Caspian Journal of Environmental Sciences
Online ISSN: 1735-3866
Print ISSN: 1735-3033

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

Heru Widoyo[1], Zahraa Yassen Mohammed[2], Andrés Alexis Ramírez-Coronel[3], Acim Heri Iswanto[4], Usman Thattarauthodiyil[5], Ameer S. Alkhayyat[6], Mohammad Karimi[7], Mahmoud Bahmani[8], Zohre Eftekhari[9*]

1. Computer Science Department, Bina Nusantara University, Jakarta, Indonesia
2. Medical Laboratory Techniques Department, Al-Maarif University College, Iraq
3. Azogues Campus Nursing Career, Health and Behaviour Research Group (HBR), Psychometry and Ethology Laboratory, Catholic University of Cuenca, Ecuador
4. Public Health Department, Faculty of Health Science, University of Pembangunan National Veteran Jakarta, Jakarta, Indonesia
5. Department of Musculoskeletal & Sports Injuries Rehabilitation, Batterjee Medical College, Jeddah, Saudi Arabia
6. Medical Laboratory Technology Department, College of Medical Technology, The Islamic University, Najaf, Iraq.
7. Department of Infectious Disease, Imam Reza Hospital, Amol Mazandaran, Iran
8. Biotechnology and Medicinal Plants Research Centre, Ilam University of Medical Sciences, Ilam, Iran
9. Biotechnology Department, Pasteur Institute of Iran, Tehran, Iran

** Corresponding author's Email: z_eftekhari@pasteur.ac.ir*

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*, *Nigllea 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; Karimi *et al*. 2021; Al-Awade *et al*. 2022; Pantsari *et al.* 2022). 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

Caspian Journal of Environmental Sciences, Vol. 21 No. 5 pp. 1289-1298 Received: May 16, 2023 Revised: June 23, 2023 Accepted: Aug. 03, 2023
DOI: 10.22124/CJES.2023.7431

Publisher: University of Guilan,

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, H_2 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, Nigllea 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	*Zingiber officinale*	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 *et al*. 2020; (Rathinavel *et al*. 2020)
Lesser galangal/ kholanjan	*Alpinia officinarum*	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 *et al*. 2017; Goswami *et al*. 2020)
Cinnamon	*Cinnamomum zeylanicum*	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 *et al*. 2020)
Black caraway/ black seed	*Nigllea sativa*	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	*Citrus paradise*	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 *et al*. 2020)
Bay tree/ barge boo	*Laurus nobilis* 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 *et al*. 2012)
Purple coneflower/ Sarhkargol	*Echinacea purpura*	Asteraceae	Sarhkargol extract has antiviral properties against H_1N_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 signified anti-inflammatory effects in the animal model by inhibition of the NF-kB 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.

REFERENCES

Al-Awade, HAR 2022, Effect of smoking on infection with COVID-19. *Caspian Journal of Environmental Sciences,* 20: 407-411, DOI: 10.22124/cjes.2022.5588.

Alhumaid, S, Al Mutair, A, Al Alawi, Z, Alhmeed, N, Zia Zaidi, AR & Tobaiqy, M 2020, Efficacy and safety of lopinavir/ritonavir for treatment of COVID-19: A systematic review and meta-analysis. *Tropical Medicine and Infectious Disease,* 5: 180.

Alimohamadi, Y, Sepandi, MT, & Hosamirudsari, H 2020, Determine the most common clinical symptoms in COVID-19 patients: A systematic review and meta-analysis. *Journal of Preventive Medicine and Hygiene,* 61: 304.

Azimi, A 2020, TMPRSS2 inhibitors, bromhexine, aprotinin, camostat and nafamostat as potential treatments for COVID-19. DOI: 10.13140/RG.2.2.18254.28484

Blonska, M, Czuba, ZP, & Krol, W 2003, Effect of flavone derivatives on interleukin-1β (IL-1β) MRNA expression and IL-1β protein synthesis in stimulated RAW 264.7 macrophages. *Scandinavian Journal of Immunology,* 57: 162-66.

Bouchentouf, S & Noureddine, M 2020, Identification of compounds from *Nigella sativa* as new potential inhibitors of 2019 novel coronasvirus (Covid-19): Molecular docking study. *ChemRXIV*, DOI: 10.26434/chemrxiv.12055716.v1

Cheng, L, Weikang ZH, Ming LI, Jie H, Shuzheng B, Qiang X & Zhaocheng M 2020, Citrus fruits are rich in flavonoids for immunoregulation and potential targeting ACE2. 202002.0313.v1

Dorgham, K, Avidan, UN, Maxens, D, Charles-Edouard, D, Hans, L, & Guy, G 2021, Considering personalized interferon beta therapy for COVID-19. *Antimicrobial Agents and Chemotherapy*, 65: e00065-21.

Carrasquero, A, Maythe, S, & Petra Beatriz, N 1998, Antioxidant activity of grapefruit seed extract on vegetable oils. *Journal of the Science of Food and Agriculture,* 77: 463-467.

Djillali, A 2021, Corticosteroids for COVID-19. *Journal of Intensive Medicine*, 1: 14-25.

Eroglu, E & Cigdem, T 2021, Overview of Favipiravir and Remdesivir Treatment for COVID-19. *International Journal of Pharmaceutical Sciences and Research*, 12: 1950-1957.

Fan, A Yin, Sherman, G & Sarah, F 2020, Chinese Herbal Medicine for COVID-19: Current evidence with systematic review and meta-analysis. *Journal of Integrative Medicine*, 18: 385-394.

Farag Mohamed, A, Haidy AG, Andreas, GH & Ludger AW 2014, Metabolomics driven analysis of six *Nigella* species seeds via UPLC-QTOF-MS and GC-MS coupled to chemometrics. *Food Chemistry*, 151: 333-342.

Farias, APP, Monteiro, ODS, da Silva, JKR, Figueiredo, PLB, Rodrigues, AAC, Monteiro, IN & Maia, JGS 2020, Chemical composition and biological activities of two chemotype-oils from *Cinnamomum verum* J. Presl growing in North Brazil. *Journal of Food Science and Technology*, 57: 3176–83.

Ferner, RE, & Aronson, JK, 2020a, Chloroquine and Hydroxychloroquine in Covid-19. *Bmj*. British Medical Journal Publishing Group. 2020b. Remdesivir in Covid-19. *British Medical Journal Publishing Group.*

Ghosh, D, 2020, A Cinnamon-derived procyanidin type-a compound: a potential candidate molecule against coronaviruses including COVID-19. *Journal of Ayurveda Case Reports*, 3: 122.

Giamperi, L, Fraternale, D, Bucchini, A & Ricci, D, 2004, Antioxidant activity of *Citrus paradisi* seeds glyceric extract. *Fitoterapia*, 75: 221-24.

Goswami, D, Kumar, M, Ghosh, SK, & Das, A 2020, Natural product compounds in *Alpinia officinarum* and Ginger are potent SARS-CoV-2 papain-like protease inhibitors. https://chemrxiv.org/engage/api-gateway/chemrxiv/assets/orp/resource/item/60c74992842e653981db2d97/original.

Hashemian, SMR, Farhadi, T, & Velayati, AA, 2021, A Review on Favipiravir: The Properties, Function, and Usefulness to Treat COVID-19. *Expert Review of Anti-Infective Therapy*, 19: 1029–37.

Hatami, A, Hajiloo, A, Bayati, R, Kakavand, P, Nasrollahi, AH, Yarahmadi, AH, Nourmohammadi, MJ & Asadi, H 2022, Public COVID-19 vaccination acceptance: A narrative review of correlated factors. *Advancements in Life Sciences*, 27; 9: 143-150.

Hoffmann, M, Kleine Weber, H, Schroeder, S, Krüger, N, Herrler, T, Erichsen, S, Schiergens, TS et al. 2020, SARS-coV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*, 181: 271-280.e8. https://doi.org/10.1016/j.cell.2020.02.052.

Huang, Y, Chan, Y, Xin, FX, Wei, X & Shu, WL 2020, Structural and functional properties of SARS-coV-2 spike protein: Potential antivirus drug development for COVID-19. *Acta Pharmacologica Sinica*, 41: 1141-49, https://doi.org/10.1038/s41401-020-0485-4.

Hudson, JB 2012, Applications of the phytomedicine *Echinacea purpurea* (purple coneflower) in infectious diseases. *Journal of Biomedicine and Biotechnology*.

Karimi, M & Gholami Ahangaran M 2021, A brief report on current evidence of traditional chinese medicine in the treatment of patients infected with SARS-CoV-2. *Plant Biotechnology Persa*, 10: 34-36.

Khan, FA, Stewart, I, Fabbri, L, Moss, S, Robinson, K, Smyth, AR & Jenkins, G 2021, Systematic Review and Meta-Analysis of Anakinra, Sarilumab, Siltuximab and Tocilizumab for COVID-19. *Thorax*, 76: 907-919.

Khan, MS & Ahmad, I, 2019, Herbal medicine: Current trends and future prospects. In new look to phytomedicine, Elsevier, pp. 3-13.

Khazdair, MR, Ghafari, SH & Sadeghi, M 2021, Possible therapeutic effects of *Nigella sativa* and its Thymoquinone on COVID-19. *Pharmaceutical Biology*, 59: 694-701.

Konno, K, Sawamura, R, Sun, Y, Yasukawa, K, Shimizu, T, Watanabe, W, Kato, M, Yamamoto, R & Kurokawa, M 2011, Antiviral activities of diarylheptanoids isolated from *Alpinia officinarum* against Respiratory Syncytial Virus, Poliovirus, Measles Virus, and *Herpes simplex* Virus Type 1 *in vitro*. *Natural Product Communications*, 6: 1934578X1100601222.

Lamb, YN 2022, Nirmatrelvir plus Ritonavir: First approval. *Drugs*, 1-7.

Lem, FF, Opook, F, Lee, DJH, Chee, FT, P Lawson, FP & Chin, SN 2021, Molecular mechanism of action of repurposed drugs and traditional chinese medicine used for the treatment of patients infected with COVID-19: A Systematic Scoping Review. *Frontiers in Pharmacology*, 11: 585331.

Lin, A, Won Lee, H, Kim, A & Soo Lee, M 2020, Herbal medicine for the management of COVID-19 during the medical observation period: A review of guidelines. *Integrative Medicine Research*, 9: 100465.

Jafarzadeh, A, Jafarzadeh, S & Nemati, M 2021, Therapeutic potential of ginger against COVID-19: Is there enough evidence? *Journal of Traditional Chinese Medical Sciences,* 8: 267-279.

Johns, M, George, S, Taburyanskaya, M & Poon, YK 2022, A Review of the Evidence for Corticosteroids in COVID-19. *Journal of Pharmacy Practice,* 35: 626-637.

McCreary, EK & Derek, CA, 2020, Efficacy of Remdesivir in COVID-19. *Jama* 324: 1041–1042.

Montoya, C, González, L, Pulido, P, Atehortúa, L & Robledo, SM 2020, Identification and quantification of limonoid aglycones content of citrus seeds. *Revista Brasileira de Farmacognosia,* 29: 710–14.

Muhammad Nadeem, F, Muhammad Issa Khan, M & Hussain, SH, 2012, Nutritional and therapeutic potential of sunflower seeds: A review. *British Food Journal*, 6: 3.

Monique, A, Cardozo, V, D McLaren, M, Garber, A, Remy, D, Baker, J, Gratton, A, Kala, MA, Monteiro, S & Warder, C, 2021, A systematic review on the effects of echinacea supplementation on cytokine levels: Is there a role in COVID-19? *Metabolism Open,* 11: 100115.

Monique, A, Cooley, K, Richard Saunders, P, Carè, J, Anheyer, D, N Medina, D, Cardozo, A, Remy, D, Hannan, N & Garber, A, 2020, The Effect of *Echinacea* spp. on the prevention or treatment of COVID-19 and other respiratory tract infections in humans: A rapid review. *Advances in Integrative Medicine* 7: 203–17.

Obetam, U, 2020, Anti-COVID-19 Properties of ginger (*Zingiber officinale*) assisted Enugu—Nigerian People during the pandemic. *Journal of Bacteriological Infectious Diseases*, no. 3.

Oun, AA, Shin, GH &, Kim, GT 2022, Antimicrobial, antioxidant, and PH-sensitive polyvinyl alcohol/chitosan-based composite films with Aronia extract, cellulose nanocrystals, and grapefruit seed extract. *International Journal of Biological Macromolecules*.

Pandey, S, Pathak, SK, Pandey, A, Ashok Salunke, A, Chawla, J, Sharma, A, Sharma, S, Thivari, P & Ratna, H 2020, Ivermectin in COVID-19: What do we know? *Diabetes & Metabolic Syndrome,* 14: 1921.

Pantsari, T, Ali, MM, Ghouri, MH, Alharbi, AM & Alfahemi H 2022, Role of antiviral drugs in management of mild and moderate Coronavirus disease-19: A systematic review. *Advancements in Life Sciene*, 9: 270-276.

Patrakar, R, Mansuriya, M & Patil, P 2012, Phytochemical and Pharmacological Review on Laurus Nobilis. *International Journal of Pharmaceutical and Chemical Sciences,* 1: 595-602.

Prasanth, DSNBK, Murahari, M, Chandramohan, V, Prasad Panda, S, Rao Atmakuri, L & Guntupalli, CH, 2021, In Silico Identification of Potential Inhibitors from Cinnamon against Main Protease and Spike Glycoprotein of SARS CoV-2. *Journal of Biomolecular Structure and Dynamics,* 39: 4618-4632.

Ranjini, HS, Udupa, EGP, U Kamath, S, Setty, M, Hadapad, B & Kamath, A 2016, An in vitro study of *Cinnamomum zeylanicum* as natural inhibitor of angiotensin-converting enzyme (Ace) on Sheep (*Ovis aries*) Tissues. *Asian Journal of Pharmaceutical and Clinical Research*, 9: 249-252.

Rathinavel, T, Palanisamy, M, Palanisamy, S, Subramanian, A & Thangaswamy, S 2020, Phytochemical 6-Gingerol–A promising drug of choice for COVID-19. *International Journal on Advanced Science, Engineering and Information Technology*, 6: 1482-1489.

Roviello, V & Roviello, GN 2021, Lower COVID-19 Mortality in Italian Forested Areas Suggests Immunoprotection by Mediterranean Plants. *Environmental Chemistry Letters*, 19: 699–710.

San Chang, J, Chih Wang, K, Feng Yeh, C, En Shieh, D & Chai Chiang, L 2013, Fresh ginger (*Zingiber officinale*) has anti-viral activity against human respiratory syncytial virus in human respiratory tract cell lines. *Journal of Ethnopharmacology,* 145: 146-151.

Sawamura, R, Shimizu, T, un, Y, Yasukawa, K, Miura, M, Toriyama, M et al, 2010, *In vitro* and *in vivo* anti-influenza virus activity of diarylheptanoids isolated from *Alpinia officinarum*. *Antiviral Chemistry and Chemotherapy,* 21: 33-41.

Sawamura, R, Sun, Y, Yasukawa,K, Shimizu, T, Watanabe, W & Kurokawa, M 2010, Antiviral Activities of Diarylheptanoids against Influenza Virus in Vitro. *Journal of Natural Medicines*, 64: 117–20.

Sethia, R, Prasad, M, Mahapatra, SJ, Nischal, N, Soneja, M & Garg, P 2020, Efficacy of Famotidine for COVID-19: A Systematic Review and Meta-Analysis. *MedRxiv*.

Shah, S, Das, S, Jain, A, Misra, DP & Negi, VS 2020, A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in Coronavirus disease-19 (COVID-19). *International Journal of Rheumatic Diseases,* 23: 613–19.

Shao, X, Lishuang, Lv, Tiffany Parks, Hou Wu, Chi-Tang Ho, & Shengmin Sang, 2010, Quantitative analysis of ginger components in commercial products using liquid chromatography with electrochemical array detection. *Journal of Agricultural and Food Chemistry* 58: 12608-12614.

Signer, J, R Jonsdottir, H, Albrich, W, Strasser, M, Züst, R, Ryter, S, Ackermann Gäumann, R, Lenz, N, Siegrist, D & Suter, A 2020, Author Correction: In vitro virucidal activity of echinaforce®, an *Echinacea purpurea* preparation, against coronaviruses, including common cold coronavirus 229e and SARS-CoV-2. *Virology Journal*, 17: 1-4.

Silva, A, da, A, Wiedemann, LSM & Veiga Junior, VF 2020, Natural Products' Role against COVID-19. *Rsc Advances*, 10: 23379-23393.

Silva, JKRda, Figueiredo, PLB, Byler, KG & Setzer, WN 2020, Essential oils as antiviral agents, potential of essential oils to treat SARS-CoV-2 infection: An in-silico investigation. *International Journal of Molecular Sciences*, 21: 3426.

Sonawane, KD, Barale, SS, Dhanavade, MJ, Waghmare, ShR, Nadaf, NH, Kamble, SA, Mohammed, AA, Asiya M Makandar, Fandilolu, PM & Dound, AS 2021, Structural insights and inhibition mechanism of tmprss2 by experimentally known inhibitors camostat mesylate, nafamostat and bromhexine hydrochloride to control SARS-Coronavirus-2: A molecular modeling approach. *Informatics in Medicine Unlocked*, 24: 100597.

Srivastava, AK, Kumar, A & Misra, N 2020, On the inhibition of COVID-19 protease by indian herbal plants: An in-silico investigation. *ArXiv Preprint ArXiv:2004.03411*.

Sun, Y, Kurokawa, M, Miura, M, Kakegawa, T, Motohashi, Sh & Yasukawa, K 2016, Bioactivity and synthesis of diarylheptanoids from *Alpinia officinarum*. *Studies in Natural Products Chemistry*, 49: 157-87.

Tiwari, P, Jena, S, Satpathy, S & Sahu, PK 2019, Nigella Sativa: Phytochemistry, Pharmacology and Its Therapeutic Potential. *Research Journal of Pharmacy and Technology*, 12: 3111-3116.

Tomar, O, Akarca, G, Gök, V & Ramadan, MF 2020, Composition and antibacterial effects of laurel (*Laurus nobilis* L.) leaves essential oil. *Journal of Essential Oil Bearing Plants*, 23: 414-421.

Vazirian, M, Alehabib, S, Jamalifar, H, Fazeli, MR, Najarian Toosi, A & Khanavi, M 2015, Antimicrobial effect of Cinnamon (*Cinnamomum verum* J. Presl) bark essential oil in cream-filled cakes and pastries. *Research Journal of Pharmacognosy*, 2: 11–16.

Venkatasubbaiah, M, Dwarakanadha Reddy, P & Satyanarayana, SV 2020, Literature-based review of the drugs used for the treatment of COVID-19. *Current Medicine Research and Practice*, 10: 100–109.

Vimalanathan, S, & Hudson, J 2014, Anti-influenza virus activity of essential oils & vapors. *American Journal of Essential Oils and Natural Products*, 2: 47–53.

Wang, Y, Rong Zhao, M, Gao, LJ, Gao, XF, Wang, DP & Cao, JM 2020, SARS-CoV-2: Structure, biology, and structure-based therapeutics development. *Frontiers in Cellular and Infection Microbiology* 10 (November): 1–17. https://doi.org/10.3389/fcimb.2020.587269.

Wehbe, Z, Wehbe, M, Iratni, R, Pintus, G, Zaraket, H, Yassine, HM & Eid, AH 2021, Repurposing ivermectin for COVID-19: Molecular aspects and therapeutic possibilities. *Frontiers in Immunology*, 12: 663586.

Yakhchali, M, Taghipour, Z, Ardakani, MM, Alizadeh Vaghasloo, M, Vazirian, M & Sadrai, S 2021, Cinnamon and Its possible impact on COVID-19: The viewpoint of traditional and conventional medicine. *Biomedicine & Pharmacotherapy*, 143: 112221.

Yan Qing, Z, Liu, L, Mu Xue, H, Wang, R, Zeng, QQ, Wang, Y, Ye, WC & Zhang, QW 2018, A review of the botany, phytochemical, and pharmacological properties of Galangal. *Natural and Artificial Flavoring Agents and Food Dyes*, 351-396.

Yuen, KS, Ye, ZW, Fung, SY, Chan, ChP & Jin, DY 2020, SARS-CoV-2 and COVID-19: The most important research questions. *Cell and Bioscience*, 10: 1-5, https://doi.org/10.1186/s13578-020-00404-4.

Zahra, A, Hussain, T & Sherwani, SK, 2018, Life after COVID-19 outbreak: Expectations and thoughts. *Advancements in Life Sciences*. 2;7:208-214.

Zakaryan, H, Arabyan, E, Adrian, Oo & Zandi, K 2017, Flavonoids: promising natural compounds against viral infections. *Archives of Virology*, 162: 2539–51.

Zareie, A, Soleimani, D, Askari, Gh, Jamialahmadi, T, Guest, PC, Bagherniya, M & Sahebkar, A 2021, Cinnamon: A promising natural product against COVID-19. In *Identification of Biomarkers, New*

Treatments, and Vaccines for COVID-19, 191–95. Springer.

Zareie, Bushra, Roshani, A, Mansournia, MA, Rasouli, MA & Moradi, G 2020, A model for COVID-19 prediction in Iran based on China parameters. *Archives of Iranian Medicine*, 23: 244–48. https://doi.org/10.34172/aim.2020.05.

Zeraatkar, D, Ellen C, Diaz Martinez, JP, Qasim, A, Mangala, SO, Kum, E, Bartoszko, JJ, Devji, T, Agoritsas, T, & Lamontagne, F 2021, Tocilizumab and Sarilumab alone or in combination with corticosteroids for COVID-19: A systematic review and network meta-analysis. *MedRxiv*.

Bibliographic information of this paper for citing:

Widoyo, H, Mohammed, ZY, Ramírez-Coronel, AA, Iswanto, AH, Thattarauthodiyil, U, Alkhayyat, AS, Karimi, M, Bahmani, M, Eftekhari, Z 2023, Herbal therapy in Covid-19: A systematic review of medicinal plants effective against Covid-19. Caspian Journal of Environmental Sciences, 21: 1289-1298.