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Role of Iranian Medicinal Plants in the Prevention of COVID-19

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Review Article

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Abstract:

One of the essential approaches to preventing the spread of COVID-19 is disease prevention methods. In this regard, medicinal plants are valuable. In this study the mechanisms and effects of effective medicinal plants for the prevention of COVID-19 in the Iranian pharmaceutical market were investigated. For this purpose, search terms *Herbal Medicine*, *Phytotherapy*, *Traditional Medicine*, *Complementary Medicine*, *Alternative Medicine*, *Integrative Medicine*, *Prevention*, *SARS-CoV-2*, and *COVID-19* were used to retrieve relevant publications indexed in *Scopus*, *ScienceDirect*, *Google Scholar*, and *PubMed* until May 2021. After obtaining articles related to medicinal

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plants, articles that addressed plants in Iran were included in the review, then the mechanisms of their actions in the prevention of COVID-19 were investigated. According to the extracted studies, plants such as *Zataria multiflora* Boiss., *Camellia sinensis* (L.) Kuntze, *Echinacea* spp., *Aloe vera* (L.) *Burm.f*, *Nigella sativa*, eucalyptus spp., *Cichorium intybus* L., *Syzygium aromaticum* (L.), *Glycyrrhiza glabra* L., *Allium sativum* L., and *Crocus sativus* L. are effective in preventing COVID-19, which are found in the domestic market of Iran. These plants seem to effectively prevent COVID-19 with three fundamental mechanisms: anti-inflammatory and antioxidant effects, immunomodulatory effects, and inhibiting virus attachment to the host cell.

Keywords: Herbal Medicine, Phytotherapy, COVID-19, Prevention, SARS-CoV-2

INTRODUCTION

Coronavirus disease of 2019 (COVID-19) is a highly contagious disease known as the third epidemic of the 21st century (1). According to the World Health Organization, since May 24, 2021, the number of patients diagnosed was 167,653,596, and the number of deceased patients was 3,480,642 worldwide (1). Clinical manifestations of COVID-19 range from asymptomatic or mild symptoms such as fever, cough, sore throat, headache, nasal congestion, and diarrhea to severe pneumonia, acute respiratory distress syndrome, multiple organ dysfunction syndrome and sepsis-related death. Effective prevention is obligatory to limit the spread of COVID-19 and prevent similar pandemics in the future. Vaccines, monoclonal antibodies, immunomodulators and antiviral drugs available in the pharmaceutical market are the most promising choices to prevent the disease (2-4). To fill the gap in response to treatment and future vaccines, preventing measures can reduce the transmission of the virus in the community and lead to more efficient control of the spread of the disease.

Due to the extremely rapid spread of COVID-19, the lack of approval of specific pharmacological treatments for this emerging disease, the economic problems caused by current prevention methods such as quarantine, and the complications of the disease that may remain with the patient for the rest of life, a practical, optimal and economical prevention methods are urgently needed. Recently, there have been significant advances in antiviral herbal remedies due to growing concerns about drug resistance and limited developments in discovering antiviral drugs. In almost all countries, herbs

have historically been widely used as traditional therapies for diseases and infections due to their wide range of therapeutic properties and minimal or no side effects. Since synthetic antiviral medicines are not accessible for most viral agents, efforts are aimed to seek out new and alternative medicines from different herbal compounds (5). Regarding the above-mentioned and the tendency of people to consume natural remedies, we will introduce the plants available in the Iranian medicinal plants market that can be used as a medicinal plant to prevent COVID-19.

MATERIALS AND METHODS

In this narrative review, the search terms *Herbal Medicine*, *Phytotherapy*, *Traditional Medicine*, *Complementary Medicine*, *Alternative Medicine*, *Integrative Medicine*, *Prevention*, *SARS-CoV-2*, and *COVID-19* were used in combination were used to retrieve relevant publications indexed in *Scopus*, *ScienceDirect*, *Google Scholar*, and *PubMed* until May 2021. The retrieved articles were screened using the abstract and keywords. Then, the full texts of eligible articles were reviewed, and articles that addressed plants in Iran were included in the review.

RESULTS AND DISCUSSION

Using medicinal plants to prevent COVID-19 requires knowledge of the virus life cycle. SARS-CoV-2 is a single-stranded RNA-coated virus, which is similar to SARS-CoV-1 with respect to host entry mechanisms. The virus targets cells by binding to a viral structural protein (spike protein) to the angiotensin-converting enzyme 2 (ACE2), inserting endosomes into cells. Four receptors have been identified for ACE2. Most of ACE2 biological activities are mediated by type I (AT1R) receptor and the type II (AT2R) receptor. The AT1R receptor has been identified in alveolar type II cells, alveolar macrophages, vascular smooth muscle cells, bronchial epithelial cells, endothelial cells, and fibroblasts in the lung, while AT2R has been detected in respiratory epithelial cells associated with dense staining of the brush border, cartilage, vascular endothelial cells, macrophages, some mucosal glands, and fibroblasts (3, 6-9).

Transmembrane protease serine 2 (TMPRSS2) is a type 2 host protease

that helps the virus enter the cell through the spike protein. When the virus enters the cell, viral peptides and RNA are synthesized, and new virus particles are assembled and released. Inhibiting the entry and proliferation of virus-infected cells and modulating the immune system can be a potential goal of pharmacotherapy (10).

The plant or any other substance used for prevention should not have adverse side effects and endanger health. For example, compounds that can target host enzymes involved in virus pathogenicity should be used in more urgent cases, such as treatment, so as not to endanger their regular biological activity. In addition, the required dose of the plant or preventative compound should not be toxic to the body. The plant or compound selected for disease prevention should be as usable and accessible as possible to all age groups. It should be noted that many herbs are contraindicated for pregnant women and should not be used without consulting a general practitioner or pharmacist.

Medicinal plants' mechanisms for preventing COVID-19 infection are classified into three categories; immunomodulators, inhibitors of virus attachment to the host cell, and antioxidants. However, medicinal plants may work through all of these mechanisms because they contain different active ingredients. It is therefore sensible that a plant may fall into all three of these categories (Figure 1).

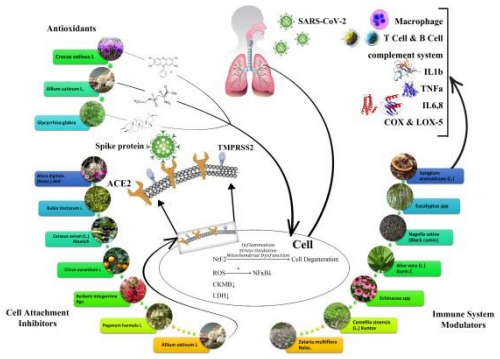

Figure1: The recommended mechanisms for preventing COVID-19 infection by medicinal plants include immunomodulators, inhibitors of virus attachment to host cells, and antioxidants.

a. *Inhibitors of virus attachment to the host cell*

Given the mechanisms of the viral pathogenicity, it is obvious that preventing the virus from entering the host is an important prophylactic approach. The bioactive properties of foods and plants against influenza virus and SAR-CoV-1 have been reported in

in vitro, *in ovo*, and *in vivo* studies, although few clinical trials have been performed on the impacts of specific foods and plants against SAR-CoV-1 and influenza virus (11). Because influenza and SAR-CoV-1 and SAR-CoV-2 belong to the same family, potent plants in preventing SAR-CoV-1 and influenza may be adequate to prevent COVID-19.

The mechanism for inhibiting influenza A virus is to inhibit virus replication or penetration into Madin-Darby Canine Kidney (MDCK) cells (12). Plants showing their antiviral properties by preventing the virus from entering the cell can prevent viral diseases. Some essential oils such as cinnamon leaf, bergamot, lemon balm, and thyme have anti-influenza activity (13). Combining essential oils also prevents the influenza virus by inactivating virus attachment capability and viral protein transport in MDCK cells (14).

According to the study of Ziaei et al., rhubarb (*Rubia tinctorum* L.), marshmallow [*Alcea digitata* (Boiss) Alef] and wild cherry [*Cerasus avium* (L.) Moench] have 100% inhibitory effects on ACE. *Citrus aurantium* L., barberry (*Berberis integerrima* Bge), pecanum (*Peganum harmala* L.), and garlic (*Allium sativum* L.) also inhibit ACE by 70% (15). Therefore, it seems that these herbs can be used to prevent COVID-19 after *in vitro* and *in vivo* studies. It should be taken into account that ACE inhibitors may upregulate receptors and increase susceptibility to COVID-19 infection in the long term (16). As a result, patients recieving ACE inhibitors should not use these herbal remedies.

Nevertheless, it should be noted that because ACE2 is expressed in lung immune cells, COVID-19 may still reach target cells using other receptors or other cell entry methods, which need further investigation (17).

b. *Immunomodulators*

An operative host immune response, including innate and acquired immunity to SARS-CoV-2, is critical to controlling and eliminating the viral infection. The severity and outcome of COVID-19 may be related to the overrun of proinflammatory cytokines, known as cytokine storms, leading to acute respiratory distress syndrome.

Unfortunately, the particular pathophysiology and treatment, specifically for severe COVID-19, remains unclear. Preliminary studies have shown that immunomodulatory or immunosuppressive therapies such as hydroxychloroquine, interleukin-6 (IL-6) and IL-1 antagonists, frequently used in rheumatology, may be measured as treatments of choice for COVID-19, especially in severe cases (18). Therefore, plants with immunomodulatory effects should be taken into further consideration.

i. *Zataria multiflora* Boiss.

The study of Taheri et al. showed the improvement of humoral and mucosal immunity parameters, increase in the expression of immunity-related genes, the capacity of plasma, and liver antioxidants in salmon receiving a hydroalcoholic extract of *Z. multiflora* (19). The effects of *Z. multiflora* powder on modulating the immune system of fishes exposed to the insecticide lambda-cyhalothrin have also been reported (20). *Z. multiflora* seems to strengthen the immune system by increasing the proliferation of lymphocytes and white blood cells, enhancing phagocytosis (21) and modulating cytokine gene expression (22).

ii. Green tea [*Camellia sinensis* (L.) Kuntze]

C. sinensis has been reported to enhance the humoral immune response (increase serum lysozyme and serum antiprotease), cellular response (increase leukocyte myeloperoxidase content and protection of reactive nitrogen species) (23), and to upregulate the expression of immune-related genes in fishes (24).

***iii. Echinacea* spp.**

Echinacea regulates the immune system by activating macrophages and influencing cytokine expression (25). Numerous studies have also shown that *Echinacea* can activate innate immune cells by increasing the number of immune cells, granulocyte migration, macrophage phagocytic capacity, cytotoxicity of natural killer cells, and cytokine production (26-31).

iv. *Aloe vera* (L.) Burm. f.

According to Mehrabi et al., supplementation of fishes with *A. vera*

improves non-specific immune parameters (lysozyme activity and complement system). The plant upregulates the expression of genes of Tumor Necrosis Factor-alpha (TNF-α), IL-1β, IL-6 and IL-8 (32). *A. vera* reduces the respiratory leukocyte burst and the hemolytic activity of the complement system induced by transplantation. It can also increase serum lysozyme concentrations and regulate innate immunity by activating the complement system (33).

v. Black seed (*Nigella sativa*)

The main active ingredient of *N. sativa*, thymoquinone, can regulate inflammatory responses such as TNF-α, nuclear factor kappa-light-chain-enhancer (NF-κB) of activated B cells, and IL-1, 6, 10, and 18 (34, 35). Besides this, *N. sativa* can inhibit the cyclooxygenase (36) and 5-lipoxygenase pathways in arachidonic acid metabolism. It means that *N. sativa* affects leukocytes and eosinophils, and modulates inflammatory responses (37). Because inflammation is an important factor for COVID-19 (38), *N. sativa* probably has a beneficial impact on the disease.

***vi.* Eucalyptus spp.**

Eucalyptus essential oil can be used as an immunoregulatory agent against infections due to the enhancement of the innate immune response (39, 40). In addition, studies have shown that eucalyptus oils and the active ingredient of eucalyptus, eucalyptol, can reduce the release of proinflammatory cytokines from monocytes and macrophages, thereby having a beneficial effect on pneumonia and infection (40, 41).

***vii.* Chicory *(Cichorium intybus* L.)**

C. intybus, a member of Asteraceae family, is used as a medicinal plant as well as a food additive. *C. intybus* has immunomodulatory activities. In an animal model of ethanol-induced immunotoxicity, *C. intybus* augmented circulating leukocytes and the weight of lymphatic system organs, indicating an enhancement of immune function (42). In addition, *C. Intybus*, as a dietary supplement, can affect plasma protein profiles and lead to decreased levels of proinflammatory markers such as C-reactive protein (CRP) (43). *C. intybus* root is rich in inulin-type fructans,

which are considered probiotics (43). Nowadays, the substantial role of the natural intestinal flora in many diseases, including immune complications, has attracted the attention of researchers (44). Therefore, in addition to the immunoregulatory effects of *C. intybus*, inulin in this herb may also have a modulating effect on the natural intestinal flora.

viii. Clove *(Syzygium aromaticum* L.)

S. aromaticum has been shown to produce modulatory effects on mouse white blood cell function and damaged macrophages over inflammation or oxidative stress damage. In animal models in which the immune system was suppressed, seven days administration of *S. aromaticum* essential oil (400 mg/kg) could improve humoral immunity and cell mediation (45). This observation suggests that in people taking immunosuppressive drugs, *S. aromaticum* may potentially prevent COVID-19-induced immunosuppression. However, further clinical trials must be conducted to confirm this argument.

c. *Antioxidants*

Reactive oxygen species (ROS) and nitrogen metabolites play a complex part in numerous diseases and metabolism regulation. Because viruses proliferate in living cells, these metabolites act as host defense mechanisms and affect the growth of viruses. Low level of ROS is involved in mitogenic activation, and the early phase of lytic and non-lytic virus pathogenesis is similar to mitogenic cell activation. ROS may also activate viral replication through NF-κB activation, but it has been acknowledged that oxidants are also involved in killing CD4 T cells through apoptosis. Antioxidants, along with agents contributing to the devastating effects of cytokines and lipid mediators, may play a role in treating viral infections. Not only can these factors relieve the symptoms of the disease, but they can also reduce the long-term effects of chronic oxidative stress that are produced along with the development of cancer in some viral infections (46).

i. Licorice (*Glycyrrhiza glabra* L.)

G. glabra is a common plant containing over 20 triterpenoids and about 300 flavonoids, and has many

potential therapeutic effects as an antiviral medicine (47, 48). Glycyrrhizin in *G. glabra* can also prevent viral binding and penetration in fighting against SARS-CoV (49). *G. glabra* extracts have been observed to exert cardioprotective properties, both *in vitro* and *in vivo*, by improving the defense mechanisms of endogenic antioxidants (50, 51). It can be therefore argued that *G. glabra* is a multipurpose remedial plant with direct antiviral and protective activities on susceptible organs in SARS-CoV-2 infection, and consequently deserves further investigation as an adjunct therapy for this disease.

ii. *A. sativum*

The remarkable various therapeutic activities of *A. sativum* are due to the organosulfur components (52). Diallyl sulfide, allicin, and alliine can reduce the inflammatory factors of infected cells by inhibiting oxidative stress (53, 54). Generally, *A. sativum* and its organosulfur components serve as multifunctional treatments for numerous tissues susceptible to SARS-CoV-2-induced damage and may be useful for primary or secondary prevention in these patients.

iii. Saffron (*Crocus sativus* L.)

C. sativus is a herbal plant of Iridaceae family, whose aroma has medicinal properties. This plant is one of the native medicinal plants of Iran. Aqueous *C. sativus* extract has shown cardioprotective properties in animal models of ISO-induced heart impairment by reducing Creatine Kinase-MB (CK-MB) and Lactate Dehydrogenase (LDH) leakage from cardiomyocytes and improving endogenic antioxidants in cardiac tissue (55, 56).

The most significant effects of most herbs and their chemicals include anti-inflammatory activity and antioxidant effects. These mechanisms involve several cellular and subcellular pathways, including NF-κB, Nuclear factor erythroid 2–related factor 2 (Nrf2), or the balance of inflammatory and anti-inflammatory cytokines and endogenic enzymatic/non-enzymatic antioxidant defense mechanisms. Given that such cascading protective mechanisms are found in almost all body organs, the valuable effects of

chemicals in one tissue can be generalized to other tissues. For example, if a compound has shown a stimulatory impact on Nrf2 signaling in heart tissue, the same action can be supposed in renal tubules or lung tissue (53).

Aerosolized tea tree oil has been reported to inhibit airborne viral particles in the H11N9 subtype of the avian influenza virus (54). Currently, there are few studies on the possibility of vapor forms of essential oils. Sterilizing the air without harming human health using essential oils can be an effective method to prevent COVID-19. Nevertheless, the minimum concentration of essential oil required to inhibit SARS-CoV-2 should be examined.

CONCLUSION

Scientific reports support numerous medicinal plants available in the Iranian pharmaceutical market such as *Z. multiflora, C. sinensis, echinacea, A. vera, N. sativa,* eucalyptus, *C. intybus, S. aromaticum, glycyrrhiza, A. sativum* and *C. sativus* because they have already been investigated *in vitro*, *in vivo*, and in clinical trials. Since these plants are available and widely known, applying them after additional clinical trials under the supervision of physicians, pharmacists, and nutritionists can improve public health.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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CONFLICT OF INTERESTS

None.

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