

Herbal therapy in Covid-19: A systematic review of medicinal plants effective against Covid-19

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ABSTRACT

In 2019, a new disease called Covid-19 was detected in Wuhan located in China which caused seriously disease or death at any age. This disease has various symptoms such as fever, chills, cough, sore throat, headache, body pain, muscle pain, diarrhoea, and vomiting. In this review study, articles related to the subject were searched using scientific sites such as Medline, PubMed, and Google Scholar using the keywords of traditional medicine, medicinal plants, and Covid-19. After downloading the articles, irrelevant articles were removed and related articles were reviewed. According to the results obtained from the review of the literature, the effective medicinal herbs including *Zingiber officinale*, *Alpinia officinarum*, *Cinnamomum zeylanicum*, *Nigella sativa*, *Citrus paradise*, *Laurus nobilis* L. and *Echinacea purpura* were the most important medicinal herbs used in treatment of Coronavirus. Antiviral chemical drugs usually inhibit the virus by disrupting the key protein and viral virulence factors. Probably, medicinal plants inhibit corona virus with a mechanism similar to the chemical drugs. Therefore, it is possible to produce effective herbal medicines as alternative for synthetic drugs and reduce the pain and suffering from Covid-19 in patients.

Keywords: Coronavirus, Covid-19, Medicinal plants, Therapy.

Article type: Review Article.

INTRODUCTION

A novel coronavirus which calls severe acute respiratory syndrome coronavirus 2, initiated the outbreak of coronavirus disease (Covid-19) in China, in December 2019, has now spread worldwide and become pandemic (Zareie *et al.* 2020; Yuen *et al.* 2020; Al-Awade *et al.* 2022; Pantsari *et al.* 2022; Karimi *et al.* 2021). SARS-coV-2 is a RNA-enveloped single-stranded virus whose entire genome encodes different amino acids, structural, and non-structural proteins (NSPs). The non-structural proteins, e.g., C30 Endopeptidase, papain-like protease, and RNA replicase are encoded by the open reading frames region, while structural proteins are encoded by the surface or spike (S), envelope (E), membrane (M), and nucleocapsid proteins (N) genes (Wang *et al.* 2020). The S protein of the virus interact with the host cell which rearranges the construction and the virus fuses to the host cell

membrane that binds to polysaccharide molecules, specifically negatively polysaccharides, to get away from the host immune system due to the entry of the host cells (Huang *et al.* 2020; Hatami *et al.* 2022). The spike of SARS-coV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors, penetrating and infecting host cells which a protease enzyme prepares the virus to complete entry into the cell. Subsequently, it uses a transmembrane serine protease 2 (TMPRSS2) to complete the infectious steps that are necessary to bind the spike protein as a receptor to ACE2 (Zahra *et al.* 2018; Huang *et al.* 2020). Due to the pandemic, a specific Covid-19 therapeutic and vaccine designed based on proteins is crucial (Hoffmann *et al.* 2020). While the design variety of biological and chemical products, new methodologies, and knowledge expansion over time especially in the Covid-19 pandemic, some cultures, still emphasize herbal medicines evaluation for the treatment of re-emerging diseases. Two years into the pandemic, it has become apparent that emerging an effective antiviral against the severe acute respiratory syndrome coronavirus 2 (SARS-coV-2) is a challenge due to the virus infectivity, mutations, and disease progression. Based on virus life cycle studies, early administration of a highly effective antiviral agents is needed to management the infection and preserve host cells. The drugs being tested to treat Covid-19 categories in two mechanisms: (i) Targeting the viral replication cycle and (ii) Aiming to control the symptoms of the disease. During the SARS-coV-2 pandemic different chemical and biological drugs recommended and prescribed for treatment of the Covid-19 which some of them include (Lem *et al.* 2021):

1) Chloroquine and hydroxychloroquine have inhibition heme polymerase effect in Malaria. In Covid-19, it is supposed that the drugs block glycosylation of host receptors and prevent the production of viral proteins (Shah *et al.* 2020; Ferner and Aronson 2020a).

2) Lopinavir, ritonavir, IFN-B, and ribavirin which are the human immunodeficiency virus protease inhibitors and use against coronaviruses via inhibition of 3-chymotrypsin-like protease (Venkatasubbaiah *et al.* 2020; Alhumaid *et al.* 2020; Dorgham *et al.* 2021).

3) Nafamostat and camostat are serine protease inhibitors which approved in Japan for using against pancreatitis. In vitro studies showed that both of them block the entry of SARS-coV-2 by acting as an antagonist to the serine protease TMPRSS2 (Azimi 2020; Sonawane *et al.* 2021).

4) Famotidine, H₂ receptor antagonist, is also been investigated as a possible treatment, during severe Covid-19 along with the other therapeutic agents. The mechanism of famotidine action is not clear. Famotidine possibly binds to a papain-like protease that is encoded by the SARS-coV-2 genome. It is essential to the entry of SARS-CoV-2 to the host cells (Sethia *et al.* 2020).

5) Ivermectin is a lipophilic macrolide prescribe as anti-parasitic drug that acts by binding glutamate-gated chloride ion channels, leading to depolarization of the cells and paralysis or death of the parasite. In Covid-19, it is thought to work by binding and disrupting cell-transport proteins used to go into the nucleus (Pandey *et al.* 2020; Wehbe *et al.* 2021).

6) Corticosteroids are used to offset the potential 'cytokine storm' that leads to lung injury and acute respiratory distress syndrome (ARDS) in some patients. These molecules inhibit the expression of various genes encoding inflammatory molecules (Annane 2021; Johns *et al.* 2022).

7) Tocilizumab and sarilumab, both monoclonal-antibody antagonists of the IL-6 receptor, are used in some patients with Covid-19, those experience severe forms of the illness with elevated levels of IL-6. A multiplicity drugs that block different cytokines such as IL-6 are being tested in clinical trials of Covid-19 treatment that are generally used to treat rheumatoid arthritis (Zeraatkar *et al.* 2021; Khan *et al.* 2021).

8) Nowadays, remdesivir is the FDA-approved drug for the treatment of Covid-19 patients. It acts as a nucleoside analogue and inhibits the RNA-dependent RNA polymerase (RdRp) of coronaviruses (McCreary & Angus 2020).

9) Two antiviral drugs, nirmatrelvir and ritonavir, are authorized to treat symptomatic adults with mild to moderate Covid-19 who are at high risk of serious illness. Nirmatrelvir is a new main protease (Mpro) inhibitor to block the SARS-CoV-2 Mpro enzyme activity, while ritonavir is an antiretroviral protease inhibitor and a strong cytochrome P450 (CYP) 3A inhibitor (Lamb 2022).

10) Favipiravir is a nucleoside analogue that can be triphosphorylated in cells to become active and helps as a substrate of virus RNA-dependent RNA polymerase (RdRp). Favipiravir has a wide range of antiviral activity including arenaviruses, bunyaviruses as well as influenza viruses, and its sensitive or resistant strains to marketed neuraminidase and M2 inhibitors. Due to its selective inhibitory effect on influenza viruses, it is considered a useful compound for the elimination of SARS-coV-2 as confirmed by *in vitro* and *in vivo* studies (Eroglu & Toprak 2021; Hashemian *et al.* 2021).

In all of the world, scientists search to find out an effective drugs or vaccine. A few countries, such as China, Iran, and India, with long histories of traditional medicine use, have also discovered the role of traditional and conventional medicine along with new therapeutic drugs. The history of traditional medicine using back to ancient times which during centuries remains as the main accessible and affordable treatment for the population in different countries. Nowadays, herbal medicine as the main component of traditional remedy have been transformed into conventional drugs that are sold in drugstores worldwide (Ang *et al.* 2020; Fan *et al.* 2020). Medicinal plants have been known for their therapeutic or protective effects against a broad range of microorganisms, such as viruses, fungi, bacteria, and parasites. Due to SARS-coV-2 pandemic, many plants are currently undergoing investigation to reveal their new therapeutic efficacies and safety. The Iranian culture, coming from Middle East nation, rich in plant flora, also appears to be interested in offering the use of herbal medicine based on local traditional knowledge. Due to attempting to restrict the disease spread and alleviate the long Covid-19 side effects, herbal medicine research as the potential use of complementary remedies including traditional remedies, finished herbal products, supplements, and food products against Covid-19 can be helpful.

MATERIALS AND METHODS

The scientific articles selected were based on relation to respiratory diseases published within the last two years (2020-2022). The open access search engines referred included: Science Direct, Google Scholar, PubMed, Web of Sciences, and Scopus. The plants listed were selected according to the country of origin which has close relation to Iran climate, the scientific name, local name, botanical family, and the mechanism of effect.

RESULTS

According to the results obtained from the review of the literature, the medicinal herbs *Zingiber officinale*, *Alpinia officinarum*, *Cinnamomum zeylanicum*, *Nigella sativa*, *Citrus paradise*, *Laurus nobilis* L., and *Echinacea purpura* were the most medicinal herbs used to treat the coronaviruses. In Table 1, the aforementioned plants are given along with their mechanisms.

DISCUSSION

Coronavirus disease-19 (Covid-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-coV-2) that was first originated from Wuhan City in China. Around 582 million of Covid-19 cases have been reported across the world and 6.4 million deaths occurred among them by August 15, 2022. The main symptoms of Covid-19 include fever, cough, dyspnoea, chills, muscle pain, headache, sore throat, loss of taste or smell, vomiting, difficulty breathing, and pressure in the chest (Alimohamadi *et al.* 2020). The development of antiviral drugs and effective vaccines without side effects to treat patients will take months or years to complete. To date, there is no specific, effective and proven conventional medicine to manage patients affected by Covid-19 with the exception of remdesivir which approved by FDA (Ferner & Aronson 2020b). So, herbs without or with low side effects can make available valuable sources of natural components that exhibit immunomodulatory, anti-inflammatory, anti-oxidative, and antiviral properties with positive effects on the organs affected by the coronavirus (Khan & Ahmad 2019; Ang *et al.* 2020). Ginger contains various components, including fatty oil, protein, carbohydrates, crude fibre, ash, water and approximately volatile oil. Chemically, based on analytical methods, ginger contains over 400 different composites. On the other hand, the pharmacological effects of ginger are basically attributed to its terpenes (zingiberene, sesquiphellandrene, bisabolene, farnesene, limonene, cineole, linalool, geranial, and curcumin) and phenolic (gingerols, paradols, shogaols and zingerone) compounds (Shao *et al.* 2010). Terpenes have several pharmacologic properties such as anti-cancer, anti-oxidant, anti-inflammatory, anti-viral, and anti-bacterial effects. At the same time, ginger-derived phenolic compounds bind to the viral protease and prevent virus replication. The other components include gingerol- or shogaol-related compounds such as 1-dehydrogingerdione, 6 and 10 gingerdione, gingerdiols and diarylheptanoids (Shao *et al.* 2010; Obetam 2020; Rathinavel *et al.* 2020). Fresh ginger reveals antiviral effects against human respiratory syncytial virus (HRSV), adenovirus, and rhinovirus. *In vitro* evaluations showed that the aqueous extract of fresh ginger inhibits the attachment and penetration of HRSV to the human carcinoma cell lines (San Chang *et al.* 2013). It has been suggested that fresh ginger can block viral attachment and permeation into host cells via interacting with proteins besides stimulation the secretion of interferons (IFN) from infected-epithelial cells and inhibition viral replication in the lower parts of the respiratory tract. So, based on previous studies, it has been recommended that in Covid-

19 patients, fresh ginger can ameliorate the clinical symptoms due to its anti-inflammatory effects and inhibition the viral replication (Rathinavel *et al.* 2020; Jafarzadeh *et al.* 2021).

Table 1. Medicinal plants effective against coronaviruses.

Plant Name	Scientific Name	Family	Therapeutic Effect	References
Ginger	<i>Zingiber officinale</i>	Zingiberaceae	It has been shown that ginger extraction has more viral inhibition potential than chloroquine and hydroxychloroquine, which are used in the treatment of Covid-19, due to its active compounds such as ginrol and shogavel. In another research conducted on the compound 6-ginrol, it was observed that this compound has a high tendency to bind the virus-infected cell proteins, including RNA polymerase, and prevents the virus from multiplying. So in the theory of density function, it is considered as a promising drug for Covid-19.	(Srivastava <i>et al.</i> 2020; (Rathinavel <i>et al.</i> 2020)
Lesser galangal/ kholanjan	<i>Alpinia officinarum</i>	Zingiberaceae	In the research conducted on the extract of the rhizome of this plant, it has been observed that according to the root compounds, these composites are able to inhibit the Covid-19 infection through molecular connections. So, it is considered as a promising natural product against the Covid-19 virus.	(Zakaryan <i>et al.</i> 2017; Goswami <i>et al.</i> 2020)
Cinnamon	<i>Cinnamomum zeylanicum</i>	Lauraceae	In the research conducted in this field, it has been determined that an enormous part of cinnamon essential oils consist of cinnamic aldehyde and eugenol, exhibit high anti-influenza properties. Given the hemagglutinin protein of the virus and the affinity of cinnamic aldehyde and eugenol, it seems that this plant can also be useful in the treatment of Covid-19 and other respiratory diseases.	(Vimalanathan & Hudson 2014; da Silva <i>et al.</i> 2020)
Black caraway/ black seed	<i>Nigella sativa</i>	Ranunculaceae	The compounds in the seeds of the Black caraway include niglidin, niglidin, niglimine, carvacrol, alpha-hydrin, thymol, thymoquinoin, dithymoquinin, and thymohydroquinone, each of these compounds can have a preventive effect. However, the two compounds, i.e., niglidin and alpha hydrin by binding to the main protease have revealed the greatest effect on Covid-19 and have been able to inhibit this virus.	(Bouchentouf & Missoum 2020)
Grapefruit	<i>Citrus paradise</i>	Rutaceae	The fruit and its skin contain valuable compounds such as acids, flavonoids, volatile compounds, terpene hydrocarbons, vitamin C, potassium, iron, and calcium. Investigators have observed that the fruit of this plant is able to reduce the load of corona family viruses. In addition, it is a protease inhibitor in HIV and it has been shown that grapefruit skin and other citrus fruits have anti-Covid-19 properties due to their flavonoid compounds.	(Cheng <i>et al.</i> 2020)
Bay tree/ barge boo	<i>Laurus nobilis</i> L.	Lauraceae	One of its main ingredients is alpha-tocopherol 1,8-cineole, exhibiting an antiviral effect, and investigators have shown that the essential oil of barge boo inhibits the SARS-coV-2 virus better than glycyrrhizin.	(Patrakar <i>et al.</i> 2012)
Purple coneflower/ Sarhkargol	<i>Echinacea purpura</i>	Asteraceae	Sarhkargol extract has antiviral properties against H ₁ N ₁ influenza and SARS virus, and also displays the power to inhibit the SARS-coV-2.	(Hudson 2012)

Alpinia officinarum is one of the most popular herbal medicines, belonging to Zingiberaceae family. It is native to Iran, south west of Asia, and China and is cultivated for food consumption in some countries. New pharmacological studies have indicated that *A. officinarum* exhibits anti-bacterial, anti-viral, anti-tumour, anti-oxidant properties (Sawamura, Sun, *et al.* 2010; Konno *et al.* 2011). Diarylheptanoid is the main component of *A. officinarum*. However, flavonoids and volatile oils such as alpha-pinene, cineole, linalool, sesquiterpene, and lactones are the most important bioactive compounds. In previous studies, Diarylheptanoids isolated from *A. officinarum* have been shown to inhibit activity of biosynthesis of prostaglandin, leukotrienes, and pro-inflammatory mediators. Subsequently, antiviral activity of diarylheptanoids has been reported against influenza virus, measles virus, respiratory syncytial virus, poliovirus, and *Herpes simplex* virus type 1 using a plaque reduction assay (Sawamura, Shimizu, *et al.* 2010; Sawamura *et al.* 2010; Konno *et al.* 2011). In a new study, the

antiviral effects of galangal diarylheptanoid were assessed against numerous types of influenza virus. The results showed that active compound was effective *in vitro* against all virus types and also revealed protective effects on induced the murine model of influenza. Nevertheless, diarylheptanoids showed a dose-dependent manner on inhibition of viral RNA and antigen expression. However, it was not effective on the viral invasion (Sawamura *et al.* 2010). Galangin exhibits significant anti-inflammatory effects in the animal model by inhibition of the NF- κ B pathway, decrease the monocyte chemoattractant protein (MCP)-1 and vascular cell adhesion molecule (VCAM)-1 of lung tissue, both of which participate in leukocytes chemotaxis besides immune-regulatory properties. So, galangal species appear to display direct antiviral properties and protective effects on the main organs damaged in SARS-CoV-2 infection (Blonska *et al.* 2003; Sun *et al.* 2016; Zhou *et al.* 2018). *Cinnamomum verum* J. Presl, a popular universal spice belonging to the Lauraceae family, is commonly known as true Cinnamon or Darchini. Cinnamaldehyde, linalool, β -caryophyllene, eugenol, methyl cinnamate, cinnamyl acetate, and procyanidin-A are the foremost components of Cinnamon and its essential oil (Vazirian *et al.* 2015; Farias *et al.* 2020). In public beliefs, Cinnamon has been known to be effective in corona disease as it is considered effective in traditional medicine for different lung diseases. A molecular docking analysis on key protein targets of SARS-coV-2 predicts interaction of Cinnamon essential oil components such as eugenol, linalool, β -caryophyllene, and eugenyl acetate with the virus targets in the organs. Even if the interactions were moderately weak, however, they may have synergistic effects on inhibiting the coronavirus (Yakhchali *et al.* 2021; Zareie *et al.* 2021). *In silico* analysis of various phytochemicals from different Cinnamon species showed that two components of cinnamon include Tenuifolin and Pavetannin C1 showed a higher binding affinity to the SARS-coV-2 spike protein (Prasanth *et al.* 2021). The other study revealed that the *Cinnamomum zeylanicum* methanolic extract inhibited angiotensin-converting enzyme inhibition in sheep kidney, lung, and testis. Reducing ACE activity was practically similar to the captopril in the kidney (Ranjini *et al.* 2016). Phenolic compounds, caffeic acid, cinnamic acid, gallic acid, and eugenol extracted from *C. zeylanicum* exhibited an inhibitory effect on trypsin. As angiotensin-converting enzyme (ACE2) and type 2 transmembrane serine protease (TMPRSS2) are expressed in target cells in SARS-coV-2 infection. These outcomes may suggest that Cinnamon can be recommended as an anti-viral medicine against SARS-coV-2 along with other drugs (Ghosh 2020) (da Silva Antonio, Wiedemann, and Veiga-Junior 2020). *N.sativa* contains various compounds including terpenes, flavanoids, sterols, tannins, coumarins, phenolic compounds, alkaloids, glycosides, saponins fatty acids, and volatile oils. The bioactive constituents of *N. sativa* include terpenes such as thymoquinone, dithymoquinone, carvone, limonine, trans-anethol, nigellicine, nigellicimine, and α -hederin (Farag *et al.* 2014). As *N.sativa* possesses anti-viral, anti-oxidant, anti-inflammatory, anti-coagulant, immunomodulatory, bronchodilatory, anti-histaminic, antitussive, and analgesic activities, it would be a possible herbal candidate to treat the patients with Covid-19. In addition, *N. sativa* has also shown anti-hypertensive, anti-obesity, anti-diabetic, anti-hyperlipidemic and anti-ulcer activities that can help the Covid-19 patients with long side effects. Additionally, nigellidine and α -hederin have potential inhibitory effects on SARS-coV-2 (Tiwari *et al.* 2019; Khazdair *et al.* 2021). Grapefruit seed extract (GSE) has antimicrobial properties and virucidal activity on avian influenza virus and Newcastle disease virus. However, it was not able to show virucidal activity against the nonenveloped virus such as infectious and bursal disease virus (Anjum *et al.* 2012). To date, there are a few studies reporting the antiviral activity of GSE, and based on our knowledge, no confirmed evidence was found about the direct activity of GSE against SARS-coV-2. Also, recent studies have suggested that GSE has antioxidant capacity. Previous study showed that GSE could reveal antioxidant activities by enhancement serum SOD, GSH-PX, and CAT and by decreasing serum MDA (Armando *et al.* 1998). On the other hand, GSE exhibits a high inhibition effect against the Gram-negative and -positive bacteria. Due to its high bactericidal effect and its proved safety, the extract is extensively used in the food industry to reduce bacterial growth in food due to storing for long period. Despite the vast literature, the exact mechanisms of action against SARS-coV-2 is vague. However, the ability of GSE to directly counteract SARS-coV-2 infection using virucidal and antioxidant activities has been evaluated by some authors (Giamperi *et al.* 2004; Oun *et al.* 2022). Since the GSE, belongs to the class of limonoids with significant virucidal and antioxidant activity, so GSE components such as obacunone, limonin, and nomilin are effective against SARS-coV-2. Furthermore, nomilin was also capable to significantly decrease ROS production and oxidative-induced mitochondrial membrane damage. So GSE containing citrus limonoids could both directly target the virus and protect the hosting cell from ROS damage (Montoya *et al.* 2020). *Laurus nobilis* L. is used as a valuable flavouring agent in the food industry. It is a bush that is native to the Mediterranean area and

cultivated in a range of Asian countries, Europe, and the Americas. This plant is used in traditional medicine for the treatment of carminative, stomach ache, amenorrhea, colic, condylomata, epilepsy, hysteria, polyps, sclerosis, spasms and nerves system disorders. Laurel contains several compounds with antioxidant activity. Both the water extract and the non-polar fraction of leaves have been revealed to possess high antioxidant activity, mainly due to its polyphenol and terpenes content (Patrakar *et al.* 2012). The chemical composition of the laurel leaves has been extensively studied. 1,8-Cineole, α -terpinyl acetate, α -terpineol, sabinene, terpinen-4-ol, α -pinene, β -pinene, methyleugenol, and γ -terpinene have been recognized to be the main compounds of laurel (Tomar *et al.* 2020). A positive therapeutic effect of bornyl acetate, isolated from leaves and fruits of *L. nobilis* L., has been reported for the treatment of lung inflammation in an animal model of acute lung injury. The alpha-pinene was effective for treatment of allergic rhinitis and also β -caryophyllene has demonstrated anti-inflammatory activity. So, during Covid-19 pandemic condition, the Mediterranean and Middle East native plants could be recommended for physician besides routine therapeutic agents (Roviello & Roviello 2021). Studies on *Echinacea* extracts have shown beneficial actions in the treatment of viral respiratory infections by a direct virucidal activity against several respiratory viruses, the pro-inflammatory response, reduction in the excessive secretion of mucin by airway cells, and potentially positive effects on cellular gene expression. A combination of these beneficial activities could reduce the amount of virus in lung tissue, and their transmission. It also leads to improvement of the virus-induced signs (Signer *et al.* 2020). The alkylamides, its derivatives or caftaric acid isolated from *Echinacea* have inhibitory effect on spike protein, the serine protease (TMPRSS-2), and non-structural proteins (NSPs) of SARS-coV-2. Notably, different binding sites were identified for different compounds of *Echinacea* indicating synergistic effects of the complex substance mixture in treatment of Covid-19 (Aucoin *et al.* 2020; Aucoin *et al.* 2021). In conclusion, medicinal plants have excessive potential value and can be recommended for treatment of Covid-19 based on the therapeutic approaches, several of them have also been confirmed by pharmacological studies in modern medicine and recommended by physician. The currently available data, regarding these medicinal plants, provide foundational evidence. Nevertheless, some data obtained from literature review, future preclinical / clinical studies are necessary to confirm the safety and efficacy of these plants for the management of SARS-coV-2 infection.

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