Therapeutic Options for the SARS-CoV-2 Virus: Is There a Key in Herbal Medicine?

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Abstract

SARS-CoV-2 has been responsible for over 500 million cumulative cases all over the world since December 2019 and has marked the third introduction of a highly pathogenic virus after SARS-CoV and MERS-CoV. This virus is in a winning situation because scientists are still racing to explore effective therapeutics, vaccines, and event treatment regimens. In view of progress in current disease management, until now none of the preventive/treatment measures can be considered entirely effective to treat SARS-CoV-2 infection. Therefore, it is required to look up substitute ways for the management of this disease. In this context, herbal medicines could be a good choice. This article emphasizes the antiviral potential of some herbal constituents which further can be a drug of choice in SARS-CoV-2 treatment. This article may be a ready reference for discovering natural lead compounds and targets in SARS-CoV-2 associated works.

Introduction

The recent eruption of β coronavirus (CoV-19) started in early December 2019 in Wuhan city of China. A large population of pneumonic patients was identified leading to the death of thousands of patients globally caused by CoV-19. The very popular name of CoV-19 by the World Health Organization is severe acute respiratory syndrome Corona virus-2 (SARS-CoV-2).[1] Till July 15th, 2022, over 565.5 million infected cases have been reported, of which, more than 6.3 million have lost their life.[2]

Coronavirus (CoVs) was identified for the first time in 1960 under the family *Coronaviridae*. Four types of CoVs have been discovered to date, among which α and β CoVs tend to circulate in mammalians and δ and γ CoVs in birds.[3,4] Till now six subtypes of human vulnerable CoVs have been recognized of which two CoVs, namely HCoV-229E and HCoV-NL63, belong to α CoVs while HCoV-HKU1, HCoV-OC43, SARS-CoV, and MERS-CoV are β CoV.[5] All identified human susceptible CoVs have low pathogenicity, except SARS-CoV and MERS-CoV. Several deaths were recorded due to the outbreak of SARS-CoV[6] and MERS-CoV[7] in 2003 and 2012, respectively. Crossing the boundaries SARS-CoV-2 has represented a pandemic risk globally.

A report stated that SARS-CoV-2 has long genomes (up to 32 kb), which are in the same β CoVs clade as bat CoV RaTG13

(96.2% genomic similarity) and SARS-CoV (79.5% genomic similarity).[8] SARS-CoV-2 is a positive sense single-stranded

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RNA. Several proteins, like spike (S), membrane (M), nucleo-capsid (N), and envelope (E), are protected in the viral structure and characterized by their unique function. S protein is a surface protein that forms homotrimeric spikes on the virus surface which functionally regulate the binding and fusion of the virus into the host cell through their subunits S1 and S2. M and E proteins give the virus its shape and a matured viral envelope. Apart from this function, the E protein is also involved in the production of virus-like particles. Unlike other proteins, N protein is present inside the envelope and binds with RNA to make nucleocapsids.[9,10]

Since the beginning of the SARS-CoV-2 outbreak, numerous studies have been conducted showing potential applications for the prevention and recovery management of the disease. Herbal medicines have shown appreciable results in improving the clinical condition associated with the disease, not only by regulating the pro- and anti-inflammatory cytokines, but also by showing alleviated antiviral activities.[11] Thus, the aim of this review article is to summarize some selected phytoconstituents which have been traditionally used to treat various infectious diseases, so that their application may be explored for the effective management of SARS-CoV-2 infection.

Mechanism of Viral Infection

SARS-CoV-2 uses its spike (S)protein to internalize with the human angiotensin-converting enzyme 2 receptor (hACE2), which is found on ciliated lung epithelia.[8] The S proteins of the virus mediate the membrane fusion process through hACE2 to infect human cells (Figure 1). Further, the internalization of S protein and the hACE2 receptor facilitate the fusion and infection by bringing the viral and cellular membranes close.[12] After entering the cell, the envelope of SARS-CoV-2 is removed and virus RNA is released into the cytoplasm of the host cell.

RNA of SARS-CoV-2 directly enters into the ribosome of the host cell for translation. Therefore, it can directly produce the essentially required proteins to replicate in the host cell cytoplasm. The RNA-dependent RNA polymerase (RdRp) enzyme first transcribes the negative strand which is used to translate additional proteins and replication of new positive-stranded RNA genomes for the reproduction of newer viruses. The large polyprotein translated by the host ribosome is slashed by its own proteases into multiple proteins.[13] The nucleocapsid protein N binds with the helical RNA and enters into the lumen of the endoplasmic reticulum, where it is enveloped by lipid, spike protein S, and envelope protein E. Further, these newly formed viruses in the host cell are transported to the cell membrane through Golgi vesicles and exocytosed into extracellular space to infect new cells.[13] This process increases the viral load in the infected individual and the infected person starts showing symptoms and becomes a carrier of the virus also. Subsequently, the person-to-person spread of infection is initiated by contact with infected individuals.[14] It is also evident that SARS-CoV-2 may be present in the feces of infected individuals

and even after the patient is cured, thereby indicating a feco-oral route of viral transmission as well.[15]

Potential Antiviral Herbal Constituents

The application of phytoconstituents for antiviral indications is not new. Various published reports have shown the potential applications of herbal products in various diseases associated with viruses such as hepatitis, influenza, HIV, and SARS-CoV. Here, we summarize various phytoconstituents which have been explored against viral infection and further could be used for the effective management of SARS-CoV-2.

Hesperidin

Hesperidin (formerly called vitamin P, $C_{22}H_{34}O_{15}$) is a bioflavonoid and a by-product of various citrus fruits like sweet orange (*Citrus aurantium*), lemon (*C. limon*), grapefruit (*Witis vinifera*), mandarin (*C. unshiu*), and Cala mansi (*C. mitis*). In addition to citrus fruits, it is also present in sufficient quantities in non-citrus fruits like prickly ash (*Zanthoxylumavicennae*), indigofera (*Indigoferatinetoria*), and peppermint (*Mentha piperita*).[16] Hesperidin is a glycoside composed of an aglycone (hesperetin) and a disaccharide (rutinose), thus called hesperetin 7-*O*-β-rutinoside[17] (Figure 2a).

Hesperidin has been of considerable interest due to its pharmacological activities. Garg et al proved its application for treating various diseases associated with increased permeability of blood capillaries and manifested in symptoms like edema, hypertension, and bleeding. Various reports support that hesperidin reduces capillary permeation and gives symptomatic relief in such diseases, including diabetes, hemorrhoids, scurvy, ulcer, bruising, and tuberculosis.[18] Reports also suggest its application because of its anti-lipidemic,[19] antihypertensive, diuretic,[20] and neuroprotective activities.[16] Hesperidin also regulates the levels of various inflammatory markers like interleukin (IL) and tumor necrosis factor-α (TNF- α).[21,22]

Hesperidin could be a choice of phytoconstituent to treat SARS-CoV-2 infection because of its capacity in controlling capillary permeation and inhibiting various inflammatory markers (IL and TNF-α). A recent report[23] has shown ACE2 receptor affinity of some flavonoids, including hesperidin, using molecular docking. The study implied that these flavonoids could play a potential role in SARS-CoV-2 treatment. A similar computational study[24] inferred that hesperidin might be a 3-chymotrypsin-like protease inhibitor. Using docking methodology, an interfering mechanism of S protein with ACE2 receptor was established. Another published report confirmed the low binding energy of hesperidin with the ACE2 receptor compared to Nelfinavir[25] and can be used against SARS-CoV-2 infection. In another study, the phytoconstituent was screened against the modeled structure of the receptor binding domain of the S protein and ACE2 receptor. The pharmacokinetic parameters of hesperidin were analyzed using various modelling software and showed good
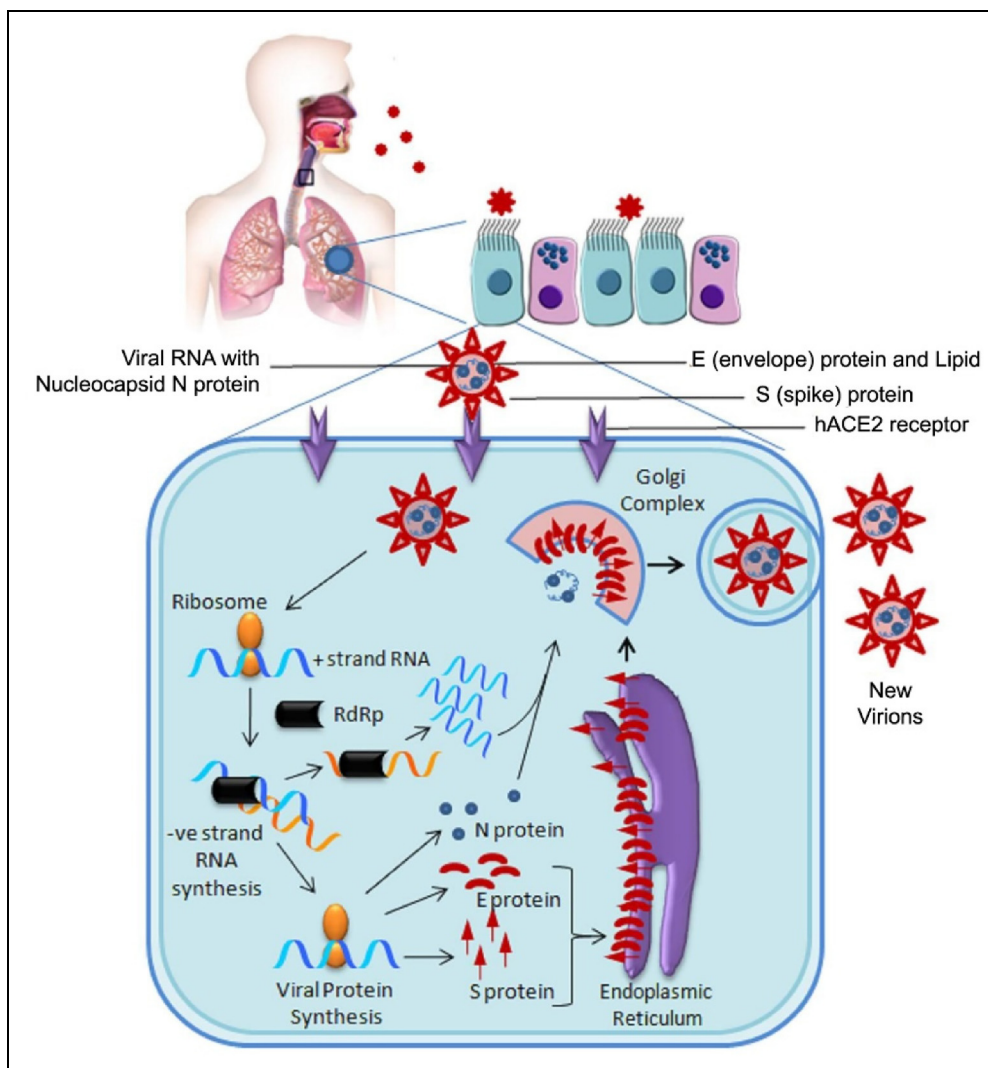
Figure 1. Schematic diagram of the viral infection process in lung epithelial cells.

pharmacokinetics properties, minimal toxicity, and good bioavailability.[26] A report of a clinical study also confirmed that the application of 1 g hesperidin daily showed a reduction of 14.5% of symptoms associated with SARS-CoV-2 infection in 216 symptomatic non-vaccinated subjects.[27]

Quinonemethide Triterpenoids

Quinonemethide triterpenoids (QMTs) are secondary metabolites present specifically in plants belonging to the family Celastraceae, which is comprised of approximately 90 tropical and subtropical genera of shrubs and lianes.[28] The name of this family (Celastraceae) is due to the presence of celastrol, an atripterine belonging to the quinine methides. In nature, QMTs are also considered a chemotaxonomic biomarker of the family. QMTs are the most common class of celastroloids, consisting of a quininemethide chromophore with a triterpenoid skeleton (Figure 2b).

To date, QMTs have been investigated for many therapeutic effects, such as anticancer, anti-inflammatory, and antileukemia activity.[29] A published report demonstrated the inhibitory activity of some QMTs (celastrol, pristimerin, and tingenone isolated from *Triterygium regelii*) against SARS-CoV. Molecular docking simulation was used to investigate the interaction of QMTs with the active site of SARS-CoV and their potential effectiveness was shown by low values for docking energy.[30] With the genomic similarity of SARS-CoV and SARS-CoV-2, QMTs may also be considered as potential therapeutic agents against SARS-CoV-2.

Emodin

Emodin [6-methyl-13,8-trihydroxyanthraquinone (Figure 2c)] is a natural anthraquinone derivative. It is isolated from different medicinal plants of Asian and European origin, namely, *Aloe vera*, Himalayan rhubarb (*Rheum austral*), buckthorn (*Rhamnus* species), rhubarb (*Rheum barbarum,* and *R rhaponticum*),
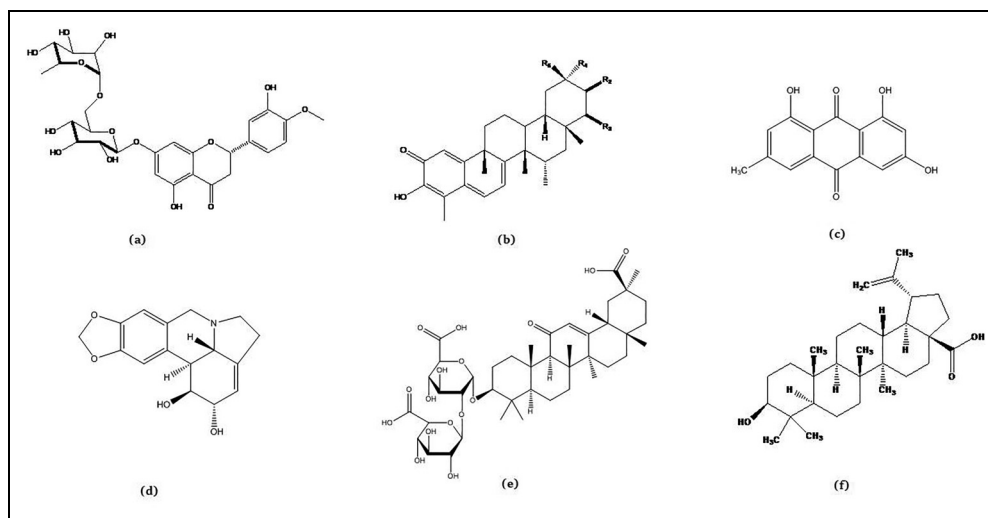
Figure 2. Chemical structure of (a) hesperidin, (b) quinine methide triterpenoids, (c) emodin, (d) lycorine, (e) glycyrrhizic acid, and (f) betulinic acid.

Japanese knotweed (*Reynoutria japonica* syn. *Polygonum cuspidatum*), and Chinese rhubarb (*Rheum palmatum*).[31,32]

Emodin has shown several therapeutic values including hepatoprotective, anticancer, and antimicrobial activities.[31] Its antiviral activity against different viruses is well documented. Inhibitions of virus replication were studied on Hep-2 cells, using MTT and plaque reduction assays. Emodin exhibited potent inhibitory effects against both the selected viruses. However, it did not block the absorption of the virus into cells and could not inactivate the viruses directly.[33] In another work, the application of emodin against coxsackievirus B4 was shown.[34]

A recent report stated the inhibition of SARS-CoV and HCoV-OC43 by emodin.[35] Batista et al have also proved the virucidal effect of emodin against the Zika virus. At a 40 μM concentration, emodin inhibited the infectivity by 83.3%.[36] Li et al, in a review article, have mentioned that emodin can be used against viroporin-like protein B2 of picornaviruses.[37] Rheum emodin was also reported to be active against enterovirus 71, which can cause encephalitis and acute flaccid paralysis.[38,39] A very recent study by Horvat et al also demonstrated the antiviral activity of emodin derivatives against human CoVs NL63.[40] However, longstanding use of emodin may cause renal toxicity, hepatotoxicity, and reproductive toxicity.[31]

Lycorine

Lycorine is a pyrrolophenanthridine alkaloid (Figure 2d) found in various Amaryllidaceae species.[41] It was first isolated from *Narcissus pseudo-narcissus* and, therefore, initially called narcissia, but was later named lycorine. This alkaloid is reported to possess different pharmacological activities namely antiparasitic,[42] antibacterial,[43] anti-inflammatory,[44] anti-tumor,[45] and antiviral.[46] Lycorine is reported for increasing the survival of mice infected with human enterovirus-71. The possible mode of action of lycorine is a viral replication inhibitory effect by blocking the elongation of the viral polyprotein.[47]

Lycorine is also reported as a potent therapeutic substance against SARS-CoV and avian influenza (H5N1) virus.[48] Guo et al demonstrated the mechanism of 32 lycorine derivatives against the hepatitis C virus.[49] Another report also suggested that lycorine can interfere with the replication of poliovirus.[50] A cellular study conducted by Zhang et al, also confirmed the SARS-CoV-2 inhibitory activity of lycorine. However, only an extensive clinical study can confirm the application of lycorine in the management of the disease.[51]

Glycyrrhizic Acid

Glycyrrhizic acid, obtained from liquorice root (*Glycyrrhiza glabra*), is a saponin that is also known as glycyrrhizin or glycyrrhizinic acid. This is a well-recognized phytoconstituent from ancient times used for the treatment of several viral infections.[52] This is an amphiphilic molecule (Figure 2e).[53]

Wang et al have reported the activity of glycyrrhizic acid against coxsackievirus A16 and enterovirus 71. The antiviral activity was evaluated using Vero cells.[54] Glycyrrhizic acid has also been reported for the treatment of hepatitis C.[55,56] Viral entry and replication steps were blocked when treated with glycyrrhizic acid. An antiviral effect against porcine parvovirus has been reported by Li et al. A potent, dose-dependent inhibitory effect was seen when the virus was treated before infection.[57]

Lin et al have published the inhibitory potential of glycyrrhizic acid and some other derivatives against Epstein-Barr virus infection.[58] The phytoconstituents also demonstrated an inhibitory effect against rotavirus replication.[59] Glycyrrhizic acid is also reported to inhibit many viruses infecting the respiratory system, namely influenza A, H1N1, and SARS-associated

CoVs.[60–62] Glycyrrhizic acid and its derivatives showed potential against SARS-associated CoVs when tested against two clinical isolates.[62] The above data showed good support regarding the potential application of glycyrrhizic acid in combating COVID-19. More randomized clinical trials will be required to obtain a precise conclusion.

Betulinic Acid

Betulin, a pentacyclic triterpene, is obtained from the outer bark of *Betula* species, family *Betulaceae* (Figure 2f). Betulinic acid,[63] which can be obtained from ethanolic and methanolic extracts of *Betula* species,[64] possesses various pharmacological activities like anticancer,[65,66] antibacterial,[67] antiplasmodial,[68] and antileishmanial.[69] Various studies have suggested the inhibitory activity of betulinic acid against many viruses, such as HIV-1NL4-3 and HIV-1JRCSF.[70] In one study, betulinic acid derivatives were used against the HIV virus.[65] In some other

Table 1. Possible Mechanism of Action of Various Phytoconstituents as Antiviral Agents.

Phytoconstituents	Possible mechanism of action	Reference
Hesperidin	Prevents SARS-CoV-2 internalization with the host cell by showing affinity to the three main protein receptors of SARS-CoV-2 (SARS-CoV-2 protease domain, the receptor binding domain of the spike glycoprotein, and the receptor binding domain of ACE2 at the protease domain	81
Quinonemethide triterpenoids	3C-like protease (3CLpro) inhibitor	30
Emodin	Inhibits the ion channel formed by the 3a protein and thus prevents virus release	31
Lycorine	Although the exact mechanism is unclear, the antiviral effect may be due to the reproduction inhibition by hindering viral polymerase activity or extension of the viral polyprotein during protein synthesis	47
Glycyrrhizic acid	Inhibition of virus replication in the host cell. It also inhibits adsorption and penetration of the virus in the early steps of the replicative cycle	62
Betulinic acid	3C-like protease (3CLpro) inhibitor	76
Lectins	They bind with SARS surface proteins, which are heavily glycosylated, and inactivate them from binding to host cells.	79

studies, the compound showed significant inhibitory potential against ECHO-6 virus,[71] and A549 cells infected with influenza A/PR/8 virus.[72] Some analogues of betulinic acid also display anti-Human Papilloma Virus type 11 activity.[73] A study conducted on the antiviral activity of natural products against CoVs suggested that betulinic acid may be considered active against SARS-CoV 3CLpro.[74] Molecular docking analysis was conducted on natural products and the study suggested that betulinic acid has the potential to inhibit the replication and 3CLpro target of 2019-nCoV with a binding energy of 4.23.[75,76] Considering the previous reports, these phytoconstituents may be future therapeutic agents against 2019-nCoV due to their additional anti-inflammatory action and significant activity against SARS-CoV.

Lectins

Lectins are naturally-occurring glycoproteins. Some foods with higher levels of lectins include beans, peanuts, lentils, tomatoes, potatoes, eggplants, vegetables, and wheat. Lectins protect plants during development.

Concanavalin A (ConA), a phytagglutinin detected in jack beans (*Canavalia ensiformis*), was found to be active against CoVs in previous studies. The plant is widely distributed in northeast India, south Asian countries, and North America. In India, this plant is cultivated for domestic use. ConA is responsible for the interim inactivity of the virus by binding glycosylated membrane proteins that enable viruses to recognize host cells.[77] The various biological features associated are related to the lectin's carbon binding characteristics. The Con A monomer is made from 237 amino acids (Mr ≈ 26500 Da) and is positioned in two anti-parallel b-sheets. This has high glucose/mannose carbohydrate empathy, especially in carbohydrates with a high level of 3,6-di-*O*-(α-D-mannopyranosyl)-D mannose. The tetramer Con A differentiates into its canonical dimer below pH 6.5. A high pH/metal ion binding is known to be the monomer–dimer–tetramer equilibrium, which indicates that there is a large decrease in the number of hydrogen intermediates bindings of Con A.[78]

Carrington and collaborators (1985) found that ConA has up to 15% protein and a circular homology is evident in comparing the sequences of amino acids from different species.[78] ConA easily binds with the virus, and, after treatment with conA, the virus loses its hemagglutination properties and infectivity is transiently interrupted. The application of ConA is nevertheless limited by its extreme hepatotoxicity.[79] Ahmed et al (2022) demonstrated the role of various lectins exhibiting antiviral activities, especially against SARS-CoV. However, extensive clinical evidence is required to support the statement[80] (Table 1).

Anti-Malarialphytoremedies

According to an international study by thousands of doctors, anti-malarial medicines are the best CoVs treatment currently

available. From 30 countries, and about 2000 doctors surveyed, 37% said that they were the most efficient virus therapy. Doctors in Europe, the USA, and China were given permission to prescribe hydroxychloroquine to SARS-CoV-2 patients when the epidemic was spiralling and there was no treatment at all. Some phytoremedies can also be looked at for the treatment of CoVs when considering the potential of anti-malarial medicines.

Artemisinin, which is obtained from *Artemisia annua* leaves, is perhaps the most powerful natural anti-malarial source. Artemisinin is only used in conjunction with other anti-malarial drugs consisting of Artemisinin Combination Therapy, owing to weak pharmacokinetic properties and careful attempts to curtail monotherapy resistance. In the developing world, Artemisinin involves a small return on the plant and higher costs for secondary anti-malarial drugs in Legislation. Apparently, this is the only way to treat the malaria parasites with increased drug resistance such as chloroquine and hydroxychloroquine.[82,83] Data obtained from a randomized and controlled clinical study revealed the efficacy of artemisinin-piperaquine for the treatment of COVID-19, with 10.6 ± 1.1 days mean time to reach an undetectable viral RNA level for the treatment group and 19.3 ± 2.1 days for the control group.[84]

Chinese Remedies Against SARS-CoV

Some Chinese herbs are known for their antiviral effects and have, therefore, been investigated for their potential function against SARS-CoV75.[85] Many studies showed that they decrease the expression of inflammatory markers and regulate the TLR7/NF-κB pathway to show antiviral effects.[86] Gao *et al* studied the anti-inflammatory and immunoregulatory potential of Yupingfeng powder. The study showed that the formulation was effective against external pathogens such as SARS-CoV infection. Furthermore, humoral and cellular immune function in mice with immunosuppression also improved with the formulation.[87] Another Chinese formulation, named Lianhuaqingwen capsule, is one of the most prescribed Chinese formulations to treat respiratory tract infections. This formulation effectively suppresses the inflammatory cytokines and thereby may be a promising option for controlling the influenza virus.[88] A clinical trial conducted on COVID-19 infected patients revealed the effectiveness of Lianhuaqingwen by showing rapid recovery as compared to the control group.[89]

A large number of herbal extracts show efficiency against SARS-CoV, some of them being *Lycoris radiata, Artemisia annua, Pyrrosia lingua,* and *Lindera aggregata. Lycoris radiata* extract was the most active. Bioassay-guided chromatographic separation of the extract led to the isolation of lycorine, which inhibited SARS-CoV at a concentration of 15.7 nM. Lycorine showed a high specificity index against HepG2 cell lines.[90] Another work, reported by Lau and coworkers, shows the inhibition of two main SARS-CoV proteins (3CLpro and RdRp) by the aqueous extract of *Houttuynia cordata.*

Additionally, the extract also increased the cell count of CD4 + and CD8 +, indicating its immune/stimulation function.[91] Recent results indicate that three alkaloids, tetrandrine, fangchineoline, and cephoranthine substantially prevent viral-induced cell death. The replication of HCoV-OC43, along with S and N protein expressions, was significantly suppressed by alkaloidal treatment.[92] A total of 221 phytochemicals were screened for SARS-CoVantiviral activity; 10 diterpenes, 2 sesquiterpenes, 2 triterpenes, five lignans, and curcumins were shown to have an inhibitory activity.[76]

Here we have summarized some of the previously reported phytoconstituents being used as antivirals for other CoVs infections. The inhibitory mechanisms of these phytoconstituents may also be replicated for the prevention of COVID-19. However, extensive research and clinical evaluation are required to establish these phytoconstituents as effective tools against COVID-19 infection.

Conclusion

Herbal drugs have been useful in various viral infections. Many phytoconstituents have exhibited excellent antiviral properties and the mechanism of their action against different viruses has been reported. In the case of the outbreak of the COVID-19 pandemic, a situation for which there were no available drugs, and completely effective vaccines, many herbal molecules that have shown potent anti-SARS-CoV activity may find application. However, clinical studies of some phytoconstituents, such as hesperidin, emodin, artemisinin, lycorine, and lianhuaqingwen, have shown exciting anti-SARS-CoV efficacy. However, still more phytoconstituents should be studied through proper clinical trials to find more effective anti-SARS-CoV treatments.

Ethical Approval

This study does not directly involve humans or other organisms as it is a review study.

Consent for Publication

All authors consented to submitting the manuscript to Natural Product Communications.

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