



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Review Article

Exploring Herbal Immunomodulators as Potential Therapeutic Agents for Long COVID

Needa Sheikh*, Vaidehi Nikure, Mohd. Shaklain, Ganesh Akone, Iftesham Ansari, Nujba Farah, Rubina Sheikh, Dr. Sayyadd Sajauddin

Central India College of Pharmacy, Lonara, Nagpur

ARTICLE INFO

Published: 11 Nov 2025

Keywords:

Long COVID, SARS-CoV-2, Post-COVID Condition, Herbal Immunomodulators, Dysfunctioning in Long Covid, Post Acute Sequelae of Covid-19 (PASC)

DOI:

10.5281/zenodo.17582163

ABSTRACT

Long COVID has become a significant global health issue, affecting millions who continue to experience symptoms long after they have recovered from the initial SARS-CoV-2 infection. It includes fatigue, cognitive problems, inflammation, and immune issues. This condition has revealed serious gaps in diagnosis, treatment, and healthcare preparedness. Current medical care primarily aims to manage symptoms since there is no specific medication and standard therapy available. Recent research suggests that herbal immunomodulators might help manage Long COVID. These plant-based substances can restore immune balance, reduce inflammation, lower oxidative stress, and offer antiviral protection. Early studies show that herbs like *Withania somnifera* (Ashwagandha), *Tinospora cordifolia* (Giloy), *Curcuma longa* (Turmeric), *Ocimum sanctum* (Tulsi), *Glycyrrhiza glabra* (Licorice), *Bacopa monnieri* (Brahmi), *Camellia sinensis* (Green tea), and *Panax ginseng* have promise due to their immune-boosting and antioxidant properties. Although these results are encouraging, further large-scale clinical trials and standardized formulations are needed to confirm their safety and effectiveness. Combining herbal immunomodulators and Ayurvedic Rasayana therapies with modern medicine could offer a balanced, affordable, and sustainable way to manage Long COVID. This approach might help with recovery, lessen symptoms, and improve the quality of life for people affected worldwide.

INTRODUCTION

Understanding the Prevalence and Impact of Long COVID

Since the COVID-19 pandemic began, many people around the world have experienced long-lasting symptoms after being infected with the SARS-CoV-2 virus. This condition, known as Long COVID, involves ongoing health issues that

***Corresponding Author:** Needa Sheikh

Address: Central India College of Pharmacy, Lonara, Nagpur

Email ✉: needasheikh46@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



can last for months and affect many areas of life. The rise of Long COVID has revealed significant gaps in healthcare systems, research, and public health communication. It underscores the need for a better understanding and management of chronic conditions linked to infections.

How Common is Long COVID?

It is difficult to estimate how many people suffer from Long COVID because there is no clear diagnostic test and definitions vary in research and clinical practice. Symptoms can differ widely and overlap with other health problems, which often results in underdiagnosis or misdiagnosis. Many patients face challenges in getting their condition recognized by healthcare providers. Current research indicates that between 10% and 35% of individuals infected with COVID-19 may develop Long COVID symptoms. If we take a conservative estimate of 10%, it is thought that at least 65 million people worldwide have experienced Long COVID. In the United States, recent surveys show that about 17.6% of adults have dealt with Long COVID at some point, with approximately 6.9% currently experiencing ongoing symptoms that last three months or longer. The prevalence of Long COVID varies by region. For instance, in the U.S., rates range from as low as 1.9% in the Virgin Islands to as high as 10.6% in West Virginia. These differences reflect variations in population, healthcare access, and reporting.

Long COVID is also linked to mortality. In the U.S., official records indicate that Long COVID was listed as an underlying or contributing cause in over 5,000 deaths since the pandemic began. The risk of death associated with Long COVID is higher among older adults, men, and certain racial and ethnic groups, such as American Indian and Alaska Native populations. However, these figures may not fully capture the true impact because

Long COVID was not consistently recorded on death certificates early in the pandemic

Need for a Clear Definition

Defining Long COVID is challenging because it involves various symptoms and health issues that can have different causes. Many of these symptoms are not unique and may appear in other disorders as well. Researchers and healthcare professionals are still trying to fully understand Long COVID, as it is a relatively new condition with many unanswered questions. New information about its symptoms, duration, and effects on the body keeps emerging. Because Long COVID is complex, it is important to have a clear and consistent way to define and diagnose it. Although Long COVID is a new condition, many definitions have been suggested. When researchers examined 295 studies published before October 2022, they found that each study described Long COVID differently. This made it difficult to compare the results. The variation complicates efforts to understand the condition better. Currently, there is no single accepted definition or standard method to assess Long COVID, which makes research and treatment more challenging

Definitions of Long COVID Across Organizations

Different health organizations have provided working definitions of Long COVID, with some differences in time frame, terminology, and symptom descriptions.

- **Office of the Assistant Secretary for Health (OASH, 2022):** Long COVID describes a condition where symptoms either continue or newly develop four or more weeks after the initial infection. It can affect multiple systems, may relapse or worsen over time, and is not a



single condition but a group of overlapping entities with different causes and outcomes.

- **Centres for Disease Control and Prevention (CDC, 2023):** The CDC describes Long COVID as a range of health problems that persist or recur after infection. Symptoms may start at least 4 weeks after infection and can occur in anyone, even if the initial infection was mild or unnoticed.
- **National Institutes of Health (NIH, 2024):** The NIH uses the term Post-Acute Sequelae of SARS-CoV-2 infection (PASC) to describe ongoing or new symptoms after COVID-19, sometimes even if the initial infection was asymptomatic.
- **World Health Organization (WHO, Adults) (2022):** The post-COVID condition is defined as symptoms lasting at least 2 months that begin within 3 months of infection and cannot be explained by another diagnosis. Common symptoms include fatigue, shortness of breath, and cognitive issues, which affect daily functioning.
- **World Health Organization (WHO, Paediatrics) (2023):** For children and teenagers, Long COVID is defined as symptoms that begin within three months of infection and continue for at least two months. Reported symptoms include fatigue, loss of smell, anxiety, and impacts on school, behaviour, social interaction, and development.
- **NICE/SIGN/RCGP (UK, 2022):** Ongoing symptomatic COVID-19 is defined as symptoms that continue for 4 to 12 weeks after the initial infection. When these symptoms persist beyond 12 weeks without another identifiable cause, the condition is

referred to as post-COVID-19 syndrome. Together, these are often called “Long COVID.”

- **Global Perspective:** Many countries and organizations have created their own definitions. For example, the EpiCore network (2023) compiled a list of global definitions that show how Long COVID is classified in different ways.
- **Reimbursement Codes:** To support healthcare and research, official coding has been developed. In the United States, doctors use the ICD-10 code U09.9 to record cases of “post-COVID-19 condition, unspecified.” In the United Kingdom, health professionals follow the coding system outlined by NICE, SIGN, and RCGP.

Modern Medicine: Limitations in the Management of Long COVID

1. Predominantly Symptom-Oriented Care

Currently, there is no FDA-approved drug or standard treatment for Long COVID. Clinical practice mainly relies on supportive care to manage symptoms. This includes pulmonary rehabilitation, occupational therapy, psychological counselling, and nutritional support. Trials with antivirals and monoclonal antibodies have generally been disappointing. They mostly show no significant difference compared to a placebo. As a result, researchers at UCSF and other institutions are starting to move away from traditional virus-focused strategies. They are exploring new treatment options, including immunomodulatory drugs like baricitinib and bezisterim, to see if they can help manage Long COVID.



2. Reliance on Alternative and Supportive Measures

Since there is no cure, clinicians often recommend vitamin supplements like vitamin D and B-complex. They also suggest lifestyle changes and rehabilitation strategies as supportive options. Some drugs, including low-dose naltrexone, dexamethasone, intravenous immunoglobulins (IVIg), metformin, statins, and omega-3 fatty acids, are being studied for their potential to reduce ongoing inflammation and metabolic issues. However, the evidence for these treatments is still limited and varies. This makes it hard to apply them universally.

3. Lack of Standardized Therapy Due to Symptom Diversity

One of the main difficulties in treating Long COVID is that patients have a range of symptoms that can change. This variety complicates diagnosis and management. Patients may experience fatigue, brain fog, respiratory problems, inflammation in the blood vessels, and cardiovascular or neurological signs. Symptoms often follow a relapsing pattern, with periods of improvement followed by setbacks. The symptoms vary so widely from person to person that a single standardized treatment approach is

often ineffective. Management needs to be tailored to each patient's specific needs.

PATHOPHYSIOLOGY OF LONG COVID

Persistent Viral Reservoirs

In some patients, SARS-CoV-2 does not completely disappear after the initial infection. Instead, small viral particles or RNA fragments can hide in certain organs like the gut, brain, lungs, and lymph nodes. These hidden viral pieces are not enough to cause a new infection, but they keep stimulating the immune system. This situation makes it seem like the body is constantly fighting off something. Over time, this ongoing immune activation leads to low-grade inflammation that never fully shuts down. Patients often experience fatigue, stomach problems, and neurological issues because of this lingering viral material. For example, if viral reservoirs remain in the intestine, they may disturb the gut microbiome, leading to bloating or digestive problems. Similarly, persistence in the brain may lead to symptoms like brain fog and headaches.

This mechanism is important because it shows that Long COVID is not simply "in the mind." It may be linked to real biological factors that continue to irritate the immune system long after the original infection has cleared.

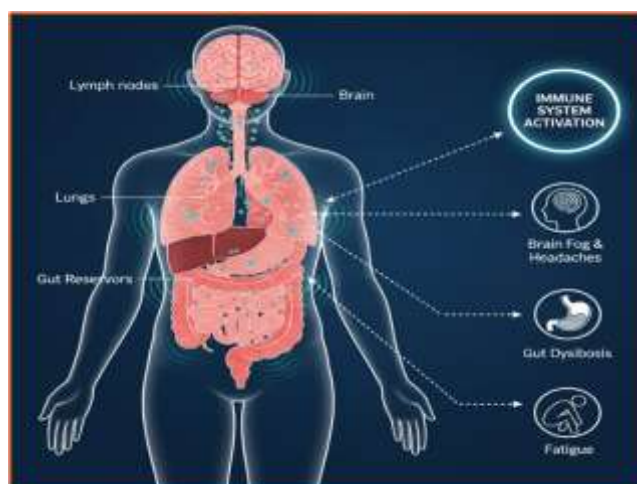


Figure 1: Persistent Viral Reservoirs & Long Covid Pathophysiology

Immune Dysregulation

Patients with Long COVID often experience an imbalance of T-cells and B-cells, as well as unusual antibody responses. Instead of shutting

down after the virus is gone, the immune system stays active and produces inflammatory chemicals. This odd immune response may explain symptoms such as ongoing fatigue, body aches, and brain fog.

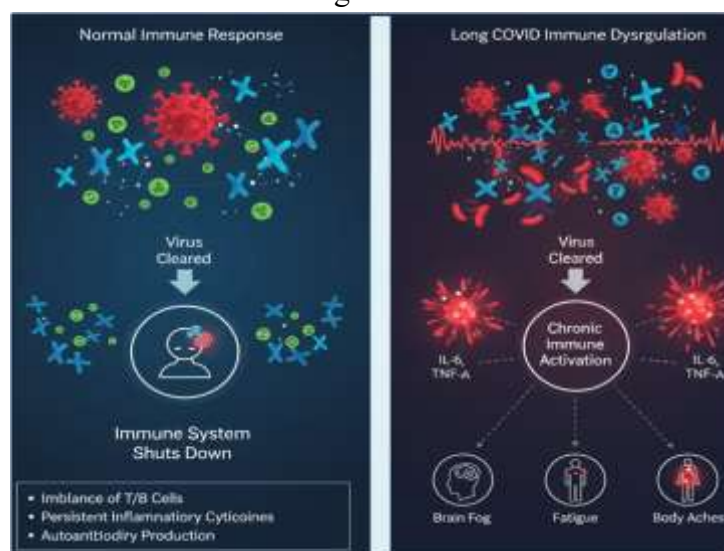


Figure 2: immune Dysregulation in long covid

Chronic Inflammation

Studies have shown that people with Long COVID have high levels of inflammatory molecules like IL-6, TNF- α , and IL-1 β . These molecules harm

tissues and increase oxidative stress, which makes symptoms worse. Ongoing inflammation is thought to be a key cause of Long COVID symptoms.

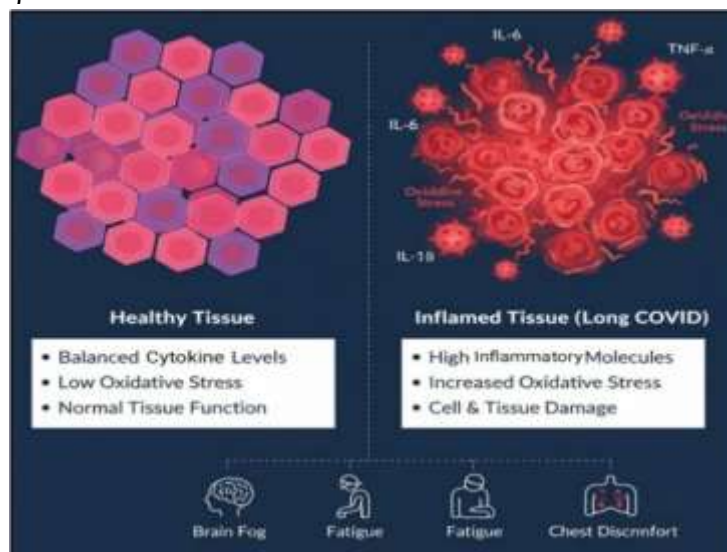


Figure 3: Chronic Inflammation in Long COVID

Endothelial Dysfunction and Microclots

COVID-19 directly harms the endothelial lining of blood vessels. In Long COVID, this damage

persists, leading to abnormal clotting and less oxygen reaching tissues. Many patients have microclots in their blood. This may help explain

symptoms like fatigue, breathlessness, and chest discomfort.

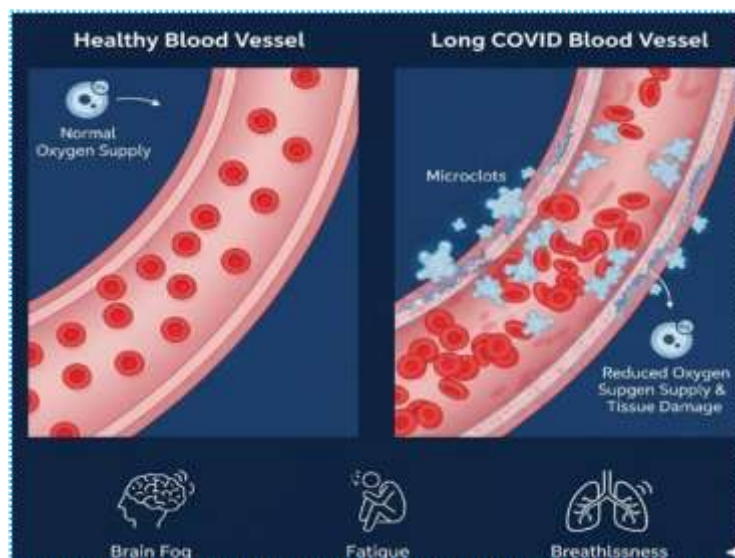


Figure 4: Endothelial Dysfunction and Microclots in Long COVID

Mitochondrial Dysfunction

The virus is believed to impact mitochondria, the energy producers of our cells. Damaged mitochondria have a hard time generating energy.

This can result in extreme fatigue, muscle weakness, and difficulty exercising. Many Long COVID patients experience these symptoms. It resembles what is seen in chronic fatigue syndrome.

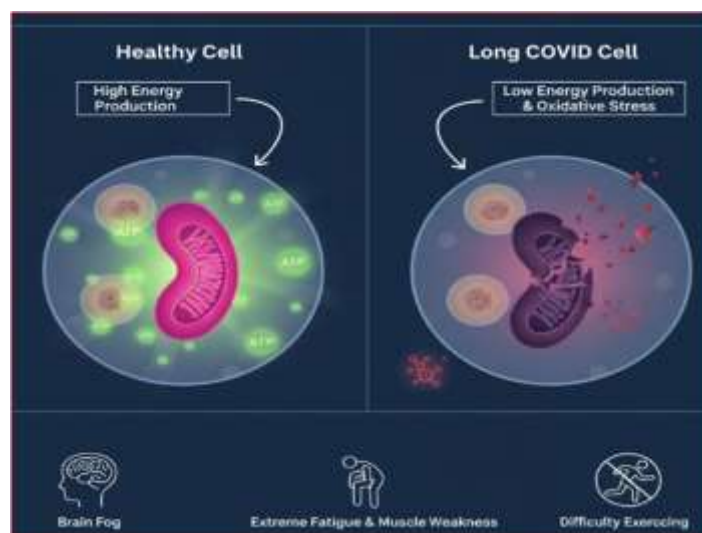


Figure 5: Mitochondrial dysfunction in Long COVID

Autoimmunity

In some cases, the immune system mistakenly creates autoantibodies that attack the body's own

tissues. This autoimmune response can cause joint pain, neurological symptoms, and organ damage in Long COVID patients.

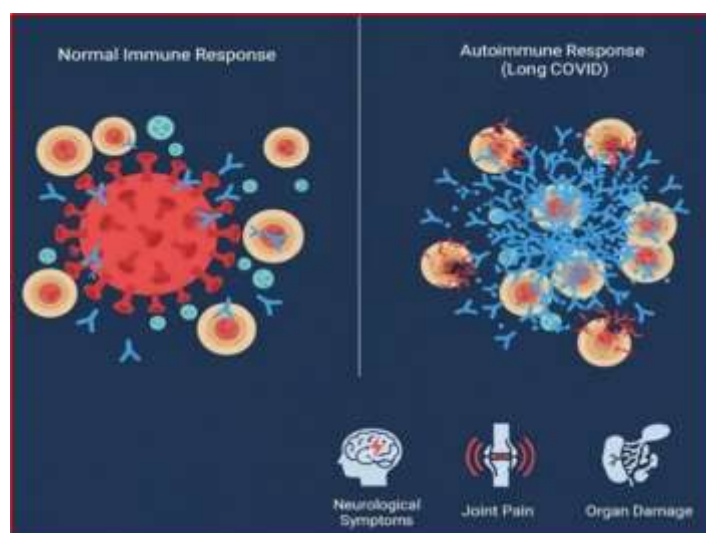


Figure 6: autoimmunity in Long COVID

Neuroinflammation

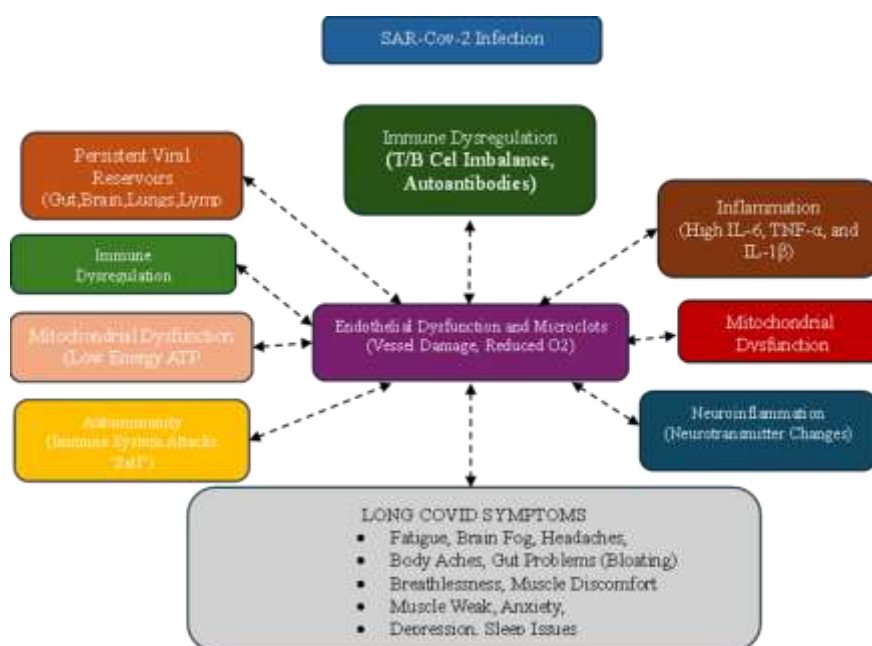
Long COVID often impacts the brain. Evidence indicates persistent neuroinflammation and changes in neurotransmitter signalling. These

factors can account for memory problems, difficulty concentrating, anxiety, depression, and sleep issues. This is why brain fog is one of the most common complaints.



Figure 7: neuroinflammation in Long COVID

Flow Chart : Adapted From References



Why Herbal Immunomodulators?

Herbal Immunomodulators in the Management of Long COVID

Long COVID is becoming more widely understood as more than just the ongoing presence of the SARS-CoV-2 virus in the body. It is seen as a post-viral syndrome where the immune system does not return to its normal state and shows signs of imbalance. This dysfunction often leads to chronic, low-grade inflammation that can show up in various symptoms. Patients frequently report persistent fatigue, cognitive issues like "brain fog," muscle and joint pain, sleep problems, and mood-related difficulties that greatly impact their quality of life.

Because there are few standard treatment options for these remaining symptoms, researchers and doctors are looking at herbal immunomodulators. These plant-based agents are thought to work on the immune system in a gentle and regulatory way. They may help control harmful overreactions while also supporting weakened immune functions. By reducing inflammation, restoring immune balance, and providing antioxidant

support, they may offer a safer and more holistic way to recover for individuals facing Long COVID.

Mechanisms of Action of Herbal Immunomodulators

1. Managing Chronic Inflammation and Immune Dysregulation

One of the key features of Long COVID is ongoing, low-grade inflammation that lasts long after the initial infection has cleared. This continuous inflammatory response likely plays a major role in symptoms like fatigue, brain fog, muscle aches, and joint stiffness. In many patients, the immune system seems unable to turn off its defense mechanisms, keeping the body in a constant state of stress.

Herbal immunomodulators have been suggested as a supportive therapy because they may help restore immune balance. These plants contain bioactive compounds (phytoconstituents) that influence immune signalling pathways and assist in regulating the body's response:

a) **Controlling Cytokine Levels:** During Long COVID, levels of pro-inflammatory cytokines such as IL-6 and TNF- α are often high. This can worsen inflammation and tissue damage. Certain medicinal herbs have natural compounds that can lower or normalize these cytokine levels, preventing the immune system from overreacting.[14]

b) **Enhancing Anti-Inflammatory Responses:** Some herbs can also boost the production of anti-inflammatory cytokines like IL-10 while dampening harmful pathways. This change helps the immune system return to a more balanced state, reducing symptoms and aiding healing.

c) Together, these findings suggest that herbal immunomodulators may not only calm excessive immune activation but also promote the type of protective responses needed for recovery from Long COVID.

2. Boosting and Balancing Immune Function

In Long COVID, the immune system often becomes unbalanced. Some immune pathways are too active, while others are too weak. This imbalance makes it harder for the body to fight infections and slows recovery. Herbal immunomodulators are particularly helpful because they act as adaptogens. They help restore balance by fine-tuning both the innate and adaptive parts of the immune system.

a) **Innate and Adaptive Immunity:** Some medicinal herbs can increase the activity of macrophages, T-cells, and natural killer (NK) cells, which are essential for both innate and adaptive responses. By boosting these functions, herbal immunomodulators not only improve resistance against pathogens but also help maintain long-term immune strength.

b) **Phagocytosis and Pathogen Clearance:** Phytochemicals in herbs can improve phagocytic activity. This is the process where immune cells engulf and destroy pathogens. This leads to more effective removal of infectious agents and cellular debris, which ultimately reduces the level of lingering inflammation.

3. Antioxidant and Antiviral Properties

Oxidative stress significantly contributes to the ongoing symptoms of Long COVID. When the body produces too many reactive oxygen species (ROS) and has weak antioxidant defences, it results in cellular damage, mitochondrial problems, and long-lasting inflammation. This oxidative stress makes fatigue and muscle weakness worse and might slow down immune recovery.

a) **Neutralizing Free Radicals:** Herbal immunomodulators have many polyphenols, flavonoids, and terpenoids that serve as natural antioxidants. These compounds neutralize free radicals, reduce lipid peroxidation, and protect cells from oxidative damage. By decreasing oxidative stress, they help restore energy metabolism and support overall recovery.

b) **Inhibiting Viral Replication:** Many herbal agents also have direct antiviral effects in addition to their antioxidant activity. For instance, Glycyrrhiza glabra (Licorice) contains glycyrrhizin, a triterpenoid saponin that can disrupt viral replication and prevent viruses from entering host cells. Licorice's combined antioxidant and antiviral qualities make it a valuable option for managing post-viral syndromes like Long COVID.[14]

Supporting Studies:



Several studies indicate that herbs with strong antioxidant effects can lower oxidative stress during viral illnesses. This helps reduce the risk of chronic inflammation and tissue damage. [14]

A systematic review of herbal medicines used for COVID-19 patients found that some herbal formulations not only eased symptoms but also shortened hospital stays and recovery times. This indicates their potential as supportive therapy.

4. Safety and Accessibility

One of the main factors that influence the acceptance of herbal immunomodulators is their safety and availability. Unlike many synthetic drugs, which often come with a higher risk of side effects over time, herbal medicines are usually seen as safer when taken with proper medical advice. This makes them particularly useful for managing chronic conditions like Long COVID, where treatment can last for several months.

a) Affordability and Availability: Herbal remedies are often cheaper than standard drugs. They are widely available through traditional medicine systems, local markets, and even as over-the-counter supplements. This easy access allows many people, especially in low- and middle-income

countries, to incorporate herbal medicine into their daily health routines.

b) Safety and Long-Term Use: When used correctly, many herbal medicines have a strong safety record. Their use in traditional medical practices for centuries builds a sense of cultural trust and acceptance. Patients dealing with Long COVID may prefer herbal options because they provide supportive care with low toxicity, especially compared to long-term pharmaceutical treatments.

5. Herbs Frequently Reported in Literature

- Withania somnifera (Ashwagandha):** Adaptogen with immunomodulatory activity; under clinical trial for Long COVID.
- Tinospora cordifolia (Giloy):** Enhances phagocytic activity, widely used in Ayurveda.
- Curcuma longa (Turmeric):** Curcumin shows strong antioxidant and anti-inflammatory actions.
- Zingiber officinale (Ginger):** Contains gingerols with antioxidant and anti-inflammatory potential.
- Glycyrrhiza glabra (Licorice):** Glycyrrhizin studied for antiviral activity

KEY HERBAL IMMUNOMODULATORS IN LONG COVID

Sr. No.	Herbs	Biological Name	Active compounds	Mechanisms	Relevance in Long COVID:	Pictures
1.	Ashwagandha	<i>Withania somnifera</i>	Withanolides (withaferin A, withanolide D, withanosides).	Immunomodulatory: balances Th1/Th2 responses and improves lymphocyte growth. Anti-inflammatory: blocks NF-κB and pro-inflammatory	Clinical studies show improvements in fatigue, sleep, and anxiety, addressing common long COVID symptoms.	

				cytokines (IL-6, TNF- α) ^[1] . Adaptogenic and anxiolytic: regulates the hypothalamic-pituitary-adrenal (HPA) axis, which lowers cortisol.		
2.	Guduchi / Giloy	<i>Tinospora cordifolia</i>	Tinosporaside, berberine-like alkaloids, polysaccharides.	Improves macrophage absorption of pathogens. Reduces cytokine storm mediators ($\downarrow$ IL-6, $\downarrow$ TNF- α , $\downarrow$ IL-1 β). Regulates MAPK and NF- κ B signalling pathways.	Helps reduce ongoing inflammation and immune dysfunction	
3.	Turmeric	<i>Curcuma longa</i>	Curcumin.	Strong blocker of NF- κ B and TLR-4 signalling. Acts as an antioxidant and reduces lung fibrosis caused by infections. Lowers pro-inflammatory cytokines	Improves systemic inflammation and stops pulmonary fibrosis.	
4.	Tulsi / Holy Basil	<i>Ocimum sanctum</i>	Eugenol, ursolic acid, apigenin, rosmarinic acid.	Adaptogenic (lowers stress by regulating cortisol). Antiviral activity (computer studies suggest interference with spike-ACE2 binding). Functions as an antioxidant and helps alleviate inflammation	Useful for stress, anxiety, and mild respiratory symptoms	
5.	Licorice / Mulethi	<i>Glycyrrhiza glabra</i>	Glycyrrhizin, liquiritin, flavonoids.	Immunomodulatory: Reduces pro-inflammatory cytokines and boosts interferon production. Protects lung tissue from damage caused by reactive oxygen species (ROS).	Helpful for respiratory inflammation and post-viral lung issues	

6.	Brahmi	<i>Bacopa monnieri</i>	Bacosides (A & B), bacopasaponins.	Neuroprotective: reduces oxidative stress and increases brain plasticity. Improves memory through cholinergic modulation and antioxidant defense.	Helpful for cognitive dysfunction, brain fog, and memory loss	
7.	Green Tea Polyphenols	<i>Camellia sinensis</i>	Epigallocatechin-3-gallate (EGCG).	Antiviral (inhibits coronavirus replication in lab tests), antioxidant, and lowers pro-inflammatory cytokines.	May help reduce viral presence and chronic inflammation	
8.	Ginseng	<i>Panax ginseng</i>	Ginsenosides (Rg1, Rb1, Re).	Improves energy use in mitochondria, balances Th1/Th2 immune response, and lowers fatigue.	Clinical data supports its role in post-viral fatigue syndrome	
9.	Aloe vera	<i>Aloe barbadensis miller</i>	Acemannan, aloe-emodin, aloin.	Boosts immune response with polysaccharides, acts as an antioxidant, and has anti-inflammatory effects.	Limited systemic evidence, but useful as supportive care for gastrointestinal symptoms and overall immune health	

EVIDENCE FROM RESEARCH / CLINICAL TRIALS (selected studies-in vitro→ clinical)

Sr. No.	Herb	Design	Intervention	Key Findings	Relevance to Long COVID
1	Tinospora cordifolia	Pilot clinical study	Ayurvedic add-on (Tinospora + Piper longum)	Reduced hospital stay and improved recovery time in COVID-19 patients	Supports immune modulation and inflammation reduction
2	Tinospora cordifolia	Randomized open-label study	Tinospora cordifolia extract	Improved clinical and molecular markers in mild COVID-19 patients	Enhances immune response and reduces inflammation
3	Curcuma longa	Triple-blind randomized clinical trial	Turmeric and ginger supplementation	Reduced inflammatory	Anti-inflammatory effects beneficial in Long COVID

				markers in COVID-19 patients	
4	Curcuma longa	Review of curcumin effects	Curcumin	Inhibited virus entry and replication; modulated immune response	Potential therapeutic role in Long COVID management
5	Bacopa monnieri	Clinical trial	Bacopa monnieri supplementation	Improved psychological health during COVID-19	May alleviate cognitive symptoms in Long COVID
6	Bacopa monnieri	Clinical studies review	Bacopa monnieri extract	Enhanced cognitive function and reduced anxiety and depression	Supports cognitive recovery in Long COVID
7	Aloe vera	In vitro study	Aloe vera compounds	Inhibited SARS-CoV-2 main protease activity	Potential antiviral activity in Long COVID
8	Aloe vera	Molecular docking study	Aloe vera compounds	Strong binding to SARS-CoV-2 NSP-16; potential inhibitor	May aid in viral inhibition in Long COVID
9	Ashwagandha	Pilot clinical trial	Ashwagandha and Shunthi (Zingiber officinale)	Reduced recovery time and improved viral clearance in mild COVID-19	Immunomodulatory effects beneficial in Long COVID
10	Ashwagandha	Randomized double-blind placebo-controlled trial	Ashwagandha root extract (1000 mg daily)	Aims to assess efficacy in promoting recovery from Long COVID	Potential therapeutic option for Long COVID

**Comparison table: Herb → Active compound
→ Mechanism → Long COVID symptom
targeted**

Herb	Active Compound(s)	Mechanism	Long COVID Symptom Targeted
Withania somnifera (Ashwagandha)	Withanolides	Immunomodulatory, anti-inflammatory, anxiolytic; ↓ NF-κB signalling, ↓ cortisol levels	Fatigue, anxiety, sleep disturbances, general immune weakness
Tinospora cordifolia (Guduchi / Giloy)	Tinosporaside, berberine-like alkaloids, polysaccharides	Enhances macrophage phagocytosis; ↓ IL-6, TNF-α, IL-1β; modulates MAPK & NF-κB pathways	Persistent inflammation, immune dysregulation, fatigue
Curcuma longa (Turmeric)	Curcumin	Inhibits NF-κB and TLR-4 signalling; antioxidant; antifibrotic; ↓ ROS and pro-inflammatory cytokines	Pulmonary fibrosis, chronic inflammation, oxidative stress

Ocimum sanctum (Tulsi)	Eugenol, ursolic acid	Adaptogenic, antiviral, anti-stress; modulates cortisol and immune response	Stress, anxiety, immune weakness, respiratory issues
Glycyrrhiza glabra (Licorice / Mulethi)	Glycyrrhizin	Antiviral; immunomodulatory; ↓ pro-inflammatory cytokines; protects respiratory tract	Respiratory inflammation, immune dysfunction
Bacopa monnieri (Brahmi)	Bacosides	Neuroprotective; antioxidant; cholinergic modulation	Brain fog, memory loss, cognitive dysfunction
Green tea (Camellia sinensis)	EGCG (Epigallocatechin gallate)	Antioxidant; antiviral; modulates immune signalling	Oxidative stress, persistent inflammation
Panax ginseng (Ginseng)	Ginsenosides	Immunomodulatory; anti-fatigue; antioxidant	Fatigue, immune weakness
Aloe vera	Acemannan, polysaccharides	Immunostimulatory; antiviral; anti-inflammatory	Immune weakness, mucosal inflammation

FUTURE PROSPECTS AND CHALLENGES IN LONG COVID MANAGEMENT

1. Need for More Clinical Trials on Long COVID Patients

Many studies have looked at treatments for Long COVID, but there is still a big gap in high-quality, large clinical trials. A study by Kim et al. (2024) showed that it is possible to run a trial using three herbal medicines to treat symptoms like fatigue and cognitive issues. However, the study stressed the need for larger trials to confirm these findings and create standard treatment protocols.

2. Standardization of Herbal Extracts

The effectiveness of herbal treatments often suffers due to the lack of standardization in their preparation. Sachan et al. (2016) pointed out that standardizing herbal products based on active ingredients is vital for ensuring consistency and effectiveness across different batches. This standardization is important for gaining clinical acceptance of herbal medicines. It helps ensure that the treatments are reliable and safe.

3. Possibility of Polyherbal Formulations and Ayurvedic Rasayana for Long COVID

Ayurvedic Rasayana therapies are known for their healing and immune-boosting benefits. They show promise in dealing with post-COVID issues. A detailed review by Ali et al. (2022) examined several Ayurvedic Rasayana formulations, such as Swasari Ras, Tulsi Ghanvati, and Anu Taila, which have proven effective for treating post-COVID symptoms. These formulations aim to improve immunity and restore balance in the body, addressing various health problems linked to Long COVID.

CONCLUSION

Long COVID is an increasing health problem worldwide. It includes ongoing symptoms such as fatigue, difficulty thinking, breathing issues, and mental distress. These symptoms can persist for months after the initial infection. The condition is complicated, involving issues with the immune system, ongoing inflammation, oxidative stress, blood vessel problems, and brain inflammation. This situation emphasizes the urgent need for effective treatments. Currently, healthcare mainly focuses on managing symptoms, and there are few standardized treatment options available. This gap in care for Long COVID is significant. Herbal immune boosters have emerged as potential



supplementary treatments since they can target several issues. Plant compounds like withanolides (from *Withania somnifera*), tinosporaside (from *Tinospora cordifolia*), curcumin (from *Curcuma longa*), eugenol and ursolic acid (from *Ocimum sanctum*), glycyrrhizin (from *Glycyrrhiza glabra*), bacosides (from *Bacopa monnieri*), and EGCG (from green tea) have shown benefits such as antioxidant, anti-inflammatory, antiviral properties, stress relief, and brain protection. These effects address the primary issues related to Long COVID, including fatigue, inflammation, immune system imbalance, breathing difficulties, and cognitive challenges. While there is some promising early research and a few small clinical studies, strong evidence from large, well-conducted trials is still needed. It's crucial to standardize herbal extracts and assess combinations of herbs or Ayurvedic Rasayana treatments to guarantee consistent effectiveness and safety. With more research and validation, herbal immune boosters could offer a sustainable, affordable, and holistic approach to managing Long COVID. This could provide hope for better recovery and improved quality of life for millions globally.

REFERENCES

1. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Global Health; Board on Health Sciences Policy; Committee on Examining the Working Definition for Long COVID, editors. *A Long COVID Definition: A Chronic, Systemic Disease State with Profound Consequences* [Internet]. Washington (DC): National Academies Press (US); 2024 Jul 9 <https://www.ncbi.nlm.nih.gov/books/NBK605678/>
2. Washington Post. Two experimental drugs failed to treat long covid. What's next? 2025. Available from: <https://www.washingtonpost.com/wellness/2025/05/16/long-covid-treatments-trial-immune-system>
3. San Francisco Chronicle. UCSF says monoclonal antibodies failed to treat long COVID in landmark study. 2025. Available from: <https://www.sfchronicle.com/health/article/ucsf-monoclonal-antibodies-long-covid-20323832.php>
4. Mahmud R, et al. Management strategies for post-COVID-19 syndrome: current perspectives. *Front Med.* 2022;9:951306 . Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9513068>
5. Huang Y, et al. Long COVID treatment strategies: current status and future directions. *Front Med.* 2024;11:39599909 . Available from: <https://pubmed.ncbi.nlm.nih.gov/39599909>
6. Shouman W, et al. Therapeutic approaches for long COVID: current evidence and future directions. *Viruses.* 2024;16(11):1795. Available from: <https://www.mdpi.com/1999-4915/16/11/1795>
7. Self Magazine. How long do long COVID symptoms last? 2023. Available from: <https://www.self.com/story/how-long-covid-symptoms-last-long-haulers>
8. Stein SR, et al. SARS-CoV-2 infection and persistence throughout the human body and brain. *Nature.* 2022;612:758–763. <https://doi.org/10.1038/s41586-022-05542-y>
9. Phetsouphanh C, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2



- infection. *Nat Immunol.* 2022;23:210–216.
<https://doi.org/10.1038/s41590-021-01113-x>
10. Peluso MJ, et al. Inflammatory biomarkers persist up to 12 months after COVID-19. *Nat Med.* 2023;29:1103–1113.
<https://doi.org/10.1038/s41591-023-02297-6>
11. Pretorius E, et al. Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC). *Cardiovasc Diabetol.* 2021;20:172.
<https://doi.org/10.1186/s12933-021-01359-7>
12. Singh KK, et al. Mitochondrial dysfunction in Long COVID: Mechanistic insights and potential therapeutic targets. *Curr Opin Physiol.* 2023;33:100626.
<https://doi.org/10.1016/j.cophys.2023.100626>
13. Wang EY, et al. Diverse functional autoantibodies in patients with COVID-19. *Nature.* 2021;595:283–288.
<https://doi.org/10.1038/s41586-021-03631-y>
14. Mousa H.A., et al. Medicinal Herbs: Promising Immunomodulators for the Treatment of Infectious Diseases. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10745476>
15. Cicero A.F.G., Gigliotti F.F. Plant-Derived Nutraceuticals and Immune System Modulation: An Evidence-Based Overview <https://www.mdpi.com/2076-393X/8/3/468>
16. Kumari R., Kaur H. Herbal Immunomodulators: A Powerful Preventive Weapon for COVID-19. <https://www.researchgate.net/publication/348483089>
17. Singh S.K., Prasad R.D. A Review on Herbal Plants as Immunomodulators. <https://www.researchgate.net/publication/327326478>
18. Ang H.M., Tan K.J. Efficacy of Herbal Medicines on Length of Stay and Conversion Outcomes in COVID-19 Patients: <https://www.frontiersin.org/articles/10.3389>
19. Sahoo J., Jena S. Herbal Plants as Immunity Modulators Against COVID-19. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7830038/>
20. ISRCTN12368131. Ayurveda for Enhancing Recovery from Long COVID <https://www.isrctn.com/ISRCTN12368131>
21. National Institutes of Health – Ashwagandha Fact Sheet. <https://ods.od.nih.gov/factsheets/Ashwagandha-HealthProfessional>
22. Chandrasekhar K, et al. A prospective, randomized double-blind study of safety and efficacy of high-concentration Ashwagandha root extract in reducing stress and anxiety in adults. *Indian J Psychol Med.* 2012. <https://pubmed.ncbi.nlm.nih.gov/23439798/>
23. Sharma U, et al. Immunomodulatory activity of *Tinospora cordifolia*. *Phytother Res.* 2012. <https://pubmed.ncbi.nlm.nih.gov/22253025/>
24. Sharma P, et al. *Tinospora cordifolia* and immunomodulation in COVID-19: A review. *Saudi J Biol Sci.* 2022;29(12):103451. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11699423/>
25. Hewlings SJ, Kalman DS. Curcumin: A review of its effects on human health. *Foods.* 2017. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5664031/>
26. Tomeh MA, Hadianamrei R, Zhao X. Curcumin as a Natural Antioxidant in COVID-19: Molecular Mechanisms and Therapeutic Implications. *Front Pharmacol.* 2021;12:643494. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8247651/>
27. Cohen MM. Tulsi—*Ocimum sanctum*: A herb for all reasons. *J Ayurveda Integr Med.* 2014.

- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4296439/>
28. In silico antiviral activity of Tulsi compounds against SARS-CoV-2. <https://pubmed.ncbi.nlm.nih.gov/32528307/>
29. Cinatl J, et al. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. *Lancet*. 2003. <https://pubmed.ncbi.nlm.nih.gov/12814717/>
30. Fiore C, et al. Antiviral effects of Glycyrrhiza species. *Phytother Res*. 2008. <https://pubmed.ncbi.nlm.nih.gov/18446856/>
31. Stough C, et al. Neuropsychological outcomes of 90-day Bacopa monnieri supplementation in healthy humans. *Psychopharmacology*. 2001. <https://pubmed.ncbi.nlm.nih.gov/11515715/>
32. Pase MP, et al. The cognitive-enhancing effects of Bacopa monnieri. *J Altern Complement Med*. 2012. <https://pubmed.ncbi.nlm.nih.gov/22414231/>
33. Ohishi T, et al. Anti-inflammatory properties of EGCG—the major catechin in green tea. *Curr Drug Targets*. 2016. <https://pubmed.ncbi.nlm.nih.gov/26398887/>
34. Scaglione F, et al. Efficacy and safety of Ginseng extract in fatigue. *J Ethnopharmacol*. 1990. <https://pubmed.ncbi.nlm.nih.gov/2084006/>
35. Hamman JH. Composition and applications of Aloe vera leaf gel. *Molecules*. 2008. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6245421/>
36. Kataria S, et al. Efficacy of Tinospora cordifolia in COVID-19: Pilot Clinical Study. *Sci Direct*. 2022. <https://www.sciencedirect.com/science/article/pii/S097594762100098X>
37. Verma S, et al. Immune modulation by Tinospora cordifolia extract in COVID-19. *PMC*. 2023;10696694. <https://pubmed.ncbi.nlm.nih.gov/38049897/>
38. Saleh A, et al. Effects of turmeric and ginger supplementation in COVID-19. *Nature*. 2025;415(16092):xx-xx. <https://www.nature.com/articles/s41598-025-16092-4>
39. Zahedipour F, et al. Curcumin as an antiviral and anti-inflammatory agent. *PMC*. 2020;7276879. <https://pubmed.ncbi.nlm.nih.gov/32430996/>
40. Shetty AK, et al. Bacopa monnieri and psychological health in COVID-19. *PMC*. 2021;8696156. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8696156/>
41. Gościński G, et al. Cognitive effects of Bacopa monnieri. *Nutrients*. 2025;17(11):1939. <https://www.mdpi.com/2072-6643/17/11/1939>
42. Mpiana PT, et al. Antiviral activity of Aloe vera. *PMC*. 2020;7833182. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7833182/>
43. Shaji J, et al. Molecular docking of Aloe vera compounds against SARS-CoV-2. *ChemRxiv*. 2021. <https://chemrxiv.org/engage/api-gateway/chemrxiv/assets/orp/resource/item/6107b2b1d03b3d822f0493f9/original/recognition-of-aloe-vera-compounds-as-potential-inhibitors-of-sars-co-v-2-nsp-16-molecular-docking-approach-for-drug-development.pdf>
44. Singh N, et al. Ashwagandha supplementation in mild COVID-19. *ClinicalTrials.gov*. 2023. <https://pubmed.ncbi.nlm.nih.gov/37482107/>
45. Mallinson DJ, et al. Ashwagandha root extract in Long COVID recovery: RCT protocol. *PMC*. 2025;10403319. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10403319/>



46. Kim TH, et al. Herbal medicines for long COVID: A phase 2 pilot clinical trial. *Sci Rep.* 2024;14:12345. Available from: <https://www.sciencedirect.com/science/article/pii/S2405844024139515>
47. Sachan A, et al. Medicinal Plants in COVID-19: Potential and Limitations. *Front Pharmacol.* 2021;12:611408. Available from: <https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2021.611408/full>
48. Ali AAM, et al. Ayurvedic formulations: Potential COVID-19 therapeutics? *PMC.* 2022. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9020642/>
49. T. C. Q. Shahril Raza Khan*, “Early Onset of Alzheimer’s Disease it’s Variant and its Herbal Managerial Tools,” Sept. 2025, doi: 10.5281/ZENODO.17165676.

HOW TO CITE: Needa Sheikh, Vaidehi Nikure, Mohd. Shaklain, Ganesh Akone, Iftesham Ansari, Nujba Farah, Rubina Sheikh, Dr. Sayyadd Sajaudin, Exploring Herbal Immunomodulators as Potential Therapeutic Agents for Long COVID, *Int. J. of Pharm. Sci.*, 2025, Vol 3, Issue 11, 1741-1758. <https://doi.org/10.5281/zenodo.17582163>

