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### A Comprehensive Review of Herbal Recommendations with the Potential to Inhibit COVID-19 Infection

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ARTICLE INFO	ABSTRACT
<p><b>Article type:</b> Review Article</p> <p><b>Article history:</b> Received: 19 Aug 2023 Revised: 08 Oct 2023 Accepted: 28 Oct 2023 Published: 24 Nov 2023</p>	<p><b>Background:</b> The outbreak of Coronavirus Disease 2019 (COVID-19) has originated from Wuhan, China and rapidly spread all over the world. This disease is caused by a coronavirus termed Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) that mainly infects the human respiratory tract. Herbal agents including <i>Atractylodes lancea</i>, <i>Ephedra</i>, <i>Curcumin</i>, and <i>Echinacea purpurea</i> had immunomodulatory effects and antiviral activities on other respiratory viruses including Influenza virus. They strengthen the innate immunity through increasing the phagocytic activity and anti-inflammatory activity. These herbs could be used as a complementary therapy to prevent entry of</p>

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COVID-19 and improve immune system. This review delves into the role and therapeutic compounds of various herbal agents in relation to immunity, their effectiveness in treating other viral respiratory illnesses, and their potential influence on COVID-19 disease.

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## Introduction

The history of medicinal plants is in sync with the history of human civilization. From a long time ago, help was taken from nature for the treatment of diseases, and physicians used plants whose effects were obtained through experience as medicine. Currently, medicinal plants are used to treat and control infectious and non-infectious diseases. The transmission of data about medicinal plants has been gradually transferred from generation to generation and has been integrated with human knowledge about the rationality. The use of medicinal plants has been widespread in almost all cultures. Today, the safety, quality and effectiveness of medicinal plants has long been a challenging and key issue in industrialized and developed countries. However, knowing the sources of medicinal plants and their effects is one of the most important needs of the medical community (1).

According to the report of the World Health Organization (WHO), 80% of developing countries need medicinal plants for health and treatment needs. Many researches have been done regarding the effect of medicinal plants on bacterial, fungal and viral infections. There are many herbs that have been proven effective against viruses and infections (Table 1) (2). Antimicrobial compounds in medicinal plants may inhibit the growth of bacteria, viruses, fungi, and protozoa by different mechanisms than existing antimicrobials and may also have significant clinical value in the treatment of resistant microbial strains. The utilization of compounds derived from medicinal plants has attracted a lot of attention owing to less side effects and no microbial resistance. The antibacterial impacts of

medicinal plants are related to their phenolic compounds, which can stop the growth of bacteria by binding to bacterial proteins or by reducing pH. Infections are often associated with oxidative stress, and herbal medicines can potentially improve infections by leveraging their antioxidant effects (3). According to the reports, extracts of medicinal plants have an inhibitory effect on the proliferation of viruses such as herpes simplex virus type 2 (HSV-2), human immunodeficiency virus (HIV), hepatitis B virus and infections related to smallpox virus and severe acute respiratory syndrome virus (SARS) (4). Development and research on medicinal plants can lead research pharmacists to design new drugs. These plants are a valuable source of bioactive substances, antioxidants, flavonoids and phenolic substances and have good impacts on health (5).

Several patients were infected with new coronavirus (SARS-CoV-2) since December 2019 (6). WHO first declared a public health emergency on January 30, 2020, and more than 57.8 million cases of COVID-19 were reported, worldwide (7).

SARS-CoV-2 enters host cells by binding spike glycoprotein mainly to the human cell surface receptor- Angiotensin-converting enzyme 2 (ACE2) (8). Some manifestations of SARS-CoV-2, such as pulmonary inflammation and coagulation, are partially due to the increased effects of Angiotensin II (8). These extra pulmonary manifestations may occur owing to the widespread release and proliferation of SARS-CoV-2 caused by direct viral poisoning or immune pathological consequences of infection, such as endothelial cell damage, thrombosis-associated inflammation, and impaired immune response (9). It appears that all ages of the population are susceptible to SARS-CoV-2 infection, and the

average age of onset of this infection is approximately 50 years (10). Symptoms of COVID-19 include dyspnea, fever, dry cough, vomiting, anorexia, and diarrhea (11).

Medicinal plants against COVID-19 can be a good candidate not only for curing COVID-19 infection, but also preventing this disease. Many herbal products have immunomodulatory and antiviral properties; hence, their discovery can be a turning point in the prevention and control of COVID-19. Due to frequent epidemic waves, there is a requirement to develop specific drugs for SARS-CoV-2 infection. The findings show the suitability of traditional medicine as a treatment for COVID-19 (12). The present study sought to discuss the effects of several plants on COVID-19 and other respiratory diseases.

### *Ocimum sanctum*

*Ocimum sanctum* is an annual and aromatic plant that grows annually or perennially in some regions. This plant is native to India and the Indian subcontinent. It is also found in Southeast Asia, North Africa, and the Oceanian Islands. In traditional medicine, it relieves pneumonia, is an analgesic and allergy drug, purifies the blood, is a diuretic, reduces blood sugar and lipids, and has anti-infective properties (13). This plant is an immunomodulator and strengthens the body against infections. *O. sanctum* (Tulsi), as a sacred plant, is used for its medicinal properties according to Ayurvedic scriptures. These multiple therapeutic effects include adaptogenic, immunomodulatory, antimicrobial, cardio protective, and anti-inflammatory effects. Its leaves are useful for treating rheumatism, bronchitis, and fever. The plant is also considered an elixir of life owing to its healing power. It boosts the immune response by enhancing cellular and humoral immunity. Eugenol and Ursolic acid are its main compounds. Ursolic acid is a five-ring triterpenoid that has antiviral, anti-inflammatory, anti-tumor, antimicrobial, anti-hyperlipidemic,

anti-ulcer, hepatoprotective, antifungal, and anti-malarial activities (14). It has been reported that dihydrodieuginol B and tulsinol A, B, C, D, E, F, G of *O. sanctum* can be used as potential inhibitors for papain-like protease (PLpro) and the main protease of the SARS virus. Since the majority of the world's population is in quarantine and under life-threatening, researchers need to find an effective drug more quickly., further studies are needed to search for drugs to target viral systems without many side effects for the human population. Ayurveda formulation can play a crucial role in creating safe and non-toxic therapies. *O. sanctum* is expected to significantly inhibit SARS-CoV-2 main protease (Mpro or Clpro3). Using the molecular docking and molecular dynamics simulation studies, Withanoside V, Somniferin, Tinocordisid, Withanine, Ursolic acid, and Isorientin 4'-O-glucoside 2"-O-hydroxybenzoate in this plant inhibit the SARS-CoV-2 Mpro activity (15). The immunotherapy potential of the aqueous extract of *O. sanctum* leaves was examined in subclinical bovine mastitis. The somatic cell count, total bacterial count (TBC), differential leukocyte counting of milk, phagocytic activity and index, and leukocyte lysosomal enzymes, such as myeloperoxidase and acid phosphatase content, were evaluated after the intra-breast infusion of the aqueous extract of its leaves. The results indicated that the aqueous extract of the *O. sanctum* treatment decreased TBC and increased the number of neutrophils and lymphocytes by increasing the phagocytic activity and index. Similarly, the content of lysosomal enzymes in the Polymorphonuclear leukocytes (PMNs) of milk significantly increased in animals treated with the extract. According to such findings, the crude aqueous extract of *O. sanctum* (leaf) has antibacterial and immunomodulatory properties, too (16). The threat of the flu is prevalent as a destructive and threatening viral infection, worldwide. The ability of the virus to undergo genetic modification causes unpredictable changes

in its antigens, and consequently, the immune response leads to recurrent epidemics of febrile respiratory diseases every 1 to 3 years.

*O. sanctum* has been found to have adaptogenic, anti-inflammatory, antibacterial, anti plasmodial, immunomodulatory, and antioxidant properties. It increases levels of Interferon gamma (IFN $\gamma$ ) and interleukin-4, along with T-helper cells (Th cell) and natural killer cells (NK cells) (17). Ursolic acid is a major component of *O. sanctum* (18) and has activities, such as protection against lipid peroxidation and antiviral activity. The United States Food and Drug Administration (FDA) has approved two classes of drugs to treat influenza virus infection: M2 ion channel blockers and Neuraminidase inhibitors (NAIs). Oseltamivir is a prodrug of NAIs approved by the United States FDA. *O. sanctum* extract is complexed with PC to facilitate drug solubility. Other medicinal extracts like PC-complexed curcumin have better absorption, increased bioavailability, and improved pharmacokinetics (19).

#### *Phyllanthus emblica*

*Phyllanthus emblica* Linn, commonly known as Indian gooseberry (*Phyllanthus emblica*), is a member of the *Euphorbiaceae* family, is widely grown in the tropics of China, India, Indonesia, and the Malay Peninsula and is used in many traditional medicine systems, such as Chinese medicine and Indian Ayurveda. It is an important herbal medicine used in Greek (Graceo-Arabic) and Ayurvedic medical systems. This plant is used both as a medicine and as nutrition. *P. emblica* is highly nutritious and can be a major food source of vitamin C, amino acids, and minerals. This plant also contains phenolic compounds, tannins, phyllembelic acid, phyllembelin, rutin, curcuminoids, and emblico. The plant is used for medicinal purposes, particularly its fruit, which is used as potent rasiana in Ayurveda, and in traditional medicine to treat diarrhea, jaundice, and inflammation. It has effective anti-inflammatory,

neutropic, antioxidant, anti-cancer, adaptogenic, anti-diabetic, antimicrobial, antiviral, and immunomodulatory effects (20, 21). Phytochemical research on *P. emblica* leads to separation of two new flavonoids, kaempferol 3-O- $\alpha$ -L-(6''-methyl)-rhamnopyranoside and kaempferol-3-O- $\alpha$ -L-(6'-ethyl)-rhamnopyranoside. Their structure was determined based on extensive spectroscopic studies, including 2D NMR experiments (20). Regarding the effect of this plant on COVID-19, organic emblica herbal tea cannot significantly affect RT-PCR results or the degree of lung involvement. However, it improves the clinical symptom severity and CRP levels and may shorten the recovery time of symptoms and it causes the recovery of patients suffering from the disease of COVID-19 (22). Among sixty-six compounds of this plant, chlorogenic acid, quercetin, and Myristicin were most effective in indicating the highest binding energy against selected SARS-CoV-2 protein targets. The study of the network pharmacological analysis of the roles of these compounds in modulating the immune response, inflammatory cascade, and cytokine storm through pathways confirmed different signaling pathways. High-performance liquid chromatography (HPLC) on *P. amarus* and *P. urinaria* indicated the presence of filantin, hypofilantin, and polar compounds, such as Gallic acid and Ellagic acid. Corilagin and Geraniin significantly inhibited the phagocytic activity of human phagocytes (23).

#### *Echinacea purpurea*

*Echinacea purpurea* is an important medicinal plant that is native to North America and is widely used in the pharmaceutical, cosmetic, and health industries. Although, it is not native to Iran it has been considered by researchers in agriculture and horticulture and has been recently cultivated in experimental and commercial farms Iran. This herbaceous plant is perennial, belongs to the family *Asteraceae*, and has short rhizomes, and

straight and more or less branched dark brown to matte white roots. Due to the presence of anthocyanin in this plant, the stems are light green, blue or red. Evidence indicates that *Echinacea* supplementation may reduce the duration and severity of acute respiratory infections. No study was conducted on the use of *Echinacea* in the prevention or treatment of conditions similar to COVID-19, and few side effects have been reported, demonstrating that this herbal treatment is reasonably safe. As *Echinacea* may increase the immune system function, there is a concern that it can worsen an over-activation of the immune system in the cytokine storm. However, clinical tests reveal that *Echinacea* reduces the level of immune molecules involved in the cytokine storm (24). In COVID-19, cytokine storms can lead to acute respiratory distress syndrome (ARDS) with a mortality rate of 40% (25). Storm-related cytokines include pro-inflammatory interleukins (IL)-6, IL-8, IL-1B, IL-12, and Tumor Necrosis Factor-alpha (TNF- $\alpha$ ), while other cytokines, including IL-10, are anti-inflammatory. It plays a role in reducing the activity of suppressing agents of the immune system. who need intensive care admission and have higher levels of cytokines TNF $\alpha$  and IL-6. Disruption of this plant can cause a considerable stimulation of the immune system that in turn can cause a cytokine storm. Several studies have found that *Echinacea* stimulates innate immune cells. There are several modes by which the extracts induce these effects by boosting the immunity of cells, granulocyte migration, the ability of macrophage phagocytosis, and NK cell cytotoxicity, as well as by increasing cytokine production (26). Several other studies have demonstrated that changes in mRNA and protein levels of cytokine genes in humans could treat blood samples, dendritic cells, and human monocytes cultured with *E. purpurea*. This plant also stimulates adaptive and acquired immune systems by both humoral and cellular immunity through the stimulation of CD4s (27). The extract derived from the aerial elements of *E. purpurea*

have significant antiviral use in contrast to various viruses. Although numerous studies have revealed that *E. purpurea* extract has antiviral activity against numerous viruses, there is no confirmation of its mechanism of action. Viral infections may predispose the airways to secondary bacterial infections that can lead to the adverse progression of predominantly self-limiting diseases. Complex respiratory infections include pneumonia, bronchitis, sinusitis, acute otitis media, and sepsis that cause high morbidity and mortality rates. Some pathogenic consequences of viral infections, such as expression of bacterial adhesion receptors and impaired physical barrier integrity due to inflammation, may create favorable conditions for concomitant infections. Influenza A virus (H3N2) is a major pathogen causing secondary bacterial infections and inflammation that lead to pneumonia. Furthermore, the herbal medicine *E. purpurea* is widely used to prevent and treat viral respiratory infections. Recent clinical data indicate that it may also prevent complications of secondary infection (28). According to research in a rat model, this plant appears to change the course of respiratory infections, including the flu. Rats infected with A/WSN flu under the treatment with the polysaccharide extract of *E. purpurea* lost less weight than untreated rats did; however, they had similar pulmonary viral titers. Rats treated with *Echinacea* had lower systemic and pulmonary KC and IL-10 levels, and lower systemic IFN- $\gamma$  levels due to influenza infection, revealing that *E. purpurea* changes the clinical course of influenza infection in rats through the modulation of cytokines rather than direct antiviral activity (29).

### *Curcumin*

*Curcuma longa* (turmeric), a natural polyphenolic compound extracted from the roots of the *C. longa* rhizome (*Zingiberaceae* family), has various therapeutic properties, including antioxidant, antimicrobial, anti-proliferative, anti-inflammatory, neuroprotective, and

cardioprotective properties. *Curcumin*, the yellow pigment of turmeric, has been widely used in our traditional Indian herbal medicine to treat many diseases related to infection and inflammation for decades. The habitats of this plant are India and South Asia (30). *Curcumin* has been reported to have antiviral activity against different viruses, such as HIV, HSV-2, HPV, Influenza virus, Zika virus, Hepatitis virus, and Adenovirus. Previous studies conducted by researchers on the anti-cancer effect of *curcumin* have found that it prevents the proliferation of tumor cells, metastatic invasion and the spread of cancer cells (31). Human respiratory syncytial virus (RSV) causes respiratory tract infections and is a leading cause of death in children under 5 years of age (32). The use of *curcumin* against RSV infections prevents the RSV proliferation and germination of human nasal epithelial cells and increases the epithelial barrier function, while it no longer affects the RSV in lung cells. *Curcumin* is an effective antiviral agent against many enveloping viruses, including respiratory viruses, such as influenza A and respiratory syncytial viruses. *Curcumin* inhibits the binding of the hemagglutinin, influenza A virus, a homotrimer membrane glycoprotein, to host cell receptors (33). Turmeric applies antiviral activity against many types of viruses, including SARS-CoV-2 by multiple mechanisms, such as direct interaction with viral membrane proteins, impaired viral envelope, inhibition of viral proteases, and induction of antiviral responses of the second host. This plant protects against lethal pneumonia and ARDS by targeting NF- $\kappa$ B, inflammation, IL-6 trans-signaling, and HMGB1 pathways. *Curcumin* is safe in both healthy and sick people and is well tolerated. Consequently, the accumulated evidence indicates that it may be a potential prophylactic treatment for COVID-19 in clinical and public health settings (34). The medicinal properties of turmeric are attributed primarily to the three main curcuminoids, namely *curcumin*, Dimethoxycurcumin, and Bisdemethoxycurcumin. *Curcumin*

(diferuloylmethane) is the most abundant bioactive curcumin in turmeric. Furthermore, animal model findings indicate that curcumin supplement interferes with several respiratory diseases, particularly ARDS, acute lung injury, pneumonia, pulmonary fibrosis, and sepsis by modulating inflammation and oxidative stress (35).

#### *Astragalus membranaceus* (*Agastache rugosa*)

*Astragalus membranaceus* commonly known as Mongolian milkvetch in English and Common Name of this plant is (Huang Qi). *A. membranaceus* belong to Leguminosae family, derived from dried root of *A. membranaceus* Bge (36). *A. membranaceus* widely distributed in China, Korea, Mongolia and Russia. The height of the plant is 50–150 cm, include a long and straight cylindrical root, branched and erect stems in upper parts or elliptical leaves. *A. membranaceus* is well-known for skin reinforcing, vital-energy tonifying, abscess-draining, diuretic and tissue generative actions (37). *A. membranaceus* widely used to prevent some acute chemotherapy side effects and liver fibrosis in East Asia. As an herbal medicine, protect neurons and prevent inflammation is one of its applications, therefore, it is potent for diseases such as Parkinson's disease and Alzheimer's disease. Other therapeutic activities including anti-viral anti-cancer, and immunomodulatory effects. This medicinal plant has effects such as antiviral activity and regulating the body's immune function, which regulates the mucus secretion of the respiratory system and strengthens the immune function of the respiratory system (38). This plant works by suppressing pro-inflammatory cytokines such as IL-6 and TNF-alpha, which have been identified in the cytokine storm of ARDS as one of the main causes of death caused by COVID-19 (39).

#### *Glycyrrhiza*

*Glycyrrhiza glabra* is derived from ancient Greek term glykos, meaning sweet, and rhiza, meaning

root. The common name of *G. glabra* is mulaithi in north India and licorice and sweet wood. *G. glabra* was native to northern Africa, Eurasia and western Asia (40) The Pharmacological effects of this plant including :

1) Effect on memory and learning: the results of studies showed the aqueous extract of root *G. glabra* improve learning and memory in a certain dose (41).

2) Anti-depressant effect: p-chlorophenylalanine as an inhibitor of serotonin synthesis. In this study they concluded that probably the aqueous extract of this plant exerts its anti-depressant properties by increasing epinephrine and norepinephrine (42).

3) Antimicrobial effects: the methanolic extract of *G. glabra* showed antimicrobial activity except *Pseudomonas aeruginosa*.

4) Anticancer effect: the results showed the inhibition proliferation of HT-29 cell line (43).

Other Pharmacological effects including: 5) Antioxidant effect, 6) Effect on respiratory system, 7) Protective effects, 8) Anti-inflammatory effect, 9) Effect in gastric duodenal ulcers, and 10) Effect on smooth muscles.

It has also been shown that *G. glabra* has the ability to inhibit virus absorption and penetration, and in addition, it can interfere with the proliferation and/or cytopathogenic effect of many respiratory viruses. It is very important to prevent the development of ARDS in COVID-19 patients, and anti-inflammatory and antiviral intervention is needed for this problem. *G. glabra* has anti-viral and anti-inflammatory effects and also has the ability to stimulate the autophagy mechanism in cells, which is very important in COVID-19 patients (44). According to published research, Glycyrrhiza has the potential to bind to ACE2 and also has cytokine modulating activity. In addition, it can prevent intracellular ROS accumulation caused by viral infection (44). Glycyrrhiza has an inhibitory effect on the excessive production of airway mucus by inhibiting the transcription of the MUC5AC gene. Therefore, it can reduce the lack

of oxygen and improve clinical symptoms in COVID-19 patients (44).

### *Rheum palmatum*

*Rheum palmatum* is Chinese rhubarb and belongs to family Polygonaceae. The rhizomes and roots of the *R. palmatum* in late autumn or in winter, when the leaves and stems were withered, have been collect (45). Anthraquinones and tannins as the main materials in this plant exhibit a variety of pharmacological properties such as laxative, hepatoprotective antibacterial, antiviral, antimetastatic and antidiabetic effects (46). Uçar et al., examined the effect of *R. palmatum* on COVID-19 and published that *R. palmatum* inhibit the attachment of virus to cell, entry into cell, formation syncytial, reduce inflammation of the body's airways, stimulation of immune system and increase interferons secretion. It is predicted that *R. palmatum* would be useful for treatment in COVID-19 patient (47).

### *Isatis tinctoria*

The commonly name of *Isatis tinctoria* is known as woad and belongs to *Brassicaceae* family. *I. tinctoria* is a short-lived perennial or herbaceous biennial species, less or more hairless to hairy, with an erect stem and greyish. The height is up to 120 cm, branched above and simple below. The root is cylindrical, externally greyish-yellow, slightly tortuous, lenticellate transversally, wrinkled longitudinally (48). Biological studies based on ethnopharmacological uses of this plant demonstrated medicinal properties effective including anti-inflammatory, antiviral, anti-tumour (49). Also, other biological activities including antimicrobial, analgesic, and antioxidant. In connection with the effect of this plant on the COVID-19, Emine Akalın discussed *Isatis tinctoria* has antiviral effect in two ways:

1) Inhibition of viral replication

2) Inhibit adsorption the *Forsythia suspensa* of virus to cell surfaces (50).

#### *Atractylodes macrocephala*

*Atractylodes macrocephala* is named as “Baizhu” in China, “Baekchul” in Korea and “Byakujutsu” in Japan, a herbal drug that commonly used as a food and medicinal herb for thousand year (51). *A. macrocephala* is also known as Wuzhu, Yuzhu, Dongbaizhu, Zhongzhu, and Zhezhu among others. *A. macrocephala* can grow rapidly at 22–28 °C, and favors conditions during the growing season (52). pharmacological activities of *Atractylodes macrocephala* include improving gastrointestinal function, anti-inflammatory activity, anti-tumor activity, anti-aging activity, anti-osteoporotic activity anti-oxidative activity, antibacterial activity, protection against Alzheimer's disease, anti-obesity activity and energy-enhancing metabolism. This plant is one of the ingredients of Qingfei Paidu decoction, which is a traditional Chinese medicine treatment for the disease of COVID-19 (53).

#### *Bupleurum chinense*

Because of the secondary metabolite in its roots have many pharmacological effects, so the dried roots of this plant in traditional Chinese medicine are called *Bupleuri Radix*. The Common name of this plant is "bee chia hu" in China; "saiko" in Japan and "si ho" in Korea. *Bupleurum chinense* is an herb that grows usually in China, but cultivated in other areas. The main active component of this plant is Saikosaponin that has many pharmacological activities, including analgesic, anti-inflammatory, anti-depressant, anti-bacterial, liver protection, and anti-cancer. *B. chinense* has other effects such as dispersing fever, soothing the liver and relieving depression. Qiao Zhang et al discussed the relationship between Gut Microbiota and COVID-19 (GM). so GM regulation help to treatment of COVID-19 patients and *B. chinense*

have a certain role on GM regulation and immunity system. *B. chinense* polysaccharides have notable pharmacological efficacy (54). Polysaccharides properties including their structural and physicochemical features, such as types of glycosidic bond, monosaccharide composition, spatial conformation and molecular weight. Moderate structural modification, such as acetylation, carboxymethylation, sulfation and phosphorylation could produce variants of polysaccharides with efficient pharmacological properties protect against oxidative damage and ROS (55).

#### *Azadirachta indica (neem)*

*Azadirachta indica* belongs to the order Rutales, genus Meliaceae, subfamily Melioideae, genus *Azadirachta*, species *Indica* which is used as an herbal remedy for many diseases in countries such as China, Greece, and India (56). *A. indica* tree is also known by various names, including Indian lilac, *Azadirachta*, Margosa, Neeb, Tamar, Kohomba, Dogonyaro, nimb, Vaypum, and Bevu (57). The therapeutic effects of this plant are due to the presence of many compounds such as Nimbin, nimbidol, nimbidin, sodium nimbinat, nimbolinin, salinnin, and quercetin. The leaves contain Nimbin, nimbandiol, nimbanene, nimbolide, and ascorbic acid. Ethanol extracted from the plant leaves has antibacterial effects against *Staphylococcus aureus* and MRSA (58). Animal studies have shown that this plant exerts various anti-cancer effects on different molecular pathways, including p53, NF- $\kappa$ B, P13K /Akt Bcl-2, and VEGF (59). *A. indica* treats many diseases and disorders, including nausea, vomiting, cough, fatigue, intestinal worms, gonorrhea, urinary tract infections, and leprosy. In vitro and in vivo studies have shown that this plant has therapeutic effects against the Newcastle virus (NDV). It also has anti-cancer, immune-regulating, wound-healing, antifungal, antimalarial, antiviral, antibacterial effects, antioxidant, anti-diabetic, and anti-inflammatory (59). Studies have shown that *A.*



*indica* reduces pain and inflammation. This plant eliminates free radicals and prevents cell damage. It also significantly reduces pro-inflammatory cytokines and regulates CD + 4 and CD8 + levels (60). Sound therapeutic effects have been reported against COVID-19. The compounds extracted from this plant inactivate viral proteases (61). This plant's anti-inflammatory and antiviral properties have made it a good target for preventing COVID-19. Capsules prepared with the compounds of this plant can be used at a dose of 50 mg twice a day. These capsules are used to avoid infection in people who have been in contact with a sick person or have a high risk of developing the disease (62).

#### *Eurycoma longifolia*

*Eurycoma longifolia* is a plant native to Southeast Asia and belongs to the Simaroubaceae family. It is also known as "Tongkat Ali" in Malaysia, "Pasakbumi" in Indonesia, "Cay ba Binh" in Vietnam, and "Ian-don" in Thailand. It is used alone or with other plants to prevent and treat many diseases (63). Numerous chemical compounds have been extracted from this plant, especially from its roots, including quinissoin, tannin, eurycomanone, eurycomanol, phenolic, and triterpenes. It can be named (63). The compounds extracted from the leaves and stems of this plant have an antibacterial effect against a wide range of bacteria (except *Escherichia coli* and *Salmonella typhi*). An antibacterial effect has not been seen in the compounds extracted from the root of this plant. This plant has sexual enhancing effects for men, anti-aging, anti-cancer, and improving fertility (64). It is also used to increase energy, increase flexibility, and treat diabetes, anxiety, chills, fever, leukemia, and syphilis. Consumption of this plant can increase sperm concentration and motility and improve fertility in men (65). Studies have also shown that the leaves of this plant also have therapeutic effects. This plant increases the body's immune system against pathogens and can be used as a suitable treatment for COVID-19 (66).

#### *Gymnanthemum amygdalinum*

*Gymnanthemum amygdalinum* belongs to the Asteraceae family and was formerly called "Vernonia amygdalina Delile". There is of the United States, tropical regions of Africa, and Asia. In India, the genus *Gymnanthemum* has three species (*G. extensum*, *G. pectiniforme*, *G. amygdalinum*). The plant has anti-fever, antimalarial, anti-worm, and anti-constipation effects. Studies have shown that the compounds extracted from the plant have antimicrobial, anti-parasitic, anti-diabetic, and antioxidant effects. Among the extracted compounds, we can name Sesquiterpene lactone, Saponin, Polyphenol, and Flavonoid. Antipyretic, anti-diarrheal, and headache treatments have also been reported for this plant. This plant has shown promising effects on increasing the number of CD4 + and improving the immune status (67). There is insufficient evidence on the efficacy of *G. amygdalinum* against COVID-19, despite various studies demonstrating antiviral, anti-inflammatory, and immunomodulatory effects of this plant.

#### *Isatis indigotica*

*Isatis indigotica* is a plant belonging to the genus *Isatis*. This plant contains alkaloids, Organic acids, flavonoids, nucleosides, amino acids, and steroids, and the use of leaves and roots. It is common in traditional Chinese medicine. Some chemical compounds in this plant, such as indigotin, Indirubin, 2-hydroxy-3-butenyl thiocyanate, Epigotrin, organic acids, and many amino acids are effective in treating the flu. Anti-HIV compounds are also found in the leaves of this plant (68). This plant is also called Chinese woad and has Antiviral activity, especially against SARS-CoV-2 (69). The root of this plant contains 20 types of poly Phenol (including Indigo, Indirubin, Indican, Sinigrin, quercetin, naringenin, aloe-emodin, Daidzein,

Emodin, and Chrysophanol). The compounds extracted from the root of this plant have antiviral activity against viruses such as rabies, influenza, and human acquired immunodeficiency virus, as well as some others. These compounds have antiviral activity against the poliovirus, Vaccinia, HSV1, and HSV2. Compounds such as Indigo, aloe-emodin, Sinigrin, and hesperetin have inhibitory activity against the significant proteases of the SARS CoV-1. This plant's four chemical compounds (Indigo, Daidzein, hesperetin, and Sinigrin) have inhibitory effects against SARS CoV-2 proteases. Sinigrin and hesperetin bind more than lopinavir to viral proteases (70). Seven phenolic compounds (aloe-emodin, hesperetin, quercetin, naringenin, Daidzein, Emodin, and chrysophanol) have inhibitory activity against 3CLpro in SARS CoV-2. Only two combinations of They have dose-dependent inhibitory activity, namely aloe-emodin and hesperetin. Studies also show Quercetin has been shown to prevent SARS-CoV-2 from entering cells in the body. Among all the mentioned compounds, hesperetin and Sinigrin have an excellent effect on inhibiting SARS-CoV-2,3CLprp (71).

#### *Malva sylvestris*

*Malva sylvestris*, a member of the *Malvaceae* family, is a biennial, rarely annual, herbaceous plant that originates in southern Europe and Asia but is found as a weed in most parts of the world and in soils rich in needs food rich in humus, loam, and sand. Phenols and fatty acids are the main constituents of this plant, and phytochemical studies of this plant. Flavonols, folic acid, and flavonoids have medicinal and biological activities. Therapeutic applications of this plant include cough treatment, inflammatory diseases of mucous membranes, nonspecific dermatitis, stomach pain, and sore throat, antibacterial, anti-inflammatory, and potent antioxidant and anti-cancer. It also has little nerve-strengthening properties and is a popular herb for treating and aiding respiratory

diseases. It has healing properties that can help with upper respiratory tract mucosal problems. This plant contains mucous material that covers the inflamed tissue with a protective layer (71). Research has shown that most polysaccharide-derived carbohydrates are found in *M. sylvestris*, particularly pectins, exhibit antioxidant and anti-diabetic properties and even regulate blood insulin. Its leaves are rich in flavonoids, which justifies their healing properties in traditional medicine. Due to its richness in essential *M. sylvestris* is rich in essential fatty acids such as Omega-3 and omega-6 and can play a role in preventing various diseases, including coronary heart disease, diabetes, and cancer. Also, a substance called sulfite oxidase in the leaves of *M. sylvestris* is involved in the oxidative breakdown of sulfur-containing amino acids, and its absence may lead to death. Stem extracts of this plant have limited bacteriostatic effects against the growth of plankton and *Staphylococcus aureus*. Inflorescences and leaf extracts of this plant are involved in treating gastric ulcers and gastric cancer due to their anti-*Helicobacter pylori* effects (71). The oil of this plant has antibacterial activity, especially against gram-positive bacteria, as the resulting compound is rich in fatty acids, mainly unsaturated fatty acid linolenic acid n-3PUFA, and possibly the target of n-3 PUFA can be cell membrane because fatty acids can penetrate the bacterial cell membrane and disrupt the normal function of the cell membrane, leading to bacterial death. In general, this plant is used by traditional healers for the prevention and treatment of respiratory diseases such as flu, colds, and even COVID-19, and it has been found that its consumption strengthens the innate immunity (72).

#### *Mentha piperita*

Peppermint, scientifically known as *Mentha piperita*, is a perennial, hairless, strong-smelling plant of the *Lamiaceae* family, also known as "Mentha balsamea wild", a combination of blue mint and mint. This plant, native to Europe and the

Middle East, is now widespread in many parts of the world and is cultivated in temperate regions of Europe, Asia, the United States, India, and the Mediterranean countries (73). Traditionally, mint infusion, its leaves, or essential oils can be used as an antispasmodic in the gastrointestinal tract and anticonvulsant and expectorant. This plant contains menthol (40.7%), menthone (23.4%), menthyl acetate, 1.8 cineole, limonene, beta-pinene, and beta-caryophyllin. It also contains phenolic compounds that are effective in the food industry because they delay the oxidative breakdown of lipids. The leaves of this plant are used to treat colds, nausea, vomiting, diarrhea, constipation, and inflammation of the mouth, throat, and liver. It also has antioxidant, antimicrobial, antiviral, anti-inflammatory, and anti-cancer properties. In traditional Islamic medicine, antiviral properties and their effects on the respiratory system have been used as adjunctive therapy for patients with COVID-19 and had a statistically significant positive effect on SpO<sub>2</sub> in COVID-19 patients (74). Evidence shows that this plant reduces pulmonary inflammation due to its antioxidant properties by directly inhibiting hydroxyl and other radicals in the upper and lower respiratory tissues and can also reduce tissue damage, immune responses, and complications. The presence of molecular compounds in this plant could affect the expression of the Nrf2-regulated antioxidant gene in mucosal cells and help their innate defense against factors that cause inflammation through oxidant-related pathways. One of the fastest responses of these genes, HO-1, is more pronounced in the nasal tissues of people treated with the oil of this plant. With a significant reduction in aspartate transaminase, alanine transaminase, alkaline phosphatase, uric acid, urea, creatinine, bilirubin, and malondialdehyde superoxide, it has a protective effect against hepatotoxicity caused by carbon tetrachloride (CCl<sub>4</sub>) (75).

### *Nigella sativa*

*Nigella sativa*, which belongs to the *Ranunculaceae* family, grows worldwide, especially in the eastern Mediterranean countries. Its seeds are used as spices and food flavors in some regions, including Germany, France, and Asia (76). This plant is traditionally used to treat asthma, cough, flu, eczema, anti-diarrhea, and appetite stimulants (77) and also has very beneficial effects in the treatment of people with HIV and HCV (78). In Greece, this plant is used to cure oligomenorrhea, induce menstruation and improve fertility. Studies in vitro and in vivo show that this plant has positive effects on diabetes, high blood pressure, and high cholesterol, all associated with cardiovascular disease, and toxic, anti-apoptotic, and anti-metastatic effects against various types of cancer (79). This plant contains different chemical compounds, including phenolic compounds, terpenes, flavonoids, coumarin, alkaloid, fumaric, fatty acids, saponin, and volatile oils. *Nigella sativa* also has antifungal activity (80). Numerous studies have shown the effect of this plant on the respiratory system, lung parenchyma, energy stimuli, fatigue, and lethargy. Black seed is used to treat respiratory disorders such as asthma and bronchial obstruction. This plant prevents the narrowing of the airways by preventing histamine secretion. This plant increases anti-inflammatory cytokines and decreases pro-inflammatory cytokines and improves the effects of cytokine storms (81). It can also modulate the function of Th1 and Th2. Studies have shown that this plant improves the treatment of rheumatism by modulating the function of T lymphocytes. The effect of this plant on the immune system and respiratory system can indicate its impact on the treatment of COVID-19. Thymoquinone in this plant blocks (the ACE2 COVID-19 receptor) and prevents the virus from entering the pneumocytes. Studies have shown that *Nigella sativa* contains active compounds such as nigellimine and thymoquinone, preventing the virus from entering pneumocytes and creating pores for more zinc uptake (Zn<sup>2+</sup>), which can increase the host's

immune response to the virus. Prevent virus replication by blocking viral RdRps. Nigellidine is an alkaloid in *Nigella sativa* that blocks 6LU7, and  $\alpha$ -Hederin, a saponin, can stop 2GTB. Hederagenin binds to 6UL7, 6Y2E, ACE2, and the active site GRP78 as type d saponin. Nigellidine has high energy d to bind to COVID-19 enzymes and proteins. According to studies, some proteins in this plant, including Nigellidine,  $\alpha$ -hederin, Hederagenin, thymohydroquinone, and thymoquinone, prevent the virus from entering adrenal cells and lung cells. The compounds in this plant increase the amount of pro-inflammatory mediators, including IL-2, IL-4, IL-6, and IL-12, which ultimately increases the level of IFN- $\gamma$ . Thymoquinone in this plant increases the serum level of IgG1 IgG2a and improves lung function in respiratory disorders (82)

### *Ephedra*

These plants grow in Hebi, Shanxi, and the Inner Mongolia Autonomous Region of China. This growth can help stop coughing and alleviate dyspnea through its potential to ventilate and descend the lung.. There are many different kinds of compounds extracted from the *Ephedra* species include alkaloids, flavonoids, polysaccharides, tannins and others. several invivo and invitro studies on compounds of *Ephedra* species showed anti-bacterial, anti-oxidant, anti-cancer, anti-inflammatory and anti-viral activity etc. *Ephedra* has inhibitory effect on growth of influenza A virus through acidification of intracellular components including of lysosomes and endosomes and thereby restrict the proliferation of influenza A virus (83). It can also significantly inhibited the mRNA expression levels of related genes in signalling pathways of TLR3, TLR4 and TLR7 which are accompanied with the down-regulation of TNFA level and the up regulation of IFNB levels (83). Kai Gao et.al showed that *Ephedra*-bitter almonds can directly inhibiting the COVID-19 virus and play an active role in immune response regulations,

promoting body repaired and consequently prevent and treat COVID-19. *Ephedra*-bitter almonds complete its regulatory role against COVID-19 through the patterns of multi-component-target-pathway. In traditional medicine *Ephedra sinica* is widely used in Asia in order to treat lung disease. Recent surveyes have found that *Ephedra sincica* could significantly subside the symptoms and alleviate the destructive effects of COVID-19. *Ephedra sinica* has three active compounds including of 4,6-dihydroxyquinoline-2-carboxylic acid, 4-hydroxyquinoline-2-carboxylic acid and 4-hydroxy-6-methoxyquinoline-2-carboxylic acid. The ethanol extracts of these compounds could effectively inhibit the interaction between ACE2 and the SARS-CoV-2 spike protein receptor-binding domain (SARS-CoV-2 RBD) (84).

### *Pelargonium sidoides*

*Pelargonium (Pelargonium sidoides)* is a genus of flowering plants, which has a worldwide distribution in temperate to subtropical zones.it is also known as African geranium, which long used in South African traditional medicine. Also it is sometimes used in cough and cold remedies to reduce the severity of illness. *P. sidoides* can help alleviate the symptoms of upper respiratory tract infections such as bronchitis, sinusitis, and common cold (2). EPs 7630, DC is a prodelphinid-rich extract from *p. sidoides*, showed dose-dependent anti-influenza activity against H1N1 pandemics. It has also immunomodulatory and antiviral properties, reduce the duration of disease and limiting the severity of the symptoms of different types of upper respiratory viruses. Root extracts of *p. sidoides* have anti-influenza activities through the inhibition of virus intery and key viral enzyme activities. Several studies showed that *P. sidoids* root extract EPs 7630 has immunomodulatory and antiviral effect it can inhibit influenza A virus replication (5). Compared to SARS-COV, MERS-COV, SARS-COV2 growth can significantly inhibited at a non-toxic

concentration with an IC<sub>50</sub> of 1.61 µg/ml of EPs 7630 which has different types of immunomodulatory functions, can efficiently reduce COVID-19 associated cytokines (IL-8, IL-13, TNF-α), chemokines (CXCL9, CXCL10) and entry inhibition of SARS-COV-2 (85).

#### *Psoralea corylifolia*

*Psoralea corylifolia* is one of the most popular plants which is used in Indian and Chinese traditional medicine to treat various disease. Psoralen is one of the extracts which exist in the seeds of this plant. The plant has different types of effects such as antibacterial, antitumor, antioxidant, antifungal, anti-inflammatory and immunomodulatory activity. There have been reported a wide range of chemical compounds which are founded in different parts of the plant including psoralen, isopsoralen, bakuchial, psoralidin, bakuchalcone, bavachinin, flavones, volatile oils and lipids. papain-like protease (PLpro) is a key enzyme in SARS-CoV that has an active role in SARS virus replication. *P. corylifolia* seed extracts showed high activity against the SARS-CoV-2 PLpro with an IC<sub>50</sub> of value of 15 µg/ml (86).

#### *Atractylodes lancea*

*Atractylodes lancea* is distributed in East Asia and used as one of the important plants in many countries. It is used to treat diseases such as rheumatism, digestive disorders, night blindness,

influenza, gastric atony, nausea, etc (87). *A. lancea* has recently received a lot of attention due to its many active substances, including bioactive sesquiterpenoid and polyacetylene glycosides. Also, Hinesol extracted from it inhibits the growth and induces the apoptosis of human leukemia HL-60 cells. Phenols and polyethylenes extracted from the rhizome of *A. lancea* have anti-inflammatory activity. According to research, *A. lancea* has an inhibitory effect on human rotavirus, H3N2 viruses and influenza A virus. Also, *A. lancea* is rich in volatile oils and is effective against various diseases, including COVID-19. Recently, this plant is frequently used to treat patients suffering from COVID-19 and in China it ranks first among medicinal plants for the treatment of COVID-19 (88).

#### *Poria cocos*

It is a traditional medicinal plant that is mostly seen around pine trees in East Asia and countries like China and Korea. It is also often used as one of the main ingredients in traditional Chinese medicine prescriptions. *Poria cocos* contains polysaccharides, triterpenes, and steroids. This plant is used to treat chronic gastritis, cataracts, stomach pain, edema, nephrosis, dizziness, vomiting. The compounds in *Poria cocos* are among the compounds used in traditional Chinese medicine used to treat COVID-19. Based on the complex components of *Poria cocos*, it is difficult to accurately determine the effect of a single substance on COVID-19 (89).

**Table 1.** Possible herbal medicines recommended for prevention and treatment of COVID-19.

Herbs (Refs.)	Other Functions	Mode of action
<i>Ocimum sanctum</i> (14)	Pneumonia, Rheumatism, Bronchitis, Fever	Enhance immune response, Increasing levels of interferon gamma and IL-4

<i>Phyllanthus emblica</i> (20)	Diarrhea, Jaundice, Inflammation	Improve clinical symptoms and CRP levels, Modulation of immune response, Inflammatory cascade and cytokine storm
<i>Echinacea purpurea</i> (26)	Common cold, Influenza, Upper respiratory tract infections, Urinary tract infections	Decreased levels of immune molecules involved in cytokine storm, Stimulation of innate immune cells
<i>Curcumin</i> (30)	Infectious diseases, Inflammatory diseases, Metabolic syndrome, Arthritis, Anxiety, Hyperlipidemia	Inhibition of influenza A virus hemagglutinin binding to host cell receptors. Preventing the proliferation of tumor cells, metastatic invasion and its spread.
<i>Astragalus membranaceus</i> ( <i>Agastache rugosa</i> ) (37)	Parkinson, Alzheimer, Skin reinforcing, Vital-energy tonifying, Abscess-draining, Liver fibrosis	Suppression of pro-inflammatory cytokines IL-6 and TNF-alpha
<i>Glycyrrhiza</i> (42)	Respiratory disorders, Hyperdipsia, Epilepsy, Fever, Sexual debility, Paralysis, Stomach ulcers, Rheumatism, Skin diseases, Hemorrhagic diseases, Jaundice	Anti-inflammatory effect by inhibiting phospholipase A2, Suppression of cyclooxygenase activity and formation of prostaglandin E2, Inhibition of hepatic aldosterone metabolism
<i>Rheum palmatum</i> (46)	Tissue edema, Necrosis, Inflammation	Preventing: virus attachment to the cell, entry into the cell, syncytial formation
<i>Isatis tinctoria</i> (49)	Inflammation, Tumor, The pain, Viral and microbial diseases	Prevention of virus replication, Inhibition adsorption of virus to cell surfaces
<i>Atractylodes macrocephala</i> (52)	Improve the function of the digestive system, Alzheimer, cancer Osteoporosis, Antibacterial and anti-inflammatory activity	Induce apoptosis and the differentiation of macrophage lineages, Increased phagocytosis and upregulated caspase-3, caspase-9, CD14, and CD68, Immunomodulatory effect
<i>Bupleurum chinense</i> (54)	Inflammation, Pain, antioxidant activity, Depression, Fever	Preventing damage to important cellular components caused by ROS
<i>Azadirachta indica</i> (56)	Nausea, Vomit, Cough, Intestinal worms,	Reduction of pro-inflammatory cytokines, Adjust lymphocyte count, Inactivate viral proteases

	Urinary tract infections	
<i>Eurycoma longifolia</i> (63)	Sexual dysfunction, Aging, Malaria, Cancer, Diabetes, Anxiety	Improving the immune system against pathogens
<i>Gymnanthemum amygdalinum</i> (67)	Fever, Cough, Constipation, Hypertension, Anti-inflammatory	Increase in lymphocyte count
<i>Isatis indigotica</i> (68)	Detoxification, Reduce inflation, Remove the heat	Preventing the virus from entering the host cell and inhibiting its proteases
<i>Malva Sylvestris</i> (71)	Cough, Inflammation of mucous membranes, Sore throat, Stomach ache, Flu and colds	Improve innate immunity
<i>Mentha piperita</i> (75)	Nausea, Vomit, Indigestion, Irritable bowel syndrome	Antioxidant properties through direct inhibition of hydroxyl and other radicals in upper and lower respiratory tissues
<i>Nigella sativa</i> (77)	Asthma, Cough, Flu, Eczema, Anti-diarrhea, Appetite stimulants	Increase anti-inflammatory cytokines and decrease pro-inflammatory cytokines, modulate Th1 and Th2 function, anti-apoptosis and anti-metastasis
<i>Ephedra</i> (83)	Asthma, Bronchitis, Hay fever, Colds and flu	Restriction of influenza A virus replication through acidification of intracellular components.
<i>Pelargonium sidoides</i> (85)	a cold Flu bronchitis	Acts as a mucolytic agent by stimulating mucus secretion.
<i>Psoralea corylifolia</i> (86)	skin diseases Dysentery diarrhoea	inhibitors main protease (Mpro) , RNA-dependent RNA polymerase (RdRp), and ACE-2
<i>Atractylodes lancea</i> (88)	Rheumatism Digestive disorders Night blindness Influenza Gastric atony Nausea	Anti-inflammatory activity, Inhibition of growth and induction of apoptosis of HL-60 human leukemia cells
<i>Poria cocos</i> (90)	Anti-obesity, Gastrointestinal, Fatty liver, Catarrh,	Inhibit main protease Mpro

	Edema,	
<i>Semen Armeniaca</i> <i>Amarum(XingRen)</i> (90)	Cough, Anti-inflammatory, Influenza A, Asthma	Suppresses inflammatory damage, inhibit SARS-CoV-2 by binding to two main structures CoV spike (S) glycoprotein (6SVB) and CoV 3CL hydrolase

### *Semen armeniaca amarum (XingRen)*

*Semen Armeniaca Amarum* is a plant with a warm nature, low toxicity and contains an effective substance called amygdalin, which after being used orally, this plant turns into hydrocyanic acid and benzaldehyde, and these compounds cause an inhibitory effect. *Semen armeniaca amarum* is used to treat cough and asthma. This plant was used together with other herbal medicinal compounds approved in Chinese medicine to treat the COVID-19 virus, which showed that this plant suppresses inflammatory damage. These plants inhibit the virus by binding to two main structures CoV spike (S) glycoprotein (6SVB) and CoV 3CL hydrolase (90).

### Conclusion

According to previous studies, herbal medicines might have the capabilities to stimulates innate immune cells, macrophage phagocytosis, and regulate proinflammatory cytokines. Due to various antiviral activity against different respiratory viruses in host cells, these properties of herbal agents have made them a useful treatment against COVID-19. The use of herbal agents is recommended as prevention and faster recovery of COVID-19 patients, but considering that their use might be associated with side effects in some individuals, therefore their administration should be under the supervision and prescription of a clinician.

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