



Ayurvedic approach of some indigenous flora in curbing SARS–CoV–2 infection: II. Traditional medicinal plants for strengthening of immune system and treatment of COVID–19

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Abstract

The coronavirus disease 2019 (COVID–19) caused by the virus Severe Acute Respiratory Syndrome Corona Virus 2 (SARS–CoV–2) has resulted in massive loss of valuable human lives, extensive destruction of livelihoods and financial crisis of unprecedented levels across the globe and declared a global pandemic in early 2020. The traditional medicine and ayurvedic therapy used in India since ancient times for its multifactorial pharmacological, medicinal, antimicrobial, immunomodulatory and adaptogenic effects, and even during current pandemic as well after recommendation of Ministry of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy), Government of India. The commencement of 1206 Ayur Raksha Clinics and associated Task Forces in Indian states during 1st quarter of 2020 improves the reach and penetration of Ayurvedic preventive, therapeutic and convalescent care strategies for the COVID–19 pandemic. Keeping in view the immunomodulatory, immune system boosting and anti SARS–CoV–2 (anticovid) potential only best eight indigenous flora [*Azadirachta indica* A. Juss (Neem), *Ocimum sanctum* L. (Tulsi), *Tinospora cordifolia* Thunb. (Giloy), *Withania somnifera* L. (Ashwagandha), *Piper betle* L. (Betel vine), *Cinchona officinalis* L. (Kunain), *Glycyrrhiza glabra* L. (Licorice) and *Andrographis paniculata* Burm. (Kalmegh)] Amongst several known and recommended medicinal plants were considered in the current manuscript. The ethnomedicinal, pharmacological and clinical significance of these medicinal floras well explored to prove the profound efficacy against SARS–CoV–2 and immunity boosting potential for strengthening of immune system and treatment of COVID–19. Thus, the espousal of the efficient medical flora as profound immunity booster in different formulation like oral pills, powder, decoction or even crude form in daily life is an utmost requirement for the improvement of immune system, treatment, prevention and control of COVID–19 infection.

Keywords: indigenous flora, traditional medicine, Anticovid, COVID–19, immunity booster, SARS–CoV–2

Introduction

According to the World Health Organization (WHO), viral diseases continue to emerge and represent serious issue to public health (Azhar *et al.*, 2019) [31]. The ongoing coronavirus disease–2019 (COVID–19) pandemic situation caused by new strain of coronavirus (CoV) known as severe acute respiratory syndrome coronavirus 2 (SARS–CoV–2) got worldwide attention and became the utmost priority of the global health community due to the higher rate of human–to–human transmission (Flaxman *et al.*, 2020; Sood *et al.*, 2020; Wang *et al.*, 2020) [14,32,39]. Earlier to current pandemic, there were six CoVs (HCoV–229E, HCoV–OC43, HCoV–NL63, HKU1, SARS–CoV and MERS–CoV) to be known to infect humans and cause mild upper respiratory disease, and in rare cases, some of them can cause severe infection in infants, young children, and elders (Chen *et al.*, 2020; Singhal, 2020; Upadhyay *et al.*, 2020a) [8, 31, 37]. SARS–CoV–2 spreads from person to person through close communities when COVID–19 patients breathe out, cough and sneeze tiny droplets that contain the virus. These droplets can enter the mouth or nose of someone without the virus, causing an infection to occur (Dan *et al.*, 2020; Junejo *et al.*, 2020) [11, 20]. The most common symptoms of COVID–19 include: fever, breathlessness, cough, sore throat, headache, muscle pain, chills and loss of taste or smell (Carlos *et al.*, 2020; Upadhyay *et al.*, 2020b; Wang *et al.*, 2020) [7, 38, 39]. Some of the commercially available antiviral medicine such as remdesivir, ribavirin, ritonavir, lopinavir either alone or with the combination of antipyretics and analgesics like chloroquine, hydroxychloroquine, and interferon–alpha supported with mechanical ventilation or extracorporeal membrane oxygenation found to have effective potential in treating SARS–CoV–2 infection and management of COVID–19 even during the absence of the vaccines and also in the present time when more than a dozen vaccines have already been approved around the globe (Dan *et al.*, 2020; De Wit *et al.*, 2020; Khan *et al.*, 2021; Upadhyay *et al.*, 2021; Yadav *et al.*, 2021) [11, 12, 22, 35, 40]. But these medicines and vaccines are not the permanent solution for

COVID-19 management; therefore people must have the ability to give a fight against this deadly virus by boosting their immune system using medicinal /herbal plants in daily life which may prevent the risk of this COVID-19 infection.

Traditional or conventional medicine is the sum total of the knowledge, skill, and practices based on the theories, beliefs, and experiences of indigenous to different cultures, used in the maintenance of health and prevention, diagnosis, improvement or treatment of physical and mental illness. Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products that contain as active ingredients parts of plants, or other plant materials, or combinations (Upadhyay *et al.*, 2022) [36]. The traditional immunity boosters are the prime concern in current scenario along with the internal purification process through yoga and meditation. Thus, the Traditional and Complementary Medicine (T&CM) is an important and often underestimated health resource with many applications, especially in the prevention and management of lifestyle-related chronic diseases, and in meeting the health needs of rising populations. Keeping in view the aforesaid interesting and valid points, the Govt. of India also directed to AYUSH ministry for the application of traditional herbal medicines and herbal produce along with various supplementary formulation as immunity booster against coronavirus in COVID-19 patients (Ayush, 2020) [2]. Despite the need for clinical studies to investigate the exact effects, the practical results are promising and therefore, the World Health Organization (WHO) welcomes innovations around the world including repurposing drugs, traditional medicines and developing new therapies in the search for potential treatments for COVID-19. Therefore, the present review article have discussed briefly about medicinal plants and herbs that may help in combating the dispersal, infectivity and morbidity of COVID-19 along with current challenges and its future perspectives.

Medicinal Plants Strengthening the Immune System in COVID-19 Patients

There are immense varieties of herbal medicines derived from several medicinal plants effective in management of life threatening diseases caused by the viruses. The most effective medicinal plants helpful in immunity boosting, so that the infection and morbidity due to SARS-CoV-2 in COVID-19 patients can be effectively managed are including *Azadirachta indica* A. Juss (Neem), *Ocimum sanctum* L. (Tulsi), *Tinospora cordifolia* Thunb. (Giloy), *Withania somnifera* L. (Ashwagandha), *Piper betle* L. (Betel vine), *Cinchona officinalis* L. (Kunain), *Glycyrrhiza glabra* L. (Liquorice) and *Andrographis paniculata* Burm. (Kalmegh) (Table 1).

a. *Azadirachta indica* A. Juss (Neem)

The plant is commonly found in tropical and semi-tropical regions. Almost each and every part of the plant such as roots, bark, leaves, fruits, seeds, and oil are used for various medicinal purposes like in curing bacterial, viral or any other disease. The neem has antibacterial, antimalarial, antifungal, anti-inflammatory, hepatoprotective, wound healing, antidiabetic, neuroprotective and anticancerous properties (Kumar *et al.*, 2018) [23]. The key chemical constituents of neem include limonoids and terpene. Nimbidin, gallic acid, catechin and gedunin, cyclic trisulfide and margolone, margolonone, isomargolonone are responsible for anti-inflammatory, antifungal and antibacterial properties respectively (Bhowmik *et al.*, 2010)^[6]. However, azadirachtin obtained from neem oil has strong insecticidal and anti malarial activities. The extract of dry neem leaf showed profound antifungal potential and found to be very effective against dermal issues like ringworm, scabies and eczema (Kumar *et al.*, 2018) [23]. The aqueous leaf extract is found to be effective against measles virus, chicken pox, chikungunya and vaccinia virus and thus have a strong antiviral property (Bhowmik *et al.*, 2010; Kumar *et al.*, 2018)^[6,23]. However, taking neem leaf in excess can cause an adverse impact on sexual activity by reducing the sperm count in body (Srivastava *et al.*, 2020) [33]. On the basis of aforementioned therapeutic potential, the recommended doses of neem and its derivatives may be an important factor in the prevention of droplet borne current viral pandemic COVID-19 and SARS-CoV-2 infection.

b. *Ocimum sanctum* L. (Tulsi)

It is an indigenous plant cultivated for the religious and traditional medicine purposes. Most of the parts of the plant including leaves, stem, flower, root, seeds, even entire plant have been used in medicinal purposes since ancient times. Tulsi is denoted as “Elixir of Life” in Ayurveda due to its healing capability and promising potential in curing variety of diseases like, bronchitis, rheumatism, asthma, skin disorders, parasitic and microbial infections, gastric and hepatic disorders etc. It has antibacterial, antiviral, antidiabetic, anticarcinogenic, anti-inflammatory, cardioprotective properties and also acts as an immunomodulatory agents or immune system booster (Jamshidi *et al.*, 2017) [17]. This is already being in used for treatment of pneumonia, pain, diarrhoea, cough, fever and other disease caused by DNA viruses [herpes viruses (HSV), hepatitis virus, adenoviruses (ADV)] and RNA viruses (enterovirus 71, coxsackie virus CVB1) which shares the most common symptoms of COVID-19 (Chiang *et al.*, 2005) [9]. Apigenin and ursolic acid are the main active antiviral components present in the extract of tulsi. A double blinded randomized study for the immunomodulatory effect revealed that there was a significant increase in the percentage of immune cells like helper T- cells (HT cells) and Natural Killer (NK) cells (Mondal *et al.*, 2011) [26]. The binding affinity of 7 photophilic compounds from Tulsi, i.e., tulsinol A, B, C, D, E, F, G, and dihydrodieuginol B, with SARS CoV-2 receptors was well documented which inhibited the replication of SARS-CoV-2 with ACE2 (Angiotensin-converting enzyme 2) blocking properties (Shree *et al.*, 2020) [30]. Thus based on the earlier published reports, the role of tulsi extract in

prevention and control of COVID-19 has been confirmed (Shree *et al.*, 2020) [30]. Therefore, authors wish to recommend the Tulsi as a profound traditional medicine in the treatment of COVID-19.

c. *Tinospora cordifolia* Thunb. (Giloy)

It is one of the most flexible restoring bushes, found in the tropical regions of the Indian subcontinent and almost all the parts of plant i.e., roots, leaves and stem are used for medicinal purposes in Ayurveda (Sharma *et al.*, 2012; Sharma *et al.*, 2019) [28, 29]. Giloy is considered to be one of the best Rasayana comprising various biologically important phytochemicals like alkaloids, lactones, steroids, sesquiterpenoid, diterpenoid, aliphatic compounds, phenols, polysaccharides and flavonoids (Sharma *et al.*, 2012; Sharma *et al.*, 2019) [28, 29]. The giloy known for its antidiabetic, anti-inflammatory, antioxidant, antispasmodic, anti-arthritic, anti-allergic, antimicrobial, anti-osteoporotic, antistress, antitoxic, antiHIV, anticancer, wound healing and immunomodulatory properties (Sharma *et al.*, 2012; Sharma *et al.*, 2019) [28, 29]. Giloy contains alkaloid components like tinosporin, tetrahydropalmatine, choline, palmatine and magnoflorine helpful in protection from aflatoxin-induced nephrotoxicity. Oral intake of giloy decoction play important role in boosting the immune system and its herbal formulation with tulsi, ginger and kaalimirsch has been found to be very effective against cough, fever and COVID-19 infection (AYUSH, 2020; Shree *et al.*, 2020) [2, 30]. Therefore, authors conclude that, giloy plays a very interesting and effective activity in prevention and control against COVID-19 infection.

d. *Withania somnifera* L. (Ashwagandha)

Ashwagandha or Indian ginseng is native to India and its roots and berries principally employed for medicinal plant purposes in the Indian Ayurvedic system (Jinu, 2019) [19]. Ashwagandha is best called for its anti-inflammatory, antitumor, antiviral, antistress, anti-oxidant, mind boosting, immune enhancing and rejuvenating properties (Jinu, 2019) [19]. The most important chemical constituents in Ashwagandha is withanolides that further contain triterpenelactones-withanolides, withaferin A & D, alkaloids, steroidal lactones, tropine and cuscohygrine (Jinu, 2019; Shree *et al.*, 2020) [19, 30]. Based on the literature review, withanone promotes to bind ACE2-RBD complex and blocks or weakens the COVID-19 entry and virulence in the body. The molecular docking studies have stated that as per YASARA scoring, out of 28 compounds of Indian ginseng, only the major components withanoside V and somniferine have shown significant binding affinity to native corona virus (Shree *et al.*, 2020; Tripathi *et al.*, 2021) [30, 34]. Thus the roots extract and event root husk because of profound antiviral property can blocks the host protein interactions and potentially to give a fight against the novel Corona virus by boosting the immunity as well.

e. *Piper betle* L. (Betel vine)

Betel or Paan (Tambool) is Southern or Southeast Asian in origin and leaves known for its medical significance and may be consumed directly for chewing purposes as well. Since the ancient era, tambool is an essential part of punch amrita present in earth and used from birth to death ceremonies in hindu rituals. It has anti-apoptotic, anti-oxidant, anti-inflammatory, anticancer and antimicrobial properties. The leaves extract of betel consist of hydroxyl chavicol, ally pyrocatechal, eugenol, chlorogenic acid, chavibetol, edible natural phenols (oil), various antioxidants, vitamins like A, B, C and variety of essential oils which help in boosting immune system and thus help the body in fighting against bacterial and viral infection (Badrul *et al.*, 2013; Akter *et al.*, 2014; Pawar *et al.*, 2017) [4, 1, 27]. Due to presence of essential oil in leaves, it helps in respiratory catarrhs and gives great relief from cough and heals breathing issues. The betel leaf ingredients in herbal and natural combination with commercially available influenza specific antiviral has been tested and predicted to have a synergistic effect. This formulation will support in reducing the effective dose of antiviral drug, drug cost pressure on patients and development of resistant viral strains. As betel vine may play a very important role in boosting immune system of body thus, may prevent the risk of viral infections (Badrul *et al.*, 2013; Akter *et al.*, 2014; Pawar *et al.*, 2017) [4, 1, 27]. Therefore, herbomineral combination of betel leaf or even paan itself may be effective in combating the current pandemic situation and therapeutic treatment for COVID-19 patients by synergistic and immune system boosting approaches.

Table 1: Ethnomedicinal significance and immune system boosting characteristics in phytochemicals of medicinal plants.

Common Name	Botanical Name	Phytochemicals	Ethnomedicinal Properties
Nimtree or Neem	<i>Azadirachta indica</i> A. Juss (Sapindales: Meliaceae)	Limonoids; terpene; nimbidin; gallic acid; catechin; gedunin; cyclic trisulfide; margolone; margolonone; azadirachtin; isomargolonone	Antibacterial, antimalarial, antifungal, anti-inflammatory, hepatoprotective, wound healing, antidiabetic, neuroprotective, antiviral and anticancerous.
Holy basil or Tulsi	<i>Ocimum sanctum</i> L. (Lamiales: Lamiaceae)	Apigenin; ursolic acid	Antibacterial, antiviral, antidiabetic, anti-carcinogenic, anticovid, anti-inflammatory, cardioprotective, hepatoprotective, immune booster, immunomodulatory, treatment of

			bronchitis, asthma, pneumonia, cough, fever, pain, diarrhoea, rheumatism, skin disorders, parasitic and microbial infections, gastric and hepatic disorders several viral diseases.
Giloy or Guduchi	<i>Tinospora cordifolia</i> Thunb. (Ranunculales: Menispermaceae)	Alkaloids; lactones; steroids; sesquiterpenoid; diterpenoid; aliphatic compounds; phenols; polysaccharides; flavonoids; tinosporin; choline; palmatine; tetrahydropalmatine; magnoflorine	Antidiabetic, anti-inflammatory, antioxidant, antispasmodic, anti-arthritic, anti-allergic, antimicrobial, anti-osteoporotic, antistress, antitoxic, antiHIV, anticancer, wound healing, immunomodulatory, nephroprotective, antipyretic, immune system booster, antiviral and anticovid.
Indian ginseng or Ashwagandha	<i>Withania somnifera</i> L. (Solanales: Solanaceae)	Triterpenelactones–withanolides; Withanolides; withaferin A; withaferin D; withanoside V; somniferine; alkaloids; steroidal lactones; tropine; cuscohygrine	Anti-inflammatory, antitumor, antistress, antioxidant, mind boosting, immune enhancing, antiviral, anticovid and rejuvenating properties
Betel vine or Paan	<i>Piper betle</i> L. (Piperales: Piperaceae)	Hydroxychavicol; hydroxyl chavicol; ally pyrocatechal; eugenol; chlorogenic acid; chavibetol; edible natural phenols (oil); vitamin A; vit. B; vit. C; essential oils	Anti-apoptotic, anti-oxidant, anti-inflammatory, anticancer, immunity booster, laxative, appetizer, and antimicrobial
Kunain or Cinchona plant	<i>Cinchona officinalis</i> L. (Gentianales: Rubiaceae)	Quinine; chloroquine; hydroxychloroquine	Antiparasitic, anti-inflammatory, antimalarial, antiarrhythmic, antispasmodic, antiprotozoan, antiviral, antipneumonia, antiHIV, immunity booster and anticovid.
Liquorice or Licorice	<i>Glycyrrhiza glabra</i> L. (Fabales: Fabaceae)	Glycyrrhizin; glycyrrhizic acid; glycyrrhizinic acid; pyrazofurin; ribavirin, 6-azauridine; mycophenolic acid	Antifungal, antibacterial, anti-inflammatory, antioxidant, antiulcer, antidiabetic, antidiuretic, effective skin whitening and anticovid properties.
Kalmegh or Chiretta	<i>Andrographis paniculata</i> Burm. (Lamiales: Acanthaceae)	Flavonoids; andrographolide; diterpenes; noriridoides; xanthones; andrographolide	Antimicrobial, antiprotozoan, anti-inflammatory, antidiabetic, antioxidant, an immune stimulant, hepato-renal protective and anticovid properties.

f. *Cinchona officinalis* L. (Kunain)

The kunain plant is native to montane forests in Colombia, Ecuador, Peru and Bolivia. The bark of kunain is principally used for medicinal purposes due to presence of a rich alkaloid named quinine. It has antiparasitic, antimalarial, antiarrhythmic, antispasmodic, anti-inflammatory and antiprotozoan properties. Chloroquine is the synthetic form of quinine and prescribed in the treatment of malaria since ancient times. Chloroquine's antiviral properties has been investigated by scientist against HIV and then against SARS-CoV-1 which structurally quite more similar to novel SARS-CoV-2 (Barnard *et al.*, 2006)^[5]. Chloroquine is one of the important drugs in the list of essential medicines created by WHO from kunain has showed the effectiveness of against SARS-CoV in mice infection model and also helpful in degradation of lethal viral infection caused by human corona virus OC43 which is closely related to SARS (Barnard *et al.*, 2006; Keyaerts *et al.*, 2009)^[5,21]. The targeted role of chloroquine's against SARS-CoV-2 has been and showed a decline in disease course, improved lung imaging findings, pneumonia worsening and increased virus negative seroconversion with no side effects as compared to control group (Ayush, 2020; Gao *et al.*, 2020)^[2,15]. The chemoprophylaxis with hydroxychloroquine (400mg twice on day 1, then 400mg once a week thereafter) for asymptomatic health-care workers treating patients with suspected or confirmed COVID-19, and for asymptomatic household contacts of confirmed cases is highly recommended by the Indian Council of Medical Research, under the Ministry of Health and Family Welfare as well (Ayush, 2020; MOHFW, 2020)^[2,25]. Therefore, authors wish to state on the basis of reviewed literature, kunain and its derivatives like quinine, chloroquine and hydroxychloroquine may be highly effective against COVID-19 infection by increasing the success rate and shortening morbidity and mortality rate by strengthening immune system fighting against infection.

g. *Glycyrrhiza glabra* L. (Liquorice)

Liquorice plant is native to Western Asia, Southern Europe and its roots and rhizomes are best known for the medicinal significance since ancient times especially in Europe and Western Countries. Liquorice acquire excellent antifungal, antibacterial, anti-inflammatory, antioxidant, antiulcer, antidiabetic, antidiuretic and effective skin whitening properties. The principal phytochemicals extracted from the liquorice roots roots and rhizomes are glycyrrhizin, glycyrrhizic acid or glycyrrhizinic acid. It is also used to treat various diseases like asthma, cough, cold and chronic obstructive pulmonary disease (Cinatl *et al.*, 2003; Hoeyer *et al.*, 2005)^[10, 16].

The chief compound glycyrrhizin (a triterpene saponine) was found beneficial against COVID-19 infection by strong affinity to angiotensin converting enzyme 2 which down regulates pro-inflammatory cytokines and also blocks the inhibition of accumulation of intracellular ROS, thrombin, hyperproduction of airways exudates and induces endogenous interferon (Cinatl *et al.*, 2003; Hoeyer *et al.*, 2005; Luo *et al.*, 2020)^[10,16,24]. The antiviral capabilities of glycyrrhizin and its active compounds like pyrazofurin, ribavirin, 6-azauridine and mycophenolic acid has been well documented through clinical trials against two corona virus clinical isolates by inhibiting the replication of SARS-CoV-2 virus (Luo *et al.*, 2020)^[24]. Thus, liquorice may be beneficial in the prevention and cure against the corona virus infection.

h. *Andrographis paniculata* Burm. (Kalmegh)

Kalmegh is known as the “King of bitters”, and native to India and Sri Lanka. The stem and leaves extract of Kalmegh constitute many important phytochemicals such as flavonoids, andrographolide, diterpenes, noriridoides and xanthenes. The plant is well known for its antimicrobial, antiprotozoan, anti-inflammatory, antidiabetic, antioxidant, an immune stimulant and hepato-renal protective properties (Jayakumar *et al.*, 2013)^[18]. Therefore, it has been employed in the treatment of life threatening diseases like cancer, blood pressure, ulcer, leprosy, bronchitis, influenza, diabetes and malaria since traditional times (Jayakumar *et al.*, 2013)^[18]. The literature reports have revealed its inhibitory role against SARS-CoV-2 proteases using an silico methodology and molecular docking focusing on an important compound andrographolide which could be helpful in the possible treatment of COVID-19 (Enmozhi *et al.*, 2020; Yadav *et al.*, 2021)^[13,40]. Based on its pharmacodynamics properties, high solubility and target accuracy, this plant and its derivatives may proposed as an efficient immunity booster and augmented fighting against SARS-CoV-2 infection.

Conclusions

The COVID-19 pandemic is an unprecedented health challenge affecting human existence across the globe. Despite the scientific and medical community's unparalleled efforts to sequence, diagnose, treat, and prevent COVID-19, there is ample evidence for the development of sequelae to the primary disease known as Post-Covid syndrome and Long Covid-19. It has been observed that recovering SARS-CoV-2 patients suffer from persistent and often, debilitating symptoms extending several months past their initial diagnosis. COVID-19 has brought a major change in the delivery of healthcare, that is, self-care and health: by all, for all. There are studies, which establish the fact that many people in some Asian countries, particularly in India, have adopted complementary, alternative, and traditional health-care practices. Considering the persistence of disabling symptoms over a long period of time, even after recovering from the Covid-19 infection and its enduring risk of a possible surge, the need for boosting immune status cannot be undermined. With the current scientific understanding a healthy immune system is pivotal for preventing progression of the disease and for speedy recovery. The Ministry of AYUSH recommended the ‘Ayush Kada or Kwatha (Tulsi + Dalchini + Ginger, + Black pepper + Draksha), Kabasura Kudineer (Kabasura), Golden Milk (Turmeric), Guduchi (Giloy), Ashwagandha (Indian ginseng) and Chyavanprash as profound immunity booster for the speedy recovery and reduced infection in healthy people. Therefore, the present review was planned to summarise the information based on the earlier published literature of medicinal plants playing key role in prevention and control of many life threaten diseases and this deadly COVID-19 as well. The ayurvedic and tradition medicine approaches in the present time will help in keeping the country and world in a fit and healthy environment.

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Conflicts of Interest

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