



HERBAL IMMUNOMODULATORS IN THE MANAGEMENT OF COVID-19 AND IT'S POST-INFECTION COMPLICATIONS

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ABSTRACT

Over 71 million cases and 1.6 million deaths have been attributed to the global transmission of COVID-19, which is caused by SARS-CoV-2, as stated by the WHO. Serious post-COVID ramifications have affected several organ systems. This research analyses how natural products from Ayurveda and Traditional Chinese Medicine (TCM) and herbal immunomodulators can help deal with these problems, which include mental health issues, renal failure, heart failure, liver damage, lung damage, and parkinsonism. Important plants with antiviral and immunomodulatory qualities include *Bacopa monnieri*, *Tinospora cordifolia*, *Ocimum sanctum*, and *Curcuma longa*. They execute this by blocking viral proteases, lowering pro-inflammatory cytokines, and enhancing immunological responses. Bioactive substances such as apigenin, quercetin, piperine, and hesperidin exhibit potential in alleviating cytokine storms and organ damage.

Conventional methods, such as AYUSH-recommended herbal formulations and dietary treatments, help to support immune function and improve symptoms. Plant-derived immunomodulators present a worthwhile, low-toxicity alternative for managing COVID-19, warranting additional clinical investigation to confirm their efficacy and safety despite the drawbacks of synthetic medications due to side effects.

**Keywords: Ayurveda, Traditional Chinese Medicine (TCM), herbal immunomodulators,
COVID-19**

OVERVIEW

The coronavirus disease 2019 (COVID-19) has spread wildly over the world since it first appeared in Wuhan, China. The World Health Organization (WHO) first declared COVID-19 a public health emergency on January 30, 2020, and on March 11, 2020, it was declared a global pandemic. To date, the WHO has reported over 71 million confirmed cases and over 1.6 million fatalities. The seventh known member of the Coronaviridae family, the novel coronavirus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is responsible for COVID-19. Coronavirus is transmitted from person to person by close contact with infected individuals via respiratory droplets from sneezing or coughing, physical contact, and aerosol transmission. COVID-19 infection causes a variety of vague symptoms, including fever, cough, headache, myalgia or tiredness, less common gastrointestinal issues, and, in severe cases, progressive respiratory failure [1]. A key element of preventative medicine during this COVID-19 pandemic has been immunomodulators. Products or substances that strengthen immune system components are known as herbal immunomodulators. Currently, scientific research worldwide is focusing on how different therapeutic plant compounds affect the immune system [2].

Post-COVID Complications

The symptoms and complications following COVID-19 infection have gained serious attention, which includes respiratory, musculoskeletal, cardiovascular, and neuropsychiatric issues. The intricacy of the recovery process is shown by research showing that a significant percentage of post-COVID patients have persistent symptoms such as exhaustion, dyspnea, joint discomfort, and anxiety. The need for effective medicines, including herbal immunomodulators, that may help alleviate these sequelae is urgent, and understanding these problems is crucial for directing therapeutic approaches.

Current therapeutics for COVID-19 infections

There are currently no precise medications that can treat COVID-19 patients that are exact to SARS-CoV-2. Nevertheless, it has been established that a number of medications linked to immune modulators, antiparasitic, antimalarial, antiviral, antibacterial, corticosteroids, and anticoagulants have been used as alternates to consider SARS-CoV-2 virus infections [3, 4]. For example, in emerging nations, COVID-19 infections are healed with ivermectin and doxycycline [3]. This would restrict the explanation of the clinical facts that may be attributed to this medication [5]. Worldwide, COVID-19-infected patients have been medicated with

hydroxychloroquine and azithromycin, with various outcomes [4]. Remdesivir and favipiravir sped up the Stimulation of patients in the clinical examination, but they also affected cardiovascular adverse effects such bradycardia, atrial fibrillation, hypotension, and cardiac arrest were recorded for remdesivir, but favipiravir was associated with a longer QT interval [6]. As a result, using these antiviral medications may be stimulating in cardiovascular practice [6]. COVID-19 patients have also been medicated with immunomodulators including convalescent plasma, baricitinib, and tofacitinib [7].

Natural products' function in treating post-COVID problems

- **Heart failure:** Following a COVID infection, some patients with heart problems even exhibited signs of mild to severe cardiac damage due to a hyperactive immune response. A study from the University of Frankfurt in Germany found that more than 78% of patients underwent cardiac issues and 60% of patients with COVID-19 had cardiac inflammation [8]. Rasayana, an Ayurvedic medication, has anti-inflammatory, anti-stress, and antioxidant properties that help patients' cardiac health [9]. In COVID-19 patients, curcumin from *C. longa* had anti-inflammatory properties and

inhibited the release of pro-inflammatory cytokines, IL-1, IL-6, and TNF- α [10].

- **Lung injury:** Recent cohort research found that 85% of COVID-19 intensive care unit patients have ARDS, as defined by the Berlin Criteria. Lung compliance and oxygenation were markedly enhanced by two well-established supportive therapies for ARDS: prone breathing and low tidal volumes [11]. In light of this, it is possible that the COVID-19-associated cytokine release syndrome is the source of two different inflammatory pathways, one of which would enable thromboembolic events and the other would encourage parenchymal lung damage, resulting in a "dual-hit" lung injury [12]. Because of their anti-inflammatory and antioxidant properties, a number of phytomolecules produced from plants have been shown to be advantageous in treating acute lung infections by modulating the NF- κ B, MAPK, and Nrf2 signalling pathways [13].
- **Kidney failure:** A recent research study involving 701 patients from a hospital in Wuhan found that 5.1% of patients admitted for COVID-19 experienced acute renal damage [14]. The virus spread through the

bloodstream to the kidney during the infection, where it harmed renal resident cells, causing proteinuria, haematuria, and elevated levels of blood urea nitrogen, serum creatinine, uric acid, and D-dimer [15]. Serum BUN and creatinine levels substantially dropped in thirty-eight individuals with mild chronic renal failure who received 1 g of *Rheum palmatum* L. (Chinese rhubarb) root extract daily [16]. According to a study, *Urtica dioica* L. seed may be a powerful herbal remedy for people with renal failure because it lowers serum creatinine levels and lessens symptoms [17].

- **Mental problems:** SARS-CoV-2 can have both neuro-invasive and neuro-virulent features. Significant stressors that patients with COVID-19 must deal with include the fear of dying from a life-threatening illness, discomfort from medical procedures, endotracheal intubation, communication problems, and a feeling of powerlessness [18]. Coping with psychological post-COVID ailments can be aided by the use of Indian herbs and herbal formulations, such as Brahmi (*B. monnieri*), Shankhpushpi (*Convolvulus prostratus* Forssk.), Giloy (*T.*

cordifolia), Malkangni (*Celastrus paniculatus* Willd.), Tulsi (*O. tenuiflorum*), Ashwagandha (*W. somnifera*), and others. *paniculatus* seed oil interacted with dopamine D2 receptors, serotonergic receptors, and GABAB receptors to produce notable antidepressant-like effects. Additionally, it reduced the levels of plasma corticosterone and inhibited MAO-A.

- **Liver injury:** The dysregulated liver function observed in COVID-19 patients may be explained by direct infection of hepatic cells caused by ACE2 expression in the liver, bile duct cells, and cholangiocytes [19]. Furthermore, 76% of COVID-19 patients who had high-dose antibiotics along with hepatotoxic antiviral drugs and steroids developed liver abnormalities and liver damage [20]. *Lawsonia inermis* L. (leaves), *E. officinalis*, *Eclipta alba* (L.) Hassk. (leaves), *Clitoria ternatea* L. (leaves), *Cassia angustifolia*, *T. cordifolia* (leaves, stem, and root), and *Momordica charantia* L. (fruit) *Abrus precatorius* L. (seeds), *Argemone mexicana* L. (leaves), and *M. Vahl* (leaves) normalized high bilirubin, ALT, ALP, and AST levels in vivo [21]. *Solanum xanthocarpum*'s fruits When

rats were given paracetamol and azithromycin, Schrad and H. Wendl. were able to normalize the blood parameters (SGOT, SGPT, ALP, and TB) more effectively than *Juniperus communis* L. fruit [22].

Herbal plants as immunomodulatory activities

As prospective medications for COVID-19, a variety of medicinal herbs are employed. Rare, important herbs that provide the human body with robust immunity are suggested by Indian Ayurvedic practitioners. Turmeric (*Curcuma longa* L), Neem (*Azadirachta indica* A. Juss), Tulasi (*Ocimum sanctum*), Amalaki (*Embllica*

officinalis Gaertn), Guduchi (*Tinospora cordifolia* (Willd iers), Liquorice (*Glycyrrhiza glabra* L), Almond (*Prunus amygdalus*), Kutki (*Picrohiza kurroa* Royle ex Benth) Ginger (*Zingiber officinale* Roscoe), Harisnagar (*Nyctanthes arbor-tristis*), Broccoli (*Brassia oleracea* L), Satavar (*Asparagus racemosus* Willd). These are some vital herbs.

These are first-level Ayurvedic herbs that are crucial for strengthening immunity in the human body and reducing the risk of infection because the immune system is the main and most important defence against this new viral virus (**Figure 1**).

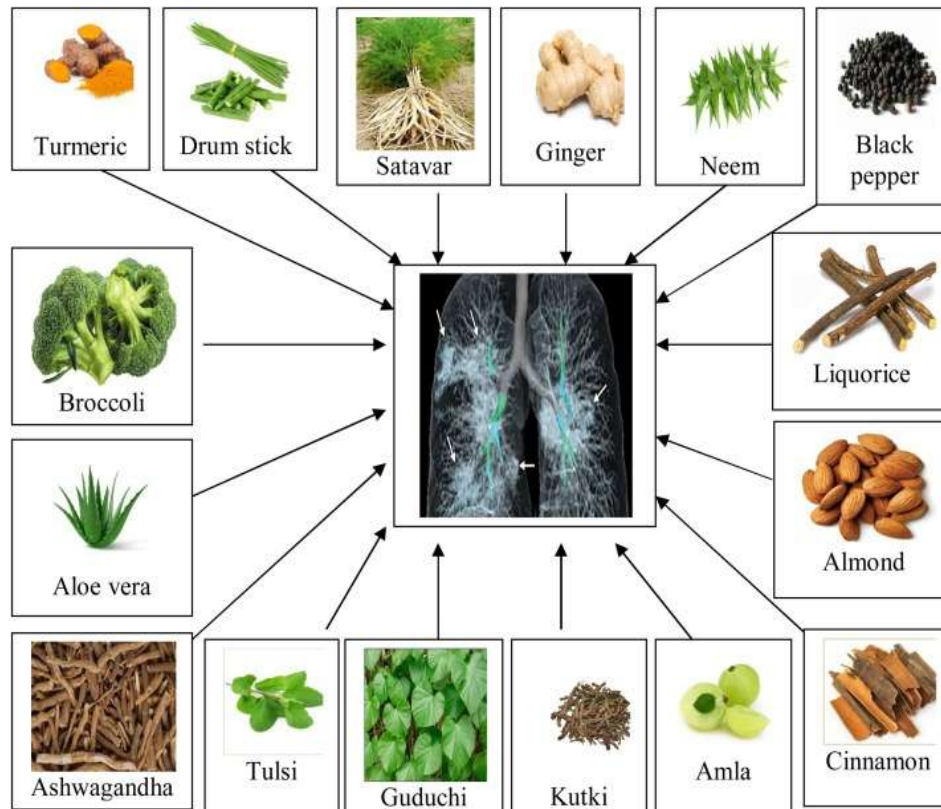


Figure 1: Herbal plants
(<https://doi.org/10.1016/j.hermed.2021.100501>)

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

Neem leaves are considered the best option for combating COVID-19 due of their immunomodulatory properties as well as their potent antiviral properties. An aqueous extract neem bark efficiently prevented Herpes Simplex virus type-1(HSV-1) in natural recipient cells and being evaluated as a potential antiherpetic microbicide [23]. Neem leaf phytochemicals had lately displayed that it is efficient against the COVID-19 virus. This was testified in a molecular docking evaluation in which it was shown that the components' binding affinities were excessively high against the COVID-19 core protease.

2. Tulsi (*Ocimum sanctum* L.)

Tulsi is widely available in India and is considered a sacred herb in Ayurveda. By increasing IFN- γ , IL-4, T-helper cells, and NK cells, as well as by enhancing phagocytic action and the phagocytic index, the leaves have an immunomodulatory effect. Further studies used as an in vitro cytotoxicity assay to determine the antiviral property of several *Ocimum sanctum* extracts against orthomyxovirus and also paramyxovirus. Last year, A study that used molecular docking and molecular dynamics (MD) modelling discovered that phytochemicals from *Ocimum sanctum* could inhibit SARS-CoV-2's main protease, Mpro [24].

3. Ashwagandha (*Withania somnifera* (L.) Dunal)

An evergreen shrub native to India is ashwagandha. The plant was recently used as an effective COVID-19 therapy. Previously, a study utilising the MTT assay shown strong action against viruses from the ashwagandha leaf aqueous extract against the hepatitis C virus (HCV). Human protein kinase N2 (PKN2, PRKCL2) and NS5B RNA-dependent RNA consumed molecular docking to settle the activity [25].

4. Ginger (*Zingiber officinale* Roscoe)

Ginger is proper to Zingiberaceae clan. In a herbal remedy used to treat respiratory conditions, ginger root was found to be an immunomodulator in a recent study. Because of its antiviral properties, the rhizomes of ginger are presently one of the initial medications for COVID-19 infections. Using the MTT assay, earlier studies displayed them to be a long-lasting therapy to inhibit the Chikungunya virus [26].

5. Turmeric (*Curcuma longa* L.)

Turmeric is a prominent multipurpose plant of the Zingiberaceae family. In a late study of non-randomized phase 2 consisting of seven patients with endometrial cancer, Curcumin, a phytoconstituent, was examined for immunomodulatory results via T cell activation and shown a substantial immune-stimulating action [27].

6. Aloe (*Aloe barbadensis* Mill)

Aloe is the multifunctional plant that is proper to the Liliaceae family and it is well-known Universally. The juice contains a number of important active ingredients, including aldopentose, polysaccharides, aloin, and para-coumaric acid (glucomannan, acemannan, mannose derivatives hemicellulose).. It has strong antiviral properties. Scientific clinical studies have displayed that aloe polysaccharides extracted from the leaves are effective against the H1N1 influenza virus [28].

Currently, natural compounds with hopeful immunomodulatory capability have become adequately responsive. The improvement of plant-derived immunomodulatory medicines with enhanced absorption and far less toxic effects has provided a unique approach to lowering the practical cytokine outburst syndrome in COVID-19.

Colchicine: Colchicine has been associated to a considerably higher risk of clinical harm in COVID-19 patients. It was proposed that colchicine therapy for outpatients could reduce the harm caused by hospitalization, morbidity, mortality, and the requirement for critical therapy and special care [29].

Hesperidin: The flavanone glycoside hesperidin is identified in a diversity of citrus fruits. Consistent to a latest in-silico docking study, hesperidin had recorded the

highest docking score when pursuing SARS-CoV-2 Spike and ACE2 receptors, which precluded the virus from entering human lung cells. Furthermore, infants and young children vulnerable to rotavirus were also given hesperidin as a remedy to help them against the virus through immunomodulation; the hesperidin's IC50 was 10 μ M [30]. Thus, hesperidin and hesperidin ZnO nanoparticles were beneficial for additional SARS-CoV-2 testing.

Oleuropein: A phenolic compound, oleuropein exist in olive oil, fruit, and leaves. Oleuropein prevented SARS-CoV-2's NSP15 endoribonuclease action in docking tests. Its antioxidant and anti-inflammatory possessions have been well examined. Oleuropein was initiated in a study utilising rats to inhibit lipoxygenase activity and leukotriene B4 production [31].

Customized conventional applications

- Many traditional activities can be instructed to build They are thought to as first-line defences against COVID-19 and boost the body's immunity through home quarantine (AYUSH) advise the following self-care practices (AYUSH, 2020)
- Immunity can be raised by eating home-cooked meals tested with spices like garlic (*Allium sativum*), turmeric (*Curcuma longa*), cumin

(*Cuminum cyminum*), and coriander (*Coriandrum sativum*).

- Once or twice a day, sip on a steamy herbal tea with raisins, dried ginger, black pepper, cinnamon, and Tulsi.
- One or two times a day, mix half a teaspoon of turmeric powder with hot milk.
- Before going to bed at night, inhale steam from a very hot water that has been imparted with juicy caraway seeds or mint leaves.
- Take clove powder and honey two to three throughout the day to help avoid coughs or throat infections.

Other noteworthy conventional uses that are easy to use execute at home are as follows:

- To improve immunity, take honey and cinnamon powder first thing in the morning.
- Consuming to support immunity, mix one tablespoon of ginger juice with one glass of hot water. treat throat infections.
- Consuming one spoonful of ghee and Ginger paste and half a teaspoon of black pepper powder with hot rice can help heal colds, coughs, and throat infections.
- To increase immunity in the morning, mix one spoonful of honey with garlic.

- To strengthen your immunity, drink a glass of hot water with a teaspoon of lemon juice.
- To boost immunity, take one spoonful of coleus leaf extract mixed with black jeera (black cumin) powder every morning.
- To treat respiratory tract problems and throat infections, Mix a half-spoonful of honey with the juice of Tulsi leaves.
- To enrich immunity, have hot milk with two to three saffron flowers along with half a spoonful of almond seed powder after meals.

CONCLUSION

The global impact of COVID-19, which was produced by SARS-CoV-2, has highlighted the urgent need for effective treatment strategies to manage the acute illness and its long-term effects. Ayurvedic and TCM natural medicines like *Ocimum sanctum*, and *Curcuma longa* have promise antiviral and immunomodulatory qualities. Plant-derived substances like piperine, hesperidin have the potential to reduce inflammation, stop cytokine storms, and help people recover from post-COVID complications like parkinsonism, mental health issues, heart failure, liver damage, lung injury. Ayurvedic methods, such as the use of herbal remedies and lifestyle changes like yoga and food adjustments, also improve

symptom management and immunological resistance. However, in order to confirm the effectiveness, safety, and ideal doses of these natural chemicals, thorough clinical investigations are necessary. Combining traditional knowledge with recent scientific evidence could lead to readily accessible, low-toxicity therapy options for the intricate issues brought on by COVID-19 and its aftereffects.

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