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Review Article

Medicinal Plant Extracts and Herbal Formulations: Plant Solutions for the Prevention and Treatment of COVID-19 Infection

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Abstract

The highly valued area of traditional medicine includes medicinal plants and the chemical compounds found in them that have therapeutic potential as effective remedies for a variety of health issues. However, with respect to their active compounds and therapeutic value, many medicinal plants from various environments fall under the category of being underexplored. Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), was initially presented in November 2019. It was eventually labeled a pandemic, with an alarming number of deaths (6.987 million) and is still active. Alternative therapies are receiving more attention as a means of improving immunity and managing symptoms over the long term, despite the well-established scientific community's quick success in implementing COVID-19 vaccinations. As an alternative strategy for COVID-19 management, traditional medicine therapies that comprise medicinal plants and extracts, formulations, and bioactive metabolites are currently receiving much interest. The usefulness of these herbal medicine interventions to manage COVID-19 infection has been the subject of recent studies, which are discussed here. In conclusion, we propose using plant extracts and their formulations as an alternative approach to treat COVID-19. This review may also instigate the development of anti-SARS-CoV-2 prophylactics from the active phytochemicals of these extracts.

Introduction

Since the initial detection of coronavirus disease 2019 (COVID-19) in November 2019, the disease has persisted and spread globally as a pandemic. The initial uncertainties and worries surrounding this outbreak have been addressed as the newly created vaccines are successfully used going forward and as worldwide treatment procedures become more established. However, this virus is still infecting many people with different waves, and it remains unclear how long it will remain prevalent. Additionally, certain underdeveloped nations may not be able to apply the internationally recognized treatment modalities due to insufficient medical resources.[1] The virus that causes COVID-19, severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), has continued to evolve, and several variants like Omicron (B.1.1.529) and its subvariants (BA.1, BA.2, BA.3, BA.4, and BA.5) have emerged due to mutation. Omicron recombinant subvariants (XBD, XBB, XBF, *etc.*) also have been developed. These variants have created different waves and COVID-19 surges in different parts of the world. The variants BA.2 and BA.2.38 in India, BF.7 and XBB.1.5 in China and the USA are examples of such cases.[2–6] Therefore, strategies for enhancing immunity and managing symptoms over the long term are required in addition to the ongoing strategies to avoid becoming infected. According to the medical conditions of each nation, herbal medicine interventions, which comprise phyto-

Keywords: Traditional medicine; Herbal extracts; Formulations; COVID-19.

Abbreviations: ACE2, angiotensin-converting enzyme-2; CAM, complementary and alternative medicine; COVID-19, coronavirus disease 2019; E, envelope; HSPA5, heat shock protein A5; M, membrane; MERS-CoV, Middle East respiratory syndrome-related coronavirus; N, nucleocapsid; ORFs, open reading frames; PLpro, papain-like protease; RdRp, RNA-dependent RNA polymerase; SARS-CoV-2, Severe Acute Respiratory Syndrome-related Coronavirus 2; S, spike; TMPRSS2, Transmembrane protease serine 2; 3CLpro, chymotrypsin-like protease.

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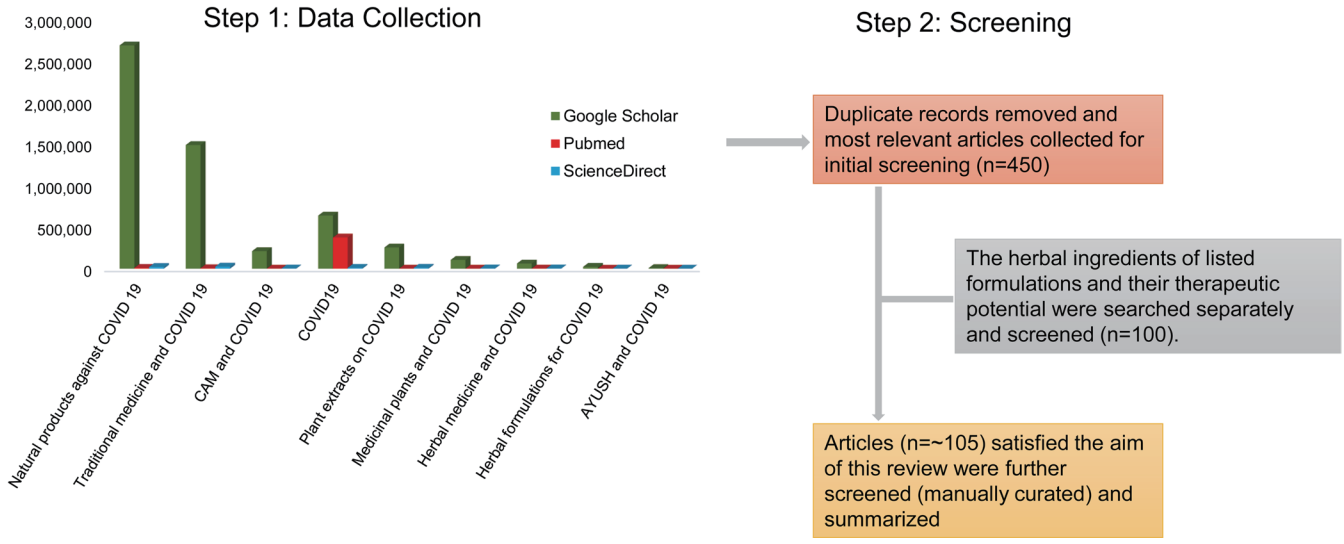

Fig. 1. Study flow diagram. CAM, complementary and alternative medicine.

chemicals, medicinal plant extracts, and herbal formulations, can be established as an alternative option for COVID-19. Approximately 80% of people worldwide still turn to traditional treatments for their medical problems.[7] In different countries, spicy herbs and medicinal plants with enormous potential are a part of their diet, which helps them to survive different ailments and reduce the impact of COVID-19.[8,9] Hence, the use of herbal remedies has been advised for COVID-19 prevention as well as treatment.[10] Even in the early phases of the COVID-19 epidemic, China gave herbal therapy prominence, and 90% of the patients who received treatment recovered.[11,12] The Chinese traditional medicines Lianhuaqingwen and ShufengJiedu have also been advocated for COVID-19 due to their efficacy against SARS-CoV-1 and influenza A virus subtype (H1N1).[13] India holds the unique distinction of having its own recognized traditional medicine; this system, which is predicated on certain medical beliefs, offers a way to achieve a healthier way of life with traditional and accepted ideas about preventing illness and enhancing well-being. The conventional applications of Indian medicinal herbs and herbal preparations can thus be repurposed to provide new therapeutic strategies for COVID-19 prevention. Numerous well-known immunity-modulating Indian traditional plants and formulations have been used for centuries to treat allergies and respiratory problems. Such formulations for COVID-19 management have been specified and recommended by the Ministry of AYUSH of the Government of India. Three nations-South Korea, China, and India-have released guidelines regarding traditional therapies for the management and prevention of COVID-19.[14] Recently, with the aid of a clinical study, the potential of the herbomineral drug fifatrol to alleviate the symptoms of SARS-CoV-2 (omicron variant) infection in the North Indian population has been established.[15] We have previously published a review article covering the curative potential of phytochemicals on COVID-19 infection.[2]

In this review, an attempt is put forward to explore the potential applications of medicinal herbs, their extracts, and formulations in the prevention of COVID-19 infection. Active phytochemicals, including both primary and secondary metabolites, with great health advantages are found in abundance in medicinal plant extracts and formulations. Among them, secondary metabolites (terpenoids, alkaloids, and phenolics) have been extensively researched for their potential medicinal uses, and some of them have been developed into natural product medications. To mitigate the current risk of COVID-19, it is crucial to take these natural sources into account to identify natural solutions against COVID-19 as well as to develop their active ingredients as COVID-19 prophylactics. Hence, this review is instructive because it highlights these aspects.

Methods

The present state of research on medicinal herbs and COVID-19 infection is reviewed thoroughly in this article. For this review article, a literature search was conducted using PubMed Central, Google Scholar, and ScienceDirect. The keywords used were as follows: COVID-19; traditional medicine and COVID-19; plant extracts on COVID-19; CAM and COVID-19; herbal medicine and COVID-19; AYUSH and COVID-19; medicinal plants and COVID-19; herbal formulations for COVID- 19 and natural products against COVID-19. The botanical components of the selected formulations and their medicinal potential were also searched. The article search was carried out from January 2022 to June 2023, and the collected articles underwent screening. Articles that adhered to the objectives of this review underwent additional screening and were meticulously summarized (Fig. 1).

SARS CoV-2

On 11 March 2020, COVID-19 was officially declared a global pandemic by the World Health Organization.[16] The virus that causes COVID-19, SARS-CoV-2, started spreading rapidly at the end of 2019 and, as of now (December 18, 2023), there are 772,386,069 confirmed cases of COVID-19 and 6,987,222 deaths due to COVID-19 worldwide.[17] As a result of asymptomatic instances that could aid in the spread of the pandemic, the true number of infected individuals is likely greater than the reported number.[18] SARS-CoV-2 is a single-stranded RNA virus that belongs to the family *Coronaviridae* and the order Nidovirales. SARS-CoV-2 has genetic structural similarity to that of SARS-CoV and Middle East respiratory syndrome-related coronavirus (MERS-CoV).[18,19] Four structural proteins, including the spike (S), envelope (E),

membrane (M), and nucleocapsid (N) proteins, are present in SARS-CoV-2. The virus has a genetic makeup of 13–15 (12 functional) open reading frames (ORFs) that have approximately 30,000 nucleotides. The genome has 11 protein-coding genes with 12 expressed proteins. The genomic structure of the ORFs closely resembles that of SARS-CoV and MERS-CoV. The ORFs 1a and 1b code for the polyproteins pp1a and pp1ab, respectively. Virally encoded proteinases further process these polyproteins to produce 16 proteins that are highly conserved across all CoVs in the same family.[19] The S protein promotes host-cell attachment, whereas the envelope protein plays a role in virus assembly, host-cell membrane permeability, and virus–host cell interaction. The membrane protein is known to be the main organizer of the coronavirus assembly process, while the nucleocapsid protein takes part in the helical ribonucleocapsid complex processing.[19–21] It has been demonstrated that there are six mutations in the genome of SARS CoV-2, with three in the ORF1ab gene, two in the S gene, and one in ORF7b and ORF 8. Usually, SARS-CoV-2 enters the human body via the nose, mouth, or eyes.[20] The SARS-CoV-2 S glycoprotein has a receptor-binding domain that can identify the target receptor. For SARS-CoV-2, the receptor angiotensin-converting enzyme-2 (ACE2) is preferred.[22] Meanwhile, enzymes such as cathepsin or transmembrane protease serine 2 (TMPRSS2) help in the hydrolysis of the S protein, resulting in membrane fusion and the release of viral nucleotides into the host cytoplasm. As a continuation, different molecular mechanisms are employed to build the new RNA and the proteins of the virus that make up its envelope. These receptors, proteases, and the proteins involved in the replication and proliferation of the virus are great targets for antiviral prophylactics.[18] Proteases, mainly chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro), nonstructural protein 12, and RNA-dependent RNA polymerase are some of the main targets.[18,19] There are three distinct phases of SARS-CoV-2 viral infection: the asymptomatic phase, the nonsevere symptomatic phase, and the severe infection period.[20] Although the mechanism underlying COVID-19 is not yet known, patients infected with this virus exhibit nonspecific symptoms that can vary from asymptomatic to deadly pneumonia and even fatality. The most typical signs, which are comparable to those of SARS-CoV and MERS-CoV infections, include fever, dyspnea, nonproductive cough, fatigue, myalgia, diarrhea, normal or reduced leukocyte counts, lung damage, and radiographic evidence of pneumonia.[14] Although SARS-CoV and the novel SARS-CoV-2 share a striking amount of similarities, the latter is spreading more quickly than the former, which might be due to the structural variations of the S proteins.[23]

Medicinal plant extracts and herbal formulations inhibiting SARS-CoV-2: Possible mechanism of action

Medicinal plant extracts and formulations contain vast amounts of active compounds with enormous health benefits. These phytomolecules include both primary and secondary metabolites. Among these, secondary metabolites, such as phenolics, alkaloids, and terpenoids, are widely studied for their therapeutic potential including antiviral activity, and some of them have emerged as natural product drugs. Hence, it is important to consider these natural sources to address the current threat of COVID-19, and researchers have started to concentrate on this topic. The medicinal plant extracts and herbal formulations containing highly active phytochemicals likely inhibit SARS-CoV-2 mainly through 3CLpro, PLpro, TMPRSS2, ACE2 receptor, RNA-dependent RNA polymerase, and heat shock protein A5 (Fig. 2). The nonstructural proteins 3CLpro and PLpro, which are encoded in the SARS-CoV-2 genome, are crucial for the replication of the virus. TMPRSS2 is the host enzyme that allows entry of the virus into the host cells. ACE2 is a functional receptor for SARS-CoV that contributes to S protein-mediated infection. RNA-dependent RNA polymerase is a crucial viral replicase that catalyzes the synthesis of complementary RNA strands using the viral RNA template. Heat shock protein A5 is the host cell receptor that is recognized by the S protein of the virus.[2,24] Thus, these can be useful targets for developing prophylactics from natural sources. We have published a review article related to studies on phytochemicals that inhibit COVID-19 through these targets.[2]

Medicinal plant extracts on COVID-19 infection

The most important sources of biomolecules that can be screened from plant parts are thought to be plant extracts. Such biomolecules are extracted from medicinal plants by employing a variety of extraction techniques and solvents.[25] Many researchers have studied and recognized the beneficial effect of traditional medicinal plants about their extracts and formulations to manage human SARS-CoV-2. A remarkable inhibitory effect of the ethanolic extract from *Psoralea corylifolia* seeds was established against PLpro of SARS-CoV, with a low half-maximal inhibitory concentration (IC_{50}) value of 15 μg/mL.[26] The anti-SARS-CoV-PLpro and 3CLpro effects of ethanolic extract from *Salvia miltiorrhiza* (88% and 60% inhibition for PLpro and 3CLpro, respectively, at an extract concentration of 30 μg/mL) and the anti-SARS-CoV-3CLpro activity of ethanolic extract from *Torreya nucifera* leaves (62% at 100 μg/mL) have also been reported.[27,28] The SARS-CoV-2 genome encodes two nonstructural proteins, 3CLpro and PLpro, which are essential for viral replication and may enable researchers to concentrate on these proteins as possible candidates for the development of therapeutics against SARS-CoV-2 infection.[24] Proteins involved in the life cycle of SARS-CoV-2 may be good targets for antiviral medications. As a result, SARS-CoV-2 infection may be prevented by drugs that can work as an inhibitor against these proteins.[21] Using a cell-based assay, the anti-SARS-CoV effects of 200 Chinese herbal extracts were evaluated. Among these extracts, six of them (*Dioscorea batatas*, tuber; *Cassia tora*, dried seed; *Gentiana scabra*, dried rhizome; two extracts of *Cibotium barometz*, dried rhizomes; and *Taxillus chinensis*, dried stem with leaf) effectively inhibited the growth and replication of SARS-CoV at concentrations between 25 and 200 μg/mL. This study revealed that the extracts of *D. batatas* tuber (IC_{50}: 44 μg/mL) and *C. barometz* rhizome (IC_{50}: 39 μg/mL) noticeably inhibited SARS-CoV-3CLpro protein.[29] In addition, an in-house library of compounds from the rhizomes of *Alpinia officinarum*, *Zingiber officinale*, and *Curcuma longa* was prepared, and their inhibitory effects against SARS-CoV-2-PLpro were studied through *in-silico* docking. The results indicated that eight phytochemicals from *A. officinarum* and *Z. officinale* demonstrated a strong binding affinity for the SARS-CoV-2-PLpro conformer.[30] These findings highlighted the fact that plant extracts are a source of active molecules that can act as COVID-19 prophylactics. We have already published a review article explaining the potential of different phytomolecules on COVID-19 management.[2] A recent computational study also has revealed that vitamin B12 is more efficient than other vitamins against almost all drug targets of SARS-CoV-2.[31] A search for the most potent natural product drug against SARS-CoV-2 through *in-silico* methods including molecular docking, properties, as well as aquatic and nonaquatic toxicity studies has

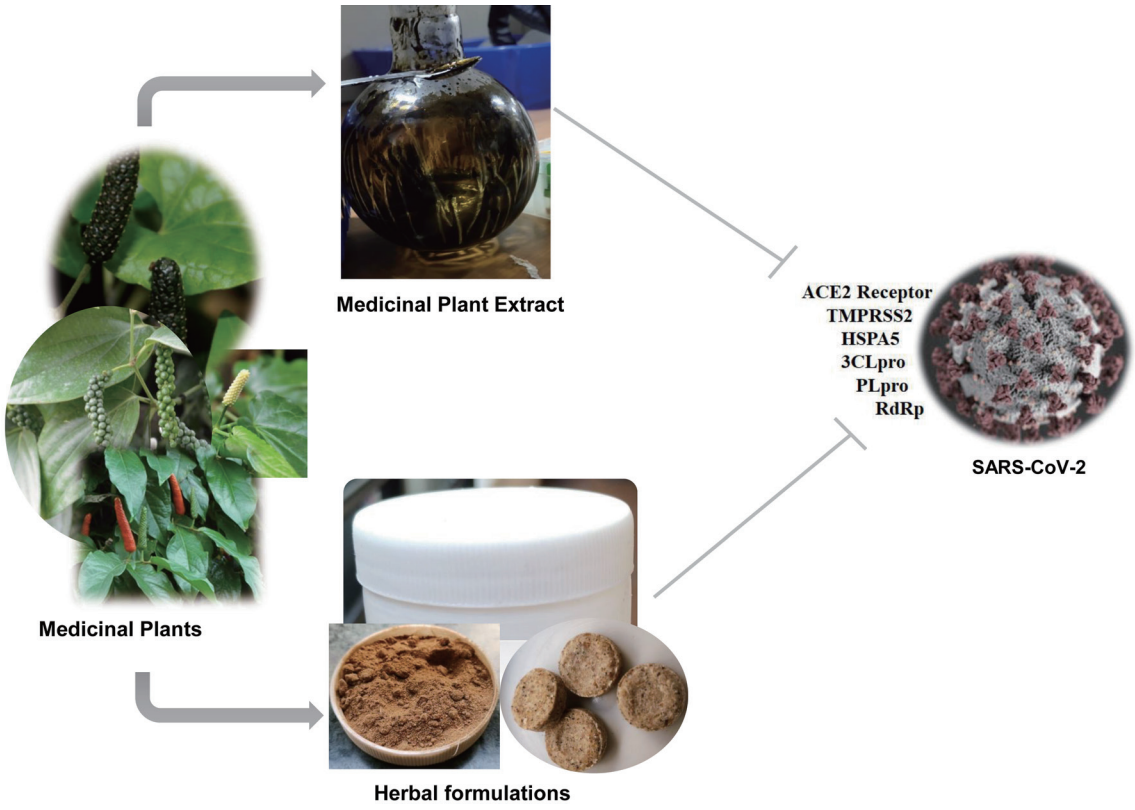

Fig. 2. Schematic representation of medicinal plant interventions and their possible targets to prevent COVID-19. ACE2, angiotensin-converting enzyme-2; COVID-19, coronavirus disease 2019; HSPA5, heat shock protein A5; PLpro, papain-like protease; RdRp, RNA-dependent RNA polymerase; SARS-CoV-2, severe acute respiratory syndrome-related coronavirus 2; TMPRSS2, transmembrane protease serine 2; 3CLpro, chymotrypsin-like protease.

been conducted and found dieckol as the most potent bioactive compound.[32] Moreover, clinical trials regarding the potential of natural products to halt the progression of COVID-19 have been reported. The efficacy of seed oil from *Nigella sativa*, which is known for immune-boosting properties and antiviral activity, was investigated in hospitalized adult COVID-19 patients through an open-label randomized clinical trial. Faster recovery of symptoms with *N. sativa* seed oil supplementation than usual care alone for patients with mild COVID-19 infection was noticed.[33] Table 1 lists the reported medicinal plants against COVID-19 infection.[26–29,33]

Herbal formulations on COVID-19 infection

AYUSH formulations

The traditional medical system in India is among the most ancient and has a pivotal role in health care services. There is a myriad of medicinal plants in India with indispensable therapeutic values, and they are also an essential part of many traditional formulations such as Chyawanprash and Triphala. Since ancient times, medicinal plants like ginger, ashwagandha, cinnamon, tulsi, turmeric, and amla have long been utilized as herbal treatments for a variety of illnesses.[14]

The recognized traditional medicines of India including Ayurveda, Yoga, and Siddha along with the alternative medicines Unani and Homeopathy, which flourished in India, form AYUSH.[34] Natural products originating from plants, animals, or minerals are the basis for the pharmacological modalities of these systems. So, if we use such herbal medications in prescribed doses by following the usage guidelines, these traditional medicines are safe to use and can cure many diseases.[35] Many traditional AYUSH formulations, well known for immunomodulation, have been in practice for centuries against respiratory tract diseases and allergic problems. Such formulations are listed and recommended by the Ministry of AYUSH of the Government of India for their prophylactic uses for COVID-19 management and include Ayurvedic, Unani, and Siddha approaches.[14] With the technical assistance of the Indian Council of Medical Research, the Ministry of AYUSH, the Council of Scientific and Industrial Research, and the Ministry of Health and Family Welfare, clinical trials in India for AYUSH formulations like Yashtimadhu, AYUSH-64, and Ashwagandha have been initiated on patients and individuals who have close contact with those with COVID-19.[14] The formulations from Ayurveda, Unani, and Siddha recommended by AYUSH for the management of COVID-19 are summarized in Table 2.[14,36–85]

Ayurvedic formulations

Ayurvedic formulations recommended by AYUSH include AYUSH Kwath, Samshamani Vati, AYUSH-64, Agasthya Hareetaki, and Anuthaila.[14] The AYUSH Kwath formulation contains four herbs (*Cinnamomum zeylanicum*, stem barks; *Ocimum sanctum*, leaves; *Piper nigrum*, fruits; and *Zingiber officinale*, rhizomes) and is available in the market as powder and tablet forms.[14,86] These herbs are immune boosters and are effective natural solutions to many viral diseases.[36–38] Therefore, the Ministry of AYUSH has approved the use of AYUSH Kwath against COVID-19 infection.[39–41]

Table 1. Medicinal plants (in terms of their extracts/oil) effective against COVID-19 infection

Source plant	Plant Part	Plant extract/ oil	Reference	SARS-CoV protein inhibited
Cassia tora	Dried seed	Continuous extraction with water, ethanol, methanol, and *n*-hexane	29	3CLpro
Cibotium barometz	Dried rhizome	Continuous extraction with water, ethanol, methanol, and *n*-hexane	29	3CLpro
Dioscorea batatas	Tuber	Continuous extraction with water, ethanol, methanol, and *n*-hexane	29	3CLpro
Gentiana scabra	Dried rhizome	Continuous extraction with water, ethanol, methanol, and *n*-hexane	29	3CLpro
Nigella sativa	Seed	Seed oil	33	Clinical trial on COVID-19 patients
Psoralea corylifolia	Seed	Ethanol extract	26	PLpro
Salvia miltiorrhiza	Root	Ethanol extract	27	PLpro and 3CLpro
Taxillus chinensis	Dried stem, with leaf	Continuous extraction using water, ethanol, methanol, and *n*-hexane	29	3CLpro
Torreya nucifera	Leaf	Ethanol extract	28	3CLpro

COVID-19, coronavirus disease 2019; PLpro, papain-like protease; SARS-CoV, severe acute respiratory syndrome-related coronavirus; 3CLpro, chymotrypsin-like protease.

Samshamani Vati is the aqueous extract from the medicinal plant *Tinospora cordifolia* and is useful against all types of fevers.[14,42] Further, this Ayurvedic formulation has antipyretic, immunomodulatory, antiviral, and anti-inflammatory effects.[42–45] AYUSH recommended a 500-mg Samshamani Vati tablet twice daily with warm water for 15 days for asymptomatic COVID-19 patients and mild COVID-19-positive individuals.[87]

AYUSH-64 is a tablet containing *Picrorhiza kurroa* (rhizomes), *Swertia chirayita* (whole plant), *Alstonia scholaris* (bark), and *Caesalpinia crista* (seed pulp).[14] Its constituents are reported to have antiviral, anti-asthmatic, and immune-boosting properties.[46–50] As AYUSH-64 has antimalarial action,[51] it is proposed to be effective against populations with a high risk of coronavirus infection. Hence, AYUSH recommended this tablet for COVID-19 patients (two 500-mg tablets twice daily for 30 days in warm water for asymptomatic individuals and two 500-mg tablets three times daily for 30 days in warm water for mild COVID-19-positive individuals).[87]

Agasthya Hareetaki is a Rasayana popularly known as Avaleha kalpana. This is a formulation of more than 15 herbal ingredients, including *Inula racemosa*, *Piper longum*, *Piper chaba*, *Mucuna prurita*, *Sida cordifolia*, *Aegle marmelos*, *Plumbago zeylanica*, *Terminalia chebula*, *Hordeum vulgare*, *Clerodendron serratum*, *Achyranthes aspera*, *Hedychium spicatum*, *Convolvulus pluricaulis*, *Tribulus terrestris*, *Solanum surattense*, *Solanum indicum*, *Uraria picta*, *Desmodium gangeticum*, *Premna mucronata*, *Stereospermum suaveolens*, *Gmelina arborea*, and *Oroxylum indicum*and commonly used against respiratory tract infections.[14,88] As its ingredients have anti-asthmatic, anti-oxidant, anti-inflammatory, antiviral, and immunomodulatory activities, this formulation is suggested for the management of COVID-19-related symptoms.[52–61] AYUSH recommended 5 g of Agasthya Hareetaki twice daily with warm water for COVID-19 symptom management.[89]

Anuthaila is an Ayurvedic oil preparation of about 25 herbs, including *Aquilaria agallocha* (heartwood), *Aegle marmelos* (root), *Berberis aristata* (stem), *Asparagus racemosus* (root), *Cedrus deodara* (heartwood), *Cinnamomum zeylanicum* (stem bark), *Cinnamomum tamala* (leaf), *Coleus vettiveroides* (root), *Cyperus rotundus* (rhizome), *Desmodium gangeticum* (whole plant), *Cyperus scariosus* (rhizome), *Embelia ribes* (fruits), *Elettaria cardamomum* (seed), *Glycyrrhiza glabra* (root), *Hemidesmus indicus* (root), *Nelumbo nucifera* (flower), *Leptadenia reticulata* (root), *Nymphaea stellata* (flower), *Santalum album* (heartwood), *Pluchea lanceolata* (root), *Solanum indicum* (whole plant), *Uraria Picta* (whole plant), *Solanum surattense* (whole plant), *Vetiveria zizanioides* (root), *Sesamum indicum* (oil), and *Vitex negundo* (seed).[90] The ingredients *L. reticulata* and *S. indicum* are effective against asthma, allergic responses, bronchitis, cough, throat trouble, fever, migraine, malaria, respiratory infections, and the common cold, thus justifying the use of Anuthaila for COVID-19.[14,62,63] Further, since ancient times, Anuthaila oil has been used for nasya, to cure skin dryness, graying of hair, a disorder of body parts above the clavicle, wasting in the cervical region, and emaciation of the shoulder and chest muscles.[90] AYUSH recommended two drops of Anuthaila daily in the morning in each nostril for the management of COVID-19 symptoms.[89]

In addition to the aforementioned Ayurvedic formulations, the Ministry of AYUSH (Government of India) highlighted the Ayurvedic health supplement chyawanprash as an immunity booster during the COVID-19 pandemic. Chyawanprash is a synergistic combination of around fifty medicinal herbs and spices. Apart from its role as an immune booster, this blend has beneficial anti-inflammatory, anti-oxidant, and cytoprotective effects and is also known to improve the health of the respiratory system.[91–93]

Unani formulations

Unani formulations recommended by AYUSH include Tiryaq-e-Arba, Arq-e-Ajeeb, Khamira-e-Banafsha, Laooq-e-Sapistan, and Habb-e-Bukhar.[14,94] Tiryaq-e-Arba contains four herbal ingredients (*Laurus nobilis*, *Gentiana lutea*, *Commiphora myrrha*, and *Aristolochia longa*) and has antidote and antispasmodic properties.[64] Its ingredients are reported as effective antiviral agents, including anti-SARS-CoV activity.[65,66] Thus, Tiryaq-e-Araba could emerge as an active antiviral medicine against COVID-19.

Table 2. AYUSH-recommended formulations for COVID-19 management

Formulation	Ingredients	Therapeutic potential of ingredients/formulation	References
Ayurvedic formulations			
AYUSH Kwath	*Cinnamomum zeylanicum*, *Ocimum sanctum*, *Piper nigrum*, *Zingiber officinale*	Antileishmanial, immunomodulatory, antiviral, and antiproliferative	36–41
Samshamani Vati	*Tinospora cordifolia*	Antipyretic, immunomodulatory, antiviral, and anti-inflammatory	42–45
AYUSH-64	*Alstonia scholaris*, *Caesalpinia crista*, *Picrorhiza kurroa*, *Swertia chirayita*	Antiviral, anti-asthmatic, immune-boosting, and antimalarial	46–51
Agasthya Hareetaki	*Achyranthes aspera*, *Aegle marmelos*, *Clerodendron serratum*, *Convolvulus pluricaulis*, *Desmodium gangeticum*, *Gmelina arborea*, *Hedychium spicatum*, *Hordeum vulgare*, *Inula racemosa*, *Mucuna prurita*, *Oroxylum indicum*, *Piper chaba*, *Piper longum*, *Plumbago zeylanica*, *Premna mucronata*, *Sida cordifolia*, *Solanum indicum*, *Solanum surattense*, *Stereospermum suaveolens*, *Terminalia chebula*, *Tribulus terrestris*, *Uraria picta*	Antiviral, anti-oxidant, anti-asthmatic, anti-inflammatory, and immunomodulatory	52–61
Anuthaila	*Aegle marmelos*, *Aquilaria agallocha*, *Asparagus racemosus*, *Berberis aristata*, *Cedrus deodara*, *Cinnamomum tamala*, *Cinnamomum zeylanicum*, *Coleus vettiveroides*, *Cyperus rotundus*, *Cyperus scariosus*, *Desmodium gangeticum*, *Elettaria cardamomum*, *Embelia ribes*, *Glycyrrhiza glabra*, *Hemidesmus indicus*, *Leptadenia reticulata*, *Nelumbo nucifera*, *Nymphaea stellata*, *Pluchea lanceolata*, *Santalum album*, *Sesamum indicum*, *Solanum indicum*, *Solanum surattense*, *Uraria Picta*, *Vetiveria zizanioides*, *Vitex negundo*	Effective against asthma, allergic response, bronchitis, cough, throat trouble, fever, migraine, malaria, respiratory infections, and common cold	14,62,63
Unani formulations			
Tiryaq-e-Arba	*Aristolochia longa*, *Commiphora myrrha*, *Gentiana lutea*, *Laurus nobilis*	Antidote, antispasmodic, and antiviral	64–66
Arq-e-Ajeeb	Camphor, menthol, Thymol,	Antiviral and anti-inflammatory	14,67–69
Khamira-e-Banafsha	*Viola odorata*	Antiretroviral, anti-inflammatory, and effective for respiratory tract and chest infections	14,70,71
Laooq-e-Sapistan	*Cordia myxa, Ziziphus jujuba*	Anti-inflammatory, antiviral, and effective for chest infection	14,72–74
Habb-e-Bukhar	*Bambusa Bambos*, *Cinchona officinalis*, *Tinospora cordifolia*	Antimalarial, antiviral, and immune-boosting	75–77
Siddha formulations			
Nilavembu Kudineer	*Andrographis paniculata*, *Chrysopogon zizanoides*, *Cyperus rotundus*, *Mollugo cerviana*, *Piper nigrum*, *Plectranthus vettiveroides*, *Santalum album*, *Trichosanthes cucumerina*, *Zingiber officinale*	Immunomodulatory, anti-asthmatic, antimicrobial, anti-allergic, antiviral, and effective against chikungunya, dengue fever, malaria, typhoid, and viral fevers	14,37,40, 78–83
Adathodai Manapagu	*Adathoda vasica*	Immune-boosting and for treating respiratory disorders	84,85
Kabasura Kudineer	*Anacyclus pyrethrum*, *Andrographis paniculata*, *Clerodendron serratum*, *Coleus aromaticus*, *Costus speciosus*, *Cyperus rotundus*, *Hygrophila auriculata*, *Justicia adhatoda*, *Piper longum*, *Sida acuta*, *Syzygium aromaticum*, *Terminalia chebula*, *Tinospora cordifolia*, *Tragia involucrata*, *Zingiber officinale*	Anti-allergic, antiviral, immunomodulatory, and effective for respiratory tract infections	14,37,57, 82,83

COVID-19, coronavirus disease 2019.

AYUSH recommended using the Tiryaq-e-Arba formulation at a dose of 3–5 g with lukewarm water.[94]

Arq-e-Ajeeb is a liquid formulation of menthol, thymol, and camphor.[14] Thymol has antiviral activity, particularly for the herpes simplex virus.[67,68] Menthol is reported for its anti-inflammatory efficacy.[69] The Unani physicians used Arq-e-Ajeeb for treating Swine flu and set a very successful treatment history.[14] These shreds of evidence enhance the possibility of using Arq-e-Ajeeb against COVID-19; thus, AYUSH recommended inhaling 2–5 drops of Arq-e-Ajeeb for respiratory tract infection.[94]

Khamira-e-Banafsha is a semi-solid Unani preparation that is primarily used as an expectorant for colds and coughs. It is also effective for respiratory tract and chest infections, whooping cough, bronchitis, fever, and other conditions. It is made by adding the decoction of *Viola odorata* flowers to a base of sugar or sugar with honey.[14] Moreover, research has shown that *V. odorata* can reduce the viral load and boost the effectiveness of antiretroviral medications.[70] It is also effective for the prevention of lung damage and is suggested as a safer medicinal agent in the treatment of inflammatory conditions of the lung.[71] The literature stated above is in favor of using it to manage COVID-19. AYUSH recommended Khamira-e-Banafsha for dry cough at a dose of 5 g and 10 g twice daily for those aged 6–12 years old and above 12 years old, respectively.[94]

Laooq-e-Sapistan is a semisolid, sugar-based polyherbal preparation of Unani medicine. It has been proven to be effective against whooping cough, phlegm, and colds. It further reduces inflammation of the pharynx and tonsils. The main ingredient is the sticky, jelly-like mass of ripened fruit of *Cordia myxa*, which has been shown to have anti-inflammatory and antichest infection properties.[14,72] Ziziphus fruit (*Ziziphus jujuba*), another important constituent, contains betulinic acid, which is reported to have antiviral efficacy.[14,73,74] These literature reports thus support the exploration of Laooq-e-Sapistan for COVID-19 infection, and AYUSH recommended Laooq-e-Sapistan for dry cough (5 g and 10 g twice daily for those aged 6–12 years old and above 12 years old, respectively).[94]

Habb-e-Bukhar is a polyherbal Unani formulation in tablet form that is given to treat malarial fever and elephantiasis.[14] It is made up of three ingredients (*Bambusa Bambos*, *Cinchona officinalis*, and *Tinospora cordifolia)*. The ingredient *C. officinalis* is rich in the alkaloids quinine, quinidine, cinchonidine, and cinchonine, and these natural products are potent antimalarial agents.[75] *T. cordifolia,* another constituent of Habb-e-Bukhar, is reported to be an effective antiviral agent against the herpes simplex virus and also to have immune-boosting efficacy.[76,77] Thus, Habb-e-Bukhar is recommended by AYUSH to be taken twice daily for high fever (250 mg for those aged 6–12 years old and 500 mg for those older than 12 years old).[94]

Siddha formulations

Siddha formulations recommended by AYUSH include Nilavembu Kudineer, Adathodai Manapagu, and Kabasura Kudineer.[14] Nilavembu Kudineer is a polyherbal formulation containing *Andrographis paniculata* (whole plant), *Chrysopogon zizanoides* (root), *Santalum album* (bark), *Zingiber officinale* (rhizome), *Piper nigrum* (fruit), *Cyperus rotundus* (root tuber), *Mollugo cerviana* (whole plant), *Plectranthus vettiveroides* (root), and *Trichosanthes cucumerina* (whole plant).[78] It plays a protective role against chikungunya and dengue fever and also acts as an immunomodulator.[79] Recent studies have revealed its efficacy as an antimicrobial and antiviral remedy, which makes this formulation suitable to treat malaria, typhoid, and viral fevers.[14,78,80] Research also has shown that most of its components are immune-boosting, antiviral, anti-asthmatic, and anti-allergic agents.[37,40,81–83]

Adathodai Manapagu is composed of the leaves of *Adathoda vasica*, which contain alkaloids like vasicine—the active ingredient in many cough syrups.[14] This herb has been a well-established Indian traditional medicine since ancient times, particularly for treating various respiratory disorders.[84] Its extract further enhances the host immunity.[85]

Kabasura Kudineer is another Siddha formulation that works well for common respiratory ailments like the flu and cold. In addition, Siddha practitioners suggest Kabasura Kudineer for fever, severe phlegm, and dry cough.[14] It is made up of 15 herbal ingredients, including *Zingiber officinale* (rhizome), *Syzygium aromaticum* (flower bud), *Piper longum* (fruit), *Tragia involucrate* (root), *Hygrophila auriculata* (root), *Anacyclus pyrethrum*(root), *Terminalia chebula* (fruit rind), *Coleus aromaticus* (leaf), *Justicia adhatoda* (leaf), *Costus speciosus* (root), *Clerodendron serratum* (root), *Tinospora cordifolia* (stem), *Andrographis paniculata* (whole plant), *Cyperus rotundus* (root tuber), and *Sida acuta* (root).[78] These ingredients have a unique role in treating respiratory tract infections, allergies, and viruses, and they have an immunomodulatory capacity.[37,57,82,83] Hence, the Ministry of AYUSH advised using Kabasura Kudineer to treat COVID-19 symptoms. AYUSH suggested Nilavembu Kudineer and Kaba Sura Kudineer as antiviral medications (60 mL, twice a day after food) and Adathodai Manapagu (for adults: 10–20 mL with warm water, twice a day after food) for the management of COVID-19-related symptoms.[95]

Formulations from traditional Chinese medicine

Chinese traditional medicine is also a collection of multi-ingredient herbal remedies and has been well known for the well-being of humans, notably for treating infectious diseases since ancient times.[96] When the COVID-19 outbreak first started, herbal remedies were extensively discussed and researched across China to reduce the spike in the number of infections. Its efficacy in reducing the severity of COVID-19 has been endorsed by frontline healthcare workers and the Chinese regulatory agency.[24] More recently, researchers have presented scientific evidence supporting the impact of these herbal remedies on COVID-19 control. Lianhuaqingwen is a traditional Chinese mixture of 13 herbs and is well known for treating fever, fatigue, cough, influenza, pneumonia, bronchitis, and the early stage of measles. As a result, the Chinese National Health Commission suggested using this herbal remedy to manage or treat COVID-19.[97,98] The remarkable *in vitro* antiviral activities of seven (forsythoside A, arctiin, isoliquiritigenin, gallic acid, kaempferol, secoxyloganin, and rutin) among 61 compounds from the Lianhuaqingwen herbal mixture, with IC_{50} values from 4.9 ± 0.1 μg/mL (kaempferol) to 47.8 ± 1.5 μg/mL (secoxyloganin), have been reported.[99] Later, the anti-SARS-CoV-2 activity of the Lianhuaqingwen herbal mixture in Vero E6 cells was assessed by cytopathic effect inhibition and plaque reduction approaches, and it was observed that the SARS-CoV-2 replication in Vero E6 cells was inhibited by this herbal blend (IC_{50}: 411.2 μg/mL). Additionally, they demonstrated that the mixture can dose-dependently inhibit the production of proinflammatory cytokines such as interleukin 6, tumor necrosis factor-alpha, chemokine ligand 2/monocyte chemoattractant protein 1, and C-X-C motif chemokine ligand 10.[97]

A combination strategy of lopinavir/ritonavir (Kaletra®) and arbidol with Shufeng Jiedua Chinese traditional medicine was tested in four COVID-19 patients. Following treatment, three of the patients reported improvements in pneumonia-related symp-

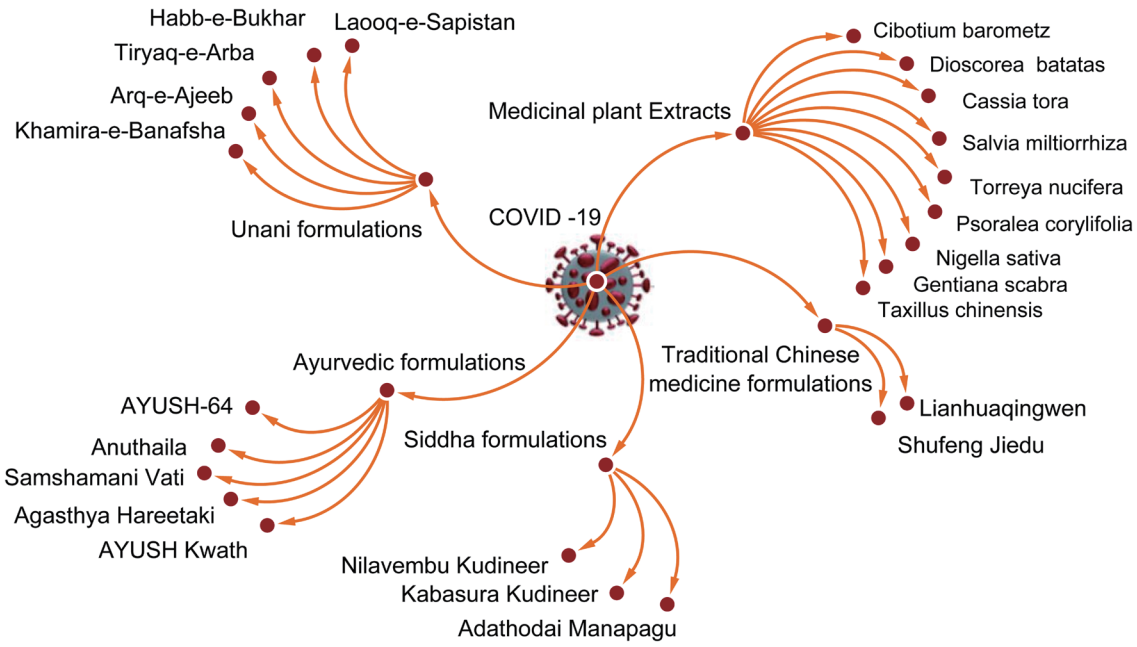

Fig. 3. Schematic representation of medicinal plants (in terms of extracts) and their herbal formulations against COVID-19. COVID-19, coronavirus disease 2019.

toms. Two of them were discharged after becoming COVID-19 negative, and one of them was COVID-19 negative at the first test. There also was improvement in the remaining patients with severe pneumonia.[100] Most recently, it was found that the Chinese herbal remedy Liu-Shen capsules inhibited SARS-CoV-2 viral infection through downregulation of the expression of inflammatory cytokines and regulation of the nuclear factor kappa B/mitogen-activated protein kinase signaling pathway *in vitro*.[101]

The medicinal plants (in terms of extracts) and their herbal formulations against COVID-19 infection are schematically illustrated in Figure 3.

Conclusion

Herbal medicine interventions are still seen as potential solutions to prevent and/or cure several ailments, and now the focus is on COVID-19. Herbal extracts contain a vast array of natural components that are underutilized in conventional therapies and might potentially serve as an endless source of therapeutic materials. Natural-origin chemicals can now be used more than in the past decades, largely as nutritional supplements and nutraceuticals, owing to new developments in science and medicine. This review, which examined COVID-19 from different angles in terms of medicinal plants, their extracts, and formulations, will be useful because there is growing interest in discovering treatments for long-term symptom relief and immunity-boosting to combat COVID-19. This review thus highlighted that traditional medicine formulations and extracts with active ingredients can be explored as a potential source to develop natural anti-SARS-CoV-2 drugs. Further experimental research is suggested to prove the detailed efficacy of these extracts and herbal formulations against COVID-19. A comprehensive approach needs to be used to examine their toxicity and consumption duration. Furthermore, novel methods of processing and formulation may enhance their solubility, transport mechanisms, and therapeutic properties, enabling their adaptation as antiviral functional foods and medications. Furthermore, novel strategies for the characterization of active phytochemicals of these extracts and formulations need to be devised for developing natural medications to treat COVID-19. Herbal extracts and formulations may have synergistic health benefits (anti-allergic, antiviral, anticancer, anti-inflammatory, etc.) due to naturally occurring phytochemical combinations; this is something to consider, but further research is needed.

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Conflict of interest

The authors declare no conflicts of interest, financial or otherwise.

Author contributions

Conceptualization, data curation, methodology, writing, reviewing, and editing original draft (DS); writing, reviewing, and editing

original draft and reference formatting (JPJ); figure preparation, reference formatting, reviewing, and editing original draft (MD); reviewing and editing original draft (SPD); supervision (CJ).

Data sharing statement

The data used in support of the findings of this study are available from the corresponding author upon request.

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