Biomedical Research and Therapy, 8(7):4461-4475

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Review

Pharmacological intervention of various Indian medicinal plants in combating COVID-19 infection

Niti Yashvardhini[1], Samiksha[1], Deepak Kumar Jha[2,*]

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ABSTRACT

Coronavirus pandemic is progressing rapidly causing an eruption of successive waves around the globe due to its ability to cause recurrent mutations, making the prevention and control measures extremely essential. The success of therapeutic benefits of natural plants and herbs are well-known to humans since ancient times. Medicinal plants play an important role in curing human diseases due to the presence of phytochemicals and bioactive compounds. India is known for its heritage of medicinal plants, and Traditional Indian Medicines (TIM) have shown the potential to treat several diseases. The review highlights the detailed information of various Indian medicinal plants and their potential therapeutic role as an antiviral and immunomodulatory therapeutics. Ministry of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy) has already issued several health advisory and routinely use of medicinal plants to strengthen the immune system to fight against COVID-19. Various medicinal plants, such as *Ocimum sanctum*, *Withania somnifera*, *Tinospora cordifolia*, *Curcuma longa*, *Zingiber officinalis*, *Azadirachta indica*, *Piper nigrum*, *Nigella sativa*, *Allium sativum*, *Glycyrrhiza glabra* with their antiviral properties against several viruses including SARS-CoV-2 virus have been discussed in the review, which might be an effective prophylaxis against COVID-19. Special emphasis has been given on the antiviral activities of these plants against SARS-CoV-2, highlighting their efficacy as potential drug candidates.

Key words: Antiviral, Coronavirus, Medicinal plants, Phytochemicals, SARS-CoV-2

BACKGROUND

Over the centuries, plants and herbs are used as an important source of medicines[1]. According to WHO, traditional medicines have always been the major source of treatment in primary healthcare system of communities. Right from the evolution of human civilization, the practice of use of medicinal plants have been documented for the purpose of curing human ailments[2]. The use of medicinal plants take us 5000 years back, providing the primitive evidence of use of traditional medicines in Indian, Chinese, Egyptian, Roman, Greek and Syrian texts[3]. The vast knowledge of the medicinal values of plants today is the result of long evolution through trials and error when everything was based on experimentations due to which man learned the healing properties of medicinal plants in barks, seeds, fruiting bodies and other parts of plant[4]. The use of traditional medicines depend on local availability of natural resources and their indigenous knowledge[5]. About 80% of the health needs of the world's population is facilitated by herbal medicine, and that too in rural areas of developing countries[6]. In majority of the developing countries, herbal medication has sustained its popularity, as modern medications are limited in those regions[7]. According to the reports of WHO, 80% of the population in Africa depends on traditional medicines for health care.

India has always been a land of plants and possesses a rich history of traditional healing system, especially the use of plants and herbs. India has the rich diversity of medicinal plants and Indian herbs are extensively used for the medicinal properties throughout the world[8]. Forests of India are the major source of therapeutic medicinal plants, contributing to about 90% of the herbs and medicinal plants, with Gujarat, Haryana, Rajasthan, Andhra Pradesh, Uttrakhand and Tamil Nadu being the leading producers of herbal plants in India[8]. The ancient literatures of India, such as Rigveda, Charak Samhita, Atharvaveda and Sushruta Samhita, talk about the practices of medicinal plants to treat diseases[3]. In India, around 17,000-18,000 flowering species are found, among which 6,000-7,000 species are considered to have medicinal values[3]. Apart from the medicinal uses, herbal plants are the source of livelihood to a large section of population of India[9]. Around 70% population of rural India depends on medicinal plants as a source of treatment of various diseases[10]. Indians have been using medicinal plants to cure several diseases, treating the wounds and inflammation.

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History

- Received: Jul 15, 2021
- Accepted: Jul 28, 2021
- Published: Jul 31, 2021

DOI : 10.15419/bmrat.v8i7.685

Check for updates

BioMedPress
The Open Access Publisher

Cite this article : Yashvardhini N, Samiksha, Jha D K. **Pharmacological intervention of various Indian medicinal plants in combating COVID-19 infection**. *Biomed. Res. Ther.;* 8(7):4461-4475.

Medicinal plants possess several properties and are known to cure some common prevalent diseases, such as malaria, tuberculosis, diarrhoea, asthma and pneumonia [11]. During the outbreak of epidemic diseases, such as malaria, cholera, small pox in the colonial era, traditional plants were continued to be used in India for medicinal purposes [1]. Medicinal plants are used against diseases like diabetes, intestinal disorders, parasitic infections, skin disorders, gastrointestinal disorders, neurological disorders, piles, skeletal diseases, viral infections *etc.* [12]. Infectious diseases across the world are the major causes of mortality and are increasing alarmingly within the last few years [13]. Viral diseases have become a major health concern throughout the world and the emergence of COVID-19 in late 2019 has resulted in a global pandemic.

The Indian Traditional System of Medicines is one of the ancient medical practice in the world [14]. There are several medicinal plants native to India, which are used as antiviral and immune stimulant [14]. Various plants, such as *Tinospora cordifolia, Glycyrrhiza glabra, Azadirachta indica, Andrographis paniculata, Calotropis gigantea, Ocimum sanctum, Curcuma longa, Withania somnifera, Zingiber officinale, Allium sativum, Moringa oleifera etc.* are known to possess the antiviral and immunomodulatory properties which boost the immune system [15–17]. The phytochemicals found in plants and the compounds specific to plants, such as flavonoids, saponins, alkaloids, quercetin, catechins and polysulphates play an important role in the inhibition of viral entry of viruses, which further inhibits their replication, causing damage to their nucleocapsid and genetic material [16]. Therefore, with the help of traditional practices of Indian medicinal plants, new treatment methods can be developed to combat the effects of COVID-19.

A BRIEF OVERVIEW OF CORONAVIRUS

Coronavirus disease 2019 (COVID-19) originated in Wuhan, Hubei Province, China in late December, 2019 [18]. It is a positive, single-stranded virus, appearing in a crown shape when seen under an electron microscope, as it has spike glycoprotein on the envelope [19]. Coronavirus comes under the broad realm of Riboviria, having a total of 39 species [20] (**Figure 1**).

The virus has the largest genome (26.4-31.7kb) among all the RNA viruses known till date [21]. It has a 5'-cap structure and 3'poly A tail with 14 open reading frames (ORFs) which encode 27 proteins [22]. There are four structural proteins of the virion, known as S (Spike), E (Envelope), M (Membrane) and N (Nucleocapsid); the S, E and M proteins together constitute

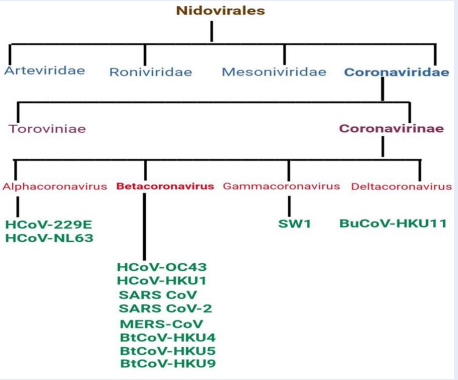

Figure 1: **Classification of Coronavirus.**

the viral envelope, while the protein N holds the RNA genome [23]. The viral envelope plays a major role in the assembly and release of virus, promoting viral pathogenesis [24].

Symptoms of SARS-CoV-2 includes fever, coughing and shortness of breath, but in severe infection, it can lead to pneumonia, multi-organ failure, severe acute respiratory syndrome and even death [25,26]. Clinical reports reveal that the most distinctive comorbidities of SARS-CoV-2 were hypertension and diabetes mellitus [27]. SARS-CoV-2 binds to the host cells through the ACE 2 receptor (Angiotensin converting enzyme 2), which is facilitated by spike glycoprotein, and the process is set with the help of a protease called TMPRSS2 [28,29]. After further endocytosis followed by uncoating, components of SARS-CoV-2 with the aid of host cell machinery produce new viruses. As a result of stimulation of SARS-CoV-2, the host immune system releases cytokines following inflammation through activation of dendritic cells, NK cells, macrophages, and neutrophils, which can result into sepsis, multiple organ failure, septic shock and even death [30]. The expression of ACE 2 is high in heart, kidney, blood vessels, lungs and intestine [31]. Multiplication of viruses induce cellular responses comprising of innate and adaptive immune cells [32,33]. Neutrophils produces injury to lungs and adaptive immune cells, mainly the T cells (Cytotoxic $CD8^+$ T cells), which not just kill the virus, but also causes injury to lungs [34,35]. This triggers the progression of systemic inflammatory response called cytokine surge, in which there is an extensive increase in the number of cytokines (TNF-α, IL1, IL6, IL10 *etc.*) which thereby causes inflammation and cell death of Type 1 and Type 2 cells in the alveoli [36]. This causes the interruption in transportation of oxygen, resulting in apoptosis in alveoli of the lungs and hence causes Acute

Respiratory Distress or Syndrome (ARDS)[37]. Transmission of SARS-CoV-2 virus occurs from human to human through respiratory droplets during coughing and sneezing[38].The high affinity of S-protein of SARS-CoV-2 to bind ACE 2 is 10 - 20 fold greater than S protein of SARS-CoV, due to which SARS-CoV-2 spreads rapidly[31].

In the race to curb the spread of the novel Coronavirus, several strategies and measures are being implemented from social distancing to drugs and vaccine discoveries. In addition, traditional herbal medicines are also being explored side by side as there is still huge dependence on medicinal plants as complementary medicines[39]. As we know that SARS-CoV-2 affects weak, immune compromised people, herbal medicines can play a potential role in boosting the immune system and possess antiviral properties which can curb the effects of COVID-19, lowering down the death rates worldwide[40].

STATUS OF MEDICINAL PLANTS OF INDIA

Humans depend on nature and its source for survival and sustenance. Plants have been one of the important sources of medicines, and in India, curative properties of plants take us back to the age of the Rigveda (2500 to 1600 B.C.)[1]. Traditional herbal medicines hold a long history in treating various infectious diseases due to the presence of anti-bacterial, anti-viral, anti-inflammatory and immunomodulatory properties, which make them effective against a wide array of diseases[39,41,42]. India has a rich traditional healing system, and *Hortus Malabaricus,* the oldest printed book on Indian Medicinal Plants, enlists the use of the medicinal plants. The most ancient written evidence of usage of medicinal plants for the preparation of medicine has been found from Nagpur on Sumerian clay slab, which dates back to 5000 years ago[4]. In India, there are more than 1.5 million practitioners who use traditional medicine system for healthcare, and more than 1500 herbal formulations are sold as dietary supplements[10,43]. 1000 species of medicinal plants are reported in India, among which 540 species are herbs, 100 are shrubs, 160 climbers, 200 species are trees, orchids are 15 species and ferns and conifers are 20[44]. 70% of Indian medicinal plants are found in tropical forests of Eastern and Western Ghats, Himalayas, Aravali Vindhya range and Chota Nagpur Plateau[45].

Despite the progress of modern medical and pharmaceutical research, the use of medicinal plants are still significant and common, and the Indian Traditional

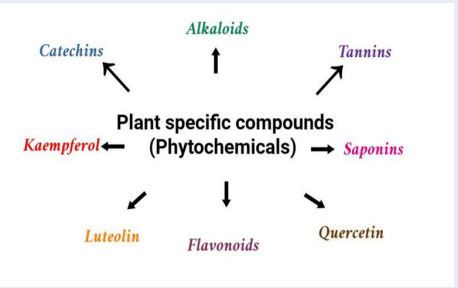

Figure 2: Types of plant specific compounds (Phytochemicals).

System of Medicines (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy (AYUSH)) uses herbs and plants for treatment of various diseases[1] (**Table 1**). Studies reveal that plant derived compounds (Phytoconstituents), extracts of parts of plant such as roots, stems, barks, flowers, fruits and seeds, help in treating common to rare infections[15] **(Figure 2).**

National Medicinal Plant Board (NMPB), established in India in November 2000 by Government of India, acts as a primary board for coordinating all matters related to medicinal plants, their growth, export, conservation and cultivation. This board is located in Department of AYUSH of Ministry of Health and Family Welfare, Government of India[3].

Table 1: List of some common medicinal plants found in India

Local Name	English Name	Botanical Name	Parts used	Applications
Tulsi	Holy basil	*Ocimum sanctum*	Leaves	antiallergic, antidiabetic
Methi	Fenugreek	*Trigonella foenum*	Seeds	constipation, diabetes
Dalchini	Bark Cinnamon	*Cinnamomum zeylanicum*		antibacterial, antiseptic
Amla	Indian gooseberry	*Embilica officanalis*	Fruit	constipation, antioxidant, fever, diabetes, hyperacidity
Mulethi	Licorice	*Glycrrhiza glabra*	Roots	digestive disorders, ulcers, bronchitis
Pyaj	Onion	*Allium cepa*	Bulb	prostate cancer, stomach cancer
Ghritkumari	Aloe	*Aloe barbadensis*	Leaves	laxative, wound healing, skin burns, ulcers
Ashwagandha	Indian ginseng	*Withania somnifera*	Roots, leaves	restorative tonic, stress, nerves disorders, aphrodisiac
Elaichi	Lesser Cardamom	*Elettaria cardomomum*	Pod and seeds	nausea, vomiting, dry cough
Babool	Gum arabic tree	*Acacia arabica*	Bark, root, gum, leaves, pods, seeds	oral care, bleeding gums, wounds
Lehsun	Garlic	*Allium sativum*	Bulb	ringworm, dysentery, wounds, heart diseases
Neem	Margosa tree	*Azadirachta indica*	Root, bark, flower	cough, diabetes, skin diseases, arthritis, bronchitis
Chirayata	Bitter stick, East Indian Balmony	*Andrographis paniculata*	Whole plant	fever and jaundice
Harad	Chebulic Myrobalan	*Terminalia chebula*	Fruits, roots, bark	digestive disorders, eye and skin diseases
Doob	Bermuda grass	*Cynodon dactylon*	Leaves	jaundice, antidiarrheal
Adrak	Ginger	*Zingiber officinale* Rosc.	Rhizome	antioxidant and anti-arthritic
Giloe/Guduchi	Heart-leaved moonseed	*Tinospora cordifolia*	Stem	fever, urinary diseases, dyspepsia
Sadabahar	Madagascar Periwinkle	*Catharanthus roseus*	Whole plant	leukaemia, hypertension, antispasmodic
Sarpgandha	Indian snake-root	*Ranwolfia serpentina*	Root	hypertension, insomnia
Jyotishmati	Staff tree	*Celastru spaniculatus*	Seeds	gout, neurological disorders, rheumatism
Laung	Clove	*Syzygium aromaticum*	Dried flower buds, leaves, and stems	analgesic, antioxidant, antitumor, antiviral, antifungal, anti-inflammatory and antibacterial activity
Haldi	Turmeric	*Curcuma longa*	Rhizome	anti-inflammatory, hematuria, hemorrhage, flatulence, jaundice, menstrual difficulties

Continued on next page

Table 1 continued

Local Name	English Name	Botanical Name	Parts used	Applications
Guggul	Indian bdelliumtree	*Commiphora wightii*	Bark	urinary infections, ascites, piles, arthritis, swellings ulcers and in skin diseases
Bhringaraj	False daisy	*Eclipta prostrata* L.	Whole plant	hepatotoxicity
Paan	Betel	*Piper betle*	Leaf	anti-inflammatory, anti-apoptotic, anti-oxidant, anticancer and antibacterial activity
Peepal	Sacred fig	*Ficus religiosa*	Bark, leaves, fruit, seeds, latex	constipation, gynecological diseases and skin diseases
Datura	Thorn apples	*Dhatura stramonium*	Leaves and fruits	asthma, cardiac pains

Table 2: List of some common medicinal plants of India having antiviral properties

Plants (Scientific Name)	English name	Family	Effective against virus	References
Withania somnifera	Indian ginseng	Solanaceae	HSV-1	46
Hibiscus sabdariffa	Roselle	Malvaceae	Measles	47
Glycyrrhiza glabra	Liquorice	Fabaceae	Japanese encephalitis, Polio	48,49
Phyllanthus amarus	Indian gooseberry	Euphorbiaceae	Polio	50
Ocimum sanctum	Holy Basil	Lamiaceae	Vaccinia	51
Alpinia officinarium	Lesser galangal	Zingiberaceae	H1N1	52
Zingiber officinale	Ginger	Zingiberaceae	Hepatitis C	53
Chrysanthemum morifolium	Florist's daisy	Asteraceae	HIV-1	54
Gardenia sp.	Cape jasmine	Rubiaceae	Influenza	55
Cinnamomum cassia	Chinese cassia, Chinese cinnamon	Lauraceae	HIV-1, HIV-2	56
Allium sativum	Garlic	Alliaceae	SARS	57
Vitex trifolia	Indian wild pepper	Lamiaceae	SARS-CoV	58
Avicenna marina	Gray mangrove	Avecennaceae	Fowl pox	59
Punica granatum	Pomegranate	Puniaceae	Influenza	60
Nigella sativa	Black cumin	Ranunculaceae	Newcastle	50
Sorghum bicolor	Great millet	Poaceae	HSV-1	61

ANTIVIRAL ACTIVITY OF INDIAN MEDICINAL PLANTS

Earth contains around 10^{31} viruses, and they are ubiquitous even in the marine environment, as nearly 5000 viral genotypes are present in every 200 L of water[62,63]. Viral diseases are increasing throughout the world and are a matter of great concern[64]. They enter the body and redirect body's metabolism to produce multiple copies of their genome and proteins[65]. Plants contain a variety of bioactive constituents, such as alkaloids, phenolic compounds, saponins, flavonoids, lignans and other bioactive components which make them a suitable treatment option against viral infections[64,66,67]. Studies reveal that compounds, such as andrographolide, glycyrrhizic acid, curcumin as well as extracts of *Azadirachta* have antiviral activities[68]. Antiviral activities of plants like *Allium sativum, Helichrysum aureonitens*, *Quillaja saponaria*, *Pterocaulon sphaedatum* are well known[65]. Antiviral activities of 38 Indian plants have been reported in 32 papers to be effective against human immunodeficiency virus (HIV)[68]. In another study by Mehrotra *et al.*[69] neutralizing activity of *Phyllanthus amarus* has been reported against hepatitis virus. Ahmed and Verma[70] studied the genus *Phyllanthus* (Euphorbiacae) and worked on plants namely *P. amarus, P. niruri, P. fraternus. P. maderaspatensis, P. emblica, P. debelis, P. acidus, P. urinaria, P. sellowianus, P. stipulatus, P. corcovadensis, P. chamaecristoides, P. caroliniensis, P. tenellus, P. orbiculatus, P. acuminatus, P. myrtifolius, P. discoides, P. virgatus and P. mummuariifolius,* which showed pharmacological and phytochemical properties of the genus exhibiting diverse biological activities such as antihepatotoxicity, anti-HIV, anti-carcinogenic and anti-inflammatory properties. Indian plants, such as *Acacia nilotica* (Family-Fabaceae), *Avicenna marina* (Family-Avecennaceae), *Cissus quadrangularis* (Family-Vitaceae), *Ipomea carnea* (Family-Convolvulaceae), *Aristolochia bracteolate* (Family-Aristolocheaceae), *Trigonella foenumgraecum* (Family-Fabaceae), *Prosposis chilensis* (Family-Mimosaceaeare), *Trebulus terrestris* (Family-Zygophyllaceae) and *Maerua oblongifolia* (Family-Capparidaceae) are found to possess antiviral properties against pox viruses *in-vitro*[59] **(Table 2).**

Rhizophora mucronata (Family- Rhizophoraceae) was assessed for its antiviral activities against Human immunodeficiency virus (HIV) *in vitro* cell culture system and the polysaccharide extracted from the bark of *Rhizophora mucronata* was found to be inhibiting the viral cycle as it protected MT-4 cells from HIV induced cytopathogenicity and inhibited expression of HIV antigens[71]. Fiore *et al.*[72] reported antiviral activity of *Glycyrrhiza* spp. (Licorice) against HIV-1, SARS related Coronavirus, hepatitis B virus, vaccinia virus and vesicular stomatitis virus, as it reduces transportation of the virus to the membrane and sialyation of surface antigen of hepatitis B virus inhibits fusion of the viral membrane of HIV-1 with the cell by reducing membrane fluidity. It also induces interferon gamma in T cells and inhibition of phosphorylating enzymes in the infection by vesicular stomatitis virus.

Azadirachta indica, commonly known as neem (Family- Meliaceae), native to Indian subcontinent, is another promising plant having active component azadirachtin and other constituents such as nimbidol, sodium nimbinate, gedunin, salannin, quercetin, nimbolinin, nimbin and nimbidin, and holds a long history of use in traditional medicines throughout the world[73]. Extracts of neem have shown antiviral activity on viruses such as vaccinia, Buffalo pox, chikunguniya, herpes, measles *etc*[68].

Central Drug Research Institute, Lucknow (CDRI) screened top 11 families for their pharmacological activities, and the rank of 11 families on the basis of their antiviral activities were found to be in this order: Euphorbiaceae > Fabaceae > Asteraceae > Fagaceae > Myrtaceae > Rubiaceae > Rosaceae > Caesalpineaceae > Lamiaceae > Lauraceae > Anacardiaceae[68].

INDIAN MEDICINAL PLANTS EFFECTIVE AGAINST COVID-19

Medicinal plants are known to have antiviral properties and several health benefits and their bioactive constituents may provide help in designing novel alternative and supplementary treatment for COVID-19[74]. Due to less cost, easier availability and no side effects, majority of the Indian population rely upon herbal medicines[40]. Several plants of Indian origin have been quoted to possess antiviral activity against SARS-COV-2[75]. Certain medicinal plants have been recommended by India for prevention and prophylaxis of coronavirus, such as *Tinospora cordifolia*, *Zizyphus jujube*, *Cydonia oblonga*, *Cordiamyxa* and *Andrographis paniculata*[76]. The medicinal drugs for coronavirus can be derived from turmeric, ginger, tulsi, fenugreek, cloves, cinnamon and fennel seeds[77]. As per the study conducted by Srivastava *et al.*[78], 18 different species of Indian herbal plants were assessed in the pursuit of potent COVID-19 inhibitors through *in silico,* and the inhibition potentials of the

plant were in order as follows: harsingar > aloevera > giloy > turmeric > neem > ashwagandha > redonion > tulsi > cannabis > black pepper, on the basis of lipophilicity, aqueous solubility and binding affinity. Molecular docking study against Mpro and ACE 2 showed that phytochemicals present in plants, such as *Curcuma longa, Ocimum gratissimum, Syzygium aromaticum, Piper longum, Phaseolus vulgaris, Artemisia absinthium and Inula helenium* have better binding energy with Mpro and ACE-2 as studied by Joshi *et al.*[79].

In another research done by Maurya and Sharma[80], phytochemicals and bioactive compounds present in tulsi, haldi, giloy, ginger, cloves, lemon, ashwagandha and ginger were assessed using molecular docking approach against SARS-CoV-2. The compounds in herbs were docked with viral capsid spike and protease to study their antiviral activities, and the phytochemicals were found potentially efficient in inhibiting different stages of SARS-CoV-2 infection and its target proteins. As studied by Shree *et al.*[81], the compounds obtained from *Withania somnifera*, *Tinospora cordifolia* and *Ocimum sanctum* could bind to SARS-CoV-2 Mpro and was found to decrease the viral transcription and replication serving as a potential inhibitors .

Ocimum sanctum

Family: Labiatae; Lamiaceae

English Name: Holy Basil, Sacred Basil

Ayurvedic Name: Tulasi, Surasaa, Bhuutaghni, Sulabhaa, Manjarikaa, Suravalli, Bahumanjari, Devadundubhi, Apet-raakshasi, Shuu-laghni, Graamya, Sulabhaa

Unani: Tulasi

Siddha: Tulasi, Nalla-Tulasi

Habitat: Grown throughout Indian houses, gardens and temples.

In Ayurveda, Tulsi is known as 'Elixir of Life' due to its curative properties and several heath ailments such as bronchitis, asthma, gastric and hepatic disorders, microbial infections, rheumatism *etc.*[40]. *O. sanctum* is used as a nervine tonic and adaptogen, and is known for its stress releasing properties and improving health conditions during cancer[82,83]. Compounds including phenolics, flavonoids, phenylpropanoids, essential oil, fixed oil, terpenoids, coumarins and fatty acid derievatives are found in tulsi. Extracts of methanol and dichloromethane from *O. americanum, O. basilicum and O. sanctum* exhibit an anti-HSV activity as reported by Caamal-Herrera *et al.*[84], Tang *et al.*[85] and Ghoke *et al.*[86] reported the antiviral activities of *O. sanctum* methanol extract (terpenoids and polyphenols) against DENV1 and H9N2. Tulsi contains Tulsinol (A, B, C, D, E, F, G) and dihydrodieugenol-B which inhibits COVID-19 main protease and papain like protease, and also possess ACE 2 blocking properties with immune-modulatory feature[87,88]. According to the research done by Mohapatra *et al.*[89] the ethanolic extract of aerial parts of Holy Basil contain flavonoids and polyphenolic acids especially luteolin-7-O-glucuronide and chlorogenic acid may bind covalently to the active residue Cys145 of main protease of SARS-CoV-2 and inhibit the viral enzyme irreversibly when screened *in silico*.

Withania somnifera

Family: Solanaceae

English name: Winter Cherry, Indian ginseng, Poison gooseberry

Ayurvedic name: Ashwagandhaa, Ashwakanda, Gandharva-gandhaa, Varadaa, Balyaa, Turaga, Turagagandhaa, Haya-gandhaa, Turangagandhaa, Vaajigandhaa, Gokarnaa, Vrishaa, Varaahakarni, Varadaa, Balyaa, Vaajikari

Unani: Asgandh

Siddha: Amukkuramkizhangu

Habitat: Throughout the drier and semitropic parts of India

Ashwagandha means "the smell and strength of a horse", referring to its aphrodisiac properties. Roots of *W. somnifera* is used as an anti-inflammatory medicine for swellings, tumours and as a sedative; root contains alkaloids such as withanine, psuedowithanine, somnine, somniferinine and withaferin A[90]. Withaferin A obtained from Ashwagandha is used to treat common cold, gynaecological disorders and infertility issues[77]. They are known to enhance nitric oxide synthase activity of macrophages and restore immune homeostasis[91]. They can reduce interleukin-1, interleukin-6 and tumour necrosis factor[92–94]. Antioxidant and immune-modulatory effects of Ashwagandha have been studied over the last two decades, and the studies claim it to be effective in boosting immune response and in inhibiting viral replication[95,96]. Grover *et al.*[97] studied this plant through molecular docking approach, and reported the potential role of withaferin A against HSV by inhibition of DNA Polymerase enzyme. Balkrishna *et al.*[98] reported that withanone (a compound found in *W. somnifera*) docked the binding interface of ACE 2-RBD (Receptor Binding Domain) complex, reduced the electrostatic component of binding free

energies of ACE2-RBD complex and destabilized the salt bridges at the interface centre, significantly decreasing their occupancies. As Ashwagandha prevents cytokine storms as well as viral infections, it can be a potential candidate for treatment of SARS-CoV-2[91]. Withanolides, a group of bioactive compound found in *W. somnifera,* are potent immunity boosters; Withanolide _G, Withanolide_I and Withanolide_ M have the highest binding affinity with PLpro, 3CLpro and spike proteins respectively[99]. It can prove to be effective against SARS-CoV-2 through modulation of host Th-1/Th-2 immunity[87].

Tinospora cordifolia

Family: Menispermaceae

English name: Heart leaved moonseed

Ayurvedic name: Guduuchikaa, Guluuchi, Amrita, Amritaa, Amritalataa, Amritavall, Chinnaruuhaa, Chinnodbhavaa, Madhuparni, Vatsaadani, Tantrikaa, Kundalini, Guduuchisattva (starch)

Unani: Gilo, Gulanchaa. Sat-e-Gilo

Siddha: Seenil, Amrida-valli

Habitat: Tropical India and the Andamans

It is considered as the best rasayana due to its strong flexibility, and the herb is known to play an important role in boosting immune system[77]. *T. cordifolia* methanol extracts possess anti-bacterial properties against *Staphylococcus aureus, Klebsiella pneumoniae, Proteus vulgaris, Salmonella typhi, Shigella flexneri, Salmonella paratyphi, Salmonella typhimurium, Pseudomonas aeruginosa, Enterobacter aerogene, Serratia marcesenses* and *Escherichia coli*[100]. The antiviral properties of *T. cordifolia* against H1N1 and Chikungunya virus have already been documented by researchers[101]. The immune-modulatory property of *Tinospora* is well documented due to presence of compounds magnoflorine, tinocordiside, syringin, 11-hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain and cordifolioside[100,102]. It is known as the nectar of life[103]. According to Sagar and Kumar[101], the binding efficacy of natural components Berberine, Isocolumbin, Magnoflorine and Tinocordiside isolated from *T. cordifolia* were assessed using *in silico* tools against four SARS-CoV-2 targets (Receptor binding domain (6M0J), surface glycoprotein (6VSB), RNA dependent RNA polymerase (6M71) and main protease (6Y84)), and all the four compounds showed high binding efficacy against all the four targets, making giloy a potential herb for the management of COVID-19 infection.

Curcuma longa

Family: Zingiberaceae

English name: Turmeric

Ayurvedic name: Priyaka, Haridruma, Kshanda, Gauri, Haridraa Kaanchani, Krimighna, Varavarnini, Yoshitapriyaa, Kshanda, Hattavilaasini, Naktaahvaa, Sharvari

Unani: Zard Chob

Siddha: Manjal

Habitat: Grown all over India, particularly in West Bengal, Tamil Nadu and Maharashtra

Turmeric is a herbaceous, perennial, rhizomatous plant, and is widely used in Ayurveda, Siddha and traditional Chinese medicines[104]. Curcumin (diferuloylmethane), the natural polyphenolic compound found in *C. longa,* makes up the major curcuminoid (77%), while curcumin II and curcumin III make up 17% and 3% respectively[105]. Curcumin exhibits therapeutic properties, such as antimicrobial, antiviral and anti-inflammatory activities[91]. The antiviral activity of curcumin is well documented, and evidences suggest that it has inhibitory effects against viruses, such as herpes simplex virus, respiratory syncytial virus, vesicular stomatitis virus, flock house virus and parainfluenza virus type 3[106]. Curcumin relieves congestion and pain, and improves breathing process in patients with sinusitis[107]. Turmeric acts as a natural cleanser of the respiratory tract. Curcumin contains anti-thrombotic properties, which aid in cleansing mucous in the lungs, thereby supporting proper oxygen supply to the entire body[108].

Das *et al.*[109] reported that curcumin isolated from turmeric can neutralize the entry of SARS-CoV-2 viral protein. The study used *in silico* approach, which demonstrated the binding of curcumin to RBD site of viral S protein along with the viral attachment sites of ACE 2 receptor. Curcumin can suppress pulmonary edema and fibrosis-associated pathways associated with COVID-19 infection[110]. It has several molecular mechanisms and inhibitory effects on toll like receptor, inflammatory cytokines, chemokines and bradykinin[111]. Diacetylcurcumin isolated from *C. longa* have been found more effective on SARS-CoV-2 (Mpro) compared to Nelfinavir[112]. Immunity and protective defence against COVID-19 infections boosted in many hospitalized patients in India due to the uptake of curcumin with vitamin C and Zinc[113]. Therefore, curcumin could be considered as a preventive herb in the inhibition of transmission of COVID-19.

Zingiber officinalis

Family: Zingiberaceae
English name: Ginger
Ayurvedic name: Aardraka, Aadrikaa, Shrngibera, Shrngavera, Katubhadra
Unani: Zanjabeel-e-Ratab, Al-Zanjabeel
Siddha: Allam, Lokottai, Inji
Habitat: Indigenous to Southeast Asia; cultivated mainly in Kerala, West Bengal, Andhra Pradesh, Uttar Pradesh and Maharashtra

Ginger is used as a common traditional medicinal plant having therapeutic properties, such as antibacterial, antioxidant, antiviral, analgesic and antipyretic properties[114]. The phytocompound 6-gingerol obtained from ginger depicts ginger as a promising candidate for drug discovery against COVID-19, as it proved to have the highest binding affinity with multiple targets of SARS-CoV-2, such as viral protease, RNA binding proteins and viral proteases through DFT (Density Functional Theory) study[115]. Ginger is known to strengthen body's defense mechanism by improving the antioxidant property. 6-Shogaol, an important compound obtained from ginger, helps the patient in relieving respiratory issues[77]. Aqueous extract of fresh ginger showed antiviral activity against human respiratory syncytial virus in human respiratory tract cell lines (Hep-2(human laryngeal carcinoma) and A549 (Adeno carcinomic human alveolar)), reducing the plaque count[14]. According to Chang *et al.*[116], ginger stimulates IFN-β secretion which counteracts viral infection. Reduction in total nasal symptom scores (TNSS) in patients suffering from rhinitis allergy was also reported by taking oral alcoholic ginger extract[117].

Azadirachta indica

Family: Meliaceae
English name: Neem tree, Margosa tree
Ayurvedic name: Arishtaphala, Pichumarda, Pichumandaka, Tiktaka, Sutiktak, Paaribhadra, Nimbaka, Arishta
Unani: Aazaad-Darakht-e-Hindi
Siddha: Vemmu, Veppu, Veppan, Arulundi
Habitat: local to Burma; found all over India

Neem extract compounds have antiviral, anti-inflammatory, anti-hyperglycaemic, anti-carcinogenic, anti-mutagenic, anti-ulcer and anti-oxidant effects[118]. The important phytochemicals present in neem are limonoids and terpene[119]. Antiviral activity of aqueous neem leaf extract is well documented against measles, Chikungunya and vaccinia virus[120]. Earlier studies have revealed that neem and its phytoconstituents play an important role in scavenging of free radical generation and prevents the pathogenesis of diseases[73].

Baildya *et al.*[121] studied the inhibitory potential of neem extracts on PLpro (papain like protease) of SARS-CoV-2 through molecular docking and molecular dynamics simulation, and it was found that desacetylgedunin (DCG) found in neem showed the highest binding affinity towards PLpro. The bioactive compound found in neem, such as Azadiradione, Epiazadiradione, Nimbione, and Vepnin were assessed by Sharon[122] through Autodock 4.2, and Pymol and was found to be potential inhibitor of COVID-19 Mpro (6Y2E, 6LU7, and 2GTB).

Nigella sativa

Family: Ranunculaceae
English name: Black Cumin, Small Fennel
Ayurvedic name: Kaalaajaaji, Kalikaa, Prthvikaa, Sthulajiraka, Sushavi, Upkunchikaa
Unani: Kalonji, Kamaazaruus
Siddha: Karumseeragm
Habitat: Cultivated in Assam, Punjab, Bengal and Bihar

Prophet Muhammad quoted, 'In the black cumin, there is a cure for every disease except death,' and the Holy Bible denotes black cumin as a 'curative black seed'[123]. The phytoconstituents found in black cumin are terpenes such as dithymoquinone (DTQ), carvone, thymoquinone (TQ), limonine, trans-anethol, and p-cymene, indazole alkaloids like nigellidine and nigellicine, isoquinoline alkaloids including nigellicimine, nigellicimine-N-oxide and α-hederin[124]. It is known for its curative properties, including jaundice, diabetes, cough, bronchitis, fever, gastrointestinal, conjunctivitis, asthma and rheumatism[125].

Studies have shown that TQ has an inhibitory property on SARS-CoV-2 protease, and has shown good antagonism to ACE 2 receptors[126]. Koshak and Koshak[127] reported that at least eight *in silico* studies have demonstrated that compounds of *N. sativa* have moderate to high affinity with SARS-CoV-2 enzymes and proteins.

Piper nigrum

Family: Piperaceae
English name: Black Pepper
Ayurvedic name: Maricha, Vellaja, Uushna, Suvrrita
Unani: Filfil Siyaah, Safed
Siddha: Milagu, Milaguver
Habitat: Locally found in the Indo-Malaysian region, cultivated in Western Ghats, Karnataka, Maharashtra, Assam and Kerala

It is known as the 'King of Spices'. Piperine found in black pepper is widely known for its antitumour, anti-asthmatic, antihypertension and anticarcinogenic properties[128]. The alkaloid constituents present in black pepper gives it the characteristic strong smell[129]. According to Choudhary *et al.*[130], peperine isolated from black pepper can be effective against proliferation of viral particles, as it can block RNA packaging inside the capsid protein. Researchers from Department of Physics at IIT, Dhanbad conducted a computational study and found that Piperine found in black pepper can inhibit SARS-CoV-2 virus. The phenolic compunds Kadsurenin L and methysticin found in *Piper nigrum* was found inhibiting COVID-19 main protease as studied by Davella *et al.*[131].

Allium sativum

Family: Liliaceae, Alliaceae

English name: Garlic

Ayurvedic name: Lashuna, Yavaneshta, Ugragandha, Rasona, Mahaushadh, Arishta

Unani: Seer, Lahsun

Siddha: Ullippoondu, Vellaippondu

Habitat: Cultivated all over India

The beneficial properties of garlic are known to humans from ages. The chemical constituents of garlic, which are responsible for its peculiar smell and taste, are mainly sulphur-based, such as S-allyl cysteine, alliin, vinyldithiin, ajoene, diallylpolysulfides, and some non-sulphur, such as saponins, maillard reaction products and flavonoids[40]. Garlic acts as an immunomodulatory by stimulating WBC, such as NK cells and macrophages[132]. Garlic induces cytokine secretion and increases $CD4^+$ and $CD8^+$ cells[133]. Shojai *et al.*[134]reported that concentration of 0.1 ml of garlic clove extract showed *in vivo* inhibitory effects against SARS-CoV-1 multiplication, possibly due to the blocking capacity of extract towards its structural proteins. Alliin found in *A. sativum* showed the highest binding ability, with the target protein of SARS-CoV- 2 (6LU7) when studied *in silico* by Pandey *et al.*[135]. Bioactives found in garlic and the serine-type protease found in SARS-CoV-2 form hydrogen bonds in the active site regions suppressing the outbreak of COVID-19, and it can act as a preventive measure against COVID-19 infection[136].

Glycyrrhiza glabra

Family: Papilionaceae; Fabaceae

English name: Licorice, Liquorice

Ayurvedic name: Yashtimadhu, Madhuyashtyaahvaa, Madhuli, Madhuyashtikaa, Atirasaa, Madhurasaa, Madhuka, Yastikaahva, Yashtyaahva, Yashti, Yashtika, Yashtimadhuka

Unani: Asl-us-soos, Mulethi

Siddha: Athimathuram

Habitat: Native to the Mediterranean regions. Now cultivated in Punjab, Jammu and Kashmir, and South India.

Glycyrrhizic acid, found in the roots of *Glycyrrhiza-glabra*, is the active antiviral compound which possesses antiviral activity against HIV, herpes simplex viruses and human and animal coronavirus[137]. Zhong *et al.*[138] documented the viral replication inhibitory property of licorice for various viruses, such as influenza, HIV, H1N1, hepatitis B and C.

Zhang *et al.*[139] assessed licorice, demonstrating that it contains three orally antiviral natural components which inhibit Mpro, S-proteins, 3C like protease and papain like protease of SARS-CoV-2. Licorice extract inhibits the main protease of SARS-CoV-2, and glycyrrhizin shows a high binding affinity and better ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties compared to other constituents of licorice[40]. Luo *et al.*[140] discussed the pharmacological action of glycyrrhizin, as it binds to ACE-2, inhibits accumulation of intracellular reactive oxygen species (ROS), inhibits hyperproduction of airway exudates and induction of endogenous interferons[141]. van de Sand *et al.*[142] demonstrated that glycyrrhizin inhibits 3CL protease of SARS-CoV-2. Different concentrations of glycyrrhizin 30 μM and 2000 μM and the complete protease inhibitor GC376 were dissolved with 90 ng Mpro in 30 μL 0.5 M DTT buffer at room temperature for 30 mins, after which the 3CL Protease substrate was added, and the activity of protease was measured after overnight incubation at the wavelength 360 nm/460nm (exc/em). It was found that glycyrrhizin inhibited Mpro activity completely at a concentration of 2000 μM, and at 30 μM concentration, it reduced its activity to 70.3%.

CONCLUSION

India has always been known for its rich biodiversity and extensive varieties of plants, which are found from Himalayas to the marine and desert to the rain forests. The present study revealed the status of medicinal plants and herbs of India and their various therapeutic benefits. Use of herbal medicines is not only safe and cost-effective, but it is also free from side effects. AYUSH system of medication emphasizes on simple natural remedies for the improvement and development of strong immune system.

Efforts should be made to explore and promote the knowledge of healing through such medicinal plants. The proper use of medicinal plants against COVID-19 could safeguard lives of several people reducing the risks of infection, thereby minimizing the rate of mortality.

ABBREVIATIONS

3CLpro: 3- Chymotrypsin Like Protease
ACE 2: Angiotensin converting enzyme 2
ADMET: Absorption, Distribution, Metabolism, Excretion, and Toxicity
ARDS: Acute Respiratory Distress or Syndrome
AYUSH: Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy
DCG: Desacetylgedunin
DFT: Density Functional Theory
DTQ: Dithymoquinone
NMPB: National Medicinal Plant Board
PLpro: Papain Like Protease
RBD: Receptor Binding Domain
ROS: Reactive Oxygen Species
TIM: Traditional Indian Medicines
TMPRSS2: Transmembrane Protease Serine 2
TNSS: Total Nasal Symptom Scores

ACKNOWLEDGMENTS

None.

AUTHOR'S CONTRIBUTIONS

All authors equally contributed in this work. All authors read and approved the final manuscript.

FUNDING

None.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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