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Plant Therapy of Corona Virus

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Abstract

COVID-19 caused by SARS-CoV-2 is declared global pandemic. The virus owing high resemblance with SARS-CoV and MERS-CoV has been placed in family of beta-coronavirus. Effective management strategy with potential drug availability will break the virus transmission chain subsequently reduce the pressure on the healthcare system. Extensive research trials are underway to develop novel efficient therapeutics against SARS-CoV-2. In this review, medicinal plants are discussed which could serve as potential candidates for drug development against COVID-19 infection.

Keywords: SARS-CoV-2; Virus; Bat fever; Wuhan; Human health

Introduction

COVID-19 appeared in late December in Chinese city, Wuhan (Hubei province) [1]. This rapidly spread worldwide and has infected 3.78 million peoples globally causing 265 thousand deaths (as per 07-05-2020). Following the severity of pandemic, WHO declares public health emergency around the globe on 30 January 2020 [2] and has estimated a 4% case fatality rate (CFR) for COVID-19.

This virus has affected many persons in China and spread to other countries in a noticeably short time. There are not yet effective treatments that target the 2019-nCoV. Development of these treatments may require months or years, meaning that a more immediate treatment or control mechanism should be found if possible. Herbs used in traditional Chinese medicine present a potentially valuable resource to this end. The coronavirus encodes more than one dozen proteins, some of which are essential to viral entry and replication. Among these proteins, the most well-studied are papain-like protease (PLpro), 3C-like protease (3CLpro) and spike protein.

Coronavirus spike protein uses angiotensin converting enzyme 2 as a receptor to help the virus enter cells. These three proteins make attractive targets for drug development [3]. CoV is a single stranded RNA virus belong to the Coronaviridae family and is enveloped. Its family embodies quite a lot of species causing infections of upper respiratory tract and gastrointestinal infections in birds and mammals. Humans complications include cold, SARS and pneumonia. The well-known human CoV (HCoV) embodies -NL63, HCoV-229E, -HKU1, -OC43 and the more extensively identified severe acute respiratory syndrome coronavirus (SARS-CoV) which caused a global danger with very high mortality in 2003. The World Health Organization (WHO) selected Middle East respiratory syndrome coronavirus (MERS-CoV) as a sixth type of HCoV infection linked with elevated casualty. There is not a single unambiguous treatment available for CoV infection and lot of research work going for evolution of preventive vaccines. Thus, the current situation necessitates the urgency to develop antivirals for effective prophylaxis and treatment of CoV infection.

Viral infections play an imperative role in human diseases, and latest outbreaks in the initiation of globalization and easiness of travel have underscored their prevention as a grave issue in conservation community health. Despite the advancement done in immunization and development of drugs, numerous viruses be deficient in preventive vaccines and competent antiviral therapies, which are frequently inundated by the generation of viral run-away mutants. Herbal drugs and purified natural products afford a wealthy supply for novel antiviral drug development. Identification of the antiviral mechanisms from these

natural agents has shed light on where they interact with the viral life cycle, such as viral entry, replication, assembly, and release, as well as on the targeting of virus host specific interactions.

Antiviral effects from several natural products and herbal medicines against corona viruses was identified. Natural products include Saikosaponins (A, B2, C, D) which act by inhibiting viral attachment and their subsequent penetration stages done mainly by Saikosaponin B2 against HCoV-22E9. Lycoris radiata and its active component lycorine, Artemisia annua, Pyrrosia lingua, and Lindera aggregata against SARS-CoV their mechanism is not clear. Phenolic compounds of Isatis indigotica and Amentoflavone isolated from Torreya nucifera against SARS-CoV and their mechanism is SARS-CoV 3CL protease inhibitor Myricetin and scutellarein against SARS-CoV and the mechanism is SARS-CoV helicase inhibitor. Houttuynia cordata water extract against SARS-CoV and the mechanism is SARS-CoV 3CL protease inhibitor; viral polymerase inhibitor [4]. Some important medicinal plants having antiviral activity against CoV infection is given in **Table 1**.

Table 1: Important medicinal plants having antiviral activity against CoV infection.

Medicinal plants having antiviral activity against CoV infection
Bupleurum spp
Heteromorpha spp
Scrophularia scorodonia
Lycoris radiata
Artemisia annua
Pyrrosia lingua
Lindera aggregata
Isatis indigotica
Torreya nucifera
Houttuynia cordata

Researchers all around the world are exploring new pathways along with formulation of new drugs on daily basis to ameliorate the COVID-19 infection [5]. Medicinal plants serve as potential candidates for drug development of various illnesses [6]. A lot of research has been done previously on medicinal plants and have explored presence of various bioactive and phytochemicals that could help to alleviate the infection. In order to combat current worsen conditions, WHO has recommended to maintain social distancing, detect and isolate affected personnel's, minimize human-animals interaction to avoid viral transmission, accelerate research and diagnosis, disseminate correct figure and statistics among public to avoid social and economic unrest. For developing effective prophylaxis of COVID-19, exploring the basic viral mechanism is a pre-requisite. Recent studies have exhibited high similarity between genome sequence of SARS-CoV-2, SARS-CoV and bat derived coronavirus [7]. Developing long term strategies for preventing further outbreaks of such pandemic is the need of hour. In this review, potential impacts of several medicinal plants for efficient cure of COVID-19 has been highlighted. Under this review, we suggest that the plant derived drugs could serve as an alternative to cope with SARS-CoV-2.

Herbal Remedies

Herbal remedies have long been used to treat infections and viruses, such as the common cold, influenza, fever, and even herpes. Some are thought to enhance the immune system and put the body in a healthier position to fight infections. Others are believed to be powerful antivirals that block certain viruses from replicating in the body.

But just because we have seen some promise with other illnesses does not mean people should assume herbal remedies provide the same benefit with COVID-19. Every virus is unique in its structure and behaviour. The herbs that seem to work for other viral infections will need to be tested to see if they also hold up against COVID-19. There is not enough data on herbs and COVID-19 Historically, there has been a major lack of evidence surrounding natural medicines. For one, it has been difficult to secure the necessary funding to study the health effects of plants and herbs. Research has also been somewhat inconsistent. There are so many parts of a plant the root, stem, leaf, flower, and it is hard to get studies that consistently analyse the same portion of a plant. There could be unwanted side effects

Licorice paste, when applied to a herpes sore, can prevent the virus from replicating and stop it in its tracks, But it also has a major downside it can activate a hormone in the body called aldosterone which causes fluids retention and can actually induce hypertension and it can interact with other medications that a patient's on and block their absorption in the body and prevent them from acting. Certain herbs, if misused, could boost the immune system even more and lead to "a cytokine storm," or a fatal overactive immune response. One of the biggest problems, is that many herbal and natural remedies are low quality.

The complicated secondary metabolism of plants has been the source of countless medicinal compounds and leads for drug discovery. It is little surprise then that plant products and their analogues have been employed as an early line of defence against COVID-19. On 17 February, the Chinese State Council announced that chloroquine phosphate a structural analogue of quinine, originally extracted from the bark of cinchona trees can be used for treating COVID-19 patients. This anti-malarial also has broad-spectrum antiviral activity and regulatory effects on the immune system.

Another compound from herbal remedies recruited to control COVID-19 is diammonium glycyrrhizinate, an extract of liquorice roots. Liquorice, Glycyrrhiza glabra, has long been employed against coughs and colds as well as to settle disturbed digestion, while diammonium glycyrrhizinate has anti-inflammatory activity and is used to treat liver damage caused by hepatitis B [8].

Combination of diammonium glycyrrhizinate and vitamin C as a COVID-19 therapy

Several patent herbal drugs, such as Huoxiang Zhengqi capsules, Lianhua Qingwen capsules and Radix isatidis granula, are being proposed as treatments, the latter two having also been used during the SARS-CoV outbreak in 2003. Boli Zhang, a leading traditional Chinese medicine expert advising on COVID-19 management, claims that such herbal medicines have been especially useful in improving symptoms such as coughing, weakness and digestive system disorders as well as alleviating anxiety. Compared to chemical drugs, herbal medicines and plant natural products are less understood mechanistically, but several clinical investigations have been started to evaluate their effects more precisely

In routine drug development, researchers first discover a drug molecule with potential therapeutic activity against a certain target, then optimize its structure and validate its function using in vitro experiments followed by animal and clinical trials. By contrast, many herbal drugs have been used in clinics for hundreds or thousands of years, and thus their safety and effects have been repeatedly tested; chloroquine phosphate has been used to treat malaria for over 70 years.

Anti-viral herbal medicines have been used in many historic epidemics, for example the previous two coronavirus outbreaks (SARS-CoV in 2013 and MERSCoV in 2012), seasonal epidemics caused by influenza viruses and dengue virus. Extracts from Lycoris radiate, Artemisia annua and Lindera aggregate, and the natural products isolated from Isatis indigotica, Torreya nucifera and Houttuynia cordata, showed anti-SARS effects. The plant flavone baicalein can prevent dengue virus entry into the host and inhibit post-entry replication6. Additionally, natural products from Pelargonium sidoides roots and dandelion have anti-influenza activities, as they inhibit virus entry and key viral enzyme activities [9-11].

The high level of mutations of IBV [12] leads to the emergence of new serotypes and genotypes and limits the efficacy of routine prevention. Eight out of 16 extracts D. canadense, M. piperita, M. officinalis, O. vulgaris, T. vulgaris, H. officinalis, S. officinalis, and S. montana were chosen based on the results of the antiviral effect assay.

Many investigations of plant extracts have been performed with different coronaviruses. The main targets were proteins involved in coronaviral replication, proteases, and ion channel conductance [12].

Several scientific publications have encouraged the use of polyphenolic compounds in the treatment and prophylaxis of chronic diseases [13]. The mixture of the geometric isomers and enantiomers of rosmarinic acid is accumulating in the families Lamiaceae Lindl, Asteraceae.

Most large quantities of rosmarinic acid have been determined in the genus of plants such as Salvia L, Perilla L, Melissa L, and Echinacea Moench. Rosmarinic acid has antioxidative, anti-inflammatory, antimutagenic, antibacterial and antiviral effects against the herpes simplex virus [14-17].

The desmodium canadense herb contains flavonoids such as apigenin, apigenin-7-O-glucoside, luteolin, rutin, 2- vicenin, vitexin, isovitexin, vitexin rhamnoside, orientin, homoorientin, quercetin, hyperoside, astragalin and kaempherol [18]. In addition, it also contains saponins and phenolic acids (chlorogenic acid, vanillic, 4- hydroxycinnamic, ferulic and caffeic). The Desmodium herb exhibits antioxidant, antibacterial, anti-inflammatory, hepatoprotective, diuretic and analgesic activity [18]. C-glycosides of flavonoids are known to exhibit antioxidant, hepatoprotective, anti-inflammatory and antiviral effects [19].

Herbal treatments used in Traditional Chinese Medicine and Africa

Herbal treatments used in traditional Chinese medicine were explored to treat coronavirus infections during the Sars-CoV and Mers-CoV outbreaks. Initial studies in China showed the alcoholic extract of sweet wormwood (Artemisia annua) was the second most potent herbal medicine used on the 2005 Sars-CoV.

Treatments containing an artemisinin derivative, artemisinin-based combination therapies (ACTs), are now standard treatments worldwide for malaria. Artemisia annua extracts show extraordinarily little toxicity and artemisinin-based drugs are widely used to treat malaria even in newborns [20].

According to the current clinical guideline in China and the experiences in the treatment of SARS or Middle East Respiratory Syndrome (MERS) patients, both conventional medicine and traditional Chinese medicine (TCM) are used for the treatment of patients with infection of SARS-CoV-2 in China. A high-profile research published in the Lancet reported that glycyrrhizin, a major active constituent liquorice root which is the most frequently used Chinese herb, potently inhibited the replication of clinical isolates of SARS virus. Another Chinese herbal compound baicalin also had the anti-SARS activity. 3-chymotrypsin-like protease (3CLpro) is vital for replication of virus, and thus represents a promising drug target for the development of therapeutics agents for SARS-CoV as well as other human coronaviruses including SARS-CoV-2. It was reported that following TCM herbal extracts had the capacity to inhibit the enzymatic activity of SARS 3CLpro: Chinese Rhubarb extracts (IC50: 13.76 ± 0.03 μg/mL) , water extract of Houttuynia cordata [21,22], flavonoid extracted from litchi seeds [23] and beta-sitosterol (IC50: 1210μM) extracted from the root extract of Isatis indigotica [24].

Further, following herb-derived naturally occurring compounds including sinigrin (IC50: 217μM), indigo (IC50: 752μM), aloe-emodin (IC50: 366 μM), hesperetin (IC50:8.3 μM) [25], quercetin (IC50: 73μM), epigallocatechin gallate (IC50: 73μM), gallocatechin gallate (IC50: 47 μM) [26], herbacetin, rhoifolin and pectolinarin [27] were able to inhibit the SARS 3CLpro activity. Moreover, the flavonoids namely herbacetin, isobavaschalcone, quercetin 3-β-D-glucoside, and helichrysetin had the potential to block the enzymatic activity of MERS-CoV 3CL protease [28].

Africa has a long history of traditional medicine and practitioners that play an important role in providing care to populations. Medicinal plants such as Artemisia annua are being considered as possible treatments for COVID-19 and should be tested for efficacy and adverse side effects. WHO is working with research institutions to select traditional medicine products which can be investigated for clinical efficacy and safety for COVID-19 treatment?

Medicinal Herbs

A variety of phytoconstituents derived from medicinal herbs have been extensively studied for antiviral activity. These herbal sources have been reported individually or in combinations across many citations studied. Activities against rabies virus, Human immunodeficiency virus, Chandipura virus, Japanese Encephalitis Virus, Enterovirus, Influenza A/H1N1 and other influenza viruses were discovered during the literature search.

Herbal sources provide researchers enormous scope to explore and bring out viable alternatives against viral diseases, considering non-availability of suitable drug candidates and increasing resistance to existing drug molecules for many emerging and re-emerging viral diseases.

According to a World Health Organization (WHO) report, 80% of the population in developing countries depends on traditional plants for health requirements [29,30]. Natural products such as herbal plant extracts (used in Ayurveda as mentioned in Charaka Samhita and Susruta Samhita or other traditional medicine practices), plant derived compounds (also known as phytoconstituents), extracts of specific plant parts (roots, stem, bark, flowers, fruits and seeds), dietary supplements and nutraceuticals find wide application in treating ailments ranging from common to rare infectious and non-infectious diseases. According to reports, one quarter of the commonly used medicines contain compounds isolated from plants. Majority of the antiviral herbs were found containing active components such as flavones, alkaloids and polyphenols, which play an important role against viruses. A classic example of a lead from herbal sources that got translated into potential anti-infective drug candidate is emetine (isoquinoline alkaloid obtained from the underground part of Cephaelis ipecacuanha, and related species), used both as an amoebicidal drug and for the treatment of abscesses due to Escherichia histolytica infections. Quinine is yet another important drug of plant origin derived from the bark of Cinchona tree with a long history of use [31].

The COVID-19 (Coronavirus disease 2019) spreads primarily through droplets of saliva or discharge from the nose. But the potential problem will continue to

persist until the development of an effective viral vaccine. In this pandemic situation, due to delay in vaccine development, there is an urge to manufacture of herbal medicines. Recently many common Indian plants have been investigated for their role in disease amelioration. Active compounds from these plants can be incorporated into respiratory masks to furnish them with inherent antiviral properties. fibrous filtration with three-layered masks using the compounds from medicinal plants for viral deactivation [32] (**Table 2**).

Table 2: Medicinal herbs.

Medicinal plant	Compound	Activity
Andrographis paniculata	Andrographolide	Antiviral potential
Acacia nilotica	Quercetin	Inhibition HIV-PR
Vitex negundo	Sabinene	Inhibitory action against HIV
Clitoria ternatea	Delphinidin-3-O-glucoside	Antiviral properties
Gymnema sylvestre	Tartaric acid	Inhibition of viral DNA synthesis
Vitex trifolia	Casticin	Immunomodulatory & Anti-inflammatory effect on lungs
Strobilanthes cusia	Lupeol	Inhibitory action towards HCoV-NL63

Traditional medicine in Ghana and WHO

According to the World Health Organization (WHO) about 80% of developing countries depend on traditional medicines for their primary health care needs [33]. In Ghana, traditional medicine, particularly herbal medicines, is an important component of the health care system of the people The WHO has a keen interest in documenting the use of medicinal plants by indigenous people from different parts of the world.

In total, 52 species of plants belonging to 28 plant families were documented. Of the 28 families of plants, members of the Fabaceae, Euphorbiaceae, Asteraceae, and Sapindaceae were the most used ones (12% in each case) in the herbal medicines. The use of members of the above families in herbal medicines is widely known in Ghana [34]. It is widely known that members of the families contain secondary metabolites such as tannins, phenolics, and alkaloids that are responsible for their bioactivity.

Two of the species of plants reported being namely, Pteridium aquilinum (L.) Kuhn and Pteridium esculentum (Forst.) Nakai, were ferns whereas the rest of the plants were vascular plants. Species most commonly reported being used were Aloe vera L. and Paullinia pinnata L.Leaves formed 57% of the herbal medicines documented. Other plant parts used were fruits, barks, and whole plants Leaves are commonly used in herbal medicines because they represent the site of most photosynthetic activity in plants and they also contain extremely high concentrations of secondary metabolites [35].

Treatment

Treatment of COVID-19 can be distributed into two categories based on the target, one that act on strengthening the human immune system while the second which directly attack coronavirus itself. Regarding the first option, the inherent immune system is known to respond against pathogenesis by inhibiting the replication and contamination of coronavirus [36]. This is majorly ascribed to function of “interferon” namely protein which enhances the immunity by altering or blocking the signal pathways of cells essential for viral replication thus exhibits anti-viral effect.

The purpose of using plant materials is stimulation and strengthening of immune system against virus caused inflammation. Several medicinal plants have been reported for exhibiting anti-coronaviral activity (a surrogate of SARSCoV). These includes Clitoria ternatea, Leucas aspera, Indigofera tinctoria (AO), Vitex trifolia, Gymnema sylvestre, Cassia alata, Abutilon indicum, Sphaeranthus indicus, Gymnema sylvestre and Evolvulus alsinoides [37].

Vitex trifolia and Sphaeranthus indicus has decreased inflammation of cytokines via modulating NF-kB pathway which is often involved in respiratory disorders in SARS-CoV [38,39]. Similarly, Clitoria ternatea is known to inhibit metalloproteinase (ADAM17) which is involved in ACE shredding. This could be achieved by utilizing Clitoria ternatea as ACE-2 shredding is linked with virus production [40]. Plants with ability to inhibit virus replication are often preferred as promising options to be adopted against viral outbreaks. Thus, Glycyrrhiza glabra and Allium sativum [41,42] could serve as alternate options for COVID-19 cure. Clerodendrum inerme Gaertn, a potential herb in cure of SARS-CoV-2 inactivates the viral ribosome and protein translation [43]. Moreover, Strobilanthes Cusia inhibits RNA genome formation thus targets the HCoVs [44].

Table 3: Plant species with their active molecule known for possessing anti-viral activities.

Plant Name	Active constituent	Mechanism of Action
Platycodon grandiflorum	Platycodin D	Inhibit viral replication and proinflammatory cytokine expression
Zingiber officinalis	6-gingerol	Anti-viral potential
Mentha piperita	Menthol and essential oils	Virucidal impact by incrementing virion density
Camellia japonica	Oleanane triterpenes	Blocking viral replication via affecting key structural protein synthesis
Isatis indigotica	Sinigrin and Hesperetin	Inhibited viral cleavage activity
Glycyrrhiza glabra	Glycyrrhizin	Induces Glycyrrhiza glabra nitrous oxide synthase which in turn blocks viral replication
Peganum harmala	L Harmine	Inhibit viral replication
Rosmarinus officinalis	Carnosic acid	Blocks viral replication
Moringa oleifera	Quercetin and kaempferol	Blocks initial stages of viral replication
Rheum palmatum L.	Polyphenols	Significant inhibition of protease activity
Vitis vinifera	Resveratrol	Reduced expression of nucleocapsid (N) protein, also lowers the apoptosis induced by virus
Houttuynia cordata	Quercetin	Virucidal activity, inhibits ATPase of multidrug resistance- protein
Punica granatum	Punicalagins and Ellagitannin	Inhibition of ACE
Strobilanthes callosa	Phytosterols and Phenolic Compounds	Blocking of virus entry
Azadirachta indica	Azadirachtin	Virucidal activity
Eugenia jambolana	Ellagic acid, Isoquercetin, Kaemferol	Inhibition of protease activity
Vitex negundo	Viridiflorol and linalool	Inhibition of virus
Strobilanthes cusia	Quinazolinone alkaloids and monoterpenes	Blocking of virus replication
Vitex trifolia	1, 8-cineole	Inhibition of virus

Andrographis paniculate, an annual herbaceous plant possesses strong anti-viral properties [45]. All these proteins and molecules have active roles in SARS-COV pathogenesis and likely to have too in SARS-CoV-2 [46,47]. Several other plants have also exhibited inhibitory role against HIV infections, they could also serve as promising candidates for COVID-19 drug development. These plants involve Eugenia jambolana [48], Acacia nilotica and Euphorbia granulate [49]. Some plants like Ocimum sanctum [50], Solanum nigrum [51] and Vitex negundo [52,53] owing capability of targeting reverse transcriptase activity of HIV could also be used for potential development of COVID-19 drug.

During pandemics, timeliness is basic prerequisite for any drug development thus natural products could serve as suitable and effective option since their safety is well-known so it can be instantly evaluated for combating patients. Therefore, we build a list of plant species with their active molecule known for possessing anti-viral activities and these could be suitable choices for combating the situations from COVID-19 pandemic (**Table 3**).

Conclusion

Ongoing pandemic of COVID-19 has become the most severe and gruesome viral infection faced by human so far. Most of countries around the globe has taken preventive measures mainly countrywide lockdowns in addition with social distancing and self-quarantine that could help to break transmission string and lowers the inflow of new COVID-19 positive cases. This review highlights the crucial value of plants with antiviral capacity and known to treat various respiratory diseases from decades. Thus, significant pathological role of plant species could help in quest for COVID-19 drug development.

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