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Coronavirus Disease (COVID-19): A Review of Antiviral Potential Herbal Medicines

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Abstract: In Wuhan, China, a severe acute respiratory syndrome caused by coronavirus-2 (SARS-CoV-2) has emerged, causing serious symptoms in patients such as fever, dry cough, and exhaustion. This fatal pandemic spreads over the globe, causing significant infections in humans, mainly in the respiratory tract. To date, researchers have paid close attention to new therapeutic methods, particularly promising antiviral medicines and vaccines. Especially, existing synthetic antivirals have been used against viruses that prevent replication, entry into the cell, and transmission of the virus. These antiviral agents have been the subject of the basis of drug discovery studies that directly affect COVID 19. Since the COVID-19 outbreak, a variety of conventional herbal remedies have been employed either alone or in combination with current medications to treat infected people with encouraging results. Flavonoids, lectins, polysaccharides, alkaloids, terpenes, lectins and essential oils are some natural ingredients with demonstrated antiviral activity. These secondary metabolites have been shown to be effective against a wide range of viruses in the studies on this subject. In this review, we investigated the potential herbal medicines against various RNA, and DNA viruses, including SARS-CoV-2. We also investigated the bioactive substances from medicinal plants and their potential antiviral efficacy.

Keywords: Antiviral, SARS-CoV-2, herbal medicines, COVID-19, 2019-nCoV

1. Introduction

Many traditional medicinal plants have been found to have potent antiviral properties, and some of them have already been used to treat viral infections in animals and humans. After Second World War, Europe's interest in developing antiviral agents grew, and in 1952, the Boots drug business in Nottingham, England, investigated the activity of 288 plants against the influenza A virus in embryonated eggs (Jassim and Naji, 2003). Global public health crises that endanger the world's health and lives as a result of the disease's onset and transmissibility have a significant impact on worldwide health and lives. For decades, scientists have been attracted to contagious diseases caused by coronaviruses (CoVs) in humans (Aanouz et al., 2020).

The coronavirus disease (COVID-19) is a novel strain that has never been identified in humans or the earth before. It was found in China in 2019. The World Health Organization formally classified the Covid-19 outbreak a pandemic on March 11, 2020, because to the disease's widespread global distribution and severeness (Açıkgöz and Günay, 2020; Kılıç and Aydın Eryılmaz, 2022). New therapeutic approaches, including vaccine development (AstraZeneca, Moderna Inc., Johnson & Johnson/Jannsen, and Pfizer-BioNTech) new antiviral drug discovery [lopinavir–ritonavir, remdesivir, favipiravir, interferon-alpha (IFN-α), ribavirin, and arbidol] and combination therapy methods, have attracted great interest so far. In particular, existing synthetic antivirals were used against viruses that prevent replication, entry into the cell and transmission of the virus. These antiviral agents have been the basis of drug discovery studies directly affecting COVID-19 (Saxena, 2020; Akindele et al., 2022). Numerous studies demonstrate that employing herbal remedies alone or in combination with conventional ones to treat COVID-19-infected people can yield favorable effects (Mathai et al., 2022). Some herbal remedies can lower mortality and also significantly heal minor and major symptoms. These plants exhibit antiviral, antioxidant, anti-inflammatory, and immunity-enhancing properties, making them a prospective COVID-19 therapeutic alternative (Luo et al., 2020). Recent research has shown that using naturally occurring bioactive substances, different herbal extracts, and extracted components can have an anti-COVID effect by directly preventing virus entry or multiplication. The angiotensin converting enzyme-2 receptor and the serine protease transmembrane protease serine 2, both of which are required for SARS-CoV-2 to infect human cells, have both been discovered to be inhibited by certain substances. According to reports, these compounds can block specific proteins like papain-like proteins and chymotrypsin-like proteases involved in the life cycle of the SARS-CoV-2 virus (Benarba and Pandiela, 2020; Mathai et al., 2022).

In this review, medicinal plants and their bioactive compounds with antiviral properties that may be effective in COVID 19 were evaluated.

2. Potential Herbal Medicines Against COVID-19

2.1. *Hippeastrum* sp.

The genus *Hippeastrum* Herb. (Amaryllidaceae) comprises about 70 species worldwide, and is widely found in the Brazilian region. The plants belonging to the genus mainly contain alkaloids and possess potent biological activities, such as antiacetylcholinesterase, antiproliferative and antimalarial. Alkaloids, such as licorine, galantamine, and tazettin have been found as attractive, and promising secondary metabolites due to their antiviral activities. It was revealed that the hybrid of *Hippeastrum* species plays an antiviral role against Human Immunodeficiency Virus (HIV: HIV-1, and HIV-2) by inhibiting fusion activity (Kaur et al., 2020). When the antiviral activities of the natural products of the hybrid against human coronavirus strains were investigated, the plant has been found to act by preventing virus attachment at the end of the virus replication cycle. In addition to this, the hybrid agglutinin, the mannose-specific lectin, was determined that it could be responsible for the antiviral effect against coronavirus. The hybrid agglutinin was also shown to inhibit the coronaviruses, together with arteriviruses, and torovirus (Van der Meer et al., 2007).

2.2. *Galanthus nivalis* L.

Galanthus nivalis agglutinin, which is a plant lectin, has been found to be effective against the virus-like synthetic antinidoviral agents, such as pradimycin-A and cyanovine-N (Van der Meer et al., 2007). *G. nivalis* agglutinin was found to have antiviral activity, as well as show a synergistic effect against feline coronavirus in combination with synthetic antiviral nelfinavir. These works displayed that *G. nivalis* agglutinin possesses the antiviral effect by inhibiting the replication of the virus (Hsieh et al., 2010). The lectins are known that they inhibit the hepatitis C virus, with glycosylenic envelope proteins. In a study on mechanistic evaluation of inhibition of hepatitis C virus, the antiviral properties of cyanovirin-N, *Microcystis viridis* lectin, and *G. nivalis* agglutinin were tested, and their IC_{50} values were detectedas 0.6 nM, 30.4 nM, and 11.1 nM, respectively (Kachko et al., 2014; Izquierdo et al., 2016).

2.3. *Narcissus pseudonarcissus* L.

The genus *Narcissus* L., belonging to the family Amaryllidaceae, majorly contains many alkaloids, especially lycorine, which has antiviral activity against some DNA and RNA viruses (Bastida et al., 2011; De Andrade et al., 2012). Lycorine was firstly isolated from *Narcissus* sp. in 1877. According to the literature on lycorine, it was observed to have antiviral effects against poliomyelitis, coxsackie, adend herpes type 1 viruses, as well as anti-SARS-CoV potentials (Bastida et al., 2011).

In a study conducted in 1990, *N. pseudonarcissus* agglutinin was discovered as an effective agent against HIV infection. Later, it was found to have an inhibitory effect on the adsorption of rabies virus (RNA virus) in another study. In addition, it was reported that the antiviral effect of *N. pseudonarcissus* agglutinin against the rubella virus was shown in the same study (Marchetti et al., 1995).

2.4. *Lycoris radiata* Herb.

The genus *Lycoris* Herb. endemic in the East Asian region, is known as an ornamental plant, and possesses great importance because of its medicinal use (Huan et al., 2011). *Lycoris* sp. is used against sore throat, burns, rheumatoid arthritis, food, and snake poisoning, laryngeal complications, and carbuncles in Traditional Chinese Medicine (TCM) (Huan et al., 2011; Tsang et al., 2017). *L. radiate,* from the Amaryllidaceae family, principally contains benzylphenethylamine alkaloids. In a study on this plant, among fifteen bioactive alkaloids of the bulbs of *L. radiate*, lycorine, haemanthamine, hippeastrine, and 11-hydroxyvittatine were found to have anti-Avian Influenza virus activity. It was also reported that these compounds inhibited the Influenza A Virus subtypes, such as H5N1, H3N2, H1N1, and H9N2. It was also explained that lycorine, and haemanthamine showed an inhibition effect on cytoskeleton alternation occurring in the cells infected with H5N1 (Tsang et al., 2017). In another study on more than 200 plants used in TCM, *L. radiate* extract showed the highest antiviral activity against SARS-CoV, and interferon-alpha was used as a positive control. In addition, lycorine was majorly identified as responsible for the antiviral activity of the plant (Li et al., 2005).

2.5. *Allium* L. sp.

The genus *Allium* L., which is commonly represented by *A. sativum* L., *A. cepa* L., *A. porrum* L., and *A. ascalonicum* L., was mostly used as a nutritional value, and medicinal source due to its therapeutic effects. It contains volatile components with organic sulfur, and important non-volatile bioactive constituents, such as flavonoids, lectins, etc. In the literature, the antiviral effects of alicin, diallyl trisulfide, and ajoene have also been demonstrated until now. In one of the studies on the essential oil of *A. sativum*, 18 compounds were identified, 17 of which are organosulfur derivatives. It was also observed that organosulfur compounds inhibited PDB6LU7 of SARS-CoV-2 and ACE2 receptors in the host cell. The highest content of the essential oil (51.3%), consisting of the compounds allyl disulfide and allyl trisulfide, which showed the most potent inhibitory effect on SARS-CoV-2 (Thuy et al., 2020). Otherwise, *A. porrum* was found as ineffective against adenovirus replication, in contrast to this A. *ascalonicum* was demonstrated to have strong antiviral activity against the adenovirus (Chen et al., 2011). Moreover, in a study, that investigated on antiviral activities of the plant lectins, the most promising lectin against the SARS-CoV-induced cytopathic was found to be mannose-specific agglutinin isolated from *A. poruum* with an EC_{50} value of 0.45 µg ml^{-1}. It was also reported that the mannose-specific agglutinin isolated from *A. ursinum* possessed antiviral activity against SARS-CoV (EC_{50}= 18 µg ml^{-1}) (Keyaerts et al., 2007).

2.6. *Colocasia esculenta* L. Schott

One of the plants from the Arecaleceae family, *Colocasia esculenta* has been widely investigated for various biological activities, such as antimicrobial, anthelmintic, antifungal (Reyad-ul-Ferdous et al., 2015). It was observed that the aqueous extract of *C. esculenta* showed strong antibacterial activity against various gram-positive, and gram-negative bacterial strains. The antifungal activity of *C. esculenta* was also found to be high against *Aspergillus niger* and *Candida albicans* (Singh et al., 2011; Reyad-ul-Ferdous et al., 2015). In addition, tarin, purified from the crude extract of *C. esculenta* as mitogenic lectin contains glycoprotein (2-3% carbohydrate). The binding of tarin to specific antigens containing high and complex mannose glycans can be considered as a potential antiviral agent (Pereira et al., 2015).

2.7. *Urtica dioica* L.

A perennial herbaceous plant, *Urtica dioica* spreads to the temperate and tropical regions of Europe, Asia, and America. The plant has important uses in the treatment of cardiovascular disorders, and benign prostatic hyperplasia, as well as for antidiabetic, and diuretic properties (Virgilio et al., 2015; Dhouibi et al., 2020). In addition to this, the methanol extract of *U. dioica* was shown to have strong inhibitory effects on the replication of dengue virus serotype 2. Its active fraction was detected as polyphenolic compounds, including quercetin, and kaempferol glycosides, as well as chlorogenic acid (Flores-Ocelotl et al., 2018). Moreover, *U. dioica* agglutinin is a small lectin isolated from *U. dioica* rhizomes and possessed specific antiviral activity. *U. dioica* agglutinin has been found to show antiviral activity by blocking the replication of viruses, such as HIV (HIV-1 and HIV-2), anti-human cytomegalovirus (CMV), respiratory syncytial virus (RSV) (Balzarini et al., 1992; Dhouibi et al., 2020). *U. dioica* agglutinin, which is a chitin-binding lectin, is capable of inhibiting HIV, related to mannose-binding lectins (Hom et al., 1995). Aqueous extract of *U. dioica* showed good inhibitory effects against feline immunodeficiency viruses, with 84% inhibition at high concentrations of the extract (Manganelli et al., 2005). In another antiviral study by using *in vitro / in vivo* techniques, *U. dioica* agglutinin was shown inhibitory effect on infection with SARS-CoV virus, by binding to SARS-CoV S- glycoproteins in the early stages of the replication cycle. It was also revealed that the lectin reduced the spread of the virus to infected cells (Kumaki et al., 2011).

2.8. *Morus alba* L., and *Morus nigra* L.

The genus *Morus* L. (Moraceae) has been found to exhibit antiviral activity against herpes simplex virus (HSV), rhinovirus, rotavirus, HIV, and various respiratory viruses, and it has been determined that the activity is due to its high flavonoid content (Du et al., 2003). *M. alba,* well known in TCM, and recorded in Chinese

Pharmacopoeia, is a famous medicinal plant. Mori cortex, known as "Sang-Bai-Pi", is used for anti-inflammatory, antihypertension, hypoglycemic, and diuretic purposes. It is also reported that it is beneficial for heart, lung diseases, and asthma in the literature (Du et al., 2003; Geng et al., 2012). The compound, Mulberrofuran G, was isolated from *M. alba* roots and showed potential antiviral activity by inhibiting DNA replication of Hepatitis B (Geng et al., 2012). It was also found that aqueous extract of *M. alba* with flavonoid-rich content showed strong antiviral activity against the dengue virus. *M. alba* extract was also shown to have prophylactic effects in high doses (Maryam et al., 2020). Moreover, the effect of *M. alba* juice was examined against the influenza virus. As a result of this study, the juice was considered to act by inhibiting the binding of surface proteins to cellular receptors of the host (Kim and Chung, 2018).

M. nigra, known as black mulberry in English, is distributed in Africa, South America, and Asia. It has been used in Unani medicine as an antitussive, antihypertensive, expectorant, and diuretic effect. In addition, its root consists of an alkaloid, deoxynojirimycin, as an active component that was considered to be effective against the Acquired Immune Deficiency Syndrome (AIDS) virus (Kumar and Chauhan, 2008; Mohiuddin et al., 2011). The compound, kuwanon-L, isolated from the root extract of *M. nigra,* was demonstrated to have an inhibitory effect on HIV-1 replication by binding to multiple viral targets (Esposito et al., 2015; Martini et al., 2017).

2.9. *Glycyrrhiza glabra* L.

One of the most popular plants in TCM, *Glycyrrhiza glabra*, contains more than 20 triterpenoids, and about 300 flavonoids. The plant, belonging to the Fabaceae family, has therapeutic effects on ulcers, colds, and coughs (Akbudak and Şen, 2021; Öztoprak and Özyazıcı, 2022). It is widely used as an expectorant in the treatment of upper respiratory tract infections, due to the main components of the roots, glycyrrhizin, and glycyrrhetinic acid (Gangal et al., 2020). The antiviral activity of glycyrrhizin, triterpenic saponoside, against various viruses, such as HIV, Hepatitis-C, and HSV was approved by studies (Wang et al., 2015). However, *in vitro* studies have shown that root extracts have antiviral effects against viruses, such as SARS-related coronavirus, respiratory syncytial virus, vaccinia virus, arboviruses, and vesicular stomatitis virus (Gangal et al., 2020). Additionally, the binding affinities of 27 natural compounds including licorice, glabridin, glycoumarin, glycyrrhizin, and liquiritigenin to 6LU7, and 6Y2E which are SARS-CoV-2 proteases, were investigated using molecular docking method. When the results were evaluated, it was found that the binding affinities of the glabridin, glycoumarin, glycyrrhizin, and liquiritigenin were as -8,0;-7,1, -7,5; -7,1, -7,2; -8,4, -7,7;-6,9 kcal mol^{-1}, respectively (6LU7; 6Y2E). The binding affinity of Saquinavir was -9,2; -7,9 kcal mol^{-1} which is a synthetic anti-HIV drug (Sampangi-Ramaiah et al., 2020).

2.10. *Nigella sativa* L.

Nigella sativa known as black cumin in Türkiye was revealed that it acts on the virus by reducing the coronavirus replication. According to the literature, nigellidine, and α- hederin were isolated from *N. sativa*, and had the best potential to act as SARS-CoV-2 treatment (Ulasli et al., 2014). Some of *N. sativa* compounds, including as nigellidine (Banerjee et al., 2021; Maiti et al., 2022), α-hederin (Ulasli et al., 2014; Dorra et al., 2019; Mir et al., 2022), rutin and nigellamine A2 (Baig and Srinivasan, 2022), hederagenin (Barakat et al., 2013; Oyero et al., 2016), thymohydroquinone (Romano and Tatonetti, 2019; Esharkawy et al., 2022; Mani et al., 2022), thymoquinone (Barakat et al., 2010; Onifade et al., 2013a,b; Xu et al., 2021), caryophyllene oxide, β-bisabolene (Duru et al., 2021), dithymoquinone (Ahmad et al., 2021; Pandey et al., 2021; Rizvi et al., 2021) were shown to have diverse mechanisms of action against SARS-CoV-2 using *in vitro, in vivo,* and *in silico* investigations (Koshak and Koshak, 2020). Therefore, it was considered that these phytoconstituents could be potential inhibitors of SARS-CoV-2. In another study, Molecular Operating Environment software was used to dock components from *N. sativa* and medications now undergoing clinical testing with the primary proteases in CoVs. When nigellidine and α-hederin are docked into the 6LU7 and the 2GTB active sites, they were found as promising agents for the potential to treat COVID-19 as compared with hydroxychloroquine, favipiravir, and chloroquine (Bouchentouf and Missoum, 2020).

In addition, clinical studies on the use of *N. sativa* against SARS-CoV-2 have common been proceeding (Ulasli et al., 2014). It was reported that the use of *N. sativa* oil by adult patients with mild COVID-19 was linked to a stronger probability of reduction in symptoms and a quicker recovery (Koshak et al., 2021). Clinical studies to treat/prevent COVID-19 were revealed in a review, performed in various countries, Saudi Arabia, Pakistan, Tunisia, the United States, and Egypt. According to the clinical studies on prevention or treatment of COVID-19, a 500 mg capsule, including *N. sativa* and/or *N. sativa* oil in adequate dose was usually utilized and *N. sativa* was also combined with honey, or Omega 3. In addition, *N. sativa* is described in the scientific literature for patent as an immunomodulator, antioxidant, anti-inflammatory, a source of anti-SARS-CoV-2 phytochemicals and having lung-protective properties (Imran et al., 2022).

2.11. *Crocus sativus* L.

Crocus sativus belongs to the Iridaceae family, had a wide range of biological activities, such as antibacterial, antimicrobial, emmenagogue, antiviral, antioxidant antihyperglycemic, and antihyperlipidemic. As for the phytochemical research on *C. sativus*, crocin, picrocrocin, crocetin, and safranal were considered as the main constituents responsible for its biological activities above-mentioned (Rahmani et al., 2017). Moreover, *in vitro* study reported that crocin prevented replication of HSV before, and after entering into host cells. It also suppressed the penetration of HSV into the host cell. Similarly, it was shown that picrocrocin possessed antiviral activity by inhibiting the entry, and replication of the virus (Aanouz et al., 2020).

2.12. *Nicotiana tabacum* L.

Nicotiana tabacum (Solanaceae) contains various secondary metabolites, such as phenolic compounds, lignans, isocoumarins, sesquiterpenes, diterpenoids, and alkaloids. Its major compound was detected as nicotine. Nicotine mainly plays an important role in the cigarette industry. Otherwise, the plant is also used in TCM as an anesthetic, sedative, antispasmodic, diuretic, emetic, antibacterial, antiviral, antiasthma, anticonvulsant, antifungal, and insecticide due to its major components of it. In addition, the anti-HIV activity of the phenolic compounds of the plant including the phytochemical determination of its composition was demonstrated in the literature (Chen et al., 2012; Rawat and Mali, 2013; Shang et al., 2015).

2.13. *Nerium oleander* L.

The positive inotropic effects of cardioactive heterosides in medicinal plants, such as *Digitalis* sp., *Nerium s*p., and *Theveatia* sp. have been known for many years. As for these natural compounds in modern therapy, Anvirzel™, a cancer drug, that contains an aqueous extract of *N. oleander*, has oleandrin as the active compound. Anvirzel™ / oleandrin exhibited an antiviral effect by inhibiting the ability of HIV-1 infection to the target cell (Singh et al., 2013). Inhibitory effects of cardioactive heterosides like digoxin, digitoxigenin, and lanatoside C on human adenovirus were found to be significant. In addition, antiviral effects of digitoxigenin against HSV, and HIV have been reported in the studies (El Sayed, 2000; Saha et al., 2019). In Morocco, the inhibitory effect of 67 natural compounds against SARS-CoV-2 was investigated using molecular docking. It was founded that crocin (*C. sativus*), digitoxigenin (*N. oleander*, and *Theveatia* sp.), and *β*-Eudesmol (*L. nobilis*) showed strong inhibitory activities against the virus (Aanouz et al., 2020).

The lack of available treatments for COVID-19 has prompted researchers and professionals in the pharmaceutical and herbal medicines to conduct in-depth study on plant-based products, particularly those that have already demonstrated antiviral characteristics. Table 1 shows that other herbal medicinal plants act on various viruses with their mechanism of actions, and virus types.

3. Conclusions

Several secondary metabolites, such as flavonoids, lectins, polysaccharides, alkaloids, terpenes, and essential oils are natural origin compounds that have proven antiviral activity. In the studies on this issue, these secondary metabolites have been found effective against broad spectrum viruses. Therefore, these metabolites are thought to be important to the discovery of new agents against the rapidly spreading COVID-19, which causes fatal results worldwide.

According to the literature, some medicinal plants, such as *Hippeastrum* hybrid, *Galanthus nivalis*, *Narcissus pseudonarcissus*, *Lycoris radiata*, *Allium porrum*, *Allium ursinum*, *Cymbidium* hybrid, *Listeria ovata*, and *Epipactis helleborine*, inhibit viral attachment at the end of the replication cycle. It was found that major compounds, which can be responsible for this effect, are mannose-binding lectins, agglutinin derivatives.

As a result, natural agents and herbs with immunomodulatory properties should be examined more in the future. Furthermore, clinical trials on the efficacy and safety of possible natural compounds and herbs are required to treat COVID-19.

Table 1. Other herbal medicines with their mechanism of action

Plant	Virus type	Mechanism of action	Reference
Cymbidium hybrid *Listera ovata* L. *Epipactis helleborine* L. *Tulipa* hybrid	HIV-1, HIV-2, CMV, RSV, and influenza A virus	They carry carbohydrate-binding agents for targeting viruses	Balzarini et al. (1992), Mani et al. (2020)
Phyllanthus sp.	HSV-1 and HSV-2	Potentially effective in the early infection and replication phase of the virus	Anbazhagan et al. (2019), Anand et al. (2021)
Tribulus terrestris	SARS-CoV	Inhibitory activity against SARS-CoV PL^{pro}	Song et al. (2014)
Houttuynia cordata Thunb.	SARS-CoV	Inhibiting SARS-CoV-like protease, and RNA polymerase	Lau et al. (2008)
Withania somnifera L.	SARS-CoV-2	Inhibitory activity against M^{pro} of SARS-CoV-2	Tripathi et al. (2021), Anand et al. (2021)
Camellia sinensis L.	SARS-CoV-2	Inhibitory activity against M^{pro} of SARS-CoV-2	Ghosh et al. (2020), Anand et al. (2021)
Azadirachta indica A. Juss	SARS-CoV-2	Inhibitory activity against M^{pro} of SARS-CoV-2	Anand et al. (2021)
Tinospora cordifolia (Willd.) Miers	SARS-CoV-2	Inhibitory activity against $3CL^{pro}$ of SARS-CoV-2	Chowdhury (2021)
Pisum sativum L. *Lens culinaris* Medik. *Lathyrus ochrus* L. *Canavalia ensiformis* L. *Pterocarpus angolensis* DC. *Vicia faba* L.	SARS-CoV-2	SARS-CoV-2 spike envelope binding activity	Konozy et al. (2022)
Ammoides verticillate Desf. (Components of essential oils)	SARS-CoV-2	Potential inhibitors to the ACE_2 receptor of SARS-CoV-2	Abdelli et al. (2020)

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The authors declare that they have contributed equally to the article. All authors declare that they have seen/read and approved the final version of the article ready for publication.

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Declaration of Conflicts of Interest

All authors declare that there is no conflict of interest related to this article.

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