



LETTER TO THE EDITOR

Herbal medicines utilized in the management of COVID-19

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ABSTRACT

COVID-19 management is becoming a popular topic of research among drug developers, researchers, and scientists because the coronavirus is a rapidly dividing virus that spreads by injecting its genome into the genes of other organisms and multiplying there. As a result, it depends on other organisms for its growth which makes it more challenging to eradicate the disease-causing agent. The Coronaviridae family of viruses includes the enveloped, positive-sense single-stranded RNA virus known as coronaviruses (CoV). Different species of the CoV family cause infections of the upper respiratory tract and gastrointestinal tract in mammals and birds. People typically get the common cold from it, but it can also result in complications such as pneumonia and SARS. The more well-known severe acute respiratory syndrome coronavirus, which in 2003 posed a serious threat with a high mortality rate, is one of the recognized human coronaviruses (HCoV), along with HCoV-229E, -OC43, -NL63, -HKU1, and others. The Middle East respiratory syndrome CoV, a sixth kind of HCoV infection with a high mortality rate, was described by the World Health Organization in 2012. Numerous herbal extracts have been used to treat clinical indications related to the respiratory system as ayurvedic medicine has a treatment for a wide variety of illnesses and complex medical diseases. Therefore, a variety of herbal remedies and purely natural substances can greatly help in the creation of novel antiviral treatments. *Tinospora cordifolia*, *Curcuma longa*, *Ocimum basilicum*, and *Allium sativum* are a few herbs utilized in COVID-19. In this work, an effort has been made to assess problems and potential treatment with the help of herbal medicine.

KEY WORDS: Antiviral, Immunomodulatory, Medicinal plants, SARS-CoV-2

INTRODUCTION

The World Health Organization reports that since December 2019, Wuhan in China has been home to a novel coronavirus illness (COVID-19), a virus from the Coronaviridae family.^[1] Initially, this virus spread from animal to human, and when the number of afflicted people dramatically increased, the Chinese health authorities recorded human-to-human transmission.^[2] The predominant signs and symptoms of this illness, which is characterized by severe and progressive pneumonia, are fever, dyspnea, dry cough, exhaustion, headaches,

and ageusia.^[3,4] Nevertheless, research suggests that patients with COVID-19 may also experience other neurological issues in addition to anosmia. Headache, myalgia, light-headedness, encephalitis, stroke, epileptic seizures, and Guillain-Barre syndrome are a few of these neurological side effects.^[5] The severe acute respiratory syndrome (SARS-CoV-2) coronavirus, a new member of the coronavirus family Coronaviridae, is the reason

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behind COVID-19.^[6] The single-stranded RNA (ssRNA) virus known as SARS-CoV-2 (severe acute respiratory syndrome) has a diameter of 80–120 nm. With a 3–4% fatality rate, the coronavirus-2 has emerged as a global epidemic affecting people.^[7]

According to studies, there is some similarity between SARS-CoV-2 and SARS-CoV, the virus that was found to cause Middle Eastern respiratory syndrome (MERS) in 2012 and the severe acute respiratory syndrome (SARS) in 2002. A significant known genetic difference between SARS-CoV-2 and other viruses is that it has the largest RNA genome and positive-sense ssRNA.^[8] The pathogenic implications of SARS-CoV-2 for producing organ damage are still unknown, but in comparison to SARS-CoV, it has a strong affinity for the host surface protein Angiotensin Converting Enzyme-2 (ACE2) that is required for virus infectivity.^[9] Antiviral medications now used to treat SARS and MERS are routinely used to treat COVID-19 as well, though, because of how strikingly similar the genetic sequence of COVID-19 is to that of SARS-CoV-2.^[10]

A potential source of treatment for preventing the COVID-19 pandemic is herbs, through natural products.^[11] It has also garnered attention in some specific versions to support the immune system or treat respiratory problems using medicinal herbs, natural substances, or preparations with antiviral and anti-inflammatory qualities.^[12] According to a study, medicinal plants and bioactive substances that have shown antiviral activity against SARS-CoV-1 and MERS-CoV may also be helpful against SARS-CoV-2.^[13,14] This review's main objective is to provide an overview of herbal medications as antiviral and immunomodulatory utilized in COVID-19 pandemic. The literature search was conducted using several platforms, including SciFinder, PubMed, Scopus, and Google Scholar.

CORONAVIRUS

Coronaviruses (CoV) are single-stranded, enclosed RNA viruses that range in size from 80 to 120 nm. They can be classified into one of four groups: α , β , γ , and δ . Only six different coronavirus types could infect people before the detection of COVID-19. The seventh was COVID-19, a member of the coronavirus family. The four CoV-human coronaviruses (HCoV)-OC43, HCoV-229E, HCoV-NL63, and HCoVHKU1-cause comparatively mild respiratory infections and are less harmful than the two CoV, SARS-CoV and MERS-CoV, which are better adapted to infecting humans. They dispersed two deadly diseases. SARS-CoV and COVID-19, however, are very similar in terms of homology and pathophysiology. The COVID-19 virus has evolved to survive in bats, which have a higher body temperature than humans, making it more temperature resistant than the SARS-CoV.^[15] The four main structural proteins of the coronavirus are designated as S (Spike),

E (Envelope), N (Nucleocapsid), and M (Membrane). ACE2 serves as the receptor for COVID-19, which spreads to cells by way of a receptor-binding domain (RBD) in the spike protein.^[16]

MEDICINAL PLANTS

Since the very beginning of time, traditional plants have been employed by herbal therapists to treat human and animal ailments, particularly in the Asia-Pacific region. On a global scale, people still use herbs as medicine and their products for wellness and general healthcare. There are over 2,500 natural plant species that can be used to diagnose various illnesses and disorders.^[17,18] As a result, there is hope that natural products (also known as secondary metabolites or phytochemicals) derived from medicinal plants may include phytochemicals that can either kill the SARS-CoV-2 virus, prevent it from multiplying, or boost the immune system's ability to fight it.^[19] The Indian subcontinent's traditional medical system, Ayurveda, sometimes known as "The Science of Life," is focused on a holistic approach to life, health, and healing. In Ayurvedic texts, a range of rejuvenating techniques that provide biological sustenance to bodily tissues is discussed.^[20] The identification of medicinal compounds from plants revealed intriguing sources for potential and cost-effective therapy, which could speed up the medication research process in times of disaster. Numerous plants are listed in the AYUSH system of medicine which were traditionally used in the treatment of headache, fever, sore throat, cough, and runny nose and were also found to have beneficial effects on SARS-CoV-2.^[21] In addition, herbal remedies have assisted in reducing the symptoms of contagious illnesses like SARS-CoV-2. There is evidence that suggests herbal formulations may be useful in lowering the risk of COVID-19. Regarding the use of herbal medicine as a complementary therapy for COVID-19, several recommendations for herbal therapy have been given.^[22] Several ethnomedicinal plants, including *Murraya koenigii*, *Euphorbia hirta*, *Curcuma longa*, *Zingiber officinale*, *Adhatoda zeylanica*, *Acalypha indica*, *Allium sepa*, *Coriandrum sativum*, *Ocimum basilicum*, and some others, have been mentioned as having the effective medicinal potential to cure colds, coughs, and breathing problems.

ANTIVIRAL ACTIVITIES OF SOME HERBAL DRUGS

During global emergencies, plants are the ideal source for locating prospective and affordable pharmaceuticals. In the course of virus epidemics, utilizing these natural compounds could hasten the drug development phase.^[23] Many viral illnesses, such as measles, poliomyelitis, rabies, and yellow fever, are now under control and extremely

infrequent. This is because of public health initiatives like vaccinations. However, several new viruses often appear, which have terrible consequences for both an individual and society.^[24] A group of RNA viruses called CoVs cause a variety of illnesses in mammals, including humans. CoVs frequently cause mild-to-moderate upper respiratory infections in humans, which can be fatal.^[25] As a result, the quest for novel antiviral medications is currently concentrating on plant-derived metabolites in addition to synthetic combinations. Several plant metabolites can halt viral reproduction without harming the host's physiology or creating significant negative side effects.^[26] Since a long time ago, medicinal plants have been used to treat human viruses. Various herbal plants are effective against viral infections in the form of leaf powder, decoctions, infusions, pastes, and tablets. Most of the plants have antiviral characteristics that can combat human infections.^[27] The complexity of plants' secondary metabolism is what gives them their wide range of therapeutic properties. The effectiveness of plant-based chemical compounds can only be comprehended if they are taken in their purest forms or in combination to make compound medications, even though it is relatively simple to utilize herbal medicine as a whole plant crude extract, decoction, or tea. There are a lot of chemical substances that have been extracted from plants that are effective antiviral medications.^[28]

Since a certain section of cinchona trees (*Chincona calisaya*) from the Andean Mountain woods contains bioactive substances that can treat fever, the trees are very beneficial. Jesuit missionaries made the initial discovery of this beneficial effect, which later spread to other parts of the world.^[29] For many centuries, quinine alkaloids, which are produced by the tree's bark, were a successful cure for malaria. Quinine works in a way that is comparable to that of the synthetic antimalarial drug chloroquine, which is used to treat malaria. It is referred to as a chloroquine analog.^[30] Quinine gained popularity because it had a comparable effect to the antimalarial medication chloroquine. The use of antimalarial medications for malaria eventually gave way to their usage as strong inhibitors for viral infection. According to a large body of evidence, some antimalarial drugs may have been studied and proved to offer certain advantages against viral infection.^[31] Chloroquine, for instance, has shown antiviral activity against the SARS-CoV infection.^[32] The SARS-CoV-2 viral load in COVID-19 patients is found to be decreased by the combination of azithromycin and hydroxychloroquine in a clinical investigation. Given this data, it is possible to predict that quinine, a chloroquine equivalent, will be effective in curing COVID-19.^[33]

Scutellaria baicalensis has a pharmaceutical substance called baicalin, which acts as a sensitizer and an anti-apoptotic.^[34] The antiviral activity of baicalin against SARS-type viruses, with an effective concentration (EC₅₀) value of 12.5 g/mL lowers the virus-forming unit by 50% within

2 days.^[35] As the incubation time beyond 2 days, the activity decreased. Since SARS-CoV and the current COVID-19 virus (SARSCoV-2) are identical, baicalin is expected to have a comparable antiviral impact on the current virus. Using UV spectrophotometry to measure ACE inhibition, baicalin was found to be potent *in vitro* inhibitor of the ACE, with an IC₅₀ value of 2.24 mM. Baicalin's low toxicity makes its potential use as a medication or treatment for COVID-19 looks promising.^[36] *S. baicalensis* (Lamiaceae) root contains the flavonoid scutellarein, which has been demonstrated to block the nsP13 helicase of SARS-CoV-2 by changing its ATPase activity.^[37] Baicalin and baicalein, two further distinct flavone glycosides of *S. baicalensis*, have been found in pharmacology studies to have potential therapeutic actions in response to COVID-19. Clinical trials are still needed to precisely pinpoint the therapeutic effects of *S. baicalensis* extract.^[38]

Over 5000 years have passed since the usage of *Cannabis sativa* for medical purposes began in central Asia.^[39] A phytocannabinoid called cannabidiol (CBD), which makes up around 40% of the extract, was first discovered in *C. sativa* in 1940. In COVID-19 target tissues, ACE2 expression has been demonstrated to be influenced by CBD. The down-regulation of ACE2, which is connected to receptor-mediated entry into human lung epithelial cells, is the suggested treatment for COVID-19. For use in antiviral testing, Canadian researchers have developed over 800 different *C. sativa* lines and extracts with high CBD content. Several *C. sativa* extracts have also been shown to block the serine protease TMPRSS2, which is necessary for SARS-CoV-2 entrance into host cells.^[40] Although preclinical research suggests that CBD may be useful in treating viral illnesses such as hepatitis C, Kaposi sarcoma, and SARS-CoV-2, clinical proof is currently absent.^[41]

In comparison to the entire alkaloid extract, the isolated lycorine alkaloid from *Lycoris radiata* strongly inhibited SARS-CoV (BJ-001). However, lycorine derived from plants inhibited SARS-CoV (BJ-001) less effectively than lycorine made synthetically.^[42]

Growing naturally in India and South-east Asia, turmeric (*C. longa* L.) is a member of the ginger (*Zingiberaceae*) family. This plant's rhizomes are rich in secondary metabolites, which are primarily bioactive compounds such as polyphenols, sesquiterpenes, steroids, and curcuminoids.^[43] Another indication of curcumin's antiviral properties is its capacity to control several molecular targets involved in cellular processes like transcription regulation and the activation of signaling pathways. Curcumin is a prime contender for an anti-viral medication due to its ability to target numerous cellular pathways and further impede the growth and replication of viruses. Curcumin binds to and inhibits target receptors linked to virus infection, such as the spike glycoprotein RBD, SARS-CoV-2 protease, and PD-ACE2, according to a molecular docking study.^[44,45]

A member of the *Piperaceae* family, Piper is known as the king of spices due to its overpowering aroma. Brazil, Indonesia, and India are just a few of the tropical nations that grow black pepper. The bioactive chemicals found in *Piper nigrum* are utilized in medicine, as preservatives, and in perfumery. Black pepper contains the potent alkaloid piperine, which is commonly utilized in traditional medicine.^[46] *P. nigrum* extracts in methanol and chloroform have been shown to have antiviral properties against the enteric virus vesicular stomatitis and the human parainfluenza virus in human cell lines. The presence of a higher amount of alkaloids in the chloroform extract was discovered to increase the anti-viral activity of *P. nigrum*.^[47] According to a docking-based study, piperdardiine and piperazine are two of black pepper's bioactive compounds that are highly effective against the COVID-19 virus and can be utilized to treat the disease.^[48]

Tinospora cordifolia (giloy), a plant belonging to the Menispermaceae family, is mainly found in Asian countries including Myanmar, China, Sri Lanka, and India. Guduchi is the name of an Indian medicinal plant that is incorporated into Ayurvedic drug compositions to treat several ailments. *T. cordifolia* has been widely used as an effective treatment for a variety of illnesses, including anemia, diabetes, skin issues, urinary disorders, jaundice, and other maladies, due to its medicinal value.^[49] In molecular docking research, one of the phytochemicals found in giloy, tinocordiside, demonstrated inhibition of the major SARS-CoV-2 protease.^[50] Surface glycoprotein (6VSB), RBD (6M0J), RNA-dependent RNA polymerase (6M71), and major protease (6Y84) were the four main Giloy-isolated SARS-CoV-2 targets. All four of these targets were exceptionally resistant to the drugs berberine, isocolumbin, magnoflorine, and tinocordiside.^[51]

A labdane diterpenoid called andrographolide is primarily extracted from the herbaceous plant extract of *Andrographis paniculate* (green chiretta). Due to its component's exceptional biological activity, which includes anti-virus, anti-hyperglycemia, anti-bacteria, anti-tumor, anti-parasite, and properties, it has been used in a variety of medicinal procedures.^[52] Through the influence of the viral 3-chymotrypsin-like cysteine protease, andrographolide was discovered to be a potential SARS-CoV-2 inhibitor. Andrographolide is often quite plentiful, inexpensive, and non-cytotoxic, although further research is needed into its potent antiviral efficacy against various viruses.^[53]

Polygonum cuspidatum, *Aloe vera*, *Cassia obtusifolia*, *Rheum palmatum*, and *Polygonum multiflorum* are a few herb species that naturally contain emodin, which has the IUPAC name 1,3,8-trihydroxy-6-methylanthraquinone. The aforementioned plants have a lengthy history of use in traditional remedies in many regions of the world, especially in Eastern Asia. Many researchers are still looking into their therapeutic benefits and healing potential.

Emodin was found to have a wide range of therapeutic benefits, including neuroprotective, anti-osteoporotic, anti-allergic, antiviral, antibacterial, immunosuppressive, anti-diabetic, and hepatoprotective effects.^[54] Inhibiting SARS-CoV S protein binding to ACE2 and S protein-pseudo typed retrovirus infectivity to Vero E6 cells is what is predicted of emodin, a crucial component of the *Rheum* and *Polygonum* genera. According to the aforementioned techniques, emodin is a fascinating anti-SARS-CoV chemical and might be a promising therapeutic option for the novel SARS-CoV.^[55]

IMMUNOMODULATORY ACTIVITIES OF SOME HERBAL DRUGS

Immunomodulators are substances that can change either the innate or adaptive components of immunity. They may be created artificially, naturally, or biologically.^[56] By causing or activating immune system components, immunostimulants are immunomodulators that improve immunological responses to infections.^[57] Due to a growing understanding of the immune system modulation technique to treat infectious diseases, particularly viral infections, the immunomodulating capabilities of medicinal plants have been extensively explored in recent years. Various plants are already used in traditional medicine to treat and prevent viral infections, either by directly combating the virus or by in some other manner strengthening the body's defense mechanisms. These medicinal plants' terpenoids are believed to possess promising efficacies in suppressing SARS-CoV-2 replications. Lycorine, homoharringtonine, and emetine are examples of alkaloidal substances that have anti-coronavirus activities. The major viral replication enzymes are inhibited by other identified natural chemicals, such as emodin, baicalin, lguesterin, cryptotanshinone, salvestrols, and sotetsuflavone, which stop the spread of the viruses.^[58]

Acute respiratory distress syndrome, is lethal and is brought on by a sudden onset of extensive lung inflammation.^[59] Therefore, it starts with an immune defense-based protective phase where an immune response boost is required, and then it moves into an inflammation-driven harmful phase when it is repressed.^[60] Several medicinal herbs are used as potential COVID-19 treatment agents. Ayurvedic practitioners in India recommend a few key plants for building robust immunity in people. Ayurvedic medicines help strengthen immunity in the human body and also help to avoid infection because the immune system plays a key and major role in the defense against this particular viral illness. Some herbs Amalaki (*Emblica officinalis* Gaertn.), Ashwagandha (*Withania somnifera*), Kutki (*Picrorhiza kurroa* Royle ex Benth), Drum stick (*Moringa oleifera* Lam.), Guduchi (*T. cordifolia* Willd. Miers), Neem (*Azadirachta indica* A. Juss), Tulsi (*Ocimum sanctum* L.).^[61]

The phagocytic activity measured by the carbon clearance test, the myelosuppression model brought on by cyclophosphamide, and the immunomodulatory action on the humoral and cell-mediated immunological response to ovalbumin of *A. indica* flowers extract. By inducing both humoral and cell-mediated immunity as well as a non-specific immunological response through macrophage phagocytic activity, the results demonstrated considerable immunomodulatory activity.^[62]

Amalaki is a member of the Phyllanthaceae family, and its fruits are among the most significant for us as immunomodulators to treat recurrent respiratory infections in people. The fruit's primary flavonoids include kaempferol, ellagic acid, and gallic acid, and it also contains significant amounts of other active ingredients including Vitamin C.^[63] Due to the fruit's abundance of Vitamin C, it is mostly used to boost immunity against COVID-19. The phytochemical Phyllaemblicin B, which was isolated from the roots, had the inhibitory capability for the Coxsackie virus and demonstrated efficacy against herpes simplex viruses 1 and 2.^[64]

Ashwagandha, a key herb in Ayurveda, is sometimes referred to as Indian ginseng and Indian winter cherry. It is used to regulate stress, fight pathogenic agents, and promote good physical and mental health. Ashwagandha increases the macrophages' ability to synthesize nitric oxide, which aids in strengthening immune cells. WSG, a protein from the *W. somnifera* plant, has significant antibacterial action.^[65] By having immuno-suppressive or immune-stimulating properties, ashwagandha aids in the restoration of immune homeostasis. Tumor necrosis factor, interleukin (IL)-1, and IL-6 are the main causes of COVID-19. By increasing interferon-gamma (IFN-gamma responses) and decreasing the number of these components, ashwagandha promotes anti-inflammatory activity and antiviral immunity. By modifying host Th-1/Th-2 immunity, Ashwagandha may be an effective agent in the treatment of COVID-19 infection. When used with the Diphtheria, Pertussis, Tetanus vaccine, ashwagandha extract provides effective immune responses that protect against the lethal effects of diphtheria and pertussis toxins.^[66]

Guduchi, also known as "Amrita," which means to resurrect dead cells, is one of the best Rasayanas. Its immuno-modulatory characteristics help the body's innate defenses fight COVID-19 infections. For the treatment of retroviruses and other viral illnesses, tinosporin, a diterpenoid, has very potent antiviral properties.^[67] Immunomodulatory proteins found in the guduchi stem boost the number of macrophages and their phagocytic activity.^[68] As a preventive and prophylactic medicine for COVID-19, it is advised to take 500 mg of Guduchi ghana vati, also known as Sanshamani Vati, which is a supplement that includes an aqueous extract of *T. cordifolia*.^[69]

C. domestica, sometimes known as turmeric, is a common culinary spice in India. The major component purified from the rhizome is curcumin, a polyphenolic molecule. Curcumin can be found in a variety of commercial preparations and is used successfully to treat several medical conditions. Through immunomodulation mechanisms, curcumin has demonstrated exceptional effectiveness in the treatment of cerebral malaria.^[70] Significant human diseases such as the flu virus, SARS-CoV-2, HCV, and HIV have all been successfully treated with curcumin. Curcumin is effective against several serious human infections, including HIV, HCV, SARS-CoV-2, and the influenza virus.^[71]

Among the most well-liked plant remedies in North America and Europe is *Echinacea purpurea*, which exhibits promising effects against viral infections. This variety of herbs is popular among Native Americans for treating respiratory illnesses.^[72,73]

Innate cytokines IL-2, IL-10, IL-7, TNF-, chemokines IP10, MCP-1, and MIP-1A were found in high concentrations in intensive care unit patients with severe COVID-19 clinical features. Based on this knowledge, it is feasible to infer that a cytokine storm situation is related to the severity of COVID-19 symptoms. When several cytokines are released in COVID-19 after echinacea administration, it might be taken into account. Hence, it will undoubtedly boost the number of pro-inflammatory cytokines brought on by echinacea.^[74,75]

Java turmeric is an herbal plant known as, or *Curcuma xanthorrhiza* Roxb, and is a quite popular in Southeast Asian nations. This plant is a member of the *Curcuma* and *Zingiberaceae* families. Java turmeric is an Indonesian native that has spread to and grown naturally in Malaysia, Sri Lanka, the Philippines, Thailand, and the Philippines. In addition, it has been utilized as a food additive to improve food flavor.^[76] Because xanthorrhizol can prevent pro-inflammatory cytokines, it may be used to treat COVID-19. COVID-19 patients are vulnerable to CRS. Therefore, giving xanthorrhizol to a COVID-19 patient with or without CRS may lessen their pro-inflammatory response. However, as there has not been a study done with xanthorrhizol in COVID-19 as of yet, its administration must be done carefully and thoughtfully. Giving xanthorrhizol to patients with COVID-19 runs the risk of exacerbating their conditions. The utilization of xanthorrhizol being the prevention and treatment of COVID-19 still has to be improved, especially in the context of clinical trials.^[14]

CONCLUSION

Medicinal plants have always performed a key part in the treatment and prevention of many illnesses. Coronavirus disease pandemic was massive public health crisis and due to the unavailability of medication and vaccination

herbs and their potential preventive action has helped to fight against this pandemic. Therefore, here we conclude that most of the herbal drugs have shown their greatest potential against coronavirus diseases as antiviral and immunomodulatory drugs.

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