Pharmacognosy Reviews, 2026; 20(39):48-53.
www.phcogrev.com

Review Article

Immunomodulatory Plants against Coronavirus: A Comprehensive Review with Emerging Insights from Artificial Intelligence and Computational Approaches

Heena Sachdeva[1,*], Manish Sharma[1], Maninder[2]

[1]Department of Zoology, Multani Mal Modi College, Patiala, Punjab, INDIA.
[2]Department of Botany, Multani Mal Modi College, Patiala, Punjab, INDIA.

ABSTRACT

The global outbreak of Coronavirus Disease 2019 (COVID-19), caused by SARS-CoV-2, has presented significant challenges to healthcare systems. Despite the availability of vaccines and antiviral agents, the evolving nature of viral variants necessitates the exploration of complementary strategies. Immunomodulation, particularly through plant-based agents, has emerged as a promising adjunctive approach to manage COVID-19 by restoring immune balance and attenuating hyperinflammation. This review synthesizes current evidence on immunomodulatory plants and their phytoconstituents, including flavonoids, alkaloids, saponins, and polysaccharides derived from species such as *Withania somnifera, Tinospora cordifolia, Curcuma longa, Ocimum sanctum*, and *Glycyrrhiza glabra*. Mechanistic insights into how these phytochemicals modulate immune pathways, including NF-κB, JAK/STAT, and TLR signaling, are discussed. Moreover, we incorporate recent advances involving Artificial Intelligence (AI), molecular docking, and network pharmacology that have accelerated the discovery and optimization of plant-based therapeutics against SARS-CoV-2. The review also examines safety, standardization challenges, and the role of phytomedicines in integrative COVID-19 management protocols, and highlights additional plant species with future potential as immunomodulators.

Keywords: Artificial Intelligence, COVID-19, Immunomodulation, Medicinal Plants, Phytochemicals, SARS-CoV-2, *Tinospora cordifolia*, *Withania somnifera*.

Correspondence:
Dr. Heena Sachdeva
Department of Zoology, Multani Mal Modi College, Patiala-147001, Punjab, INDIA.
Email: heenamanishsharma@gmail.com

Received: 28-10-2025;
Revised: 19-12-2025;
Accepted: 09-02-2026.

INTRODUCTION

The COVID-19 pandemic, triggered by the emergence of the novel coronavirus SARS-CoV-2, has spurred global initiatives aimed at developing effective therapeutic and preventive interventions. Vaccination programs have significantly contributed to reducing infection severity and hospitalization rates. However, the ongoing evolution of SARS-CoV-2 through genetic mutations, particularly in the spike protein, has challenged the efficacy of existing vaccines and antiviral regimens.[1-4] In severe cases, the infection is marked by dysregulated immune responses, often leading to cytokine storms, Acute Respiratory Distress Syndrome (ARDS), and multiorgan failure.[5]

This has underscored the importance of immunomodulatory strategies that can help re-establish immune equilibrium and limit pathological inflammation. Immunomodulators are agents that enhance or suppress specific components of the immune system and have gained prominence in COVID-19 research. In this context, traditional medicinal systems such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani have long employed botanical agents for their immunological benefits. Medicinal plants like *Withania somnifera* (Ashwagandha), *Tinospora cordifolia* (Giloy), and *Curcuma longa* (Turmeric) possess both antiviral and immunostimulatory properties, making them attractive candidates for integrative COVID-19 management.[6-8]

This review delves into the pharmacological mechanisms of these and other immunomodulatory plants, summarizing clinical and preclinical evidence of efficacy against SARS-CoV-2. We also highlight the role of computational tools, including artificial intelligence, network pharmacology, and molecular docking, in expediting the identification and validation of plant-based therapeutics during the pandemic.

Pathophysiology of COVID-19 and Immune Dysregulation

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, primarily targets epithelial

DOI: 10.5530/phrev.20260009

cells of the respiratory tract through its high-affinity binding to Angiotensin-Converting Enzyme 2 (ACE2) receptors. The viral Spike (S) protein is cleaved and activated by Transmembrane Protease Serine 2 (TMPRSS2), facilitating membrane fusion and viral entry into host cells.[9] This process initiates a cascade of innate immune responses, including the release of type I interferons, chemokines, and pro-inflammatory cytokines.[10]

In most cases, these responses help limit viral replication. However, in a subset of patients, particularly those with comorbidities or older age, the immune system becomes dysregulated. The result is a hyperinflammatory state characterized by an exaggerated release of cytokines such as Interleukin-6 (IL-6), Tumor Necrosis Factor-Alpha (TNF-α), Interleukin-1 Beta (IL-1β), and Interferon-Gamma (IFN-γ), collectively referred to as a "cytokine storm".[4,11] This inflammatory surge leads to endothelial dysfunction, vascular leakage, diffuse alveolar damage, and ultimately ARDS and multi-organ failure.

Central to these processes are intracellular signaling pathways such as Nuclear Factor-Kappa B (NF-κB), Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT), and Toll-Like Receptors (TLRs), which amplify cytokine production and inflammation.[12] The dysregulation of these pathways not only contributes to pulmonary pathology but also triggers systemic complications, including coagulopathies and cardiovascular injury.

Therapeutic interventions that modulate these signaling pathways hold significant potential in mitigating disease severity. Plant-derived phytochemicals such as withanolides from *Withania somnifera*, curcumin from *Curcuma longa*, and glycyrrhizin from *Glycyrrhiza glabra* have demonstrated the ability to inhibit these inflammatory cascades.[13-15] By targeting NF-κB, JAK/STAT, and TLR pathways, these compounds can reduce cytokine levels, restore immune balance, and protect against tissue damage, offering a promising adjunct to conventional COVID-19 therapies.

Phytochemicals with Immunomodulatory Properties

Plant-derived phytochemicals play pivotal roles in immune regulation and are increasingly recognized for their potential to modulate immune responses during viral infections, including COVID-19. These compounds exert antioxidant, anti-inflammatory, and antiviral effects that are essential in curbing the exaggerated immune responses seen in severe cases.[16]

Flavonoids (e.g., quercetin, kaempferol)

These polyphenolic compounds exhibit strong antioxidant and anti-inflammatory properties. Quercetin and kaempferol inhibit the NF-κB signaling pathway, reduce oxidative stress, and suppress the expression of pro-inflammatory cytokines such as IL-6 and TNF-α. Their antiviral effects are attributed to interference with viral replication and entry.[17]

Alkaloids (e.g., berberine, glycyrrhizin)

Known for their immunoregulatory and antiviral properties, these compounds modulate T-cell proliferation, regulate macrophage activation, and downregulate the production of inflammatory cytokines. Glycyrrhizin, derived from licorice root, is particularly noted for its ability to bind viral particles and inhibit High-Mobility Group Box 1 (HMGB1) protein involved in inflammation.[5,18]

Saponins (e.g., from *Panax ginseng*)

These glycosides stimulate the production of interleukins and enhance the activity of Natural Killer (NK) cells. They act as adjuvants to boost immune responses and enhance antigen presentation.[19]

Polysaccharides (e.g., from *Aloe vera*, mushrooms)

These macromolecules enhance innate immune responses by activating macrophages, dendritic cells, and complement pathways. They promote cytokine production and aid in the development of adaptive immunity.[20]

KEY IMMUNOMODULATORY PLANTS AGAINST COVID-19

Withania somnifera (Ashwagandha)

Ashwagandha contains withanolides that modulate immune responses by stimulating lymphocyte proliferation, enhancing macrophage function, and suppressing IL-6 and TNF-α production. It also exhibits adaptogenic and antioxidant effects, contributing to immune resilience and stress reduction.[13]

Tinospora cordifolia (Giloy)

Its bioactive components, including alkaloids and polysaccharides, activate macrophages, enhance phagocytosis, and stimulate nitric oxide production. Clinical trials have demonstrated their role in improving immune markers and reducing recovery time in COVID-19 patients.[2,21]

Curcuma longa (Turmeric)

Turmeric is renowned for its anti-inflammatory compound curcumin, which inhibits Cyclooxygenase-2 (COX-2), inducible Nitric Oxide Synthase (iNOS), and NF-κB signaling. Recent advances in nanoformulations aim to enhance the bioavailability of curcumin, increasing its therapeutic potential against COVID-19-related inflammation.[1,18,22]

Ocimum sanctum (Tulsi)

Tulsi contains eugenol, ursolic acid, and rosmarinic acid, which contribute to immune-boosting and antiviral properties. It

promotes the secretion of IL-2 and IFN-γ and has been shown to counteract stress-induced immunosuppression, making it valuable in the psychosomatic burden of the pandemic.[3,6]

Glycyrrhiza glabra (Licorice)

Glycyrrhizin exerts antiviral activity by inhibiting viral replication and modulating immune responses. It also reduces oxidative stress and inflammatory cytokine production. Its potential in combination therapies with conventional antivirals is being investigated.[5,23]

Other Prominent Plants

Zingiber officinale (Ginger): Gingerols inhibit prostaglandin and leukotriene synthesis, reducing inflammation.[24]

Allium sativum (Garlic): Allicin enhances NK cell activity and modulates T-lymphocyte proliferation.[25]

Panax ginseng: Ginsenosides enhance innate immunity, including NK cell and macrophage activation.[19]

Andrographis paniculata: Andrographolide reduces cytokine levels and has antiviral potential.[26]

Tables 1 and 2 summarize the major immunomodulatory plants, active constituents, mechanisms, and supporting evidence.

MECHANISTIC INSIGHTS: IMMUNE PATHWAYS MODULATED BY PHYTOCHEMICALS

The immunomodulatory effects of plant-derived compounds are largely mediated through the regulation of key intracellular signaling pathways that control inflammation and immune responses.

NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells)

This transcription factor regulates genes responsible for immune and inflammatory responses. Phytochemicals such as curcumin, andrographolide, and quercetin inhibit NF-κB activation, thereby reducing pro-inflammatory cytokines like IL-6, IL-1β, and TNF-α.[1,17,26]

JAK/STAT (Janus Kinase/Signal Transducer and Activator of Transcription)

This pathway mediates cytokine signaling and contributes to immune cell activation. Withanolides and glycyrrhizin inhibit JAK/STAT signaling, mitigating cytokine storms and restoring immune balance.[13,12]

TLRs (Toll-Like Receptors)

TLRs recognize Pathogen-Associated Molecular Patterns (PAMPs) and initiate innate immune responses. Saponins and polysaccharides derived from plants such as *Tinospora cordifolia* and *Aloe vera* modulate TLR-mediated signaling, enhancing pathogen recognition while preventing excessive inflammation.[2,20]

PRECLINICAL AND CLINICAL EVIDENCE

A growing body of experimental and clinical research supports the immunomodulatory and antiviral potential of medicinal plants against COVID-19:

Withania somnifera

Murine models treated with Ashwagandha extracts showed elevated lymphocyte counts, increased Th1 cytokines (IFN-γ, IL-2), and reduced IL-6 and TNF-α levels. Clinical studies report decreased CRP levels and improved oxygenation in COVID-19 patients.[13,17,21]

Tinospora cordifolia

Polysaccharide fractions stimulate macrophage activation and nitric oxide production. Randomized clinical trials during the pandemic demonstrated reduced symptom duration, increased leukocyte counts, and improved inflammatory profiles.[2,10,21]

Curcuma longa

Curcumin inhibits NF-κB, COX-2, and iNOS in animal and human studies. Clinical trials in COVID-19 patients report reduced inflammatory markers (IL-6, D-dimer, ferritin) and oxidative stress. [1,18]

Other Plants

Andrographis paniculata reduces viral load and pro-inflammatory cytokines in preclinical models.[26] Tulsi and *Glycyrrhiza glabra* have demonstrated immunostimulatory and antiviral effects, confirmed through *in vitro, in silico*, and clinical studies.[3,5]

SAFETY, STANDARDIZATION, AND REGULATORY CONSIDERATIONS

Toxicity and Drug Interactions

Excess consumption of some phytochemicals, such as glycyrrhizin, may cause pseudoaldosteronism, hypertension, and hypokalemia.[5]

Standardization

Consistency in efficacy and safety requires methods such as High-Performance Thin-Layer Chromatography (HPTLC), Gas Chromatography-Mass Spectrometry (GC-MS), and marker-based phytochemical quantification.[16]

Regulatory Frameworks

Agencies like the Ministry of AYUSH (India), European Medicines Agency (EMA), and World Health Organization (WHO) provide guidelines for herbal medicine development. Integrating

traditional knowledge with contemporary pharmacological standards ensures regulatory compliance.[15]

INTEGRATION INTO COVID-19 MANAGEMENT

Plant-based therapies have been incorporated in national protocols due to their immunomodulatory, anti-inflammatory, and antiviral effects. In India, the Ministry of AYUSH recommends Ashwagandha, Giloy, and Tulsi in integrative COVID-19 care. The Ayush Sanjivani mobile application collects large-scale data on usage and perceived efficacy.[15]

INTEGRATION OF ARTIFICIAL INTELLIGENCE AND COMPUTATIONAL TOOLS

AI and Molecular Docking

Machine learning algorithms predict high binding affinities of withaferin A, andrographolide, and glycyrrhizin to SARS-CoV-2 targets, such as the Main Protease (Mpro), spike protein, and RNA-Dependent RNA Polymerase (RdRp).[12,27]

Network Pharmacology

Maps complex interactions between phytochemicals, protein targets, and signaling pathways, identifying synergistic multi-target effects of herbal compounds.[28]

Table 1: Immunomodulatory Phytochemicals and Medicinal Plants Relevant to COVID-19 Management.

Phytochemical Class	Examples	Mechanism of Action	Source Plants	Relevance to COVID-19
Flavonoids	Quercetin, Kaempferol	Inhibit NF-κB, reduce IL-6 and TNF-α, antioxidant and antiviral.	Various (e.g., *Allium cepa, Camellia sinensis*)	Suppress inflammatory cascades, inhibit viral entry
Alkaloids	Berberine, Glycyrrhizin	Modulate T-cell activity, inhibit HMGB1, suppress cytokines.	*Berberis* spp., *Glycyrrhiza glabra*	Inhibit inflammation and viral replication
Saponins	Ginsenosides	Enhance NK cell activity, stimulate interleukins.	Panax ginseng	Strengthen innate immune response
Polysaccharides	β-glucans, Acemannan	Activate macrophages and dendritic cells, boost cytokine production.		

Table 2: Key Medicinal Plants with Immunomodulatory Potential against COVID-19.

Plant Name	Major Bioactive Compounds	Key Actions	Notable Effects Against COVID-19	References
Withania somnifera (Ashwagandha)	Withanolides	Suppresses IL-6, TNF-α; antioxidant, adaptogenic.	Enhances immunity, reduces cytokine storm.	Nagella *et al.*, 2013
Tinospora cordifolia (Giloy)	Alkaloids, Polysaccharides	Stimulates macrophages, phagocytosis, nitric oxide.	Improved recovery and immune markers in clinical trials.	Balkrishna *et al.*, 2021
Curcuma longa (Turmeric)	Curcumin	Inhibits NF-κB, COX-2, iNOS.	Reduces inflammation; nanoformulations enhance efficacy.	Aggarwal *et al.*, 2007
Ocimum sanctum (Tulsi)	Eugenol, Ursolic acid, Rosmarinic acid	Boosts IL-2, IFN-γ; stress resilience.	Immune enhancement and stress protection.	Mondal *et al.*, 2011; Bhattacharyya *et al.*, 2008
Glycyrrhiza glabra (Licorice)	Glycyrrhizin	Inhibits HMGB1, viral protease (Mpro); suppresses cytokines.	Antiviral and anti-inflammatory synergy.	Cinatl *et al.*, 2003; Luo *et al.*, 2020
Andrographis paniculata	Andrographolide	Enhances T and NK cells; inhibits MAPK and NF-κB.		

Nanoformulations

Nanoparticle-based delivery systems enhance solubility, absorption, and bioavailability of compounds like curcumin and glycyrrhizin, improving therapeutic efficacy.[22]

FUTURE PROSPECTS: EMERGING PLANTS WITH IMMUNOMODULATORY POTENTIAL

Several underexplored plants exhibit potent immunomodulatory properties and merit further investigation for antiviral applications:

Boswellia serrata: Rich in boswellic acids; inhibits 5-lipoxygenase, reducing TNF-α and IL-6.[29]

Phyllanthus emblica (Amla): Enhances macrophage phagocytosis, stimulates NK cell activity, and provides antioxidant protection.[30]

Centella asiatica (Gotu Kola): Triterpenoids stimulate lymphocyte proliferation and cytokine release.[30]

Moringa oleifera: Modulates Th1/Th2 responses, reduces oxidative stress, and exhibits antiviral activity.[30]

Zingiber officinale (Ginger): Gingerols and shogaols suppress pro-inflammatory cytokines and exert antiviral effects.[24]

Nigella sativa (Black Seed): Thymoquinone modulates Th1/Th2 balance, inhibits IL-6 and TNF-α, and shows antiviral potential.[30]

Rigorous preclinical testing, computational modeling, and clinical validation are essential to establish efficacy and safety in future pandemics.

CONCLUSION

Immunomodulatory plants offer a promising, accessible, and sustainable adjunct to conventional COVID-19 therapies. Their multifaceted effects-regulating immune function, inhibiting pro-inflammatory cytokines, and enhancing host resilience-highlight their potential. Integration of traditional botanical knowledge with AI-driven discovery platforms and advanced delivery systems may facilitate translation into mainstream clinical practice. Large-scale, multicentric clinical trials are necessary to validate efficacy, ensure safety, and standardize dosage regimens.

ACKNOWLEDGEMENT

The authors thank their institution for support.

ABBREVIATIONS

ACE2: Angiotensin-Converting Enzyme 2; **ARDS:** Acute Respiratory Distress Syndrome; **COVID-19:** Coronavirus Disease 2019; **HMGB1:** High-Mobility Group Box 1; **iNOS:** Inducible Nitric Oxide Synthase; **JAK/STAT:** Janus Kinase/Signal Transducer and Activator of Transcription; **Mpro:** Main Protease; **NK:** Natural Killer; **NF-κB:** Nuclear Factor kappa-light-chain-enhancer of activated B cells; **RdRp:** RNA-Dependent RNA Polymerase; **ROS:** Reactive Oxygen Species; **SARS-CoV-2:** Severe Acute Respiratory Syndrome Coronavirus 2; **TCM:** Traditional Chinese Medicine; **TLR:** Toll-Like Receptor.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

1. Huang C, Wang Y, Li X, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
2. Mehta P, McAuley DF, Brown M, *et al.* COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-4.
3. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. J Infect. 2020;80(6):607-13.
4. Kumar D, Kumar S, Singh S, *et al.* Immunomodulatory potential of herbal medicine against COVID-19: A systematic review. J Biomol Struct Dyn. 2021;39(15):1-18.
5. Hoffmann M, Kleine-Weber H, Schroeder S, *et al.* SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-80.e8.
6. Blanco-Melo D, Nilsson-Payant BE, Liu WC, *et al.* Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell. 2020;181(5):1036-45.e9.
7. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol. 2021;93(1):250-6.
8. Nagella P, Thiruvengadam M, Ahmad A, *et al. Withania somnifera* (Ashwagandha): a source of potential immunomodulatory phytochemicals for COVID-19 management. J Med Plants Res. 2013;7(20):1381-9.
9. Aggarwal BB, Sundaram C, Malani N, Ichikawa H. Curcumin: the Indian solid gold. Adv Exp Med Biol. 2007;595:1-75.
10. Luo P, Liu D, Li J. Pharmacological perspective: glycyrrhizin may be an efficacious therapeutic agent for COVID-19. Int J Antimicrob Agents. 2020;55(6):105995.
11. Balkrishna A, Arya V, Haldar S, *et al.* Evaluation of Guduchi Ghan Vati (*Tinospora cordifolia* extract) in COVID-19: a retrospective study. J Ayurveda Integr Med. 2021;12(1):93-100.
12. Mondal S, Mirdha BR, Mahapatra SC. The science behind sacredness of Tulsi (*Ocimum sanctum* Linn.). Indian J Physiol Pharmacol. 2011;55(4):313-31.
13. Bhattacharyya D, Sur TK, Jana U, *et al.* Controlled programmed trial of *Ocimum sanctum* leaf on generalized anxiety disorders. Nepal Med Coll J. 2008;10(3):176-9.
14. Cinatl J, Morgenstern B, Bauer G, *et al.* Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet. 2003;361(9374):2045-6.
15. Raut AA, Rege NN, Tadavi FM, *et al.* Exploratory study to evaluate tolerability, safety and activity of Ashwagandha in healthy volunteers. J Ayurveda Integr Med. 2012;3(3):111-14.
16. Verma A, Ghosh S, Pandey A, *et al. Withania somnifera* supplementation improves immune parameters in COVID-19 patients: a clinical study. Phytomedicine. 2021;93:153821.
17. Sahebkar A, Javadi B, Hatamipour M, *et al.* Curcumin: A promising adjunctive treatment for COVID-19. Phytother Res. 2021;35(3):1237-45.
18. Isbrucker RA, Burdock GA. Risk and safety assessment on the consumption of Licorice root (*Glycyrrhiza* sp.), its extract and powder as a food ingredient, with emphasis on the pharmacology and toxicology of glycyrrhizin. Regul Toxicol Pharmacol. 2006;46(3):167-92.
19. Patwardhan B, Mutalik G, Tillu G. Integrative Approaches for Health: Biomedical Research, Ayurveda and Yoga. Elsevier; 2020.
20. WHO. WHO Traditional Medicine Strategy 2014-2023. World Health Organization; 2019.
21. Ministry of AYUSH, Government of India. Ayurveda's immunity boosting measures for self-care during COVID-19 crisis. 2020. Available from: https://www.ayush.gov.in/
22. Ahmad S, Gilani SS, Akhter M, *et al.* Molecular docking and machine learning for COVID-19 therapeutics from medicinal plants. J Biomol Struct Dyn. 2021;39(11):3954-66.
23. Zhou Y, Wang F, Wang Z, *et al.* Network pharmacology to identify the mechanisms of herbal compounds in COVID-19 treatment. Phytomedicine. 2020;79:153323.
24. Chen H, Feng Y, Zhang N, *et al.* Quercetin inhibits TNF-α-induced HUVECs apoptosis via regulation of the ROS-mediated pathway. Phytother Res. 2010;24(4):595-601.
25. Ammon HP. Boswellic acids: biological actions and molecular targets. Curr Med Chem. 2016;23(2):237-61.

26. Scartezzini P, Speroni E. Review on some plants of Indian traditional medicine with antioxidant activity. J Ethnopharmacol. 2000;71(1-2):23-43.
27. James JT, Dubery IA. Pentacyclic triterpenoids from the medicinal herb, *Centella asiatica* (L.) Urban. Molecules. 2009;14(10):3922-41.
28. Leone A, Spada A, Battezzati A, *et al. Moringa oleifera* seeds and leaves: nutritional profile and health-promoting properties. J Food Sci. 2015;80(9):R1960-71.
29. Rahmani AH, Shabrmi FM, Aly SM. Active ingredients of ginger as potential candidates in the prevention and treatment of diseases via modulation of biological activities. Int J Physiol Pathophysiol Pharmacol. 2014;6(2):125-36.
30. Bouchentouf S, Missoum N. Identification of compounds from *Nigella sativa* as new potential inhibitors of 2019 Novel Coronavirus (COVID-19): Molecular docking study. ChemRxiv. 2020;preprint.

Cite this article: Sachdeva H, Sharma M, Maninder. Immunomodulatory Plants against Coronavirus: A Comprehensive Review with Emerging Insights from Artificial Intelligence and Computational Approaches. Pharmacog Rev. 2026;20(39):48-53.