even developed AIDS. In a different study (Ikegami et al. 1989), HIV-positive individuals without AIDS took glycyrrhizin for 1–2 years, and none of them developed AIDS-related symptoms. Glycyrrhizin causes an immediate improvement in immunological function in HIV-positive and

AIDS patients. Another study where glycyrrhizin was administered intravenously to symptom-free HIV-positive individuals reported that the patients' T-helper cell counts increased and their liver function improved (Mori et al. 1989). In another study where AIDS patients were administered glycyrrhizin intravenously for 30 days (Hattori et al. 1989), a decrease or absence of the P24 antigen indicating active disease was observed. These studies on HIV-positive and AIDS patients have produced favorable findings.

12.4.4 Gynecological Issues

Another common application of glycyrrhiza is in the treatment of gynecological conditions, specifically premenstrual syndrome (PMS) and menopause. Given that glycyrrhizin has antiestrogenic actions and inhibits the breakdown of progesterone, administration of glycyrrhiza 2 weeks before the onset of menstruation may lessen PMS symptoms. Clinical research demonstrated that herbal combinations containing glycyrrhiza are also beneficial for dysmenorrhea (Tanaka 2003). The potential of glycyrrhiza isoflavones to impede serotonin reuptake suggests that they may also have antidepressant effects in PMS (Ofir et al. 2003).

12.4.5 Others

Glycyrrhiza can be used to treat nearly all inflammatory and allergy conditions. In a double-blind clinical trial on postoperative sore throat (Agarwal et al. 2009), patients who had elective lumbar laminectomy were placed into two groups: gargling glycyrrhiza in water or water only before anesthesia. The occurrence and intensity of postoperative sore throat and post-extubation cough were lessened in the glycyrrhiza group compared to the water group.

Aphthous stomatitis is also a common ulcerative oral disease and DGL may promote healing effectively. In a study (Das et al. 1989), patients were directed to DGL mouthwash and most patients saw huge improvement within day 1 and complete recovery of the ulcers by day 3.

A review examined the potential use of the active components of glycyrrhiza in the treatment of rheumatoid arthritis via the cyclooxygenase (COX)-2/thromboxane A2 (TxA2) pathway (Huang et al. 2016). These active components have the potential to enhance the effects of non-steroidal anti-inflammatory drugs or disease-modifying antirheumatic drugs and also reduce their side effects by inhibiting the COX-2/TxA2 pathway, making them a potential add-on therapy for the treatment of rheumatoid arthritis.

12.5 Potential of Glycyrrhizae Radix et Rhizoma for the Management of COVID-19

The world is currently dealing with the coronavirus disease 2019 (COVID-19) pandemic, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As glycyrrhiza is widely accessible and generally safe, it is frequently used in traditional Eastern medicine to treat COVID-19 infections. Glycyrrhizin was found to have the potential to lessen the severity of a COVID-19 infection by hindering the number of entry sites and providing an anti-inflammatory mechanism independent of angiotensin-converting enzyme 2 (ACE2) (Murck 2020).

12.5.1 ACE2 Receptor as SARS-CoV-2 Entry Receptor

SARS-CoV-2 shares a high percentage of the genetic sequence of the SARS-CoV and has a similar cell entry receptor that is the angiotensin-converting enzyme II (ACE2) (Zhou et al. 2020). In the meantime, the SARS-CoV-2 infection shares many clinical resemblances with the SARS-CoV infection (Wang et al. 2020). Due to the similarities between SARS-CoV and SARS-CoV-2, the clinical experience and clinical research from SARS-CoV can be referred to treat SARS-CoV-2.

Recent studies suggest that SARS-CoV-2 and human ACE2 have strong correlations (Xu et al. 2020a; Wan et al. 2020). Letko et al. findings further validated that ACE2 is the receptor for SARS-CoV-2 as their findings found that the SARS-CoV-2 receptor-binding domain could only enter cells expressing ACE2 (Letko et al. 2020). Therefore, targeting ACE2 could be a hopeful potential method for preventing SARS-CoV-2 infection since virus entry depends on the host cell receptor.

12.5.2 Glycyrrhiza Anti-inflammatory Actions toward ACE2

Glycyrrhiza may be a good candidate for treating COVID-19 and merits additional investigation in light of the experience and lessons learned from the fight against SARS. Glycyrrhizin, a triterpene saponin with a variety of biological actions and pharmacological effects, has been in vitro shown to be active against SARS-associated coronavirus (Cinatl et al. 2003). Glycyrrhizin is reported to work best when given before and after the viral adsorption phase as it can prevent viral attachment and penetration (Fujii et al. 2004). Additionally, glycyrrhizin can obstruct the replication and/or cytopathogenic effects of several respiratory viruses (Cinatl et al. 2003; Michaelis et al. 2011).

ACE2 plays a protective role for lung tissue by inhibiting the lipopolysaccharide (LPS)-induced toll-like receptor 4 (TLR4) pathway, where ACE2 overexpression could reduce the LPS-induced inflammation (Kaparianos and Argyropoulou 2011;

Ye and Liu 2020). Consequently, the downregulation of ACE2 may be considered concerning. Here, the immunomodulatory properties of glycyrrhizin are important for its antagonistic action of TLR4-dependent mechanisms, as glycyrrhetinic acid has a TLR4 antagonistic action that lowers inflammation in a variety of tissues, including the lung (Yu et al. 2005). Additionally, in an LPS model of inflammation, glycyrrhizin caused a decrease in TLR4 expression in the heart and lung, accompanied by a considerable decrease in the secretion of cytokines (Seo et al. 2017). Accordingly, in a mice study (Yu et al. 2005), glycyrrhizin protects against the acute respiratory distress syndrome (ARDS) caused by the TLR4 activator. In a mouse model of *Streptococcus* aureus infection (Yao and Sun 2019), intraperitoneal treatment of glycyrrhizin also significantly reduced the expression of inflammatory markers in the lungs. These findings are consistent with other studies where glycyrrhizin or glycyrrhetinic acid could inhibit inflammatory pathways via TLR4 (Thakur et al. 2017; Vitali et al. 2015). Overall, glycyrrhizin may induce anti-inflammatory actions by inhibiting TLR4 activities while regulating ACE2 (Ingraham et al. 2020).

12.5.3 Other Potential Roles of Glycyrrhiza in COVID-19 Infection

Glycyrrhizin possesses cytokine-modulating activity and may potentially boost the immunological response (Xu et al. 2018). The proinflammatory cytokines are overproduced during a cytokine storm, which can worsen pathological damage in hosts (Liu et al. 2016). The severity of the disease was linked to the cytokine storm observed in critically ill COVID-19 patients (Huang et al. 2020). Therefore, it is crucially important to identify patients with cytokine storms and to intervene as soon as possible. During the SARS outbreak, glucocorticoids were frequently used in individuals with cytokine storm. Glucocorticoids have an anti-inflammatory impact and are prescribed to alleviate respiratory distress brought on by cytokine storms, but they also have an immunosuppressive effect that reduces the immune system's ability to remove viruses (Fujii et al. 2004). To avoid or lessen excessive cytokine storms in COVID-19 patients, glycyrrhizin is therefore anticipated to be administered in the early stages of the disease for a longer period with fewer side effects.

Antioxidants may be supportive in treating the cytokine storm brought on by infection since reactive oxygen species (ROS) influence inflammatory response (Liu et al. 2016). The buildup of intracellular ROS brought on by viral infection can be prevented by glycyrrhizin (Tong et al. 2020). Glycyrrhizin can inhibit the generation of ROS and inhibit the activation of signaling pathways which are known to be related to virus replication (Michaelis et al. 2011). Additionally, cytokine storms or prolonged inflammation due to SARS-CoV-2 can activate the complement and coagulation cascades, which may lead to the failure of many organs (Wang et al. 2020). Studies have shown that glycyrrhizin selectively inhibits thrombin

(Francischetti et al. 1997; Mendes-Silva et al. 2003). These findings suggest that glycyrrhizin may be effective against COVID-19 via multiple sites of action.

Conversely, bilateral diffuse alveolar damage with cellular fibromyxoid exudates can be seen in histological findings of COVID-19 (Xu et al. 2020b), where the impaired alveolar function may lead to hypoxia; therefore, inhibiting the hyperproduction of airway exudates is a promising strategy for preventing severe hypoxia. Notably, glycyrrhizin could also inhibit airway mucus hyperproduction (Nishimoto et al. 2010). Hence, glycyrrhizin may reduce hypoxia and alleviate clinical symptoms in individuals with COVID-19.

Additionally, glycyrrhizin could induce endogenous interferon which would prevent the transmission of viruses by preventing DNA and RNA viruses from replicating and by eradicating viral infections (Abe et al. 1982; Wang and Fish 2019). Hence, glycyrrhizin may also have an indirect effect in treating COVID-19. Besides, antiviral drugs for COVID-19 may also lead to drug-induced liver injury. In this context, glycyrrhizin could also play an adjunctive role in treating COVID-19 due to its hepatoprotective properties.

12.6 Conclusions

Glycyrrhiza may be a promising herb for the treatment of COVID-19. Over the years, total saponins or saponin monomers from glycyrrhiza have been explored and identified to have a variety of biological properties, including anti-inflammatory, antibacterial, antiviral, hepatoprotective, anticancer, and antioxidant actions. However, these pharmacological investigations on glycyrrhiza currently only include bioassays of a small number of saponin monomers. Additional research is required to examine the biological activity of additional triterpene saponins using in vitro and in vivo models. Due to the various pharmacological effect of glycyrrhiza, this herb is worth conducting more research to further validate its value in managing COVID-19, which is not necessarily to treat or prevent the disease, but to reduce the severity and symptomatology of COVID-19. Nevertheless, as the findings on biological actions drawn from in vivo and in vitro studies may not correspond with real-life clinical efficacy in patients, further assessments are needed to identify the optimal dosage and treatment regimen for the adequate application of glycyrrhiza in managing COVID-19.

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Chapter 13
COVID-19-Induced Kidney Disease: Ethnopharmacological Intervention to Ameliorate Kidney Damage and Improve Kidney Function

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Abbreviations

ACE2	Angiotensin-converting enzyme 2
ADME	Absorption, distribution, metabolism, excretion
AKI	Acute kidney injury
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CAT	Catalase
CBP	Complete blood picture
CCl_4	Carbon tetrachloride
COVID-19	Coronavirus disease 2019
CRRT	Continuous renal replacement therapy
CXCL	C-X-C motif chemokine ligand
DPP4	Dipeptidyl peptidase 4
eGFR	Estimated glomerular filtration
ERK	Extracellular signal related-kinases

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FGF	Fibroblast growth factor
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GPx	Glutathione peroxidase
GSH	Glutathione
ICU	Intensive care unit
IFN	Interferon
IL	Interleukin
IP10	Interferon gamma-induced protein 10
JAK	Janus kinase
KIM-1	Kidney injury molecule 1
L-FABP	Liver-type fatty acid-binding protein
MAPK	Mitogen-activated protein kinases
MCP	Monocyte chemoattractant protein
MDA	Malondialdehyde
MIP	Macrophage inflammatory protein
MNC	Mononuclear cells
mTOR	Mammalian target of rapamycin
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
PDGF	Platelet-derived growth factor
RBC	Red blood cell
RdRp	RNA-dependent RNA polymerase
RNA	Ribonucleic acid
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOD	Superoxide dismutase
STAT	Signal transducers and activators of transcription
TCM	Traditional Chinese Medicine
TGF	Transforming growth factor
TLR	Toll-like receptors
TMPRSS2	Transmembrane serine protease 2
TNF	Tumor necrosis factor
VEGF	Vascular endothelial growth factor

13.1 Introduction

The world saw an unprecedented event that began in the late December of 2019; a pandemic like never before; coronavirus disease 2019 (COVID-19). The first wave lasted till 2020, and the second, more fatal wave in 2021. Even now, many countries are still experiencing subsequent waves, India is now seeing a rise in cases and it is said to be the fourth wave. By late 2021, vaccines were rolled out and vaccination drives began. Notwithstanding, COVID-19 still possess a serious health threat.

The causative agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily infects the lungs, the respiratory system being the main target for COVID-19 disease. However, other organs and systems are known to be affected; the digestive system, renal system, cardiovascular system, and neural system, to name a few. Sometimes, SARS-CoV-2 directly infects the organs of these other systems. The inflammation produced in the body as a result of the SARS-CoV-2 infection is also responsible for negative effects on the other organ systems.

13.2 COVID-19 and Kidney Disease

The effect of COVID-19 disease on the renal system is undeniable, patients who have no history of kidney problems have been observed to develop kidney damage and reduction/loss of kidney function. A significant contributing feature is that a large group of severe COVID-19 patients also exhibit chronic co-existing conditions such as high blood pressure and diabetes, which greatly increase the risk of kidney disease (Coronavirus: kidney damage caused by COVID-19 2022). Studies have shown that kidney disease is prevalent in some COVID-19 patients at the time of admission itself, and many others develop acute kidney injury (AKI) during hospitalization (Cheng et al. 2020). According to the Kidney Disease Improving Global Outcome (KDIGO) criteria, the incidence of acute kidney injury in COVID-19 patients is 3–9% (Armaly et al. 2021). Reports of AKI in hospital settings, however, tell a different story; this rate of incidence varies and is often significantly higher. In hospital settings, AKI could be anywhere from 0% to 14.7%, the pooled incidence rate is 7%; and in ICU settings, this is higher still, 8.3–28.8%, pooled incidence rate being 19%, as evidenced by a meta-analysis of nine studies (Kaye et al. 2021). A study of 5994 hospitalized COVID-19 patients admitted to 13 academic and community hospitals in a metropolitan for about a month reported the occurrence of 36.6% AKI; 1993 patients suffered from AKI (Hirsch et al. 2020). A retrospective observational study of 3993 COVID-19 patients reported the incidence of 46% AKI; 1835 patients developed kidney injury (Chan et al. 2021). 23 out of 85 confirmed COVID-19 patients (27%) were found to suffer from AKI in one retrospective analysis (Batlle et al. 2020). In another prospective cohort study with 701 hospitalized COVID-19 patients, AKI was observed in 5.1% of patients (Armaly et al. 2021). Yet another observational retrospective study on 193 COVID-19 patients reported the occurrence of 23.3% AKI (Cheng et al. 2020). A single-center case series of 138 hospitalized patients the existence of 3.6% AKI among all patients (Allemailem et al. 2021). In another cohort, out of 63 COVID-19 patients, 32 patients (50.79%) had AKI (Wang et al. 2020). In a multi-centered retrospective observational study with 193 COVID-19 patients, among 128 non-severe COVID-19 patients, 12 (9%) had AKI. In the same study, among 65 severe COVID-19 patients, 43 (66%) suffered from AKI (Braun et al. 2020). A report of a study (single-centered, retrospective, observational study) of 710 critically ill COVID-19 patients, out of the 52 patients admitted into the ICU, 15 (29%) developed AKI (Li et al.

2020) A large cohort of 1099 COVID-19 patients reported a surprisingly low occurrence of AKI; 0.5% (Yang et al. 2020).

Several indications have been reported that point to altered kidney function and kidney injury during COVID-19 disease. Proteinuria, haematuria, altered CBP profiles, and reduction in estimated glomerular filtration (eGFR) have been reported in many COVID-19 patients (Armaly et al. 2021). The number of patients exhibiting proteinuria was varied, over a wide range of 26–63% in the different studies; 63% in 51 patients, 60% of 147 patients, 59% (on admission) of 193 patients, 53.9% of 193 patients, 43.9% (on admission) of 701 patients (Armaly et al. 2021; Kaye et al. 2021; Cheng et al. 2020; Braun et al. 2020; Guan et al. 2020; Gagliardi et al. 2020). Haematuria was also reported in COVID-19 patients, with different studies recording varying percent of incidence; 48% of 147 patients, 44% in 193 patients (on admission), 40.9% of 5449 patients, 26.7% out of 701 patients (on admission), 22.3% of 193 patients (Armaly et al. 2021; Kaye et al. 2021; Hirsch et al. 2020; Cheng et al. 2020; Braun et al. 2020). Studies revealed both proteinuria and haematuria to be independent risk factors of in-hospital mortality in COVID-19 patients. COVID-19 patients also exhibited elevated levels of blood urea nitrogen (BUN); in 31% of 193 patients, 14% of 193 patients, and 13% of 701 patients (Armaly et al. 2021; Li et al. 2020; Gagliardi et al. 2020). Along with the occurrence of proteinuria and haematuria, elevated blood urea nitrogen, serum creatinine, uric acid, and D-dimer were found to be significantly associated with mortality, as revealed with univariate Cox regression analysis of COVID-19 patients. Data from the same study also indicated an approximately 5.3 times increase in mortality risk in COVID-19 patients who developed AKI (Kaye et al. 2021; Meena et al. 2020). A dose-dependent relationship was observed between in-hospital mortality and the stage of AKI. The mortality risk in COVID-19 patients with stage 3 AKI was at least four times, a study on 701 patients reported (Cheng et al. 2020). In the study of 5994 COVID-19 patients, out of the 1993 patients who developed AKI during hospitalization, 35% (694) died; among these, 91% had stage 3 AKI, 64% stage 2 AKI, and 34% had stage 1 AKI (Hirsch et al. 2020).

One study reported the results of post-mortem autopsies conducted on six COVID-19 patients. The main damage in the kidney was found to be in the tubulointerstitium, which showed acute tubular necrosis of varying levels, luminal brush border sloughing, degeneration of vacuole, and lymphocyte infiltration to different proportions. In three of the cases, viral infection associated-syncytia was noted. The study also reported dilated capillary vessels without any severe glomerular injury, at the glomerular level (Diao et al. 2021). Another autopsy study of 26 COVID-19 patients revealed that some exhibited kidney damage. The changes identified through light microscopy include injury to the proximal tubule in association with loss of brush border, degeneration of vacuole (non-isometric), and necrosis (Su et al. 2020).

13.3 SARS-CoV-2 and the Kidneys

Some studies have reported the presence of the SARS-CoV-2 constituents—viral proteins and viral-like particles within the kidney. One study reported that in the tubular structures of the kidneys, the nucleocapsid protein and spike protein of SARS-CoV-2 were present, as revealed by immunohistochemical analysis. Both antigens were found to be restricted to ACE2-positive tubules; this was ascertained by immunofluorescence double staining. Viral RNA accumulation in the tubules was also found, as detected by in situ hybridization assay (Diao et al. 2021). Another study using electron microscopy revealed that in the podocytes and renal tubular epithelial cells, coronavirus-like particles having distinctive spikes were seen. The same study reported that the renal tubular epithelia were positive, on staining with SARS-CoV-2 nucleoprotein antibody (Su et al. 2020). Post-mortem analysis was carried out on 63 patients COVID-19 patients. Among the 63 patients, 32 had AKI. Out of these 32, the presence of RNA of SARS-CoV-2 was detected in the kidneys of 23 patients. This study also reported that this occurrence of SARS-CoV-2 RNA in the kidney was found to be associated with both, older age and a higher number of co-morbidities. Additionally, the presence of RNA in the kidney was significantly associated with a reduction in the survival time of patients. The same study also performed an extended analysis, SARS-CoV-2 was isolated from the autopsied kidneys of patients and was infected into cells in vitro. 48 hours post-cell infection, there was a 1000-fold increase in viral RNA, indicating the presence of highly infective virus from the kidneys of patients, even after death (Braun et al. 2020). A biopsy study of a COVID-19 patient who developed AKI was significant, electron microscopy revealed the presence of vacuoles with several spherical particles (50 to 110 nm), surrounded by spikes (9 to 10 nm) in podocyte cytoplasm. These particles could be viral inclusion bodies, that have been reported with SARS-CoV-2 infection (Kissling et al. 2020).

13.4 Mechanisms for Kidney Involvement in COVID-19

13.4.1 Direct Cellular Entry

To enter host cells, SARS-CoV-2 binds to its obligate receptor, angiotensin-converting enzyme II (ACE2). ACE2 is expressed on the cells in the lungs (alveolar type II cells), keratinocytes of the esophagus, epithelial cells of the stomach, cholangiocytes of the liver, colonocytes, small intestine and rectum, and also on the surface of kidney cells. The renal proximal tubular cells and podocytes express ACE2 receptors. It is interesting to note that ACE2 is more highly expressed in the brush border apical membrane of the proximal tubules than in the lung tissue. The ACE2 expression in the podocytes is considerably lower. In addition to the ACE2 receptor, the transmembrane protease serine 2 (TMPRSS2) of the host also plays a

critical role in facilitating SARS-CoV-2 entry into the host cells. TMPRSS2 is involved in cleaving the viral S glycoprotein, aiding in the entry of SARS-CoV-2 into the cells. While the expression of TMPRSS2 in the proximal tubules in the kidney is relatively low, expression of the same by the distal tubules is more. Cathepsin B/L, cysteine proteases, DPP4, and glutamyl aminopeptidase expressed in the kidneys are suggested to be alternative viral S priming proteases for the TMPRSS2 in the proximal tubule (Ahmadian et al. 2021). It is hypothesized that SARS-CoV-2 enters the glomerular and arteriole capillaries, initially infecting the glomerular endothelial cells. Podocytes are subsequently infected, through the glomerular filtration barrier. SARS-CoV-2 eventually the proximal tubule surface and then infect the proximal tubular epithelium (Yin and Zhang 2020).

13.4.2 Role of ACE2 and Subsequent Injury

Conversion of angiotensin II to Ang (1-7) is facilitated by the action of both soluble and insoluble ACE2. Ang (1-7) plays a significant role in controlling inflammation, vasoconstriction, and thrombosis. During acute lung injury, Ang II is increased, and during AKI, ACE2 is downregulated. This can cause the activation of the type I angiotensin receptor and a decrease in Ang (1-7) production. Both pulmonary inflammation and coagulation, which further aggravates AKI can result from the binding of angiotensin II to type I receptors. Entry of SARS-CoV-2 downregulates the expression of ACE2, consequently increasing the effects of Ang II and inhibiting the protective and anti-inflammatory of ACE2 in patients. COVID-19 patients with co-existing conditions such as cardiovascular diseases, diabetes, hypertension, and older age additionally exhibit ACE2 deficiency. In such patients, there can be a dysregulation between the protective angiotensin (1-7) and adverse AT1 roles in the renin-angiotensin system (RAS). ACE2 is also involved with the kallikrein–kinin system (KKS). An important member of this system, bradykinin has a key role to play in the process of inflammation. ACE2 brings about the hydrolysis and inactivation of [des-Arg973] BK (DABK), which is the active metabolite of bradykinin. COVID-19 can cause a decrease in the levels of ACE2, thus promoting KKS activation via BKB1R, the bradykinin B1 receptor. This results in increased recruitment of leukocytes and a surge of fluid in the lungs, aggravating the disease further and making resolution difficult (Batlle et al. 2020; Ahmadian et al. 2021).

13.4.3 Hyperinflammation and Dysregulated Immune Response Triggered Injury and Loss of Function

It has been established that COVID-19 patients exhibit a dysregulated immune response, resulting in an extensive cytokine and chemokine release, also called a

cytokine storm, that promotes the body to exist in a state of hyperinflammation. In patients with COVID-19, a significant increase in plasma levels of cytokines IL-6, IL-1β, TNF, IL-1RA, IFNγ, IL-7, IL-9, IL-10, G-CSF, GM-CSF, PDGF, FGF, VEGF, and chemokines IP10, CXCL8, MCP1, MIP1α, MIP1β can be observed, when compared with healthy individuals. This sort of dysfunctional immune response causes a failure in viral clearance. The ensuing continuous viral replication promotes the exaggerated inflammatory response and increased cytokine production. Other contributing factors include pyroptosis (an inflammatory form of programmed cell death) and ACE2 receptor mediated-increase in cytokines IL-6 and MCP1 (triggered by increased angiotensin II following the disruption of RAS) (Peter et al. 2021a). It is suggested that endothelial dysfunction, microcirculatory derangement, and tubular injury in the kidney are a consequence of the interaction of a large amount of circulating cytokines and chemokines with the kidney-resident cells (Soliman 2021). Different signaling pathways, JAK/STAT, TLR, NF-κB, mTOR, MAPK/ERK, and TGFβ are dysregulated that furthering the disease progression by promoting hypercytokinemia, hyperinflammation, thrombosis, and vasoconstriction. Hypercytokinemia and hyperinflammation induced by SARS-CoV-2 lead to the development of AKI in COVID-19 patients and can cause mortality (Ahmadian et al. 2021; Peter et al. 2021b).

13.4.4 Dysregulation of Complement System, Hypercoagulation and Vascular Consequences

SARS-CoV-2 is also established to induce coagulopathy in the host. Increased clotting, disseminated intravascular coagulation, pulmonary infarction, and thrombosis were reported in severe COVID-19 patients. Irreversible kidney damage occurs as microvascular thrombosis and acute necrosis (both tubular and cortical), causing fibrinoid necrosis and glomerular ischemia. Dysfunction of the complement system has also been reported as a result of SARS-CoV-2 infection. In severe COVID-19, the dysregulated complement system promotes the disease state in the body. Widespread complement activation that is characterized by activation of C3, generation of C3a, fragment deposition of C3, and an increase in serum levels of C5a are observed in patients with severe COVID-19. All these events in turn stimulate histamine, leukotrienes, and prostaglandins, which eventually increase hypersensitivity symptoms, hypotension, hypoxia, flushing, and vasodilation. The complement and coagulation pathways stimulate each other, increasing disease severity (Ahmadian et al. 2021).

13.4.5 Organ Crosstalk

There are reports of the existence of crosstalk in ARDS, between the lung and kidney. ARDS can cause the development of AKI. The inflammatory and immune reactions during ARDS promote an increased release of circulating factors. Interaction of these with kidney-resident cells causes damage, resulting in AKI. Crosstalk between other organ systems and the kidney, like the cardiovascular system can also contribute to the development of AKI in COVID-19 patients. COVID-19-induced myocarditis leads to an impairment of cardiac output, compromised end-organ perfusion, and concomitant right-ventricular dysfunction, which ultimately causes diastolic dysfunction and venous congestion. This can be transmitted back to the kidney, resulting in kidney congestion, further compromising the process of perfusion. Additionally, hypoperfusion, hypotension, and renal vein congestion which are responsible for the reduction in the glomerular filtration rate (GFR) are associated with acute viral myocarditis and cytokine cardiomyopathy. Hypovolaemia, sepsis, and nephrotoxicity, known risk factors of cardiovascular comorbidity can also mediate AKI. This kind of dysfunction in one organ during infection leads to impairment in the other and increases disease severity (Ahmadian et al. 2021).

13.4.6 Other Factors

There are other factors also that come into play in patients with COVID-19 patients which can increase the risk of injury to the kidney. Increased severity of disease makes for longer in-hospital stays, ICU requirement, mechanical ventilation, hemodynamic instability, nephrotoxic drugs, and sepsis, factors that strongly contribute to kidney injury. In such patients, septic AKI acts synergistically with other mechanisms of kidney damage (Soliman 2021) (Fig. 13.1).

13.5 Addressing COVID-19 Related Kidney Injury

Case study data and various reports clearly show that there is a substantial number of patients exhibit kidney involvement as one of the disease manifestations of COVID-19. Reports also confirmed that AKI and reduced renal function are implicated in COVID-19 mortality rates, AKI is a predisposing factor to disease severity and in-hospital mortality. Consequently, successful management of COVID-19 involves effective treatment of COVID-19-induced kidney injury. As of now, there is still no specific treatment for COVID-19-induced AKI. Currently, the treatment of AKI in COVID-19 patients is just a supportive treatment procedure, the KDIGO supportive care guidelines are followed—nephrotoxic drugs are avoided, serum creatinine levels and urine output are monitored regularly and

Fig. 13.1 Factors contributing to the development of AKI during/post COVID-19

hemodynamic monitoring is carried out, if possible. Renal replacement therapy (RRT) is started early, to mitigate the damage and promote early resolution (Kaye et al. 2021).

13.6 The Lacuna

Although the occurrence of COVID-19-associated AKI is substantial and there is no doubt of the detrimental role it plays in the recovery of the patient, there is no specific treatment that is prescribed. At its best, the treatment is just medical management. Renal replacement therapy (RRT) and continuous renal replacement therapy (CRRT) are carried out, if necessary. However, the optimal time to initiate the RRT of CRRT on the patient has to be decided at the discretion of the physician. Before initiating the therapy, there should be careful consideration of fluid and volume overload management, and management of hyperkalemia and metabolic acidosis. Moreover, another factor to be considered is the continuous dependence on the therapy post-discharge. Some disadvantages of these therapies include the risk of transmission, especially in such a pandemic situation, the lack of resources like hospitals with fewer ICU beds, and the need for experienced personnel.

13.7 Medicinal Plants

Medicinal plants offer a viable solution for the lacuna presented above. Medicinal plants with established nephroprotective activity, and anti-inflammatory and antiviral activity can be suitable adjuvants in the therapy of COVID-19-induced AKI.

13.8 Nephroprotective Plants with Probable Anti-SARS-CoV-2 Activity

13.8.1 Boerhavia diffusa *Linn*

Bierhavia diffusa is a very well-known Indian medicinal plant, natively known as "*punarnava*." The use of *B. diffusa* as a medicinal plant is not restricted to the Indian subcontinent, it is also a native medicinal plant in different parts of Africa and South America. It is a perennial herb, and the whole plant, the leaves, and roots in particular have been utilized for hepatoprotective, gastrointestinal, respiratory, nephrological, and gynecological indications. Well known for the anti-inflammatory and immunomodulatory activity it possesses, *B. diffusa* is the major ingredient for over 35 different ayurvedic formulations. Several researchers have scientifically evaluated the pharmacological effects of the different parts of *B. diffusa* plant and have also successfully isolated bioactive compounds from it. In addition to ecdysteroids, flavonoids, flavonoid glycosides, lignans, purine nucleosides, steroids, and xanthones found in *B. diffusa*, a new class of isoflavonoids called rotenoids were isolated from its roots. Decoctions of the root, tender shoot, leaves, and the whole plant have been used for improving the renal system function. Decoction of the root and leaves have been used to treat inflammation and edema (*Boerhavia diffusa* n.d.; Mishra et al. 2014).

In a study conducted on male Wistar rats, gentamycin-induced AKI was produced. The efficacy of *B. diffusa* aqueous root extract in ameliorating kidney injury and improving kidney function was studied. High doses of gentamycin caused elevated levels of BUN, serum creatinine, and histopathological damage in rat models. Pre-treatment with 200 and 400 mg/kg/day *B. diffusa* extract, resulted in significantly lower serum creatinine and BUN levels, comparable to the standard treatment group (ALA-α-lipoic acid). AKI in gentamycin-treated rats was indicated by the presence of both, tubular necrosis and desquamation which involved more than half of the proximal tubules (median grade: 3). Significant difference was observed in the ALA and *B. diffusa* (200 mg/kg/day)-treated rats. In rats treated with ALA, prominent tubular epithelial necrosis and desquamation involving less than half of cortical tubules (median grade: 2) were observed. *B. diffusa* (200 mg/kg/day)-treated rats exhibited desquamation of tubular epithelial cells in small foci (median grade: 1) (Sawardekar and Patel 2015). Male Wistar albino rates were

subject to kidney injury induced by acetaminophen. An increase in BUN, serum creatinine and structural damage; degeneration of epithelial cells, tubular necrosis, glomerular damage, and congestion indicated kidney injury in the animal models. Dose-dependent attenuation of elevation of both serum creatinine and BUN levels was observed on pre-treatment with *B. diffusa* aqueous extract (200 and 400 mg/kg/day). Moreover, pre-treatment with the aqueous extract of *B. diffusa* brought about a significant attenuation to renal cell damage, only minimal damage to the typical renal architecture was observed in these two groups (Pareta 2011).

An in silico study analyzed the efficacy of nine specific phytochemicals from *B. diffusa* to bind to and consequently inhibit SARS-CoV-2 main protease. Molecular docking analysis was carried out for boeravinone j, bioquercetin, biorobin, boerhavisterol, trans-caftaric acid, 2–3-4 beta-ecdysone, kaempferol, liriodendrin, quercetin. The least binding energies were obtained with biorobin; − 8.17 kcal/mol, bioquercetin; − 7.97 kcal/mol and boerhavisterol; − 6.77 kcal/mol. ADME studies were used to test the drug-likeness of biorobin, bioquercetin, and boerhavisterol. Among the three, the most suitable, following Lipinsky's rule was boerhavisterol. This suggests the potential therapeutic activity of *B. diffusa* for COVID-19 (Rutwick Surya and Praveen 2021).

13.8.2 Hygrophila auriculata *(Schumach.) Heine*

Hygrophila auriculata (K. Schum) Heine (syn.) *Asteracantha longifolia* Nees (syn) *Hygrophila spinosa* T. Anders. is an Indian medicinal plant well described in Ayurveda. A stout, erect herb found in wet places, native to Tropical and South Africa, the Indian subcontinent and Indo-China. The ashes, roots, and seeds of *H. auriculata* are widely used in traditional medicine to treat a wide range of ailments; inflammation, rheumatism, hepatic obstruction and jaundice, pain, gout, urinary infections, and edema (*Hygrophila auriculata* n.d.; Shanmugasundaram and Venkataraman 2006). The potency of the different plant parts of *H. auriculata* has been evaluated scientifically by different researchers. From the aerial parts of *H. auriculata*, lupeol, stigmasterol, and butelin have been isolated. Fatty acids have been reported to be present mainly in the seeds (Vijayakumar et al. 2006).

Gentamycin-induced kidney injury was produced in a group of study albino Wistar rats, and the efficacy of pre-treatment with *H. auriculata* methanol extract (200 and 400 mg/kg body weight; 8 days) was evaluated. Significant reduction in BUN, serum uric acid, and creatinine levels could be observed in the H. *auriculata*-pre-treated group. Animals in this group also exhibited recovery of the epithelial cell when compared to the non-treated group, which showed dilated tubules and degeneration of epithelial lining (Neharkar and Gaikwad 2019). Male Sprague-Dawley rats were treated with gentamycin to induce kidney injury for the study of the nephroprotective activity of the whole plant ethanolic extract of *H. auriculata.* Pre-treatment with *H. auriculata* ethanolic extract (250 mg/kg, po from ninth day to day 30) was found to cause a reduction in serum creatinine, 14 days post-

treatment, and on the 30th day, serum creatinine was similar to healthy control rats. Gentamycin-induced increase in blood urea also was prevented, when measured on the 30th day, there was not much difference between the *H. auriculata* pre-treatment group and the healthy control group. Gentamycin was found to induce marked kidney damage, extensive proximal tubular necrosis, epithelial lining loss, edema; interstitial and perivascular and in the interstitium multiple focal collections of mononuclear cells. Definite changes in the glomeruli were observed. The group administered with 50 mg/kg ethanolic extract of *H. auriculata* exhibited areas of tubular degeneration and necrosis, perivascular edema, and tubulo-interstitial mononuclear cell infiltrates, throughout the cortex at different foci. The group treated with 250 mg/kg *H. auriculata* ethanolic extract showed much better outcomes, and varying degrees of regeneration with only slight degenerative changes. Small foci of mononuclear cell infiltration confined to the subcapsular area were scattered. The epithelial cells of the proximal convoluted tubules were almost intact. These findings confirm the therapeutic action and nephroprotective potential of *H. auriculata* (Kariyil et al. 2010).

Molecular docking analysis was carried out with two phytoconstituents of *H.* auriculata; apigenin 7-O-glucoside and cucurbitacin B. The binding of these to the N-domain and RBD domain was analyzed with Autodock Vina with Pyrx v0.8 platform, Pymol v2.5, Ligplot+ v2.2.4 and Discovery Studio Visualizer v21.1.0.20298. The phytochemicals of *H. auriculata* showed effective inhibition of the mutated N-Domain; the binding affinity for apigenin 7-O-glucoside was −6.5 kcal/mol and that of cucurbitacin B was −6.2 kcal/mol. Among the two, cucurbitacin B had a lower binding affinity. The compounds were studied in the Molinspiration server, ADMETlab 2.0 to analyze the adsorption, digestion, drug-likeness metabolism, excretion, lethal dosage, toxicity (ADMET) and toxicity (Bharathi et al. 2022). In another analysis of potent inhibitors of SARS-CoV-2 main proteases $3CL^{pro}$ (6 LU7) by in silico approach, luteolin 7- rutinoside from *H. auricualata* docked with $3CL^{pro}$, energy value exhibited −134.6 kcal/mol. This comprises of van der Waal interaction; −98.9 kcal/mol and hydrogen bonding interaction; −36.23 kcal/mol. This suggests that the individual phytoconstituents may be considered for formulations to effectively target SARS-CoV-2, thus treating COVID-19 (Vincent et al. 2020).

13.8.3 Phyllanthus niruri *L.*

Phyllanthus niruri is a perennial, tropical herb native to Tropical and Subtropical America (*Phyllanthus niruri* n.d.). It is a well-known traditional medicinal plant in South and South-East Asia, used for a wide range of indications such as diarrhea, dyspepsia, jaundice, genitourinary infections, and renal stones. In Ayurvedic

and Unani medicine, the leaves and fruits are used in the treatment of gall stones and jaundice, and the Malay system of medicine is employed for treating cough and kidney diseases. *P. niruri* is used in the alleviation of liver injury secondary to various hepatotoxic agents in TCM (traditional Chinese Medicine). Extensive scientific research has been carried out to validate the ethnopharmacological activities of *P. niruri.* Several important bioactive compounds have been isolated and characterized from *P. niruri*. *P. niruri* is rich in alkaloids, coumarins, flavonoids, lignans, phenylpropanoids, tannins, and terpenes. Some bioactive compounds isolated and characterized from *P. niruri* include phyllanthin, nirtetralin, niranthin, nirurin, nirurifl avone, nirphyllin, phyllnirurin (Lee et al. 2016).

Nephroprotective activity of *P. niruri* was studied using albino Wistar rats treated with gentamycin to produce kidney injury. Two doses of whole plant methanolic extract of *P. niruri* were used for the study, 200 mg/kg and 400 mg/kg, administered from the tenth to the 19th day of study. Treatment with gentamycin causes a decrease in body weight and urine volume and an increase in the weight of the kidney. Treatment with *P. niruri* protects from these effects, urine volume and kidney weight are almost the same in the control group and the *P. niruri* 400 mg/kg treatment group. Serum creatinine and protein, BUN are also significantly lower in the *P. niruri* treatment group. Gentamycin brought about glomerular congestion, and treatment with *P. niruri* showed moderate tubular degeneration and normal glomeruli and Bowman's capsule (Reddy et al. 2015).

The ability of two phytoconstituents of *P.* niruri; phyllanthin and hypophyllanthin to bind to spike glycoprotein (6LZG) and main protease (5R7Y) was determined using Molegro Virtual Docker 6.0. Both phytoconstituents possessed increased binding affinity to the COVID-19 inhibition sites when compared to their native ligand; 6LZG and 5R7Y. The rerank score of phyllanthin and hypophyllanthin was lower than 6LZG and 5R7Y, suggesting that they possess a greater interaction than the native ligands, both for spike glycoprotein (possible entry inhibitor) and main protease (potential translation and replication inhibitor) (Marhaeny et al. 2021).

13.8.4 Punica granatum *L.*

Punica granatum, commonly called pomegranate is a tree, native ranging from the Middle East region to the Himalayas in the Northern part of India. All over the Mediterranean region of Asia, Caucasus, northern Africa, and Europe, pomegranate was naturalized and its cultivation has been in process since ancient times. The fruit is a delicacy and is consumed for good taste and is also one of the few fruits advised to be eaten even during ill health. Pomegranate juice is also well consumed. Dried fruit is also used both, in foods and as a spice condiment (Lim 2012; *Punica granatum* n.d.). Pomegranate is known for its medicinal properties, it has been an inherent part of different traditional systems of medicine; Islamic, Persian,

Ayurveda, and Chinese. Traditionally, pomegranate is used for the treatment of diabetes, hypertension, peptic ulcer, different types of cancers, atherosclerosis, hyperlipidemia, and oral diseases (Ge et al. 2021). Extensive studies have been carried out on the parts of the pomegranate plant and numerous phytochemicals have been isolated and characterized. Some phytochemicals isolated are; from the roots; norpseudopelletierine, sedridine, hygrine and norhygrine, from the bark; punicotannic acid, punicalin and punicalagin, punicacorteins A, B, C, and D, from the leaves; punicafolin, granatins A and B, corilagin, strictinin, from the flowers; punicanolic acid, urolic and maslinic acids, ellagic acid, from the fruits; polyphenols, 35 dimers of flavanol-anthocyanin adducts, different ellagitannins, anthocyanin pigments and from the seeds; high contents of α-tocopherol and γ-tocopherol, estrogens, and glycosides have been reported (Lim 2012).

Kidney injury was induced in male Wistar rats using gentamycin. The nephroprotective activity of methanol *P. granatum* leaf extract was accessed, and three concentrations were studied, 100, 200, and 400 mg/kg *p.o. Kidney injury was indicated by elevated levels of* serum creatinine, and urea, degeneration of tubules alongside an increase in TNF-α, lipid peroxidation, and a decrease in the activity of antioxidant enzymes activity. Administration of methanolic extract of *P. granatum* along with gentamycin was found to protect the kidneys from the nephrotoxic effects of gentamicin. The best activity was found in the group of rats treated with the highest concentration of *P. granatum* extract, 400 mg/kg; indicated by a significant reduction in levels of serum creatinine and BUN and an increase in the concentration of serum albumin. Histopathological studies revealed substantial kidney injury on treatment with gentamycin; acute vacuolar degeneration, destruction and hyalinization of arterioles, tubular collapse, scarring and matrix-rich expansion of interstitium and tubule distortion, presence of mononuclear cells (MNCs) in the renal sections and edema. Treatment with *P. granatum* leaf extract was found to reduce the intensity of vacuolar degeneration, edema, and infiltration of MNC and also improve renal morphology. Substantial improvement of renal tubules and a reversal of many of the histopathological changes, evidenced by the preservation of tubular histology was observed in the 400 mg/kg methanol leaf extract treatment group. An enhancement of thickening in the basement membrane and glomerular size was also caused as a result of gentamycin treatment. Treatment with methanol extract at doses of 200 mg/kg and 400 mg/kg could effectively bring about a decrease in this gentamycin-induced increase of both, basement membrane thickening and glomerular size. Additionally, renal TNF-α levels were also altered. Gentamycin induced a considerable increase in the renal levels, but treatment with methanolic extract of *P. granatum* (at all three concentrations, 100, 200, and 400 mg/kg) reduced renal TNF-α levels substantially (Mestry et al. 2020). Another study employed carbon tetrachloride (CCl_4) to induce kidney injury in male CD4 albino mice and evaluated the nephroprotective effects of the *P. granatum* peel aqueous extract. Kidney damage was indicated by the elevated levels of serum creatinine and urea.

Histopathological evaluation showed significant degenerative changes, both in the glomerulus and Bowman's capsule with cells revealing evidence of necrosis and vacuolization in mice treated with CCl_4. Treatment with an aqueous extract of *P. granatum* peel in CCl_4-treated mice led to a significant decrease in serum urea and creatinine. Mice treated with *P. granatum* extract retained intact histological architecture in the kidney, with reduced damaged areas when compared to non-treated animals. In the *P. granatum* + CCl_4-treated group, some glomeruli seemed to be moderately congested, and a few tubules exhibited mildly swollen epithelial cells with normal nuclei. The renal tissue of the *P. granatum* + CCl_4-treated mice had a medium reduction in the content of collagen fiber as compared to the group treated with only CCl4. Reduced expression of Caspase-3 in the renal tissue was also noted in the animals treated with an aqueous extract of *P. granatum* as compared to non-treated animals. The study also analyzed the levels of mRNA expression of SOD (superoxide dismutase), catalase (CAT), and glutathione peroxidase (GPx). Substantial variation of gene expression levels of all the genes in the CCl4 and PPE + CCl4 treatment groups was observed. Treatment with *P. granatum* extract increased SOD and GPx expression, even slightly more that in the control animal group. CAT expression was increased in the *P. granatum*-treated groups but was notably lesser than in the control group (Emam et al. 2020).

The efficacy of the hydroethanolic extract of *P. granatum* as an antiviral drug against SARS-CoV-2 was studied. Three different concentrations of extract, ranging from 0.04 mg/mL to 1 mg/mL, were found to inhibit Spike and ACE2 interactions in a dose-dependent manner, up to 74%. Three individual polyphenols of *P. granatum*; punicalagin (PC), gallic acid (GA), and ellagic acid (EA) were tested to ascertain which had the most impact on the binding of Spike to ACE2. While GA did not have any effect on this binding, PC showed the most effect, with 49% inhibition, and EA with 36% inhibition. Further investigations studying the chemical interactions between the extract and Spike and extract and ACE2 were carried out. Though *P. granatum* extract bound to both proteins, the interaction with the Spike was tenfold strong as compared to that with ACE2. Gene expression analysis also revealed that *P. granatum* extract downregulates the expression of ACE2 and TMPRSS, the genes responsible for the virus access into the cells. Additionally, at a concentration of 0.2 mg/ml, *P. granatum* extract was able to inhibit the activity of one of the main proteins, 3CL protease, which is involved in viral replication by up to 80%. Among the individual phytoconstituents, PC exhibited the highest inhibition of enzymatic activity; 50% followed by EA; with 10% inhibition, and GA showed no inhibition of protease activity. This suggests that pomegranate juice is effectively reducing viral infection and replication and can be part of a formulation to treat COVID-19 (Tito et al. 2021).

13.8.5 Tribulus terrestris *L.*

Tribulus terrestris is an annual shrub, widely distributed in the Subtropical, Mediterranean, and desert climatic regions of the world, India, China, Mexico, Spain, southern USA, Mexico, and Bulgaria (Chhatre et al. 2014). It is commonly known as Devil's thorn and Puncture vine (Tribulus terrestris 2022). It has been used in folk medicine, extensively by Indian, Japanese, Bulgarian, Korean, and Chinese civilizations. It is known to possess a host of pharmacological properties; immunomodulatory, anti-inflammatory, anticariogenic, anticancer, diuretic, antidiabetic, hepatoprotective, hypolipidemic, cardiotonic, analgesic, antispasmodic, antiurolithic, aphrodisiac, absorption enhancing, antibacterial, anthelmintic, and larvicidal activities. Several important phytochemicals have been isolated from *T. terrestris;* protodioscin, neoprotodioscin, prototribestin from the aerial parts; tribufuriside D, tribufuroside E, tribulosaponin A, polianthoside D from the fruits (Ștefănescu et al. 2020).

Inbred male Balb/c mice were subject to kidney injury by the administration of cisplatin. Three doses of ethanolic extract of *T. terrestris;* 100, 300, and 500 mg/kg body weight were administered to assess the nephroprotective activity. While there were no significant differences in the body weight in the 300 and 500 mg/kg treatment groups, the animals in the 100 mg/kg treatment group showed a reduction in body weight. All three *T. terrestris*-treatment groups showed no significant difference in kidney weight, unlike the animals treated with cisplatin alone. Substantial kidney damage occurred with cisplatin treatment; cortical tubular necrosis, medullar tubular necrosis, and Bowman's space enlargement. Administration of *T. terrestris* extract brought about a dose-dependent reduction in kidney damage; with minimum damage seen in the 500 mg/kg treatment group, with scores closest to those of the control (Raoofi et al. 2015). Another study assessed the nephroprotective activity of the hydroalcoholic activity of *T. terrestris*, employing mercuric chloride to induce kidney injury. The study animals were male Wistar rats, and three doses of *T. terrestris* used; 100, 200, and 300 mg/kg/day for 7 days. Renal function was evaluated by checking BUN and serum creatinine levels. Dose-dependent reductions in the levels of serum creatinine and BUN were observed in the animals treated with *T. terrestris* extract; the highest reduction was observed with the 300 mg/kg dose, indicating improved renal function. A similar dose-dependent increase in GSH levels, GPx activity, inhibition of SOD activity, and suppression of renal MDA levels was noted on treatment with *T. terrestris* extract. AKI was effectively induced by cisplatin, as confirmed by the increase in KIM-1 and L-FABP levels. *T. terrestris* at lower concentrations; 100/200 mg/kg was ineffective in bringing about a significant reversal of the increased KIM-1 and L-FABP levels. *T. terrestris* extract at a higher concentration of 300 mg/kg was found to be efficacious in bringing about a substantial reduction in the levels of both KIM-1 and L-FABP. Histopathological studies revealed that treatment with *T. terrestris* resulted in 50–75% intact/viable

tubular epithelium. Some necrosis could be observed, representing grade 1 protection using *T. terrestris.* This shows *T. terrestris* is effective in attenuating the nephrotoxic effects of mercuric chloride (Yadav et al. 2019).

The methanolic extract of the fruits of *T. terrestris* (different doses1, 10, 100, 1000 μM) exhibited substantial inhibition against the papain-like protease (PLpro). Six cinnamic amides isolated from the fruit of *T. terrestris* were assayed for their ability to inhibit SARS-CoV PLpro. All six compounds showed significant inhibitory activity, with IC50 values ranging between 15.8 and 70.1 μM. Terrestrimine was the most effective inhibitor, with an IC50 of 15.8 μM (Song et al. 2014).

13.8.6 Urtica dioica *L.*

The most common species of the Urticaceae family and one of the most studied medicinal plants worldwide, *Urtica dioica* is a unique herbaceous perineal flowering plant that has stinging hairs. It is widely distributed in the Indian Subcontinent, Europe, and a few regions in Africa. *U. dioica* is commonly called nettle; it is famous for its hairy, toothed leaves and for its sting. The stinging hair of the nettle has a bulbous tip, that breaks off leaving a sharp needle-like tube piercing the skin and injecting acetylcholine and histamine. This causes a burning and itching sensation that can sometimes last up to 12 hours (Dhouibi et al. 2020; Urtica dioica 2022). Traditionally, *U. dioica* is used to treat allergies, rheumatic conditions, urinary tract disorders, benign prostate hyperplasia, and as an anti-haemorrhagic agent. *U. dioica* is also used for cosmetic preparations; anti-dandruff and hair loss lotions. The leaves are eaten raw/blanched, steamed/fried and added to food items such as soups, sauces, pesto, quiches, purées. Formulations of *U. dioica* are also used to prepare homeopathic medications. Some of the pharmacological activities of *U. dioica* include anti-inflammatory, diuretic, anti-asthmatic, cardiovascular, astringent, depurative, anticancer, galactogogue, and stimulating effects. Phytosterols, lignans, isolectins, coumarins, triterpenoic acids, and monoterpendiols have been isolated from the roots of *U. dioica.* Rutin, quercetin-3-*O*-glucoside and kaempferol-3-*O*-glucoside were found in the leaves and stalks and rutinosyl flavonols, chlorogenic acid, and caffeoyl malic acid were reported from the leaves (Esposito et al. 2019).

AKI was induced in the study animals; male Wistar rats via the administration of gentamycin, for 8 days. The preventive effect of methanolic leaf extract of *U. dioica*, at a dose of 200 mg/kg/day, administered for 8 days was assessed in study animals. Kidney injury was indicated in the animals treated with gentamycin alone, they exhibited a substantial increase in BUN, plasma creatinine, urinary sodium excretion, fractional excretion of sodium and potassium, and MDA levels. Considerable renal damage was also found in the animals treated with gentamycin alone; tubular cells necrosis, production of intraluminal protein casts (grade 3), vacuolization of renal tubular cells (grade 4), increase in space of Bowman's capsule, decreased RBC count and dispersion of cells into the lumen of the tubule (grade 3). On the other hand, animals co-treated with methanol extract of *U. dioica* showed lower levels of

BUN and plasma creatinine, reduced excretion of urinary sodium, reduced fractional excretion of sodium and potassium and lower MDA levels. Improved renal blood flow, clearance of creatinine, urine osmolarity, and FRAP levels were also characteristic of the *U. dioica*-treated group. A substantial decrease in renal injury was also observed in *U. dioica*-treated animals. Decrease in cellular necrosis, decrement of the Bowman's space, increased number of RBCs in the glomeruli, and only grade 1 level of generation of protein casts within the lumen of the tubule and dispersion of cells into the lumen of the tubule (grade 1; $p < 0.001$) and grade 2 vacuolization of renal epithelial cells was observed (Hajihashemi et al. 2020). A similar study evaluating the nephroprotective activity of *U. dioica* was carried out in rabbits. Gentamycin was used to induce nephrotoxicity. Ethanolic of the whole *U. dioica* plant, at a dose of 200 mg/mL was used. Co-treatment with *U. dioica* extract was found to ameliorate the negative effects of gentamycin on the kidney. Serum creatinine, BUN, and MDA levels were lower in the co-treated group, values of BUN were almost equal to that of the control. Extensive kidney damage was seen in the gentamycin-treated group. Swelling of the renal corpuscle, increased urinary spaces, urinary pole destruction, degeneration of the epithelium of collecting tubules and Henle loop characterized by the presence of varying degrees of tubular epithelial vacuolar degeneration, diminished brush border, attenuation, loss of epithelial cellular detail with the abundant epithelium of proximal and distal convoluted tubules containing a massive cytoplasmic aggregation of hyaline droplet and slight interstitial hemorrhage. On the contrary, co-treatment with gentamycin and *U. dioica* showed almost normal kidney morphology. There were only a few focal hydropic regions of swelling of tubular epithelial cells, indicating the partial to complete protective role of *U. dioica* against the nephrotoxicity of gentamicin (Salih 2015).

SARS-CoV replication was inhibited by *U. dioica* agglutinin (UDA) in a dose-dependent manner in a study conducted in Vero 76 cells. Decreased yields of the virus (of Urbani strain) by 90% were also observed in UDA-treated Vero 76 cells. In vivo analysis was also carried out, by infecting BALB/c mouse models with SARS-CoV-1. UDA at doses of 5, 10, and 20 mg/kg/day were administered for 4 days. Treatment with UDA protected the mice against weight loss as a result of SARS-CoV, lower lung pathology scores, and protection from death. Further analysis revealed that UDA probably curbs infection with SARS-CoV by targeting the early stages of the replication cycle; virus adsorption or penetration. UDA also neutralizes the infectivity of the virus by possibly binding to the spike (S) glycoprotein of SARS-CoV. Binding studies suggested that the binding sites for UDA are plausibly the *N*-acetylglucosamine-like residues that are present on the glycosylated envelope glycoproteins, thus preventing the attachment of SARS-CoV to cells (Kumaki et al. 2011).

13.8.7 Vitis vinifera *L.*

Although *Vitis vinifera* distribution natively ranges from South Central and South-East Europe to Central Asia and North Iran, it has been introduced to several places around the globe; India, Korea, Afghanistan, Pakistan, Bangladesh, and some parts of Africa, Europe, and the USA. Commonly referred to as grape wine or parsley wine, it is a woody climber with coiled climbing tendrils (Vitis vinifera 2022). *V. vinifera* is one of the oldest domesticated plants, which is consumed for both, its nutritional and medicinal values. Since ancient times, it is known for its medicinal value, traditional systems of medicine around the world have chronicled the use of *V. vinifera* for different indications; Ayurveda for inflammation and cardiovascular diseases, in Malatya the fruit is suggested to aid the formation of blood, in Elazığ for the treatment of anemia, in Iran for ailments and memory problems, in Pakistan as a carminative, in Tuscany, the drink derived from the fruit is used as a digestive, a Persian physician chronicled its used for oral health and in Cyprus the alcohol marinade is used as a poultice, mouthwash, and liniment. Grape skin is a source of polyphenols, proanthocyanidins, flavan-3-ols, and resveratrol. The fruit is rich in antioxidant phenolics, anthocyanins, catechins, quercetin, resveratrol, procyanidins, epigallocatechin, and epigallocatechin-3-gallate (Ardid-Ruiz et al. 2020; Al-Warhi et al. 2022).

The potency of grape seed extract to protect against renal dysfunction was assessed in female albino rats. Dexamethasone was administered, which brought about kidney dysfunction, as evidenced by the high amounts of serum creatinine and uric acid. Two concentrations of aqueous grape seed extract were used for analysis; 200 and 400 mg/kg BW. A dose-dependent reduction in the levels of creatinine and uric acid was observed in the grape seed extract treatment groups. In fact, in the 400 mg/kg group, the levels of creatinine and uric acid were very similar to that of the control. Treatment with grape seed extract, especially at a dose of 400 mg/kg was able to effectively ameliorate the reduction in weight gain due to dexamethasone administration. The relative weight of the kidney also was improved in the grape seed treated group, when compared to the group that was administered only dexamethasone. This indicates that grape seed extract positively affects plausible renal alteration on the administration of medication like dexamethasone (Hasona et al. 2017). The nephroprotective activity of grape juice was evaluated in male Wistar rats that were fed on a high cholesterol diet. High cholesterol diet led to renal dysfunction, as evidenced by increased BUN, serum creatinine, and urea with altered morphology in the kidney; dilated proximal tubules with acidophilic casts in their lumina. Peritubular capillaries were also congested and dilated. The group of rats administered with grape juice exhibited lower levels of BUN, serum creatinine, and urea. Most tubules in this animal group appeared intact, only some were affected. Only a few peritubular capillaries were congested in the grape juice-treated group (Ali et al. 2015).

A study on the antiviral activity of *V. vinifera* leaf extract against SARS-CoV-2 by plaque reduction assay showed very promising results. Virus pre-treatment

Fig. 13.2 Nephroprotective plants with antiviral activity (All plant images taken from Indian Biodiversity Portal)

(treatment before infection on the cell monolayer) and co-treatment (incubated with SARS-CoV-2 in addition to target cells) was found to yield the best results. Only a slight antiviral effect was noted when cells were treated first with extract and subsequently infected (cell pre-treatment), and when the extract was added after HSV-1 infection (post-treatment). This suggests that *V. vinifera* leaf extract acts on viral particles directly, and blocks interaction with the cell membrane. *V. vinifera* extract also strongly decreased the expression of S post-SARS-CoV-2 infection until a concentration of 10 μg/mL was reached, and it resumed being expressed in a dose-dependent manner at lower concentrations (Zannella et al. 2021).

The images of the plants with nephroprotective activity and probable anti-SARS-CoV-2 activity described above may be found in Fig. 13.2. Some more medicinal plants with nephroprotective activity and potential effect on COVID 19 (preventive&/treatment) are described in Table 13.1

13.9 Conclusion

One of the lethal manifestations of COVID-19 is the occurrence of acute kidney injury. AKI not only complicates and prolongs treatment but also accounts for poor prognosis and high mortality rates. Moreover, some patients who develop AKI may not regain renal function even post-discharge. This makes AKI a serious complication and warrants extensive study, in pursuit of suitable cures and efficient management systems. Medicinal plants open up fascinating horizons of treatment; nephroprotective plants have been in use via different indigenous systems of medicine. Medicinal plants constitute vital ingredients for formulations of different Ayurvedic and traditional Chinese medicines. Scientific evaluation has also validated the use of many of these plants and individual phytochemicals have been isolated and characterized. Some nephroprotective plants and phytochemicals also exhibit antiviral properties, in particular against SARS-CoV and SARS-CoV-2. The advantage of the use of medicinal plants is undisputable, with minimum side effects,

Table 13.1 Medicinal plants with nephroprotective activity and potential COVID-19 effects (preventive&/treatment) (Mukherjee et al. 2022)

S. No.	Medicinal plant	Mode of action	Reference
1	*Azadirachta indica* A.Juss.	Oral administration of crude aqueous leaf extract improved malaria-induced renal injury. Treatment with extract for 4 days brought levels of creatinine and BNU to near normalcy. Absence of any toxic effects on treatment A pilot, double-blind, randomized controlled trial showed the prophylactic effect of neem capsules; it effectively decreased the risk of COVID-19 infection Bark extract effectively inhibits in vitro infection and replication of SARS-CoV-2 and m-CoV-RSA59 and also reduces gene expression of envelope and nucleocapsid genes. In vivo, bark extract attenuates neuroinflammation and hepatitis by inhibiting viral replication and spread. Isolated fractions of NBE enriched in Nimbin isomers showed effective inhibition of m-CoV-RSA59 infection in vitro. In in silico analysis, NBE targets spike and RdRp of m-CoV and SARS-CoV-2 with great affinity	Somsak et al. (2015), Nesari et al. (2021), Sarkar et al. (2022)
2	*Magnolia officinalis* Rehder and E.H.Wilson	95% ethanolic extract of the bark ameliorated kidney damage in a high-fat fed mouse model. Significant reduction in albumin-to-creatinine ratio, reduction in glomerular enlargement, and renal tubular epithelial damage over a 6 months treatment period. Reduced levels of TNF-α, plasminogen activator inhibitor in treated mice Honokiol, a phytoconstituent from the bark of *Magnolia sps.* was found to inhibit the replication of SARS-CoV-2 in Vero E6 cells and human A549 cells. Honokiol was also effective in inhibiting newer variants of SARS-CoV-2 such as Omicron	Cui et al. (2013), Salgado-Benvindo et al. (2023)
3	*Syzygium aromaticum* (L.) Merr. and L.M. Perry	Ameliorative effect of clove bud hydroalcoholic extract on contrast-induced acute kidney injury established. A significant difference in degradation, flattening, necrosis of renal tubular cells and dilation of the tubular lumen in treated and non-treated groups	Nasri et al. (2020), Li et al. (2022)

(continued)

Table 13.1 (continued)

S. No.	Medicinal plant	Mode of action	Reference
		Water and ethanol extract of *Syzygium aromaticum* exhibited a dose-dependent suppression of SARS-CoV-2 spike protein binding to ACE2 and inhibition of ACE2 activity	
4	*Andrographis paniculata* (Burm. f.) Nees	In vitro treatment of human tubular epithelial cells (HK-2 cells) with andrographolide effectively averts renal tubular cell damage induced by high glucose. Additionally, andrographolide was also found to suppress mitochondrial dysfunction and NLRP3 inflammasome activation, thus protecting the progression of diabetic tubular injury and fibrosis A significant inhibition in infectious virions production (IC_{50} of 0.036 μg/mL and 0.034 μM respectively), determined by the plaque assay on treatment (postinfection) of andrographolide and *A. paniculata* in Calu-3 cells infected with SARS-CoV-2 was observed, indicating anti-SARS-CoV-2 activity	(Liu et al. 2021; Ngiamsuntorn et al. 2021)
5	*Tinospora cordifolia* (Willd.) Miers	Feeding diabetic rats with 5% bark of *T. cordifolia* effectively modulates changes in the kidney (increased glomerular area, glomerular filtration rate) Saponarin, a phytoconstituent of *T. cordifolia* exhibited a very promising result in computational binding studies with the main protease of COVID-19, with a binding affinity of −8.75 kcal/mol. The binding affinity of the experimental drug Remdesvir was found to be –8.65 kcal/mol	Joladarashi et al. (2012), Mulpuru and Mishra (2021)
6	*Cinnamomum zeylanicum* L.	Pre-treatment with an aqueous extract of cinnamon bark results in significant protection against kidney injury in acetaminophen-treated rats. Significant restoration of urea and creatinine levels and normalization of renal tissue architecture was observed on pre-treatment with cinnamon Two phytoconstituents from *Cinnamomum zeylanicum*, cinnamyl acetate and caryophyllene oxide exhibited high binding affinities with the main protease of COVID-19, –5.38	Hussain et al. (2019), Mulpuru and Mishra (2021)

(continued)

Table 13.1 (continued)

S. No.	Medicinal plant	Mode of action	Reference
		kcal/mol and –5.25 kcal/mol. The binding affinity of the experimental drug, Favipiravir was also determined, –5.76 kcal/mol	
7	*Piper nigrum* L.	Administration of ethanolic extract of fresh seeds (pre-treatment) was found to normalize levels of urea, creatinine, albumin, total protein, blood urea nitrogen levels and normalize histoarchitecture of kidney in study rats Computational studies revealed that piperine has a very high binding affinity (−7.0 kCal/mol) toward the RNA-binding pocket of the SARS-CoV-2 nucleocapsid	Gaikwad and Zodape (2019), Choudhary et al. (2020)
8	*Mucuna pruriens* (L.) DC.	Long-term treatment (90 days) with *M. pruriens* extract resulted in improved levels of serum ALT, urea and creatinine levels in study animals. Molecular docking using Biovia Discovery Studio was performed to study the binding of phytoconstituents from *M. pruriens*. High positive values of -CDocker energy and -CDocker interaction energy were observed with *M. pruriens* constituent, dopamine. This suggests that dopamine could possibly deactivate the nucleocapsid protein N-terminal RNA binding domain 6M3M enzyme, and consequently interrupting the life cycle of SARS-CoV-2	Concessao et al. (2020), Mishra and Swain (2020)
9	*Allium sativum* L.	Treatment with ethanolic extract of garlic resulted in improved kidney function and as evidenced by improved parameters (urea, creatinine, blood urea nitrogen) to near-normal levels. A significant decrease (60–70%) of viral RNA and infectious viral particles in SARS-CoV-2 infected Vero E6 and Calu-3 cells treated with allicin was observed. Treatment with allicin in infected Calu-3 cells also brought about a reversal in several host pathways to levels similar to that of uninfected cells. Allicin also brought about a reduction in the abundance of structural proteins N, M, S, and ORF3 in the host–virus proteome	Anusuya et al. (2013), Mösbauer et al. (2021)

(continued)

Table 13.1 (continued)

S. No.	Medicinal plant	Mode of action	Reference
10	*Chrysanthemum indicum* L.	Ethanolic extract was potent in both in vitro and in vivo studies, improving cell viability and renal function index, respectively. The herb was found to inhibit SARS-CoV-2 virus	Kim et al. (2015), Mukherjee et al. (2022)
11	*Zingiber officinale* Roscoe	Treatment with ginger restored renal function makers (creatinine clearance, reabsorption rate of urine albumin, creatinine, and urea levels), restoration and regeneration of glomeruli, renal tubules, and cells in cadmium-treated rats 6-gingerol, a phytochemical found in ginger exhibited high binding affinity (binding energy −2.8764 KJ/mol to −15.7591 KJ/mol) with several COVID-19 viral protein targets	Gabr et al. (2019), Rathinavel et al. (2020)
12	*Echinacea purpurea* L. Moench	Decrease in AST, blood urea nitrogen, and total and direct bilirubin in rats treated with hydroalcoholic extract of aerial parts of *E. purpurea*. The ability of *E. purpurea* to prevent SARS-CoV-2 infection was studied in a randomized, open, controlled, exploratory clinical study. In the test group, participants received *E. purpurea* extract (Echinaforce). 5 out of 60 individuals from this group contracted COVID-19 as opposed to 8 out of 60 in the control group. During viral infection, an increased dose of Echinaforce was given as treatment regime. This treatment was found to reduce overall viral load and there were fewer COVID-19-related hospitalizations when compared to the control group.	Rezaie et al. (2013), Kolev et al. (2022)
13	*Curcuma longa* L.	Protective effect against kidney injury and helps maintain normal kidney morphology in renal ischemic rat models Effective neutralization of SARS-CoV-2 at subtoxic concentrations in Vero E6 and human Calu-3 cells was observed on treating with root extract of turmeric, dissolved turmeric capsule content and pure curcumin. Curcumin treatment brought about a substantial decrease in SARS-CoV-2 RNA levels in cell culture supernatants	Aggarwal and Harikumar (2009), Bormann et al. (2021)

(continued)

Table 13.1 (continued)

S. No.	Medicinal plant	Mode of action	Reference
14	*Glycyrrhiza glabra* L.	The active compound of licorice, glycyrrhetinic acid reduces the frequency of hyperkalemia and serum potassium concentration in dialysis patients The aqueous root extract of *G. glabra* showed a potent protective effect against COVID-19 in hamsters infected with SARS-CoV-2. Prophylactic treatment exhibited protection against loss in body weight, a decrease (35–40%) in viral load in the lungs, and reduced lung pathology. Reduced mRNA expression of proinflammatory cytokines and plasminogen activator-1 was also observed in vivo. In vitro, the extract reduced Th2 and Th17 differentiation and IL-4 and IL-17A production	Ferrari (2009), Rizvi at al. (2022)

and offer high efficacy. This review aims to shed light on COVID-19-induced AKI and selected medicinal plants that can possess nephroprotective and antiviral activity. The use of these plants and their extracts is promising; they can be employed for the development of effective drugs with little or no side effects to combat COVID-19-induced AKI efficiently.

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Chapter 14
Phytochemicals and Nutraceuticals Targeting SARS-CoV-2: An In Silico Analysis

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14.1 Introduction

A new coronavirus was reported in December 2019, which is called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19) (Ko et al. 2020). Since its emergence, it caused a menace to humankind and spread to nearly every country and area in the world (John Hopkins University 2020). COVID-19 was proclaimed a pandemic by the World Health Organization (WHO) as it threatened human life and caused huge economic losses throughout the world. Although immunization is a positive step, it might not completely guard against the illness; as a result, it will still be necessary to create potent COVID-19 treatment and prevention.

Traditional medicines which employ plant extracts, nutraceuticals, and other plant products remain the base for present-day drug discovery and development programs (Veeresham 2012). Plant phytochemicals, dietary supplements, and functional foods are nutraceuticals that also imbibe medicinal properties within them (Varzakas et al. 2016). Plethora reports are available for COVID-19-related research and the hunt for phytochemicals from varied sources grows exponentially.

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Behl et al. (2021) have indicated the importance of plant-based functional foods in combating human viral diseases elaboratively. They have discussed the importance of flavonoids, chalcones, coumarins, phenolic compounds, etc., and plant sources such as ginger, garlic, moringa, mint leaves, etc., in alleviating the provoking of viral diseases.

A recent study on the application of Ayurvedic Kadha for the management and prevention of SARS-CoV-2 was reported by Maurya and Sharma et al. (2022). The role of phytochemicals found in the Kadha in controlling the viral infection and multiplication in the host cells was investigated using in silico approach. Most of the phytochemicals found in the herbs ashwagandha, black pepper, clove, tulsi, and giloy were effective in inhibiting COVID-19.

Qazi et al. (2021) have specifically studied the antiviral activity of phytochemicals from *Aeglemarmelos*, *Vetiveriazizanioides*, *Moringa oleifera*, and *Punica granatum* against protein targets such as 3CLpro and RNA-dependent RNA polymerase through docking and molecular dynamics simulation studies. They have provided lead molecules from the above functional food sources that may hinder viral replication and transcription.

Considering the medicinal significance of the phytochemical compounds against COVID-19 targets, in this chapter, we discuss the research on virtual screening of around 744 phytochemicals from 37 different plant species for specific COVID-19 targets such as SARS-CoVMpro, MERS-CoVMpro, SARS-CoV2 MPro, Spike glycoprotein, RNA-dependent RNA polymerase, NSP16, NSP10, NSP3 NSP15, and NSP9. Furthermore, in order to understand the effect of phytochemicals from Indian-based functional foods that are used day-to-day and their impact on SARS-CoV-2 targets, main protease, and spike glycoprotein have been investigated using the docking approach.

14.2 Methodology

The general methodology followed in exploring the inhibitory activity of phytochemicals on covid targets using in silico approach is shown in Fig. 14.1. A druggable target for SARS-CoV-2 is identified through a literature review or by using biological sequence databases. Small molecules or ligand molecules are curated from plant phytochemical databases like Dr. Duke's database (1992–2016)/Pubchem database (Kim et al. 2019). The experimentally determined tertiary structures of the proteins were retrieved Protein Data Bank (Berman et al. 2000). Identified targets and ligands are prepared in minimized energy conformation with proper bond angles and distances to improve the docking accuracy. The binding /active sites of the protein targets were identified using the CASTp server (Tian et al. 2018), which is the site the ligand molecule is set for docking. Tools like PyRx 0.8 (Dallakyan and Olson 2015) are used for virtual screening/docking of the phytochemicals using Auto dock/Auto vina module. Docked complexes are analyzed using Discovery Studio Visualizer (BIOVIA) (Accelrys Inc., San Diego, CA, USA).

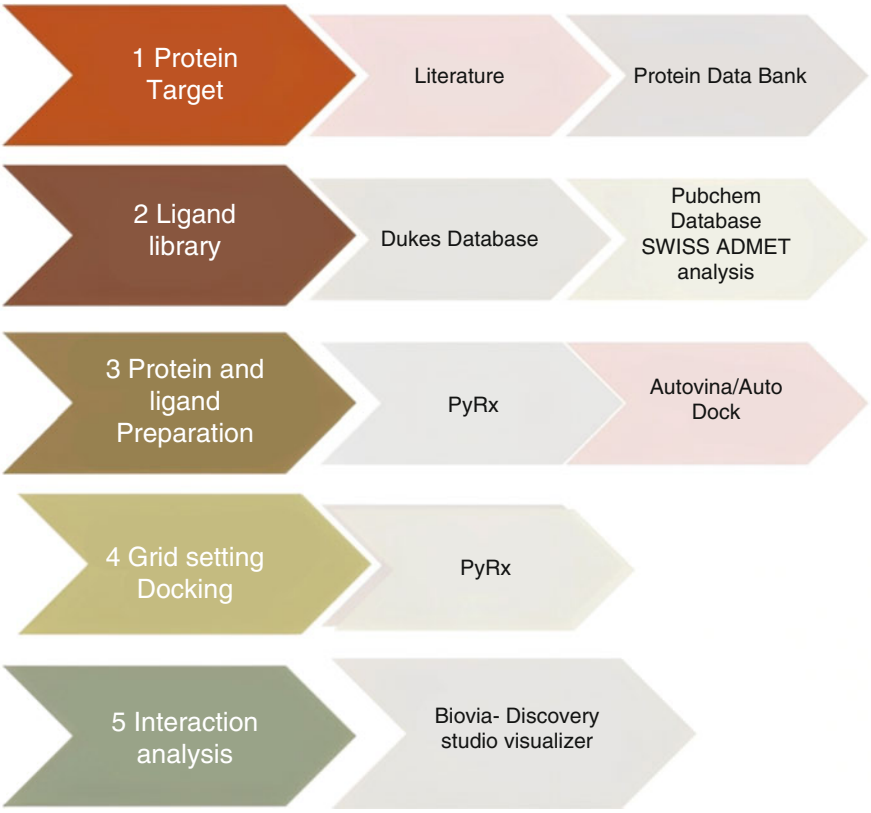

Fig. 14.1 General methodology followed in the identification of phytochemicals that may inhibit SARS-CoV-2 targets using in silico approach

14.3 In Silico Screening of Medicinal Compounds Against CoVID-19 Targets

Our traditional medicines implementing Ayurveda, Siddha, and Unani aged around 5000 years ago remain the golden base behind the current drug discovery programs. Nallusamy et al. (2021) have performed a detailed study on phytochemicals to combat COVID-19 in the identification of novel molecules that could act as an inhibitor of SARS-CoV-2 targets. Auto Vina wizard available in PyRx (Dallakyan and Olson 2015) was used for screening 744 ligands (chemical compounds and bioactive compounds from medicinal herbs) against seven major protein targets. Active site residues were predicted using the CASTp server for the above-mentioned targets are given in Table 14.1. Phytochemicals from "Kabasurakudineer" (Siddha medicine prescribed for immunity booster, AYUSH Board of Government of India) were also included for ligand library preparation. Furthermore, a comparison of the medicinal compounds with that of already existing drugs such as

Table 14.1 Amino acid residues of coronavirus binding sites

Protein Name	Amino acids at the active site (binding site)
Main protease—SARS-CoV-2 (PDB ID: 5R81)	24 T, 25 T, 26 T, 27 L, 41 H, 44 C, 45 T, 46 S, 49 M, 140 F, 141 L, 142 N, 143 G, 144 S, 145 C, 163 H, 164 H, 165 M, 166 E, 167 L, 168 P, 187 D, 188 R, 189 Q, 190 T, 192 Q
Spike protein (PDB ID: 6M0J)	*Chain E*—403 R, 405 D, 406 E, 408 R, 409 Q, 415 T, 416 G, 417 K, 420 D, 421 Y, 449 Y, 453 Y, 456 F, 493 Q, 494 S, 495 Y, 496 G, 497 F, 50 1 N, 502 G, 503 V, 504 G, 505 Y
NSP 12 (PDB ID: 6 M71)	164 D, 166 V, 167 E, 429 F, 430 K, 431 E, 436 E, 437 L, 438 K, 439 H, 440 F, 441 F, 442 F, 452 D, 455 Y, 456 Y, 494 I, 496 N, 497 N, 499 D, 500 K, 501 S,503 G, 507 N, 511 K, 540 T, 541 Q, 542 M, 543 N, 544 L, 545 K, 546 Y, 547 A, 548 I, 549 S, 550 A, 551 K, 553 R, 554 A, 555 R, 556 T, 557 V, 558 A, 559 G, 565 T, 568 N, 569 R, 572 H, 573 Q, 576 L, 577 K, 580 A, 588 V, 589 I, 590 G, 591 T, 592 S, 593 K, 594 F, 598 TRP, 601 M, 602 L, 616 G, 617 TRP, 618 D, 619 Y, 620 P, 621 K, 622 C, 623 D, 624 R, 665 E, 667 V, 676 K, 680 T, 681 S, 682 S, 683 G, 684 D, 685 A, 686 T, 687 T, 688 A, 689 Y, 691 N, 756 M, 758 L, 759 S, 760 D, 761 D, 762 A, 763 V, 792 V, 793 F, 795 S, 797 A, 798 K, 79 C, 800 TRP, 810 H, 811 E, 812 F, 813 C, 814 S, 815 Q, 816 H, 833 D, 835 S, 836 R, 837 I, 840 A, 841 G, 843 F, 844 V, 845 D, 847 I, 848 V, 854 L, 855 M, 857 E,858 R, 859 F, 861 S, 862 L, 864 I, 865 D *C Chain*—3 M, 4 S, 7 K, 40 L, 41 L, 43 K
NSP10 - NSP16 (PDB ID: 6W4H)	6841 N, 6844 K, 6845 Y, 6867 H, 6868 F, 6869 G, 6870 A, 6871 G, 6872 S, 6873 D, 6878 P, 6879 G, 6896 S, 6897 D, 6898 L, 6899 N, 6900 D, 6901 F, 6911 G, 6912 D, 6913 C, 6928 D, 6929 M, 6930 Y, 6931 D, 6932 P, 6933 K, 6947 F, 6968 K
NSP3 (PDB ID: 6 W02)	6 F, 7 S, 8 G, 10 L, 11 K, 12 L,18 I, 19 K, 20 N, 158 K, 161 Y, 162 D, 165 V, 168 F
NSP15 (PDB ID: 6 W01)	69 E, 71 K, 90 K, 196 T, 198 S, 199 R, 200 N, 201 L, 202 Q, 252 L, 255 L, 259 F, 266 L, 268 D, 272 M, 273 D. 274 S, 275 T, 277 K, 279 Y, 295 V, 296 I, 297 D
NSP9 (PDB ID: 6W4B)	13 M, 33 Y, 38 G, 39 G, 40 R, 42 V, 57F, 58 P, 59 K, 60 S, 66 I, 68 T

hydroxychloroquine, chloroquine, and ivermectin was performed to quench the drug-likeness behavior of the molecules against SARS-CoV-2 targets.

Out of the 605 phytochemicals from 37 plant species, 33 phytochemicals from 22 plant species were reported as the best inhibitors with higher binding affinities against seven targets of SARS-CoV-2. Among the above-mentioned 22 plant species, four plants were found to be constituents of "Kabasurakudineer."

Plantwise comparison of phytochemicals that may inhibit SARS-CoV-2 targets using a docking approach highlighted the following plants, *Vitex negundo*, *Solanum nigrum*, *Pedalium murex, Azadirachta indica*, *Terminalia chebula*, *Cissus quadrangularis*, *Clerodendrum serratum*, and *Ocimum basilicum* as predominant entities among the chosen 37 plants. Moreover, phytochemicals such as amentoflavone, catechin-o-gallate, agasthisflavone, and chlorogenin showed higher binding affinity against multiple targets of CoVID-19.

Amentoflavone reported docking scores of −9.3 kcal/mol, −8.3 kcal/mol, −7.4 kcal/mol, −8.5 kcal/mol, and −8.2 kcal/mol for the SARS-CoV-2 targets such as NSP 12, NSP 9, NSP 3, NSP10-NSP16, and spike protein, respectively. Biological activities such as antitumor, antiviral, anti-inflammatory, antioxidative, antidiabetic, and antifungal have been observed for amentoflavone (Yu et al. 2017). Also, it was found to have antisenescence activity in the cardiovascular and central nervous systems (Park et al. 2011).

In the case of agathisflavone, binding affinity values of −8.9 kcal/mol, −8.2 kcal/mol, −8.2 kcal/mol, and −6.6 kcal/mol were predicted on docking with targets NSP 12, SARS-CoV-2 main protease, spike protein, and NSP 3, respectively. Figure 14.2 provides the interaction pattern of RdRp and Spike glycoprotein with ivermectin, agathisflavone, and amentoflavone.

Catechins are the class of compounds that are generally reported in antiviral studies due to their property of increased affinity toward cellular membranes (Kaihatsu et al. 2018). Catechin-o-gallate showed significant binding interactions with the affinity values of −7.3 kcal/mol, −6.6 kcal/mol, −7.9 kcal/mol, and −8.5 kcal/mol against spike protein, NSP3, NSP 12 (RNA-dependent RNA polymerase), and NSP 15, respectively. Chlorogenin which is a constituent of *Solanum torvum* also showed higher binding affinity against multiple targets such as NSP9 (−8.2 kcal/mol), MPro (−7.7 kcal/mol), and NSP16-NSP10 (−7.6 kcal mol), respectively.

14.4 Docking Studies on Food Phytochemicals against SARS-CoV-2 Main Protease (MPro) and Spike Glycoprotein

A total of 63 food crops with 4462 phytochemicals were screened against SARS-CoV-2 MPro and spike glycoprotein to understand the antiviral property of day-to-day food phytochemicals that can help to withstand the adverse effect of COVID-19. For this study, chosen crops were categorized into seven types vegetables, fruits, supplements, spices, pulses, millet, and herbs mainly based on their properties and usage. Details of the number of plants taken under each category are provided in Table 14.2. Information on the phytochemicals, PubChem id, and the plant part are given in Supplementary Table 14.S1.

14.4.1 Docking Experiment and Drug-Like Molecule Prediction

In silico screening of phytochemicals for SARS-CoV-2 antiviral activity was performed using PyRx (0.8) AutoDock module (Dallakyan and Olson 2015). Except

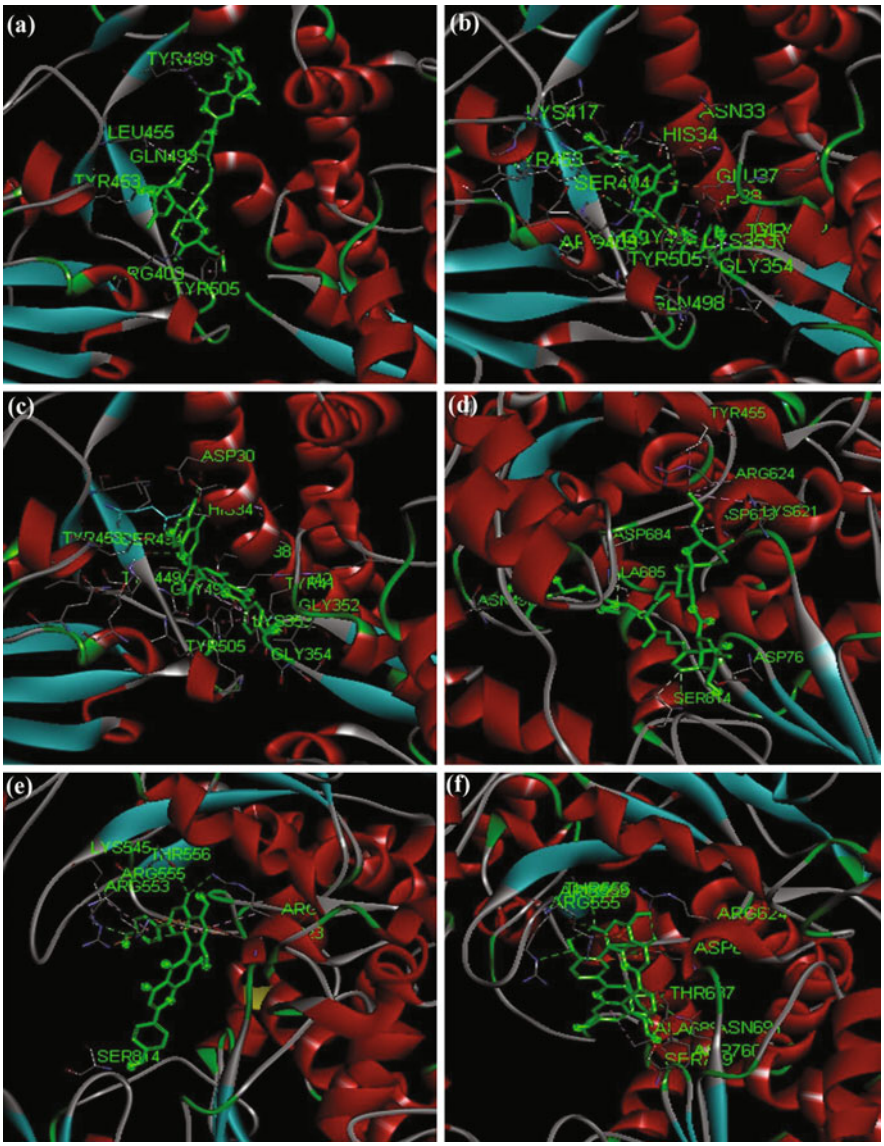

Fig. 14.2 Docked complex structures showing the interaction of spike protein with that of (**a**) ivermectin, (**b**) agasthisflavone, (**c**) amentoflavone and NSP12 with that of (**d**) ivermectin, (**e**) agasthisflvaone, (**f**) amentoflavone

for the docking protocol, all the methods are similar to the previously discussed article by Nallusamy et al. (2021). Details of food phytochemicals were collected from Duke's database and their structures were obtained from the PubChem database. The protein structure was prepared by adding hydrogen atoms by Autodock to

Table 14.2 Information on the number of plants in each category that was used for phytochemical curation is provided

S. No	Name	Number of plants
1	Vegetables	15
2	Fruits	11
3	Supplement	3
4	Spices	7
5	Pulses	4
6	Millets	3
7	Herbs	20
	Total	63

make macromolecule modulation and energy minimization was carried out using SWISS PDB Viewer. The ligand was prepared to the lowest energy conformation using the uff force field available in PyRx software. PyRx (0.8) AutoDock module was used for the generation of pdbqt files of ligands and proteins. Docking was performed using Autodock wizard with the parameters which include Genetic Algorithm runs (100), number of individuals in the population (150), Maximum number of generations (27000), and rate of crossover (0.8). A threshold of −5.0 kcal/ mol was set to streamline the process of identification of antiviral compounds. In the present study, compounds are considered active when their binding affinity value is equal to or greater than −5.0 kcal/mol. All the analyses were performed based on this threshold value.

Fig. 14.3 provides the details of the numbers of phytochemicals curated under each category and the number of phytochemicals that score binding affinity greater than or equal to −5.0 kcal/mol against the spike glycoprotein and MPro. Tables 14.3 and 14.4 provide the details of the docking score and the compounds that are predicted as lead-like inhibitor molecules against SARS-CoV-2 MPro and spike protein. The best three compounds from each category are discussed elaborately in the present chapter for both the target proteins.

14.4.1.1 Vegetables

Oleanolic acid (*Cyprus rotundus*), Gibberellin-a-3 (garlic), and Tocopherols (drum stick) were identified with best binding affinity scores of −11.4 kcal/mol, −9.4 kcal/mol, and − 7.8 kcal/mol, respectively, for the target spike glycoprotein. In the case of MPro, oleanolic acid, gibberellin-a-3, and rotundifoline (mint leaves) were reported as inhibitors with the highest binding affinity of (−12.7 kcal/mol), −11.9 kcal/mol, and − 9.4 kcal/mol, respectively.

Oleanolic Acid: *Cyprus rotundus*

The antiviral activity of essential oils from *Cyprus rotundus* has a proven role against hepatitis B virus (HBV) and also has hepatoprotective characteristics (Wu and

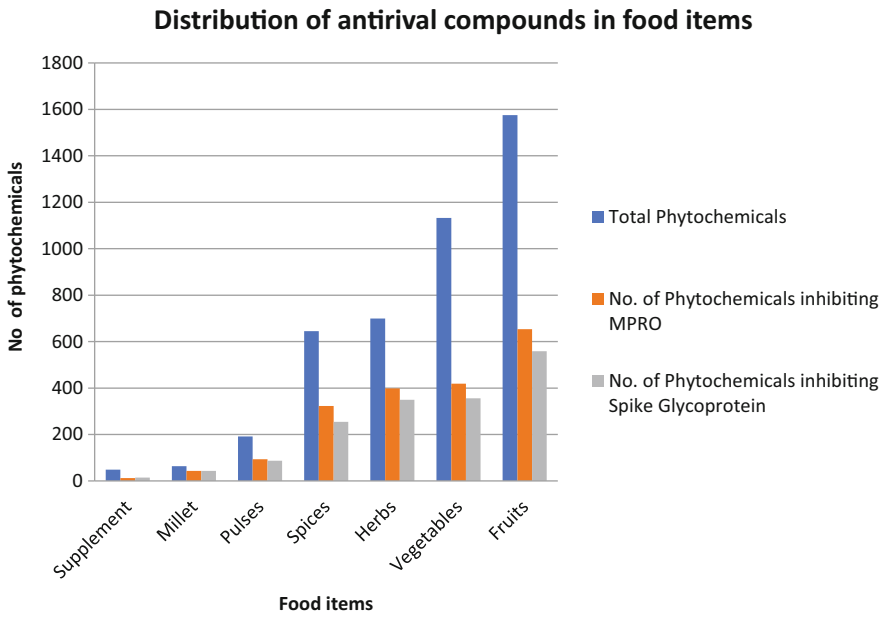

Fig. 14.3 Details of phytochemicals studied under each food category and their inhibition potential statistics based on docking score are given

McGoogan 2020; Khwaza et al. 2018). Animal and test-tube studies have displayed the antiviral nature of oleanolic acid against herpes viruses, HIV influenza, and hepatitis, which is a component of *C. rotundus*.

Giberellin-a-3- Garlic

Garlic (*Allium sativum* L.) is a commonly consumed food and has been used as medicine against a number of virus diseases such as HIV, HSV 2, pneumonia, and rotavirus, etc. (Rouf et al. 2020; Bayan et al. 2014).

Tocopherols- Leaf- Drum Stick

Moringa olefiera is one of the most important traditional plants with medicinal value where most of its parts are edible using which many Indian dishes are prepared. Apart from its antiviral property, it is used to treat many medicinal properties like anemia, headache, malaria, diabetes, tuberculosis, etc. (Biswas et al. 2020; Siddiqui et al. 2022). Moreover, tocopherol has been reported for its drug-likeness property against SARS-CoV-2 spike glycoprotein using docking and simulation approaches by Siddiqui et al. (2022).

Table 14.3 Screening of top three phytochemicals for each food category against SARS-CoV-2 spike protein

Phytocompound	Pubchem id	Plant parts	Plant	Binding affinity Kcal/mol
Vegetables				
Oleanolic acid	10,494	Tuber, bulb	*Cyprus rotundus*,	−11.4
Gibberellin-a-3	52,921,570	Bulb	*Allium sativum*	−9.4
Tocopherols	14,986	Leaf	*Moringa oleifera*	−7.8
Spices				
Crataegolic acid	73,659	Flower	*Syzygiumaromaticum*	−12
Zingiberol	5,317,270	Rhizome	*Zingiber officinale*	−8
Gamma-eudesmol	6,432,005	Rhizome	*Zingiber officinale*	−8
Sesquiterpenes	53,790,872	Leaf	*Cinnamomum verum*	−7.9
Millet				
Violanthin	448,438	Finger millet	Finger millet	−7.6
Narigenin	442,428	Finger millet	Finger millet	−7.5
Orientin	5,281,675	Finger millet	Finger millet	−7
Flavonoids	53,787,266	Pearl millet	Pearl millet	−7
Pulses				
Delta-tocopherol	92,094	Seed	*Arachis hypogaea*	−7.8
Vitamin E	14,985	Seed	*Arachis hypogaea*	−7.7
Cajanone	325,518	Plant	*Cajanus cajan*	−7.5
Herbs				
Maslinic acid	73,659	Leaf	*Eucalyptus globulus*	−12
Triterpenoid	451,674	Leaves	*Abutilon indicum*	−11.6
Oleanolic acid	10,494	Leaf	*Eucalyptus globulus*	−11.4
Oleanolic acid	10,494	Leaf	*Ocimum basilicum*	−11.4
Oleanolic acid	10,494	Leaf	*Ocimum tenuiflorum*	−11.4
Fruits				
Corilagin	73,568	Fruit	*Phyllanthus emblica*	−12
Citrusin-ii	102,082,877	Fruit	*Citrus sinensis*	−11.8
Oleanolic acid	10,494	Pericarp	*Vitis vinifera*	−11.4
Supplements				
Coronene	9115	Ghee	Ghee	−7.4
Riboflavin	493,570	Plant	Spirulina	−7.1
Epoxygedunin	6,708,724	Ghee	Ghee	−7.1

Rotundifoline: Mint Leaves

Rotundifoline is a novel compound with antiviral activity obtained from the present analysis of food phytochemicals.

Table 14.4 Screening of top three phytochemicals for each food category against SARS-CoV-2 MPro

Phytocompound	Pubchem id	Plant part	Plant	Binding affinity kcal/mol
Vegetable				
Oleanolic acid	10,494	Tuber, bulb	*Cyprus rotundus*	−12.7
Gibberellin-a-3	52,921,570	Bulb	*Allium sativum*	−11.9
Rotundifoline	139,055,911	Leaves	*Mentha piperita L* Mint leaves	−9.4
Spices				
Crataegolic acid	73,659	Flower	*Syzygiumaromaticum*	−12.3
Sesquiterpenes	53,790,872	Leaf	*Cinnamomum verum*	−8.7
Sesamin	72,307	Flower, root	*Piper longum*	−8.3
Millet				
Vitexin	5,280,441	Panicle	Finger millet	−8.2
Isoorientin	114,776	Panicle	Finger millet	−7.8
Isovitexin	162,350	Panicle	Finger millet	−7.4
Pulses				
Alpha-amyrin	73,170	Root	*Cajanus cajan*	−8.3
Vitamin e	14,985	Seed	*Arachis hypogaea*	−7.8
5,7,2′-trihydroxyisoflavone	44,257,268	Root	*Cajanus cajan*	−7.6
Herbs				
Nimbinene	44,715,635	Leaf	*Azadirachta indica*	−13.1
Nimbandiol	157,277	Leaf	*Azadirachta indica*	−12.9
Triterpenoid	451,674	Leaves	*Abutilon indicum*	−12.8
Fruits				
Citrusin-ii	102,082,877	Fruit	*Citrus sinensis*	−15.1
Corilagin	73,568	Fruit	*Phyllanthus emblica*	−14.2
Limonexic-acid	5,321,283	Fruit	*Citrus sinensis*	−13.3
Supplement				
Coronene	9115	Ghee	Ghee	−7.4
Epoxygedunin	6,708,724	Ghee	Ghee	−7.1
Riboflavin	493,570	Plant	Spirulina	−7.1
Spathulenol	92,231	Honey	Honey	−5.8

14.4.1.2 Spices

Among the spices category, crataegolic acid (*Syzygiumaromaticum)* scored good binding affinity of −12.0 kcal/mol and − 12.3 kcal/mol (Fig. 14.4b) for spike glycoprotein and MPro, respectively. Other compounds such as zingiberol (*Zingiber officinale)*, gamma-eudesmol (*Zingiber officinale)*, and Sesquiterpenes (Cinnamon) were reported for the spike glycoprotein. Sesquiterpenes (−8.7 kcal/mol) was also reported as an inhibitor for the MPro target, scoring high among the top three

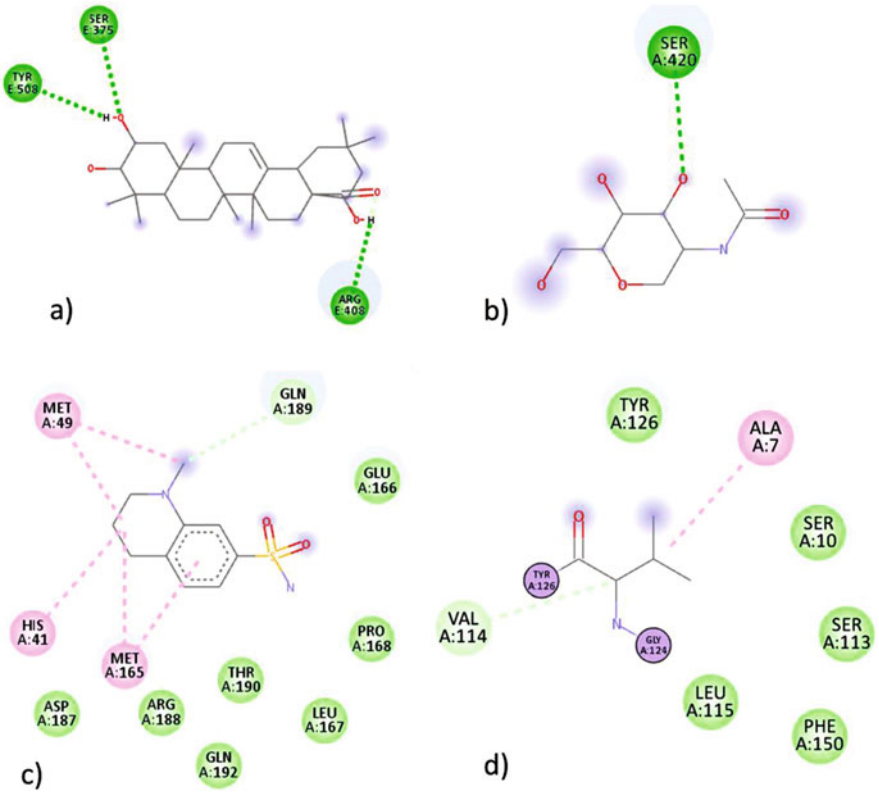

Fig. 14.4 Docked complex structures of spike protein with (**a**) Corilagin, (**b**) Crataegolic acid (**c**) Citrusin-ii (**d**) Corilagin

inhibitors. Sesamin from *Piper Longum* was the third-highest inhibitor among the screened compounds.

Crataegolic Acid-*Syzgiumaromaticum*

Syzygium aromaticum L (Clove) is a well known dietary spice that has been used for several years in traditional medicine for many disorders such as respiratory ailments, antiviral, and anti-inflammatory properties (Vicidomini et al. 2021).

Zingiber officinale

Zingiber officinale Roscoe (Ginger) is an important spice in many food items and remains the constituent of phenolic compounds, terpenes, polysaccharides, lipids, organic acids, and raw fibers (Mao et al. 2019; San Chang et al. 2013). Ginger also

has the important property of smoothing the airway muscle for easier breathing (Townsend et al. 2013).

Zingiberol (Baliga et al. 2011) remains the main constituent of ginger rhizome aroma and is identified as a potent compound against spike glycoprotein. Furthermore, another compound from ginger, namely, gamma-eudesmol was observed to have the highest binding affinity against spike glycoprotein which was also reported by Tran et al. (My et al. 2020) reported as one of the active inhibitors for SARS-CoV-2 MPro through computational studies.

Sesquiterpenes-Cinnamon

Cinnamon which is an essential oil was found to have strong antiviral activity against a wide range of pathogenic viruses (Allahverdiyev et al. 2004). Cinnamon contains the phytochemical sesquiterpenes which are major class terpenes.

Piper longum

Piper longum L. (Long pepper) is recognized as one of the important constituents of indigenous medicines. It has varied pharmacological activities such as antiviral, anticancer, immunomodulatory, cardioprotective, antimicrobial, antifungal, bioavailability-enhancing and antioxidant (Choudhary and Singh 2018). Sesamin from long pepper has reported −8.3 kcal/mol binding affinity against MPro.

14.4.1.3 Millets

A total of 63 phytochemicals from three millets, namely proso millet, finger millet, and pearl millet were taken for screening the anti-SARS-CoV-2 inhibitors. Phytochemicals from finger millet (violanthin, narigenin, orientin, vitexin, isoorientin, and isovitexin) and pearl millet (Flavonoid) have the highest score against spike glycoprotein and MPro targets. Major phytochemicals from finger millet have been reported as top binding inhibitors of covid targets. Minor cereals such as finger millets and pearl millets are highly enriched with phytochemicals, vitamins, calcium, dietary fiber (Hassan et al. 2021), and polyphenol compounds. Additionally, it possesses antidiabetic, antitumorigenic, atherosclerogenic effects, antioxidant, and antimicrobial properties (Devi et al. 2014).

Violanthin was reported as a SARS-CoV-2 MPro inhibitor (Vincent et al. 2020) that may have a role in reducing shortness of breath, sore throat, etc. Naringenin is an important flavonoid known for its biological activities such as antioxidant, anti-inflammatory, and antiviral properties (Tsiani and Den Hartogh 2019). Orientin and isoorientin were reported for several activities including antioxidant, antiaging, antiviral, antibacterial, anti-inflammation, vasodilatation and cardioprotective, antiadipogenesis, antinociceptive, radiation protective, neuroprotective, and

antidepressant-like effects (Lam et al. 2016). Vitexin and isovitexin were used in conventional Chinese medicines, where they have many properties such as antioxidant, anticancer, anti-inflammatory, antihyperalgesic, and neuroprotective effects (He et al. 2016).

14.4.1.4 Pulses

Four pulses such as ground nut, sprouted green gram, black gram, and pigeon pea containing 191 phytochemicals were virtually screened for their anti-covid properties. Peanut (Delta-tocopherol, Vitamin E) and pigeon pea (Cajanone, alpha-amyrin, 5,7,2′-trihydroxyisoflavone) were the two pulses that reported the highest binding affinity phytochemicals with the chosen SARS-CoV 2 targets, respectively.

Oil seed - Arachis hypogaea (Peanut)

Arachis hypogaea L. is an important commercial crop worldwide that has been used for the production of oil and it serves as an important source of protein. Its pharmacological attributes lie in heart disease, body weight management, anticancer, antiviral, and antidiabetes properties (Harrod et al. 2022). Delta-tocopherol is well known for its medicinal value such as anticancer, lysosomal storage disorders, and anti-inflammatory properties. Its derivative D-α-tocopherol polyethylene glycol succinate (TPGS) (Makau et al. 2018) was identified as a potential antiviral compound against SARS-CoV-2 and β-coronaviruses that showed strong synergy with remdesivir through in silico screening and in vitro viral inhibition assay studies. A fat-soluble antioxidant, vitamin E stops the production of reactive oxygen species when fat undergoes oxidation. Furthermore, the role of vitamin E in the prevention of chronic diseases is being investigated (Huang et al. 2007).

Cajanus cajan (Pigeon Pea)

Pigeon pea is used in Chinese and Brazilian traditional medicine known for their nutritional and medicinal properties such as antioxidant, antidiabetic, antimicrobial, DNA damage protective, and xanthine oxidase inhibitory properties and to treat cough (Mathew et al. 2017). This study has reported the antiviral properties of three compounds mentioned above which are constituents of the pigeon pea against SARS-CoV-2 targets. Cajanone is one of the well-studied antimycobacterial compounds (Coronado-Aceves et al. 2017) and is predicted to have antiviral properties in the present study. Alpha-amyrin () possesses antioxidant, anti-inflammatory, antiarthritis, and antiviral properties. 5,7,2′-trihydroxyisoflavone has shown its relevance to an anti-covid property in the cited literature (Sainz-Cort and Heeroma 2020).

14.4.1.5 Herbs

Maslinic acid/Crataegolic acid (−12.0 kcal/mol), Triterpeniod (−11.6 kcal/mol), and Oleanolic acid (−11.4 kcal/mol) are the top three phytochemicals reported for the target spike glycoprotein. *Eucalyptus globulus* (Martin 2005), *Abutilon indicum* (Abat et al. 2017), *Ocimum basilicum* (Shahrajabian et al. 2020), and *Ocimum tenuiflorum* (Prakash and Gupta 2005) are medicinal plants that are well known for their pharmacological activities have reported the above-mentioned phytochemicals variedly.

For the MPro target, nimbinene (13.1 kcal/mol), nimbandiol (−12.9 kcal/mol), and triterpenoid (−12.8 kcal/mol) were predicted as inhibitors. Nimbinene and nimbandiol are phytoconstitutents of *Azadirachta indica* (Alzohairy 2016), which is a plant of traditional medicinal value used generation over generations.

14.4.1.6 Fruits

Orange (Gonçalves et al. 2017) has a proven record of antiviral activity, and this study has found two compounds, namely citrusin-ii and limonexic acid (only MPro) were predicted as inhibitors of SARS-CoV-2 targets. Citrusin -ii (Fig. 14.4c) was predicted to have the highest binding score of −15.1 kcal/mol among all the screened plant metabolites of various food categories against the target MPRO. Limonexic acid (−13.3 kcal/mol for spike protein), which is a limonoid (Tundis et al. 2014), has shown anticancer, antibacterial, antifungal, antimalarial, and antiviral activities.

Oleanolic acid from grapes was listed in the top three predicted inhibitors of spike glycoprotein. Grapes juice was reported to have antiviral properties (Cliver and Kostenbader Jr 1979) in a number of studies. Among the 417 phytochemicals investigated in grapes, 174 and 193 phytochemicals have shown binding affinity equal to or more than −5.0 kcal/mol for spike and MPro targets. Among all the other fruits investigated in the present study, grapes had the maximum phytochemicals and maximum predicted inhibitors within the cutoff value of −5.0 kcal/mol.

Corilagin, which is a phytoconstituent of gooseberry (an Indian traditional medicinal plant) and an anti-SARS-CoV-2 inhibitor (Yang et al. 2021) exhibited a binding score of −12.0 kcal/mol and −14.2 kcal/mol for MPro and spike glycoprotein (Fig. 14.4a, d), respectively.

14.4.1.7 Supplements

In supplementary food items phytochemical investigation, epoxygedunin, riboflavin and spathulenol from ghee, spirulina, and honey were predicted as inhibitors against MPro, spike glycoprotein. A smaller set of 49 phytochemicals were studied under this category. Regarding the properties of the reported phytochemicals, spathulenol

(do Nascimento et al. 2018) has antioxidant, anti-inflammatory, antiproliferative, and antimycobacterial properties in earlier studies. Riboflavin, which is a B vitamin, is known for its antioxidant, antiaging, anti-inflammatory, antinociceptive, and anticancer properties (Suwannasom et al. 2020). Epoxygedunin (James and Thomas 2019) was observed to have anticancer properties from earlier reported studies.

Plants that possess a higher number of antiviral molecules have been analyzed in which only the top ten plants are discussed. Grape (193 and 174), Pepper (83 and 74), Orange (72 and 72), Ginger (71 and 63), Carrot (67 and 71), Onion (62 and 56), Eucalyptus (61 and 63), Fenugreek (56 and 59), and *Piper longum* (53 and 49) are the plants reported to have a higher number of phytochemicals that inhibits both MPro and spike glycoprotein protein targets. Banana and papaya were observed to have 49 phytochemicals each with a binding affinity score of more than −5.0 kcal/mol against spike glycoprotein alone, whereas wheatgrass reported 58 phytochemicals showing an antiviral property specific to MPro. Fruits, vegetables, spices, and herbs are the categories of the above-mentioned plants which possess a higher number of anti-covid phytochemicals compared to pulses, supplements, and millet. Information on the total number of phytochemicals and antiviral activity based on the docking score are given in the Supplementary Fig. 14.S1.

Network illustrates (Fig. 14.5a) the compounds that may inhibit spike glycoprotein and MPro. Interestingly, eleven compounds such as coronene, riboflavin, sesquiterpenes, giberellin-a3, corilagin, crategolic acid, oleanolic acid, triterpenol, epoxygedunin, citrusin-ii, and vitamin E have shown highest binding affinity against both spike glycoprotein and Mpro targets.

To understand the distribution of phytochemicals with antiviral properties among the chosen 63 plants, the percentage of antiviral molecules was computed for each plant based on the ratio of a total number of compounds and a total number of compounds with a docking score equal to or greater than −5.0 kcal/mol. A total number of compounds that have reported binding affinity equal to or greater than −5.0 kcal/mol are considered antiviral molecules. Figure 14.5b shows the presence of the highest number of phytochemicals in the millets and the least number in the supplement food items such as ghee, honey, and spirulina. The second and third highest were observed with herbs and pulses, respectively. This statistic provides knowledge on the phytochemicals present in the particular food and their antiviral efficiency on comparison within seven food categories taken for this analysis.

14.5 Conclusion

Virtual screening of thousands of food nutraceuticals and phytochemicals resulted in the prediction of potent inhibitors from daily consumed food items. Although the present work is based on predictions, they provide us the clue to explore the phytochemicals that can be further taken for drug testing and clinical trials. Naturally occurring phytochemicals have a good impact on human health with fewer hazards/side effects in comparison to synthetic chemicals. Plants contain vital

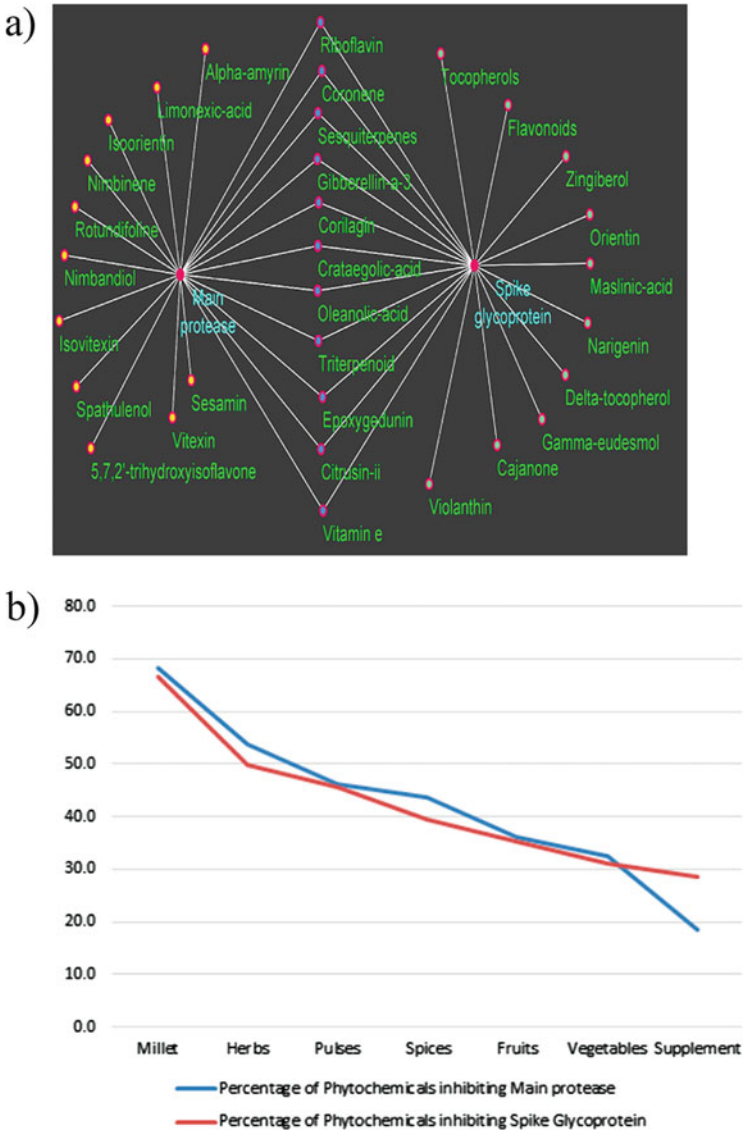

Fig. 14.5 (**a**) Network diagram of predominant inhibitors having the highest docking score unique and common to main protease and spike glycoprotein, respectively (**b**) Percentage value forecasting the impact of different food categories and their antiviral property

phytochemicals that emphasize healthy food habits and lifestyles to combat severe viral diseases such as COVID. It is essential to consume all food items in different categories in different combinations that may have a synergistic effect to inhibit the function of viral targets. Some of the food items are neglected totally from our dining due to the changing lifestyle. In this line, millets, which are high nutrient enriched

small grains have drawn the attention of the globe has invoked the announcement of "International millet year in 2023" to create awareness among the public. Food remains the hub of most of the antiviral molecules and it enlightens the way of healthy living by combating several diseases and symptoms.

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Chapter 15
Therapeutic and Prophylactic Effects of Plant Derivatives Against SARS CoV-2

Vinotha Viswanathan and Vaseeharan Baskaralingam

15.1 Introduction

The single-stranded enveloped RNA virus family is known as coronavirus which are belonging to the Coronaviridae family. Coronavirus has caused respiratory tract, gastrointestinal tract, and neurological diseases (Wu et al. 2020; Bhavaniramya et al. 2022b). As stated by WHO (World Health Organization), COVID-19 was caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) which cause severe health risk worldwide. The family of coronaviridae has Letovirinae and Orthocoronavirinae as subfamilies. Among, Orthocoronavirinae consist of α, β, γ, and δ coronaviruses. Amidst, α and β viruses infect mammals while the γ and δ variants affect the avians and are also opportunistic to mammals. Herein, SARS-CoV-1 and 2 belong to the β variants (Cui et al. 2019; Amanat and Krammer 2020; Harrison et al. 2020). SARS-CoV-2 (Fig. 15.1) mainly causes acute respiratory distress (ARDS), pneumonia, renal failure, and finally death. Fever and cough are the common symptoms of SARS-CoV-2 (Fig. 15.2a). However, asymptomatic conditions have also been recorded recently (Wang et al. 2020; Chan et al. 2020). The mode of transmission of SARS-CoV-2 is highly through respiratory droplets, person-to-person or any surfaces contact, and oral transmission from fecal (Fig. 15.2b) (Otter et al. 2016; Harrison et al. 2020).

During the pandemic condition, SARS-CoV-2 was recognized as a major public health emergency by the unit of WHO as it is been a key threat to the human population. Moreover, it influences the global economy. The SARS-CoV-2 infection is been a threatened disease globally due to its easy and rapid transmission between human populations through droplets (Srivastava and Saxena 2020; Ghosh et al.

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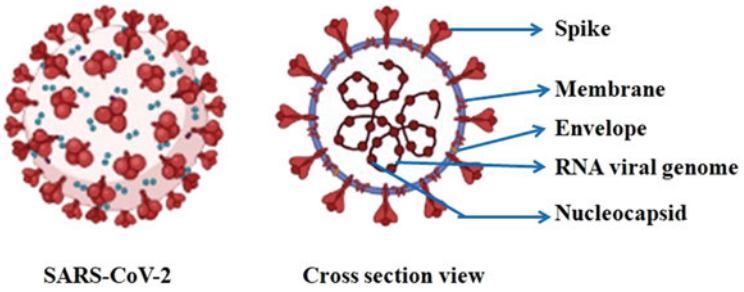

Fig. 15.1 Structure of Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2)

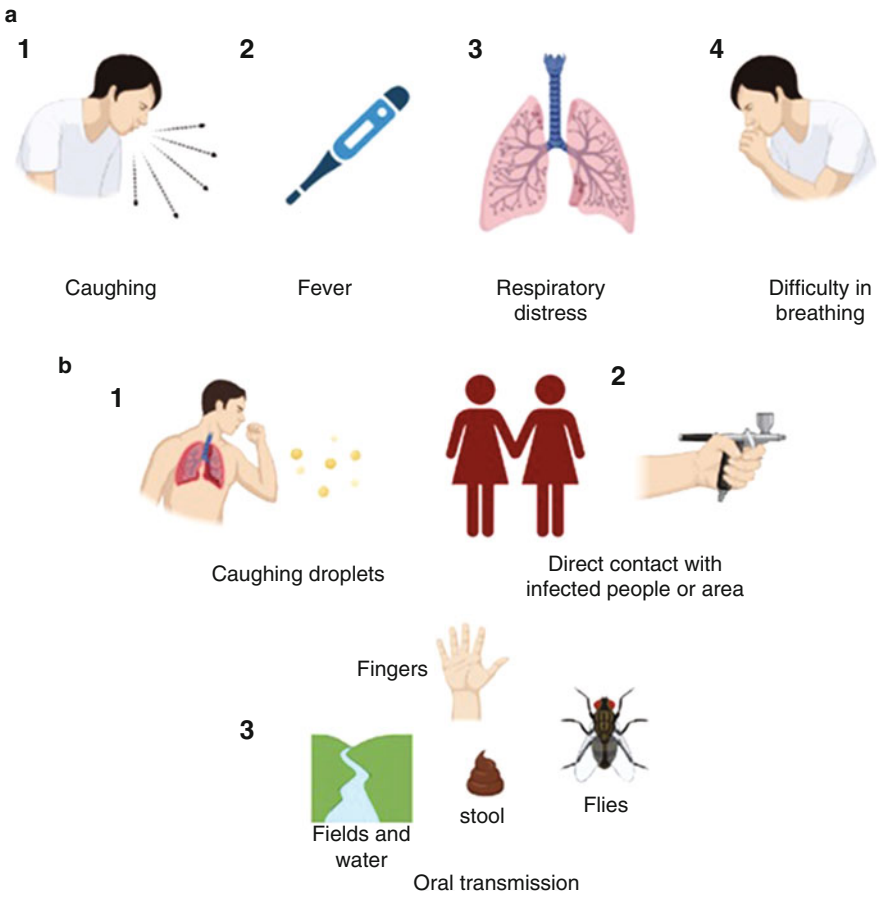

Fig. 15.2 (**a**) Symptoms and (**b**) Transmission of SARS-CoV-2 infection

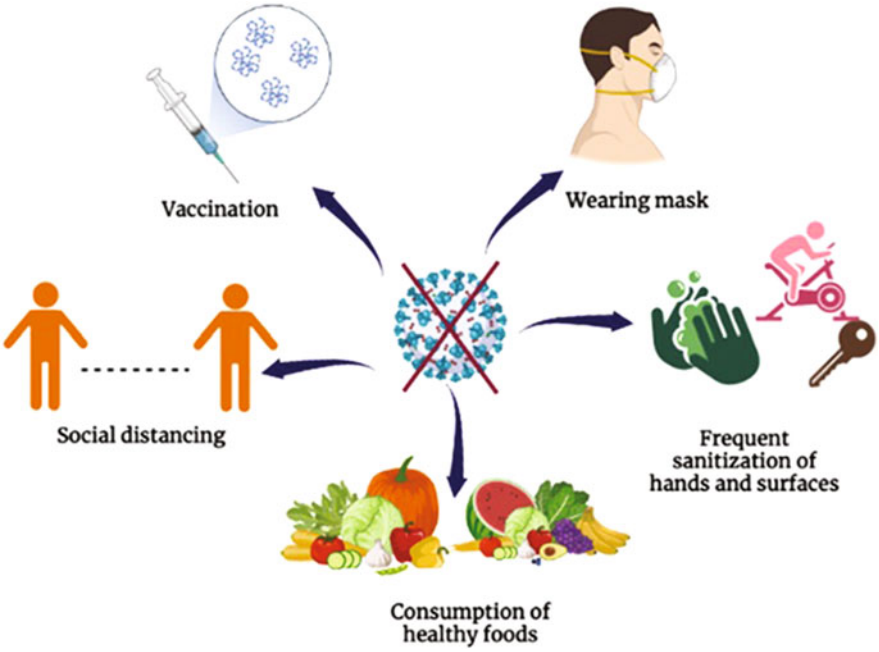

Fig. 15.3 Prevention measures of SARS-CoV-2 infection

2021). Predominantly, vaccination against COVID-19 viruses at frequent intervals helps to prevent or reduce the risk of transmission and susceptibility in the host. Moreover, the practice of frequent hand washing, using mouth covering, keeping at least 6 feet distance between people, isolation of infected people, and consumption of nutrient-rich food could enhance immunity, and avoidance of dispensable gathering might reduce the risk of COVID-19 (Fig. 15.3) (Srivastava and Saxena 2020; Prather et al. 2020; Zolezzi et al. 2021; Centers for Disease Control and Prevention 2021). Still, no approved medications are available to fight against COVID-19. Hence, the only way to defeat SARS-CoV-2 is to find a drug to fight against them at their specific receptors involved in the replication process. Nowadays, many researchers are focused on the development of a product that could target the specific receptors [i.e., angiotensin-converting enzyme II (ACE2), spike protein, RNA-dependent RNA polymerase (RdRp), nonstructural protein (Fig. 15.4)] (Elfiky 2020; Abdelli et al. 2021; Babadaei et al. 2021; Velusamy et al. 2021; Bhavaniramya et al. 2022a). Recently, Senthil Kumar et al. (2021) reported that antcins isolated from *Antrodia* species significantly restrain the ACE2 receptor.

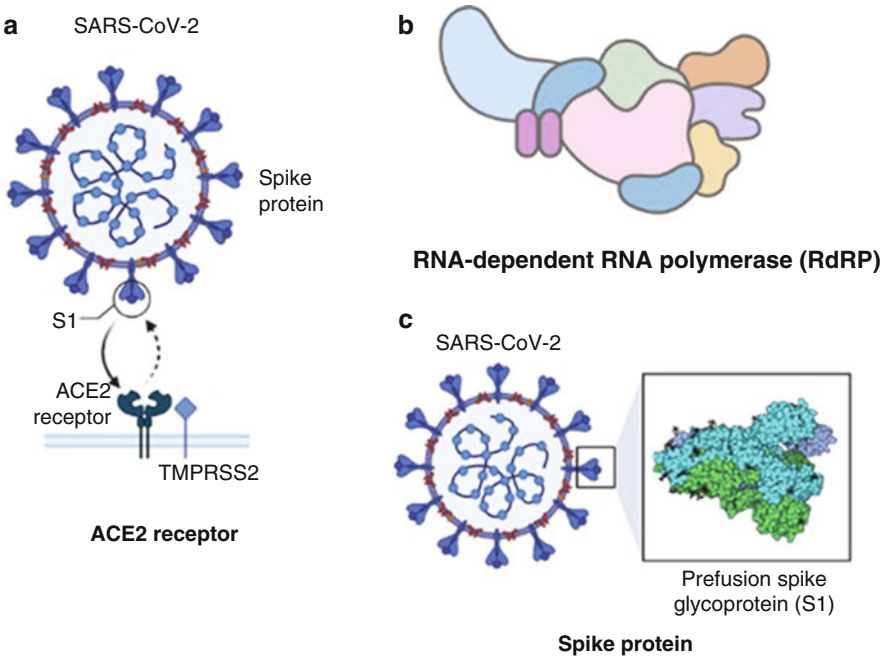

Fig. 15.4 SARS-CoV-2 recognition receptors (**a**) Angiotensin-converting enzyme II (ACE2), (**b**) RNA-dependent RNA polymerase (RdRp), and (**c**) Spike protein

15.2 Therapeutic Plants

Therapeutic plants are the ultimate agents who always participated in the day-to-day life of human beings. In the form of food, medicine, prophylactic agent, and traditional cultures the plants are taken place in the daily routine. Moreover, therapeutic plants are rich in secondary metabolites including flavonoids, phenolics, polyphenols, tannins, saponins, and alkaloids possess antibacterial, antifungal, antioxidant, anti-analgesic, anti-inflammatory, and especially antiviral activity. Typically, various parts of the plants including leaves, roots, stem or barks, flowers, and seeds were extremely utilized in the antiviral activity from ancient times (Fig. 15.5). For instance, *Scutellaria edelbergii* extract was reported for its antibacterial, anti-inflammatory, and anti-analgesic activity in Swiss albino mice (Shah et al. 2021); anti-diabetic and anti-cancer activity of *Cuminum cyminum* was also reported earlier (Mnif and Aifa 2015). Similarly, *Aloe vera* species was found to be effective in antibacterial, antiviral, and anti-cancer activities. In addition, *Aloe vera* could regulate the immune system and are a hepatoprotective agent (Gao et al. 2019). On the other side, a combination of essential oil from three different medicinal plants exhibits prophylaxis against respiratory syncytial virus (RSV) (Tseliou et al. 2019). Some therapeutic plants and their derivatives reported for antiviral properties are listed in Table 15.1.

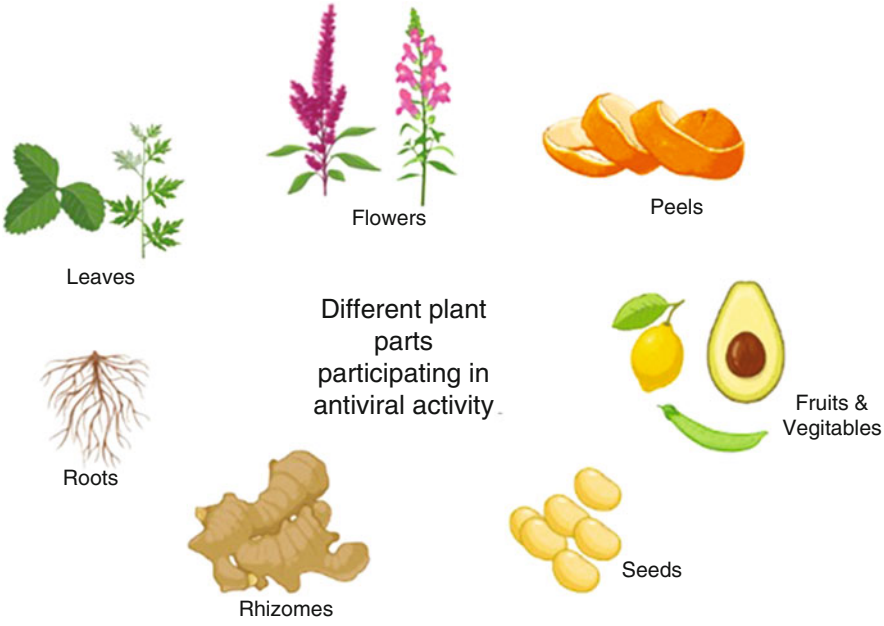

Fig. 15.5 Various parts of therapeutic plants involved in antiviral activity

15.3 The Therapeutic Effect of Plant Derivatives Against SARS-CoV-2

As stated above, therapeutic plants and their derivatives have the potential to control viral infections from ancient times. Therapeutic plant derivatives also expressed prophylactic effects against COVID-19 (Divya et al. 2020). Recently, Shree et al. (2022) reported the phyto-compounds Withanoside V and Somniferine derived from Ashwagantha, Tinocordiside derived from Giloy, and Vicenin, Isorientin 4'-O-glucoside 2"-O-p-hydroxybenzoagte and Ursolic acid from Tulsi expressed high affinity toward the virus particle. Similarly, the botanical derivatives from Amla, Bhumi Amla, and Giloy are proficiently engaging the protease binding point in COVID-19 (Murugesan et al. 2021). Identical in silico studies on the relationship between plant derivatives and the viral particle have been listed in Table 15.2. Also, the chemical structure of some therapeutic plant derivatives that can fight against SARS-CoV-2 has been illustrated in Fig. 15.6.

Table 15.1 Therapeutic plants and their derivatives reported for antiviral properties

Sl. No	Name of the plant	Part used	Nature of the sample	Plant derivatives if any	Viral infection	Reference
1	*Nepeta nepetella*		Aqueous extract	–	HSV1	Abad et al. (2000)
2	*Dittrichia viscosa*	–	Aqueous extract	–	VSV, poliovirus type 1	Abad et al. (2000)
3	*Desmodium canadense*, *Mentha piperita*, and *Thymus vulgaris*	–	Aqueous extract	–	Avian infectious bronchitis virus	Lelešius et al. (2019)
4	*Morus alba var. alba*, *Morus alba var. rosea*, *and Morus rubra*	Leaves and bark	Aqueous and methanol extract	–	Human coronavirus (HCoV 229E), and single-stranded RNA viral strains	Thabti et al. (2020)
5	*Veronica persica Poir.*	–	Methanol extract	–	HSVs 1 and 2	Sharifi-Rad et al. (2018)
6	*Antidesma bunius*, *Caseria graveolens*, *Cleistanthus patulus*, *Colebrookea oppositifolia*, *Hypericum gaitii*, *Millettia extensa*, *Protium serratum*, *Rubus ellipticus*, and *Ventilago maderaspatana*	–	Aqueous extract	–	Enterovirus-71	Panda et al. (2017)
7	*Euphorbia coopire* and *Morus alba*	Flowers and leaves	Chloroform and aqueous methanol extract	7-galloyl catechin, Gallic acid, Kaempferol 3-O-β-(6″-*O*-galloyl)-glucopyranoside, quercetin 3-*O*-*β*-(6″-*O*-galloyl)-glucopyranoside, and Kaempferol	HSV-1	El-Toumy et al. (2018)
8	*Baccharis gaudichaudiana*	Aerial parts	Organic extract	–	HSV-1	Visintini Jaime et al. (2013)

9	*Solanum nigrum*	Seeds	Methanol and chloroform extract	–	Hepatitis C virus	Javed et al. (2011)
10	*Acacia nilotica*	–	Acetone and methanol extract	–	Hepatitis C virus	Rehman et al. (2011)
11	*Zingiber officinale*	Rhizomes	Aqueous extract	–	Chikungunya virus (CHIKV)	Kaushik et al. (2020)
12	*Andrographis paniculata* and *Momordica charantia*	–	Methanol extract	–	Dengue virus serotype 1 (DENV-1)	Tang et al. (2012)
13	*Trachyspermum ammi*	Seeds	Essential oil	–	Japanese encephalitis virus (JEV)	Roy et al. (2015)
14	–	–	–	Baicalein	Dengue virus serotype 2 (DENV-2)	Zandi et al. (2012)
15	*Zingiber officinale*	Rhizome (fresh)	Hot water extract	–	Human respiratory syncytial virus (HRSV)	San Chang et al. (2013)
16	*Phyllanthus emblica*	Branches and leaves	–	Pentagalloylglucose (PGG)	Influenza A virus	Liu et al. (2011)
17	*Agrimonia pilosa*	Whole plant	Ethanol extract	–	Human influenza viruses (H1N1 and H3N2 influenza A&B subtypes)	Shin et al. (2010)
18	*Phyllanthus* spp.	–	Aqueous and methanol extract	–	DENV-2	Lee et al. (2013)
19	*Scutia buxifolia*	Leaves and stem bark	Ethanol extract	–	HSV-1	Boligon et al. (2013)

(continued)

Table 15.1 (continued)

Sl. No	Name of the plant	Part used	Nature of the sample	Plant derivatives if any	Viral infection	Reference
20	*Lagerstroemia speciosa*	Leaves	–	Ellagic acid	Human rhinoviruses (HRVs)	Park et al. (2014)
21	*Azardirachta indica*	Bark	Aqueous extract	–	HSV-1	Tiwari et al. (2010)
22	*Bletilla striata*	Rhizome	Ethanol extract	Diphenanthrenes	Influenza A virus	Shi et al. (2017)
23	*Nepeta nuda*	Aerial parts	Chloroform extract	–	HSV-1 and 2	Todorov et al. (2015)
24	*Byrsonima verbascifolia*, *Myracrodruon urundeuva*, *Eugenia dysenterica* and *Hymenaea courbaril*	Leaves	Ethanol extract	–	Rotavirus SA11	Cecílio et al. (2012)
25	*Radix isatidis*	Root and leaves	Aqueous extract	–	Scbrood virus (SBV)	Sun et al. (2021)
26	*Acorus calamus*, *Cymbopogon citrates*, and *Myristica fatua*	–	Methanol extract	–	DENV-2	Rosmalena et al. (2019)
27	*Embelia ribes*	Fruits	Ethyl acetate	–	Influenza virus A	Hossan et al. (2018)
28	*Syzygium jambos*	Leaves	Ethanol	–	HSV-1	Twilley et al. (2017)
29	*Artocarpus heterophyllus*	Leaves	Dichloromethane	–	Hepatitis C virus (HCV)	Hafid et al. (2017)

30	*Portulaca oleracea*	Aerial part	Aqueous extract	–	Influenza A viruses	Li et al. (2019)
31	*Cissampelos pariera*	–	Alcoholic extract	–	DENV – 1 to 4	Sood et al. (2015)
32	*Ocimum sanctum* and *Acacia arabica*	Leaves	Crude extract	Terpenoid (Ocimum) and polyphenol (acacia)	Avian influenza (AI) H9N2	Ghoke et al. (2018)
33	*Heracleum lehmannianum*, *H. ponticum*, *H. aconitifolium*	Root	Essential oil	–	Influenza virus A and B	Tkachenko (2007)
34	*Radix isatidis*	–	–	Clemastanin B, Epigoitrin, Phenylpropanoids portion and Phenylpropanoids, alkaloids, and organic acid combination	Influenza virus	Ping et al. (2016)
35	*Coridothymus capitatus*, *Origanum dictamnus*, and *Salvia fruticosa*	–	Combination of essential oils	–	Influenza A/H1N1 virus, influenza B and human rhinovirus 14 (HRV14)	Tseliou et al. (2019)
36	*Lavandula angustifolia* and *Salvia officinalis*	–	Essential oil	–	Avian influenza H5N1 virus	Abou Baker et al. (2021)

Table 15.2 In silico studies on the relationship between plant derivatives and SARS-CoV-2

Sl. No	Name of the plant	Plant derivatives	SARS-CoV-2 target site/Mode of interaction	Reference
1	*Curcuma longa*	Cyclocurcumin	SARS-CoV-2 (Mpro)/formation of two hydrogen bonds with amino acid residues of COVID-19 Mpro	Rajagopal et al. (2020)
2	*Withania somnifera*	Withanolide and Withanone	SARS-CoV-2 (Mpro)/quercetin-3-rutinoside-7-glucoside	Kushwaha et al. (2021)
3	*Curcuma longa*	Cuminoid and Tetrahydroxycurcumin	SARS-CoV-2 (Mpro) /hydrogen bonding	Ghosh et al. (2021)
4	*Sesamum indicum*	Sesami, Sesaminol, and Sesamolin	SARS-CoV-2 (Mpro)/formation of two hydrogen bonds with amino acid residues	Natesh et al. (2021a)
5	*Ferula asafoetida*	Farnesiferol B	SARS-CoV-2 (Mpro)/amino acid residues and indicated H-bond	Natesh et al. (2021a)
6	*Camellia sinensis*	Allocatechin-3-gallate	SARS-CoV-2 (Mpro)/amino acid residues and indicated H-bond	Ghosh et al. (2021)
7	*Heracleum candicans*	Candibirin H, Candibirin G	SARS-CoV-2 3CLpro and PLpro/ hydrogen bonding	Natesh et al. (2021b)
8	*Acacia nilotica*	Catechin 5-O-gallate, Kaempferol 3-glucoside 7-rhamnoside, Kaempferol7,4′-diglucoside	SARS-CoV-2 3CLpro and PLpro, SARS-CoV-2 spike protein/hydrogen bonding	Natesh et al. (2021b)
9	*Hypericum perforatum* L.	Hypericin, Pseudohypericin, 6,6′-biapigenin	SARS-CoV-2 3CLpro, SARS-CoV-2 spike protein and PLpro/hydrogen bonding	Natesh et al. (2021b)
10	*Tribulus terrestris* L.	Tribuloside, Tribulosin	SARS-CoV-2 spike protein/hydrogen bonding	Natesh et al. (2021b)
11	–	Deacetylnomilin, Ichangin, nomilin, and β-amyrin (Terpinoids)	SARS-CoV-2 spike and Mpro/hydrogen bonding	Giofrè et al. (2021)

(continued)

Table 15.2 (continued)

Sl. No	Name of the plant	Plant derivatives	SARS-CoV-2 target site/Mode of interaction	Reference
12	*Oxalis pes-caprae*	Caeruleanone A	SARS-CoV-2 (Mpro)/hydrophobic interaction	Gul et al. (2022)
13	*Ocimum menthiifolium*	Apigenin-7-O-rutinoside, Prunin, and Acaciin	nsp16/10 complex of SARS-CoV-2	Albohy et al. (2022)
14	*Rhus succedanea*	Amentoflavone and Agathisflavone (as biflavonoid)	SARS-CoV-2 (Mpro)/interact with catalytic residues	Lokhande et al. (2020)
15	*Camellia sinensis*	Oolonghomobisflavan-A (polyphenol)	SARS-CoV-2 (Mpro)	Bhardwaj et al. (2021)
16	*Camellia sinensis*	Epigallocatechin gallate, Gallocatechin-3-gallate, and Epicatechin gallate	SARS-CoV-2 (Mpro)/interact with catalytic residues	Ghosh et al. (2021)
17	*Nigella sativa*	Campesterol, Cycloeucalenol, alpha-spinasterol and Beta-sitosterol	N-terminal RNA binding domain and Papain-like protease of SARS-CoV-2	Siddiqui et al. (2022)
18	*Silybum marianum*, *Withania somnifera*, *Tinospora cordifolia*, and *Aloe barbadensis*	Silybin, Withaferin A, Cordioside, and Catechin and quercetin	SARS-CoV-2	Pandit and Latha (2020)
19	*Boesenbergia rotunda*	Panduratin A	SARS-CoV-2	Kanjanasirirat et al. (2020)
20	*Echinacea purpurea*	Echinaforce	SARS-CoV-2	Signer et al. (2020)

15.4 Prophylactic Effect of Plant Derivatives

It is said, "prevention is better than cure" which means prevention is a safe way to stay away from any problem, especially infections or diseases, and also this practice shields us from the severity of the problem. From ancient times, the therapeutic plants and the phyto-compounds derived from the therapeutic plants are well-known prophylactic agents as well as curative agents. Prophylaxis of SARS-CoV-2 has predominantly depending on the improvement of immunity. Some plants are a rich source of immune boosters. Specifically, the consumption of *Phyllanthus emblica* (Amla) enhances the immune system and protects from SARS-CoV-2 infection because Amla is rich in vitamin C (Kapoor et al. 2020). Magzoub (2020) suggested that the consumption of ginger (*Zingiber officinale*) juice (12 mg/250 mL) can diminish the vulnerability to SARS-CoV-2 by increasing the amount of IgM.

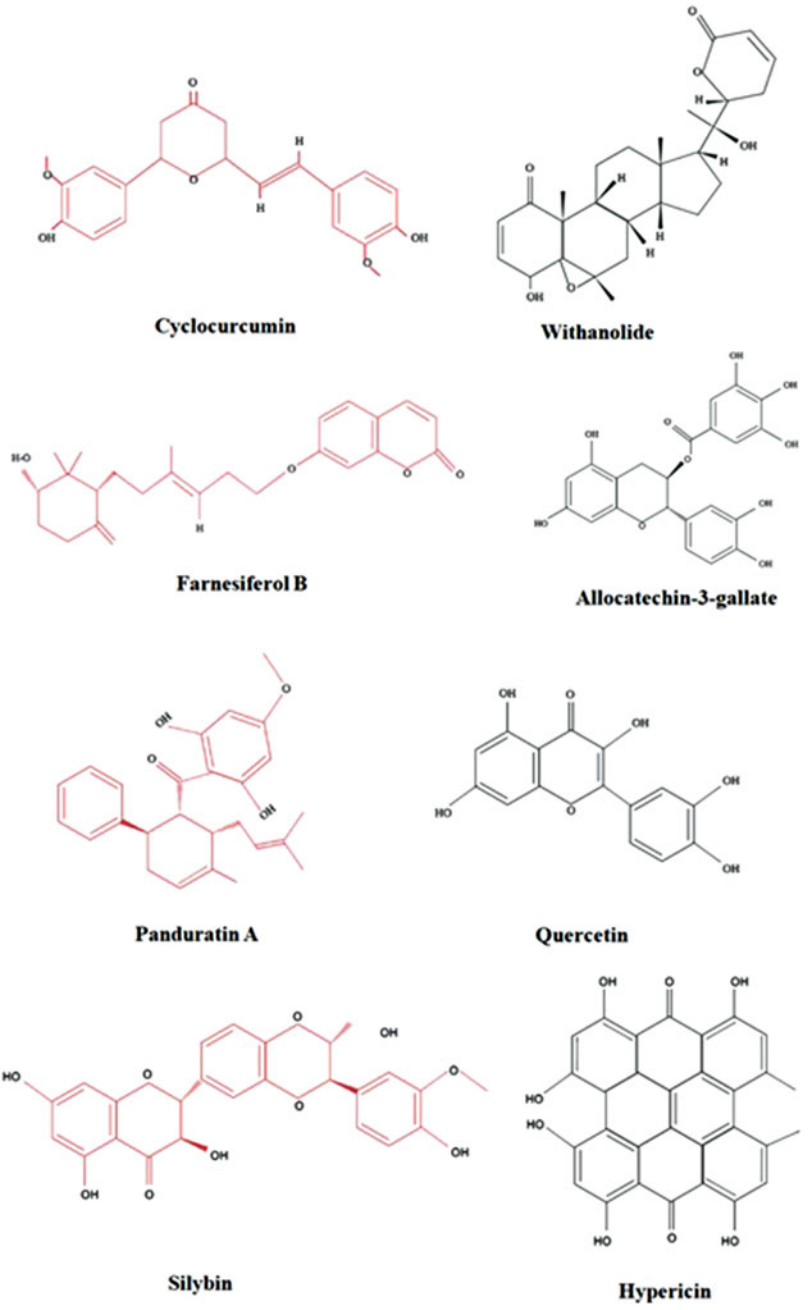

Fig. 15.6 Therapeutic plant derivatives involved in antiviral activity against SARS-CoV-2

Predominantly, the AEC2 receptor facilitates the entry of the virus inside the host; hence it is recognized as a significant receptor. Therefore, the inhibition of the AEC2 receptor is greatly preferable for prophylactic activity (Senthil Kumar et al. 2021). Previously, some in silico studies revealed that the polyphenols isolated from pomegranate peels have high affinity toward the Mpro region of SARS-CoV-2 suggesting the binding probability with ACE2, also the affinity was more stable which offers prevention of infection (Rakshit et al. 2021). Alike, pre- and post-administration of Oleandrin a phytochemical isolated from *Nerium oleander* restrain the replication of viral particles and reduce the risk of infection (Plante et al. 2020). Limited studies are available on the experiment of the prophylactic effect of plant derivatives. Hence, there is an open forum and also an immense need to experiment with the prophylactic effect of plant derivatives to develop effective alternatives to existing vaccines.

15.5 Conclusion and Prospective

From the ancient period, plants and their derivatives played a vital role in the control of many pathogenic microorganisms, especially viruses. Moreover, the therapeutic plants and their derivatives were effectively involved in the prophylactic activity. Numerous studies revealed that extracts, essential oils, and secondary metabolites from therapeutic plants could efficiently control the viral replication process. Particularly, some plant derivatives, including phenols, saponins, flavonoids, etc., could interrupt specific receptor recognition. Many in silico studies suggest the utilization of therapeutic plant derivatives to control the infection. Though, the insufficient reports on the experimental pieces of evidence on the relationship between the therapeutic plant derivatives and the SARS-CoV-2 virus have been the major limitation. Due to this reason, the development of therapeutic plant-mediated drugs/vaccine development was getting delayed. Therefore, more in vitro and clinical trials on the prophylactic and antiviral efficiency of therapeutic plant derivatives against SARS-CoV-2 infection were needed and it might be facilitated the development of target-specific and highly safe alternatives.

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Chapter 16
Therapeutic Potential of Essential Oils against SARS-CoV-2 Infection

Muhammad Adil, Pragya Tiwari, and Jen-Tsung Chen

16.1 Introduction

The present era has witnessed a tremendous global health crisis and rising mortality rates due to the ongoing coronavirus disease 2019 (COVID-19) pandemic. The SARS-CoV-2 (a new strain of coronavirus), primarily originated in China, gradually dissiminated across the world and created a major health disaster to the global economy. However, this expanding health catastrophe was effectively tackled by the high-throughput advances in medical science, via the development of various COVID-19 vaccines (Alshrari et al. 2022). In the last few years, a new variant of coronavirus has emerged and controlled with effective medications/vaccines. Moreover, another variant, B.1.167 has been currently detected in many countries including India, Canada and the United Kingdom (Sanyaolu et al. 2021). With a fast mutation and multiplication characteristics, the emergence of a more deadly and infectious viral strain (Malabadi et al. 2021) cannot be ruled out, however, with effectual healthcare and bio-based therapeutics, these challenges can be addressed and countered to a major extent.

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Herbal medicines have been traditionally used for the treatment of human diseases and are gaining recognition as effective therapeutics in the current era. Bioactive components and extracts from multiple plants have demonstrated pharmacological effects in the treatment of multiple diseases including diabetes, cancer and neurological diseases, either used individually or in combination therapies. The volatile secondary metabolites from plants, known as essential oils, are classified into distinct chemical classes as hydrocarbons (sesquiterpenes, monoterpenes, diterpenes, etc.), oxygenated hydrocarbons (terpenoids comprising phenols, aldehydes, alcohols, etc.), non-terpene compounds (eugenol, cinnamaldehyde, etc.), and other compounds (Schnitzler et al. 2011; Bora et al. 2020). Essential oils are widely used in our daily life as aromatherapeutic agents, air fresheners, perfumes and aromatic waters. Besides, essential oils also comprise an integral part of folk and traditional medicine, and exhibit multiple bioactivities including antioxidant, antimicrobial, immunomodulatory, sedative and antirheumatic properties (Brahmi et al. 2016; Dhifi et al. 2016; Bora et al. 2020). While essential oils are produced by more than 17,000 plant species, classified into diverse plant families, and extracted from multiple plant parts, namely flowers, leaves, fruits and roots, primarily an aromatic ingredient of specialized plant tissues (Schnitzler et al. 2011), with aromatic essential oils forms the basis of aromatherapy.

Plant-derived essential oils constitute a complex mixture of phytochemicals, originating from phenylpropanoids, monoterpene and sesquiterpene classes (Ma and Yao 2020; Tshibangu et al. 2020) and possess wider applications in pharmaceutical, perfume and soap industries. Regarded as a prospective strategy for tacking SARS-CoV-2 in recent times, essential oils are effective in restricting the growth of diverse pathogens, on account of their volatile components and chemical composition (Swamy et al. 2016). The use of essential oils highlights several advantages, including high lipophilicity, rapid action, small size, virucidal properties at low concentrations, high vapor pressure, low cost of preparation, and prospects as a prophylactic agent in the initial stages of viral pneumonia (Elsebai and Albalawi 2022). A key example is eucalyptol, with its vital physicochemical properties and pharmacological functions, which reveals its prospects as a drug in the prevention and treatment of COVID-19. Moreover, other major examples of essential oils as effective therapeutics against SARS-CoV-2 comprise the eucalyptus oil (jensenone and eucalyptol/1,8-cineol), garlic oil (garlicin, allitridin, ajoene), aromatic herbs (essential oils of *Laurus nobilis*, *Juniperus oxycedrus* ssp. oxycedrus), and other essential oils with potent antiviral activities (Elsebai and Albalawi 2022).

In a quest toward the discovery of potent therapeutics against SARS-CoV-2, essential oils show antiviral activity, owing to their lipophilicity, disruption of the viral membrane and viral disintegration (Elsebai and Albalawi 2022). Moreover, many bioactive components of crude essential oils act on different parts of the virus (entry in the cell, transcription, virus assembly and translation), and are gaining popularity as attractive bio-based therapeutics against SARS-CoV-2. Studies have suggested that essential oils and their bioactive molecules can be used as adjuvants for viral disease treatment, resulting in milder disease forms and improving the overall health status of patients (Damiescu et al. 2022). Consequently, randomized

clinical trials are necessary for standardizing the bioactive constituents and determining the efficacy of potent active compounds, of essential oils against SARS-CoV-2.

16.2 Physicochemical and Pharmacokinetic Characteristics of Essential Oils

Some essential oils, such as eucalyptol, have distinct physicochemical properties, causing their presence in the lungs via exhalation and exerting their pharmacological action in low doses (Usachev et al. 2013). While asymptomatic patients are crucial in the diseas transmission, eucalyptol exerts virucidal effects both on oral administration in the lower respiratory tract and inhalation in the upper respiratory tract, thus preventing the virus from spreading to other body organs (Wölfel et al. 2020). Many essential oils are commercially marketed as antimicrobials and are important alternatives to chemical agents, specifically in the mileau of rising microbial resistance to conventional drugs (Gutierrez et al. 2008). Studies have documented the effects of essential oils from *Anthemis hyalina*, *Nigella sativa* and *Citrus sinensis* on coronavirus replication and TRP gene expression (Ulasli et al. 2014).

The initial progress of SARS-CoV-2 occurs via targeting lungs and airways, the primary site of infection, therefore, it is suggested that essential oils should be administered via inhalation, causing a direct action in the lungs and other parts of respiratory tract. This administration route of essential oils provides a better option to hamper the binding interactions between SARS-CoV-2 spike proteins and their ACE-2 receptors, located in the parenchymatous lung cells (Elsebai and Albalawi 2022). In addition, lung-based delivery of potent essential oils with anti-SARS-CoV-2 function constitutes a remarkable approach for achieving the desired outcome (Dent et al. 2013). Another key advantage of inhaled drugs with reference to essential oils comprises their low molecular weights and high vapor pressures, therefore these substances are exhaled from the lungs and lead to non-specific anti-inflammatory action, further improving their pharmacological function (Dent et al. 2013). These characteristics enable the eucalyptol to persist in the lungs and cause its local virucidal effect (Sharifi-Rad et al. 2017).

With the pharmacological effects of essential oils and their constituents well reported, the application of essential oils against viral diseases is widely explored in the current era. Essential oils are capable of penetrating and subsequently rupturing the viral cell membrane by their sufficient lipophilic potential (Elsebai and Albalawi 2022). The metabolism of essential oils proceeds via multiple degradative pathways and functions of different enzymes in vivo. It is equally important to determine the chemical profiles of essential oils and their respective constituents. The safety profiles of essential oils can be elucidated by the biotransformation of essential oils in phase I metabolism (reduction, oxidation and hydrolysis etc.) and phase II metabolism (Al-Harrasi et al. 2020). In addition, studies have reported the

pharmacodynamics of multiple essential oils during in vitro conditions however, the availability of essential oils in different organs has been unknown. This necessitates a requirement to explicate the absorption, distribution, metabolism and excretion of essential oils for understanding the link between in vivo and in vitro studies. Moreover, it is also imperative to comprehend the bioavailability as well as the pharmacokinetic properties of essential oils and their constituents (Al-Harrasi et al. 2020).

16.3 Therapeutic Basis of Essential Oils with Reference to SARS-CoV-2 Infection

Apart from the symptomatic treatment in terms of anti-inflammatory, anticoagulant and antipyretic agents, monoclonal antibodies and antiviral drugs such as monlupiravir and remdesivir have been previously used against COVID-19 infection with varying success rates (Elsebai and Albalawi 2022). Essential oils exhibit diverse pharmacological spectra characterized by anticancer, antioxidant, anti-inflammatory, insecticide and antimicrobial effects (Galvan et al. 2021). Bioactive substances of various essential oils such as tea tree oil, thyme oil and eucalyptus oil are used as an adjunct to conventional therapeutic agents against flu and common cold, whereas, those of *Allium sativum*, *Echinacea purpurea*, *Echinacea angustifolia* and *Zingiber officinale* are useful for their immunostimulant potential (Damiescu et al. 2022). Essential oils from anise (*Illicium verum*), eucalyptus, sandalwood (*S. album*), chamomile (*Matricaria recutita*), and others have shown promising antiviral effects against HSV-1 and/or HSV-2 (Schnitzler et al. 2001), essential oils from *Artemisia glabella* (Seidakhmetova et al. 2002), *Origanum acutidens* (Sökmen et al. 2004), *Oenanthe crocata* (Bonsignore et al. 2004), against influenza viruses, essential oils from *Eucalyptus globulus* (eucalyptus), *Ocimum basilicum album* (tropical basil), *Lavandula latifolia* (lavender), and others against HSV-1, highlight the potential efficacy of essential oils against multiple viruses.

Essential oils have been extensively used in folk medicine on account of their miscellaneous pharmacological effects including antimicrobial, immunomodulatory, antioxidant, anti-inflammatory, mucolytic and antirheumatic properties (Brahmi et al. 2016; Dhifi et al. 2016). Moreover, spoilage bacteria and food-borne pathogens are highly susceptible to the combinations of essential oils (Gutierrez et al. 2008; Mutlu-Ingok and Karbancioglu-Guler 2017). The antiviral efficacy of essential oils has been documented against a wide range of pathologically important viruses including yellow fever virus, human and avian influenza viruses, human herpes viruses (HSV-1 and HSV-2), Zika virus, avian influenza A virus (H_1N_1), influenza A virus (H_5N_1), human immunodeficiency virus (HIV), and SARS-COV-2 (Astani et al. 2010; Schnitzler et al. 2011; Ma and Yao 2020; Rouf et al. 2020). The effectiveness of essential oils against enveloped single-stranded positive RNA viruses has been validated through in vitro assays as well as experimental studies

using animal models (Wilkin et al. 2020). Likewise, both in vitro and in vivo studies have revealed the additive pharmacological effects of oseltamivir and germacrone combination against the influenza virus (Liao et al. 2013). Moreover, the hsp1 was successfully targeted by a synergistic combination of acyclovir and 4., piperitenone oxide which is the active ingredient of *Mentha suaveolens* essential oil (Civitelli et al. 2014). Concurrent use of *Melissa officinalis* essential oil improved the antiviral effect of oseltamivir against avian influenza A virus (Pourghanbari et al. 2016). Improved clinical outcomes characterized by reduced lung pathological index, pulmonary cytokines expression and viral titers, whereas, enhanced survival rate have been associated with the synergistic pharmacological benefit resulting from the co-administration of oseltamivir and eucalyptol (Lai et al. 2017).

Immunomodulatory, mucolytic and anti-inflammatory effects are also useful to combat viral respiratory diseases including the SARS-COV-2 infection. Consequently, the use of essential oils is gradually increasing in medicine, cosmetics, pharmaceutics, food and other industries. Simply targeting the SARS-COV-2 using specific antiviral drugs may not provide a complete solution to COVID-19 infection. Therefore, essential oils characterized by anti-inflammatory, antioxidant, antimicrobial and immunomodulatory effects can properly relieve the clinical manifestations of COVID-19 infection by suppressing the pulmonary inflammatory cascade and preventing secondary bacterial infection (Wilkin et al. 2020). Based upon their high volatility and ease of inhalational administration, essential oils can be effectively used to subside sore throat, coughing, expectoration, nasal congestion and rhinorrhea (Horváth and Ács 2015; Valussi et al. 2021). The optimal antimicrobial efficacy of essential oils entails their application for disinfecting closed areas wherein enhanced proliferation of SARS-COV-2 is projected.

16.4 Major Bioactive Constituents and Pharmacological Mechanisms of Essential Oils Against SARS-CoV-2

Essential oils and their purified bioactive substances may represent a relatively less explored source of useful antiviral drugs for add-on therapy of viral infections (Wilkin et al. 2020). Whole essential oils are usually preferred over purified constituents by virtue of multiple pharmacological actions, reduced probability of microbial resistance and synergistic effects (Popa et al. 2020). Antifungal, antibacterial and antiviral activities have been documented for many essential oils and their derivative compounds (Swamy et al. 2016; Wińska et al. 2019). Sesquiterpenes and monoterpene hydrocarbons have been implicated in triggering the potential antiviral activity of essential oils (Sobrinho et al. 2021). Different pharmacological mechanisms of essential oils have been shown in Fig. 16.1. The synergistic constituents of essential oils in combination therapies, improve the efficacy of other antiviral drugs and alleviate COVID-19 symptoms (Da Silva et al. 2020). Various steps of viral replication such as cell entry, assembly, transcription and translation

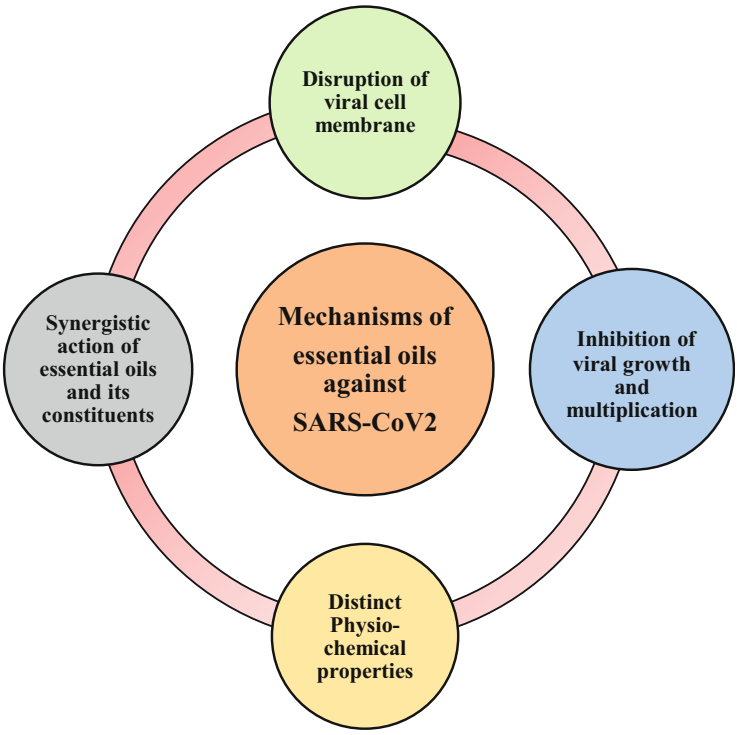

Fig. 16.1 Different mechanisms of action of essential oils against SARS-CoV-2

can be impaired by several bioactive ingredients of crude essential oils (Elsebai and Albalawi 2022). Several proteins of SARS-COV-2 have been effectively targeted using different bioactive components of essential oils including carvone, thymoquinone, camphene, limonin, carvacrol, eucalyptol and thymol (Neto et al. 2021). The majority of tested substances primarily targeted the spike protein of SARS-COV-2 that has been associated with the cell entry of virus following its attachment to specific ACE-2 receptors (Neto et al. 2021).

Molecular docking analysis revealed the synergistic inhibitory actions caused by 17 different compounds of garlic essential oil on Mpro and ACE-2 proteins of SARS-COV-2 (Thuy et al. 2020). ACE-2 antagonism has also been attributed to the principal ingredient of *Ammoides verticillata* essential oil, called isothymol (Abdelli et al. 2021). Moreover, the bioactive substance called zerumbone exhibited a high affinity for spike protein-human cell ACE-2 receptor complex (Neto et al. 2021; Sharbidre et al. 2021). Endoribonuclease which is essential for the replication of SARS-COV-2 and restricts the host defense mechanism can be efficiently inhibited using curion (Hackbart et al. 2020). Another substance known as caryophyllene demonstrated a high affinity for non-structural RNA-binding protein-9 RP1A as well as spike protein, spro (Neto et al. 2021). Likewise, the bioactive components of South Asian plant, *Melaleuca cajuputi*, including

α-eudesmol, β-selinenol, γ-eudesmol, cineol, linalool, guaiol and terpineol displayed a synergistic inhibitory effect on viral replication via interacting with ACE-2 receptor (My et al. 2020). Cysteine protease enzyme having a pivotal role in the viral replication process was successfully targeted by spatholinol, himachalol and eudismol (Neto et al. 2021). Several major ingredients of different essential oils such as pulegone, menthol, camphene, cinnamaldehyde, anethole, geraniol, thymol and carvacrol inhibited viral replication by targeting the S1 element of the spike protein (Kulkarni et al. 2020). Menthol, eugenol, carvacrol and cinnamaldehyde suppressed the synthesis of proinflammatory cytokines and recruitment of macrophages in the bronchoalveolar fluid (Wani et al. 2021). Essential oils of juniper, lemon and geranium are also known for their inhibitory effects on ACE-2 receptor of SARS-COV-2 (Kumar et al. 2020). Ethanolic preparation consisting of methyl salicylate, eucalyptol, thymol and menthol (Listerine®) demonstrated significant antiviral effect during an in vitro study (Stathis et al. 2021). Moreover, in silico evidence is available regarding the blockage of S1 unit of viral spike protein by mouth rinses comprising of pinocarveol, caryophyllene, myrtenol and carvacrol (Yadalam et al. 2021).

Different bioactive compounds, including γ-terpinene, p-cymene, limonene, thymol and isothymol, derived from the Algerian plant, *Ammoides verticillate*, were screened for their in silico ACE-2 inhibitory actions. Isothymol was found as the most effective ACE-2 receptor antagonist with its binding affinity equivalent to that of chloroquine and captopril (Abdelli et al. 2021). The diverse flora of the Amazon region has also been examined for potential antiviral efficacy against SARS-CoV-2 using the molecular docking technique. Several of the tested compounds such as humulene epoxide II, hedycaryol, guaia-6,9-diene, germacrene A, azulenol, aristochene, amorpha-4,9-dien-2-ol, allo-aromadendrene epoxide, 14-hydroxy-muurolene, α-muurolene, α-calacorene, α-cadinene, α-amorphene and (E)-α-atlantone have reflected antiviral effects (Amparo et al. 2021). Buriti oil obtained from *Mauritia flexuosa* and containing α-carotene, 9-cis-β-carotene and 13-cis-β-carotene has been implicated in interacting with the viral peptidase enzyme (Costa et al. 2021). Similarly, a palm tree known as Coco de Mer (*Lodoicea maldivica*) comprising monoterpenes, bicyclogermacrene and β-caryophyllene has been linked with antimicrobial potential (Giuliani et al. 2020). Faster recovery and suppression of clinical manifestations were documented in COVID-19 patients following the twice utilization of *Nigella sativa* oil capsules (500 mg) for 10 days (Koshak et al. 2021). Based upon their preliminary antiviral actions, the essential oils of *Melaleuca alternifolia* (tea tree) and *Laurus nobilis* are also considered as potential anti-COVID agents, requiring further pharmacological screening (Loizzo et al. 2008; Schnitzler et al. 2011).

16.5 Conclusion and Future Recommendations

Essential oils obtained from medicinal plants have been traditionally used in several parts of the world for different pharmaceutical benefits. Accordingly, the pharmacotherapeutic significance of aromatherapy seems inevitable in the milieu of SARS-COV-2 infection. Different parts of cultivated or wild plants including leaves, flowers, bark, root or fruits are used for the extraction of essential oils (Damiescu et al. 2022). Standardized preparations of certain essential oils are commercially available in the form of nasal sprays, gels, creams and capsules, and are widely used for the treatment of different viral infections (Damiescu et al. 2022). Several beneficial aspects of essential oils including high lipophilicity, smaller molecular size, rapid onset of action, wide safety margin, high vapor pressure, efficient virucidal activity, ease of synthesis and formulation, convenient oral administration, and lack of first-pass metabolism reflect their therapeutic and prophylactic significance in conjunction with the typical antiviral drugs for the treatment of viral pneumonia (Elsebai and Albalawi 2022). Essential oils can be used as an adjunct to conventional antiviral agents in countries with deprived healthcare facilities and limited availability of effective vaccines (Damiescu et al. 2022). Nevertheless, highly concentrated formulations of some essential oils can give rise to detrimental effects such as vomiting, nausea, dizziness and epileptic seizures upon oral administration (Damiescu et al. 2022). Lack of standardized dosage forms, direct cytotoxic reactions and poor solubility are some of the drawbacks that limit the widespread application of some essential oils for therapeutic purpose (Damiescu et al. 2022). Besides, some essential oils can also lead to tissue irritation or a burning sensation on the cutaneous/mucosal surface. However, the nano-emulsion formulations have considerably minimized the likelihood of undesirable effects and enhanced the therapeutic utility of essential oils (Damiescu et al. 2022).

Several commercially available essential oils have been linked with efficient antimicrobial effects and thereby necessitate further investigation of their pharmacological potential to combat the extensively rising microbial resistance (Gutierrez et al. 2008; Wińska et al. 2019; Kakhki et al. 2020). Eucalyptol is considered a promising candidate drug against SARS-COV-2 infection on account of its suitable physicochemical profile and diverse pharmacological effects (Elsebai and Albalawi 2022). The currently available in silico data regarding the antiviral efficacy of essential oils against SARS-COV-2 should be further validated using in vitro assays, animal models and clinical studies (Neto et al. 2021). Apart from the confirmation of antiviral efficacy at experimental and clinical levels, the safety profile of essential oils and their purified bioactive products also require in-depth evaluation through toxicity studies. Randomized clinical studies are required for determining the efficacy and safety of standardized essential oil formulations (Damiescu et al. 2022). Keeping in view the antioxidant, immunomodulatory and anti-inflammatory properties of essential oils against SARS-COV-2 infection, their pharmacological actions and therapeutic effects should be further explored through experimental and clinical studies (Elsebai and Albalawi 2022).

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Chapter 17
Antiviral Properties of South Indian Plants Against SARS-CoV-2

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Abbreviations

ACE2	Angiotensin-converting enzyme 2
H1N1	Influenza
HBV and HCV	Hepatitis B and C virus
HIV	Human immunodeficiency viruses
M^{pro}	Main protease
NSPs	Non-structural proteins
PL^{pro}	Papain-like protease
SARS-CoV-2	Severe acute respiratory syndrome
TNF-α	Tumor necrosis factor-α

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17.1 Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic disease that originated in Wuhan in China in December 2019 and was disclosed as a pandemic by World Health Organization in March 2020. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and it belongs to the family of Coronaviridae. Studies have highlighted that coronaviruses caused severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory disease (MERS) in 2012 (Mlozi 2022). In the past years, 40 million people were affected by COVID-19 and six million deaths were recorded across the globe. The widespread of COVID-19 is mainly due to a lack of immunity in the host because of its novel nature. COVID-19 is a life-threatening disease that has become a huge socioeconomic burden (Shanmugam et al. 2020; Kuchi Bhotla et al. 2020; Kuchi Bhotla et al. 2021a, b; Pushparaj et al. 2022; Meyyazhagan et al. 2022; Mukherjee et al. 2022).

Nucleocapsid, spike, membrane, and envelope are the four structural proteins present in the virions of COVID-19. The assembly and release of viral particles depend on the viral envelope. The spike, membrane, and envelope proteins are responsible for the development of the viral envelope, whereas the RNA genome is held by a nucleocapsid (Yashvardhini et al. 2021). The spike glycoprotein along with the TMPRSS2 aids the penetration of the virus to the Angiotensin-converting enzyme 2 (ACE2). The spike (S) protein is split into two subunits S1 and S2 by furin. The ACE2 receptor is present in various parts of the body including the heart, lungs, kidney, intestine, testis, and blood vessels. The S2 subunit is further cleaved by the action of lysosomal cathepsin or by TMPRSS2 (Boopathi et al. 2021; Jackson et al. 2022).

The viral genome is released into the cytosol of the host cell after being uncoated from the endosome. Translation of the viral genome takes place, generating viral replicase proteins from open reading frames 1a and 1b. These replicase proteins are cleaved into non-structural proteins (NSPs), such as Papain-like protease (PL^{pro}) and main protease (M^{pro}). M^{pro} facilitates the cleavage of non-structural proteins 12 (RNA-dependent RNA polymerase, or RdRp) and PL^{pro} is involved in the processing of Nsp1–3. The rearrangement of the replicase proteins promotes the replication of the viral genome and sub-genomic RNAs and also helps to translate the structural and accessory proteins needed for the construction of new viral particles (Luan et al. 2020; Harrison et al. 2020).

In the lungs, the host immune defense mechanism produces cytokines in response to inflammation, activating neutrophils, dendritic cells, and macrophages. Neutrophils, which are a type of white blood cell, can cause lung injury when they are released in large numbers. The immune response also activates T cells, which are a type of adaptive immune cell. The production of large amounts of cytokines, like interleukins and tumor necrosis factor-α (TNF-α), in response to the inflammation can lead to a cytokine storm, which can cause cell death in the alveoli and interfere with oxygen supply. This can lead to respiratory failure and other serious

complications (Channappanavar and Perlman 2017; Tomar et al. 2020). Antiviral drugs such as molnupiravir, remdesivir, paxlovid, hydroxychloroquine, and chloroquine (antimalarial), and lopinavir and ritonavir (antihuman immunodeficiency viruses, HIV) are prescribed for the treatment of COVID-19 (Chen et al. 2020).

Due to the lack of proper allopathic medication and vaccination, there is a need for an alternative approach. In ancient times, each country had a traditional medicine system that played a vital role in health care. Now the World Health Organization also has encouraged the usage of plant-based products for the treatment and management of COVID-19. The Indian traditional system of medicine is 4000 years old and is practiced throughout generations by all cultures. India is listed as one of the 12 plant diversity centers in the world. In South India, the Eastern Ghats and Western Ghats are the two significant geographic zones. The medicinal plants and their formulation from Ayurveda, Siddha, Unani, Homeopathy, and Naturopathy had a huge contribution to the management of COVID-19 (Sivasankari et al. 2013; Chopra et al. 2021).

In part, the Southern part of the Siddha medicinal system is more prevalent (Nargis Begum et al. 2009; Vijayakumar et al. 2015, 2019; Manikandan and Anand 2016; Sattanathan et al. 2020; Vijaya Anand et al. 2020). The five basic elements (Panchabootham), six tastes (Arusuvai), and three senses of humor (Mukkuttram) form the fundamental principle of Siddha medicine (Thas 2008). The clinical investigation of disease is based on the eight examinations using eyes (Vizhi), color (Niram), tongue (Naa), speech (Mozhi), pulse diagnosis (Naadi), sensation (Sparisam), urine (Moothiram), and stool (Malam) (Kannan et al. 2022). Diabetic ulcers, leprosy, eczema, vitiligo, pompholyx, alopecia, and warts are treated using Siddha medicine. Other than these herbal formulations like Nilavembu kudineer had shown efficiency against Chikungunya and Dengue virus. During COVID-19, a Siddha formulation of Kaba Sura Kudineer was approved by the Ministry of Ayush as a COVID-19 drug to improve immunity (Bala 2021).

In the current study, the literature was obtained from authenticated databases such as Springer, Nature, Biomed Central, Research Gate, ScienceDirect, Elsevier, Wiley, and PubMed for relevant content. COVID-19, SARS-CoV-2, South Indian plants, origin, pharmacological activity, ethnopharmacology, virucidal, and antiviral effects were used as the keywords to search the articles. Around 105 plants present in South India were selected from the database and scrutinized based on their antiviral property and their origin in South India. The present study is focused on documenting the important pharmacological activity, antiviral and anti-SARS-CoV-2 effect of plants present in South India.

17.2 Pharmacological and Ethnopharmacological Use

In the present study, antiviral and anti-SARS-CoV-2 properties of 22 (*Andrographis paniculata*, *Azadirachta indica*, *Tinospora cordifolia*, *Terminalia chebula*, *Phyllanthus amarus*, *Phyllanthus emblica*, *Aegel marmelos*, *Cinnamomum verum*, *Euphorbia hirta*, *Terminalia arjuna*, *Moringa oleifera*, *Syzygium cumini, Cyperus*

rotundus, *Solanum trilobatum*, *Murraya koenigii*, *Cassia fistula*, *Nerium oleander*, *Gymnema sylvestre*, *Cassia alata*, *Avicennia marina*, *Clerodendrum inerme*, and *Catharanthus roseus*) South Indian have been summarized. The phytocompounds isolated from medicinal plants and herbs, plant products, and formulations have shown effects against various human viruses including Influenza A virus and its subtypes, Hepatitis B and C virus (HBV, HCV), Polioviruses, Chikungunya virus, Zika virus, Herpes simplex virus type 1 (HSV-1), Dengue virus, and HIV, and viruses that affect the plants (tobacco mosaic virus and sunn-hemp rosette virus) and livestock (Bombyx mori nucleopolyhedrovirus). The pharmacological activity of South Indian plants is given in Tables 17.1 and 17.2 contains the ethnopharmacological uses of South Indian plants concerning treating COVID-19 (Arumugam et al. 2020; Poochi et al. 2020; Anand et al. 2021; Kuchi Bhotla et al. 2021a, b; Chandra Manivannan et al. 2022).

17.3 South Indian Plants with Antiviral Activity

The strong anti-HIV activity was exhibited by the aerial parts (aqueous extract) of the *Andrographis paniculata*. Similarly, andrographolide derived from ethanolic extract (whole plant) exhibited activity against HIV by preventing the activity of cyclin-dependent kinase and resulting in the dysfunction of the cell cycle of HIV. In vitro analysis showed that the methanolic extract of *Andrographis paniculata* has considerable activity against the Dengue virus (Hossain et al. 2014). Jadhav and Karuppayil (2021) studied andrographolide and its derivatives found in *Andrographis paniculata* for antiviral effects against HSV-1. The findings of the study denoted that pre-treated 3,14,19-triacetylandrographolide, 14-acetyl-3, 19-isopropylideneandrographolide, and 14-acetylandrographolide were the potential in suppressing the infection and complete inhibition of the viral multiplication was achieved by post-treatment.

In in vitro studies, ethanolic extract of *Andrographis paniculata* (leaves) presented antiretroviral activity against Simian retrovirus-2 (Kumar et al. 2021a, b). The andrographolide and its derivatives were found to be effective against the Influenza A virus. Cai et al. (2015) demonstrated that 14-deoxy-11,12-dehydroandrographolide compounds extracted from *Andrographis paniculata* acted against the Influenza A virus by constraining the viral replication. Another compound 14-a-lipoyl andrographolide also presented an antiviral effect against Influenza A and its subtypes by restricting the viral hemagglutinin and binding (Intharuksa et al. 2022).

HuH7 cells infected with the Hepatitis C virus were treated with a methanolic fraction of *Phyllanthus amarus*. The treatment with *Phyllanthus amarus* diminished the replication of viral RNA of the Hepatitis C virus (Mao et al. 2016). HIV replication was limited by *Phyllanthus amarus* administration in in vitro studies (Notka et al. 2004). Ghosh et al. (2022) reported that water and alcoholic extracts of *Phyllanthus amarus* significantly decreased the replication of HIV in HeLa cells.

Table 17.1 Pharmacological activity of South Indian plants

Name of plant and family	Common name	Origin	Pharmacological activity	Reference
Aegle marmelos and Rutaceae	Bael or Wood apple	Native to **India**, parts of South Asia	Antioxidant, hepatoprotective, antidiabetic/ antiobesity, cardioprotective, antipyretic/anti-inflammatory, antimicrobial, anticancer, antiulcer, and antiviral	Dutta et al. (2014)
Andrographis paniculata and Acanthaceae	Nilavembu	Taiwan, Mainland China, and **India**. Asia, Sri Lanka, Thailand, and Vietnam	Anti-inflammatory, common cold, hepatoprotective, antihyperglycemic, antihyperlipidemic, antiparasitic, antimicrobial, cardiovascular, anticancer, immunomodulatory, and antiviral	Kumar et al. (2021a, b)
Avicennia marina and Acanthaceae	Gray mangrove or white mangrove	China, **India**, Pakistan, and Egypt	Antioxidant, antidiabetic, antimicrobial, antiviral, anthelmintic, antimalarial, anticancer, anti-inflammatory, and sexual activity	ElDohaji et al. (2020)
Azadirachta indica and Meliaceae	Neem	Myanmar (earlier Burma) or Upper Myanmar, **India** Pakistan Asia, Africa, and Saudi Arabia	Antiviral, antimalarial, antifungal, antibacterial, antiarthritic, anti-inflammatory, antipyretic, antigastric, spermicidal, diuretic, antifungal, and immunomodulatory	Moin et al. (2021)
Cassia alata and Caesalpiniaceae	Candle bush	**India,** Africa, and Asia	Anticancer, antimalarial, anthelmintic, anti-inflammatory, antioxidant, antibacterial, antifungal, hepatoprotective, cardioprotective, broncho-relaxant, antiviral, antidiabetic, and antihyperlipidemic	Dewi et al. (2019)

(continued)

Table 17.1 (continued)

Name of plant and family	Common name	Origin	Pharmacological activity	Reference
Cassia fistula and Fabaceae	Golden shower	Asia, Pakistan, **India,** Sri Lanka Bangladesh, Myanmar, and Thailand	Antitussive, leukotriene inhibition, clastogenic effect, antipyretic, antioxidant, laxative, anti-inflammatory, wound healing, hepatoprotective, antifungal, antibacterial, hypocholesterolemic and hypoglycemic, antiparasitic, hypolipidemic, antifertility, antileishmaniasis, and antiviral	Danish et al. (2011)
Catharanthus roseus and Lauraceae	Madagascar periwinkle	**India,** China, and Sri Lanka	Antidiabetic, anticancer and cytotoxic, larvicidal and pupicidal, antimicrobial, antioxidant, and antiviral	Kumar et al. (2022)
Cinnamomum verum and Lauraceae	Ceylon cinnamon	Sri Lanka, **India**, Asia, China, Indonesia, Burma, the Caribbean, Australia, Africa, and Madagascar	Antimicrobial, antioxidant, anti-inflammatory, anticancer, antidiabetic, wound healing, anti-HIV, anti-Parkinson, antianxiety, antidepressant, and antiviral	Pathak and Sharma (2021)
Clerodendrum inerme and Verbenaceae	Indian privet	**India,** Northern Africa, Asia, Egypt, and Madagascar	Antioxidant, antimicrobial, anti-inflammatory, antimalarial, antiviral, antidiabetic, anticancer, and analgesic	Kar et al. (2014)
Cyperus rotundus and Cyperaceae	Korai, Korai kilangu, Muthakasu, Koraipullu	**India**, Africa, Southern Asia, and Southern, and central Europe	Analgesic, antiandrogenic, antimicrobial, cytotoxic, anticonvulsant, antidiabetic, antidiarrheal, antigenotoxic, anti-inflammatory antilipidemic and cardioprotective, antiplatelet, antiuropathogenic,	Peerzada et al. (2015)

(continued)

Table 17.1 (continued)

Name of plant and family	Common name	Origin	Pharmacological activity	Reference
			hepatoprotective, lactogenic, antidepressant, antiviral, neuroprotective, and inotropic	
Euphorbia hirta and Euphorbiaceae	Asthma-plant	**India**, Sri Lanka Asia, Madagascar Europe, and North America	Antiviral, antiallergic, antibacterial, antidiabetic, antidiarrheal, antioxidant, antitumor, anxiolytic and sedative, and diuretic	Khursheed and Jain (2022)
Gymnema sylvestre and Apocynaceae	Gurmar	**India**, Sri Lanka, Africa, Australia, Vietnam, and Malaysia	Antidiabetic, antiarthritic, dental caries, antibiotic and antimicrobial, anti-inflammatory, anticancer, cytotoxic, antihyperlipidemic, immunostimulatory, hepatoprotective, antiviral, wound healing, and ethnobotanical	Tiwari et al. (2014)
Moringa oleifera and Moringaceae	Moringa	**India**, Kenia, Ethiopia and Somalia, Northern **India**, Greeks, and Romans	Antioxidant, anticancer, anti-inflammatory, immunomodulatory, hypoglycemic, antiviral, hypolipidemic, hepatic, and kidney protective	Mahato et al. (2022)
Murraya koenigii and Rutaceae	Curry Leaf	**India**, Sri Lanka, Malaysia, and South Africa	Antibacterial, antifungal, antiprotozoal, antitrichomonal, immunomodulation, antioxidant, nephroprotective, antipyretic, anthelmintic, antiulcer, antidiarrheal, cardioprotective, antiosteoporotic, antiviral, inotropic, mosquitocidal and larvicidal, dental caries, and hypoglycemic	Goel et al. (2020)

(continued)

Table 17.1 (continued)

Name of plant and family	Common name	Origin	Pharmacological activity	Reference
Nerium oleander and Apocynaceae	Oleander	**Indo**-Pakistan subcontinent	Anticancer, antimicrobial, cardiotonic, antidiabetic, anti-inflammatory, antinociceptive, larvicidal, antiviral, hepatoprotective, and antioxidant	Ebrahimi et al. (2018)
Phyllanthus amarus and Phyllanthaceae	Indian gooseberry	**India**, American, African, Madagascar Australasian, and Asian	Antiamnesic, antibacterial, anticancer, antidiarrhoeal, gastroprotective and antiulcer, antifungal analgesic, anti-inflammatory, antiallodynic, antihematogenic, antinociceptive, antioxidant, antiplasmodial, antiviral, aphrodisiac, contraceptive, diuretic, antihypertensive, hepatoprotective, hypoglycemic and hypocholesterolemic, immunomodulatory, nephroprotective, radioprotective, and spasmolytic	Patel et al. (2011)
Solanum trilobatum and Solanaceae	Purple fruited pea eggplant	The southern region of **India** along with some other countries like Srilanka, Thailand, and Vietnam	The antimicrobial, hemolytic, protective effect, anti-inflammatory oviposition, deterrent and skin repellent, antioxidant, antibacterial, antiviral, antidiabetic, and immunomodulatory	Ranjith et al. (2010)
Syzygium cumini and Myrtaceae	Malabar plum	**India**, South Asia, Burma, Bangladesh, Pakistan, Nepal, Indonesia, and Sri Lanka	Antioxidant, anti-inflammatory, anticancer, radioprotection hyperlipidemia and cardioprotective, antidiabetic, antiviral, gastroprotective,	Ayyanar and Subash-Babu (2012)

(continued)

Table 17.1 (continued)

Name of plant and family	Common name	Origin	Pharmacological activity	Reference
			antidiarrheal, and antimicrobial	
Terminalia arjuna and Combretaceae	Arjun	**India**, Burma, Mauritius, and Sri Lanka	Coronary flow, cardiac hemodynamics, antioxidant, cardioprotective, hypolipidemic, antiviral, antiatherogenic, and blood pressure	Amalraj and Gopi (2017)
Terminalia chebula and Combretaceae	Harida, Harada, Haritaki and Harar	Asia, Bangladesh, **India**, China, Nepal, Pakistan, Vietnam, Thailand, Sri Lanka, Africa, Myanmar, Afghanistan, Brazil, and Iran	Anti-inflammatory and anti-arthritic, antioxidative, hepatoprotective, antidiabetic and antihyperglycemic, anticancer, hypolipidemic and hypo-cholesterolemic, cardioprotective, neuroprotective, gastroprotective, anticonvulsant, molluscicidal, nephroprotective, radioprotective, wound healing, antiaging, cytoprotective, antispermatogenic, antidiarrheal and antimotility, antipsychiatry, antiviral, antifungal, antiparasitic, and antibacterial	Bag et al. (2013)
Tinospora cordifolia and Menispermaceae	Guduchi	**India**, Sri Lanka, China, Thailand, Malaysia, Bangladesh, and Africa	Antidiarrhoeal, anthem, antiviral, antimicrobial, antidiarrhoeal, anticancer, anthelmintic, and antidiarrhoeal	Choudhary et al. (2013)
Phyllantus emblica and Phyllanthaceae	Amla	Asia, **India**, Nepal, Bangladesh, Pakistan, Bhutan, Sri Lanka, and China	Immunomodulatory, analgesic, antipyretic, Anti-inflammatory, anticancer, antiproliferative, antimutagenic,	Saini et al. (2022)

(continued)

Table 17.1 (continued)

Name of plant and family	Common name	Origin	Pharmacological activity	Reference
			diabetes, and associated problems, antimicrobial, neuroprotective, antiviral, antimalarial, and antioxidant	

The extracts also had activity against the reverse transcriptase, protease, and integrase enzymes of HIV. Corilagin and ellagitannins geraniin isolated compounds of *Phyllanthus amarus* are considered as the mediators of antiviral effect.

The water extract (leaves) of *Azadirachta indica* has presented inhibition against of replication of a wide range of viruses including Measles, Chikungunya, Dengue virus, and Vaccinia in in vitro and in vivo analysis (Parida et al. 2002, Subapriya and Nagini 2005). The methanolic extract (leaves) of *Azadirachta indica* extract also presented a virucidal effect against Coxsackievirus virus B4. On pre-treatment with bark extract of *Azadirachta indica* actively prevented the entry of HSV-1 (Alzohairy 2016). The methanolic extract of *Avicennia marina* was investigated for anti-HSV-1 and HIV effects. The findings revealed that *Avicennia marina* has a strong inhibition effect against HSV-1 by blocking the viral entry, but has not shown activity against HIV (Namazi et al. 2013). The methanolic and iridoid glycoside derivatives of *Avicennia marina* diminished the multiplication of the virus (Behbahani 2014). ElDohaji et al. (2020) suggested that glycerin crude extract of *Avicennia marina* has antiviral properties against Poliovirus and HSV-1.

CIP-29, a protein that induces systemic antiviral resistance derived from *Clerodendrum inerme*, has been utilized to develop systemic resistance to the Sunn-hemp rosette virus in *Cyamopsis tetragonoloba* (Prasad et al. 2014). Adhikari et al. (2021) demonstrated that *Clerodendrum inerme* and *Gymnema sylvestre* had the potential to decline the mouse coronavirus and HSV infection. In vitro analysis of methanolic extract *Gymnema sylvestre* successfully prevented HIV and HBV infections (Subashini and Rajendran 2015). The alatains A and alatains B phytoconstituents of *Cassia alata* have shown activity against the plant tobacco mosaic virus (Zhou et al. 2020). Other compounds such as alataindolein A, B, C, and D and alatachromone A have also shown antitobacco mosaic virus (Yang et al. 2022).

Moringa, a phytocompound derived from *Moringa oleifera* (seeds), was found to have antiviral properties against the Influenza (H1N1) subtype by suppressing viral plaque formation and hemolysis in RAW264.7 cells that were infected with the H1N1 virus, according to Xiong et al. (2021). The water extract of *Moringa oleifera* has the potential against the Newcastle disease virus (Tolba et al. 2022). The ethanolic and water extracts of *Moringa oleifera* are composed of high anthraquinone and flavonoids. *Moringa oleifera* has shown inhibitory activity against various viruses like Polioviruses, Cytomegalovirus, and HIV (Hamza et al. 2021). Eleven

Table 17.2 Ethnopharmacological uses of South Indian Plants

Name of the plants	References
Aegle marmelos **Leaf:** To treat abscesses, ulcers, vomiting, backache, weakness of the heart, cuts, blood sugars, acute bronchitis, dropsy, and diarrhea injuries caused by animals and beriberi. Ophthalmic infections and asthmatic complaints, cold, cough, and other respiratory complaints, hair growth, and wound healing **Root:** To treat fish poison, fevers, increases seminal fluid volume, remedy for heart palpitation and melancholia, hypoglycemia, gastric troubles, dog bite, antiamoebic, heart disorders, and rheumatism **Flowers** are used as a tonic for the intestine, stomach, antidiabetic, antidysenteric, local anesthetic, epilepsy, and diaphoretic **Fruit:** Treat diarrhea, burn cases, gastric troubles, dysentery, laxative, constipation, digestive, tonic, ulcer, brain and heart tonic, gonorrhea, intestinal parasites, lower blood pressure, epilepsy, and cure intestinal parasites, like *Ascaris lumbricoides* and *Entamoeba histolytica* **Bark:** Fish poison and fever treatment	Dutta et al. (2014)
Andrographis Paniculata **Leaf:** Antioedema activity, hepatoprotective effect, antiviral/antiretroviral, antioxidant, antimicrobial, antifertility, anti-inflammatory, antidiabetic, and anticancer **Stem:** Anticancer, antimicrobial, and antioxidant **Root:** Antimicrobial **Whole plants:** Analgesic	Kumar et al. (2021a, b)
Avicennia marina **Leaf:** Anticancer (India and Iran), antioxidant (China), simplex virus 2 (HSV-2) (Iran), weak radical scavenging (China), antiviral (Indonesia), and antibacterial (Indonesia) **Root:** Antiglycation (Pakistan) **Fruit:** Antioxidant (China)	ElDohaji et al. (2020)
Azadirachta indica **Leaf:** Antifungal, antisemitic, antihelminthic, anticlotting agent, antitumor, antituberculosis, antiviral, antiseptic, cosmetics, contraceptive, insecticides, fertilizers, insect repellents, and mosquito and nematicides **Flower:** Stimulant, analgesic, elimination of intestinal worms, and phlegm and bile suppression **Fruit:** Leprosy and intestinal worms, yield oil and cake an antibacterial effect, relieves piles, urinary disorders, intestinal worms, phlegm, epistaxis, diabetes, eye problem, leprosy, and wounds **Barks:** Antifungal, antiallergenic, antitumor, antiprotozoal, alternative, curative of fever, and analgesic **Deodorant:** **1. Gum:** Effective against skin diseases such as scabies, ringworms, ulcers, and wounds **2. Twigs:** Oral deodorant, toothache reliever, and tooth cleaners	Moin et al. (2021)
Cassia alata **Leaf:** Gonorrhea, heart failure, abdominal pains, edema and purgative, ringworm, skin problems, impetigo, favus, and other mycoses, psoriasis, syphilis sores, chronic lichen planus, herpes, shingles, scabies,	Dewi et al. (2019)

(continued)

Table 17.2 (continued)

Name of the plants	References
rash and itching, eczema, stomach pain during pregnancy and leaf decoctions, hemorrhoids, dysentery, jaundice, blood in the urine (schistosomiasis, gonorrhea), hernia, headache, and one-sided weakness or paralysis **Stem:** Antiasthma, aperients, improve the visual activity and diuretic agent. (Chinese medicine)	
Cassia fistula **Leaf:** The leaves extract is used as a laxative, used externally as an emollient, reduced mutagenicity in *E. coli*, in insect bites, a poultice is used for chilblains, rheumatism, facial paralysis, swelling, laxative properties, antiperiodic, the leaves are used in piles, jaundice, also externally skin eruptions, rheumatism ulcers, eczema, ringworms, insect bites, and pustules **Stem:** Prescribed as an astringent, febrifuge, strong purgative, tonic, fever **Root:** Chest pain, migraine, blood dysentery, joint pain, blood sugar level up to 30%, chest pain, swellings, amenorrhea, fever, retained excretions and biliousness, and heart diseases **Root bark:** Exhibits cardiac disorders, anti-inflammatory activity, rheumatic conditions, biliousness, wounds, hemorrhages, boils, and various skin diseases and ulcers **Flower:** Purgative, febrifugal, biliousness, and astringent. Antifertility activity in female albino rats. The heated pods are applied to swellings on the neck due to cold **Fruits:** Snakebite, cathartic, skin diseases, asthma, diabetes, abortifacient, antipyretic, lessens inflammation and heat of the body, demulcent, throat troubles, useful in chest complaints, diseases of the eye and gripping, liver complaints, colic, constipation, urinary disorders, and chlorosis **Seed:** Carminative, laxative, improves the appetite, antipyretic activity, cooling, biliousness, jaundice, swollen throat, skin disease, and hypoglycemic activity **Bark**: Antidysentric properties, tonic, skin complaints, the powder or decoction of the bark is administered in jaundice, leprosy, heart diseases, and syphilis	Danish et al. (2011)
Catharanthus roseus **Leaf:** Toothache, menorrhagia, blood circulation, and memory loss (India). Diabetes mellitus, amenorrhea (Philippines), Reducing toothaches, soothing insect bites, regulating blood sugar, healing wounds, cardiovascular diseases, and improving circulation and memory (Sri Lanka). Diabetes (England) and Vomitive (France). Diabetes; combat primary inertia in childbirth; (Dominica). Menorrhagia and diabetes (Australia), Anemia, Ulcers, inflammation (Myanmar), Traditionally used for diabetes (Spain), Astringent, diuretic, cough remedy (China), Diabetes, rheumatism (Mozambique), Indigestion, dyspepsia (Mauritius), Menorrhagia, rheumatism (Africa) and Toothache, fever, skin diseases, diuretic (India) **Stem:** Diabetes (West Bengal), Dysmenorrheal (Indonesia) **Root:** Menorrhagia, tonic, stomachic (India), abortion, emmenagogue, dysmenorrhea with scanty flow abortion (Philippines), diabetes	Kumar et al. (2022)

(continued)

Table 17.2 (continued)

Name of the plants	References
(Mexico), vermifuge, purgative, hemostatic, depurative and toothache remedy (France). hypertensive, febrifuge (Mozambique) vomitive, vermifuge, purgative, hemostatic toothache remedies, and depurative (Madagascar). fevers, malaria (Brazil), stomach problems (Kenya), venereal disease (Venda), and febrifuge (Australia) **Fruit:** Eyewash for the eyes of infants (Rodriguez Islands & Jamaica), asthma, tuberculosis, and flatulence (Bahamas)	
Cinnamomum verum **Leaf:** To treat asthma, rheumatism, cephalalgia, febrifuge, inflammatory diseases, and ophthalmia (China, India, Japan, Korea, and Thailand). **Root:** To treat venereal infections, coughs, elephantiasis, skin diseases, tropical burns, rheumatism, febrifuge, vermifuge, malaria, antihypertensive, sedative properties, and antidiabetic.	Pathak and Sharma (2021)
Clerodendrum **Leaf:** To treat food flavoring agents (Asia). Leukorrhea, puerperal fever, and eczema **Stem:** Rheumatic pain, dermatitis, body ache, bile, dysentery, and stomachache **Root:** Kidney stone removal, cholera, tonsillitis, vomiting, colic, flatulence in children, bone fracture, jaundice, malaria **Flower:** Blood dysentery **Fruit:** Bronchitis **Whole plant:** Bone fracture, Colic, cholera, vomiting, diarrhea, dermatitis, flatulence in children, dysentery, menstrual irregularities, dysmenorrhea, painful menstruation, emmenagogue, high fever, bronchitis, epilepsy, dysentery, galactagogue, gynecological disorder, indigestion, malaria, urinary disorders, constipation, intermittent fevers, kidney-stone removal, leprosy, itching, anthelmintic, dysentery, leukorrhea, lowering blood glucose level, puerperal fever, bile, rheumatic pain, body ache, fever, scorpion bite, skin diseases/blisters, jaundice, snake-bite, stomach, and bowel disorder, tonsillitis, urinary problems, diaphoretic, wound healing, stimulant, astringent, diuretic, tonic, vermifuge, demulcent, stomachic, and emmenagogue (India, Pakistan, and Bangladesh)	Kar et al. (2014)
Euphorbia hirta **Leaf:** Antifungal, antibacterial activities, warmed and rubbed on itchy soles, surma to cure eye sores and lower eyelids Stem: Gastrointestinal disorders (dysentery, diarrhea, intestinal parasitosis, etc.), bronchial and respiratory diseases (bronchitis, hay fever, asthma, etc.), and conjunctivitis. Tonic properties, hypotensive, anxiolytic, analgesic, antipyretic, anti-inflammatory activities, and anxiolytic **Root:** Anticancer activity, prostaglandins I2, E2, and D2, inhibits aflatoxin contamination, e incognita, snake bites, and decoction	Peerzada et al. (2015)
Gymnema sylvestre **Leaf:** Antisweet tested, diabetes mellitus, stomachic, and diuretic. Decreases gluconeogenic enzyme and pathological changes, snake-bite, stimulating insulin, inhibition glucose absorption, hypolipidemic,	Khursheed and Jain (2022)

(continued)

Table 17.2 (continued)

Name of the plants	References
antiatherosclerotic, and anti-inflammatory. Inhibit glucose absorption, antimicrobial, diabetes, obesity, dianex herbal formulation, diabecon, regulated–induced hyperglycemia, and gustatory sensation **Stem:** Cardiotonic, diuretic, digestive, stimulant, laxative, uterine tonic, and stomachic **Root:** Cardiotonic, diuretic, digestive, stimulant, laxative, uterine tonic, and stomachic	
Moringa oleifera **Leaf:** Antioxidant, antibacterial, antifungal, anti-inflammatory, cardioprotective, immunomodulatory, neuroprotective, and anticancer **Stem:** Antioxidant, antifungal, and anticancer **Root:** Antioxidants **Fruit:** Antioxidants and anticancer. **Bark:** Antioxidant **Seed:** Antifungal and anticancer	Tiwari et al. (2014)
Murraya koenigii **Leaf:** Stomachic, febrifuge, purgative, antihelminthic, antianemic, antiulcer, analgesic, antiamnesic, antinociceptive, cooling, itching, and anti-inflammation. Hair growth to cure eruption and bruises, vomiting, night blindness, hypercholesterolemia lightning, and bites of poisonous animals **Stem:** Datum for cleaning, and strengthening gums and teeth **Root:** Analgesic, antihelminthic, inflammation, cooling agent and itching, leucoderma, kidney pain, and blood disorders **Flower:** Astringent **Whole plant:** Leucoderma, diabetes mellitus, kidney pain, body aches, and vomiting **Bark:** Datum for cleaning, and strengthening gums and teeth	Mahato et al. (2022)
Nerium oleander **Leaf:** To the treatment of microbial and fungal diseases, expectorant, heart tonic, diuretic, emetic, and diaphoretic. Scabies and to reduce swellings. Snakes and other venomous bites, cure eye diseases. Nerium is emetic, cardiotonic, diaphoretic, cardiotonic, expectorant, sternutatory, diuretic, anticancer, antibacterial, and antifungal **Root:** Anticancer, skin complaints, herpes, and also ringworm infection **Fruit:** Treatment of microbial and fungal diseases, emetic, cardiotonic, diaphoretic, cardiotonic, expectorant, sternutatory, diuretic, anticancer, antibacterial, and antifungal. The hydroalcoholic and aqueous extract of the flowers is antinociceptive and cardiotonic **Bark:** Treatment of microbial and fungal diseases, expectorant, heart tonic, diuretic, emetic, and diaphoretic. Athletic, febrifuge, and intermittent fever. Oil prepared from the root bark is used in the treatment of leprosy and skin diseases of a scaly Nature **Seeds** are used as a purgative in rheumatism and dropsy **Whole plant:** Anticancer, warts, against corns, carcinoma, cancerous ulcers, hard tumors, or ulcerating	Goel et al. (2020)
Phyllanthus amarus **Leaf:** Diabetics, jaundice, gonorrhea and syphilis, malaria, skin	Ebrahimi et al. (2018)

(continued)

Table 17.2 (continued)

Name of the plants	References
diseases, menstrual, chronic dysentery, syphilis, stomachache, kidney problems, rashes, and itches **Root:** Jaundice **Whole plant:** Migraine, gonorrhea and syphilis, jaundice, malaria, skin diseases, dyspepsia, liver disease, moderate constipation, anorexia, irritable bowel syndrome, chronic colitis, aphrodisiac, urinary tract infection, diabetes, dysentery, cleaning uterus, stomach ache, health promotion, laxative, and disease prevention	
Solanum trilobatum **Leaf:** Cure snake poison and increase male fertility. Antimicrobial activity and antimitotic against fungi and bacteria and anticancer activity **Stem:** Antimitotic, anti-inflammatory, and antiulcerogenic **Root:** Treat acute and chronic bronchitis, tuberculosis, and treating cough **Flower:** Antibacterial **Fruit:** Antibacterial and treats cough	Patel et al. (2011)
Syzygium cumini **Leaf:** Strengthen the gums and teeth, dysentery with bloody discharge, and diarrhea in children **Fruit** Removes bad smell from the mouth, astringent to the bowels, stomachic, biliousness, diuretic, antidiabetic, and astringent. Astringent in chronic diarrhea and efficient **Bark:** Digestive, anthelmintic, astringent to the bowels, bronchitis, treatment of sore throat, thirst, asthma, dysentery, biliousness, blood purifier, and ulcers **Seed:** Good for diabetes and astringent to the bowels. Treat cough, cold, skin problems, fever, rashes, and the throat, mouth genitourinary tract ulcers, and intestines (Tamil Nadu)	Ranjith et al. (2010)
Terminalia arjuna **Leaf:** Earache, heart ailments (Malabar tribe and Kerala) **Fruit:** Treat wounds and blood in the urine **Bark**: To treat demulcent, astringent, cardiotonic, expectorant, antidysenteric, and styptic, useful in fracture, urinary astringent, leukorrhea, ulcers, anemia, diabetes, cirrhosis, and cardiomyopathy. To kill worms in teeth and cure headaches	Ayyanar and Subash-Babu (2012)
Terminalia chebula Fruit: Mild laxative, tonic, stomachic, antispasmodic, alterative, hemorrhoids, ophthalmia, bleeding gums, dental caries, anti-inflammatory, ulcerated oral cavity, purifying, and healing capacity for wounds, analgesics, sore throat, oral ulcers, bleeding and ulceration in gums, and dentifrice in loose gums Increase appetite, digestive aid, liver stimulant, stomachic, gastrointestinal prokinetic agent, chronic diarrhea, nervous weakness, nervous irritability, promotes the receiving power of the five senses It is adjuvant in hemorrhages due to its astringent nature and good for chronic cough, chorizo, sore throat as well as asthma. Also, it is useful in renal calculi, dysuria, retention of urine, and skin disorders with discharges like allergies, urticaria, and other erythematous disorders	Amalraj and Gopi (2017)

(continued)

Table 17.2 (continued)

Name of the plants	References
Terminalia chebula **Fruit:** Reduces swelling, hastens, healing, and cleanses wounds, ulcers, skin disorders, and erysipelas, anti-inflammatory, haritaki prevents problems of the throat and stomatitis **Bark:** Used as a diuretic and tonic for the heart.	Bag et al. (2013)
Tinospora cordifolia **Leaf:** Fever, cholera, rheumatism, snake-bite, vermifuge, syphilitic sores, wash for sore eyes, internal inflammation, wound itching, reduce thirst, increase appetite, jaundice, rheumatism, relieve body pain leaf, abdominal pain, paralysis, leprosy, and skin disease **Stem:** Snake-bite, rheumatism, vermifuge, wound itching, wash for sore eyes and syphilitic sores, internal inflammation, increase appetite, thirst, appetizer, antipyretic, stomachic, bitter tonic, mucous congætion, ears problems, treatment of stomachache, parasites, jaundice, treat fevers caused by smallpox, cholera, and malaria. Diabetes, hypertension, postpartum remedy, and muscle pain (Murut community), garo, non-garo, and prevention of intestinal disorders (Bangladesh) **Root:** Snake-bite, cholera, rheumatism, vermifuge, syphilitic sores, wash for sore eyes, internal inflammation, thirst, increase appetite, and wound itching	Choudhary et al. (2013)
Phyllantus emblica **Leaf:** Antimalarial **Root:** Eczema (China), hemostatic and astringent (Nepali). Aperient, refrigerant, and febrile condition **Flower:** Refrigerant and aperient **Fruit:** Laxative, diuretic, and inflammation of the eye **Bark:** Refrigerant, aperient, and gonorrhea	Saini et al. (2022)

compounds extracted from the methanolic extract of *Moringa oleifera* (seeds) were then evaluated against the H1NI virus. The results revealed that glucomoringin, moringa A, and vitexin had virucidal effects against the H1N1 virus (Xiong et al. 2022).

Somu et al. (2019) tested 14 fractions isolated from *Aegle marmelos* (leaves extract) for their antiviral property. Seselin exhibited significant effectiveness against Bombyx mori nucleopolyhedrovirus present in larvae of silkworms. Kaur et al. (2020) suggested *Aegle marmelos* has the strongest efficacy against HIV. Wahab et al. (2020) tested the efficiency of the methanolic extract of *Catharanthus roseus* on HSV-1. The secondary metabolites terpenoid, alkaloid, and saponin expressed anti-HSV-1 effect by decreasing plaque formation in both pre- and post-treatment. In vitro studies by Xu et al. (2015) in a hepatoblastoma cell line transfected with Hepatitis B disclosed that among the 37 sesquiterpenoids extracted from methanolic extract of *Cyperus rotundus* (roots), eudesmane-type sesquiterpenoids expressed good antiviral effect against Hepatitis B.

Ogbole et al. (2021) have reported that *Euphorbia hirta* extract (leaves) has a protective action against Enterovirus C99, Coxsackievirus A13, and Coxsackievirus

A20. The hydromethanolic extract of *Euphorbia hirta* showed activity against the Simian immunodeficiency viruses, HIV-1, and HIV-2 by decreasing the viral replication (Gyuris et al. 2009). The virucidal property of casuarinin derived from *Terminalia arjuna* (bark) reduced the cell growth, plaque formation, and virality of HSV-2 (Cheng et al. 2002). In silico analysis, compounds present in *Terminalia arjuna* were tested for antiviral effects against the Zika virus. The outcome of the results revealed that tannic acid from *Terminalia arjuna* can control the Zika virus (Priya et al. 2018). Singh et al. (2021) described that *Cinnamomum verum* extract had efficacy against the HIV protease.

The aqueous extract of *Nerium oleander* was tested against various viruses such as Reovirus type-1, Vesicular stomatitis virus, Yellow fever virus, HSV, HIV-1, and Poliovirus type-1. *Nerium oleander* was found to be constructive in controlling Polio virus type-1 by decreasing the formation of plaque (Sanna et al. 2021). Mononuclear cells infected with HIV were used in detecting the performance of *Nerium oleander* against the virus. The extract reduced the effect of the virus by diminishing the envelope protein, GP-120 expression, and replication of HIV (Singh et al. 2013). Silver nanoparticles synthesized from *Tinospora cordifolia* have expressed antiviral activity against Chikungunya virus-infected Vero cells (Sharma et al. 2019).

The methanolic extract of the *Terminalia chebula* (fruits) presented notable inhibitory activity (El-Mekkawy et al. 1995). Kurokawa et al. (1995) indicated that the extract of *Terminalia chebula* and acyclovir together can provide better protection by attenuating the infection of HSV-1. Chebulinic acid and chebulagic acid extracted from ethanolic extract of *Terminalia chebula* (fruits) were purified and examined against HSV-2. During post-viral infection in Vero cells, the phytochemical displayed a significant virucidal effect against HSV-2 by preventing viral attachment, penetration, and plaque formation. The activity of phytochemicals was found to be greater than the activity exhibited by the standard drug acyclovir (Kesharwani et al. 2017). Another research involving fruits of *Terminalia chebula* (galloyl moiety) exhibited notable effects against HIV-1 (Ahn et al. 2002).

The punicalagin and chebulagic acid isolated from dried fruits of *Terminalia chebula* showed remarkable activity against HSV-1 in lung cells by suppressing the transmission and binding of viral particles (Lin et al. 2011). The phytocompounds of *Terminalia chebula* (fruits) were assessed for anti-HCV activity two tannins (chebumeinin A and chebumeinin B) showed positive effects on the reduction of HCV (Ajala et al. 2014). Oyuntsetseg et al. (2014) reported that subtypes of the influenza virus were decreased by the treatment with an aqueous extract of *Terminalia chebula* (seeds). Mishra et al. (2018) suggested that *Terminalia chebula* has anti-HIV-1 and HSV-2 properties. Likewise, the chebulinic acid derived from flowers of *Terminalia chebula* exhibited an inhibitory effect against HSV-2 and Dengue virus by blocking the entry of the virus. However, the chebulinic acid was not effective against Chikungunya virus infection (Thomas et al. 2022).

The phytoconstituents like putranjivain A, digallic acid, 1-*O*-galloyl-*β*-D-glucose, kaempferol-3-*O*-*β*-D-glucoside, 1,6-di-*O*-galloyl-*β*-D-glucose, quercetin-3-*O*-*β*-D-glucoside found in methanolic extract of *Phyllanthus emblica* presented anti-HIV property (El-Mekkawy et al. 1995). Coxsackievirus virus B3 was combated by the

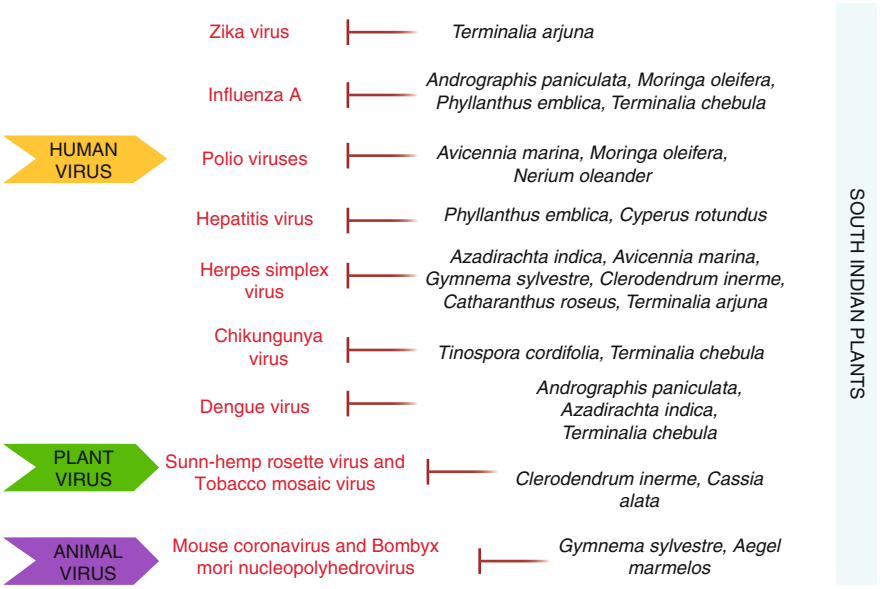

Fig. 17.1 Antiviral activity of South Indian plants

phyllaemblicin B compound derived from *Phyllanthus emblica* in both animal models and cell-based analysis (Wang et al. 2009). Phyllaemblic acid methyl, phyllaemblicin B, and phyllaemblicin C also affected Coxsackievirus virus B3 (Liu et al. 2009). 1,2,4,6-tetra-*O*-galloyl-*β*-D-glucose (phenolic compound) extracted from *Phyllanthus emblica* exhibited activity against the HBV and HSV-1 (Xiang et al. 2010, 2011). Phyllaemblicins G1–G8 and glochicoccin D, phyllaemblicin F, and phyllaemblic acid were tested for antihepatitis B properties. The findings indicate that phyllaemblicins G6–G8 have antihepatitis B activity (Lv et al. 2014).

Lv et al. (2015) revealed that glochicoccinoside D had an effect against the influenza A virus. The gel formulated from ethanolic extract of *Phyllanthus emblica* was found to have the potential of decreasing HSV-2 and HIV-1 (Mishra et al. 2018). Triphala formulation containing *Phyllanthus emblica* has repressed the action of the Dengue virus in Vero cells (Panya et al. 2021). 1,2,3,4,6-penta-*O*-galloyl-*β*-D-glucose isolated from the various parts (leaves, barks, and roots) of *Phyllanthus emblica* demonstrated virucidal effect on Influenza virus in MDCK cells. Glochicoccinoside D and phyllaemblicin B from roots of *Phyllanthus emblica* also showed an effect against the subtype (H3N2) of the Influenza virus (Saifulazmi et al. 2022) (Fig. 17.1).

17.4 Anti-SARS-COV-2 Activity of South Indian Plants

Calu-3 lung cells affected with the SARS-CoV-2 virus were used for testing the ability of *Andrographis paniculata* and its derived andrographolide. The results showed that *Andrographis paniculata* could suppress the generation of virions (Sa-Ngiamsuntorn et al. 2021). Andrographolide and andrographidine C of *Andrographis paniculata* presented higher binding toward the targets. Especially the andrographidine C had a stronger binding affinity to phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma and ACE receptors (Xie et al. 2021). SARS-CoV-2 induces host response by inducing 36 genes causing cytokine storm. The study reported that andrographolide can restrict the cytokine storm by suppressing the NFkB1 pathway (Rehan et al. 2021). Recent research by Das et al. (2022) also demonstrated that andrographolide has the efficacy to attenuate the cytokine storm by regulating interleukin 6 and TLR4-MD2. Andrographolide also could interact with various viral entry points like cathepsin L, TMPRSS-2, furin, and ACE2.

Latha et al. (2022) investigated the anti-SARS-CoV-2 activity of ethanolic extracts of *Withania somnifera*, *Centella asiatica*, *Calophyllum inophyllum*, *Zanthoxylum piperitum*, and *Andrographis paniculata* on nucleoprotein and envelope genes of SARS-CoV-2 virus. The results showed that in in vitro analysis, *Centella asiatica*, *Andrographis paniculata*, and *Withania somnifera* displayed activity against both genes. Among them, *Andrographis paniculata* had a higher activity than the standard drug (remdesivir). The compounds isolated from *Centella asiatica* (kaempferol), *Withania somnifera* (coagulin G), and *Andrograhis paniculata* (andrographidine C) have also shown better inhibitory effects against the spike protein, M^{pro}, and RdRp, respectively, in in silico method.

Wanaratna et al. (2022) examined the efficiency of the *Andrograhis paniculata* extract in individuals affected with mild SARS-CoV-2 infection. *Andrograhis paniculata* extract treatment showed betterment in levels of C-reactive protein without adverse effects. Tanwettiyanont et al. (2022) reported administration of *Andrograhis paniculata* did not show a significant reduction in pneumonia in individuals with mild SARS-CoV-2. Intharuksa et al. (2022) stated that *Andrograhis paniculata* has the capability to reduce the production of the virion and also can bind with ACE and $3CL^{pro}$ receptors.

Borkotoky and Banerjee (2021) conducted a study to examine the competency of the 70 compounds derived from *Azadirachta indica* against the proteins (envelope and membrane) of SARS-CoV-2 which are useful in the assembly of viruses. Nimbolin A (−11.2 kcal/mol) and nimocin (−10.2 kcal/mol) from *Azadirachta indica* showed a good binding affinity to envelope and membrane protein respectively. Desacetylgedunin present in seeds of *Azadirachta indica* was found to have significant binding with the papain-like protease which was revealed in in silico studies conducted by Baildya et al. (2021). Shadrack et al. (2021) reported that the virus entry site (spike-receptor binding domain (RBD)-ACE2) was obstructed by quercetin, azadirachtin H, and margocin isolated from *Azadirachta indica*.

Azadirachtin was effective the inhibiting M^{pro}, PL^{pro}, and RdRp proteins. In vivo studies, oral treatment of nimbin and its isomers derived inhibited viral production and dissemination of m-CoV-RSA59 and SARS-CoV-2 (Foka et al. 2022).

Sagar and Kumar (2020) evaluated the phytoconstituents present in *Tinospora cordifolia* against the major targets (RBD, RdRp, surface glycoprotein, and M^{pro}) important for the attachment and multiplication of the SARS-CoV-2 virus. The outcome of the study demonstrated that berberine, magnoflorine, tinocordiside, and isocolumbin showed higher binding scores against all four targets. Both M^{pro} and surface glycoprotein were potentially inhibited by isocolumbin and tinocordiside. Another in silico study by Chowdhury (2021) revealed that berberine present in *Tinospora cordifolia* can bind with $3CL^{pro}$ which is essential during the replication of the virus.

The phytocompounds present in *Tinospora cordifolia* were analyzed for anti-SARS-CoV-2 activity. Among 11 compounds scrutinized, xanosporic acid, tembetarine, cardiofolioside B, berberine, and tinosponone were found to be potential inhibitors of $3CL^{pro}$ and tinosponone had the top binding affinity to $3CL^{pro}$ (Krupanidhi et al. 2021). Mulpuru and Mishra (2021) reported that saponarin found in *Tinospora cordifolia* was effective in arresting the M^{pro} of the SARS-CoV-2 virus. Jena et al. (2021) investigated the effectiveness of phytocompounds of *Tinospora cordifolia* against the spike protein of SARS-CoV-2. The results suggested that several compounds present in *Tinospora cordifolia* have the ability to counteract the attachment of spike protein with the ACE receptor.

Sarkar et al. (2022) studied 16 compounds of *Terminalia chebula* for their anti-SARS-CoV-2 activity. The observations revealed that daucosterol, 1,3,6-trigalloyl glucose, and β-sitosterol compounds had a higher inhibitory effect against all eight (M^{pro}, PL^{pro}, non-structural protein (NSP) 10, helicase, NSP9 RNA binding protein, NSP15 endoribonuclease, RBD, and RdRp) targets. Arjunin, chebulinic acid, chebulanin, chebulagic acid, punicalin, 1,6 di-*O*-galloyl-D-glucose, 1,2,3,4,6 penta galloyl β-Dglucose, galloyl glucose, ellagitanin, terflavin C, terflavin D, casuarinin, and corilagin in *Terminalia chebula* were tested antiviral property against SARS-CoV-2. The findings revealed that the compounds of *Terminalia chebula* can be used as a therapeutic alternative for the treatment of COVID infection (Naik et al. 2021). Ghosh et al. (2022) evaluated 22 various phytochemicals present in the *Terminalia chebula* against the SARS-CoV-2 virus. The findings reported that sterols and triterpenoids have strong binding against the M^{pro}, whereas daucosterol exhibited stronger affinity.

Based on the literature, 190 phytochemicals present in *Phyllanthus amarus* were selected and docked against the M^{pro} and $3CL^{pro}$. Out of 190, 16 phytochemicals showed a good binding affinity with scores between −8.9 and −9.6 kcal/mol. Among them, quercetin-3-*O*-glucuronide and myricitrin topped the binding score (Murthy et al. 2021). Murugesan et al. (2021) recommended that astragalin, apigenin-6-*C*-glucosyl7-Oglucoside, amritoside, and pectolinarin present in *Phyllanthus amarus*, *Tinospora cordifolia*, and *Phyllanthus niruri* has an antiviral effect against the SARS-CoV-2 virus. Sree et al. (2022) demonstrated that *Phyllanthus amarus* has the potential to combat SARS-CoV-2 by acting against

the M^{pro}. The phytoconstituents of *Phyllanthus amarus* displayed better binding energy than the reference (lopinavir).

Chikhale et al. (2021) reported that chlorogenic acid, myricetin, and quercitrin found in the *Phyllanthus emblica* have the potential to act against the protein targets of the SARS-CoV-2 virus. Pandey et al. (2021) established the importance of phytochemicals present in *Phyllanthus emblica* and *Aegel marmelos* through in silico analysis. Three compounds from *Phyllanthus emblica* and two compounds from *Aegel marmelos* were analyzed and the results exhibited that (2S)-eriodictyol 7-*O*-(6″-*O*-galloyl)-*β*-D glucopyranoside from *Phyllanthus emblica* had good binding score against the RdRp of SARS-CoV-2 virus. Varnasseri et al. (2022) suggested that tea prepared using *Phyllanthus emblica* lowered the length of stay and improved the C-reactive protein and oxygen saturation level.

In silico studies of phytochemicals present in cinnamon were examined by Prasanth et al. (2021). Pavetannin C1 and tenufolin presented a higher correlation with both M^{Pro} and spike protein. Other compounds such as 6-cinnamtannin-B1, proanthocyanidin-A2, glucopyranosylprocyanidin B1, kaempferol 3-*α*-*L*-arabinofuranoside-7- rhamnoside also showed active binding to spike and M^{pro} protein. Yakhchali et al. (2021) recommended the usage of *Cinnamomum verum* in the treatment of SARS-CoV-2 because *Cinnamomum verum* is a well-known antiobstructive drug that provides great relief for lung obstruction.

Khursheed and Jain (2022) reported that methanolic extracts (leaves and roots) of *Euphorbia hirta* can inhibit the ACE. A computational approach was used by Parmar et al. (2022) to check the anti-SARS-CoV-2 effect of *Euphorbia hirta*. Myricetin was efficient in forbidding the M^{pro} and 3-o-*α*-rhamnoside, isoquercitrin, and quercetin were found to be efficient in constraining the RdRp. Rutin and euphrobianin showed significant activity against both RdRp and M^{pro}. Around 170 phytocomounds present in *Euphorbia hirta* were scrutinized using molecular docking. The results demonstrated that trigallic acid (−9.2 kcal/mol), trigalloylquinic acid (−9.0 kcal/mol), quercetin-3-*O*-rhamnoside (−9.0 kcal/mol), myricetin-3-*O*-rhamnoside (−9.0 kcal/mol), and pedunculagin II (−8.9 kcal/mol) higher affinity against the SARS-CoV- M^{pro} (Cayona and Creencia 2022).

Arjunetin present in ethanolic extract of *Terminalia arjuna* was tested against SARS-CoV-2 using docking analysis. The findings established that arjunetin showed antiviral activity by acting against the RdRp, $3CL^{pro}$, and PL^{pro}, and the binding of arjunetin was greater than the lopinavir and remdesivir control drugs (Arumugam et al. 2022). Wanarase et al. (2022) reported that N-desmethyl sildenafil and triterpenoid present in *Terminalia arjuna* could suppress the multiplication of the SARS-CoV-2 virus by inhibiting the M^{pro}.

Thirty-three bioactive compounds of ethanolic extract *Moringa oleifera* (fruit) were examined for their antiviral properties against SARS-CoV-2 infection. The outcome of the study indicated that the phytochemicals of *Moringa oleifera* were efficient in binding with spike and ACE receptors (Siddiqui et al. 2022a). Sen et al. (2022) demonstrated that flavonoids (kaempferol, isorhamnetin, and apigenin) present in *Moringa oleifera* have activity against the M^{pro}. Sivani et al. (2021) proposed that isorhamnetin-3-*O*-rutinoside and rutin antiviral compounds of *Moringa oleifera*

may have activity against the SARS-CoV-2 virus. The ethanolic extract of *Moringa oleifera* (leaf) was subjected to gas chromatography-mass spectroscopy. The β-sitosterol and β-tocopherol compounds exhibited good interaction with spike-RBD-ACE2 and spike glycoprotein, respectively (Siddiqui et al. 2022a, b). Aini et al. (2022) screened the phytoconstituents of *Moringa oleifera* and *Syzygium cumini* for the anti-SARS-CoV-2 effect. The observation showed that myricetin from *Moringa oleifera* and ellagic acid from *Syzygium cumini* were the best candidates for a therapeutic approach against the SARS-CoV-2 virus.

Kumar et al. (2021a, b) proposed that two secondary metabolites (stigmasta-5,22-dien-3-ol and β-amyrin) in *Cyperus rotundus* have the ability to attenuate the M^{pro}. The plant-specific compounds of *Solanum trilobatum* including α-solanine, solanidine, and solasodine studied for their effect against SARS-CoV-2. The findings of the study revealed that α-solanine (−203.0 kcal/mol) had higher binding energy against the M^{pro}. Other two compounds solasodine (−101.6 kcal/mol) and solanidine (−69.0 kcal/mol) also exhibited good binding affinity to the target (Anandakumar et al. 2020). Molecular docking methods were used by Wadanambi et al. (2022) to analyze the carbazole alkaloids (koenine, o-methylmurrayamine A, girinimbine, and mukonicine) found in *Murraya koenigii*. Mukonicine, o-methylmurrayamine A, koenine, and girinimbine All the phytochemicals significantly prevented the viral replication of SARS-CoV-2 by suppressing M^{pro} activation.

Dawood et al. (2021) focused on anthraquinone extracted from ethanolic extract of *Cassia fistula* (pods) to investigate the antiviral property. The anthraquinone performed well in the antioxidant assay. In silico analysis disclosed that anthraquinone (aloe-emodin and rhein) can restrict the M^{pro}. The efficacy of *Nerium oleander* and its derivative oleandrin were measured for their antiviral activity in Vero cells. The administration of oleandrin to Vero cells infected during pre- and post-infection presented a decline in the viral production of SARS-CoV-2 (Plante et al. 2021). Subramani et al. (2020) suggested that active phytoconstituents, especially the gymnemic acids of *Gymnema sylvestre* can reduce the replication of the virus by binding to the M^{pro} site. Ernawati et al. (2021) assessed the phytoconstituents of *Dendrophthoe petandra* and *Cassia alata* for antiviral activity. The authors identified that quercetin, aloe-emodin, emodin, and kaempferol from *Dendrophthoe petandra* and *Cassia alata* have the potential to act as an inhibitor for SARS-CoV-2 infection.

A new steroid versisterol from *Avicennia marina* showed strong activity against the $3CL^{pro}$ in in silico analysis (Elsbaey et al. 2022). Kar et al. (2021) used molecular docking methods to evaluate the anti-SRAS-CoV-2 property of 12 different species of *Clerodendrum* spp. M^{pro} enzyme, RdRp, and spike protein were fixed as the target sites. The compounds stigmasterol, taraxerol, and friedelin were securitized from *Clerodendrum* spp. The finding depicted that taraxerol had a better binding affinity to the target sites. The vindolininol, apparicine, and 12-chlorotabersonine of *Catharanthus roseus* were selected from the database based on their structural similarity with chloroquine and hydroxychloroquine drugs. The compounds were also checked for their pharmacokinetics and drug-likeness (Lipinski's) properties.

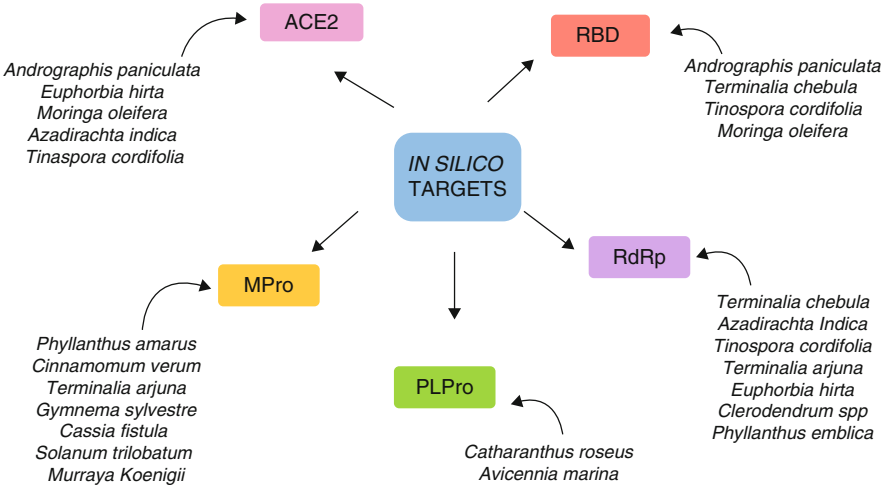

Fig. 17.2 South Indian plant effects against major in silico targets of COVID-19

The outcome of the study demonstrated that compounds have a strong binding score to the PL^{pro} and spike protein (Kalaria and Patel 2020). Figure 17.2 represents the South Indian plant effect against major in silico targets of COVID-19.

17.5 Conclusion

The outbreak of SARS-CoV-2 has become a global health crisis due to the unavailability of proper medication and vaccines. In the current scenario, an alternative or complementary treatment or medicine is mandatory to control the spread of infection. To date only, antimalarial and anti-HIV drugs are prescribed to individuals affected with COVID-19. India is the second largest populated country. It is hectic to handle a pandemic like COVID-19. Till present, around 4.5 million people were affected by COVID-19 with a death rate of 5 lakhs in India. The World Health Organization has recommended the utilization of plant-based medicine and products to tackle the virus. India holds a heritage of having traditional medicinal systems such as Ayurveda, Siddha, and Unani. Siddha medicine has been practiced in the Southern parts of India.

The current chapter has concentrated on documenting the antiviral and anti-SARS-CoV-2 effects of plants that are indigenous to South India. Many commonly available and day-to-day consumed plants and herbs including drumstick, gooseberry, neem, java plum, and green chiretta have shown activity against SARS-CoV-2. The secondary metabolites and plant extracts have exhibited better anti-SARS-CoV-2 effects against the pivotal targets of SARS-CoV-2 like M^{pro}, PL^{pro}, RdRp, spike protein, and ACE2 receptors in in silico analysis. Thus, studying

the action of secondary metabolites, formulations, and plant-based products on these targets in employing in vivo and in vitro analysis could pay a deep insight into the discovery of novel therapeutic approaches to combat COVID-19.

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Chapter 18
Immune-Boosting Plants Used in Turkish Folk Medicine and Their Potential Against COVID-19

Seyid Ahmet Sargin and Yunus Dogan

18.1 Introduction

The coronavirus disease 2019 (COVID-19) outbreak, which emerged in Wuhan, China in late 2019, is still the first contagious epidemic the world has encountered after the Spanish Flu in terms of scope and size. The virus, namely severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) with its enveloped and single-stranded RNA content, rapidly expanded into a global dimension, with rising serious mortality rates after it turned into a regional epidemic (TAS 2020). The first verified COVID-19 case in Turkey was detected on March 11. As of 10 May 2021, 5,016,141 confirmed cases and 42,746 deaths have been reported to the World Health Organization (WHO 2021). To combat this rapidly emerging threat, prevention and treatment protocols were established and some social restrictions were imposed in a very short time (Konakci et al. 2020).

The immune system is a complex system that forms the defense mechanism against diseases in a living thing, recognizes and destroys pathogens and tumor cells, and protects the body from foreign and harmful substances (Scudiero et al. 2021). Two types of immunities, innate and adaptive, play a powerful role in increased susceptibility to infections. The likelihood of being diseased depends on the effectiveness of the immune response. Therefore, low immunity results in a reduced ability to fight the pathogen and become more susceptible to disease. Most of the deaths associated with coronavirus are due to the suppressed immune system of the human body that is unable to fight against it, rather than the damage caused by

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the virus (Bhatta 2020). When the immune response is low, weak, or damaged, infections such as coronavirus attack people, especially young and older people. It also becomes an open invitation for other diseases such as diabetes, heart disease, or cancer (Arshad et al. 2020; WHO 2020). Since it is not yet a registered drug or vaccine 100% effective against COVID-19 and all its mutants or variants, the immune system is still the best defense we have. As long as the immune system is functioning normally, infections such as COVID-19 may go undetected (Chowdhury et al. 2020). It has been found that patients suffering from infectious and non-infectious diseases of the lungs are at greater risk of this viral infection due to their low immune system (Opitz et al. 2010; Khanal et al. 2020). Therefore, strengthening immunity (natural body system) can make a major contribution as a prophylactic measure against multiple pathogenic conditions as well as maintaining optimum health (Khanal et al. 2020; Nicholson 2016).

The most common symptoms are fever, headache, cough, difficulty breathing, and diarrhea. In some cases or different variants of the virus, these symptoms may also remain silent. Or, on the contrary, it might be presented as severe pneumonia causing shortness of breath, kidney failure, or even death. After the virus enters the respiratory mucosa cells of another host through droplets that are released by coughing and sneezing (or close-range speech), it releases its genetic code to initiate viral replication, then uses the following three mechanisms to circumvent the immune response: The virus implements various mechanisms to circumvent the immune response. In the first step, it inhibits the rapid expression of interferon type 1 (IFN-1), known as the "initial alarm," which modulates immune cells to the "antiviral state" in the case of the system encountering the virus. Second, it blocks IFN-1's existing signals in the system through inhibition of the phosphorylation of STAT-1 (signal converter and transcription activator 1). Its third mechanism is the dysfunctioning of the immune system through excessive and prolonged production of IFN-1 by plasmacytoid dendritic cells (pDCs). The process causes an overproduction of activated neutrophils and macrophages, resulting in lung immunopathology (e.g. acute respiratory distress syndrome) (Taghizadeh-Hesary and Akbari 2020). This, in turn, activates a rapid reaction of innate immunity and results in the release of cytokines in large amounts, which play a key role in determining the extent of the infection. They damage beneficial cells and organs in the body, including defense cells, thus causing destruction and leading to death (Scudiero et al. 2021). In severe cases, a severe immune response is observed with deep lung exudate production, which limits ventilation and can subsequently trigger an uncontrolled inflammatory response, acute respiratory distress syndrome (ARDS), and septic shock, following bilateral pneumonia (Galmarini et al. 2020). These two complications are the primary reasons for hospitalization in intensive care and mortality for COVID-19 in patients with a history of smoking and comorbidities (Kakodkar et al. 2020). Chronic obstructive pulmonary disease, including chronic inflammation of the upper respiratory tract (URI), hypertension, diabetes, malignant tumor, coronary heart disease, cerebrovascular disease, and chronic kidney disorders are among the most common of these clinical stories (Scudiero et al. 2021; Chowdhury et al. 2020).

Due to their ability to easily mutate their genetic material and gain resistance, developing a broad-spectrum antiviral drug/vaccine that is completely safe and has the potential of 100% effectiveness and it reaching the market level is difficult and quite time-consuming (Oyston and Robinson 2012). Moreover, synthetically developed antiviral drugs sometimes have harmful or even fatal side effects that can cause significant health problems (Ghildiyal et al. 2020). Indeed, a newly developed popular vaccine that received market approval a few months ago created clots as a side effect and caused deaths in vaccinated people. Within a week, its use was suspended by about 18 countries worldwide (Tobaiqy et al. 2021). Therefore, herbs and plant-based herbal remedies seem promising in reducing these side effects because to their capacity to have strong antiviral activity (Ghildiyal et al. 2020; Jahan and Onay 2020).

A healthy and proper diet can strengthen the immune system and prevent the development of diseases and immune depression. For example, antioxidants can prevent or repair damage caused by harmful agents such as viruses and free radicals. The most powerful antioxidant in the human body is glutathione (GSH). If its level in the body increases, there is a simultaneous decrease in cytokine factors such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), which cause to worsen the disease (pro-inflammatory), thereby helping the patient recover (Scudiero et al. 2021). Especially medicinal plants, due to their rich content of minerals and vitamins, regularly contribute to the healthy development of the general intestinal microbiome, which constitutes 85% of the immune system and keeps the immune system active in the fight against infections. Highlights of immune-enhancing herbs are garlic, black cumin, and licorice (Arshad et al. 2020; WHO 2020). They produce many important phytochemicals through their secondary metabolism and act as a defense against stress caused by environmental triggers and pathogens. In fact WHO's announcement that 80% of the world's population trusts them for treatment highlights this fact (Ekor 2014; Khan et al. 2021).

Herbal preparations/medicines are always defined as a therapeutic regimen that, rather than consisting of a single compound that interacts with a single target, is a concerted pharmacological intervention of several compounds that interact with multiple targets (Wang et al. 2012). The results showed that not only do they modulate pathways related to strengthening the immune system, but also modulate multiple pathways that contribute to the progression of multiple disease pathogenesis that would add beneficial effects on specific issues such as hypertension and diabetes patients (Khanal et al. 2020). After the first SARS-CoV epidemic, it has been shown in many studies that plant extracts and phytochemicals produced from plants affect the virus with different mechanisms. These consist of direct antiviral activity, immune stimulator, inflammation modulator, and symptom management. Direct antiviral activity includes inhibition of early replication through viral entry inhibition and late replication inhibition (Khan et al. 2021).

The most likely mechanism for immune enhancers is to trigger humoral and cellular immune responses (Vaghasiya et al. 2010). For example, it has been found that aqueous and methanol extracts of basil leaves and seed oil increase the immune response by increasing T-helper and natural killer cells, lymphocyte count,

phagocytic activity, neutrophil count, antibody titer, and the like (Jamshidi and Cohen 2017; Singh et al. 2017). Similar positive effects of a wide variety of flavonoids found naturally in plants, such as quercetin, naringin, hesperetin, and catechin, against severe acute respiratory syndrome coronavirus (SARS-CoV) have been reported (Khanna et al. 2020). Researchers such as Terali et al. (2020) and Bibi et al. (2020) also elucidated the inhibitory action pathway against the ACE2 enzyme receptor, which enables COVID-19 to enter host cells. Hence, Utomo et al. (2020) reported that curcumin isolated from turmeric (*Curcuma longa*) inhibits SARS-CoV-2 protease, spike glycoprotein-RBD, and PD-ACE2 receptors, based on their molecular insertion studies. As a result of their in silico studies, Jakhmola Mani et al. (2020) stated that active ingredients such as a-hederin, thymohydroquinone, and thymoquinone, obtained from the extract of *Nigella sativa* seeds, efficiently bind and block ACE2 and reduce hypoxia and inflammation caused by oxidative stress, strengthening immunity and can greatly assist in the fight against COVID-19. Also, ACE2 inhibitors have been identified in various species such as *Allium sativum, Cerasus avium, Berberis integerrima, Alcea digitata, Rubia tinctorum, Peganum harmala*, etc. (Heidary et al. 2020). It has also been disclosed that herbal blockers which can inhibit the "pathogenic" kinase (PAK1), which plays a major role in the infection of many viruses, can support the immune system and serve as potential therapeutic agents against COVID-19 (Asih et al. 2021). Also, curcumin rhizome (Nemati et al. 2020) and tea-shaped extract of *Schinus molle* (pink peppercorn) fruits (Ji et al. 2019) contribute to the blocking of PAK1, strengthening the immune system against COVID-19 and other viral infections, and its essential anti-inflammatory formulations have been reported. Conversely, Shaghaghi (2020) showed in molecular dynamic simulations with terpenoid compounds, including thymoquinone extracted from *Nigella sativa*, that thymoquinone can reduce the likelihood of infection of SARS-CoV-2 (Elfiky 2020). Therefore, it is envisaged that medicinal plants may be effective in the prevention and treatment of COVID-19, either through direct use or their isolated compounds. However, many more advanced studies are needed for optimum effective dosage formulation and usage descriptions.

The following can be given as examples of similar studies conducted in Turkey: In an in silico study conducted by Adem et al. (2020), phytochemicals such as rutin, apiin, hesperidin, diosmin, and diacetylcurcumin were identified as potent COVID-19-main-protease (Mpro) inhibitors. Yilmaz et al. (2020) reported that black mulberry (*Morus nigra*) syrup increased serum lysozyme, myeloperoxidase, superoxide dismutase, and catalase activities and expression levels of immune-related genes, increasing innate immune parameters and antioxidant-related gene expression responses. In another study, Bilen et al. (2020) revealed that the aqueous methanolic extract of lemon balm (*Melissa officinalis*) has antioxidant and cell-mediated-immune system-stimulating effects by increasing lysozyme, pepsin, and trypsin activities. Thus, they highlighted that these herbal use recipes can play a vital role in reducing the symptoms of COVID-19 infection and preventing the further spread of such pandemics.

The COVID-19 pandemic is perhaps the most dangerous and deadly epidemic in human history, due to its rapid infection ability from person to person and its high incidence of mortality. The worldwide spreading rate and the concern that vaccines will be insufficient increase the need for new and natural medicine resources that will stimulate and strengthen our immunity without causing complications such as coagulation and side effects. However, well-designed, further-clinical studies are needed to demonstrate the potential efficacy of local herbal diets and preparations that have the potential to increase immunity against SARS-CoV-2 infection (Tewari et al. 2020). Turkey has a potential worth of ore for researchers and industry who are interested in this issue because it has the richest flora of Europe and the Middle East. The country's official pharmacopoeia includes contributions from 37 countries, including the European Pharmacopoeia. The number of monographs with rich content prepared to standardize the use of commonly used herbs is increasing day by day (Şekeroğlu and Gezici 2020).

While the previous study exhibited a national-plant list that promises a potential for anti-influenza activity in Turkey, in this study, the most comprehensive national-wide inventory of important medicinal plants that make the immune system quite active and strong is presented. In addition, the repercussions of these plants in the traditional medicine works of neighboring and nearby countries and the experimental studies conducted worldwide for the above-mentioned activities were examined, and the results were presented in tables and graphs. The taxa, which have not been the subject of any experimental research, constitute a unique reserve for new investigators in the field of natural medicine.

18.2 Materials and Methods

18.2.1 Gathering Data

The study has been conducted in three different stages by using only English and Turkish terms and by searching electronic databases respected by scientific circles such as Web of Science, Scopus, ScienceDirect, PubMed, ProQuest, Medline, HighWire Press, Cochrane Library, Google Scholar, and EBSCO. As a first step, an inventory roster of herbs consumed as immune system stimulants, enhancers, or boosters in traditional Turkish medicine was displayed (Table 18.1). To reach more point-by-point data, master and doctoral dissertations carried out throughout the country (Fig. 18.1) were also embodied in the study. To this end, approximately 1000 national works were determined between January 1999 and December 2020, and a consensus reached only over 99 (Table 18.2). The therapeutic plants traditionally utilized by the nation's citizens for centuries were meticulously distinguished from those works according to the ensuing gauges and introduced in (Table 18.1). The equivalents of those plants in peer works conducted in nearby nations were examined in the stage after that. Finally, the implications of the empirical works in the global literature on immune-boosting and other similar

Table 18.1 The list of plant taxa used for immune-boosting and related activities in Turkish folk medicine

Plant name	Family	C/W/E	English name	Part(s)	Preparation(s)	Report(s)
Achillea millefolium L.	Compositae	W	Common yarrow	Leaves, flowers	Infusion	Kalafatçılar and Kalafatçılar (2010), Baytop (1999), Özer et al. (2005), Akan and Bakır-Sade (2015), Everest and Ozturk (2005)
***Achillea nobilis* L.**	Compositae	W	Noble yarrow	Aerial parts, flowers	Infusion	Çekin et al. (2016), Sargin et al. (2015), Nacakcı and Dutkuner (2015), Everest and Ozturk (2005)
Allium cepa L.	Amaryllidaceae	C	Onion	Bulbs, leaves	Eaten raw, boiling, juice with some honey	Jahan and Onay (2020), Köse (2019), Özcan et al. (2020), Uçar et al. (2020), Yeşilada (2012), Ege and Elmastaş (2020), Uzun and Kaya (2016), Çakılcıoğlu and Türkoğlu (2007), Ekşi et al. (2020)
Allium sativum L.	Amaryllidaceae	C	Garlic	Leaves, bulbs, flowers	Eaten raw, cooked, tincture (prepared with the bulbs, lemon, and vinegar)	Jahan and Onay (2020), Kalafatçılar and Kalafatçılar (2010), Köse (2019), Özcan et al. (2020), Kavaklı et al. (2020b), Uçar et al. (2020), Yeşilada (2012), Ege and Elmastaş (2020), Uzun and Kaya (2016), Çakılcıoğlu and Türkoğlu (2007), Ekşi et al. (2020)

***Althaea officinalis* L.**	Malvaceae	C/W	Common marsh	Buds, flowers	Infusion	Kalafatçılar and Kalafatçılar (2010), Baytop (1999), Ötnü and Akan (2020)
Apium graveolens L.	Apiaceae	C	Celery	Leaves, seeds	Decoction, mixture (eaten after milling with cloves and seeds of anise, turnip, radish, and mixed with honey)	Baytop (1999), Özcan et al. (2020), Sargin (2013), Uçar et al. (2020)
***Asparagus acutifolius* L.**	Asparagaceae	C/W	Wild asparagus	Aerial parts	Infusion	Çekin et al. (2016), Ege and Elmastaş (2020), Demirci-Kayıran (2019), Ozturk et al. (2017b)
***Astragalus* spp.**	Leguminosae	W	Milkvetches	Aerial parts, roots, young shoots	Infusion, eaten raw after peeling, infusion after dried and pulverized, mixture (obtained by drying and pulverizing the fresh shoots and mixing with honey), tincture (prepared with lemon and vinegar)	Kalafatçılar and Kalafatçılar (2010), Sargin (2013), Uçar et al. (2020), Tuzlacı and Doğan (2010a), Arı et al. (2015), Akbulut et al. (2017), Doğan (2008), Korkmaz and Karakurt (2014), Polat et al. (2013)
Avena sativa L.	Poaceae	C/W	Oat, common oat	Fruits, seeds	Pastry, meal	Baytop (1999), Özcan et al. (2020), Çekin et al. (2016), Yeşilada (2012)
Brassica oleracea L.	Brassicaceae	C	Cabbage, flowering cabbage, kale	Aerial parts, leaves	Decoction, meal, salad	Özcan et al. (2020), Gül and Seçkin-Dinler (2016), Gökçe (2011), Akbulut et al. (2017)
Brassica rapa L.	Brassicaceae	C	Turnip	Tubers, roots, leaves, seeds	Juice, boiling-meal, mixture (eaten after milling with cloves and seeds of anise, celery, radish and mixed with honey)	Özcan et al. (2020), Sargin (2013), Yeşilada (2012), Gökçe (2011)

(continued)

Table 18.1 (continued)

Plant name	Family	C/W/E	English name	Part(s)	Preparation(s)	Report(s)
Calendula officinalis L.	Compositae	C/W	Pot marigold, ruddles	Flowers	Infusion	Kalafatçılar and Kalafatçılar (2010), Çekin et al. (2016), Onbaşlı and Dal (2020)
Camellia sinensis (L.) Kuntze	Theaceae	C	Green tea	Leaves	Infusion	Genç (2010), Özcan et al. (2020), Yeşilada (2012), Doğan and Doğan (2020), Korkmaz et al. (2016)
Capparis spinosa L.	Capparaceae	W	Caper bush, flinders rose	Fruits, buds, roots, barks	Infusion, decoction	Baytop (1999), Genç (2010), Çekin et al. (2016)
Capsicum annuum L.	Solanaceae	C	Ornamental pepper	Fruits	Eaten raw, spice, decoction, meal	Kavaklı et al. (2020b), Uzun and Koca (2020), Sargin and Büyükcengiz (2019)
Castanea sativa mill.	Fagaceae	C/W	Chestnut, sweet chestnut	Fruits, seeds, flowers	Decoction, boiling, infusion	Köse (2019), Kavaklı et al. (2020a)
***Centaurea hyalolepis* Boiss.**	Compositae	W	Yellow star-thistle, knapweed	Flowers	Restorative paste (with honey after crashing)	Kılıç (2019), Altundag and Ozturk (2011), Tuzlacı and Doğan (2010a), Doğan (2008)
***Ceratonia siliqua* L.**	Leguminosae	C/W	Carob	Fruits	Eaten raw, boiling, molasses	Kurt and Karaoğul (2018), Biçer (2020), Doğan and Doğan (2020), Sargin and Büyükcengiz (2019)
Cichorium intybus L.	Compositae	W	Blue daisy, blue dandelion, blue sailors, blue weed	Aerial parts, roots	Infusion, decoction	Kılıç (2019), Şenkardeş (2014), Çekin et al. (2016), Özer et al. (2005), Ozturk et al. (2017b)
***Cistus creticus* L.**	Cistaceae	W	Pink rock-rose, hoary rock-rose	Leaves	Infusion	Şekeroğlu and Gezici (2020), Baytop (1999), Güneş (2010), Ege and Elmastaş

						(2020), Yeşilada et al. (2019), Doğan and Doğan (2020)
***Cistus laurifolius* L.**	Cistaceae	W	Laurel-leaved rock-rose	Leaves	Infusion	Şekeroğlu and Gezici (2020), Ege and Elmastaş (2020), Yeşilada et al. (2019), Doğan and Doğan (2020)
***Cistus salviifolius* L.**	Cistaceae	W	Sage-leaved rock-rose	Leaves	Infusion	Şekeroğlu and Gezici (2020), Baytop (1999), Ege and Elmastaş (2020), Yeşilada et al. (2019), Doğan and Doğan (2020)
Citrus spp.	Rutaceae	C/W	Oranges, lemons, grapefruits, pomelos, limes	Pericarps, fruits	Decoction, jam, eaten raw, juice, marmalade, dropped in teas and soups, gargle	Jahan and Onay (2020), Şekeroğlu and Gezici (2020), Baytop (1999), Köse (2019), Genç (2010), Özcan et al. (2020), Yeşilada (2012), Akan and Bakır-Sade (2015), Güneş (2010)
***Cota austriaca* (Jacq.) Sch.Bip.**	Compositae	W	Corn chamomile	Capitulum, flowers, aerial parts	Infusion	Kılıç (2019), Genç (2010), Şenkardeş (2014), Alkış (2019), Doğan (2014), Tetik et al. (2013), Kaval et al. (2014)
Crataegus monogyna Jacq.	Rosaceae	C/W	Hawthorn, may	Flowers, fruits, seeds	Infusion, eaten raw, infusion, eaten raw, decoction	Şenkardeş (2014), Kavaklı et al. (2020b), Olgun (2019), Paksoy et al. (2016)
***Crataegus orientalis* pall. Ex M.Bieb.**	Rosaceae	C/W	Oriental hawthorn	Flowers, fruits, seeds	Infusion, eaten raw, infusion, eaten raw, decoction	Şenkardeş (2014), Kavaklı et al. (2020b), Gençay (2007)
***Daucus carota* L.**	Apiaceae	C/W	Wild carrot, bird's nest	Seeds	Spice after milling	Özcan et al. (2020), Akan and Bakır-Sade (2015)

(continued)

Table 18.1 (continued)

Plant name	Family	C/W/E	English name	Part(s)	Preparation(s)	Report(s)
***Drosera rotundifolia* L.**	Droseraceae	C/W	Round-leaved sundew, common sundew	Flowers	Infusion	Kalafatçılar and Kalafatçılar (2010), Baytop (1999), Genç (2010)
***Echinophora tenuifolia* subsp. *sibthorpiana* (Guss.) Tutin**	Apiaceae	C/W	Turkish çördük, tarhana	Aerial parts	Soup, meal (after dried and pulverized)	Sargin (2013), Özer et al. (2005), Bulut et al. (2014)
Elaeagnus angustifolia L.	Elaeagnaceae	C/W	Silverberry	Fruits, leaves, flowers	Eaten raw, infusion	Şenkardeş (2014), Biçer (2020), Ozturk et al. (2017a)
Equisetum arvense L.	Equisetaceae	W	Field horsetail, common horsetail	Aerial parts	Infusion, foot bath	Kalafatçılar and Kalafatçılar (2010), Şanlı (2006), Everest and Ozturk (2005), Korkmaz et al. (2016)
***Eriobotrya japonica* (Thunb.) Lindl.**	Rosaceae	C/W	Loquat	Leaves	Infusion mix (with *Cydonia* leaves and *Tilia* flowers)	Baytop (1999), Hürkul and Köroğlu (2019), Sargin (2015)
***Eruca vesicaria* (L.) Cav.**	Brassicaceae	C/W	Rocket, garden rocket	Leaves	Eaten raw, salad	Deniz et al. (2010), Akan and Bakır-Sade (2015), Kavaklı et al. (2020a)
***Eupatorium cannabinum* L.**	Compositae	W	Hemp-agrimony, holy rope	Aerial parts	Infusion	Kalafatçılar and Kalafatçılar (2010), Baytop (1999), Genç (2010), Mumcu and Korkmaz (2018)
***Ferula orientalis* L.**	Apiaceae	W	–	Whole parts	Decoction, infusion after dried and pulverized	Ötnü and Akan (2020), Altundag and Ozturk (2011), Tuzlacı and Doğan (2010a), Bulut et al. (2014), Doğan (2008)

***Ficus carica* L.**	Moraceae	C/W	Common fig	Fruits	Eaten raw or dried with/without nuts	Gençay (2007), Bulut (2008), Arasan (2014)
Fragaria vesca L.	Rosaceae	C/W	Strawberry, wild strawberry	Fruits	Jam, syrup	Özcan et al. (2020), Sargin (2013), Uçar et al. (2020), Gül and Seçkin-Dinler (2016)
Glycyrrhiza glabra L.	Leguminosae	C/W	Licorice, licorice	Leaves, roots	Infusion after pulverizing, syrup	Şekeroğlu and Gezici (2020), Kılıç (2019), Kavaklı et al. (2020b), Uçar et al. (2020), Ötnü and Akan (2020), Özer et al. (2005), Akan and Bakır-Sade (2015), Tütenocaklı (2014), Yeşil et al. (2019), Mumcu and Korkmaz (2018), Akbaş and Akçakaya (2020), Küpeli-Akkol et al. (2020)
Helianthus tuberosus L.	Compositae	C/W	Sunroot, sunchoke, earth apple	Tubers	Eaten raw, salad, soup, meal	Baytop (1999), Özçelik et al. (2016)
Hordeum vulgare L.	Poaceae	C/W	Barley	Fruits, seeds	Decoction, additive (the flour is obtained after drying, and grinding is added to the meals)	Olgun (2019), Özdemir-Nath (2016), Doğan (2014)
Hypericum perforatum L.	Hypericaceae	C/W	St. John's wort	Flowering branches, aerial parts	Infusion after drying, infusion mix (with the leaves of *Urtica* spp. and *Rubus* spp)	Köse (2019), Gül and Seçkin-Dinler (2016), Özdemir-Nath (2016), Yeşilyurt et al. (2017a, b), Nacakcı and Dutkuner (2015), Sargin and Büyükcengiz (2019)

(continued)

Table 18.1 (continued)

Plant name	Family	C/W/E	English name	Part(s)	Preparation(s)	Report(s)
***Hyssopus officinalis* L.**	Lamiaceae	W	Hyssop	Flowers, flowering branches, leaves	Infusion	Jahan and Onay (2020), Çekin et al. (2016), Özer et al. (2005)
Juglans regia L.	Juglandaceae	C/W	Walnut, common walnut	Leaves, pericarp, fruits	Infusion, mixture (eaten with honey and dried fig)	Kalafatçılar and Kalafatçılar (2010), Baytop (1999), Kavaklı et al. (2020b), Nacakcı and Dutkuner (2015)
***Juniperus oxycedrus* L.**	Cupressaceae	W	Cade, cade juniper, prickly juniper	Fruits, seeds, leaves, tars, cones, gall	Decoction, infusion, distillation	Şenkardeş (2014), Deniz et al. (2010), Şanlı (2006), Akgul et al. (2018), Kökçü et al. (2015), Tuzlacı and Sadıkoğlu (2007)
***Lavandula stoechas* L.**	Lamiaceae	C/W	Spanish lavender, topped lavender	Leaves, flowering branches	Infusion	Ötnü and Akan (2020), Güneş (2010), Bulut (2008), Nacakcı and Dutkuner (2015), Bozyel and Merdamert-Bozyel (2020), Bulut and Tuzlacı (2009)
***Lepidium sativum* L.**	Brassicaceae	C/W	Garden cress	Aerial parts, seeds	Infusion, restorative paste (prepared with honey)	Baytop (1999), Deniz et al. (2010), Kavaklı et al. (2020a), Çiçek (2019), Ongan (2018)
***Linum usitatissimum* L.**	Linaceae	C/W	Flax	Seeds, fixed oils	Eaten raw, drunk	Kalafatçılar and Kalafatçılar (2010), Köse (2019), Özcan et al. (2020), Kavaklı et al. (2020b)
Malus domestica Borkh.	Rosaceae	C	Apple	Fruits	Eaten raw, juice, decoction (with pear peels after dried)	Sargin (2013), Uçar et al. (2020), Olgun (2019)

***Malus sylvestris* (L.) mill.**	Rosaceae	C/W	European crab apple	Fruits	Eaten raw, juice, decoction (with pear peels after dried)	Uçar et al. (2020), Olgun (2019), Günbatan et al. (2016), Doğan (2014)
***Malva neglecta* Wallr.**	Malvaceae	W	Cheese plant, dwarf mallow	Aerial parts	Infusion, decoction	Arasan (2014), Bulut and Tuzlacı (2013), Doğan (2014), Şenkardeş (2014), Olgun (2019)
***Malva nicaeensis* all.**	Malvaceae	W	Bull mallow, French mallow	Leaves	Decoction with the aerial parts of *Urtica dioica.*	Gençay (2007), Bulut (2008), Kızılarslan (2008), Uzun and Kaya (2016)
Malva sylvestris (L.) mill.	Malvaceae	W	Large-flowered mallow, high mallow	Leaves, aerial parts	Infusion, meal (prepared with rice, radish, onion, and butter). Another meal is prepared with the leaves, *Papaver rhoeas* petals, *Urtica dioica,* and *Spinacia oleracea* leaves	Köse (2019), Sargin (2013), Özer et al. (2005), Özdemir-Nath (2016), Bulut (2008), Kızılarslan (2008), Tuzlacı and Doğan (2010b)
Matricaria chamomilla L.	Compositae	W	Chamomile, German chamomile	Aerial parts, flowering branches, flowers	Infusion	Kalafatçılar and Kalafatçılar (2010), Genç (2010), Özcan et al. (2020), Uçar et al. (2020), Özer et al. (2005), Sargin et al. (2015), Tuzlacı and Sadıkoğlu (2007), Polat et al. (2015)
Melissa officinalis L.	Lamiaceae	C/W	Lemon balm	Aerial parts	Infusion after drying, infusion mix (with sage leaves, elder fruits, black pepper, and ginger)	Uçar et al. (2020), Özer et al. (2005), Ege and Elmastaş (2020), Yeşilada et al. (2019), Demirci-Kayıran (2019), Güneş (2017), Özhatay et al. (2009), Diken (2009)

(continued)

Table 18.1 (continued)

Plant name	Family	C/W/E	English name	Part(s)	Preparation(s)	Report(s)
***Mentha longifolia* (L.) L.**	Lamiaceae	W	Horse mint	Aerial parts	Eaten raw, infusion	Jahan and Onay (2020), Kılıç (2019, 2016), Şenkardeş (2014), Özer et al. (2005), Olgun (2019), Kurt and Karaoğul (2018), Yeşilyurt et al. (2017b), Arı et al. (2015)
Mentha pulegium L.	Lamiaceae	W	Pennyroyal, pennyrile, squaw mint	Leaves	Infusion after drying, infusion mix (with the leaves of *Petroselinum crispum* and *Origanum vulgar*e)	Jahan and Onay (2020), Köse (2019), Kurt and Karaoğul (2018), Yeşilyurt et al. (2017b)
***Mentha spicata* L.**	Lamiaceae	W	Spearmint	Aerial parts, leaves	Infusion, spice (after powdering)	Jahan and Onay (2020), Köse (2019), Deniz et al. (2010), Kurt and Karaoğul (2018), Yeşilyurt et al. (2017b), Güneş (2010, 2017)
Mentha x piperita L.	Lamiaceae	C/W	Peppermint	Leaves, aerial parts	Eaten raw, salad, spice, syrup, infusion mix-1 (with lemon juice), infusion mix-2 (with the leaves of *Petroselinum crispum* and*Origanum vulgare*)	Jahan and Onay (2020), Kalafatçılar and Kalafatçılar (2010), Kılıç (2019), Genç (2010), Şenkardeş (2014), Uçar et al. (2020), Özer et al. (2005), Gül and Seçkin-Dinler (2016), Kurt and Karaoğul (2018), Yeşilyurt et al. (2017a, b), Uzun and Koca (2020), Akay (2019), Bozyel and Merdamert-Bozyel (2020)

Mespilus germanica L.	Rosaceae	C/W	Medlar, medlar tree	Leaves, fruits	Infusion, eaten raw	Köse (2019), Gül and Seçkin-Dinler (2016), Uzun and Koca (2020)
Morus alba L.	Moraceae	C/W	White mulberry	Fruits, leaves	Syrup, molasses, churchkhela, infusion	Şenkardeş (2014), Çekin et al. (2016), Olgun (2019), Özdemir-Nath (2016), Gençay (2007), Çiçek (2019), Ege and Elmastaş (2020), Doğan (2014)
Morus nigra L.	Moraceae	C/W	Black mulberry, blackberry	Fruits, leaves	Molasses, syrup, infusion	Gül and Seçkin-Dinler (2016), Bulut (2008), Ege and Elmastaş (2020)
Myrtus communis L.	Myrtaceae	C/W	Common myrtle or true myrtle	Fruits, leaves	Eaten raw, infusion	Akan and Bakır-Sade (2015), Güneş (2010), Korkmaz et al. (2016)
Nasturtium officinale R.Br.	Brassicaceae	W	Watercress, yellowcress	Leaves, flowers	Infusion, salad, meal	Kılıç (2019), Şanlı (2006), Gençay (2007), Kocabaş et al. (2017)
***Nigella arvensis* L.**	Ranunculaceae	C/W	Wild fennel, field fennel flower	Flowers, seeds	Infusion after dried, restorative paste (with honey after crushed), spices	Kılıç (2019), Deniz et al. (2010), Güneş (2017), Arı et al. (2015), Kılıç et al. (2020)
Nigella damascena L.	Ranunculaceae	C/W	Love-in-a-mist, ragged lady	Seeds, essential oils	Infusion, eaten raw	Genç (2010), Çekin et al. (2016), Özçelik et al. (2016)
Nigella sativa L.	Ranunculaceae	C/W	Black cumin	Seeds, essential oils	Eating raw, infusion after crashing, spices	Kalafatçılar and Kalafatçılar (2010), Baytop (1999), Köse (2019), Uçar et al. (2020), Ötnü and Akan (2020), Deniz et al. (2010), Kurt and Karaoğul (2018), Biçer

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Table 18.1 (continued)

Plant name	Family	C/W/E	English name	Part(s)	Preparation(s)	Report(s)
						(2020), Arı et al. (2015), Arıtuluk (2010)
Olea europaea L.	Oleaceae	C/W	Olive	Leaves, fruits, fixed oils	Infusion, cataplasm with one tablespoon molasses, tarhana, and flour, drunk one tablespoon or added to salads	Şekeroğlu and Gezici (2020), Köse (2019), Özcan et al. (2020), Ötnü and Akan (2020), Yeşilada et al. (2019)
***Origanum onites* L.**	Lamiaceae	W	Pot marjoram, Cretan oregano	Aerial parts with flowers, flowering branches	Foot bath, infusion-1 (with sage leaves), infusion-2 (with anise and mint leaves)	Deniz et al. (2010), Kalafatçılar and Kalafatçılar (2010), Nacakcı and Dutkuner (2015), Bozyel and Merdamert-Bozyel (2020), Şekeroğlu and Gezici (2020)
Origanum vulgare L.	Lamiaceae	W	Ornamental oregano	Aerial parts with/without flowers, flowering branches	Foot bath, infusion 1 (with sage leaves), infusion 2 (with anise and mint leaves)	Şekeroğlu and Gezici (2020), Deniz et al. (2010), Özer et al. (2005), Bozyel and Merdamert-Bozyel (2020)
***Papaver rhoeas* L.**	Papaveraceae	W	Flanders poppy	Flowers, petals	Infusion with/without *Urtica dioica* leaves, meal (prepared with the leaves of *Spinacia oleracea* and *Malva* spp. or *Urtica dioica*)	Özdemir-Nath (2016), Gençay (2007), Kızılarslan (2008), Özhatay et al. (2009), Tütenocaklı (2014), Kültür (2007)
Petroselinum crispum (mill.) fuss	Apiaceae	C/W	Parsley	Leaves, aerial parts	Eaten raw, juice (with lemon), salad, infusion with/without the leaves of *Mentha spp* and*Origanum* spp.	Şenkardeş (2014), Uçar et al. (2020), Ötnü and Akan (2020), Olgun (2019), Güneş (2010), Kavaklı et al. (2020a), Çiçek (2019)
***Phoenix dactylifera* L.**	Arecaceae	C/W	Date, date palm	Fruits	Eaten raw	Baytop (1999), Genç (2010), Kavaklı et al. (2020a), Biçer (2020)

***Pinus brutia* Ten.**	Pinaceae	C/W	Calabrian pine, Turkish pine	Barks, shoots, pollens, cones, fruits, essential oils	Decoction, eaten with honey. Pickle, prepared with seeds, cones, lemons, garlic, and water. Medicinal bath, frankincense	Jahan and Onay (2020), Kalafatçılar and Kalafatçılar (2010), Genç (2010), Sargin (2013), Gürbüz et al. (2019)
***Pinus nigra* J.F. Arnold**	Pinaceae	W	Black pine	Resins, tars, essential oils	Decoction, medicinal bath, frankincense	Jahan and Onay (2020), Kalafatçılar and Kalafatçılar (2010), Genç (2010), Sargin (2013), Gürbüz et al. (2019)
***Pinus pinea* L.**	Pinaceae	C/W	Stone pine, umbrella pine, parasol pine	Fruits, pollens, essential oils	Eaten with molasses, honey, dried figs, or grapes	Jahan and Onay (2020), Genç (2010), Ötnü and Akan (2020), Gürbüz et al. (2019)
Pinus sylvestris L.	Pinaceae	W	Redwood, Scots fir	Buds, resins, cones, essential oils	Decoction, medicinal bath, frankincense	Jahan and Onay (2020), Kalafatçılar and Kalafatçılar (2010), Genç (2010), Gürbüz et al. (2019)
Portulaca oleracea L.	Polygonaceae	W	Common purslane, fatweed	Aerial parts	Eating raw, boiling, roasting	Kılıç (2019), Köse (2019), Ötnü and Akan (2020), Arasan (2014), Kocabaş et al. (2017)
Prunus avium (L.) L.	Rosaceae	C/W	Sweet cherry	Fruits stalks	Infusion, restorative paste (prepared with a cherry stalk and rye after drying and pulverizing and sweetening with honey or molasses)	Sargin (2013), Sargin et al. (2015), Özdemir-Nath (2016), Gürbüz et al. (2019), Hürkul and Köroğlu (2019), Korkmaz et al. (2016)
***Prunus cerasifera* Ehrh.**	Rosaceae	C/W	Cherry plum	Fruits	Eaten raw, infusion, decoction	Çiçek (2019), Arı et al. (2015), Hürkul and Köroğlu (2019)
***Prunus domestica* L.**	Rosaceae	C/W	Plum, European plum	Fruits	Eaten raw, compote	Ötnü and Akan (2020), Kavaklı et al. (2020a)

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Table 18.1 (continued)

Plant name	Family	C/W/E	English name	Part(s)	Preparation(s)	Report(s)
***Prunus spinosa* L.**	Rosaceae	W	Sloe, blackthorn	Fruits	Eaten raw, decoction	Şanlı (2006), Özdemir-Nath (2016), Yeşilyurt et al. (2017b), Özhatay et al. (2009)
Punica granatum L.	Lythraceae	C/W	Pomegranate	Fruits, flowers, seeds, pericarps	Eaten raw, juice, infusion, decoction	Baytop (1999), Köse (2019), Sargin (2013), Kavaklı et al. (2020b), Olgun (2019), Kurt and Karaoğul (2018), Özdemir-Nath (2016), Gençay (2007), Güneş (2010), Çiçek (2019), Arasan (2014), Tuzlacı and Sadıkoğlu (2007), Kilic and Bagci (2013), Korkmaz and Karakurt (2014), Ozturk et al. (2017a), Polat et al. (2011), Şahin (2019)
Pyrus communis L.	Rosaceae	C/W	European pear, common pear	Fruits	Eaten raw, decoction with the dried peel of the apple after dried	Güneş (2017), Akgul et al. (2018), Doğan (2014)
Rhus coriaria L.	Anacardiaceae	C/W	Tanner's sumach, Sicilian sumac	Leaves, fruits	Infusion, spice	Uçar et al. (2020), Nacakcı and Dutkuner (2015), Doğan and Doğan (2020), Özçelik et al. (2016)
Rosa × *damascena* Herrm.	Rosaceae	C/W	Rose, damask rose	Flowers	Infusion, jam, syrup, juice, pastry, vinegar	Baytop (1999), Kavaklı et al. (2020b), Çekin et al. (2016)
Rosa canina L.	Rosaceae	C/W	Dog rose, briar rose, common briar	Fruits, leaves, flowers, petals, roots, stems	Eaten raw, infusion after drying and pulverizing, infusion mix (with lemon balm,	Şanlı (2006), Kültür (2007), Sarıkan (2007), Bulut (2008), Doğan (2008),

					elderflower, plantaginis leaf, and a little honey or stevia) decoction, jam, Marmalate	Kızılarslan (2008), Özhatay et al. (2009), Deniz et al. (2010), Kalafatçılar and Kalafatçılar (2010), Kılıç (2019), Köse (2019), Şenkardeş (2014), Çekin et al. (2016), Yeşilada (2012), Sargin et al. (2015), Gül and Seçkin-Dinler (2016), Olgun (2019), Yeşilyurt et al. (2017b), Çiçek (2019), Gürbüz et al. (2019), Altundag and Ozturk (2011), Tuzlacı and Doğan (2010a), Uzun and Kaya (2016), Yeşil et al. (2019), Bulut et al. (2017), Günbatan et al. (2016), Mumcu and Korkmaz (2018), Paksoy et al. (2016), Arıtuluk (2010), Erarslan et al. (2020), Kavaklı et al. (2020a, b), Uçar et al. (2020), Ötnü and Akan (2020)
***Rosa hemisphaerica* Herrm.**	Rosaceae	W	Sulphur rose	Fruits	Eaten raw, decoction	Şenkardeş (2014), Kavaklı et al. (2020b), Uzun and Kaya (2016)
Rosmarinus officinalis L.	Lamiaceae	C/W	Rosemary	Leaves, fruits, young shoots	Infusion, syrup, jam, eaten raw	Genç (2010), Kavaklı et al. (2020b), Ötnü and Akan (2020), Yeşilada (2012), Deniz et al. (2010), Güneş (2010), Şahin (2019)

(continued)

Table 18.1 (continued)

Plant name	Family	C/W/E	English name	Part(s)	Preparation(s)	Report(s)
***Rubus caesius* L.**	Rosaceae	C/W	Dewberry	Fruits, leaves, roots	Syrup, jam, eaten raw, infusion after drying and pulverizing, infusion mix (with the leaves of *Urtica* spp. and the aerial parts of *Hypericum perforatum*)	Baytop (1999), Özcan et al. (2020), Kurt and Karaoğul (2018), Çiçek (2019), Paksoy et al. (2016)
***Rubus canescens* DC.**	Rosaceae	W	Woolly blackberry	Leaves, fruits, young shoots	Infusion, syrup, jam, Marmalate, eaten raw	Kalafatçılar and Kalafatçılar (2010), Özcan et al. (2020), Gül and Seçkin-Dinler (2016), Şanlı (2006), Özhatay et al. (2009), Kültür (2007), Tuzlacı and Doğan (2010b)
***Rubus sanctus* Schreb.**	Rosaceae	W	Holy bramble	Fruits, roots, flowers, leaves	Syrup, jam, eaten raw, decoction, infusion, jam, infusion after drying, infusion mix (with the leaves of *Urtica* spp. and the aerial parts of *Hypericum perforatum*)	Kalafatçılar and Kalafatçılar (2010), Kılıç (2019), Özcan et al. (2020), Gül and Seçkin-Dinler (2016), Şanlı (2006), Özdemir-Nath (2016), Bulut (2008), Kızılarslan (2008), Akay (2019), Hürkul and Köroğlu (2019), Tuzlacı and Doğan (2010b)
***Salvia absconditiflora* Greuter & Burdet**	Lamiaceae	E	–	Aerial parts	Infusion	Kılıç (2019), Şenkardeş (2014), Sargin (2013), Sargin et al. (2015), Yeşilada et al. (2019)
Salvia officinalis L.	Lamiaceae	C/W	Culinary sage, golden sage, garden sage	Aerial parts	Infusion after drying, infusion mix-1 (with/without the flowers or fruits of *Sambucus*	Kalafatçılar and Kalafatçılar (2010), Genç (2010), Kavaklı et al. (2020a, b),

					nigra, the leaves of *Melissa officinalis*, black pepper, and ginger). Infusion mix-2 (with flowers of *Tilia* and *teucrium*, *Urtica* and *Thymus* leave with honey)	Uçar et al. (2020), Yeşilada (2012), Akan and Bakır-Sade (2015), Yeşilada et al. (2019), Uzun and Koca (2020)
***Salvia palaestina* Benth.**	Lamiaceae	W	Palestinian sage	Aerial parts	Infusion	Kılıç (2019), Yeşilada et al. (2019), Kocabaş et al. (2017)
***Salvia tomentosa* Mill.**	Lamiaceae	W	Balsamic sage	Aerial parts	Infusion after drying, infusion mix (with flowers of *Tilia argentea* and *teucrium polium* or *Urtica dioica* and *Thymus longicaulis* leaves with honey)	Sargin (2013), Deniz et al. (2010), Sargin et al. (2015), Yeşilada et al. (2019), Alkış (2019)
***Salvia verticillata* subsp. *amasiaca* (Freyn & Bornm.) Bornm.**	Lamiaceae	W	Lilac sage, whorled clary	Aerial parts	Infusion	Köse (2019), Altundag and Ozturk (2011), Doğan (2014)
Sambucus ebulus L.	Adoxaceae	W	European dwarf elder	Fruits, roots, seeds	Eaten raw, decoction, infusion after drying and pulverizing, infusion mix (with sage, Melissa leaves, black pepper, and ginger)	Baytop (1999), Yeşilada et al. (2019), Ozturk et al. (2017a), Öztürk and Ölçücü (2011)
Sambucus nigra L.	Adoxaceae	W	Elderberry, European elder	Leaves, flowers, fruits, barks	Infusion after drying and pulverizing, infusion mix-1 (with lemon balm, plantaginis leaf, rosehip fruit powder, and a little honey or stevia). Infusion mix-2 (with sage, Melissa leaves, black pepper, and ginger)	Kalafatçılar and Kalafatçılar (2010), Ötnü and Akan (2020), Yeşilada (2012), Şanlı (2006), Ege and Elmastaş (2020), Yeşilada et al. (2019), Akbaş and Akçakaya (2020), Kökçü et al. (2015)

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Table 18.1 (continued)

Plant name	Family	C/W/E	English name	Part(s)	Preparation(s)	Report(s)
***Satureja cuneifolia* Ten.**	Lamiaceae	W	Apulian savory	Aerial parts	A glass of its infusion is drunk twice a day	Sargin (2013), Sargin et al. (2015), Güneş (2017)
***Satureja hortensis* L.**	Lamiaceae	W	Summer savory	Aerial parts, flowering branches, essential oil	Infusion, spice, lotion	Olgun (2019), Altundag and Ozturk (2011), Tuzlacı and Doğan (2010a), Doğan (2014), (2008), Tetik et al. (2013), Kılıç (2016), Polat et al. (2013)
***Satureja thymbra* L.**	Lamiaceae	W	Thyme-leaved savory	Aerial parts, flowering branches, essential oil	Infusion, spice, lotion	Sargin et al. (2015), Nacakcı and Dutkuner (2015), Sargin (2015)
Sesamum indicum L.	Pedaliaceae	C/W	Sesame	Seeds	Mixture (crushed and mixed with boiled grape juice), eaten raw	Baytop (1999), Ötnü and Akan (2020), Güneş (2017)
Silybum marianum (L.) Gaertn.	Compositae	W	Milk thistle, Marian thistle	Seeds, stems, fruits	Eaten raw after peeling, infusion	Baytop (1999), Kılıç (2019), Sargin et al. (2015), Akbaş and Akçakaya (2020)
Solanum lycopersicum L.	Solanaceae	C	Tomato	Fruits	Eaten raw or after boiling, soup, salad	Köse (2019), Özcan et al. (2020), Sargin (2013), Uçar et al. (2020), Gökçe (2011)
Spinacia oleracea L.	Amaranthaceae	C	Spinach	Leaves	Boiling, salad, pastry material. Mixture-meal (prepared with *Papaver rhoeas* petals and *Malva* spp. or *Urtica dioica* leaves)	Özcan et al. (2020), Sargin (2013), Gençay (2007), Uzun and Kaya (2016)

Taraxacum spp.	Compositae	W	Dandelions	Flowers, roots	Infusion, meal, mixture-meal (with *Allium cepa, Allium sativum, Solanum lycopersicum*, and *Capsicum annuum),* decoction, tincture (prepared with lemon and vinegar)	Kılıç (2019), Genç (2010), Gül and Seçkin-Dinler (2016), Kurt and Karaoğul (2018), Özdemir-Nath (2016)
***Thymbra capitata* (L.) Cav.**	Lamiaceae	W	Spanish oregano, cone-head thyme	Aerial parts, flowering branches, essential oil	Infusion, lotion, spice	Şekeroğlu and Gezici (2020), Kalafatçılar and Kalafatçılar (2010), Sargin et al. (2015), Doğan and Doğan (2020)
***Thymbra spicata* L.**	Lamiaceae	W	Thyme spiked	Aerial parts, flowering branches, essential oil	Infusion, lotion, spice, foot bath, bath with/without Matricaria	Şekeroğlu and Gezici (2020), Kalafatçılar and Kalafatçılar (2010), Kılıç (2019), Sargin et al. (2015), Akan and Bakır-Sade (2015), Güneş (2010), Doğan and Doğan (2020)
***Thymbra sintenisii* Bornm. & Azn.**	Lamiaceae	W	–	Aerial parts, flowers	Infusion, lotion, spice	Şekeroğlu and Gezici (2020), Kalafatçılar and Kalafatçılar (2010), Kılıç (2019), Doğan and Doğan (2020)
***Thymus fallax* Fisch. & C.A.Mey.**	Lamiaceae	W	–	Aerial parts, flowering branches, whole parts	Infusion, foot bath, bath with/without Matricaria	Jahan and Onay (2020), Şekeroğlu and Gezici (2020), Gül and Seçkin-Dinler (2016), Olgun (2019)
***Thymus longicaulis* C.Presl**	Lamiaceae	W	Creeping thyme	Flowering branches, aerial parts	Infusion	Jahan and Onay (2020), Şekeroğlu and Gezici (2020), Gül and Seçkin-Dinler (2016), Günbatan et al. (2016)

(continued)

Table 18.1 (continued)

Plant name	Family	C/W/E	English name	Part(s)	Preparation(s)	Report(s)
***Thymus praecox* Opiz**	Lamiaceae	W	–	Aerial parts, flowering branches, whole parts	Infusion, foot bath, bath with/without Matricaria	Jahan and Onay (2020), Şekeroğlu and Gezici (2020), Gül and Seçkin-Dinler (2016), Günbatan et al. (2016), Alkış (2019)
***Tilia cordata* Mill.**	Malvaceae	W	Bast, small-leaved linden	Leaves, fruits, flowers, bracts	Decoction mix (with cinnamon and cloves)	Kalafatçılar and Kalafatçılar (2010), Şenkardeş (2014), Kavaklı et al. (2020a, b), Yeşilyurt et al. (2017b), Gökçe (2011)
***Tilia platyphyllos* Scop.**	Malvaceae	W	Broad-leaved lime	Flowers, bracts	Decoction with cinnamon and cloves, infusion after drying, infusion mix (with *Salvia tomentosa* leaves), cold maceration	Kalafatçılar and Kalafatçılar (2010), Kavaklı et al. (2020b), Gökçe (2011), Bulut and Tuzlacı (2013), Bulut et al. (2017)
Tilia tomentosa Moench	Malvaceae	C/W	European white lime, silver lime, silver linden	Leaves, flowers, fruits, barks, bracts, roots	Cold maceration, infusion after drying, infusion mix (with *Salvia tomentosa* leaves)	Kavaklı et al. (2020b), Çekin et al. (2016), Kurt and Karaoğul (2018), Gürbüz et al. (2019), Gökçe (2011), Akay (2019), Bulut et al. (2017)
Tribulus terrestris L.	Zygophyllaceae	W	Caltrop, devil's-thorn	Fruits	Infusion after dried	Baytop (1999), Kılıç (2019), Şenkardeş (2014), Deniz et al. (2010), Nacakcı and Dutkuner (2015), Demirci-Kayıran (2019), Özçelik et al. (2016), Kökçü et al. (2015)

Urtica dioica L.	Urticaceae	W	Stinging nettle, perennial nettle, tall nettle, common nettle	Aerial parts (without flowering), leaves, roots, seeds	Infusion after drying, infusion mix (with/without the petals of *Papaver rhoeas* or the leaves of *Rubus* spp. and the aerial parts of *Hypericum perforatum*), the roots are eaten raw after preparing a mixture (after milling with mustard seeds and mixing with honey). Mixture-meal (with the leaves, *Papaver rhoeas* petals, and *Malva* spp. and *Spinacia oleracea* leaves). Seeds are eaten with honey	Jahan and Onay (2020), Kalafatçılar and Kalafatçılar (2010), Kılıç (2019), Köse (2019), Genç (2010), Şenkardeş (2014), Çekin et al. (2016), Yeşilada (2012), Deniz et al. (2010), Özer et al. (2005), Olgun (2019), Şanlı (2006), Özdemir-Nath (2016), Yeşilyurt et al. (2017a, b), Gençay (2007), Çiçek (2019), Uzun and Koca (2020), Demirci-Kayıran (2019), Everest and Ozturk (2005), Kızılarslan (2008), Uzun and Kaya (2016), Ongan (2018), Özçelik et al. (2016), Tütenocaklı (2014), Bulut and Tuzlacı (2009, 2013), Mumcu and Korkmaz (2018), Paksoy et al. (2016), Sarıkan (2007), Akgul et al. (2018), Doğan (2014), Kılıç et al. (2020), Tetik et al. (2013), Diken (2009), Erarslan et al. (2020), Kaval et al. (2014), Onbaşlı and Dal (2020), Polat et al. (2015)
***Urtica pilulifera* L.**	Urticaceae	W	Roman nettle	Aerial parts, leaves, seeds	Salad, pastry, infusion, restorative paste (prepared with ginger, cinnamon,	Kalafatçılar and Kalafatçılar (2010), Genç (2010), Yeşilada (2012), Sargin et al.

(continued)

Table 18.1 (continued)

Plant name	Family	C/W/E	English name	Part(s)	Preparation(s)	Report(s)
					turmeric, and *Nigella sativa* seeds after milling and mixing with honey)	(2015), Şanlı (2006), Demirci-Kayıran (2019), Everest and Ozturk (2005), Ongan (2018)
***Urtica urens* L.**	Urticaceae	W	Small nettle	Aerial parts	Infusion after dried	Kalafatçılar and Kalafatçılar (2010), Kılıç (2019), Köse (2019), Şenkardeş (2014), Yeşilada (2012), Özer et al. (2005), Yeşilyurt et al. (2017b), Bulut (2008), Demirci-Kayıran (2019), Everest and Ozturk (2005), Ongan (2018), Tütenocaklı (2014), Bulut and Tuzlacı (2009, 2013)
***Vaccinium arctostaphylos* L.**	Ericaceae	W	Caucasian whortleberry	Fruits, leaves	Eaten raw, infusion	Kalafatçılar and Kalafatçılar (2010), Baytop (1999), Genç (2010), Kubat (2019)
***Vaccinium myrtillus* L.**	Ericaceae	W	Bilberry, wineberry, whortleberry	Fruits, leaves	Eaten raw/dried, jam infusion	Kalafatçılar and Kalafatçılar (2010), Baytop (1999), Köse (2019), Özcan et al. (2020), Yeşilada (2012), Şanlı (2006), Kubat (2019)
***Viburnum opulus* L.**	Adoxaceae	W	Guelder-rose	Fruits	Eaten raw, juice	Köse (2019), Kurt and Karaoğul (2018), Ongan (2018), Tütenocaklı (2014)
Viscum album L.	Santalaceae	W	European mistle-toe, common mistletoe	Fruits, leaves, stems, aerial parts	Infusion, decoction, tincture (prepared with lemon and vinegar)	Kalafatçılar and Kalafatçılar (2010), Baytop (1999), Genç (2010), Uzun and Koca

						(2020), Bulut et al. (2017), Ozturk et al. (2017a), Öztürk and Ölçücü (2011), Polat et al. (2011)
Vitis labrusca L.	Vitaceae	C/W	Fox grape, concord grape	Fruits, seeds	Eaten raw, eaten with honey after dried and pulverized	Kalafatçılar and Kalafatçılar (2010), Biçer (2020), Kubat (2019), Sarıkan (2007)
Vitis vinifera L.	Vitaceae	C	Grapevine	Fruits, seeds	Eaten raw or dried, cataplasm (with tarhana flour), molasses, churchkhela	Kalafatçılar and Kalafatçılar (2010), Kılıç (2019), Köse (2019), Özcan et al. (2020), Sargin (2013), Şanlı (2006), Biçer (2020), Güneş (2017), Sarıkan (2007), Kılıç et al. (2020)
Withania somnifera (L.) Dunal	Solanaceae	W	Ashwagandha, Indian ginseng	Roots	Infusion after dried and pulverized	Kalafatçılar and Kalafatçılar (2010), Kubat (2019), Küpeli-Akkol et al. (2020)
Ziziphora clinopodioides lam.	Lamiaceae	W	Blue mint bush	Flowering branches, aerial parts	Infusion, spices	Sargin (2013), Sargin et al. (2015), Altundag and Ozturk (2011), Tuzlacı and Doğan (2010a)
Ziziphus jujuba mill.	Rhamnaceae	C/W	Jujube, red date	Fruits	Eaten raw or after dried, decoction mix (prepared with pear, ginger, and lemon), tincture (prepared with lemon and vinegar)	Çekin et al. (2016), Uzun and Koca (2020), Arıtuluk (2010)

C Cultured plants, *W* wild plans, *E* endemic plants, *CW* cultured and wild plants. **Boldly highlighted taxa** (which are 60 in total and their immune-boosting and other similar activity effects have not been investigated experimentally yet)

Fig. 18.1 Regional map of Turkey

activities, such as immunostimulant, immunomodulatory, immune-enhancing, and immunotherapeutic are discussed, and the results are exhibited in (Table 18.3).

18.2.2 Evaluating Data

For the primary and moment portion research, the works identified to be within the scope of the study were minutely analyzed, contrasted, and preferred with respect to the following criteria:

1. The works ought to be conducted within the borders of Turkey.
2. It must be presented in an ethnobotanical, ethnomedicinal, or ethnopharmacological framework.
3. The author must have an academic title or citation records from other scientific works must be available.
4. The plant taxa mentioned in the work should be given in the study together with their scientific and local names.

The third screening study, which compares the taxa determined as a result of the first screening with the experimental studies published in the world literature, was made based on the following criteria:

Table 18.2 Distribution of ninety-nine works selected from ethnomedical studies conducted in Turkey by region

Region	Work	Citation	Citation %	Selected Studies
Eastern Anatolia	15	53	7.5	Olgun (2019), Altundag and Ozturk (2011), Tuzlacı and Doğan (2010a), Arasan (2014), Doğan (2008, 2014), Korkmaz et al. (2016), Tetik et al. (2013), Çakılcıoğlu and Türkoğlu (2007), Kaval et al. (2014), Kılıç (2016), Kilic and Bagci (2013), Öztürk and Ölçücü (2011), Polat et al. (2011, 2013)
Marmara	12	68	9.6	Özdemir-Nath (2016), Yeşilyurt et al. (2017b), Bulut (2008), Güneş (2017), Kızılarslan (2008), Akay (2019), Özhatay et al. (2009), Tütenocaklı (2014), Bulut and Tuzlacı (2009), Kökçü et al. (2015), Kültür (2007), Tuzlacı and Doğan (2010b)
Mediterranean	12	66	9.3	Şanlı (2006), Güneş (2010), Nacakcı and Dutkuner (2015), Uzun and Koca (2020), Demirci-Kayıran (2019), Everest and Ozturk (2005), Özçelik et al. (2016), Alkış (2019), Kocabaş et al. (2017), Sargin and Büyükcengiz (2019), Ozturk et al. (2017b), Sargin (2015)
Black Sea	10	85	12.0	Köse (2019), Kavaklı et al. (2020b), Gül and Seçkin-Dinler (2016), Kurt and Karaoğul (2018), Gürbüz et al. (2019), Kubat (2019), Mumcu and Korkmaz (2018), Yeşilyurt et al. (2017a), Korkmaz and Karakurt (2014), Polat et al. (2015)
Southeastern Anatolia	10	78	11.0	Kılıç (2019), Ötnü and Akan (2020), Akan and Bakır-Sade (2015), Gençay (2007), Çiçek (2019), Yeşil et al. (2019), Akgul et al. (2018), Arıtuluk (2010), Kılıç et al. (2020), Ozturk et al. (2017a)
Aegean	9	66	9.3	Sargin (2013), Deniz et al. (2010), Sargin et al. (2015), Arı et al. (2015), Bulut and Tuzlacı (2013), Bulut et al. (2017), Sarıkan (2007), Tuzlacı and Sadıkoğlu (2007), Şahin (2019)
Central Anatolia	7	49	6.9	Şenkardeş (2014), Kavaklı et al. (2020a), Uzun and Kaya (2016), Ongan (2018), Günbatan et al. (2016), Paksoy et al. (2016), Akbulut et al. (2017)
All regions	24	246	34.4	Jahan and Onay (2020), Şekeroğlu and Gezici (2020), Kalafatçılar and Kalafatçılar (2010), Baytop (1999), Genç (2010), Özcan et al. (2020), Çekin et al. (2016), Uçar et al. (2020), Yeşilada (2012), Özer et al. (2005), Ege and Elmastaş (2020), Yeşilada et al. (2019), Biçer (2020), Doğan and Doğan (2020), Gökçe (2011), Bozyel and Merdamert-Bozyel (2020), Hürkul and Köroğlu (2019), Akbaş and Akçakaya (2020), Bulut et al. (2014), Diken (2009), Ekşi et al. (2020), Erarslan et al. (2020), Küpeli-Akkol et al. (2020), Onbaşlı and Dal (2020)
Total	99	711		

Table 18.3 Worldwide immune-boosting and other similar activity research results of the taxa detected in the study

Plant species	Active compounds effective on immune response(s) (and used parts)	Type of activity	Type of immune response	Mechanism of action	References
Achillea millefolium L.	Not specified (aerial parts)	Immune-boosting	Humoral	By reducing the levels of serum lipids and boosting the immune response. Thus, it is proposed that can be used as an antibiotic alternative	Yakhkeshi et al. (2012)
Allium cepa L.	Agglutinin (bulbs)	Immunomodulatory	The cell-mediated	By increasing the production of nitric oxide, production of pro-inflammatory cytokines, enhancing the proliferation of murine thymocytes, and elevating the expression levels of cytokines	Prasanna and Venkatesh (2015)
Allium sativum L.	Not specified (bulbs)	Immune-boosting	The cell-mediated	By increasing CD4 (cluster of differentiation 4) T lymphocytes and total WBC (white blood cells) synergistically with *Allium cepa*	Mirabeau and Samson (2012)
Apium graveolens L.	Not specified (leaves)	Immunostimulant	The cell-mediated	By increasing total white and red blood counts, hemoglobin content, and hematocrit value	Mohamed et al. (2018)
Avena sativa L.	β-Glucan (seeds)	Immunomodulatory	The cell-mediated	By increasing cytokine levels	Rösch et al. (2016)
Brassica oleracea L.	Not specified (aerial parts)	Immune-boosting, immunostimulant	Humoral and the cell-mediated	By showing significant improvement in phagocytic and bactericidal activity	Pisuttharachai et al. (2020)
Brassica rapa L.	Not specified (roots)	Immunostimulant	The cell-mediated	By stimulating their endocytic/pinocytosis activity and releasing nitric oxide, tumor necrosis factor-alpha (TNF-α), and interleukin-6 cytokines	Wufuer et al. (2020)

Calendula officinalis L.	Not specified (flowers)	Immunostimulant	The cell-mediated	By increasing the production of nitric oxide on a level comparable with that of lipopolysaccharides	Danilets et al. (2010)
Camellia sinensis (L.) Kuntze	Strictinin, catechin (leaves)	Immunostimulant, immunomodulatory	The cell-mediated	By using the phagocytic activity of macrophage-like cells as an indicator of immune function activation	Monobe et al. (2008)
Capparis spinosa L.	Quercetin and kaempferol glycosides (buds)	Immunomodulatory	The cell-mediated	Inhibiting the extracellular virus release upregulates their production of IL-12, IFN-γ, and TNF-α. It should thus be employed for the treatment of immunocompromised hosts	Arena et al. (2008)
Capsicum annuum L.	Not specified (fruits)	Immunomodulatory	Humoral and the cell-mediated	Oral administration with capsicum extract might activate the CD4+ T cells leading to cytokine production as well as CD19+ B cells in Peyer's patches	Park et al. (2010)
Castanea sativa mill.	Not specified (fruits)	Immunostimulant	The cell-mediated	Through the skin mucus and serum immune parameters were significantly increased in fish fed with CSP compared to the control	Van Doan et al. (2020)
Cichorium intybus L.	Oxycoumarins, hydroxycinnamic acids, and flavonoids (aerial parts)	Immunomodulatory	Humoral and the cell-mediated	By reducing the suppressive azathioprine effect on the cell-mediated immune response, antibody response, and phagocytosis with macrophages	Saybel et al. (2020)
Citrus spp.	Auraptene (fruits)	Immunomodulatory	Humoral and the cell-mediated	By activating splenocytes and lymphocytes from mesenteric lymph nodes and increasing IL-4, interferon-gamma (IFNγ), and TNF-α production	Nishimoto et al. (2012)
Crataegus monogyna Jacq.	Not specified (leaves)	Immunomodulatory	Humoral and the cell-mediated	By increasing the total number, percentage, and absolute count of T and B splenocytes	Lis et al. (2020)

(continued)

Table 18.3 (continued)

Plant species	Active compounds effective on immune response(s) (and used parts)	Type of activity	Type of immune response	Mechanism of action	References
Elaeagnus angustifolia L.	Not specified (fruits)	Immunostimulant	Innate, humoral, and the cell-mediated	By increasing the spleen and thymus index of mice, increasing the phagocytosis of the mononuclear phagocyte system, and stimulating hemolysin formation	Lian et al. (2009)
Equisetum arvense L.	Not specified (aerial parts)	Immune-enhancing	Innate, humoral, and the cell-mediated	By enhancement of cytokine (IL-2, INF-γ) production in Th1 cells	Yukitake and Yamamoto (2011)
Fragaria vesca L.	Gamma-aminobutyric acid (fruits)	Immunomodulatory	Innate, humoral, and the cell-mediated	By increasing IL-10 and IFN-γ in mice	Cataldo et al. (2020)
Glycyrrhiza glabra L.	Not specified (roots)	Immunomodulatory	Humoral and the cell-mediated	By increasing leukocytes, phagocytic activities, and antibody-secreting cells of the mouse spleen in combination with zinc	Mazumder et al. (2012)
Helianthus tuberosus L.	Inulin (tubers)	Immunostimulant, immunomodulatory	Humoral and the cell-mediated	By increasing total immunoglobulin and lysozyme activity	Tiengtam et al. (2017)
Hordeum vulgare L.	β-Glucan (seeds)	Immunomodulatory	The cell-mediated	By increasing cytokine levels	Rösch et al. (2016)
Hypericum perforatum L.	Germacrene D, β-caryophyllene, α-humulene (essential oils from leaves and flowers)	Immunomodulatory	Innate	By inhibiting neutrophil Ca2+ mobilization, chemotaxis, and reactive oxygen species (ROS) production	Schepetkin et al. (2020)

Juglans regia L.	Not specified (fruits)	Immunomodulatory	Innate, humoral, and the cell-mediated	By promoting macrophage phagocytosis and natural killer activity, elevating the percentages of CD3+ and CD4, upregulating the production of antibody IgM, IgA, IgG, and SIgA, and regulating cytokines, Th1 produced	Mao et al. (2020)
Malus domestica Borkh.	Catechin, procyanidin B, quercetin-3-galactoside, and quercetin xyloside (fruit peels)	Immunostimulant	Innate and the cell-mediated	By increasing the lysozyme and phagocytic activity of macrophages	Riaz et al. (2020)
Malva sylvestris (L.) mill.	Not specified (leaves)	Immunomodulatory	The cell-mediated	By acting as macrophage and T helper-1 (Th-1) activators	El Ghaoui et al. (2008)
Matricaria chamomilla L.	Not specified (flowering branches)	Immunomodulatory	The cell-mediated	Through activating immunoregulation cells of peripheral blood and increasing the sensitivity of effector cells to helper signals	Uteshev et al. (1999)
Melissa officinalis L.	Not specified (aerial parts)	Immunostimulant	The cell-mediated	By increasing lipase and lysozyme activity, and elevating pepsin and trypsin	Bilen et al. (2020)
Mentha pulegium L.	Not specified (aerial parts)	Immune-enhancing, immunostimulant	Innate	By increasing phagocytosis, lysozyme, respiratory burst, and total white and red blood cells (WBC/RBC)	Akbary et al. (2015)
Mentha x piperita L.	Not specified (aerial parts)	Immunostimulant	Humoral and the cell-mediated	By increasing erythrocytes, leucocytes, hematocrit, hemoglobin, phagocytic activity, lysozyme, anti-protease, and anti-bactericidal activities, as well as elevating serum protein and globulin levels	Talpur (2014)
Mespilus germanica L.	Not specified (leaves)	Immunostimulant	Humoral	By increasing the immunoglobulin levels and interleukin 8 levels as well as elevating the level of lysozyme activity	Hoseinifar et al. (2017)

(continued)

Table 18.3 (continued)

Plant species	Active compounds effective on immune response(s) (and used parts)	Type of activity	Type of immune response	Mechanism of action	References
Morus alba L.	2-Formyl-5-(hydroxymethyl)-1H-pyrrole-1-butanoic acid and 2-formyl-5-(methoxymethyl)-1H-pyrrole-1-butanoic acid (fruits)	Immunostimulant	The cell-mediated	By the enhancement of nitric oxide, TNF-α, and IL-12 production and the stimulation of phagocytic activity	Kim et al. (2013)
Morus nigra L.	Not specified (fruits)	Immunomodulatory	Innate	By increasing the activities of serum lysozyme, myeloperoxidase, superoxide dismutase, and catalase and increasing the expression levels of immune-related genes (interleukin 1, beta, tumor necrosis factor, immunoglobulin M, interferon-gamma and heat shock protein 70) in the spleen and antioxidant-related genes	Yilmaz et al. (2020)
Myrtus communis L.	Not specified (leaves)	Immunostimulant	Innate	By increasing the number of erythrocytes (RBCs), leukocytes (WBCs), hematocrit, and lysozyme activity	Taee et al. (2017)
Nasturtium officinale R.Br.	Not specified (leaves)	Immunomodulatory, immunostimulant	Humoral and the cell-mediated	By enhancing hemoglobin (Hb), mean corpuscular hemoglobin concentration (MCHC), lysozyme and complement activities, as well as total protein and globulin levels	Asadi et al. (2012)
Nigella damascena L.	Damascenine and β-Elemene (seed-essential oils)	Immunomodulatory	The cell-mediated	By inhibiting the release of interleukin 1 beta (IL-1β) and interleukin 8 (IL-8), decreasing matrix metallopeptidase 9 (MMP-9) production	Sieniawska et al. (2019)

Nigella sativa L.	Thymoquinone (seed-essential oils)	Immunomodulatory, immunotherapeutic	Innate and the cell-mediated	By possessing reproducible antioxidant effects through enhancing the oxidant scavenger system and augmenting the T cell- and natural killer cell-mediated immune responses	Salem (2005)
Olea europaea L.	Oleuropein (leaves)	Immunomodulatory	The cell-mediated	By inducing and maintaining high proliferation in lymphocytes	Randon and Attard (2007)
Origanum vulgare L.	Not specified (aerial parts)	Immunostimulant	Innate and the cell-mediated	By increasing serum total protein, albumin, globulin, respiratory burst activity, phagocytic activity, and serum lysozyme activity	Pourmoghim et al. (2015)
Petroselinum crispum (mill.) fuss	Not specified (aerial part-essential oils)	Immunomodulatory	The cell-mediated	Through its inhibitory effect on PHA-stimulated splenocytes which occurred due to the production of cytokines such as IFN-γ and IL-2, which are vital for T-cell proliferation and the signaling pathways	Karimi et al. (2012)
Phoenix dactylifera L.	Chlorogenic acid, caffeic acid, pelargonin, ferulic acid, trypsin (fruits)	Immunomodulatory	Humoral and the cell-mediated	By stimulating FN-γ mRNA expression significantly in mouse Peyer's patch cell cultures and increasing the number of IFN-γ + CD4+ CD49b + and IL-12 + CD11b + cells	Karasawa et al. (2011)
Pinus sylvestris L.	Not specified (cones)	Immune-enhancing	Humoral	By affecting the expansion of T cells (both CD4 and CD8) during the proliferative phase	Bradley et al. (2014)
Portulaca oleracea L.	Not specified (aerial parts)	Immunostimulant, immunomodulatory	Innate, humoral, and the cell-mediated	By enhancing splenocyte proliferation and upregulated inflammatory cytokines (IL-2, IL-12, TNF-α, and IFN-γ) and natural killer (NK) cell activity in vitro	Park et al. (2019)

(continued)

Table 18.3 (continued)

Plant species	Active compounds effective on immune response(s) (and used parts)	Type of activity	Type of immune response	Mechanism of action	References
Prunus avium (L.) L.	Not specified (fruits)	Immunomodulatory	The cell-mediated	By inducing the NO release from RAW264.7 cells and the expression of several immune-related molecular (TNFα, IL6, IL10, GCSF, iNOS, COX-2)	Cao et al. (2018)
Punica granatum L.	Not specified (pericarps)	Immunomodulatory	Humoral and the cell-mediated	By increasing antibody density to typhoid-H antigen and enhancing the inhibition of leukocyte migration	Ross et al. (2001)
Pyrus communis L.	Not specified (fruits)	Immunostimulant	The cell-mediated	By increasing phagocytic activities	Pavithra et al. (2020)
Rhus coriaria L.	Not specified (fruits)	Immune-enhancing	Innate, humoral, and the cell-mediated	By increasing the number of leukocyte (WBC) and erythrocyte (RBC), lymphocyte, monocyte, and neutrophil value as well as serum lysozyme and TNF-α and IL-1b	Slavov et al. (2013)
Rosa × *damascena* Herrm.	Not specified (petals)	Immunomodulatory	Humoral and the cell-mediated	Through Peyer's patch cells and enhanced production of IL-6 from murine macrophages	Saaby et al. (2011)
Rosa canina L.	Oleanolic acid, betulinic acid, and ursolic acid (fruits)	Immunomodulatory	Humoral and the cell-mediated	By inhibiting the lipopolysaccharide-induced interleukin-6 release	Al Sheyab et al. (2012)
Rosmarinus officinalis L.	Not specified (leaves)	Immunomodulatory	Humoral	By increasing IgM (immunoglobulin M) response at all antibody titers and proliferation of spleen cells	Capek and Hribalova (2004)
Salvia officinalis L.	3-O-methyl-galactose (aerial parts)	Immunomodulatory	The cell-mediated	By inducing the proliferation of rat thymocytes	Gharaei et al. (2020)

Sambucus ebulus L.	Not specified (leaves)	Immunostimulant	The cell-mediated	By increasing the levels of IFN-γ, IL-4, and nitric oxide and switching the host immune responses toward the Th1 response	Heidari-Kharaji et al. (2019)
Sambucus nigra L.	Cyanidin 3-glucoside and quercetin (fruits)	Immunomodulatory	The cell-mediated	By blocking viral glycoproteins as well as indirect effects by increased expression of IL-6, IL-8, and TNF	Torabian et al. (2019)
Satureja hortensis L.	Not specified (essential oils)	Immunomodulatory	Innate	Through a significant enhancement in serum lysozyme for the innate immune response of angelfish	Ghafari-Farsani et al. (2018)
Sesamum indicum L.	Not specified (seeds)	Immunomodulatory	Innate, humoral, and the cell-mediated	By increasing splenocyte proliferation, balancing the secretion of Th1 and Th2 cytokines, inhibiting the secretion of key pro-inflammatory mediators (IL-6, TNFα, and nitric oxide), and increasing the cytotoxic activity of natural killer (NK) cells	Majdalawieh et al. (2020)
Silybum marianum (L.) Gaertn.	Silymarin (seeds)	Immunomodulatory	Innate and the cell-mediated	Through the enhancement of hematological and immunological parameters including lysozyme and complement activities, total protein, and globulin levels	Ahmadi et al. (2012)
Solanum lycopersicum L.	Not specified (fruits)	Immune-enhancing	Humoral and the cell-mediated	By increasing phagocytosis, chemotaxis, and levels of immunoglobulins (TIg, IgG, IgM, and IgA)	Elwan et al. (2019)
Spinacia oleracea L.	Not specified (leaves)	Immunostimulant, immune-enhancing	Innate	Through a substantial improvement of serum protein profile, lysozyme activity, hematocrit percent, and serum superoxide dismutase enzyme (SOD)	Ayoub and Khames (2019)

(continued)

Table 18.3 (continued)

Plant species	Active compounds effective on immune response(s) (and used parts)	Type of activity	Type of immune response	Mechanism of action	References
Taraxacum spp.	Taraxasterol (not specified)	Immunomodulatory	The cell-mediated	By increasing hepatic glutathione (GSH) and superoxide dismutase (SOD) production, inhibiting the release of pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1β, interferon-γ (IFN-γ) and IL-4	Sang et al. (2019)
Thymbra spicata L.	Not specified (aerial parts)	Immunomodulatory	The cell-mediated	By increasing the decreased level of the IL-6 cytokine in response to TNF-α	Mendi et al. (2017)
Tilia tomentosa Moench	Not specified (flowers)	Immunostimulant	Innate	By increasing lysozyme activity and respiratory burst activity	Almabrok et al. (2018)
Tribulus terrestris L.	Saponins (fruits)	Immunomodulatory	The cell-mediated	By increasing phagocytic activity	Tilwari et al. (2011)
Urtica dioica L.	Quercetin-3-O-rutinoside, kaempherol-3-O-rutinoside, and isorhamnetin-3-O-glucoside (leaves and roots)	Immunostimulant	The cell-mediated	By chemotactic effects in 4, 8, and 16 μg doses and showing high intracellular killing activity	Akbay et al. (2003)
Viscum album L.	Not specified (aerial parts)	Immune-boosting	The cell-mediated	By increasing phagocytic activity and candidacidal activity of neutrophils and stimulating the levels of CD4 + CD25+ and CD8 + CD25+ T cells	Fidan et al. (2008)
Vitis labrusca L.	Arabino-3, 6-galactan (pericarp)	Immunostimulant	Innate and the cell-mediated	Results of comparisons between the taxa detected in the study and research on immune-stimulating and related activities carried out globally	Kim et al. (2010)

Vitis vinifera L.	Not specified (seeds)	Immunostimulant	Innate	By increasing nitroblue tetrazolium (NBT) activity, myeloperoxidase (MPO) activity, phagocytic activity, and lysozyme activity	Al-Atbee and Al-Niaeem (2021)
Withania somnifera (L.) Dunal	Not specified (roots)	Immunostimulant	The cell-mediated	By increasing nitric oxide (NO) production by macrophages	Iuvone et al. (2003)
Ziziphora clinopodioides lam.	Not specified (aerial parts)	Immune-boosting	The cell-mediated	By improving the immune system and blood biochemical parameters of laying hens with *Melissa officinalis* and *Tanacetum balsamita*	Nobakht et al. (2012)
Ziziphus jujuba mill.	Not specified (fruits)	Immunomodulatory, immunostimulant	Innate, humoral, and the cell-mediated	By increasing spleen and thymus indices, promoting serum hemolysin formation, and enhancing the phagocytic activity of macrophages	Zou et al. (2018)

1. It should be an experimental study (in vitro or in vivo).
2. The scientific name of the plant used should be included in the title of the work or the text.
3. One of the words "immune-boosting, immunostimulant, immunomodulator, immune-enhancing, or immunotherapeutic" should be included in the title.
4. The method of obtaining the compound or extracts used from the plant and the mechanism of action determined should be included in the text.
5. For each taxon, only one experimental study should be selected that meets the above criteria. However, in the title, studies with active compounds are preferred.

18.2.3 Data Arrangement

Accurate-scientific nomenclature with international validity of the plant taxa identified in national surveys was performed using "Turkey Plant List" (Güner et al. 2012), "The Plant List" (2021), and "International Plant Names Index" (2021) and exhibited in (Table 18.1) after arranging in alphabetical order.

The same table contains scientific names, information about pharmaceutical uses, and citation details. The English names of taxa have been added to the table using the following databases or search engines: Springer Link (https://link.springer.com/article), Encyclopedia of Life (https://eol.org), and USDA Plants (https://plants.sc.egov.usda.gov/java). The common names of plants native to Turkey and those that are considered to be a part of the "Irano-Turanian element," however, cannot be verified because they are only known in Turkey and its near surroundings and may not yet be known in English-speaking nations. The results of the research on whether the taxa listed in (Table 18.1) have been the subject of experimental studies in the world literature on their immune-boosting and other similar activities are presented in (Table 18.3). The same table also includes the scientific names of the taxa that match, active compounds (if any), parts used, kind of activity, type of immunological response, method of action, and associated citations.

18.2.4 Comparative Analysis

After determining the definitive list of plants that have the potential to stimulate or strengthen the immune system in Turkish traditional medicine, a second scanning work has been performed to comport with the resemblance percentage with peer works carried out in nearby countries, and the outcomes are submitted in (Table 18.4). Since there are very few taxa related to the immune system in the identified works, we tried to select as many works as possible from each country. However, the negative effects of repeated taxa on the total number and percentage have been avoided. For example; if taxa related to the immune system were mentioned in only three of the studies conducted in one country, only different

Table 18.4 Taxon similarity percentages in similar studies conducted in neighboring and nearby countries

Countries	Regions	Total taxa used for immunity	Similar taxa #	Similarity %	References
Albania	All	14	9	64.3	Pieroni (2008), Pieroni et al. (2005, 2014a, b), Pieroni and Quave (2014), Quave and Pieroni (2014), Tomasini and Theilade (2019)
Cyprus	All	23	14	60.9	Karousou and Deirmentzoglou (2011), Lardos et al. (2011), Özkum et al. (2013)
Bulgaria	All	16	9	56.3	Ivancheva and Stantcheva (2000), Kozuharova et al. (2013), Koleva et al. (2015)
Palestine	All	31	16	51.6	Abu-Rabia (2005), Ali-Shtayeh et al. (2011), Eid and Jaradat (2020), Jaradat (2005)
Bosnia and Herzegovina	All	22	11	50.0	Redžić (2007), Šaric Kundalic et al. (2015)
Iran	Mashhad, Azerbaijanprovince	32	16	50.0	Amiri and Joharchi (2013), Latifian and Arslanoğlu (2018), Miraldi et al. (2001), Naghibi et al. (2005)
Kosovo	Anadrini region, Albanian Alps, and South Kosovo	15	7	46.7	Mullalija et al. (2021), Mustafa et al. (2012)
Macedonia	All	15	7	46.7	Gjorgieva-Ackova et al. (2011), Pieroni et al. (2013), Rexhepi et al. (2013)
Nakhchivan	All	26	12	46.2	Ibadullayeva et al. (2015), Novruzova et al. (2015), Ozturk and Hakeem (2018)
Iraq	Northern Iraq	22	10	45.5	Ahmed (2016), Ahmad and Askari (2015), Kawarty et al. (2020), Mati and de Boer (2011)

(continued)

Table 18.4 (continued)

Countries	Regions	Total taxa used for immunity	Similar taxa #	Similarity %	References
Croatia	Northeastern Istria, Knin area, and Pannonian region	16	7	43.8	Varga et al. (2019), Vitasović-Kosić et al. (2017), Žuna-Pfeiffer et al. (2020)
Azerbaijan	All	7	3	42.9	Alakbarov (2001)
Armenia	All	12	5	41.7	Nanagulyan et al. (2020)
Syria	Aleppo	12	5	41.7	Alachkar et al. (2011), Rihawy et al. (2010)
Georgia	All	10	4	40.0	Akhalkatsi et al. (2018), Bussmann et al. (2016a, b), Martkoplishvili and Kvavadze (2015)
Greece	Thessaloniki (northern)	68	27	39.7	Hanlidou et al. (2004), Tsioutsiou et al. (2019)
Serbia	Eastern and Southeastern	63	24	38.1	Janaćković et al. (2019), Matejić et al. (2020), Popović et al. (2012), Zlatković et al. (2014), Živković et al. (2020)
Ukraine	Southwestern	35	13	37.1	Mattalia et al. (2020a, b), Sõukand and Pieroni (2016), Stryamets et al. (2015)
Lebanon	All	11	4	36.4	Arnold et al. (2015), Jeambey et al. (2009), Marouf et al. (2015), Redwan et al. (2017)
Jordan	All	26	9	34.6	Aburjai et al. (2007), Alzweiri et al. (2011), Assaf et al. (2013), Al-Quran (2014), Lev and Amar (2002)
Romania	Transylvania, Dobruja, and West Romania	36	12	33.3	Daraban et al. (2013), Papp et al. (2014), Petran et al. (2020), Pieroni et al. (2012, 2015)
Montenegro	Northern Montenegro	13	4	30.8	Menković et al. (2011, 2014)
Israel	All	30	9	30.0	Lev and Amar (2000), Said et al. (2002)

(continued)

Table 18.4 (continued)

Countries	Regions	Total taxa used for immunity	Similar taxa #	Similarity %	References
Russia	All	15	4	26.7	Shikov et al. (2017), Spiridonov et al. (2005)

taxa in these three works were included in the study. If *Melissa officinalis* was repeated for the same activity in all three, its number was considered to be 1, and it was not allowed to affect the total number as 3. The table includes country, region, the total number of taxa used for immunity, the number of similar taxa, the percentage of similarity, and references to related studies. Countries are listed in descending order of similarity percentages.

18.3 Results and Discussion

Medicinal herbs are a 1000-year-old source in a variety of traditional herbal medicine systems, from raw uses in the form of direct preparations, such as infusions, decoctions, maceration, and pastes, to the extraction of key compounds. In fact, their secondary metabolism is a phytochemical treasure with promising results for all of humanity. Therefore, as trials for testing vaccines continue, traditional herbal remedies in the form of decoctions, tea, or powders require increased clinical testing and research to alleviate symptoms (Khan et al. 2021). As in many parts of the world, people living in Turkey, especially in rural areas, have rich traditional knowledge and experience about the utilization of therapeutic plants in the avoiding and handling of assorted illnesses, but also open to serious clinical evaluation studies (Sargin 2021).

18.3.1 Regional Analysis

The dispersion of 99 works with respect to the regions where they were acquired was as follows: 15 in Eastern Anatolia (15.2%), 12 in the Mediterranean and Marmara (12.1%), 10 in Southeastern Anatolia and Black Sea (10.1%), 9 in the Aegean (9.1%), 7 in Central Anatolia (7.1%), and 24 general studies across all regions (24.2%). The reason why ethnomedicinal works related to immunity come mostly from Eastern Anatolia, Mediterranean and Marmara regions may be because

separate regional studies have been carried out for each region spread over a wide area. After all, these regions contain very different topographies.

The sectional dissolution of 711 total reports received was as follows: Black Sea: 85 (12.1%), Southeastern Anatolia: 78 (11.0%), Marmara: 68 (9.6%), Mediterranean and Aegean: 66 (9.3%), Eastern Anatolia: 53 (7.5%), Central Anatolia: 49 (6.9%), and general studies covering all regions: 246 (34.4%). The fact that the obtained taxon references come mostly from the Black Sea region may be because these regions contain locations with very high biodiversity and endemism such as Bolu, Düzce, and Artvin (Güner et al. 2012). In addition, the traditional high-plateau life, which is scattered far away from the city and district centers, and the abundant rainy climate in these regions, may have prompted the local people to use more varieties of plants (Terzioğlu et al. 2015).

The following can be said as the reason for the lowest percentages in Central Anatolia: First of all, the capital Ankara and Eskişehir, known as the city of universities, are located within the borders of the region. Therefore, widespread urbanization might be providing local people with easy access to healthcare services (Keser and Kurt 2016) and reduce the tendency to plant. Secondly, it can be shown that there are not many options for a medicinal plant even for people who are far from healthcare, due to the dominance of the plateau landform in the region, the low annual rainfall percentage (Apaydin et al. 2011), and the much lower level of plant biodiversity than other regions (Kenar et al. 2020).

18.3.2 Data Analysis

The bibliographies exploited for the choice of 128 plant taxa that are used traditionally for immunity enhancement consist of 67 articles, 23 theses, seven books, and two bulletins. These plant taxa are most commonly Lamiaceae (25 taxa, 19.5%), Rosaceae (18 taxa, 14.1%), Compositae (11 taxa, 8.6%), Malvaceae (7 taxa, 5.5%), Apiaceae and Brassicaceae (5 taxa, 3.9%), and other families (57 taxa, 44.5%). The rationale behind the Lamiaceae family is the foremost favored in Turkish folk medicine can be demonstrated as the habit of preparing many conventional immune-boosting preparations such as lotion, medical baths, spice, infusion mix, and syrup due to the family that contains the highest dosage of essential oils (Bozyel and Merdamert-Bozyel 2020) and experience of receiving good results (Başer et al. 2006) in immunostimulation and flu treatment. In addition, 44.2% of species belonging to the Lamiaceae family, 65.2% of species belonging to *Origanum* genus, 52.6% of species belonging to *Thymus* genus, and 28% of species belonging to *Satureja* genus are endemic in Turkey (Bozdemir 2019). Therefore, it is not coincidental that this family comes first in presenting the richest variety of taxa to our study.

In the works carried out in different regions of Turkey, the most common genera are *Citrus* and *Salvia* (5 taxa, 3.9%) and *Mentha, Pinus, Prunus*, and *Taraxacum* (4 taxa, 3.1%). It is not surprising that *Citrus*, *Salvia*, and *Mentha* appeared in the

first place. They are grown both naturally and culturally (for healing and ornamental purposes) in park gardens, balconies, and pots in almost every part of the country. *Citrus* species are actually an exotic genus settled in the flora of Turkey. It is seen on all roadsides and gardens, especially in the southern regions (Baytop 1999; Başer et al. 2006). Moreover, the *C. limon* species is sold as a "panacea!" or "Lemon for tea and soup!" in almost all local markets of the country. It is also always in high demand for direct use or mixtures. In particular, the infusion mixture prepared from *Mentha x piperita* (peppermint) leaves and *C. limon* peel can be said to be the most widely used traditional preparation in the country to increase body resistance against winter diseases (Sargin 2021; Tuzlacı and Eryaşar-Aymaz 2001). The other three genera, *Pinus, Prunus*, and *Taraxacum*, are also naturally distributed in a wide area in the country (Baytop 1999, 2007). *Prunus* and *Pinus* fruits and *Taraxacum* leaves have been traditionally consumed for centuries for healing and food to strengthen the body against diseases (Sargin and Büyükcengiz 2019; Ozturk et al. 2017a; Dogan et al. 2004).

Among the determined plants, 61 were wild (47.7%), 55 were wild and cultural (43.0%), 11 were cultivated (8.6%), and one (*Salvia absconditiflora*) was endemic (0.9%). In Table 18.1, these details are displayed in a column; cultivated "C," endemic "E," wild taxa as "W," and cultivated & wild "CW." The majority of plant parts are consumed as fruits (39.8%), leaves (33.6%), flowers, flowering branches, petals and capitula (32.8%), aerial parts (32.0%), seeds and cones (19.5%), roots, rhizomes and bulbs (13.3%), essential oils, fixed oils, resins, and tars (12.5%), whole parts, stems, barks and shoots (10.9%), and other parts (buds, bracts, pericarps, fruit stalks, galls, and pollens) (10.2%). Those parts were mostly used as infusion and infusion mix (80.5%), eating raw or after milling (35.2%), decoction, decoction mix, boiling (31.3%), jam, syrup, marmalate, molasses (21.9%), meal, roast, soup, pastry, cooked (18.0%), pickle, vinegar, tincture, maceration (14.8%), external uses such as foot bath, medicinal bath lotion and frankincense (14.1%), restorative paste, spices drop and additives (11.7%), churchkhela and mixtures (11.7%), drunk, juice, gargle (10.9%), and salad (7.8%). In terms of utilization parts, *Juniperus oxycedrus, Pinus brutia, Rosa canina*, and *Tilia tomentosa* (6 parts, 4, 7%), while the taxa with the most usage types are *Rubus sanctus* (8 types, 6.3%), *Citrus* spp. (7 types, 5.5%), *Mentha x piperita*, *Rosa x damascena*, *R. canina* and *Thymbra spicata* (6 types, 4.7%) are the taxa with the greatest abundance (Table 18.1).

18.3.3 Comparison of the Findings with Research from Surrounding Nations

The number of taxa that match studies from surrounding and neighboring nations out of the 128 that we specified in our research is 81; the similarity rate (from 81×100/128) was computed as 63.3%. 18 plants, including *Urtica dioica* (with 11 citations

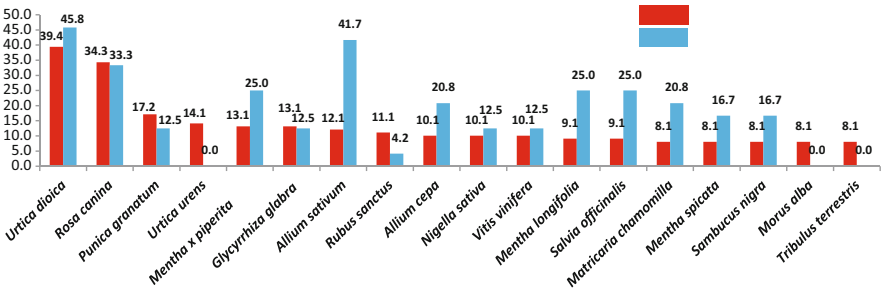

Fig. 18.2 The most reported plants are in Turkey and neighboring countries

and 45.8%), *Achillea millefolium* and *Allium sativum* (with 10 citations and 41.7%), and *Juglans regia, Rosa canina,* and *Taraxacum* spp. (8 citations and 33.3%) (Fig. 18.2), have been found as the most reported plants. These herbs may have gained popularity because they have been used for ages in Turkish traditional medicine and are more long-lasting and effective at boosting immunity. Especially, the emergence of *Urtica* spp. as the most used plant as an immune booster in 11 countries (45.8%), other than Turkey, may be because it has proven itself in the traditional medicine of many cultures rather than the fact that its distribution area is wide and easily accessible. The similarity of 63.3% between the findings of investigations carried out in 24 close and neighboring nations may confirm the powerful effectiveness of these taxa (Table 18.4). 47 plants such as *Urtica urens, Morus alba*, and *Tribulus terrestris* do not resemble at all (Fig. 18.2), may be because they are not naturally widespread in these countries because of geographical or climatic differences, or even if they do, they are not traditionally preferred for immunity.

Nevertheless, the maximum similarity was detected with Albania (64.3%), Cyprus (60.9%), and Bulgaria (56.3%), while the minimum one was with Russia (26.7%), Israel (30.0%), and Montenegro (30.8%). In countries with high similarity, there may be similarities in climate, vegetation, and landforms, as well as cultural and plant use habits from the Ottoman period. Differences in religious practices, social-cultural norms, flora, and topography may be the root causes of the poor similarity with Russia, Israel, and Montenegro (Table 18.4).

18.3.4 Evaluation of Worldwide Works in Comparison

As a result of the comparison screening of experimental studies conducted worldwide under the title of activities such as immunostimulant, immunomodulator, immune-enhancing, or immunotherapeutic, reflections of only 68 (53.1%) of 128 taxa were detected. 60 taxa (46.9%), which have not been investigated yet, are among the valuable data of this study and are shown in bold in Table 18.1. The percentage distribution of the activities mentioned in the titles of the studies is as follows: Immunomodulatory (47.1%), immunostimulant (27.9%),

immunomodulatory and immunostimulant (7.4%), immune-enhancing (5.9%), immune-boosting (5.9%), immune-enhancing and immunostimulant (1.5%), immune-boosting and immunostimulant (1.5%), and immunomodulatory and immunotherapeutic (1.5%). For only 23 taxa (18.0%) out of 68 matching taxa, the results were given with the active ingredients, while the remaining 45 taxa (35.2%) were not specified. The prominent among 39 active substances are quercetin derivatives (such as quercetin xyloside, quercetin-3-galactoside, and quercetin-3-O-rutinoside) (10.3%), β-glucan, and catechin (5.1%), respectively (Table 18.3).

The action mechanisms in the studies identified are listed according to the immune responses on which they were based: Cell-mediated (42.6%), humoral and cell-mediated (22.1%), innate only (11.8%), innate, humoral, and cell-mediated (11.8%), humoral only (5.9%), and innate and cell-mediated (5.9%), respectively. According to these three basic immune responses, it has been determined that the mechanisms were carried out in the following eight different groups: By increasing spleen and thymus indices/serum immune parameters/total white and red blood cells (WBC/RBC) (20.3%), by increasing pinocytosis, phagocytic and bactericidal activity/acting as macrophage and T helper-1 (Th-1) activators/switching the host immune responses toward Th1 response (20.3%), by increasing interleukin cytokine levels/elevating the levels of tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFNγ)/elevating the expression levels of cytokines/activating the CD4+ T cells leading to cytokine production (18.0%), by activating the CD19+ B cells in Peyer's patches/increasing total immunoglobulin/reducing the suppressive azathioprine effect on the cell-mediated immune response, and antibody response (13.5%), by promoting serum hemolysin formation and increasing lysozyme, myeloperoxidase, superoxide dismutase catalase, and superoxide dismutase activities (12.8%), by increasing production of nitric oxide (NO) on a level comparable with that of lipopolysaccharides/reducing the levels of serum lipids/inhibiting the lipopolysaccharide-induced interleukin-6 release (6.8%), by increasing respiratory burst activity/reactive oxygen species (ROS) production/increasing the hematocrit level and red blood cell count/hemoglobin content and hematocrit value (4.5%), and by increasing the cytotoxic activity of natural killer (NK) cells (3.8%), respectively (Table 18.3).

When the plant parts used for 68 taxa (53.1%) that were determined to match in the comparison of Turkey and the world literature were examined, a concordance of 94.1% was obtained. This result may have proved the accuracy and reliability of part selection and application methods of plants used as immunostimulants and enhancers in Turkish folk medicine.

18.3.5 Comparative Analysis of Effective Substances

The taxa with the largest quantities of potent substances that have been demonstrated to have immune-boosting and other associated benefits include *Phoenix dactylifera* (5 chemicals, 12.8%, out of 39), *Malus domestica* (4; 10.25%), *Cichorium intybus,*

Hypericum perforatum, Urtica dioica, and *Rosa canina* (3; 7.7%) (Table 18.3). *Phoenix dactylifera* (date palm) is widespread in a vast area from North Africa to the Middle East, parts of Central and South America, and Southern Europe for both its production and consumption of its fruit for food and healing purposes (Baytop 1999; Karasawa et al. 2011). The reason why it stands out in terms of active ingredient richness in this study may be that it is rich in fiber, mineral, and other nutritional sources, as well as its antibacterial, antifungal, and immunostimulant properties, as a widely effective folk remedy in preventing various infectious diseases and increasing body resistance (Qadir et al. 2020). As in the geographical area mentioned above, the consumption of dried fruit becomes widespread in Turkey, especially during the holy month of Ramadan. It is known that while fasting, the body compensates for the mineral and energy loss, thus keeping the immune system active (Baytop 1999, 2007; Kavaklı et al. 2020a). The study by Karasawa et al. (Karasawa et al. 2011) provides additional evidence for this finding. They investigated the immunomodulatory effects of hot water extract of ripe fruits compared to prunes and fig fruits in mice and declared that the polyphenols and polysaccharides they isolated stimulated the cellular immune system in mice. Therefore, this finding may be a shred of evidence that this taxon might be more effective than others in terms of immunomodulatory activity.

As a result of this screening, quercetin and its derivatives came to the fore with their immunomodulatory and immunostimulant activities and it was determined that they were isolated from the taxa of *Capparis spinosa, Malus domestica, Urtica dioica*, and *Sambucus nigra* (Akbay et al. 2003; Arena et al. 2008; Torabian et al. 2019; Riaz et al. 2020) (Tablsssse 18.3). The fact that quercetin and its derivatives appear to be the most prevalent effective substances may not be a coincidence. These chemicals are the best ones for boosting or activating immunity, according to numerous experimental types of research. A few of these are given below:

Colunga-Biancatelli et al. (Colunga-Biancatelli et al. 2020) provided evidence that the co-administration of vitamin C and quercetin shows a synergistic antiviral effect and enhances its efficacy due to its antiviral and immunomodulatory properties and the capacity of ascorbate to recycle quercetin. Wang et al. (Wang et al. 2020) increased the immunostimulant properties, antioxidant index, and disease resistance of zebrafish with the optimal quercetin level. Singh et al. (Singh et al. 2017) reported for the first time the in vivo immunostimulatory activity of quercetin in ovalbumin-vaccinated Balb/c mice. Their administration of quercetin showed the dominance of the Th2 immune response by increasing IgG1 antibody titers, as well as increased infiltration of CD11c + dendritic cells in the mouse peritoneum and the production of LPS-activated IL-1β and nitric oxide (NO) by peritoneal macrophages. These outcomes may validate that quercetin and its derivates are ideal aspirants for a functional nutraceutical or phytotherapy by stimulating or positively modulating immunity. Additionally, many taxa commonly employed in Turkish traditional medicine, *Avena sativa, Camellia sinensis, Hordeum vulgare*, and *Malus domestica*, have active compounds such as β-glucan and catechin. Some studies (Özcan et al. 2020; Yeşilada 2012; Ege and Elmastaş 2020; Riaz et al. 2020; Monobe et al. 2008; Rösch et al. 2016) pointed out that beta-glucan and catechin act through one or more

of the eight groups of action mechanisms mentioned above, and that these molecules could potentially give positive results in the treatment of COVID-19 in terms of immune-stimulating or accelerating activities.

18.3.6 Exotic Plants

14 medicinal exotic herbs, such as *Alpinia officinarum* (lesser galangal), *Cinchona pubescens* (quina), *Echinacea angustifolia* (coneflower), *Hibiscus sabdariffa* (hibiscus), *Malpighia emarginata* (acerola cherry), and *Vaccinium macrocarpon* (cranberry) are used for stimulating or boosting the immune system in Turkish folk medicine and traded in public markets and herbal shops. Scientific names, families, English names, used parts, preparations, native lands, and related references of these plants are introduced in Table 18.5.

The native to Southeast Asia *Citrus* species and the native to North Africa *Phoenix dactylifera* (date palm) listed in (Table 18.1) are essentially exotic taxa that were subsequently incorporated into the native flora. After being grown for centuries along the coastlines of the Mediterranean and Aegean, on highways, in parks, and gardens, they have shown a natural expansion. Other plants that have adapted to the flora during the Ottoman era are *Solanum lycopersicum* (tomato, South America), *Morus alba* and *M. nigra* (mulberry, China), *Camellia sinensis* (tea plant, native to South and Southeast Asia), *Withania somnifera* (Indian ginseng), *Capsicum annuum* (pepper, South and Central America), *Prunus cerasifera* (myrobalan plum, Japan), and *Ziziphus jujuba* (jujube, Southeast Asia) in the same table (Kaya et al. 2018; Polat and Selvi 2020).

18.4 Conclusion

Suffering from a global epidemic of COVID-19 mutants and variants, the whole world has turned its attention and hope to natural treatments that can keep the immune system active and strong. Recent studies of some medicinal plant preparations hold great prospects that they may be potential candidates to develop effective and safe immune-boosting drugs against this relentless pandemic. Initiatives in this regard will primarily be hope for millions of people with weakened immune systems due to old age and pre-existing medical problems, waiting for treatment in quarantine at home or in intensive care in a hospital. In particular, recent research on phytochemicals like quercetin, beta-glucan, and catechin makes us feel a little more optimistic about the future.

Thanks to a strong immune system, a person with good body health can easily get rid of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections without any complications. It is known that the side effects of existing synthetic drugs and the necessity of taking a certain dose while in the state of infection make

Table 18.5 Exotic plants traditionally used for immune-boosting and other similar activities in Turkey

Sc. Names	Families	English names	Parts	Preparations	Native lands	References
Alpinia officinarum hance	Zingiberaceae	Lesser galangal	Rhizomes	Spice, decoction, or infusion (after pulverizing)	Southeast Asia	Ötnü and Akan (2020), Gökçe (2011), Akbaş and Akçakaya (2020), Korkmaz and Karakurt (2014)
Cinchona pubescens Vahl	Rubiaceae	Red cinchona, quina	Barks	Decoction or infusion (after pulverizing), syrup, or liqueur prepared after pulverizing	Central and South America	Jahan and Onay (2020), Kalafatçılar and Kalafatçılar (2010), Baytop (1999), Genç (2010), Kavaklı et al. (2020b), Akbaş and Akçakaya (2020)
Cinnamomum verum J.Presl	Lauraceae	Cinnamon, true cinnamon tree	Barks	Decoction with the pulverized bark, linden leaves, and cloves. Restorative paste (prepared with the dried and pulverized bark, black pepper fruits, ginger rhizomes, nettle seeds, turmeric rhizomes, and *Nigella sativa* seeds after milling and mixing with honey)	South and Southeast Asia	Kalafatçılar and Kalafatçılar (2010), Genç (2010), Şenkardeş (2014), Kavaklı et al. (2020a, b), Şanlı (2006), Yeşilyurt et al. (2017b), Everest and Ozturk (2005), Gökçe (2011), Bulut and Tuzlacı (2013), Bulut et al. (2017)
Curcuma longa L.	Zingiberaceae	Turmeric	Rhizomes	Restorative paste (prepared with the dried and pulverized rhizomes, ginger, cinnamon, and the seeds of nettle and *Nigella sativa* after milling and mixing with honey)	Indian subcontinent and Southeast Asia	Jahan and Onay (2020), Şekeroğlu and Gezici (2020), Genç (2010), Uçar et al. (2020), Yeşilada (2012), Şanlı (2006), Ege and Elmastaş (2020), Demirci-Kayıran (2019), Doğan and Doğan (2020), Everest and Ozturk (2005), Ongan

						(2018), Akbaş and Akçakaya (2020)
Echinacea angustifolia DC.	Compositae	Narrow-leaf coneflower	Roots, rhizomes, flowers	Decoction or infusion (after pulverizing)	North America	Kalafatçılar and Kalafatçılar (2010), Genç (2010), Yeşilada (2012), Ege and Elmastaş (2020), Doğan and Doğan (2020), Kavaklı et al. (2020b), Uçar et al. (2020)
Hibiscus sabdariffa L.	Malvaceae	Roselle, carcade, hibiscus	Leaves	Infusion	West and East Africa and Southeast Asia including Northeastern India.	Kalafatçılar and Kalafatçılar (2010), Baytop (1999), Ötnü and Akan (2020), Yeşilada (2012), Akan and Bakır-Sade (2015), Arıtuluk (2010)
Malpighia emarginata DC.	Malpighiaceae	Acerola cherry	Fruits	Decoction or infusion (after pulverizing)	Central and South America	Genç (2010), Ötnü and Akan (2020), Yeşilada (2012)
Panax ginseng C.A.Mey.	Araliaceae	Asian ginseng	Roots	Decoction or infusion (after pulverizing), paste (with honey)	Russian Far East (outer Manchuria), Northeast China, and the Korean Peninsula	Jahan and Onay (2020), Kalafatçılar and Kalafatçılar (2010), Baytop (1999), Genç (2010), Kavaklı et al. (2020b), Ötnü and Akan (2020), Yeşilada (2012), Kurt and Karaoğul (2018), Gökçe (2011), Ongan (2018), Kökçü et al. (2015), Korkmaz and Karakurt (2014), Onbaşlı and Dal (2020)
Piper nigrum L.	Piperaceae	Black pepper	Unripe fruits	Infusion mix (with the dried and pulverized fruits and ginger rhizomes, melissa leaves, sage	India	Baytop (1999), Uçar et al. (2020), Özer et al. (2005), Ege and Elmastaş (2020),

(continued)

Table 18.5 (continued)

Sc. Names	Families	English names	Parts	Preparations	Native lands	References
				leaves, and elder fruits), restorative paste1 (all of them above are eaten by mixing with honey), restorative paste2 (prepared with the dried and pulverized fruits and ginger rhizomes, cinnamon, turmeric, nettle seeds, and *Nigella sativa* seeds after milling and mixing with honey)		Yeşilada et al. (2019), Demirci-Kayıran (2019), Doğan and Doğan (2020), Güneş (2017), Özhatay et al. (2009), Diken (2009)
Rheum officinale Baill.	Polygonaceae	Chinese rhubarb	Roots, rhizomes	Infusion after pulverizing, syrup, paste (with honey)	China	Jahan and Onay (2020), Kalafatçılar and Kalafatçılar (2010), Baytop (1999), Genç (2010)
Syzygium aromaticum (L.) Merr. & L. M.Perry	Myrtaceae	Cloves	Flower buds, essential oil	Pastille, infusion, frankincense, decoction mix (with cinnamon and linden leaves), mixture (eaten after milling with seeds of celery and anise, turnip, radish, and mixed with honey)	Maluku Islands	Baytop (1999), Özcan et al. (2020), Sargin (2013), Uçar et al. (2020)
Terminalia citrina Roxb. Ex Fleming	Combretaceae	–	Fruits, seeds	Paste (prepared with honey after dried and pulverized)	East India	Baytop (1999), Ötnü and Akan (2020), Kökçü et al. (2015)
Vaccinium macrocarpon Aiton	Ericaceae	Cranberry	Fruits	Eaten after dried, juice, decoction	North America	Genç (2010), Ötnü and Akan (2020), Yeşilada (2012)

Zingiber officinale roscoe	Zingiberaceae	Ginger	Rhizomes	Infusion mix (with the dried and pulverized rhizomes, melissa leaves, sage leaves, elder fruits, and black pepper), restorative paste1 (all of them above are eaten by mixing with honey), restorative paste2 (prepared with the dried and pulverized rhizomes, cinnamon, turmeric, nettle seeds, and *Nigella sativa* seeds after milling and mixing with honey)	South Asia	Baytop (1999), Uçar et al. (2020), Özer et al. (2005), Ege and Elmastaş (2020), Yeşilada et al. (2019), Demirci-Kayıran (2019), Doğan and Doğan (2020), Güneş (2017), Özhatay et al. (2009), Akbaş and Akçakaya (2020), Diken (2009)

vital organs, such as the kidney and liver, even riskier (Marra et al. 2020; Vitiello et al. 2021). In fact, new cases are added every day to the reports that dozens of people who had newly developed vaccines lost their lives due to unpredictable coagulation. Countries that were lining up to be able to supply the relevant vaccines a while ago, announced that they, therefore, ban the use of these vaccines one after another (Evenett et al. 2021). At this point, medicinal plants might almost be the rescuers of humanity, for they have been providing us with the successful results observed in immune system boosting and similar activities for centuries, provided that they are routinely utilized following the guidelines laid out in their pharmacopeias. However, there is also a misperception that herbal medicines are completely safe and have no side effects. In addition, complications that may occur in the case of the use of existing drugs are another issue that should be taken into consideration. For this reason, we strongly recommend that people and establishments that keep and sell fresh or dried medicinal herbs in public markets and shops are inspected more strictly by local governments and that they are sold to the public following international norms. In these matters, the directives, instructions, and practices of the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) can be taken as a model and the existing system can be revised. We firmly advocate the urgent need to inform the public in more detail by recording the herbal mixtures and prescriptions of traditional empirical practices with proven reliability and effectiveness after the necessary clinical tests, revealing their ingredients and active compounds through experimental studies, and updating their knowledge in their pharmacopeias. We sincerely believe that more effective results in public enlightenment will be attained if non-governmental organizations, scientific communities, and official authorities/institutions organize some sort of enlightenment seminars with the participation of local residents on plants that can be used safely against COVID-19 and similar epidemics.

Considering that Turkey has the richest flora in Europe and the Middle East and its invaluable ethnomedical history, it presents a treasure-worthy potential for those who want to do serious research on this subject. In fact, this study presents a nationally useful inventory of immune-enhancing plants that are regularly used in traditional Turkish medicine, not only against COVID-19 but for the prevention and treatment of epidemic diseases in general. We present 68 (53.1%) plants whose effective immunostimulating and strengthening properties have been confirmed in experimental studies in the world literature as ready-made material for the relevant pharmacological sectors. In addition to the 60 (46.9%) taxa that have not been searched yet, which are shown in bold in Table 18.1, the first 18 plants (Fig. 18.2), which received more citations than others about immunity enhancement in our research and were also prominent in neighboring country studies, we strongly recommend that these should urgently be subjected to clinical trials firstly. In this way, we will feel peaceful and happy if we can be instrumental in the survival of humanity from the current and future epidemics and pandemics with minimal damage, alleviation of patients' agonies, and the development of a healthier and happier generation.

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Chapter 19
A Comparison Study of Medicinal Plants Used Against SARS-CoV-2 and Those Recommended Against Malaria in Africa

Abdirahman Elmi, Ahmed Said Mohamed, Saredo Said, and Remy Bationo

19.1 Introduction

African medicinal plants have been used for thousands of years, and many of them are well-known for their health benefits and therapeutic values. They have been listed either in complete catalogs mentioning the scientific and local names, the family, the genus, and the traditional use or either through scientific articles presenting the phytochemical and biological aspects of a plant for a given biological activity. African plants are well known not only for their food resources but also for their therapeutic values. When epidemics or pandemics appear, the use of traditional medicine may have a high demand because they are natural and less expensive remedies.

In this chapter, first, the disease with a long history for humankind in Africa was discussed based on the literature of several decades. This is a very dangerous and deadly disease, normally, fewer than 5-year-old children and pregnant women are the most affected groups according to the record. It has been reported that malaria leads to more than 400,000 death per year, 92% in Africa. However, in 2018, compared to the year 2000, nearly 600,000 lives were saved due to the success of investments in fighting this disease. Nevertheless, the parasites can develop resistance to the treatments. Hence, future research needs to explore some more effective treatments and in the meantime should consider accessibility, feasibility, and cost.

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In addition to malaria, the global pandemic of coronavirus disease 2019 (COVID-19) arose in 2019 and subsequently in turn caused a serious mortality rate in Africa in the past years. In this scenario, timely vaccine and drug development is a great challenge due to the increasing number of variants found. Interestingly, a symptomatic resemblance of two diseases, i.e., COVID-19 vs. malaria, was found despite the large difference in classification, i.e., viral vs. parasitic. Subsequently, antimalarial agents or antimalarial candidates were evaluated for their potential for combating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

This chapter aims in the first part to summarize the ethnobotanical research works for SARS-CoV-2 in Africa. Then, it focuses on phytochemical analyses and the biological/clinical test of the plants with anti-SARS-CoV-2 effects. Finally, the similarities and differences between COVID-19 and malaria were comprehensively discussed.

19.2 Ethnobotany Report in Africa on Anti-Coronavirus Plants

The African continent was greatly affected by COVID-19, which is a deadly disease caused by a new type of coronavirus that is highly contagious. Unfortunately, in 2019, this disease had no treatment in the form of medicine or vaccines. Since the emergence of the SARS-CoV-2 pandemic, the global scientific community has continued to explore a cure to combat the pandemic. In the past years, many laboratories and/or pharmaceutical industries have been looking for existing molecule structures that can respond biologically to this disease or in particular also new plant-based molecules to overcome this pandemic (Llivisaca-Contreras et al. 2021; Costanzo et al. 2020). Herbal medicine research is very important and has a high potential to discover medicines for the management of COVID-19 (Elmi et al. 2020a, 2021; Lim et al. 2021; Jomah et al. 2020). Several studies have been reported and have found promising remedies (Fouedjou et al. 2021; Najem et al. 2022). Ethnobotanical studies against SARS-CoV-2 are generally carried out focusing on plants commonly used in Africa to relieve cough, fever, fatigue, and respiratory problem which are also the main and most common symptoms of COVID-19.

In 2020, Vroh conducted a study of plant diversity in traditional medicine for key symptoms of COVID-19 in sub-Saharan Africa (Vroh 2020). The result of this work identified 99 species use against frequent symptoms of COVID-19 in sub-Saharan African countries (Burkina Faso, Madagascar, Togo, Gabon, Cameroon, Benin, Senegal, Ivory Coast, and South Africa, Mozambique, Ghana, Niger, Mali, Ethiopia, Democratic Republic of Congo, Central African Republic). Fourteen of these species mentioned (*Terminalia macroptera, Terminalia catappa, Citrus limon, Anogeissus leiocarpus, Zea mays, Eucalyptus camaldulensis, Artemisia afra, Calantica cerasifolia, Lantana camara, Ocimum gratissimum, Zingiber officinale, Lippia javanica, Scoparia dulcis,* and *Crossopteryx febrifuga*) are used at the same time

for the treatment of two out of the three common symptoms and no species is used for the treatment of the three symptoms at the same time. By priority of use, 5 plants (*Zingiber officinale, Lippia javanica, Ocimum gratissimum, Citrus limon,* and *Artemisia afra*) are very common because of their diverse and common uses in traditional medicine in sub-Saharan Africa.

In the next year, a broader study was carried out by Beressa et al. in 2021, bringing together a total of 36 studies grouping the usefulness of African medicinal plants against viral infections. Among 328 screened plants showing antiviral activities, 10 plants were found to possess anti-SARS-CoV-2 activity. This work proposed a source of certain African medicinal plants, with antiviral effects that could potentially be a remedy against COVID-19 in the future (Beressa et al. 2021).

Adeleye et al. in 2021 have also reported some information focusing on the ethnomedicine identification of plants present in Africa as a means against SARS-CoV-2. This work highlighted 15 plants: *Abrus precatorius* (Iwu 2013), *Achyranthes aspera* (Sharma and Chaudhary 2015), *Allium sativum* (Thuy et al. 2020; Tijani et al. 2019; Asowata-Ayodele et al. 2016), *Annona muricata* (Roger et al. 2015; Coria-Téllez et al. 2018), *Artemisia afra* (More et al. 2012), *Azadirachta indica* (Xuan et al. 2004; Kumar and Navaratnam 2013; Borkotoky and Banerjee 2021), *Cryptolepis sanguinolenta* (Odoh and Akwuaka 2012; Osafo et al. 2017), *Curcuma longa* (Ayati et al. 2019; Taoheed et al. 2017), *Euphorbia hirta* (Jeje TO et al. 2016), *Garcinia kola* (Seanego and Ndip 2012; Ekene and Erhirhie 2014), *Glycyrrhiza glabra* (Murck 2020; El-Saber Batiha et al. 2020), *Moringa oleifera* (Bhattacharya et al. 2018; Shaji 2020), *Nigella sativa* (Koshak and Koshak 2020; Rahman 2020), *Psidium guajava* (Gutiérrez et al. 2008; Laksmiani et al. 2020), *and Zingiber officinale* (Mao et al. 2019; Prasad et al. 2020) from different African countries (Adeleye et al. 2021).

Most of these plants have shown effective or mean activity against SARS-CoV-2 to relieve the intensity of symptoms of this disease. For example, Oyebamiji et al. and Trivedi et al. in 2020 showed that *Annona muricata* seeds can be used as an inhibitor against SARS-CoV-2 (Trivedi et al. 2020; Oyebamiji et al. 2020). Also, *Curcuma longa* is a plant with potential anti-SARS-CoV-2 effects, reported both by Wen *et al.*, in 2007 (Wen et al. 2007) and Zahedipour and Coll, in 2020 (Zahedipour et al. 2020). In addition, an interesting study was also carried out in 2020 by Lin and Ying, showing the good anti-inflammatory activity of curcumin which can be used as a treatment for pneumonia in patients affected by COVID-19 infection (Liu and Ying 2020).

As respiratory perturbations are also one of the major symptoms of SARS-CoV-2. Agbor *et al.* in 2021 selected ethnobotanical scientific articles on respiratory diseases in Africa over the past 10 years (2011–2021). This review has been the subject of 14 scientific articles on different respiratory diseases which is a track to identify future anti-SARS-CoV-2 plants. It has been listed at around 143 plants belonging to 60 families, whose species of the family *Fabaceae* and *Lamiaceae* are the most cited (18 citations each). The plants that have been identified are used for about 15 diseases and/or symptoms related to the respiratory system. Among the 143 plants listed, *Ocimum gratissimum L.* (4 citations), *Entandrophragma*

cylindricum (Sprague), *Scyphocephalium ochocoa Warb, Rubia cordifolia,* and *Allium sativum L.* (3 citations each) are most popular. Based on this review, *Ocimum gratissimum* is more used against respiratory disorders and can be useful for the local management of COVID-19 (Agbor and Ndjib 2021).

Traditional medicine is also practiced in Maghreb countries (North Africa) to treat infectious diseases (Chebaibi et al. 2022). During the pandemic, ethnobotanical studies are carried out to identify natural substances against COVID-19. An ethnobotanical study was carried out in Fez city (Morocco) in 2021 (Benkhaira et al. 2021). Benkhaira *et al.* listed around 49 medicinal plants belonging to 28 botanical families, used against SRAS-CoV-2. Considering PUV (Plant Use Value), there are 4 plants used a lot, namely *Syzygium aromaticum* (0.46), *Thymus vulgaris* (0.46), *Eucalyptus globulus* (0.4), and *Artemisia vulgaris* (0.36) (Trotter and Logan 1986).

In Algeria, a recent ethnobotanical study was likewise carried out in 2022 in the region of Bejaia (Northeast of Algeria). Brahmi *et al.* counted about 23 medicinal plants (*Allium sativum, Allium cepa, Pistacia lentiscus, Pimpinella anisum, Artemisia herba-alba* (Boughendjioua et al. 2022)*, Matricaria chamomilla, Lavandula stoechas, Rosmarinus officinalis, Ocimum basilicum, Melissa officinalis, Mentha spicata, Origanum vulgare, Thymus vulgaris, Salvia officinalis, Cinnamomum verum*, *Eucalyptus globules*, *Syzygium aromaticum, Olea europaea, Pinus halepensis, Citrus x limon, Citrus sinensis, Aloysia citriodora, and Zingiber officinalis*) belonging to 12 families (Amaryllidaceae, Anacardiaceae, Apiaceae, Asteraceae, Lamiaceae, Lauraceae, Myrtaceae, Oleaceae, Pinaceae, Rutaceae, Verbenaceae, and Zingiberaceae) were listed in the Bejaia localities against COVID-19 infection. This work was done through data analysis using relative citation frequency (RFC), family importance value (FIV), and plant part value (PPV) (Orch et al. 2020). Among these plants, *Aloysia citriodora* (RFC = 0.248), *Mentha spicata* (RFC = 0.145), *Citrus limon* (RFC = 0.135), *Thymus vulgaris* (RFC = 0.118), *Zingiber officinalis* (RFC = 0.09), *Artemisia herba-alba* (RFC = 0.065), and *Eucalyptus Globules* (RFC = 0.063) are used. The leaves of these plants which are used (65%) in the form of infusion (43.6%) are administered orally (95.03%) to treat and relieve certain symptoms of COVID-19 (Brahmi et al. 2022).

Another study was conducted in Algeria, particularly in Seraidi, a region rich in medicinal plants. An ethnobotanical survey was evaluated to meet the health needs, of antiviral plants of interest over the pandemic, which is also a disease of viral origin. This survey listed 32 species (*Origanum vulgare, Thymus capitatus, Lavandula angustifolia, Thymus vulgaris, Artemisia herba-alba, Zingiber officinale, Curcuma longa, Glycyrrhiza glabra, Cinnamomum zeylanicum, Eucalyptus globules, Syzygium aromaticum, Allium sativum, Pistacia lentiscus, Allium cepa, Olea europaea, Verbena officinalis, Citrus sinensis, Citrus limon, Mentha spicata, Cupressus arizonica, Melissa officinalis, Pulmonaria officinalis, Salvia officinalis, Artemisia absinthium, Ziziphus lotus, Nigella sativa, Pinus sylvestris, Myristica fragrans, Urtica dioica, Origanum majorana, Brassica rapa,* and *Arisarum vulgare*) to belong to 20 botanical families, of which the Lamiaceae is the most represented family in terms of use as an antiviral (Salima et al. 2022). The species identified in

the Seraidi region were mentioned also in the online survey conducted by Hamdani and Houari in 2020, carried out on 500 people, including 49% suffering from COVID-19, in different regions of northern Algeria (Hamdani and Houari 2020).

Since 2019, the search for a miracle plant or phytoconstituents to help combat this new global SARS-CoV-2 pandemic has continued to grow. The African continent has largely contributed to the search for relevant means through ethnobotanical studies to combat this pandemic using traditional medicinal knowledge and its terrestrial forest wealth (Tegen et al. 2021; Belmouhoub et al. 2021).

Currently, no medicine can treat SARS-CoV-2 except vaccines, and still not effective, due to the virus variance of SARS-CoV-2. The search for plant-derived therapeutics for COVID-19 is necessary for Africa. Therefore, the encryptions of African medicinal plants, used to treat different viral infections are a priority for possible evaluations against SARS-CoV-2.

19.3 Phytocompounds from Anti-Coronavirus Plants

Secondary metabolites are molecules that are not directly involved in the growth process of living organisms, unlike primary metabolites (carbohydrates, amines, and lipids). However, their role is not secondary to the survival of the producing organisms. They are produced during the degradation of primary molecules and have various functions, in particular protection against aggressors (bacteria, viruses, etc.). Several categories of specialized metabolites are classically distinguished according to their biochemical nature and their biosynthetic origin. They can be divided into three main families such as polyphenols, nitrogen compounds, and terpene-sterols. The different types of these compounds have been studied in the fight against COVID-19 (Figs. 19.1, 19.2, and 19.3).

19.3.1 Polyphenols

Preliminary research suggests that polyphenols, a type of antioxidant found in many plants, may help protect against the virus that causes COVID-19. In vitro, kaempferol inhibits coronaviruses by blocking the 3a viral channels implicated in viral proliferation (Schwarz et al. 2014). Quercetin, epigallocatechin gallate, and gallocatechin gallate showed very promising effects against SARS-CoV 3CL (pro) with a weak half inhibition concentration of 73, 73, and 47 μM, respectively (Nguyen et al. 2012). A recent study has shown that quercetin can block the normal operations of the SARS-CoV-2 viral proteins inside human cells around 85%. This value rises to 93% if this compound is combined with vitamin D (Glinsky 2020). Other phenolic compounds showed more potent against papain-like protease (PLpro) than against 3-chymotrypsin-like protease (3CLpro). The IC_{50} of fourteen compounds (broussochalcone B, broussochalcone A, 4-hydroxyisolonchocarpin,

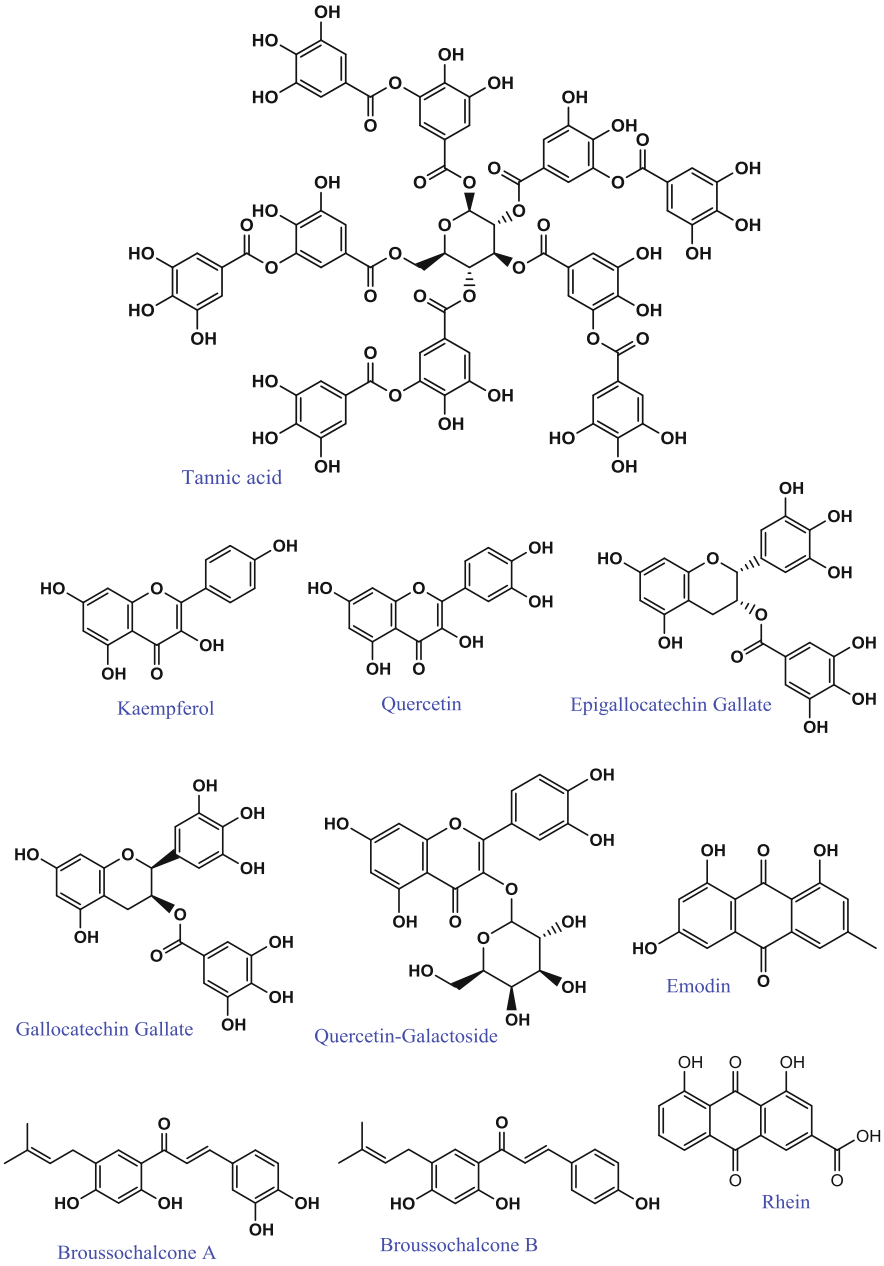

Fig. 19.1 Structure of polyphenols tested against coronavirus

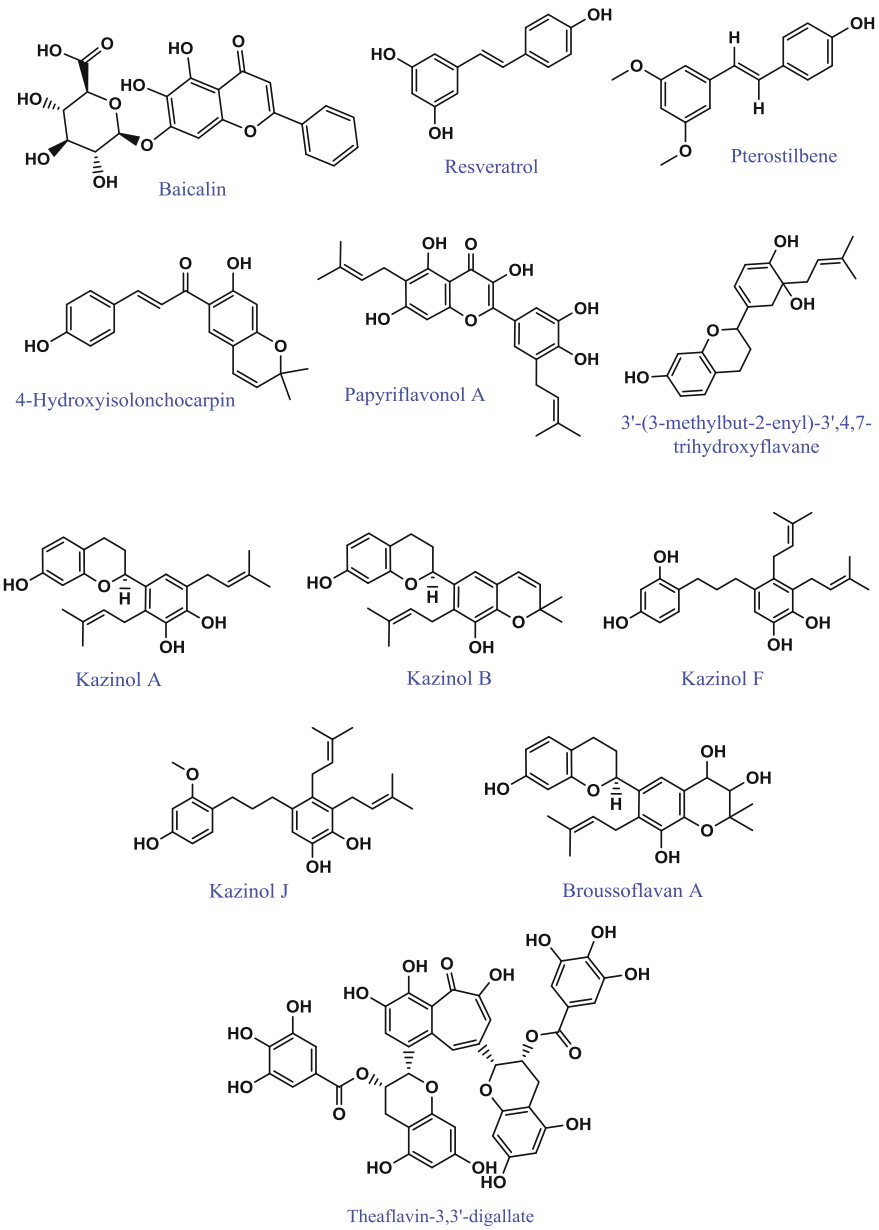

Fig. 19.1 (continued)

kaempferol, papyriflavonol A, 3′-(3-methylbut-2-enyl)-3′,4,7-trihydroxyflavane, kazinol A, kazinol B, kazinol J, broussoflavan A, kazinol F, quercetin, and quercetin-β-galactoside) ranged from 30.2 to 233.3 μM and 3.7 to 66.2 μM against SARS-CoV 3CLpro and SARS-CoV PLpro, respectively (Park et al. 2017). An in

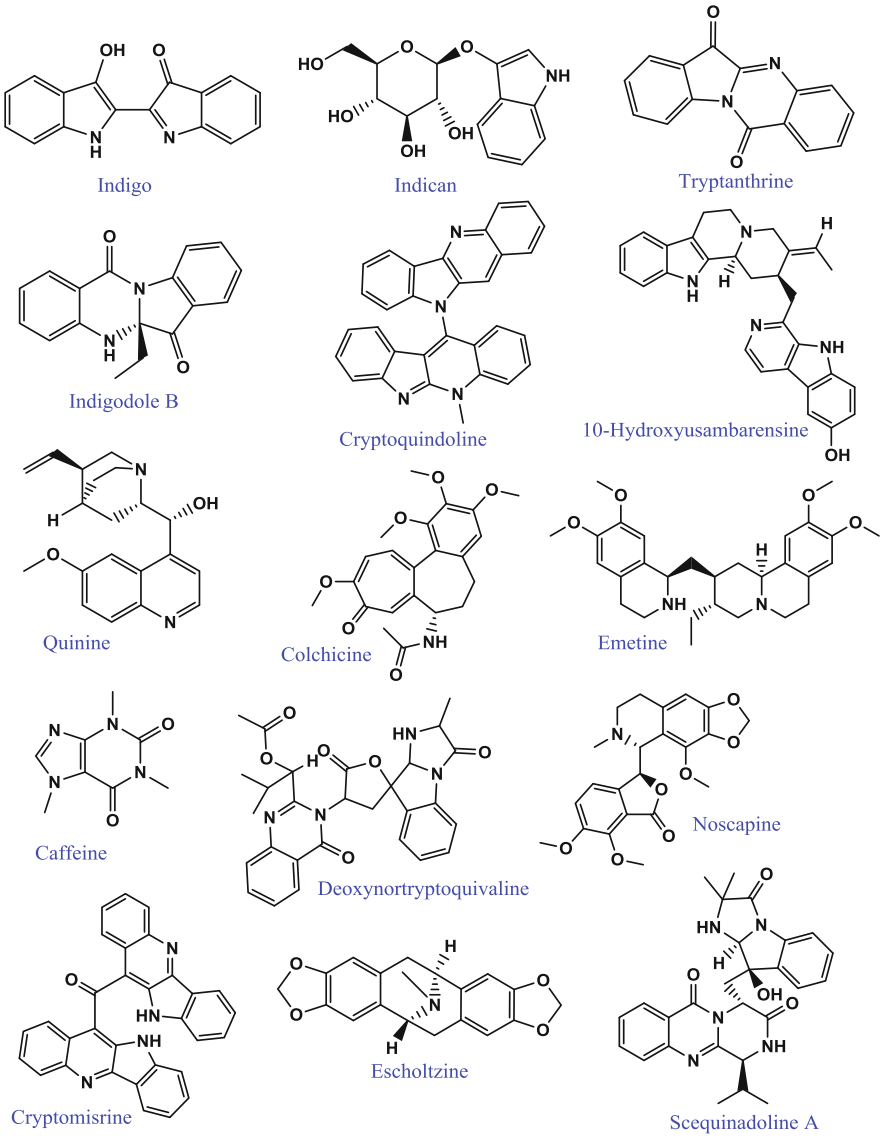

Fig. 19.2 Structure of alkaloids tested against coronavirus

silico study showed that the flavonoids from Djiboutian medicinal plants (including rutin, catechin, and kaempferol) have better binding energy, between −9.1 and − 7.25 kcal/mol, than the reference remdesivir, and hydroxychloroquine with −7.194 and − 5.816 kcal/mol, respectively, at the active site SARS-CoV-2 Mp (Elmi et al. 2020b).

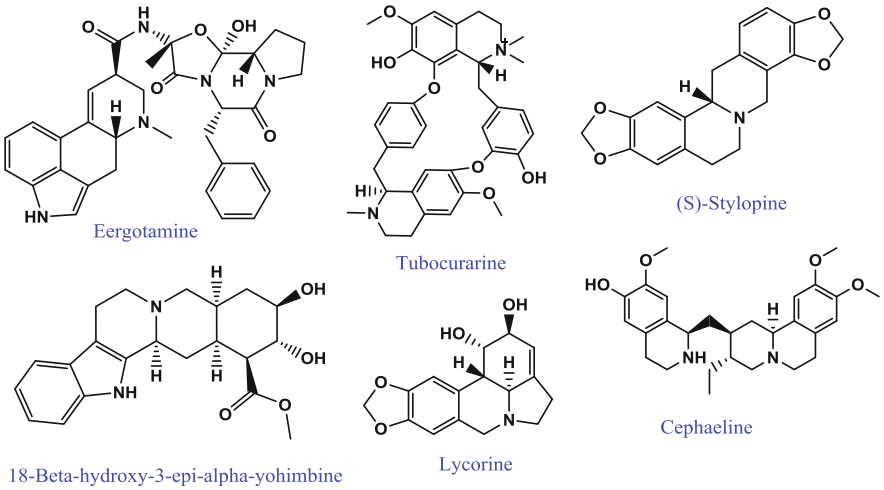

Fig. 19.2 (continued)

Catechin derivatives interact vigorously with one or both the amino acids, His41 and Cys145, from SARS-CoV-2-Mpro, a key component of this viral reproduction (Ghosh et al. 2021). Two anthraquinones, emodin, and rhein, common to the genre aloe prevent landing S-protein on ACE-II (Ho et al. 2007). Tannic acid, theaflavin-3,3′-digallate, and baicalin were demonstrated as effective viral 3CLPro inhibitors (Chen et al. 2005; Su et al. 2020). Also, resveratrol and pterostilbene are promising antiviral compounds to treat SARS-CoV-2 infection in in vitro tests using African green monkey kidney cells (ter Ellen et al. 2020).

19.3.2 Alkaloids

Indigo and Indicant isolated from *Satis indigotica* root showed efficiency in blocking the cleavage processing of the $3CL^{pro}$ (Lin et al. 2005) Tryptanthrin and indigodole B (5a *R*-ethyl tryptanthrin) present in *Strobilanthes cusia leaf* exhibited potent antiviral activity against HCoV-NL63 replication, particularly by blocking viral RNA genome synthesis (Tsai et al. 2020). In silico test 10-hydroxyusambarensin and cryptoquindoline, found in different African medicinal plants are capable to inhibit the $3CL^{pro}$ with a high score to both old and emerging SARS-CoV (Gyebi et al. 2021). Quinine, currently prescribed in Africa for malaria, has a good interaction with the Lys353 residue localized on the ACE2 receptor (Gonzalez et al. 2022), and with to NSP12 target (Sumitha et al. 2020).

The most common target in the case of alkaloids is SARS-CoV-2 Mp, with examples including 10-hydroxyusambarensine, caffeine, emetine, deoxynortryptoquivaline, ergotamine ; noscapine, cryptomisrin, escholtzine, 18-hidroxy-3-epi-alpha-yohimbine, (*S*)-stylopine, scequinadoline A and tubocurarine (Gyebi

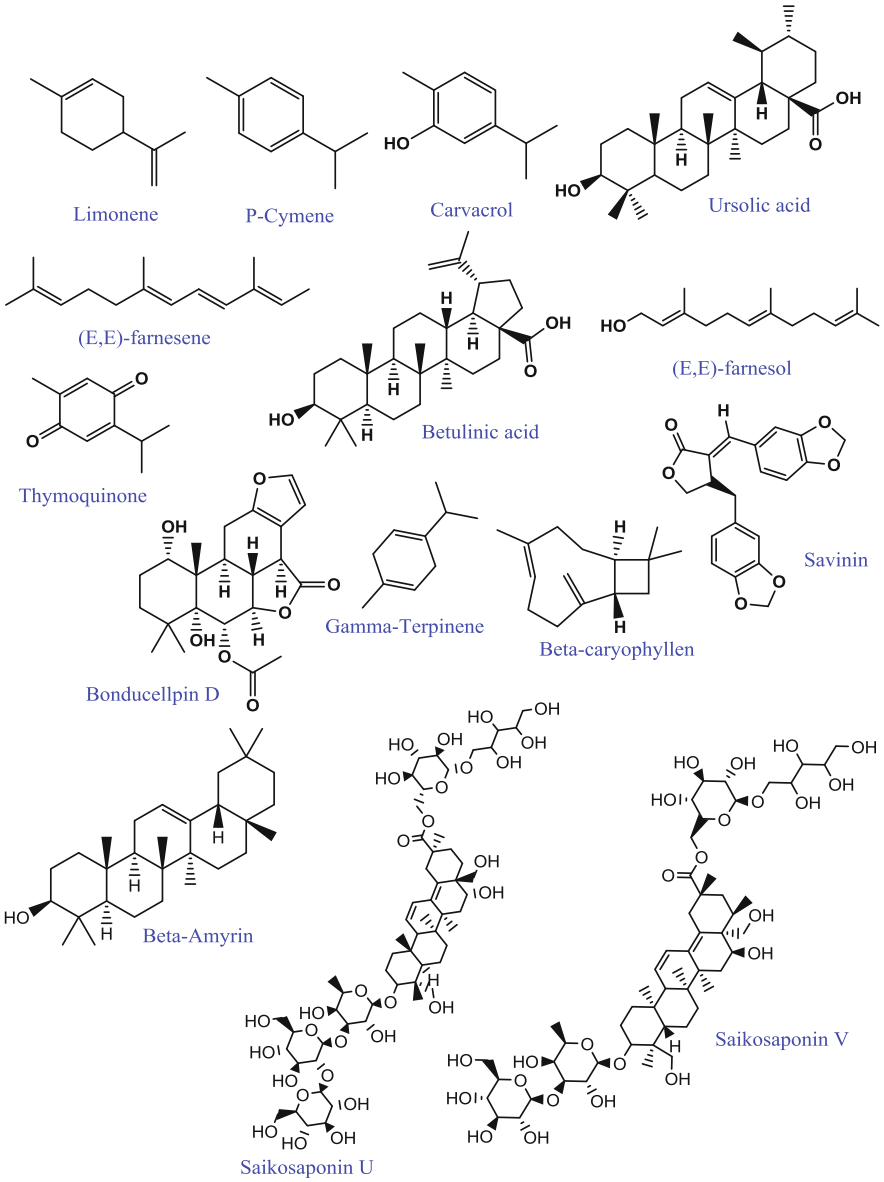

Fig. 19.3 Structure of alkaloids tested against coronavirus

et al. 2021, 2022; Borquaye et al. 2020; Das et al. 2021; Elzupir 2022; Singh and Florez 2020; Garg and Roy 2020; Gurung et al. 2020; Ismail et al. 2021; Kumar et al. 2022; Qiao et al. 2020; Quimque et al. 2021; Sisakht et al. 2021). In in vitro tests, emetine, lycorine, and cephaeline alkaloids were evaluated as inhibitors of viral protein synthesis to have cross-interactions with human ribosomes on different

catalytic sites (Ren et al. 2022). Finally, colchicine is the alkaloid that has had the largest clinical trials in different countries. Indeed, in Greece it is valued for its significantly enhanced time to treatment (Deftereos et al. 2020), in Brazil about the lower need for hospitalization maintenance (Lopes et al. 2021), in Russia, it is observed a brief and statistically significant decrease, and normalization of CRP (C-reactive protein) (Mareev et al. 2021), in Canada, USA, and Italia, a lower incidence of death or hospital admission than placebo (Tardif et al. 2021; Brunetti et al. 2020; Manenti et al. 2021). However, unfortunately, there are no studies in Africa till present.

19.3.3 Terpenoids

Limonene, *P*-cymene, and γ-terpinene extracted from *Ammoides verticillata* (Desf.) Briq., collected in western Algeria, have a good inhibition on the ACE 2 receptor of SARS-CoV-2 (Abdelli et al. 2021). Different terpenic compounds reported significant interaction on sites or receptors of SRAS-CoV such as betulinic acid and savinin (Wen et al. 2007), saikosaponin U and saikosaponin V (Sinha et al. 2021), carvacrol, ursolic acid (Sampangi-Ramaiah et al. 2020), bonducellpin D (Gurung et al. 2020), β-amyrin (Borkotoky and Banerjee 2021), β-caryophyllene (Narkhede et al. 2020), thymoquinone (Bouchentouf and Missoum 2020), (*E, E*)-farnesol and (*E, E*)-α/β-farnesene (da Silva et al. 2020).

19.4 Bioassay and Clinical Evidence

In Africa where the use of plants is very present, a rapid recourse to these resources has been observed. In emergencies, plants that have been used for thousands of years can be taken without worrying about their toxicity as opposed to newly synthesized molecules. However, due to poor scientific infrastructure, there are few confirmatory bioassays or clinical studies. Because of the similarity of the symptoms between COVID-19 and malaria, *Artemisia* sp. has been one of the most investigated plants in plant care. Extracts of this plant (aqueous and alcoholic) as well as its main molecule (artemisinin) and its derivatives (artesunate and artemether) were tested in vitro against SARS-CoV-2. The originality of this study is to test the effectiveness of these preparations or pure compounds in pre-treatment (pt) and treatment (t) after infection (Zhou et al. 2021). In both cases (pt and t), the alcoholic extract has an effective concentration of about 50% smaller than the aqueous extract at 173 μg/mL (pt)/142 μg/mL (t) and 390 μg/mL (pt)/260 μg/mL (t), respectively. Overall, artesunate had the best activity with EC_{50} of 12 μg/mL (pt) and 7 μg/mL (t). The latter molecule is a known antimalarial drug in pharmacy and this reinforces the possible link between malaria and COVID-19.

Another example is "covid organics," a preparation of *artemisia annua* in hot water promoted by the Malagasy government and distributed in several African countries. Its use was debated at the beginning of the epidemic due to the lack of tangible evidence of its efficacy, and the WHO was late in agreeing to evaluate it. Since then multiple studies have been carried out. An in vitro evaluation shows an inhibitory action of this drink with an effective half concentration (EC_{50}) of 7.73% of raw drink and with a selectivity index of 5.28 (Nie et al. 2021). Some clinical studies of natural products and their derivatives against COVID-19 are summarized in Table 19.1.

A team of Malagasy researchers with technical support from WHO conducted an efficacy and safety evaluation of artemisinin and 1,8-cineole capsule for COVID-19 patients (Rakotosaona et al. 2022). The study was a phase 3 randomized, double-blind, placebo-controlled trial involving more than 1500 patients. The median time to recovery was 14 and 21 days with the capsule or placebo treatment, respectively. According to this clinical study, none of the patients treated with CVO + C developed the severe form of this disease, and all the vital functions of their organism are preserved (kidney and liver, among others). A similar study of artemisinin combined with piperaquine showed a faster clearance of SARS-CoV-2 than control patients (Li et al. 2021). Also, different studies were performed in which pharmaceutical preparations containing artemisia plant, artemisinin, and/or its derivatives about the virological clearance (NCT04502342, ChiCTR2000033049, and PACTR202103601407640), shorter time to clinical improvement (NCT04382040, NCT04374019, and CTRI/2020/09/028044), and to avoid hospitalizations and oxygen use (NCT04530617).

Other plants and essential oils that have targeted the symptoms (NCT04501965, NCT04980573, NCT04981314, and NCT04705753) and sanitary deterioration (NCT04400890 and NCT04851821) were studied.

In Nigeria, a new compound, harpagide 5-O-β-D-glucopyranoside from *Clerodendrum volubile* leaf has a promising ability to suppress T-cell proliferation (Erukainure et al. 2022). The latter is involved in the activation of cytokine release syndrome, and studies have indicated that targeting T-cell proliferation may prevent the severe form of COVID-19 (Zhou et al. 2020a).

Three extracts of Egyptian medicinal plants (*Psiadia punctulata, Aframomum melegueta,* and *Nigella sativa*) and their isolated compounds achieved high inhibition rates between 31.5–66.4% and 63.21–73.8%, respectively, for the extracts and compounds against the major proteases of SARS-CoV-2 (Abdallah et al. 2022).

In Madagascar, (−)-6-epi-artemisinin isolated from *Saldinia proboscidea, a typical source, showed interesting* in vitro *activity against SARS-CoV-2* (Randrianarivo et al. 2021).

Table 19.1 Some clinical studies of natural products and their derivatives against COVID-19

Trial code	Preparations	Participants	Outcomes measure	Status
NCT04382040	Artemisinin+ curcumin+ frankincense (=Boswellia)	50	Time to clinical improvement	Completed
NCT04502342	Artesunate +amodiaquine	30	Virological clearance	Unknown
NCT04374019	artesunate + Artemisia annua	13	Clinical deterioration	Terminated
NCT04530617	Artemisia annua	246	Rate of hospitalizations and oxygen use	Terminated
CTRI/2020/09/028044	Artemisinin	120	Accelerated the recovery of patients	Terminated
PACTR202103601407640	Artemisinin and 1,8-cineole	276	With complete clearance of the SARS-CoV-2 virus at day 28	Terminated
ChiCTR2000033049	Artemisinin + piperaquine	41	Shorten the time to reach undetectable SARS-CoV-2	Terminated
NCT04501965	Quinquina-stevia/ azithromycin	231	Virologic clearance and COVID-19 symptoms development	Unknown
NCT04400890	Resveratrol/ vitamin D3	100	Hospitalization rates for COVID-19	Terminated
NCT04980573	Citrus essential oil	47	Fatigue symptom	Terminated
NCT04981314	Echinacea purpurea	230	Fever	Recruiting
NCT04851821	Quercetin	80	Avoid emergency/ disappearance of symptoms	Completed
NCT04705753	Essential oil mixture	20	Number of patients with symptom resolution in 14 days max	Completed
NCT04997395	Cbd and thc	30	Long covid symptoms (pain, fatigue, anxiety, oxygen saturation, etc.) attenuation	Recruitment
NCT03944447	Medical cannabis	200.000	COVID-19 infection rates in cannabis users and symptoms attenuation	Recruitment

(continued)

Table 19.1 (continued)

Trial code	Preparations	Participants	Outcomes measure	Status
NCT05228626	Zanthoxylum and Warburgia sp	584	Clinical recovery in 8 days	Not yet recruiting

19.5 Malaria and COVID-19: Common Features and Their Differences

Malaria is a parasitic disease involving the genus *Plasmodium*. It is also transmitted and spread to humans by the bite of an infected female mosquito of the species Anopheles (Talapko et al. 2019). In 2020, the WHO annual report estimated the number of deaths at 627,000 in the world, the majority in Africa (WHO 2021). The emerging disease, COVID-19, was caused by SARS-CoV-2 and coronavirus disease 2019 (COVID-19), which is a serious threat to global health (Fisher and Heymann 2020). The COVID-19 outbreak started in Wuhan, a city in China's Hubei province, at the end of December 2019 and since it has spread rapidly all over the world and caused an outbreak (Sharma et al. 2021). Then WHO declared the COVID-19 outbreak a pandemic (World Health Organization 2020). Although malaria and COVID-19 may have several similar performances, clinical diagnosis of both diseases is based on patient symptoms and physical examination findings (Fig. 19.4).

The responsible agents of these diseases are viruses (COVID-19) and parasites (malaria), respectively, living organisms that are found all around us. The rapid spread of SARS-CoV-2 throughout the world is due, among other things, to its mode of transmission (direct human-to-human), whereas the parasite responsible for malaria needs an intermediary, the mosquito. The pendency of the COVID has accelerated the search for preventive and curative vaccines. Currently, about ten vaccines have been licensed by the WHO or state agencies, while the first malaria vaccine is currently only used in a limited number of countries for children (Bejon et al. 2008; Liu and Ye 2022).

19.5.1 The Role of ACE2 in Malaria and COVID-19

SARS-CoV-2 interacts with angiotensin-converting enzyme 2 (ACE2) as a receptor for entry into human cells, resulting in the downregulation of ACE2 in infected individuals (Yan et al. 2020; Sommerstein et al. 2020). ACE2 is an enzyme that is present on the cell surface of various organs in the body (heart, lungs, kidneys, etc.) (Zhou et al. 2020b). The amount of ACE2 and its action is crucial in identifying the severity of COVID-19. ACE2 plays a major role in the renin-angiotensin system (RAS) which antagonizes the action of angiotensin-converting enzyme (ACE) by converting angiotensin II to angiotensin 1–7. Its counteraction regulates blood

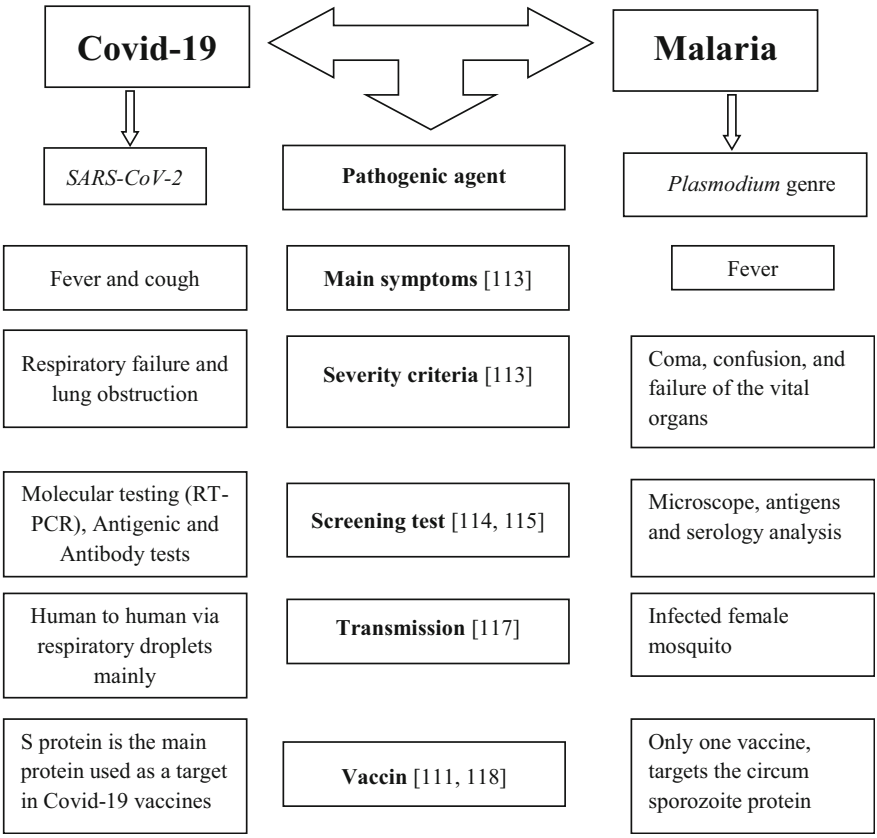

Fig. 19.4 Description of a comparison between COVID-19 and malaria

pressure by dilating blood vessels in a healthy adult (Stewart et al. 2008; Donoghue et al. 2000).

Besides some genetic variants of ACE2 are characterized by genetic deletion/insertion polymorphism (D/I). This characteristic is a good indicator of the severity of COVID-19 (Gemmati and Tisato 2020). Indeed, this polymorphism is related to an increase in Ang II concentration (Gemmati and Tisato 2020; Gemmati et al. 2020) and consequently leads to a negative disease evolution (Verma et al. 2021). In contrast, in malaria, high Ang II is beneficial because it has a parasiticidal effect and allows normal blood flow (Saraiva et al. 2011).

19.5.2 Impact the Country of the Two Diseases

The worldwide distribution of malaria and COVID-19 infections shows an inverse impact. Indeed, in highly malaria-endemic countries, including the African

continent, the impact (contagion and death) is low compared to Western countries that have eradicated malaria. Different hypotheses have been formulated, such as the demographic distribution of a predominantly young African continent or the low logistics of COVID-19 detection.

But within the continent, there is a disparity in the impact of COVID-19 which has done more damage in the North and South, while the malaria-endemic sub-Saharan region is relatively unscathed. Therefore the role of hydroxychloroquine (HCQ) and chloroquine (CQ) used against malaria in this region should be considered.

19.5.3 Natural Therapeutics

In this non-exhaustive literature search, we have listed 31 botanical families most used against malaria and COVID-19 in Africa. Eight botanical families are both popular against these two diseases, namely Combretaceae, Asteraceae, Annonaceae, Rutaceae, Meliaceae, Euphorbiaceae, Lamiaceae, and Fabaceae (Fig. 19.5).

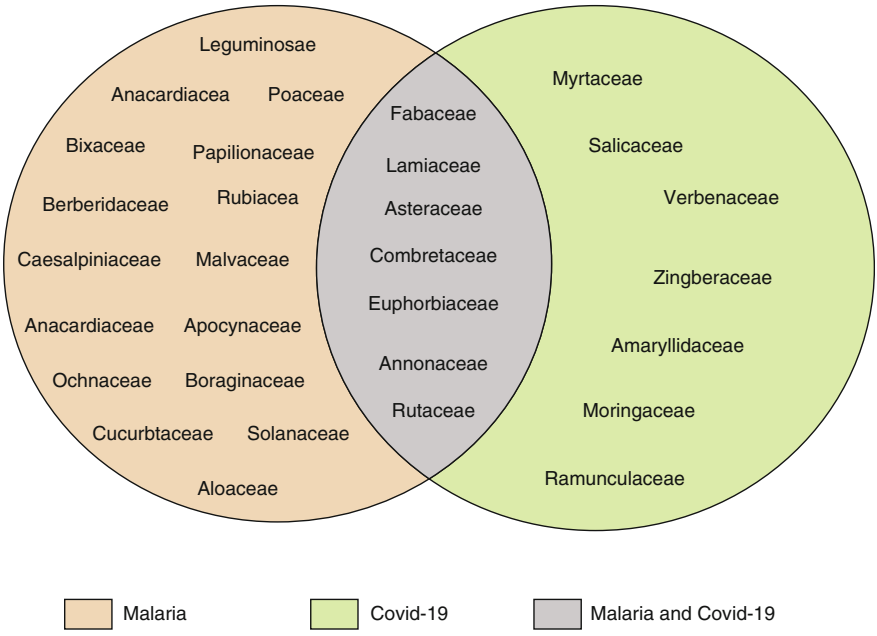

Fig. 19.5 Antimalarial major botanic family and anti-covid major botanic family plants (Asase et al. 2005; Diarra et al. 2015; Dike et al. 2012; Manya et al. 2020; Manuel et al. 2020; Opio et al. 2018; Oladeji et al. 2020; Yetein et al. 2013; Odugbemi et al. 2007)

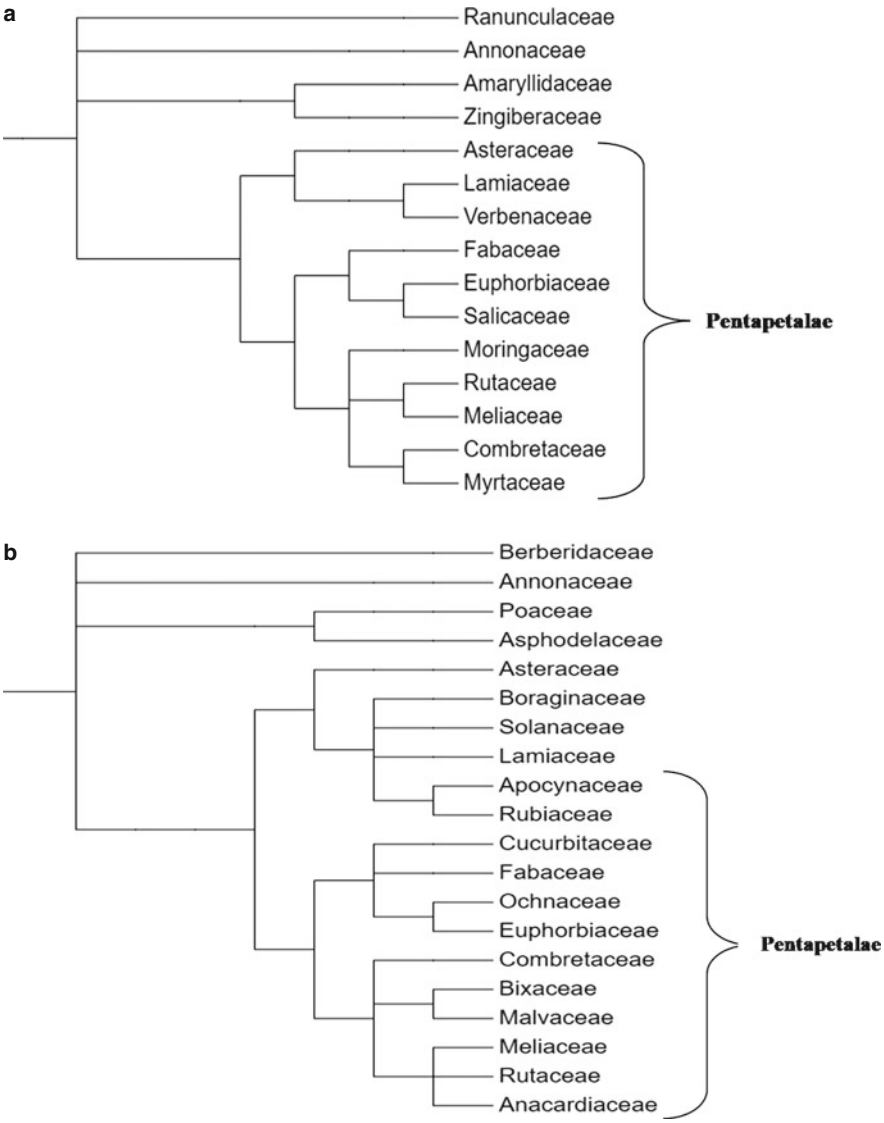

Fig. 19.6 Phylogenic organization (done by PhyloT software) of the plant families potentially used against COVID-19 (**a**) and malaria (**b**) in Africa (made with phyloT Sofware (Letunic and Bork 2021))

Most of the families listed belong to the Pentapetalae group (Fig. 19.6). The latter is the most diverse group of extant flowering plants and has a characteristic type of flower made up of whorls of five pieces each (Chanderbali et al. 2017).

19.6 Conclusion

SARS-CoV-2 has largely affected Africa even though the impact has been smaller than on other continents. Because of the high use of medicinal plants in Africa, various studies have been interested in identifying them and documenting their efficacy on patients infected by the coronavirus. The plants frequently cited are those known to be used against major symptoms of the disease such as fever, cough, and difficulty in breathing, among others. The strong similarity of symptoms with malaria has directed the search for remedies for plants and antimalarial drugs. The identification of active compounds against this new virus is rare as the targeting process usually takes a long time. However, apart from treating the symptoms, there is a high demand to explore drugs that combat protein targets of this virus.

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Chapter 20
Exploring the Potential Antiviral Properties of *Nigella sativa* L. Against SARS-CoV-2: Mechanisms and Prospects

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20.1 Introduction

The utilization of medicinal and aromatic plants is widespread among low-income communities, particularly in developing countries, as they are easily accessible and affordable (UNIDO 2006). Black cumin or *Nigella sativa* L., a plant belonging to the Ranunculaceae family, has been widely used to treat a variety of medical conditions throughout the world. Moroccan locals claim to have used this specific plant to treat a number of ailments, including cardiovascular disorders, stomachache, queasy, and arthritis (Fakchich and Elachouri 2021). *Nigella sativa* has been shown to possess a diverse range of properties, including antioxidant (Burits and Bucar 2000; Dalli et al. 2021a, b, c), antimicrobial (Dalli et al. 2021a, b, c), anti-inflammatory (Ali 2015), immunomodulatory (Salem 2005), antidiabetic (Dalli et al. 2021a, b, c, 2022), and low toxicity (Kehili et al. 2018). The existence of various bioactive substances, such as phenolic acids, flavonoids, alkaloids, and terpenoids, has been noted in *N. sativa* through several phytochemical investigations (Bourgou et al. 2010; Malhotra 2012).

Coronaviruses (CoV), a group of viruses, have been discovered to be capable of infecting livestock and inducing a range of disorders in the intestines, respiratory system, and other parts of the body, varying in severity. These viruses are responsible for a variety of illnesses in diverse wildlife species such as birds, bats, mice, giraffes, and whales. In humans, they cause both mild ailments like the common cold and more severe respiratory infections like pneumonia, resulting in substantial economic losses (Chan et al. 2013; Hasoksuz et al. 2007). Four of the seven coronavirus strains that can infect humans (HCoV OC43, HCoV 229E, HCoV HKU1, and HCoV NL63) typically cause moderate cold symptoms in persons with healthy immune systems. MERS-CoV, SARS-CoV, and SARS-CoV-2 are the three remaining coronaviruses, are all of zoonotic origin, and can all result in serious respiratory illnesses and even death. Chinese authorities informed the WHO about cases of pneumonia in China on December 31, 2019, which were later determined to be SARS-CoV-2 virus (Hasöksüz et al. 2020). The illnesses quickly spread over the world in March 2020, and the WHO proclaimed COVID a new pandemic (Salzberger et al. 2021). Similar to SARS-CoV and MERS, bats are found to be the natural reservoir for SARS-CoV-2 (Song et al. 2019); however, the difference lies in the intermediary, which is pangolins for MERS and civet cats for SARS-CoV (Prompetchara et al. 2020). Furthermore, 2.34% is the rate mortality of SARS-CoV-2, which is lower than the rates for SARS-CoV and MERS, which are 9.56% and 35.37%, respectively (Ganesh et al. 2021; Xie and Chen 2020). SARS-CoV-2 typically replicates in the upper and lower respiratory passages. Droplets and aerosols from infected asymptomatic and symptomatic patients are the main means of transmission with an incubation period of 5.7 days (Salzberger et al. 2021).

The ongoing COVID-19 pandemic has shed light on the importance of medicinal and aromatic plants as a tank of biomolecules that could help in the treatment and prevention of viral infections by SARS-CoV-2 which brings back to the surface the exploration of *N. sativa* and its derivates that are known to be endowed with high antiviral properties.

20.2 Epidemiology of COVID-19

The WHO has reported roughly 756,581,850 confirmed cases of COVID-19, including 6,844,267 deaths, according to recent numbers released on February 17th, 2023. While calculating the number of persons who have received vaccinations, it was discovered that 13,195,832,385 vaccine doses have been given globally. Corresponding to recent WHO statistics, Europe registered the highest number of confirmed cases, with a total of 272,634,146 cases since the start of the pandemic, with France as an example reporting 38,475,606 cases, followed by Western Pacific countries with 200,792,487 confirmed cases, then North and South America with a cumulative total of 189,648,697 cases, dominated by the USA with 101,496,168 confirmed cases. However, Southeast Asia has a total of 60,762,712 cases, followed by the Eastern Mediterranean countries with 23,251,360 confirmed cases. Finally, the African continent has the lowest number of confirmed cases, with 9,491,684 recorded. Regarding the number of deaths, the North and South America region has the highest number so far, with 2,923,918 deaths, followed by Europe with 2,189,540 deaths, the Southeast Asia region with 803,789 deaths, the Western Pacific countries with 402,289 deaths, then the Eastern Mediterranean countries with 349,434 deaths, and finally the African continent with 175,284 deaths. In Morocco, from 3 January 2020 to February 17, 2023, the number of COVID-19 recorded has reached more than 1,272,353 cases since the start of the pandemic with 16,296 deaths, while the total administered vaccine doses on the Moroccan territory were 55,379,860 (WHO 2023).

20.3 Molecular Basis of SARS-CoV-2 Pathogenesis

The new coronavirus, sometimes referred to as SARS-CoV-2, is a highly contagious virus that is causing the continuing COVID-19 epidemic worldwide. The virus belongs to the Coronaviridae family and exactly to the Betacoronavirus genus and is characterized by positive-sense single-stranded RNA (Zhu et al. 2020). A 30 kilobase genome makes up the SARS-CoV-2 and encodes 27 proteins, including the spike protein (S), which has 1273 amino acids and is composed of three similar chains, the envelope protein (E), the membrane protein (M), and the nucleocapsid protein (N) (Bailey-Elkin et al. 2017; Seyed Hosseini et al. 2020). Also, it was indicated the presence of hemagglutinin-esterase on the virus surface, which could help with virus entry (Boopathi et al. 2020). The S protein mediates viral entry into host cells by binding to the host cell receptor ACE2, which is expressed on the surface of human cells, particularly in the respiratory tract (Alnefaie and Albogami 2020; Boopathi et al. 2020) (Fig. 20.1). After SARS-CoV-2 enters host cells, the viral RNA genome is released into the cytoplasm, where it serves as a template for the translation of viral proteins. The viral RNA-dependent RNA polymerase (RdRp) and other viral enzymes also replicate and transcript the viral RNA genome in the cytoplasm. The replicated and transcribed viral RNA can be packaged into new virus

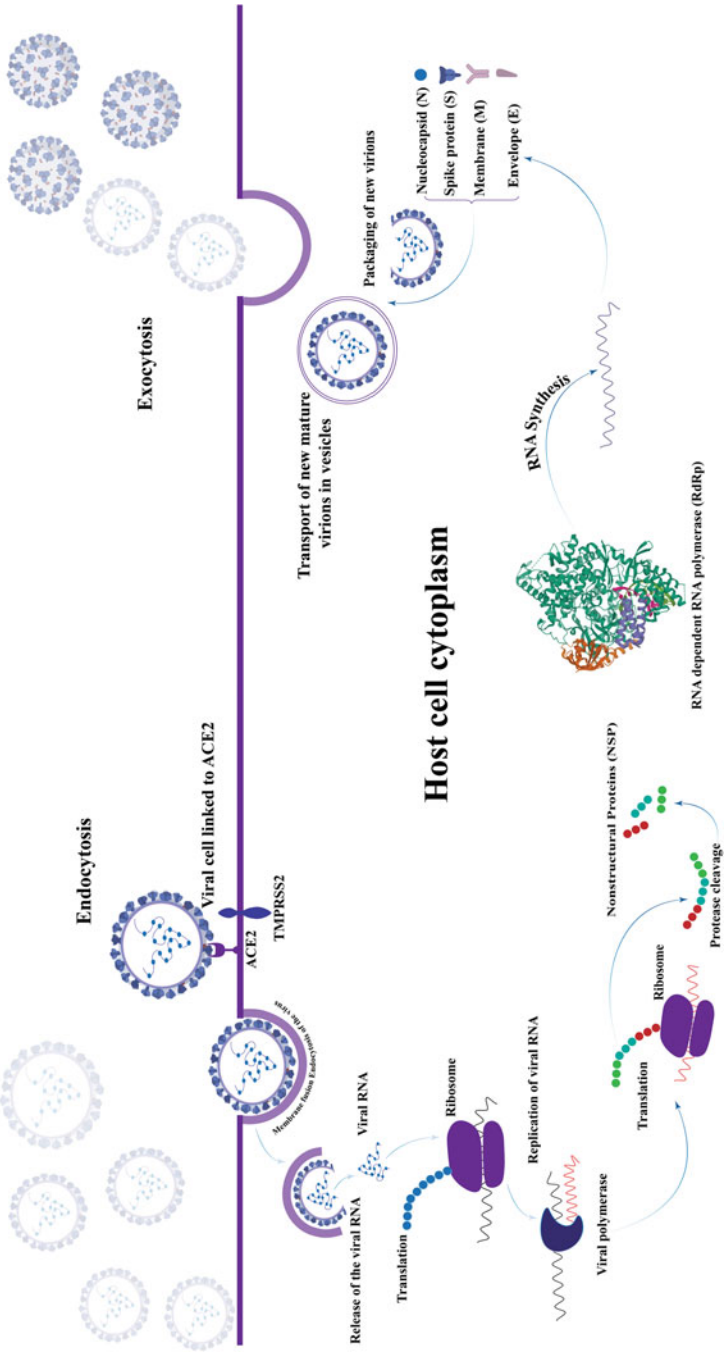

Fig. 20.1 SARS-CoV-2 structure and pathogenesis mechanism *Nigella sativa* bioactive compounds

particles, which can then infect neighboring cells and spread the infection figure. One of the challenges of SARS-CoV-2 is its ability to mutate and evolve, leading to the emergence of new variants of the virus that may have increased transmissibility and virulence, as well as potential resistance to current treatments and vaccines. The viral RdRp is error-prone meaning that it can make mistakes when copying the viral RNA, leading to the accumulation of mutations in the viral genome over time (Alnefaie and Albogami 2020) (Fig. 20.1). Non-structural proteins (NSPs), which aid in viral replication and immune system evasion, are also encoded by the SARS-CoV-2 genome. The RNA helicases, proteases, and RNA processing enzymes that make up the NSPs are essential for viral replication and translation (Boopathi et al. 2020). A trimeric transmembrane protein called S protein is essential for viral entrance into host cells. The S protein is made up of two functional subunits, S1 and S2, the former of which is in charge of receptor binding and the latter of which is in charge of membrane fusion. The S1 subunit's receptor-binding domain (RBD) interacts with host cells' ACE2 receptors to permit virus entry. Increased binding affinity to the ACE2 receptor brought on by mutations in the RBD region may boost the virus's virulence and transmissibility (Boopathi et al. 2020) (Fig. 20.1). Moreover, the presence of TMPRSS2 was found to be overexpressed in alveolar cells and also was reported to increase the binding between ACE2 and viral S proteins which facilitates viral entrance into host cells (Alnefaie and Albogami 2020). The deregulation of the host immune response, which results in the release of proinflammatory cytokines and chemokines, is one of the characteristics of SARS-CoV-2 infection. In some situations, this immunological reaction can result in multiple organ failures, severe respiratory distress, and even death. The ability of SARS-CoV-2 to inhibit interferon signaling and elude identification by innate immune cells is one of the factors contributing to the virus's ability to circumvent the host immune response and cause severe disease. The viral NSP1 protein has been shown to inhibit host translation and immune responses by binding to the host 40S ribosome and blocking the production of antiviral proteins (Yuan et al. 2021) (Fig. 20.1).

Two proteases that are essential for the replication and maturation of the virus are encoded for by SARS-CoV-2: the main protease (Mpro) and the papain-like protease (PLpro). Structure and function of SARS-CoV-2 proteases Mpro and PLpro are both cysteine proteases that are essential for the maturation of the viral polyproteins that are translated from the viral RNA (Hilgenfeld 2014). Mpro, also known as 3CLpro, cleaves the polyproteins at 11 specific sites, while PLpro cleaves at three specific sites. The cleavage of the polyproteins by these proteases releases the individual proteins necessary for the assembly of new viral particles. Mpro is a homodimeric protease that consists of two identical chains of approximately 33 kDa. The active site is situated in a cleft site between domains I and II in each of the three domains that make up the chain. The peptide link between the glutamine residue and the subsequent residue is broken when Mpro detects a specific sequence in the polyproteins that contains a glutamine residue at the P1 location. The structure of Mpro has been extensively studied, and several inhibitors have been developed that target its active site (Hilgenfeld 2014; Jin et al. 2020). PLpro is a multidomain protease that consists of three domains: an N-terminal ubiquitin-like domain (Ubl), a

protease domain, and a C-terminal domain. The protease domain contains the active site, which recognizes a specific sequence in the polyproteins, containing a leucine residue at the P1 position. PLpro cleaves the peptide bond between the leucine and the next residue. The Ubl domain of PLpro is involved in the recognition of ubiquitin and interferes with the host immune response by cleaving and removing ubiquitin from host proteins which protects the viral protein from proteolysis (Hilgenfeld 2014). Because of their significance in the SARS-CoV-2 life cycle, Mpro and PLpro are desirable targets for the creation of COVID-19 antiviral medications (Bailey-Elkin et al. 2017; Hilgenfeld 2014). The newly synthesized viral proteins in the cytoplasmic environment were inserted in the endoplasmic reticulum (ER) and then transferred intermediate compartment between the endoplasmic reticulum and the Golgi apparatus (ERGIC). Moreover, the N protein duplicated genomes make nucleocapsids in the cytoplasm, which then aggregate inside the ERGIC membrane to create new virions. Via the process of exocytosis, fresh virions are exported from infected cells to the cell membrane in smooth-walled vesicles before being secreted to infect more cells (Boopathi et al. 2020) (Fig. 20.1). The ongoing COVID-19 pandemic has highlighted the importance of molecular biology in the diagnosis, treatment, and prevention of viral infections which brings back to the surface the exploration of new alternatives that are endowed with high antiviral properties.

20.4 *Nigella sativa* Bioactive Compounds

The seeds and aerial sections of *Nigella sativa* contain bioactive substances from several natural sources, according to phytochemical analysis performed in different studies. The investigation of black cumin volatile compounds composition has demonstrated the presence of thymoquinone, thymol, carvacrol, β-cymene, α-phellandrene (Dalli et al. 2021a, b, c; Kabir et al. 2020). Among the discovered phenolic acids and flavonoids, the presence of rutin, nigelflavonoside B, flavone, apigenin, catechin, quercetin, vanillic acid, p-coumaric acid, ferulic acid, and gallic acid was also noted (Dalli et al. 2021a, b, c; Malhotra 2012; Parveen et al. 2020). Additionally, various bioactive alkaloid compounds including nigellimine, nigellimine N-oxide, nigellicine, and magnoflorine were identified and characterized using different spectral techniques such as NMR (Malik and Zaman 1992; Malik et al. 1995; Atta-ur-Rahman 1985). Additionally, saponins were also identified in *Nigella sativa* extracts such as hederagenine; nigelloside; kaempferol 3-O-rutinoside, flaccidoside (Parveen et al. 2020; Taşkin et al. 2005). Crude fiber, minerals including salt, copper, zinc, phosphorus, and calcium, as well as vitamins like thiamine, niacin, and folic acid were discovered to be present in black cumin seeds (Takruri and Dameh 1998). The GC-MS analysis of the black cumin seeds showed that several different kinds of fatty acids were present. While lauric acid, myristic acid, linolenic acid, and eicosadienoic acid were found in smaller levels and ranged in concentrations from 0.5% to 3.4%, linoleic acid, oleic acid, and palmitic acid were the main fatty acids (Fig. 20.2) (Dalli et al. 2021a, b, c; Nickavar et al. 2003).

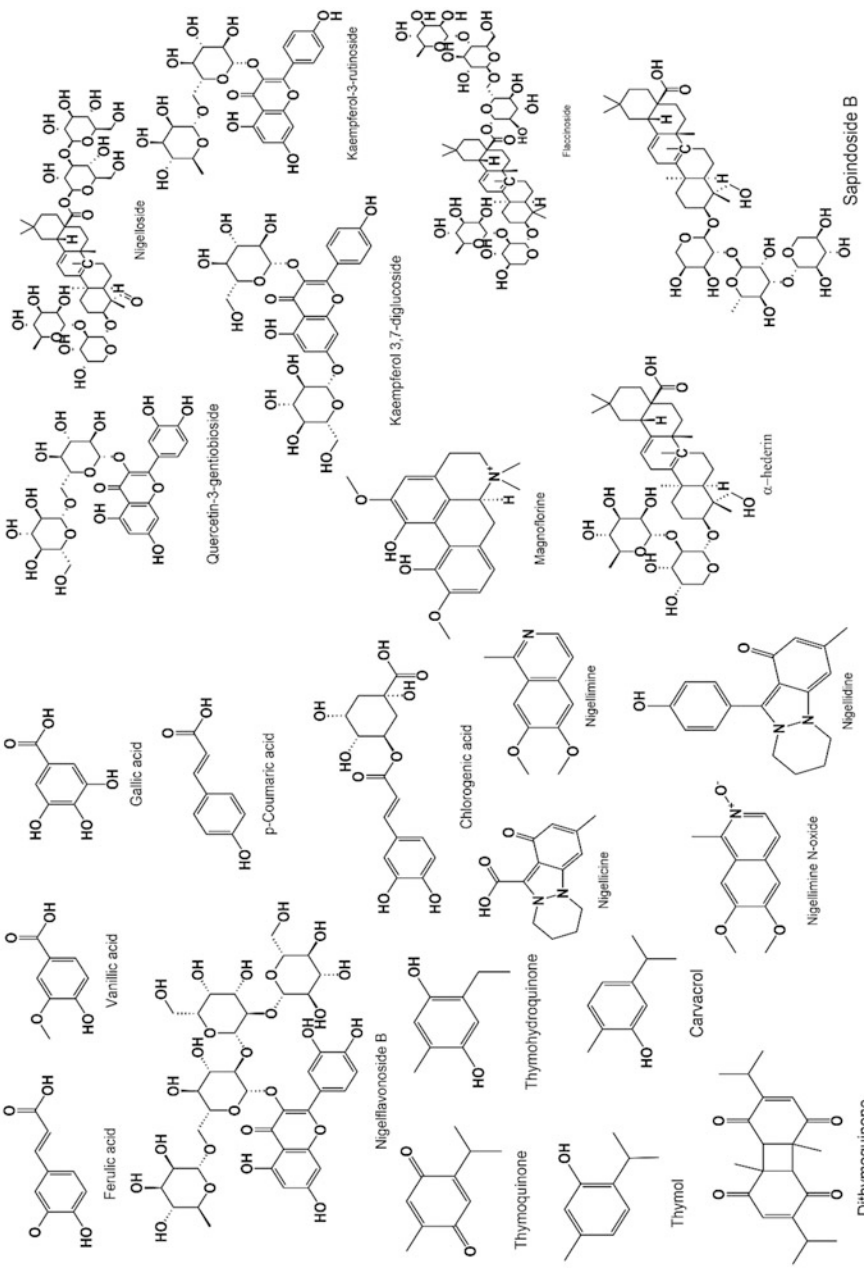

Fig. 20.2 Principal chemical compounds found in *Nigella sativa* L.

20.5 Anti-Inflammatory and Immunomodulatory Activity

In earlier reports, Eo and TQ the major compound identified in NS seeds were reported to reduce inflammation which was comparable to the data collected using indomethacin in the carrageenan model. Actually, when administered intraperitoneally at a dosage of 1.55 mL/Kg, Eo suppressed inflammation by 96.26%. Conversely, at a concentration of 5 mg/mL, TQ exhibited a greater anti-inflammatory effect by suppressing it by 104.88% (Mutabagani and El-Mahdy 1997). Similarly, it was mentioned that TQ was endowed with a great capacity to inhibit cyclooxygenase and 5-lipoxygenase pathways, the same study has demonstrated the ability of NS aqueous extract to attenuate the inflammation and to exert an important analgesic effect which was comparable to aspirin (Al-Ghamdi 2001) (Fig. 20.3). Numerous studies evaluate the NS effect on rats injected with carrageenan which is a chemical compound that can induce inflammation involving phospholipase A2 and by increasing inflammation mediators such as cytokines, serotonin, histamine, and prostaglandins. The findings showed that NSO balm stick application helped reduce the Carrageenan-induced paw edema inflammation in rats which is very obvious in the reduction of oedema. In the same context, the application of a 10% NSO balm stick gave the highest anti-inflammatory effect with an inhibition of 60.64%, also an inhibition of TNF-α, and a reduction of leucocytes (Dwita et al. 2019) (Fig. 20.3). When used in a formaldehyde-induced arthritis model, *N. sativa* has a potent anti-inflammatory effect that is comparable to aspirin which could be attributed to NSO's ability to hinder the generation of eicosanoids (Pise and Padwal 2017). Regarding the cytokines profile, it was observed that IL-1A increased after the application of fresh and stored NS oil. Also, it was observed that stored oil was able to decrease IL-1B, while fresh oil decreased IL-6. Conversely, it was reported that TQ was not able to reduce any cytokine (Bordoni et al. 2019) (Fig. 20.3). Recently it was reported that macrophages increase their phagocytosis ability after exposure to 50 and 100 μg/mL of TQ which is considered a principal mechanism allowing the engulfing of various types of antigens by breaking them down into fragments and presenting these antigen peptides on the cell membrane. This presentation enables the adaptive immune system to identify and target the antigen for the attack. This process is mainly linked to an increase and the expression of the human leukocyte antigen DR isotype and the production of interferon-gamma. These findings suggest that TQ could enhance different properties of macrophages (Alkhattabi et al. 2022). TQ administered orally to carrageenan-mice models over approximately 14 days showed outcomes that were consistent with earlier studies at doses of 50 and 100 mg/Kg. Furthermore, proinflammatory parameters were reduced due to a decrease in MDA and an increase in antioxidant indicators (Hijazy et al. 2022) (Fig. 20.3).

Patients infected with SARS-CoV-2 may experience changes in various health markers. Elevated levels of C-reactive protein, IL-6, serum ferritin, and erythrocyte sedimentation rate may be among these modifications. In addition, the numbers of CD^{4+} and CD^{8+} lymphocytes, monocytes, and platelets may drop, while IL-7, IL-10, TNF-α, and other indicators may be overproduced. Moreover, those who are

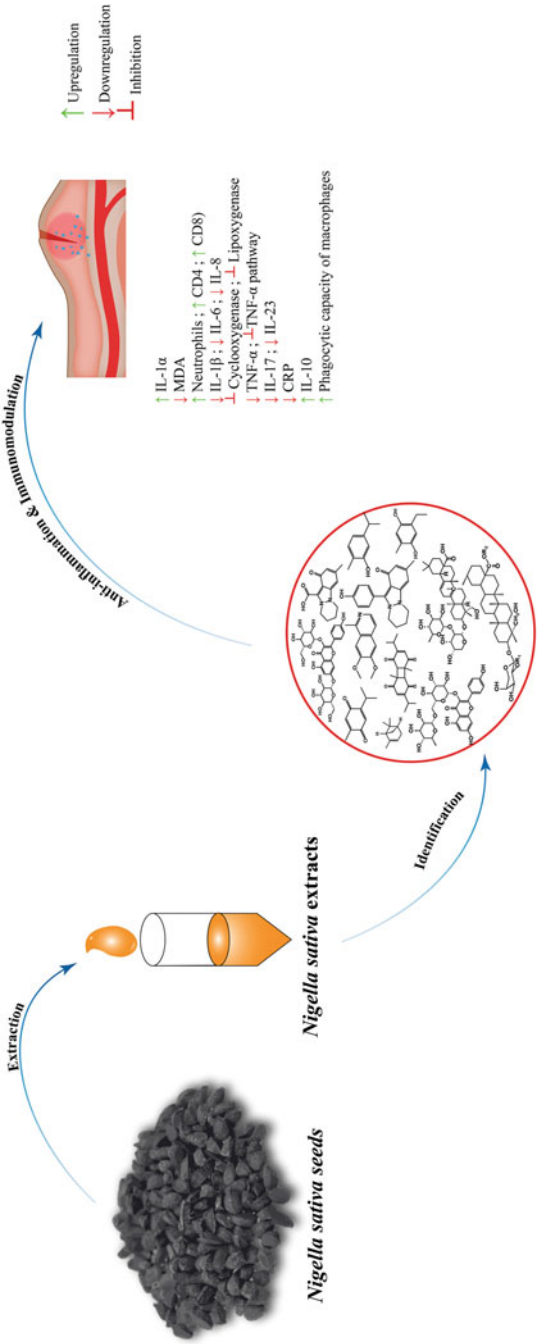

Fig. 20.3 An overview of the anti-inflammatory and immunomodulatory effects of *Nigella sativa* and its derivatives

infected may have an increase in neutrophils (Rahman 2020). Aside from its anti-inflammatory properties, consuming 2 grams of NS seeds daily for 3 months has been shown to enhance antioxidant activity and cell-mediated immunity in patients with β-thalassemia. This is evidenced by an increase in neutrophil count, as well as an increase in CD4 and CD8 counts (Fig. 20.3) (El-Shanshory et al. 2019). Moreover, the detected amount of IL-1B, IL-6, IL-8, and TNF-α dropped in various NS fractions, although IL-10 levels increased in comparison to the control. According to a molecular docking analysis of the major iNOS pathway chemicals, nigelloside C, rosmarinic acid, quercetin O-rhamnosyl-triglucoside, γ-linolenic acid, and nigellidine-4-O-sulfite exhibited the highest binding scores. Also, it was discovered that roasting had a considerable negative impact on the amount of certain bioactive chemicals with high binding affinities (Salem et al. 2023). The *Nigella sativa* EtOH extract therapy reduced the expression of the cytokine's interleukin in the study on lupus mice produced by pristane, according to the findings (IL-17, IL-6, and IL-23). Moreover, a decline in the expression of regulatory T cells that was nearly normal was observed (Hikmah et al. 2022). The supplementation with *Nigella sativa* showed an important decrease of proinflammatory cytokines in mice like TNF-α, CRP, and IL-6 in infected mice by malaria. It was also noted, an elevation of the anti-inflammatory cytokine IL-10, antioxidant makers in mice model (Gholamnezhad et al. 2021; Ojueromi et al. 2022) (Fig. 20.3).

20.6 Antiviral Properties

Many investigations were established to learn more about the effects of this panacea in order to better understand the antiviral activity of *Nigella sativa* and its derivatives. By inhibiting the angiotensin-converting enzyme 2 (ACE2), which stops viral proteins from interacting with host cells, TQ has a significant antiviral potential against COVID-19 in silico (Kadil et al. 2021) (Fig. 20.4). When black cumin seed oil was tested on patients who were hospitalized for having mild COVID-19 symptoms, Koshak et al. 2021 found that the supplementation with 500 mg/Kg reduces the average number of days needed to recover from the viral attack (10.7 days), compared to the control (12.5 days) (Koshak et al. 2021). Four of the nine bioactive compounds from black cumin that were investigated, according to theoretical findings based on molecular docking experiments, displayed high interaction with RNA-dependent RNA polymerase. For instance, compared to Remdesivir, the positive control, α-hederin showed a greater binding affinity (RdRp). The affinities of TQ, nigellicine, and nigellidine were lower than those found in α-hederin but close to those of Remdesivir (Mir et al. 2022) (Fig. 20.4). The inhibition of TMPRSS2 was among the strategies exerted to alleviate SARS-CoV-2 by inhibiting the truncation of S proteins thus blocking its endocytosis. Carvacrol demonstrated high affinity with TMPRSS2 compared to Comstat used as a control while thymol had a weak affinity (Yadav et al. 2021). Kaempferol, nigellidine, and dithymoquinone were some of the compounds with high affinity with COVID-19

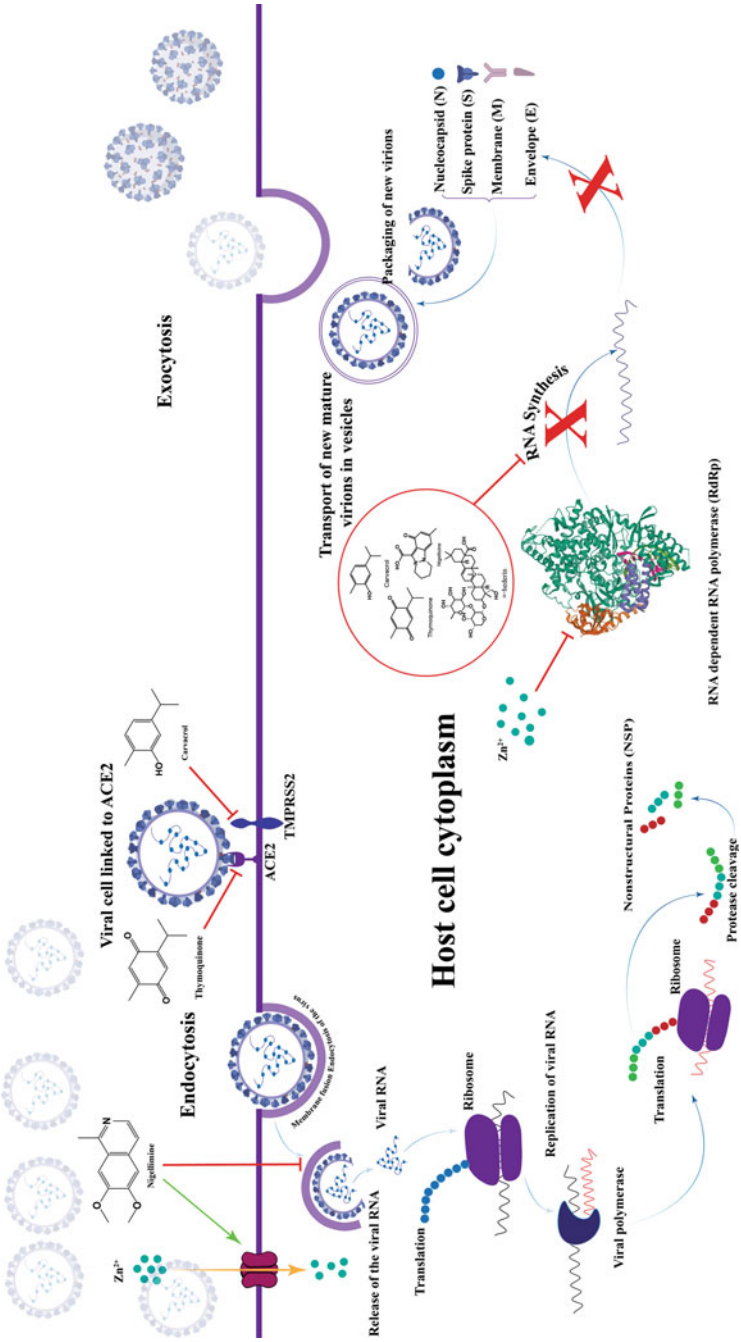

Fig. 20.4 The antiviral properties of *Nigella sativa* bioactive compounds

proteases (Ahmad et al. 2021). Likewise, *Nigella sativa* biocompounds (TQ, DTQ, nigellicine, and others) were discovered to have antiviral capabilities in addition to their antioxidant and anti-inflammatory effects. The various compounds were also found to have a high interaction with different amino acids (Baig and Srinivasan 2022; Sherwani et al. 2022) (Fig. 20.4). Similar to this, it was observed that hydroxychloroquine (HCQ) and black cumin seeds co-administration decreased toxicity and enhanced HCQ's antiviral effect against COVID-19. A number of theories contend that the alkaloid nigellimine can prevent SARS-CoV-2 from entering its host by inhibiting ACE2 (Khan 2021). In addition, it was shown that nigellimine might have similar ionophore actions to encourage zinc uptake and entry into pneumocytes, assisting in the stimulation of the immune system against SARS-CoV-2 (Rahman 2020) (Fig. 20.4). In silico analysis performed by Khan et al. revealed that TQ, a phytochemical derived from NS essential oil, could be a promising candidate to combat SARS-CoV-2 due to its interaction with the main protein active site (C145, H41), which changes the viral protein's catalytic activity which encourages the application of this molecule for clinical applications, which was checked according to the drug likeliness guidelines (Khan et al. 2024). For more accuracy, the in vitro antiviral of the various *NS* derivates was also verified. In fact, the methanolic extract induced inhibition of SARS-CoV-2 main protease by a percentage of 31.5%. Meanwhile, TQ inhibited the main protease by 63.21%. The IC_{50} value recorded was 10.26 μM. The finding reported in this study confirmed the results obtained in silico. Conversely, a low selectivity index supports the anti-SARS-CoV-2 action (Abdallah et al. 2022) (Fig. 20.4). Recently, it was indicated that the supplementation with NS and Vitamine D at different dosages during 14 days to 120 patients diagnosed to be COVID-19 positive. During the supplementation period, it was noted that the three treated groups by NS or by NS+ VitD played an important role in reducing the severity of caught, diarrhea, fatigue, and pharyngitis compared to the control group. Also, supplementation with the mentioned mixture has reduced the clearance time from the viral infection and reduced the severity and progression of the virus (Said et al. 2022). In counterpart, other studies have noted that the supplementation of 262 subjects with whole seeds or the powder of NS showed no significant changes in symptoms and inflammatory markers during 10 days of treatment which suggest that the *Nigella sativa* action requires more time to exert its antiviral effect (Bin Abdulrahman et al. 2022).

20.7 Conclusion and Future Perspectives

Available evidence suggests that due to its antiviral properties, *Nigella sativa* and its derivatives may be beneficial against SARS-CoV-2. These substances have been demonstrated to affect host immunological responses as well as viral entrance, replication, and transcription. To confirm these results and establish the ideal dosage and treatment plan, additional research is required. Future studies should focus on finding the precise active ingredients in *N. sativa* that are responsible for its antiviral

activities and thoroughly examining their mechanisms of action (in vitro, in vivo). *N. sativa* must also undergo clinical trials to determine its efficacy and safety as a potential treatment for SARS-CoV-2 and other viral diseases. Overall, Nigella sativa represents a viable route for the creation of fresh antiviral treatments and calls for additional research.

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