

*Edited Book*

# Natural Products and Herbal Strategies

*in*

# COVID-19 and Mental Health Management

*Editors*

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# **Natural Products and Herbal Strategies in Covid- 19 and Mental Health Management**

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## Preface

The COVID-19 pandemic has reshaped global healthcare systems and highlighted the urgent need for safe, effective, and multi-target therapeutic strategies. Beyond its acute respiratory manifestations, COVID-19 has revealed complex systemic involvement, including cardiovascular, metabolic, neurological, and profound neuropsychiatric complications. In particular, the emergence of post-COVID syndrome or Long COVID has brought attention to persistent conditions such as anxiety, depression, cognitive impairment, chronic fatigue, and sleep disturbances, which continue to affect millions of individuals worldwide.

Conventional pharmacotherapy, while essential in acute management, often falls short in addressing the multifactorial and interconnected pathophysiological mechanisms underlying these long-term complications. These include chronic inflammation, oxidative stress, immune dysregulation, endothelial dysfunction, mitochondrial impairment, and neurochemical imbalance. This therapeutic gap has renewed global interest in natural products and herbal medicines as complementary and integrative approaches in disease management.

Natural products derived from medicinal plants have long been a cornerstone of traditional healing systems such as Ayurveda, Unani, Traditional Chinese Medicine, and other ethnomedical practices. Modern scientific research now increasingly validates their pharmacological potential, particularly their antiviral, anti-inflammatory, immunomodulatory, antioxidant, and neuroprotective properties. These multi-target actions make herbal agents especially suitable for complex diseases like COVID-19 and associated mental health disorders.

This edited book, *Natural Products and Herbal Strategies in COVID-19 and Mental Health Management*, brings together current scientific evidence, mechanistic insights, and translational perspectives on the role of medicinal plants and natural compounds in managing viral infections and neuropsychiatric complications. It explores phytochemicals, pharmacological mechanisms, clinical evidence, and emerging technologies such as nanoformulations, systems pharmacology, and evidence-based herbal drug development.

The objective of this volume is to bridge the gap between traditional knowledge and modern biomedical science, providing researchers, academicians, healthcare professionals, and students with a comprehensive resource on herbal strategies for COVID-19 and mental health management. It also aims to encourage further research and innovation in integrative medicine for future global health challenges.

We hope this book will serve as a valuable reference and inspire new directions in phytopharmacology and integrative therapeutic research.

### Editors

Perwez Alam

Sanmati Kumar Jain

Pratyush Mishra

Swatantr Bahadur Singh

## Acknowledgements

We express our sincere gratitude to all contributing authors for their valuable scholarly contributions, scientific insights, and dedicated efforts in shaping this edited volume, *Natural Products and Herbal Strategies in COVID-19 and Mental Health Management*. Their commitment to advancing research in natural products, pharmacology, neuropharmacology, and mental health has significantly enriched the scientific depth, interdisciplinary scope, and academic quality of this book. Each chapter reflects rigorous effort in compiling evidence-based information, mechanistic understanding, and translational perspectives relevant to post-pandemic healthcare.

We sincerely thank the reviewers and subject experts for their careful evaluation, critical appraisal, and constructive suggestions. Their thoughtful comments have greatly improved the scientific rigor, clarity, coherence, and overall presentation of the chapters included in this volume. Their expert guidance ensured that the content aligns with current advances in biomedical sciences and meets high academic and publishing standards.

We extend our heartfelt appreciation to our respective academic and research institutions for providing continuous support, infrastructure, and an intellectually stimulating environment that made the completion of this work possible. The encouragement for research activities, academic freedom, and availability of laboratory and library resources played a crucial role in the successful development of this edited book.

We also acknowledge the valuable support of colleagues, faculty members, research collaborators, and laboratory staff, whose cooperation, technical assistance, and academic discussions have contributed directly and indirectly to the preparation of this volume. Their collaborative spirit and shared scientific engagement have strengthened the conceptual foundation of this work.

We also acknowledge the support of libraries, academic databases, and open-access scientific platforms, which have provided invaluable access to up-to-date research articles, clinical studies, and review literature. These resources have been essential in ensuring that the content of this volume is evidence-based and scientifically relevant.

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Finally, we express our deepest gratitude to our families and well-wishers for their unwavering encouragement, patience, and emotional support throughout the preparation of this edited book. Their constant motivation, understanding, and belief in our academic endeavors have been a continuous source of strength and inspiration.

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## Chapter 1: Immunomodulatory and Neuroprotective Roles of *Tinosporacordifolia* and *Withaniasomnifera* in COVID-19 and Stress-Related Disorders

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### Abstract

The Coronavirus Disease 2019 (COVID-19) pandemic has created unprecedented global health challenges extending beyond respiratory complications to include immune dysregulation, neuroinflammation, oxidative stress, and psychological disturbances. Increasing evidence indicates that SARS-CoV-2 infection is associated with cytokine storms, immune imbalance, neuronal injury, anxiety, depression, cognitive dysfunction, insomnia, and long-COVID syndrome. In this context, medicinal plants possessing immunomodulatory, neuroprotective, antioxidant, and adaptogenic properties have gained significant scientific interest as complementary and integrative therapeutic approaches. This chapter comprehensively explores the immunomodulatory and neuroprotective roles of (*Guduchi/Giloy*) and (*Ashwagandha*) in COVID-19 and stress-related disorders. The ethnopharmacological significance, phytochemical composition, traditional medicinal uses, and pharmacological properties of both plants are critically discussed. Special emphasis is placed on their ability to regulate inflammatory cytokines, enhance innate and adaptive immune responses, reduce oxidative stress, modulate neuroimmune pathways, and improve stress resilience. Experimental, preclinical, and clinical evidence demonstrates that *Tinosporacordifolia* exhibits potent immunomodulatory, antioxidant, anti-inflammatory, and neuroprotective activities through enhancement of macrophage and natural killer cell function, suppression of pro-inflammatory mediators, and reduction of oxidative neuronal injury. Similarly, *Withaniasomnifera* possesses remarkable adaptogenic, anxiolytic, neuroregenerative, and immunorestorative properties mediated through regulation of the hypothalamic–pituitary–adrenal axis, neurotransmitter modulation, neurogenesis, and anti-inflammatory signaling pathways. The chapter further discusses molecular docking investigations, antiviral screening studies, neurobehavioral outcomes, clinical evidence in COVID-19 supportive care, and future therapeutic perspectives involving nanotechnology-based herbal delivery systems and integrative medicine approaches. Despite promising findings, challenges related to standardization, dosage optimization, clinical validation, and herb–drug interactions remain important considerations for future research. Overall, the combined therapeutic potential of *Tinosporacordifolia* and *Withaniasomnifera* highlights their significance as multifunctional medicinal agents for managing immune dysfunction, neuroinflammation, stress-related disorders, and post-COVID complications. Continued scientific investigation and evidence-based clinical translation may facilitate the development of safe and effective phytotherapeutic interventions for neuroimmune and viral disorders.

### Keywords

COVID-19; Immunomodulation; Neuroprotection; Oxidative stress; Cytokine storm; Adaptogens Neuroinflammation; Long-COVID; Herbal medicine; Stress-related disorders; Ayurveda; Phytotherapy; Immunity.

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## 1. Introduction

The emergence of Coronavirus Disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), created one of the greatest global public health crises in modern history. Since its initial outbreak in late 2019, COVID-19 has affected millions of individuals worldwide, leading not only to acute respiratory illness but also to prolonged systemic complications involving the immune, cardiovascular, and nervous systems (World Health Organization [WHO], 2023). Although vaccination programs and therapeutic interventions significantly reduced mortality rates, post-COVID complications and long-COVID syndrome continue to represent major healthcare challenges. Persistent fatigue, cognitive dysfunction, depression, anxiety, sleep disturbances, and neuroinflammatory manifestations have been increasingly reported among recovered patients (Nalbandian et al., 2021). The pandemic also exposed vulnerabilities in healthcare systems and emphasized the urgent need for safe, affordable, and effective therapeutic approaches capable of enhancing immunity and reducing long-term complications.

Viral infections are closely associated with immune dysregulation and inflammatory disturbances that may subsequently contribute to neurological complications. SARS-CoV-2 infection activates both innate and adaptive immune responses, leading to excessive production of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin-1 $\beta$  (IL-1 $\beta$ ), a condition commonly referred to as the “cytokine storm” (Mehta et al., 2020). Excessive cytokine release can damage multiple organs and disrupt blood–brain barrier integrity, thereby contributing to neuroinflammation and neuronal injury. Studies have demonstrated that COVID-19 patients frequently exhibit neurological manifestations including headache, anosmia, encephalopathy, cognitive decline, stroke, and neuropsychiatric symptoms (Ellul et al., 2020). Furthermore, oxidative stress generated during viral infection enhances neuronal degeneration and impairs neurotransmitter balance, thereby increasing susceptibility to neurodegenerative and stress-related disorders (Heneka et al., 2020). These findings suggest a strong interrelationship between viral pathogenesis, immune dysfunction, and neurological impairment.

Apart from direct viral effects, the COVID-19 pandemic profoundly influenced mental health worldwide. Social isolation, fear of infection, economic instability, and prolonged uncertainty significantly increased the prevalence of chronic stress, anxiety, depression, and sleep disorders (Pfefferbaum & North, 2020). Chronic stress is known to dysregulate the hypothalamic–pituitary–adrenal (HPA) axis and promote excessive cortisol secretion, which subsequently suppresses immune function and aggravates inflammatory pathways. Persistent neuroinflammation associated with stress may impair neuronal plasticity, cognition, and emotional regulation (Cohen et al., 2012). Moreover, stress-induced oxidative damage can further exacerbate immune imbalance and increase vulnerability to infectious diseases. Consequently, therapeutic agents possessing both immunomodulatory and neuroprotective properties are of considerable interest in the management of COVID-19-associated complications and stress-related disorders.

In recent years, herbal medicines and traditional medicinal systems have gained significant attention as complementary and integrative therapeutic strategies. Medicinal plants containing bioactive phytoconstituents often exhibit multitarget pharmacological actions including antioxidant, anti-inflammatory, antiviral, adaptogenic, and immunomodulatory activities (Ekor, 2014). Herbal immunomodulators and adaptogens are particularly valuable because they may help restore immune homeostasis while simultaneously protecting against stress-induced physiological disturbances. Integrative medicine approaches combining conventional therapy with evidence-based herbal interventions have therefore emerged as promising strategies for enhancing overall health outcomes during and after the pandemic.

Among various medicinal plants, and have attracted considerable scientific and clinical interest due to their broad pharmacological potential. *Tinosporacordifolia*, commonly known as Guduchi or Giloy, is an important medicinal plant in Ayurveda traditionally used for enhancing immunity, reducing fever, and improving vitality. The plant contains diverse phytoconstituents such as alkaloids, diterpenoid lactones, glycosides, and polysaccharides that contribute to its immunomodulatory, antioxidant, and anti-inflammatory properties (Sharma et al., 2019). Experimental studies have demonstrated its ability to regulate macrophage activation, enhance phagocytosis, and modulate cytokine production, thereby supporting immune defense mechanisms. Additionally, *Tinosporacordifolia* exhibits neuroprotective and cognitive-enhancing effects through reduction of oxidative stress and neuroinflammatory mediators.

Similarly, *Withaniasomnifera*, commonly known as Ashwagandha, is widely recognized as a potent adaptogenic herb in traditional Indian medicine. The plant contains biologically active withanolides and alkaloids that possess anti-stress, anxiolytic, neuroprotective, and immunoregulatory properties (Singh et al., 2011). Ashwagandha has been extensively investigated for its role in reducing cortisol levels, improving stress tolerance, enhancing memory, and protecting neuronal integrity. Recent studies also suggest that *Withaniasomnifera* may inhibit inflammatory signaling pathways and support immune resilience during viral infections. Because COVID-19 is associated with both immune dysregulation and psychological stress, the combined therapeutic potential of *Tinosporacordifolia* and *Withaniasomnifera* represents a promising area of research.

The present chapter aims to critically explore the immunomodulatory and neuroprotective roles of *Tinosporacordifolia* and *Withaniasomnifera* in the context of COVID-19 and stress-related disorders. The chapter discusses their phytochemical composition, traditional applications, mechanisms of action, and experimental as well as clinical evidence supporting their therapeutic efficacy. Special emphasis is placed on their roles in regulating immune responses, reducing neuroinflammation, combating oxidative stress, and improving mental health outcomes. Furthermore, the chapter highlights future perspectives regarding integrative medicine approaches, standardization, and clinical translation of these medicinal plants in post-pandemic healthcare management.

## 2. Ethnopharmacology, Phytochemistry, and Traditional Uses

### 2.1 Ayurvedic Significance (Guduchi/Giloy)

*Tinosporacordifolia* (Willd.) Hook. f. & Thomson, commonly known as Guduchi or Giloy, is one of the most valued medicinal plants in Ayurveda. It is categorized as a “Rasayana” drug, which refers to rejuvenating therapeutics capable of promoting longevity, vitality, disease resistance, and overall well-being (Sharma et al., 2019). Classical Ayurvedic texts describe Guduchi as “Amrita,” meaning nectar of immortality, because of its broad-spectrum healing potential and ability to restore physiological balance. Traditionally, the plant has been used for the management of fever, chronic infections, metabolic disorders, inflammatory diseases, and immune dysfunctions (Upadhyay et al., 2010).

The Ayurvedic pharmacological properties of Guduchi include Tikta (bitter) and Kashaya (astringent) rasa, Guru (heavy) guna, Ushnavirya (hot potency), and Madhuravipaka (sweet post-digestive effect). These properties collectively contribute to its immunomodulatory, detoxifying, anti-inflammatory, and rejuvenating activities. During the COVID-19 pandemic, Guduchi received considerable attention in traditional and integrative healthcare systems because of its reputed immune-enhancing and antipyretic properties.

### Botanical Description and Distribution

*Tinosporacordifolia* belongs to the family Menispermaceae. It is a large deciduous climbing shrub characterized by succulent stems, aerial roots, and heart-shaped leaves. The stem surface appears grey-brown with wart-like lenticels, while the leaves are simple, alternate, and cordate in shape. The plant bears small yellowish flowers and red drupaceous fruits (Saha & Ghosh, 2012). The plant is widely distributed throughout tropical and subtropical regions of India, Sri Lanka, Myanmar, and China. In India, it commonly grows in forests, hedges, and dry deciduous areas, especially in states such as Uttar Pradesh, Madhya Pradesh, Maharashtra, and Gujarat. Guduchi often climbs on neem trees, and Ayurvedic practitioners traditionally consider neem-associated Guduchi therapeutically superior.

### Major Phytoconstituents

The pharmacological activities of *Tinosporacordifolia* are attributed to its rich and diverse phytochemical composition. The plant contains alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoids, polysaccharides, flavonoids, and phenolic compounds (Sharma et al., 2019). Important alkaloids include magnoflorine, palmatine, and berberine, which contribute to anti-inflammatory and antimicrobial activities. Diterpenoid lactones such as tinosporide, cordifolide, and columbin exhibit immunomodulatory and antioxidant effects. Polysaccharides isolated from Guduchi have demonstrated macrophage activation and enhancement of innate immune responses. Flavonoids and phenolic compounds contribute significantly to free radical scavenging and neuroprotective actions by reducing oxidative stress and inflammatory damage.

## Traditional Therapeutic Applications

Traditionally, Guduchi has been employed in Ayurveda for the treatment of fever, diabetes, gout, rheumatoid arthritis, urinary disorders, skin diseases, and respiratory infections. It is also used as a digestive tonic, hepatoprotective agent, and rejuvenator. Several traditional formulations containing Guduchi are prescribed for enhancing immunity and combating chronic fatigue.

Modern pharmacological studies support many of these traditional claims and demonstrate antimicrobial, antidiabetic, hepatoprotective, antioxidant, anticancer, neuroprotective, and adaptogenic activities of the plant (Saha & Ghosh, 2012). Furthermore, Guduchi has shown potential in regulating cytokine release and reducing oxidative stress associated with viral infections and neuroinflammatory disorders.

## 2.2 Ayurvedic Importance (Ashwagandha)

*Withaniasomnifera* (L.) Dunal, commonly known as Ashwagandha, belongs to the family Solanaceae and is regarded as one of the most important adaptogenic herbs in Ayurveda. The term “Ashwagandha” translates to “smell of a horse,” reflecting the traditional belief that the herb imparts strength, stamina, and vitality comparable to that of a horse (Singh et al., 2011). Ashwagandha is classified as a Rasayana herb and has been extensively used for rejuvenation, stress reduction, nervous system support, and enhancement of cognitive functions. Ayurvedic medicine recommends Ashwagandha for balancing Vatadosha and improving physical as well as mental resilience. Due to its adaptogenic and immunomodulatory properties, Ashwagandha gained significant popularity during the COVID-19 pandemic for managing stress, anxiety, sleep disturbances, and immune suppression.

## Botanical Characteristics and Geographical Distribution

*Withaniasomnifera* is a small woody shrub that grows up to 35–75 cm in height. The plant possesses ovate leaves, greenish-yellow flowers, and orange-red berries enclosed within a papery calyx. Its roots are thick, cylindrical, and light brown in color, which constitute the most therapeutically important part of the plant. Ashwagandha is native to India, the Middle East, and parts of Africa. It is extensively cultivated in dry subtropical regions of India, particularly in Rajasthan, Madhya Pradesh, Punjab, Uttar Pradesh, and Gujarat. The plant thrives in sandy and well-drained soils under dry climatic conditions (Mirjalili et al., 2009).

## Key Bioactive Compounds

The pharmacological activities of Ashwagandha are mainly associated with steroidal lactones known as withanolides. Important withanolides include withaferin A, withanolide D, and withanone, which exhibit anti-inflammatory, antioxidant, anticancer, and neuroprotective effects (Singh et al., 2011). Other important constituents include sitoindosides, alkaloids, steroidal saponins, flavonoids, and amino acids. Withanolides are known to modulate inflammatory signaling pathways, inhibit oxidative damage, and improve neuronal survival. Sitoindosides contribute to adaptogenic and anti-stress activities by regulating cortisol levels and enhancing resistance to stress-induced physiological alterations.

## Traditional Uses in Stress, Immunity, and Neurological Disorders

Ashwagandha has traditionally been used to manage stress, anxiety, insomnia, fatigue, infertility, muscular weakness, and age-related debility. In Ayurvedic medicine, it is considered a “MedhyaRasayana,” a category of herbs used to improve memory, intellect, and cognitive functions. Scientific studies have demonstrated that Ashwagandha possesses anxiolytic, antidepressant, neuroprotective, immunomodulatory, and anti-inflammatory properties (Chandrasekhar et al., 2012). The herb has shown efficacy in reducing cortisol levels, improving sleep quality, enhancing cognitive performance, and protecting neurons against oxidative stress-induced degeneration. Additionally, Ashwagandha may support immune resilience by modulating cytokine production and enhancing natural killer cell activity.

### 2.3 Comparative Phytochemical and Pharmacological Profile

Although *Tinosporacordifolia* and *Withaniasomnifera* belong to different botanical families, both plants exhibit remarkable similarities in their pharmacological actions, particularly in immune regulation, antioxidant defense, stress adaptation, and neuroprotection. However, differences in phytochemical composition contribute to distinct therapeutic mechanisms and clinical applications.

**Table 1. Comparative Phytochemical and Pharmacological Profile of *Tinosporacordifolia* and *Withaniasomnifera***

Parameter	<i>Tinosporacordifolia</i> (Guduchi/Giloy)	<i>Withaniasomnifera</i> (Ashwagandha)
Family	Menispermaceae	Solanaceae
Major Traditional Classification	Rasayana	Rasayana and MedhyaRasayana
Main Bioactive Constituents	Alkaloids, diterpenoid lactones, glycosides, polysaccharides, flavonoids	Withanolides, sitoindosides, alkaloids, steroidal lactones
Principal Pharmacological Activities	Immunomodulatory, antipyretic, anti-inflammatory, antioxidant, hepatoprotective	Adaptogenic, anxiolytic, neuroprotective, anti-inflammatory, immunomodulatory
Primary Therapeutic Targets	Immune dysfunction, fever, inflammatory disorders, metabolic diseases	Stress, anxiety, neurodegeneration, fatigue, cognitive impairment
Immunological Effects	Enhances macrophage activation, phagocytosis, cytokine modulation	Regulates stress-induced immune suppression and cytokine balance
Neuroprotective Mechanisms	Reduces oxidative stress and neuroinflammation	Improves neuronal survival, neurogenesis, and synaptic plasticity
Role in COVID-19 Context	Immune enhancement and inflammatory regulation	Stress reduction and neuroimmune support

Major Traditional Uses	Fever, diabetes, arthritis, infections, immunity enhancement	Stress, insomnia, weakness, aging, cognitive disorders
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The synergistic therapeutic potential of Guduchi and Ashwagandha is particularly relevant in COVID-19 and stress-related disorders because both herbs target interconnected pathological pathways involving oxidative stress, inflammation, immune dysfunction, and neurodegeneration. Guduchi primarily acts as a potent immunomodulator and anti-inflammatory agent, whereas Ashwagandha exhibits strong adaptogenic and neuroprotective effects. Together, these herbs may provide complementary benefits by simultaneously strengthening immune defenses, reducing cytokine-mediated inflammation, improving stress tolerance, and protecting neuronal integrity.

The combined use of these medicinal plants in Ayurvedic formulations may therefore offer a holistic therapeutic strategy for managing post-viral fatigue, anxiety, neuroinflammation, and immune imbalance. Nevertheless, further clinical investigations and mechanistic studies are required to validate their synergistic efficacy, optimize dosage regimens, and establish standardized therapeutic protocols for integrative healthcare applications.

### 3. Immunomodulatory Mechanisms in COVID-19 Management

#### 3.1 Immune Dysregulation in COVID-19

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, is characterized not only by respiratory complications but also by profound immune dysregulation and systemic inflammation. In severe cases, uncontrolled immune activation contributes significantly to disease progression, multiorgan dysfunction, neurological complications, and mortality (Mehta et al., 2020). The interaction between viral replication and host immune responses determines the clinical severity of infection. While an effective immune response is essential for viral clearance, excessive or dysregulated activation of inflammatory pathways may produce detrimental effects on tissues and organs.

#### Cytokine Storm and Inflammatory Cascades

One of the most critical pathological features of severe COVID-19 is the “cytokine storm,” which refers to an uncontrolled release of pro-inflammatory cytokines and chemokines. Elevated levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), interferon-gamma (IFN- $\gamma$ ), and C-reactive protein (CRP) have been associated with severe pulmonary inflammation, acute respiratory distress syndrome (ARDS), vascular injury, and multiorgan failure (Huang et al., 2020).

The excessive inflammatory response activates nuclear factor-kappa B (NF- $\kappa$ B) and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways, leading to amplification of inflammatory cascades and recruitment of immune cells into infected tissues. Hyperactivation of macrophages and neutrophils further contributes to tissue destruction through the release of reactive oxygen species (ROS), proteolytic enzymes, and inflammatory mediators. Persistent inflammation may also disrupt blood-brain barrier integrity, contributing to neuroinflammation and neurological manifestations associated with COVID-19 (Heneka et al., 2020).

## Oxidative Stress and Immune Imbalance

Oxidative stress plays a central role in COVID-19 pathogenesis. Viral infection induces excessive production of reactive oxygen species and reactive nitrogen species, which damage lipids, proteins, and nucleic acids while impairing mitochondrial function (Delgado-Roche & Mesta, 2020). Elevated oxidative stress further activates inflammatory signaling pathways, thereby creating a vicious cycle between inflammation and oxidative injury.

In severe COVID-19, antioxidant defense systems such as glutathione, catalase, and superoxide dismutase become depleted, leading to immune imbalance and cellular dysfunction. Oxidative stress also contributes to endothelial injury, thrombosis, neuronal damage, and chronic fatigue observed in long-COVID syndrome. Consequently, therapeutic agents possessing antioxidant and immunomodulatory activities are considered promising adjuncts in COVID-19 management.

## Innate and Adaptive Immune Responses

The innate immune system acts as the first line of defense against SARS-CoV-2 infection. Pattern recognition receptors such as Toll-like receptors detect viral components and stimulate the production of interferons and inflammatory cytokines. Macrophages, dendritic cells, neutrophils, and natural killer (NK) cells participate actively in antiviral defense during the early phase of infection (Vabret et al., 2020).

Adaptive immunity involves activation of T lymphocytes and B lymphocytes. CD4+ T helper cells coordinate immune responses, while CD8+ cytotoxic T cells eliminate virus-infected cells. B cells produce neutralizing antibodies against viral antigens. However, severe COVID-19 is frequently associated with lymphopenia, impaired T-cell responses, and exhaustion of immune cells, resulting in defective viral clearance and prolonged inflammation (Tay et al., 2020). Therefore, restoring immune homeostasis without excessive immune activation is a major therapeutic objective in COVID-19 treatment.

## 3.2 Immunomodulatory Actions of *Tinosporacordifolia*

### Enhancement of Macrophage and NK Cell Activity

*Tinosporacordifolia* (Guduchi/Giloy) is widely recognized for its potent immunomodulatory properties in traditional and modern medicine. Experimental studies demonstrate that Guduchi enhances macrophage activation, phagocytic activity, nitric oxide production, and antigen presentation, thereby strengthening innate immune defense mechanisms (Sharma et al., 2019).

Polysaccharides and alkaloids present in Guduchi stimulate natural killer (NK) cell activity and improve host resistance against microbial and viral infections. Enhanced NK cell function may facilitate elimination of virus-infected cells and support early antiviral immunity during SARS-CoV-2 infection. Guduchi also promotes leukocyte proliferation and improves overall immune surveillance.

## Regulation of Pro-inflammatory Cytokines

Several studies have reported that *Tinosporacordifolia* regulates inflammatory cytokines involved in cytokine storm syndrome. Bioactive constituents such as tinosporide, cordifolide, magnoflorine, and berberine suppress excessive production of IL-6, TNF- $\alpha$ , and IL-1 $\beta$  by inhibiting NF- $\kappa$ B-mediated inflammatory signaling pathways (Saha& Ghosh, 2012).

This cytokine-modulating activity is particularly important in COVID-19 because excessive inflammatory responses contribute significantly to pulmonary injury and systemic complications. By balancing immune activation and inflammatory suppression, Guduchi may help prevent progression from mild infection to severe inflammatory disease.

## Antioxidant and Anti-inflammatory Pathways

Guduchi exhibits strong antioxidant activity through scavenging of reactive oxygen species and enhancement of endogenous antioxidant enzymes including superoxide dismutase, catalase, and glutathione peroxidase. These antioxidant effects reduce oxidative tissue damage and improve cellular resilience during viral infection (Upadhyay et al., 2010).

In addition, Guduchi suppresses cyclooxygenase (COX) and lipoxygenase pathways, thereby reducing inflammatory mediator synthesis. Reduction of oxidative stress and inflammation may contribute to protection against endothelial dysfunction, pulmonary injury, and neuroinflammatory complications associated with COVID-19.

## Experimental and Clinical Evidence in Viral Infections

Experimental studies have demonstrated antiviral and immunomodulatory activities of *Tinosporacordifolia* against various infectious conditions. Molecular docking investigations suggest that certain phytoconstituents may interact with viral proteins involved in SARS-CoV-2 replication and entry processes. Clinical observations during the COVID-19 pandemic also indicated beneficial effects of Guduchi-based formulations in improving immune status and reducing symptom severity, although large-scale controlled clinical trials remain limited.

### 3.3 Immunomodulatory Actions of *Withaniasomnifera*

#### Adaptogenic and Immunorestorative Effects

*Withaniasomnifera* (Ashwagandha) is a well-established adaptogenic herb known for its ability to restore physiological homeostasis under stress conditions. Chronic stress and elevated cortisol levels suppress immune function and increase susceptibility to infections. Ashwagandha counteracts stress-induced immune suppression by regulating hypothalamic–pituitary–adrenal (HPA) axis activity and lowering cortisol levels (Chandrasekhar et al., 2012).

The herb also improves overall immune resilience by enhancing leukocyte counts, macrophage activity, and antibody responses. These immunorestorative effects are particularly relevant in COVID-19 patients experiencing stress-induced immune dysfunction and post-viral fatigue.

### **Modulation of Stress-Induced Immune Suppression**

Psychological stress significantly impairs immune competence through glucocorticoid-mediated suppression of lymphocyte proliferation and cytokine imbalance. Ashwagandha contains withanolides and sitoindosides that modulate neuroendocrine pathways and reduce stress-associated inflammatory damage.

Studies have shown that Ashwagandha improves stress tolerance, reduces anxiety, and enhances adaptive immune responses. By attenuating stress-mediated immune suppression, the herb may indirectly improve resistance to viral infections and accelerate recovery during post-COVID conditions.

### **Effects on T-cell Proliferation and Cytokine Regulation**

Ashwagandha has demonstrated stimulatory effects on T-cell proliferation, B-cell activation, and antibody production. Withanolides regulate inflammatory cytokines by suppressing IL-6, TNF- $\alpha$ , and CRP while promoting balanced immune responses (Vetvicka&Vetvickova, 2011).

The herb also modulates Th1/Th2 immune balance and improves cellular immunity. Such immunoregulatory actions may help prevent immune exhaustion and excessive inflammatory activation observed in severe COVID-19 cases.

### **Potential Antiviral and Anti-inflammatory Mechanisms**

Recent computational and experimental studies suggest that withanolides may interfere with SARS-CoV-2 entry and replication mechanisms. Withaferin A and withanone have shown potential interactions with viral spike proteins and main proteases involved in viral infectivity. Additionally, Ashwagandha suppresses inflammatory pathways including NF- $\kappa$ B and reduces oxidative stress-induced tissue injury.

Its combined antiviral, anti-inflammatory, anxiolytic, and neuroprotective properties make Ashwagandha a promising candidate for integrative COVID-19 management and recovery support.

## **3.4 Combined Therapeutic Potential in COVID-19**

### **Herbal Synergy and Polyherbal Approaches**

The combined use of *Tinosporacordifolia* and *Withaniasomnifera* may provide synergistic therapeutic benefits because both herbs target multiple interconnected pathological pathways involved in COVID-19. Guduchi primarily enhances innate immunity and suppresses inflammatory cytokines, whereas Ashwagandha predominantly acts as an adaptogen and neuroimmune regulator.

Their combined administration may therefore improve immune competence, reduce cytokine-mediated tissue damage, alleviate oxidative stress, and enhance psychological resilience simultaneously. Polyherbal formulations containing these herbs have traditionally been used in Ayurveda for respiratory infections, chronic fatigue, inflammatory disorders, and immune support.

### Role in Prevention, Recovery, and Long-COVID Management

Both medicinal plants may play supportive roles during different stages of COVID-19. During the preventive phase, their immunomodulatory effects may enhance host defense mechanisms. During active infection, anti-inflammatory and antioxidant properties may help regulate cytokine storm and oxidative injury. In post-COVID recovery, adaptogenic and neuroprotective actions may reduce fatigue, anxiety, cognitive impairment, and stress-related complications.

Long-COVID syndrome is often associated with persistent inflammation, immune imbalance, mitochondrial dysfunction, and neuropsychiatric symptoms. The combined antioxidant and immunoregulatory effects of Guduchi and Ashwagandha may therefore contribute to improved recovery outcomes and restoration of physiological balance.

**Table 2. Comparative Immunomodulatory Mechanisms of *Tinosporacordifolia* and *Withaniasomnifera* in COVID-19 Management**

Parameter	<i>Tinosporacordifolia</i>	<i>Withaniasomnifera</i>
Primary Pharmacological Nature	Immunomodulator	Adaptogen and Immunorestorative Agent
Major Active Constituents	Tinosporide, cordifolide, magnoflorine, polysaccharides	Withanolides, withaferin A, withanone, sitoindosides
Main Immune Targets	Macrophages, NK cells, cytokine pathways	T lymphocytes, stress-mediated immune pathways
Cytokine Regulation	Reduces IL-6, TNF- $\alpha$ , IL-1 $\beta$	Balances IL-6, TNF- $\alpha$ , CRP, Th1/Th2 cytokines
Antioxidant Actions	Enhances glutathione and antioxidant enzymes	Reduces cortisol-induced oxidative stress
Anti-inflammatory Mechanisms	NF- $\kappa$ B inhibition, COX suppression	NF- $\kappa$ B modulation and stress-mediated inflammation reduction
Neuroimmune Effects	Reduces neuroinflammation and oxidative neuronal injury	Improves stress tolerance, cognition, and neuroprotection
Potential COVID-19 Benefits	Immune enhancement and cytokine regulation	Stress reduction, immune recovery, antiviral support
Role in Long-COVID	Fatigue reduction and immune restoration	Anxiety reduction and cognitive recovery
Therapeutic Strength	Strong innate immune modulation	Strong adaptogenic and neuroprotective action

## Safety Considerations and Dosage Perspectives

Although both herbs are generally considered safe when used appropriately, excessive or unsupervised consumption may lead to adverse effects. Guduchi has occasionally been associated with hepatotoxicity in susceptible individuals, particularly when consumed in inappropriate formulations or excessive doses. Ashwagandha may cause gastrointestinal discomfort, sedation, or thyroid stimulation in sensitive patients.

Standardization of herbal preparations, quality control, dosage optimization, and evaluation of herb–drug interactions are essential for safe clinical application. Further multicentric randomized controlled trials are needed to establish definitive therapeutic efficacy and evidence-based dosage recommendations for COVID-19 and long-COVID management.

## 4. Neuroprotective and Anti-Stress Effects

### 4.1 Neurological and Psychological Consequences of COVID-19

Although COVID-19 was initially recognized as a respiratory illness, accumulating evidence demonstrates that SARS-CoV-2 significantly affects the central nervous system (CNS) and mental health. Neurological manifestations observed in COVID-19 patients include headache, dizziness, anosmia, encephalopathy, stroke, seizures, cognitive impairment, and neuropsychiatric complications (Ellul et al., 2020). These complications may arise through direct viral invasion, immune-mediated neuroinflammation, vascular dysfunction, and oxidative stress-induced neuronal injury.

### Neuroinflammation and Oxidative Neuronal Injury

Neuroinflammation represents one of the major pathological mechanisms underlying neurological complications associated with COVID-19. SARS-CoV-2 infection activates systemic inflammatory pathways that increase circulating levels of pro-inflammatory cytokines such as IL-6, TNF- $\alpha$ , and IL-1 $\beta$ . These cytokines can cross the blood–brain barrier or disrupt its integrity, thereby activating microglial cells and astrocytes within the CNS (Heneka et al., 2020).

Activated microglia release reactive oxygen species (ROS), nitric oxide, and inflammatory mediators that contribute to neuronal degeneration and synaptic dysfunction. Excessive oxidative stress impairs mitochondrial function, promotes lipid peroxidation, and damages neuronal proteins and nucleic acids. Persistent neuroinflammation and oxidative injury may therefore contribute to cognitive decline, memory disturbances, fatigue, and neurodegenerative changes observed in post-COVID conditions (Boldrini et al., 2021).

### Anxiety, Depression, Insomnia, and Cognitive Dysfunction

The psychological burden of the COVID-19 pandemic significantly increased the prevalence of anxiety disorders, depression, sleep disturbances, emotional stress, and cognitive dysfunction worldwide. Social isolation, fear of infection, economic instability, prolonged hospitalization, and uncertainty regarding the future contributed substantially to mental health deterioration (Pfefferbaum & North, 2020).

Many COVID-19 survivors experience persistent neuropsychiatric symptoms including “brain fog,” reduced concentration, impaired memory, chronic fatigue, and insomnia. Neurochemical imbalance, inflammatory cytokines, and HPA axis dysregulation play important roles in these conditions. Elevated cortisol and chronic stress may further impair hippocampal neuronal function and synaptic plasticity, leading to emotional and cognitive disturbances.

### **Stress-Related Disorders Associated with Pandemic Conditions**

Chronic stress associated with pandemic conditions triggered significant neuroendocrine and immune alterations. Stress activates the hypothalamic–pituitary–adrenal (HPA) axis, resulting in increased secretion of cortisol and catecholamines. Persistent elevation of stress hormones suppresses immune competence, increases oxidative stress, and enhances inflammatory signaling pathways (Cohen et al., 2012).

Long-term psychological stress may predispose individuals to depression, generalized anxiety disorder, post-traumatic stress disorder (PTSD), sleep disturbances, and neurodegenerative disorders. Therefore, therapeutic interventions capable of simultaneously reducing stress, regulating neuroinflammation, and protecting neuronal integrity are of considerable importance in post-pandemic healthcare management.

## **4.2 Neuroprotective Role of *Tinosporacordifolia***

### **Antioxidant Defense and Neuronal Protection**

*Tinosporacordifolia* (Guduchi/Giloy) possesses potent antioxidant and neuroprotective properties attributed to its alkaloids, diterpenoid lactones, flavonoids, and phenolic compounds. Experimental studies have demonstrated that Guduchi enhances endogenous antioxidant defense systems including superoxide dismutase, catalase, and glutathione, thereby reducing oxidative neuronal damage (Sharma et al., 2019).

The herb protects neuronal cells against reactive oxygen species-induced injury and inhibits lipid peroxidation in neural tissues. By reducing oxidative stress and inflammatory mediator release, Guduchi may prevent neuronal apoptosis and preserve synaptic function under pathological conditions associated with viral infections and chronic stress.

### **Cholinergic Modulation and Cognitive Enhancement**

Cognitive dysfunction and memory impairment are often associated with cholinergic deficits and oxidative neuronal damage. Studies suggest that *Tinosporacordifolia* may improve cognitive performance through modulation of cholinergic neurotransmission and enhancement of acetylcholine availability in the brain (Upadhyay et al., 2010).

Guduchi has demonstrated nootropic activity in experimental models by improving learning ability, memory retention, and behavioral performance. Reduction of neuroinflammation and oxidative stress further contributes to improved neuronal signaling and cognitive function. These properties may be particularly relevant in managing post-COVID cognitive impairment and neuroinflammatory conditions.

## Experimental Evidence in Neurodegenerative and Stress Models

Several experimental investigations have demonstrated the neuroprotective effects of Guduchi in models of neurodegeneration, stress, and cognitive dysfunction. Animal studies have shown that Guduchi extract reduces stress-induced biochemical alterations, improves behavioral parameters, and protects against neuronal degeneration.

Additionally, Guduchi has shown beneficial effects in experimental models of Parkinson's disease, Alzheimer's disease, and ischemic neuronal injury through antioxidant and anti-inflammatory mechanisms. The herb's immunomodulatory actions may also contribute indirectly to neuroprotection by suppressing cytokine-mediated neuronal inflammation.

### 4.3 Neuroprotective Role of *Withaniasomnifera*

#### Adaptogenic and Anxiolytic Effects

*Withaniasomnifera* (Ashwagandha) is widely recognized for its adaptogenic and anxiolytic properties. Adaptogens are substances capable of enhancing the body's resistance to physical, emotional, and environmental stress. Ashwagandha improves stress tolerance and reduces anxiety by regulating neuroendocrine and neurotransmitter pathways (Chandrasekhar et al., 2012).

Clinical studies have demonstrated that Ashwagandha supplementation significantly reduces stress scores, anxiety levels, and sleep disturbances while improving overall psychological well-being. The herb also exhibits sedative and mood-stabilizing properties that may help alleviate pandemic-associated mental health disorders.

#### Modulation of the HPA Axis and Cortisol Levels

The hypothalamic–pituitary–adrenal (HPA) axis plays a central role in stress responses. Chronic activation of the HPA axis results in excessive cortisol secretion, which negatively affects immune function, neuronal survival, and emotional regulation.

Ashwagandha has been shown to normalize HPA axis activity and reduce circulating cortisol levels. Withanolides and sitoindosides present in the plant modulate stress signaling pathways and improve neuroendocrine balance (Singh et al., 2011). Reduction of cortisol-mediated oxidative stress may contribute significantly to improved mental resilience and neuronal protection.

#### Neurogenesis, Synaptic Plasticity, and Memory Enhancement

Ashwagandha exhibits remarkable neuroregenerative properties. Experimental studies demonstrate that withanolides stimulate neurite outgrowth, synaptic reconstruction, and neuronal regeneration. The herb enhances hippocampal neurogenesis and improves synaptic plasticity, which are essential for learning, memory, and emotional regulation (Kuboyama et al., 2005).

Ashwagandha also improves cognitive performance by modulating cholinergic and GABAergic neurotransmission while reducing oxidative neuronal injury. These effects may help reverse memory impairment, cognitive dysfunction, and concentration difficulties observed in post-COVID syndrome.

### **Evidence in Depression, Anxiety, and Neurodegenerative Diseases**

Numerous experimental and clinical studies support the efficacy of Ashwagandha in anxiety disorders, depression, insomnia, and neurodegenerative diseases. The herb demonstrates antidepressant-like activity comparable to conventional anxiolytic agents in some experimental models.

Additionally, Ashwagandha has shown neuroprotective potential in Alzheimer's disease, Parkinson's disease, Huntington's disease, and stress-induced neuronal injury through antioxidant, anti-inflammatory, and antiapoptotic mechanisms (Kulkarni & Dhir, 2008). These findings suggest its promising therapeutic value in managing neuropsychiatric and neurodegenerative complications associated with COVID-19.

### **4.4 Mechanistic Insights**

The neuroprotective and anti-stress effects of *Tinosporacordifolia* and *Withaniasomnifera* involve multiple interconnected molecular and cellular mechanisms. These herbs act on inflammatory pathways, oxidative stress responses, mitochondrial integrity, neurotransmitter regulation, and neuroimmune interactions.

#### **Anti-inflammatory Signaling Pathways**

Both medicinal plants suppress inflammatory signaling pathways implicated in neurodegeneration and stress-induced neuronal injury. Guduchi and Ashwagandha inhibit activation of NF- $\kappa$ B, cyclooxygenase (COX), inducible nitric oxide synthase (iNOS), and pro-inflammatory cytokines including IL-6 and TNF- $\alpha$  (Heneka et al., 2020).

Reduction of inflammatory signaling decreases microglial activation and limits neuronal damage associated with cytokine-mediated neurotoxicity. These mechanisms are particularly important in COVID-19-associated neuroinflammation and long-COVID neurological complications.

#### **Mitochondrial Protection and Reduction of Oxidative Stress**

Mitochondrial dysfunction is a major contributor to neuronal degeneration and fatigue-related disorders. Both Guduchi and Ashwagandha enhance mitochondrial antioxidant defense systems and reduce ROS generation. Improvement of mitochondrial membrane stability and ATP production helps preserve neuronal viability and cellular energy metabolism.

Their antioxidant phytoconstituents also prevent lipid peroxidation, DNA damage, and apoptosis induced by oxidative stress. Such mitochondrial protective effects may improve recovery from viral-induced neurotoxicity and chronic stress.

## Regulation of Neurotransmitters and Neuroimmune Interactions

Neurotransmitter imbalance plays a major role in anxiety, depression, cognitive dysfunction, and stress-related disorders. Ashwagandha modulates GABAergic, serotonergic, and cholinergic neurotransmission, thereby improving mood stability, memory, and emotional regulation. Guduchi also contributes to cholinergic enhancement and cognitive support.

Both herbs influence neuroimmune interactions by regulating cytokine release and reducing neuroinflammatory responses. Their combined neuroimmune-modulating properties may therefore provide significant therapeutic benefits in stress-associated neurological complications and post-COVID cognitive disorders.

**Table 3. Neuroprotective and Anti-Stress Mechanisms of *Tinosporacordifolia* and *Withaniasomnifera***

Parameter	<i>Tinosporacordifolia</i>	<i>Withaniasomnifera</i>
Major Neuroactive Constituents	Alkaloids, flavonoids, diterpenoid lactones	Withanolides, sitoindosides, steroidal lactones
Primary Neuroprotective Action	Antioxidant and anti-inflammatory neuroprotection	Adaptogenic and neuroregenerative activity
Oxidative Stress Modulation	Enhances glutathione, catalase, SOD	Reduces cortisol-induced oxidative damage
Effects on Neuroinflammation	Suppresses IL-6, TNF- $\alpha$ , microglial activation	Inhibits NF- $\kappa$ B and inflammatory cytokines
Cognitive Effects	Memory enhancement and cholinergic support	Neurogenesis and synaptic plasticity improvement
Neurotransmitter Modulation	Cholinergic modulation	GABAergic, serotonergic, and cholinergic modulation
Stress-Related Effects	Reduces stress-induced oxidative injury	Decreases anxiety, cortisol, and HPA overactivation
Evidence in Neurological Disorders	Parkinsonism, cognitive dysfunction, stress models	Alzheimer's disease, anxiety, depression, neurodegeneration
Relevance in Long-COVID	Cognitive support and neuroinflammation reduction	Stress recovery and emotional stabilization

## 5. Experimental, Preclinical, and Clinical Evidence

### 5.1 In Vitro Studies

In vitro investigations play a critical role in evaluating the antiviral, immunomodulatory, antioxidant, and neuroprotective potential of medicinal plants before their translation into animal and clinical studies. Both *Tinosporacordifolia* and *Withaniasomnifera* have been extensively studied in cellular and molecular models to understand their therapeutic relevance in COVID-19 and stress-associated disorders.

## Antiviral and Immunomodulatory Screening

Several *in vitro* studies have demonstrated that *Tinosporacordifolia* possesses broad-spectrum immunomodulatory and antimicrobial activities. Extracts of Guduchi have shown the ability to stimulate macrophage activation, enhance phagocytosis, and regulate cytokine production in cultured immune cells (Sharma et al., 2019). Polysaccharide fractions isolated from the plant significantly increase nitric oxide production and improve innate immune responses, suggesting potential antiviral benefits.

Similarly, *Withaniasomnifera* exhibits potent anti-inflammatory and immunoregulatory properties in cellular models. Withanolides derived from Ashwagandha suppress inflammatory cytokines such as IL-6, TNF- $\alpha$ , and IL-1 $\beta$  while modulating immune signaling pathways including NF- $\kappa$ B and JAK/STAT pathways (Singh et al., 2011). Cell culture studies also demonstrate antioxidant protection against oxidative stress-induced neuronal injury.

During the COVID-19 pandemic, several researchers evaluated the antiviral potential of these medicinal plants against SARS-CoV-2. Extracts and phytoconstituents from Guduchi and Ashwagandha demonstrated inhibitory effects on inflammatory responses associated with viral infection and showed potential immunomodulatory activities capable of reducing cytokine-mediated damage.

## Molecular Docking and Mechanistic Investigations

Molecular docking and computational studies emerged as important approaches during the pandemic for identifying phytochemicals capable of interacting with SARS-CoV-2 proteins. Several investigations demonstrated that bioactive constituents of Ashwagandha, particularly withanone and withaferin A, may interact with viral spike proteins, angiotensin-converting enzyme 2 (ACE2) receptors, and SARS-CoV-2 main proteases involved in viral entry and replication (Balkrishna et al., 2020).

Similarly, diterpenoid lactones and alkaloids from *Tinosporacordifolia* showed promising binding affinities toward viral targets involved in replication and host inflammatory responses. Computational studies also suggest that these phytoconstituents may reduce viral infectivity while simultaneously modulating immune pathways.

Mechanistic investigations further revealed that both herbs regulate oxidative stress pathways, inflammatory mediators, mitochondrial dysfunction, and apoptosis-related signaling. Such multitarget actions make them promising candidates for integrative therapeutic strategies against COVID-19 and associated neuroinflammatory disorders.

## 5.2 In Vivo Experimental Studies

### Animal Models of Viral Infection and Stress Disorders

Animal studies provide important evidence regarding the pharmacological efficacy and mechanistic actions of medicinal plants under physiological conditions. Numerous *in vivo* studies have demonstrated the immunomodulatory, neuroprotective, anti-inflammatory, and adaptogenic properties of Guduchi and Ashwagandha.

Experimental models of viral infection have shown that *Tinosporacordifolia* enhances immune competence by stimulating macrophage function, increasing leukocyte counts, and improving antibody responses (Upadhyay et al., 2010). The plant also reduces inflammatory tissue injury and oxidative stress associated with infection-induced immune activation.

Ashwagandha has been extensively evaluated in animal models of chronic stress, anxiety, depression, neurodegeneration, and immune suppression. Administration of Ashwagandha extract significantly improves stress tolerance, reduces cortisol levels, and attenuates behavioral abnormalities induced by chronic stress (Kulkarni & Dhir, 2008).

In neurodegenerative disease models, Ashwagandha demonstrates protective effects against neuronal degeneration, oxidative damage, and cognitive impairment. Experimental evidence also indicates that both herbs may improve mitochondrial function and reduce neuroinflammatory responses associated with viral infections and stress disorders.

### Neurobehavioral and Immunological Outcomes

Behavioral studies indicate that Ashwagandha improves learning, memory, motor coordination, sleep quality, and anxiety-related behavior in animal models. Neurochemical analyses reveal modulation of GABAergic, cholinergic, and serotonergic neurotransmission, contributing to anxiolytic and antidepressant-like effects.

Guduchi has similarly demonstrated cognitive-enhancing and neuroprotective effects in experimental studies. Improvement in memory retention, reduction of oxidative neuronal injury, and suppression of inflammatory cytokines have been reported in stress and neurotoxicity models.

Immunological investigations further demonstrate enhancement of natural killer (NK) cell activity, T-cell proliferation, cytokine balance, and antioxidant enzyme levels following administration of these herbs. These findings support their potential use in managing immune dysfunction, stress-associated disorders, and post-viral complications.

**Table 4. Experimental and Preclinical Evidence of *Tinosporacordifolia* and *Withaniasomnifera***

Study Area	<i>Tinosporacordifolia</i>	<i>Withaniasomnifera</i>
In Vitro Immunomodulation	Enhances macrophage activation and cytokine regulation	Modulates IL-6, TNF- $\alpha$ , NF- $\kappa$ B pathways
Antiviral Investigations	Potential inhibition of inflammatory viral responses	Withanolides show interaction with SARS-CoV-2 targets
Antioxidant Activity	Reduces ROS and lipid peroxidation	Protects neurons against oxidative stress
Animal Stress Models	Reduces oxidative and inflammatory damage	Improves stress tolerance and reduces anxiety
Neuroprotective Effects	Cognitive enhancement and neuronal protection	Neurogenesis and synaptic reconstruction
Immunological Outcomes	Enhanced NK cell activity and	Improved T-cell proliferation and

	leukocyte function	immune resilience
Behavioral Outcomes	Improved memory and cognitive performance	Reduced depression, anxiety, and insomnia
Mechanistic Pathways	Antioxidant and cytokine regulation	HPA axis modulation and anti-inflammatory effects

### 5.3 Clinical Trials and Human Studies

#### Clinical Evidence in COVID-19 Supportive Care

During the COVID-19 pandemic, traditional medicinal systems including Ayurveda gained attention as complementary healthcare approaches. Several clinical studies evaluated the supportive role of Guduchi and Ashwagandha in improving immunity, reducing stress, and promoting recovery in COVID-19 patients. Clinical observations suggested that Guduchi-based formulations may reduce fever duration, fatigue, and inflammatory symptoms while improving immune responses in mild-to-moderate COVID-19 cases. Some studies also reported improved recovery rates and reduced symptom severity when Guduchi was used as an adjunct to conventional therapy (Ayush Ministry, 2021). Ashwagandha supplementation has been investigated for improving stress resilience, reducing anxiety, enhancing sleep quality, and supporting immune function during the pandemic. Clinical studies demonstrated reductions in cortisol levels, stress scores, and fatigue among participants receiving Ashwagandha extracts (Chandrasekhar et al., 2012). Such adaptogenic effects may be beneficial in post-COVID recovery and long-COVID syndrome.

#### Studies Related to Stress, Anxiety, Cognition, and Immunity

Numerous human studies support the efficacy of Ashwagandha in reducing anxiety, depression, chronic stress, insomnia, and cognitive impairment. Randomized controlled trials demonstrated improvements in cognitive flexibility, memory, attention, and psychological well-being following Ashwagandha supplementation. Guduchi has also shown promising effects in improving immune competence, reducing inflammatory markers, and supporting overall health. Some clinical investigations indicate beneficial effects in chronic fever, allergic conditions, metabolic disorders, and stress-associated immune dysfunction. Collectively, these studies suggest that Guduchi and Ashwagandha may provide complementary benefits in managing neuroimmune disturbances, psychological stress, and inflammatory complications associated with COVID-19.

#### Limitations and Challenges in Clinical Translation

Despite encouraging findings, several limitations restrict the clinical translation of these medicinal plants. Many available studies involve small sample sizes, short treatment durations, lack of placebo controls, and variability in herbal formulations. Differences in extraction methods, phytochemical standardization, dosage regimens, and study design complicate comparison among studies.

Another major challenge involves the limited availability of large-scale multicentric randomized controlled trials evaluating efficacy specifically in COVID-19 patients. Furthermore, mechanistic understanding of herb–drug interactions and long-term safety profiles remains incomplete.

Standardization of herbal products and evidence-based clinical guidelines are therefore essential for broader medical acceptance.

#### 5.4 Safety, Toxicity, and Herb–Drug Interactions

##### Toxicological Evaluation

Both *Tinosporacordifolia* and *Withaniasomnifera* are generally considered safe when administered at recommended therapeutic doses. Acute and subchronic toxicity studies in animals have demonstrated relatively low toxicity profiles for standardized extracts of these plants.

However, isolated reports have suggested possible hepatotoxicity associated with excessive or inappropriate use of Guduchi formulations in susceptible individuals. The exact mechanisms remain unclear and may involve contamination, adulteration, or immune-mediated reactions rather than the plant itself (Philips et al., 2021).

Ashwagandha is generally well tolerated, although mild adverse effects including gastrointestinal discomfort, nausea, sedation, and headache have occasionally been reported. High doses may influence thyroid hormone activity and should therefore be used cautiously in patients with thyroid disorders.

##### Contraindications and Precautions

Patients with autoimmune disorders, severe hepatic disease, pregnancy, or concurrent immunosuppressive therapy should use these herbal products cautiously and under medical supervision. Because both herbs influence immune function, careful monitoring may be necessary in individuals receiving immunomodulatory medications.

Ashwagandha may potentiate sedative drugs and thyroid medications, whereas Guduchi may interact with antidiabetic and immunosuppressive agents. Standardized dosage recommendations and pharmacovigilance monitoring are therefore essential for safe therapeutic application.

##### Regulatory Perspectives

The growing global interest in herbal medicine has increased the need for stringent regulatory frameworks regarding quality control, standardization, and safety evaluation. Regulatory authorities including the World Health Organization (WHO) and national AYUSH agencies emphasize the importance of scientific validation, Good Manufacturing Practices (GMP), phytochemical standardization, and toxicity assessment for herbal products. Future integration of Guduchi and Ashwagandha into evidence-based clinical practice requires harmonized regulatory guidelines, robust clinical evidence, and comprehensive safety monitoring systems.

**Table 5. Clinical and Safety Profile of *Tinosporacordifolia* and *Withaniasomnifera***

Parameter	<i>Tinosporacordifolia</i>	<i>Withaniasomnifera</i>
Clinical Applications	Immune support, inflammatory	Stress reduction, anxiety,

	disorders, fever management	cognition, immune support
COVID-19 Relevance	Supportive immunomodulatory therapy	Adaptogenic and psychological support
Evidence from Human Studies	Improved immune responses and symptom relief	Reduced cortisol, anxiety, and fatigue
Major Therapeutic Strength	Immune regulation and antioxidant defense	Neuroprotection and stress resilience
Common Adverse Effects	Rare hepatotoxicity, gastrointestinal discomfort	Mild sedation, nausea, gastrointestinal symptoms
Potential Drug Interactions	Antidiabetic and immunosuppressive drugs	Sedatives, thyroid medications
Contraindications	Severe liver disease, autoimmune disorders	Hyperthyroidism, pregnancy (high doses)
Regulatory Considerations	Need for standardization and quality control	Standardized extract validation required

## 6. Emerging Therapeutic Perspectives and Future Directions

The growing scientific evidence supporting the immunomodulatory, neuroprotective, adaptogenic, and anti-inflammatory properties of *Tinosporacordifolia* and *Withaniasomnifera* has generated considerable interest in their future therapeutic applications. The COVID-19 pandemic highlighted the urgent need for safe, multitarget, and integrative therapeutic strategies capable of addressing not only viral infection but also associated immune dysfunction, neuroinflammation, psychological stress, and long-term post-viral complications. In this context, these medicinal plants represent promising candidates for future translational and clinical research.

### 6.1 Role in Integrative and Personalized Medicine

Modern healthcare increasingly recognizes the importance of integrative medicine approaches that combine conventional therapies with scientifically validated traditional medicines. Since COVID-19 involves complex interactions among immune, neurological, metabolic, and psychological systems, multitarget herbal therapeutics may offer complementary benefits alongside standard medical care.

*Tinosporacordifolia* and *Withaniasomnifera* possess broad pharmacological actions capable of simultaneously regulating immune responses, reducing oxidative stress, alleviating neuroinflammation, and improving stress tolerance. Such pleiotropic activities are especially valuable in long-COVID syndrome, where patients often present with fatigue, cognitive dysfunction, anxiety, sleep disturbances, and persistent inflammatory symptoms (Nalbandian et al., 2021).

Personalized medicine approaches may further enhance the therapeutic utility of these medicinal plants. Individual variability in immune responses, stress susceptibility, metabolic status, and genetic background may influence therapeutic outcomes. Integration of traditional Ayurvedic constitutional concepts with modern precision medicine could therefore contribute to individualized herbal interventions for neuroimmune disorders and post-viral recovery.

## 6.2 Nanoformulations and Advanced Herbal Delivery Systems

One of the major limitations associated with herbal therapeutics involves poor bioavailability, instability of phytoconstituents, limited blood–brain barrier penetration, and inconsistent pharmacokinetic profiles. Advanced drug delivery systems and nanotechnology-based formulations may help overcome these challenges. Nanoformulations such as nanoparticles, liposomes, phytosomes, nanoemulsions, and solid lipid nanoparticles have demonstrated potential for improving solubility, stability, controlled release, and targeted delivery of herbal bioactive compounds (Rai et al., 2016). Encapsulation of withanolides and Guduchi phytoconstituents within nanocarriers may significantly enhance their neuroprotective and immunomodulatory efficacy. Particularly in neurological disorders, nanotechnology may improve blood–brain barrier permeability and facilitate targeted delivery of phytochemicals to inflamed neural tissues. Such approaches may prove highly beneficial in managing neuroinflammation, oxidative neuronal injury, and cognitive dysfunction associated with COVID-19 and chronic stress.

## 6.3 Potential Combination Therapies with Conventional Drugs

Combination therapy approaches involving medicinal plants and conventional pharmaceuticals are emerging as promising strategies in infectious and neuroinflammatory disorders. Guduchi and Ashwagandha may complement conventional antiviral, anti-inflammatory, anxiolytic, or neuroprotective therapies by enhancing immune resilience and reducing oxidative damage. Ashwagandha's adaptogenic effects may help reduce psychological stress and improve quality of life in patients undergoing prolonged pharmacological treatment, while Guduchi may contribute to immune restoration and inflammatory regulation. Their antioxidant properties may also reduce drug-induced oxidative stress and tissue injury. However, combination therapy requires careful scientific evaluation because herb–drug interactions may alter pharmacokinetic and pharmacodynamic responses. Future investigations should therefore focus on synergistic efficacy, safety assessment, dosage optimization, and mechanistic interactions between herbal phytoconstituents and conventional drugs.

## 6.4 Future Prospects in Neuroimmune Disorders and Pandemic Preparedness

The relationship between immune dysregulation and neurological disorders has become increasingly evident in recent years. Chronic neuroinflammation and oxidative stress contribute significantly to neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and depression (Heneka et al., 2020). Since Guduchi and Ashwagandha modulate both immune and neuronal pathways, their therapeutic applications may extend beyond COVID-19 into broader neuroimmune and neurodegenerative conditions.

Future pandemic preparedness strategies may also incorporate evidence-based herbal immunomodulators as supportive healthcare measures. Traditional medicinal plants with proven safety and multitarget pharmacological actions could help strengthen population-level immune resilience during emerging infectious outbreaks.

Furthermore, increasing global interest in plant-based therapeutics may encourage development of standardized phytopharmaceutical products, nutraceuticals, and preventive healthcare formulations derived from Guduchi and Ashwagandha.

### 6.5 Need for Standardization, Biomarkers, and Multicentric Trials

Despite promising experimental and clinical evidence, several challenges continue to limit the widespread clinical acceptance of herbal therapeutics. Variability in phytochemical composition due to geographical, seasonal, and processing differences significantly affects therapeutic consistency and reproducibility.

Standardization of herbal extracts based on validated biomarkers and bioactive compounds is therefore essential for ensuring quality, efficacy, and safety. Identification of reliable pharmacological biomarkers may also facilitate monitoring of therapeutic responses in immune and neurological disorders.

Large-scale multicentric randomized controlled trials are urgently needed to establish evidence-based therapeutic protocols for Guduchi and Ashwagandha in COVID-19, long-COVID syndrome, stress-related disorders, and neurodegenerative diseases. Future studies should emphasize:

- Standardized extract formulations
- Pharmacokinetic and pharmacodynamic evaluation
- Long-term safety assessment
- Herb–drug interaction studies
- Mechanistic molecular investigations
- Precision medicine approaches
- Comparative efficacy trials

Integration of artificial intelligence, systems biology, metabolomics, and network pharmacology may further accelerate discovery of novel therapeutic mechanisms and optimized herbal combinations.

**Table 6. Emerging Therapeutic Perspectives of *Tinosporacordifolia* and *Withaniasomnifera***

Emerging Area	<i>Tinosporacordifolia</i>	<i>Withaniasomnifera</i>	Future Significance
Integrative Medicine	Immune restoration and anti-inflammatory support	Stress reduction and neuroprotection	Complementary management of COVID-19 and long-COVID
Personalized Medicine	Individualized immune modulation	Personalized adaptogenic therapy	Precision herbal therapeutics
Nanoformulations	Enhanced delivery of polysaccharides and alkaloids	Improved bioavailability of withanolides	Better CNS targeting and efficacy
Neuroimmune Disorders	Neuroinflammation suppression	Neuroregeneration and synaptic support	Potential in neurodegenerative diseases
Combination Therapies	Adjunct	Adjunct anxiolytic and	Improved

	immunomodulatory support	adaptogenic support	multidimensional treatment outcomes
Long-COVID Management	Reduction of fatigue and inflammatory imbalance	Improvement of cognition and emotional health	Holistic post-COVID rehabilitation
Future Pandemic Preparedness	Population immune resilience	Stress adaptation and mental resilience	Preventive healthcare strategies
Research Priorities	Standardization and mechanistic validation	Clinical efficacy and safety trials	Evidence-based translational medicine

## 7. Conclusion

The COVID-19 pandemic emphasized the complex interrelationship between viral infection, immune dysregulation, oxidative stress, neuroinflammation, and psychological disturbances. Although SARS-CoV-2 primarily affects the respiratory system, increasing scientific evidence demonstrates its profound impact on neurological and mental health. Persistent inflammatory responses, cytokine storms, oxidative neuronal injury, chronic stress, anxiety, depression, cognitive dysfunction, and long-COVID syndrome have emerged as major post-pandemic healthcare challenges (Nalbandian et al., 2021). Consequently, there is an urgent need for therapeutic strategies capable of simultaneously regulating immune responses, reducing neuroinflammation, protecting neuronal integrity, and improving psychological resilience.

In this context, *Tinosporacordifolia* and *Withaniasomnifera* represent highly promising medicinal plants with broad-spectrum pharmacological potential. *Tinosporacordifolia* demonstrates potent immunomodulatory, antioxidant, anti-inflammatory, and neuroprotective activities through enhancement of macrophage and natural killer cell function, regulation of cytokine production, suppression of oxidative stress, and reduction of inflammatory signaling pathways (Sharma et al., 2019). These properties may contribute significantly to the management of cytokine-mediated inflammatory complications and immune imbalance associated with COVID-19.

Similarly, *Withaniasomnifera* possesses remarkable adaptogenic, anxiolytic, neuroregenerative, and immunorestorative properties. By modulating hypothalamic–pituitary–adrenal (HPA) axis activity, reducing cortisol levels, improving neurotransmitter balance, and promoting neurogenesis, Ashwagandha may effectively alleviate stress-induced neuroimmune dysfunctions and cognitive impairment (Singh et al., 2011). Its anti-inflammatory and antioxidant mechanisms further support neuronal protection against oxidative and inflammatory damage associated with viral infections and chronic stress conditions.

Experimental, preclinical, and clinical investigations collectively support the therapeutic relevance of these medicinal plants in COVID-19 supportive care and stress-associated disorders. Their multitarget pharmacological actions may provide synergistic benefits in reducing inflammatory cytokines, enhancing antioxidant defenses, restoring immune homeostasis, improving cognitive function, and promoting emotional stability. Such integrated neuroimmune modulation is particularly important in long-COVID syndrome, where persistent fatigue, anxiety, depression, insomnia, and cognitive dysfunction continue to affect patient quality of life.

The scientific significance of integrating traditional medicinal systems with modern therapeutics has gained substantial recognition during and after the pandemic. Traditional Ayurvedic knowledge offers valuable insights into holistic disease management through the use of Rasayana herbs such as Guduchi and Ashwagandha. Modern biomedical research increasingly validates many of these traditional claims through molecular, pharmacological, and clinical investigations. Integration of traditional medicine with evidence-based modern healthcare may therefore provide safer, affordable, and more comprehensive therapeutic approaches for complex multifactorial disorders involving immune and neurological pathways.

Despite promising findings, several challenges remain regarding standardization, phytochemical characterization, dosage optimization, herb–drug interaction assessment, and large-scale clinical validation. Future research should focus on multicentric randomized controlled trials, advanced herbal delivery systems, biomarker-guided therapeutic monitoring, systems biology approaches, and molecular mechanistic studies. Development of standardized phytopharmaceutical formulations and integration of nanotechnology-based delivery systems may further enhance the therapeutic efficacy and clinical applicability of these medicinal plants.

In conclusion, *Tinosporacordifolia* and *Withaniasomnifera* possess substantial therapeutic potential as multifunctional medicinal agents capable of modulating immune responses, protecting neuronal function, reducing oxidative stress, and improving stress resilience. Their emerging role in integrative medicine and post-pandemic healthcare highlights the importance of continued scientific exploration and clinical translation. Future evidence-based research may facilitate the development of novel phytotherapeutic interventions for COVID-19, long-COVID syndrome, neuroinflammatory disorders, and stress-related diseases.

## References

- Ayush Ministry. (2021). *Ayurveda interventions for COVID-19 management*. Government of India, Ministry of AYUSH.
- Balkrishna, A., Pokhrel, S., Singh, H., Joshi, M., Mulay, V. P., Haldar, S., & Varshney, A. (2020). Withanone from *Withania somnifera* as a potential drug for COVID-19 treatment. *Journal of Biomolecular Structure and Dynamics*, 39(17), 6355–6368.
- Boldrini, M., Canoll, P. D., & Klein, R. S. (2021). How COVID-19 affects the brain. *JAMA Psychiatry*, 78(6), 682–683.
- Chandrasekhar, K., Kapoor, J., & Anishetty, S. (2012). A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of Ashwagandha root in reducing stress and anxiety in adults. *Indian Journal of Psychological Medicine*, 34(3), 255–262.
- Cohen, S., Janicki-Deverts, D., & Miller, G. E. (2012). Psychological stress and disease. *JAMA*, 298(14), 1685–1687.
- Delgado-Roche, L., & Mesta, F. (2020). Oxidative stress as key player in severe acute respiratory syndrome coronavirus (SARS-CoV) infection. *Archives of Medical Research*, 51(5), 384–387.
- Ekor, M. (2014). The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. *Frontiers in Pharmacology*, 4, 177.

- Ellul, M. A., Benjamin, L., Singh, B., Lant, S., Michael, B. D., Easton, A., ... Solomon, T. (2020). Neurological associations of COVID-19. *The Lancet Neurology*, 19(9), 767–783.
- Heneka, M. T., Golenbock, D., Latz, E., Morgan, D., & Brown, R. (2020). Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. *Alzheimer's Research & Therapy*, 12(1), 69.
- Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., ... Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, 395(10223), 497–506.
- Kuboyama, T., Tohda, C., & Komatsu, K. (2005). Neuritic regeneration and synaptic reconstruction induced by *Withania somnifera* in cortical neurons. *NeuroReport*, 16(16), 1801–1805.
- Kulkarni, S. K., & Dhir, A. (2008). *Withania somnifera*: An Indian ginseng. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 32(5), 1093–1105.
- Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., & Manson, J. J. (2020). COVID-19: Consider cytokine storm syndromes and immunosuppression. *The Lancet*, 395(10229), 1033–1034.
- Mirjalili, M. H., Moyano, E., Bonfill, M., Cusido, R. M., & Palazón, J. (2009). Steroidal lactones from *Withania somnifera*, an ancient plant for novel medicine. *Molecules*, 14(7), 2373–2393.
- Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M. V., McGroder, C., Stevens, J. S., ... Wan, E. Y. (2021). Post-acute COVID-19 syndrome. *Nature Medicine*, 27(4), 601–615.
- Pfefferbaum, B., & North, C. S. (2020). Mental health and the COVID-19 pandemic. *New England Journal of Medicine*, 383(6), 510–512.
- Philips, C. A., Ahamed, R., Augustine, P., Rajesh, S., George, T., Mohanan, M., & Nair, D. C. (2021). Liver injury associated with the use of *Tinospora cordifolia* during the COVID-19 pandemic. *Clinical and Experimental Hepatology*, 7(1), 26–31.
- Rai, M., Ingle, A. P., Pandit, R., Paralikar, P., Anasane, N., Santos, C. A., & Duran, N. (2016). Nanotechnology-based anti-infectives and therapeutics. *Biotechnology Advances*, 34(5), 847–859.
- Saha, S., & Ghosh, S. (2012). *Tinospora cordifolia*: One plant, many roles. *Ancient Science of Life*, 31(4), 151–159.
- Sharma, P., Dwivedee, B. P., Bisht, D., Dash, A. K., & Kumar, D. (2019). The chemical constituents and diverse pharmacological importance of *Tinospora cordifolia*. *Heliyon*, 5(9), e02437.
- Singh, N., Bhalla, M., de Jager, P., & Gilca, M. (2011). An overview on Ashwagandha: A Rasayana (rejuvenator) of Ayurveda. *African Journal of Traditional, Complementary and Alternative Medicines*, 8(5 Suppl), 208–213.
- Tay, M. Z., Poh, C. M., Rénia, L., MacAry, P. A., & Ng, L. F. P. (2020). The trinity of COVID-19: Immunity, inflammation and intervention. *Nature Reviews Immunology*, 20(6), 363–374.
- Upadhyay, A. K., Kumar, K., Kumar, A., & Mishra, H. S. (2010). *Tinospora cordifolia* (Willd.) Hook. f. and Thoms. (Guduchi) – Validation of the Ayurvedic pharmacology through experimental and clinical studies. *International Journal of Ayurveda Research*, 1(2), 112–121.
- Vabret, N., Britton, G. J., Gruber, C., Hegde, S., Kim, J., Kuksin, M., ... Sinai Immunology Review Project. (2020). Immunology of COVID-19: Current state of the science. *Immunity*, 52(6), 910–941.

- Vetvicka, V., & Vetvickova, J. (2011). Immune enhancing effects of *Withania somnifera* (Ashwagandha). *Annals of Translational Medicine*, 3(9), 127.
- World Health Organization. (2023). *Coronavirus disease (COVID-19) pandemic*. Geneva: World Health Organization.

## Chapter 2: Antiviral and Anxiolytic Potential of *Andrographis paniculata* and *Glycyrrhiza glabra* Against SARS-CoV-2

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### Abstract

The Coronavirus Disease 2019 (COVID-19) pandemic caused by SARS-CoV-2 has emerged as a major global health crisis affecting not only the respiratory system but also immune, neurological, and psychological health. In addition to acute viral infection, COVID-19 is associated with excessive inflammatory responses, oxidative stress, immune dysregulation, anxiety, depression, insomnia, cognitive dysfunction, and long-COVID syndrome. Despite advances in antiviral therapies and vaccination programs, limitations related to drug resistance, adverse effects, accessibility, and management of neuropsychiatric complications have increased interest in medicinal plants with multitarget pharmacological activities. This chapter critically explores the antiviral and anxiolytic potential of *Andrographis paniculata* and *Glycyrrhiza glabra* against SARS-CoV-2 infection and stress-associated disorders. The ethnopharmacological significance, phytochemical composition, traditional medicinal applications, and pharmacological activities of both plants are comprehensively discussed. Special emphasis is placed on their antiviral, anti-inflammatory, antioxidant, immunomodulatory, neuroprotective, and anxiolytic properties relevant to COVID-19 management. *Andrographis paniculata*, rich in andrographolide and related diterpenoids, exhibits significant antiviral and immunomodulatory activities through inhibition of viral replication, suppression of inflammatory cytokines, and regulation of oxidative stress pathways. Molecular docking studies suggest potential interactions of andrographolide with SARS-CoV-2 viral proteins and host receptors involved in viral entry and replication. Additionally, the plant demonstrates neuroprotective and stress-relieving effects through modulation of inflammatory mediators and neurotransmitter pathways. Similarly, *Glycyrrhiza glabra* contains biologically active compounds such as glycyrrhizin, flavonoids, and saponins that exhibit antiviral, anti-inflammatory, antioxidant, and anxiolytic effects. Glycyrrhizin has shown inhibitory activity against several viral pathogens, including coronaviruses, through interference with viral attachment, replication, and inflammatory signaling. Furthermore, *Glycyrrhiza glabra* contributes to stress reduction and neuroprotection through regulation of the hypothalamic–pituitary–adrenal axis, neurotransmitter modulation, and attenuation of oxidative neuronal injury. The chapter also reviews in vitro, in vivo, preclinical, and clinical studies evaluating the efficacy of these medicinal plants in viral infections, immune dysfunction, anxiety disorders, and post-COVID complications. Emerging therapeutic perspectives including nanoformulations, integrative medicine approaches, and phytopharmaceutical development are discussed. Although existing evidence highlights considerable therapeutic promise, challenges related to standardization, clinical validation, safety evaluation, and herb–drug interactions remain important areas for future investigation. Overall, *Andrographis paniculata* and *Glycyrrhiza glabra* represent promising multifunctional medicinal agents with potential applications in COVID-19 supportive care, neuroimmune regulation, stress management, and post-viral recovery. Continued scientific research and evidence-based clinical translation may facilitate the development of novel phytotherapeutic strategies for viral and stress-related disorders.

### Keywords

COVID-19; SARS-CoV-2; *Andrographis paniculata*; *Glycyrrhiza glabra*; Antiviral activity; Anxiolytic activity; Neuroprotection; Immunomodulation; Oxidative stress; Cytokine storm; Herbal medicine; Adaptogens; Neuroinflammation; Long-COVID; Phytotherapy.

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## 1. Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged as one of the most devastating global public health emergencies in recent history. Since its initial outbreak in Wuhan, China, in late 2019, COVID-19 rapidly spread worldwide, resulting in millions of infections, deaths, economic instability, and long-term healthcare challenges (World Health Organization [WHO], 2022). The pandemic not only overwhelmed healthcare systems but also exposed the vulnerability of global medical infrastructure in managing rapidly evolving infectious diseases. Although vaccination campaigns and antiviral therapies significantly reduced mortality rates, the persistence of viral variants, long-COVID syndrome, and post-infection complications continue to present major therapeutic challenges.

SARS-CoV-2 primarily targets the respiratory system through interaction with angiotensin-converting enzyme 2 (ACE2) receptors expressed on host cells. Viral entry and replication initiate inflammatory and immune responses that may lead to acute respiratory distress syndrome (ARDS), pneumonia, endothelial dysfunction, thrombosis, and multiorgan injury (Huang et al., 2020). However, increasing scientific evidence demonstrates that COVID-19 extends beyond respiratory pathology and significantly affects neurological and psychological health. Neuroinvasion, systemic inflammation, oxidative stress, cytokine storms, and disruption of the blood–brain barrier contribute to neurological complications including headache, dizziness, encephalopathy, anosmia, cognitive dysfunction, seizures, and cerebrovascular abnormalities (Ellul et al., 2020).

In addition to neurological manifestations, the COVID-19 pandemic triggered an unprecedented rise in anxiety, depression, insomnia, chronic stress, and post-traumatic stress disorder across populations worldwide. Social isolation, fear of infection, prolonged lockdowns, economic insecurity, loss of family members, and uncertainty regarding the future significantly affected mental health (Pfefferbaum & North, 2020). Furthermore, post-COVID neuropsychiatric disorders, often associated with persistent inflammation and neuroimmune dysregulation, emerged as critical long-term complications affecting quality of life. Long-COVID patients frequently experience fatigue, cognitive impairment (“brain fog”), sleep disturbances, mood instability, and emotional distress even months after viral recovery (Nalbandian et al., 2021). These observations highlight the close relationship between viral infection, immune dysfunction, oxidative stress, and neuropsychological disturbances.

Despite considerable advances in antiviral drug development and supportive therapies, conventional pharmacological approaches exhibit several limitations including adverse effects, limited accessibility, viral resistance, high treatment costs, and inadequate management of stress-related complications. Many antiviral agents primarily target viral replication but may not effectively address associated inflammatory, oxidative, neurological, and psychological manifestations. Consequently, there is growing scientific and clinical interest in complementary and integrative therapeutic approaches involving medicinal plants with multitarget pharmacological activities.

Medicinal plants possessing antiviral, anti-inflammatory, antioxidant, immunomodulatory, and anxiolytic properties have gained substantial attention during and after the COVID-19 pandemic. Traditional medicinal systems such as Ayurveda, Traditional Chinese Medicine, and Unani medicine have long

utilized herbal formulations for respiratory infections, immune enhancement, stress reduction, and neurological disorders. Several medicinal plants contain bioactive phytochemicals capable of modulating inflammatory pathways, regulating immune responses, inhibiting viral replication, reducing oxidative stress, and improving neuropsychological health (Ang et al., 2020). Such multitarget therapeutic actions make herbal medicines promising candidates for supportive management of COVID-19 and post-pandemic stress-associated disorders.

Among these medicinal plants, *Andrographis paniculata* and *Glycyrrhiza glabra* have attracted considerable scientific interest because of their well-documented antiviral and anxiolytic properties. *Andrographis paniculata*, commonly known as “King of Bitters,” is widely used in Ayurveda and Traditional Chinese Medicine for the treatment of fever, respiratory infections, inflammation, and immune disorders. Its major bioactive constituent, andrographolide, exhibits potent antiviral, anti-inflammatory, antioxidant, and immunomodulatory activities (Hossain et al., 2021). Computational and experimental studies suggest that andrographolide may interfere with SARS-CoV-2 replication and inflammatory signaling pathways involved in COVID-19 pathology.

Similarly, *Glycyrrhiza glabra* (Licorice) is an important medicinal herb traditionally used for respiratory ailments, gastrointestinal disorders, inflammatory diseases, and stress-associated conditions. Glycyrrhizin, the principal active constituent of licorice, demonstrates broad-spectrum antiviral activity against several viral pathogens including coronaviruses (Cinatl et al., 2003). In addition to antiviral effects, *Glycyrrhiza glabra* exhibits anti-inflammatory, antioxidant, neuroprotective, and anxiolytic activities through modulation of neurotransmitter systems, stress hormones, and inflammatory mediators. These properties may be particularly beneficial in managing neuroimmune complications and psychological disturbances associated with COVID-19.

The rationale for selecting *Andrographis paniculata* and *Glycyrrhiza glabra* for this chapter is based on their dual therapeutic potential in combating viral infection and stress-related disorders. Both medicinal plants possess multitarget pharmacological actions that may contribute to antiviral defense, immune regulation, reduction of cytokine-mediated inflammation, oxidative stress suppression, neuroprotection, and psychological stabilization. Their extensive use in traditional medicine and growing scientific validation further support their relevance in integrative healthcare strategies.

Therefore, this chapter aims to comprehensively review the antiviral and anxiolytic potential of *Andrographis paniculata* and *Glycyrrhiza glabra* against SARS-CoV-2 and stress-associated disorders. The chapter discusses their ethnopharmacology, phytochemistry, antiviral mechanisms, anxiolytic and neuroprotective effects, experimental and clinical evidence, safety considerations, and future therapeutic prospects. Particular emphasis is placed on their relevance in COVID-19 supportive care, long-COVID management, neuroimmune regulation, and integrative medicine approaches. By integrating traditional medicinal knowledge with modern scientific evidence, this chapter seeks to provide a comprehensive understanding of the therapeutic significance of these medicinal plants in contemporary healthcare.

## 2. Ethnopharmacology, Phytochemistry, and Traditional Uses

### 2.1 *Andrographis paniculata*

#### Ayurvedic and Traditional Importance

*Andrographis paniculata* (Burm. f.) Wall. ex Nees, commonly known as “Kalmegh” or “King of Bitters,” is an important medicinal herb extensively used in Ayurveda, Traditional Chinese Medicine (TCM), Siddha, and various folk medicinal systems. In Ayurveda, Kalmegh is traditionally classified as a bitter tonic and febrifuge with significant therapeutic value in fever, liver disorders, respiratory diseases, infections, and inflammatory conditions (Hossain et al., 2021). Traditional healers have long used the plant for enhancing immunity, detoxification, and restoring physiological balance during infectious illnesses.

In Traditional Chinese Medicine, *Andrographis paniculata* is known for its “heat-clearing” and detoxifying properties and is widely employed in upper respiratory tract infections, influenza, sore throat, and febrile disorders. Folk medicinal practices across India, China, Thailand, and Southeast Asia also utilize the herb for malaria, gastrointestinal disturbances, microbial infections, and fatigue-related conditions.

The plant gained renewed scientific interest during the COVID-19 pandemic because of its potent antiviral, anti-inflammatory, antioxidant, and immunomodulatory activities. Traditionally, Kalmegh formulations have been administered in fever and respiratory illnesses because of their ability to reduce inflammation, support immune responses, and alleviate symptoms associated with infectious diseases.

#### Botanical Description and Distribution

*Andrographis paniculata* belongs to the family Acanthaceae and is an annual herbaceous plant characterized by slender dark green stems, lanceolate leaves, and small white flowers with purple markings. The plant generally grows up to 30–110 cm in height and possesses an intensely bitter taste due to the presence of diterpenoid lactones.

Taxonomically, the plant is classified as follows:

- Kingdom: Plantae
- Family: Acanthaceae
- Genus: *Andrographis*
- Species: *Andrographis paniculata*

The herb is widely distributed in tropical and subtropical regions of Asia including India, Sri Lanka, China, Malaysia, Indonesia, and Thailand. In India, it is extensively cultivated in states such as Uttar Pradesh, Tamil Nadu, Kerala, and West Bengal. The plant thrives in humid climatic conditions with well-drained soil and moderate rainfall (Akbar, 2011).

## Major Phytoconstituents

The pharmacological properties of *Andrographis paniculata* are mainly attributed to its diverse bioactive phytochemicals, particularly diterpenoid lactones and flavonoids.

### *Andrographolide*

Andrographolide is the principal diterpenoid lactone and the major pharmacologically active constituent of the plant. It exhibits significant antiviral, anti-inflammatory, antioxidant, hepatoprotective, immunomodulatory, and neuroprotective activities. Experimental and computational studies suggest that andrographolide may inhibit viral replication and inflammatory signaling pathways associated with SARS-CoV-2 infection (Enmozhi et al., 2021).

### *Diterpenoids*

In addition to andrographolide, the plant contains neoandrographolide, deoxyandrographolide, andrograpanin, and other diterpenoid compounds. These constituents contribute to antimicrobial, antipyretic, antioxidant, and immunostimulatory activities.

### *Flavonoids*

The herb contains flavonoids such as apigenin, luteolin, and quercetin derivatives that possess antioxidant and anti-inflammatory properties. These compounds help reduce oxidative stress and cellular injury associated with viral infections and chronic inflammation.

### *Polyphenols and Lactones*

Various polyphenolic compounds and lactones present in the plant contribute to free radical scavenging activity, immune regulation, and protection against inflammatory tissue damage.

## Traditional Therapeutic Applications

Historically, *Andrographis paniculata* has been used for a wide range of therapeutic purposes in traditional medicine.

### *Antipyretic and Anti-inflammatory Uses*

Kalmegh is traditionally recognized as a potent antipyretic herb and is commonly administered in fever, influenza, malaria, and inflammatory disorders. Its bitter diterpenoids suppress inflammatory mediators and help reduce pyrexia and tissue inflammation.

### *Respiratory Tract Infections and Immune Enhancement*

The plant is widely used in respiratory tract infections including bronchitis, sore throat, common cold, influenza, and cough. Traditional formulations containing Kalmegh are believed to improve immune

competence and resistance against microbial infections. Modern studies support its immunomodulatory role through enhancement of macrophage activity and cytokine regulation.

### ***Stress and Fatigue Management***

Traditional medicinal systems also recommend *Andrographis paniculata* in fatigue, weakness, and stress-associated disorders. Its antioxidant and adaptogenic properties may contribute to improved physiological resilience and recovery during illness.

## **2.2 Glycyrrhiza glabra**

### **Traditional and Medicinal Significance**

*Glycyrrhiza glabra* L., commonly known as Licorice or Mulethi, is one of the oldest medicinal plants used in Ayurveda, Unani, Traditional Chinese Medicine, and Middle Eastern herbal systems. The plant is highly valued because of its demulcent, anti-inflammatory, antiviral, expectorant, and rejuvenating properties (Pastorino et al., 2018).

In Ayurveda, Mulethi is classified as a Rasayana herb and is used to strengthen respiratory health, improve immunity, enhance vocal quality, and reduce inflammatory disorders. In Traditional Chinese Medicine, licorice is frequently incorporated into herbal formulations as a harmonizing agent because of its synergistic effects and ability to reduce toxicity of other herbs.

Historically, *Glycyrrhiza glabra* has been used in respiratory illnesses, gastric ulcers, liver disorders, cough, bronchitis, sore throat, and inflammatory diseases. During previous coronavirus outbreaks, glycyrrhizin attracted scientific attention because of its antiviral activity against SARS-associated coronaviruses (Cinatl et al., 2003).

### **Botanical Characteristics and Distribution**

*Glycyrrhiza glabra* belongs to the family Fabaceae and is a perennial herb with extensive underground stolons and roots. The plant grows up to 1–1.5 meters in height and bears pinnate leaves, purple to pale blue flowers, and flattened seed pods.

Taxonomic classification includes:

- Kingdom: Plantae
- Family: Fabaceae
- Genus: *Glycyrrhiza*
- Species: *Glycyrrhiza glabra*

The plant is native to Southern Europe, Central Asia, and the Mediterranean region but is now cultivated in India, China, Russia, Iran, Afghanistan, and parts of the Middle East. In India, licorice cultivation occurs mainly in Punjab, Haryana, and Jammu & Kashmir under suitable climatic conditions.

## **Key Bioactive Compounds**

The medicinal properties of licorice are attributed to various triterpenoid saponins, flavonoids, and phenolic compounds.

### ***Glycyrrhizin***

Glycyrrhizin is the principal active triterpenoid saponin responsible for the sweet taste and major pharmacological activities of licorice. It exhibits antiviral, anti-inflammatory, hepatoprotective, antioxidant, and immunomodulatory effects. Glycyrrhizin has shown inhibitory activity against SARS-associated coronaviruses and may interfere with viral replication and inflammatory responses (Cinatl et al., 2003).

### ***Liquiritigenin***

Liquiritigenin is a flavonoid compound possessing antioxidant, anxiolytic, estrogenic, and neuroprotective activities. It contributes to modulation of neurotransmitter systems and reduction of oxidative neuronal damage.

### ***Flavonoids and Saponins***

Licorice contains numerous flavonoids including glabridin, liquiritin, and isoliquiritin along with triterpenoid saponins that exhibit anti-inflammatory, antioxidant, antimicrobial, and neuroprotective effects.

### ***Isoliquiritigenin***

Isoliquiritigenin demonstrates anti-inflammatory, antioxidant, antiviral, and antidepressant-like activities. Studies suggest its role in neuroprotection through suppression of oxidative stress and inflammatory signaling pathways.

## **Traditional Therapeutic Applications**

### ***Cough, Bronchitis, and Viral Infections***

Licorice has long been used as an expectorant and soothing agent in cough, bronchitis, sore throat, asthma, and respiratory infections. Its antiviral and anti-inflammatory activities contribute to relief of respiratory tract irritation and immune support.

### ***Anti-inflammatory and Gastroprotective Uses***

Traditional medicine extensively employs licorice in gastric ulcers, gastritis, inflammatory bowel disorders, and liver diseases. Glycyrrhizin and flavonoids help reduce inflammation and protect mucosal tissues against oxidative injury.

### *Anxiety, Stress, and Neuroprotective Applications*

Licorice is also traditionally used for fatigue, stress, weakness, and nervous disorders. Experimental studies indicate that licorice flavonoids may regulate neurotransmitters, reduce stress-induced oxidative damage, and improve cognitive and emotional functions.

### **2.3 Comparative Phytochemical and Pharmacological Profile**

Both *Andrographis paniculata* and *Glycyrrhiza glabra* possess broad-spectrum pharmacological activities relevant to viral infections, inflammation, oxidative stress, and neuropsychological disorders. However, their mechanisms of action and dominant phytochemical classes differ considerably.

*Andrographis paniculata* is primarily rich in diterpenoid lactones, especially andrographolide, which strongly modulates inflammatory signaling pathways, viral replication mechanisms, and immune responses. Conversely, *Glycyrrhiza glabra* predominantly contains triterpenoid saponins and flavonoids, particularly glycyrrhizin, which exhibits antiviral, mucoprotective, anti-inflammatory, and anxiolytic activities.

Despite these differences, both medicinal plants demonstrate significant antioxidant, immunomodulatory, antiviral, and neuroprotective effects. Their multitarget therapeutic actions suggest potential synergistic applications in COVID-19 supportive care, respiratory infections, stress-associated disorders, and post-viral complications.

**Table 1. Comparative Phytochemical and Pharmacological Profile of *Andrographis paniculata* and *Glycyrrhiza glabra***

Parameter	<i>Andrographis paniculata</i>	<i>Glycyrrhiza glabra</i>
Traditional Name	Kalmegh, King of Bitters	Mulethi, Licorice
Major Traditional Systems	Ayurveda, TCM, Folk Medicine	Ayurveda, Unani, TCM
Major Bioactive Compounds	Andrographolide, diterpenoids, flavonoids	Glycyrrhizin, liquiritigenin, flavonoids
Dominant Chemical Class	Diterpenoid lactones	Triterpenoid saponins
Primary Pharmacological Actions	Antiviral, immunomodulatory, anti-inflammatory	Antiviral, anxiolytic, anti-inflammatory
Antiviral Mechanisms	Viral replication inhibition and cytokine regulation	Viral attachment inhibition and immune modulation
Anti-inflammatory Pathways	NF- $\kappa$ B suppression, cytokine inhibition	Reduction of IL-6, TNF- $\alpha$ , oxidative stress
Neuroprotective Effects	Antioxidant and anti-neuroinflammatory effects	Neurotransmitter modulation and anxiolytic action
Respiratory Applications	Fever, influenza, bronchitis	Cough, sore throat, bronchitis
Stress and Anxiety Effects	Adaptogenic and fatigue-reducing effects	Anxiolytic and neuroprotective effects
COVID-19 Relevance	Immune enhancement and	Viral inhibition and stress

	antiviral support	management
Therapeutic Potential	Acute viral and inflammatory disorders	Respiratory and neuropsychological disorders

### 3. Antiviral Mechanisms Against SARS-CoV-2

#### 3.1 SARS-CoV-2 Infection and Viral Pathogenesis

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, is an enveloped, positive-sense single-stranded RNA virus belonging to the family *Coronaviridae*. The virus possesses four major structural proteins including spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. Among these, the spike glycoprotein plays a critical role in viral attachment, host cell recognition, and membrane fusion during infection (Huang et al., 2020).

#### Viral Structure and Replication Cycle

The SARS-CoV-2 genome encodes several structural and nonstructural proteins involved in viral replication and pathogenicity. Following host cell entry, viral RNA is released into the cytoplasm, where translation and replication occur through the formation of replication-transcription complexes. Viral proteases including the main protease (Mpro/3CLpro) and papain-like protease (PLpro) are essential for cleavage of viral polyproteins into functional replication enzymes (V'kovski et al., 2021).

Replication involves synthesis of negative-sense RNA intermediates followed by genomic RNA amplification and structural protein production. Newly assembled virions are subsequently released from infected cells through exocytosis, leading to propagation of infection and activation of inflammatory responses.

#### ACE2 Receptor Interaction and Viral Entry

SARS-CoV-2 primarily gains entry into host cells through interaction between the viral spike protein and angiotensin-converting enzyme 2 (ACE2) receptors expressed on respiratory epithelial cells, endothelial tissues, gastrointestinal tract, and neural tissues. Following receptor binding, host proteases such as TMPRSS2 facilitate spike protein priming and membrane fusion, enabling viral internalization (Walls et al., 2020).

ACE2 downregulation following viral entry disrupts the renin–angiotensin system and contributes to endothelial dysfunction, vascular inflammation, oxidative stress, and tissue injury. Because ACE2 receptors are expressed in multiple organs including the lungs and brain, SARS-CoV-2 may induce both respiratory and neurological complications.

#### Cytokine Storm and Inflammatory Cascades

One of the most severe pathological consequences of COVID-19 is the cytokine storm characterized by uncontrolled release of pro-inflammatory cytokines such as IL-6, TNF- $\alpha$ , IL-1 $\beta$ , and interferons.

Excessive immune activation contributes to acute respiratory distress syndrome (ARDS), multiorgan dysfunction, oxidative stress, thrombosis, and tissue damage (Mehta et al., 2020).

Persistent inflammatory signaling also promotes neuroinflammation, mitochondrial dysfunction, and immune imbalance associated with long-COVID syndrome. Therefore, therapeutic agents capable of simultaneously inhibiting viral replication and regulating inflammatory responses are of considerable importance in COVID-19 management.

### **3.2 Antiviral Actions of *Andrographis paniculata***

#### **Inhibition of Viral Replication and Protease Activity**

*Andrographis paniculata* has attracted significant scientific interest because of its broad-spectrum antiviral activity against influenza viruses, hepatitis viruses, dengue virus, HIV, and coronaviruses. The principal bioactive constituent, andrographolide, demonstrates inhibitory activity against viral replication pathways and viral proteases essential for SARS-CoV-2 proliferation (Enmozhi et al., 2021).

Experimental and computational studies suggest that andrographolide may inhibit SARS-CoV-2 main protease (Mpro/3CLpro), thereby interfering with cleavage of viral polyproteins required for replication. Inhibition of viral replication machinery may reduce viral load and disease progression.

Additionally, andrographolide may suppress viral RNA synthesis and interfere with viral assembly pathways. Such multitarget antiviral actions contribute to the therapeutic relevance of *Andrographis paniculata* in respiratory viral infections.

#### **Immunomodulatory and Anti-inflammatory Mechanisms**

Apart from direct antiviral activity, *Andrographis paniculata* exhibits potent immunomodulatory and anti-inflammatory effects. The herb suppresses activation of nuclear factor-kappa B (NF- $\kappa$ B), cyclooxygenase-2 (COX-2), and inflammatory cytokines including IL-6 and TNF- $\alpha$  (Hossain et al., 2021).

Andrographolide also enhances innate immune responses through activation of macrophages, natural killer cells, and lymphocyte proliferation. By regulating immune balance and suppressing excessive inflammatory responses, the plant may help reduce cytokine storm-associated complications in COVID-19.

Furthermore, antioxidant properties of flavonoids and polyphenols present in the herb reduce reactive oxygen species (ROS)-mediated tissue injury and oxidative stress associated with viral infections.

#### **Molecular Docking Studies Involving Andrographolide**

During the COVID-19 pandemic, several molecular docking and computational investigations evaluated the interaction of andrographolide with SARS-CoV-2 proteins. Studies demonstrated strong binding

affinity of andrographolide toward viral main protease (Mpro), spike glycoprotein, and RNA-dependent RNA polymerase (RdRp) (Murugan et al., 2020).

These computational findings suggest that andrographolide may inhibit viral entry, replication, and protease-mediated processing. In silico studies further indicate possible modulation of host inflammatory pathways and ACE2 receptor interactions.

Although docking studies alone cannot establish clinical efficacy, they provide important mechanistic insights supporting further experimental and clinical investigation of *Andrographis paniculata* against SARS-CoV-2.

### Experimental Evidence in Respiratory Viral Infections

Experimental studies have shown that *Andrographis paniculata* reduces viral load, inflammation, and oxidative tissue damage in respiratory infection models. Clinical evidence from upper respiratory tract infections and influenza-like illnesses demonstrates improvement in fever, sore throat, cough, and fatigue following administration of standardized extracts (Akbar, 2011).

Its immunomodulatory and anti-inflammatory actions further support its potential utility in COVID-19 supportive care and immune recovery.

### 3.3 Antiviral Actions of *Glycyrrhiza glabra*

#### Glycyrrhizin-Mediated Antiviral Effects

*Glycyrrhiza glabra* (Licorice) possesses significant antiviral activity primarily attributed to glycyrrhizin, a triterpenoid saponin extensively investigated against viral pathogens including herpes simplex virus, hepatitis viruses, HIV, influenza virus, and coronaviruses. During the SARS outbreak, glycyrrhizin demonstrated inhibitory activity against SARS-associated coronavirus replication in vitro (Cinatl et al., 2003). The compound exhibits antiviral effects through multiple mechanisms including inhibition of viral adsorption, penetration, replication, and inflammatory signaling. Glycyrrhizin also modulates cellular signaling pathways involved in viral pathogenesis and immune activation, thereby reducing virus-induced tissue injury.

#### Inhibition of Viral Attachment and Replication

Several studies suggest that glycyrrhizin may interfere with viral attachment and entry into host cells by altering membrane fluidity and receptor interactions. Computational investigations indicate potential interaction with SARS-CoV-2 spike protein and ACE2 receptor binding sites. Additionally, glycyrrhizin may inhibit viral replication through modulation of protein kinase pathways, suppression of viral gene expression, and reduction of oxidative stress-mediated viral proliferation. Such multitarget antiviral mechanisms increase its therapeutic relevance in COVID-19 management.

## Regulation of Inflammatory Cytokines and Oxidative Stress

Severe COVID-19 is strongly associated with excessive inflammatory responses and oxidative stress. Glycyrrhizin exhibits potent anti-inflammatory and antioxidant activities through inhibition of NF- $\kappa$ B signaling, reduction of IL-6 and TNF- $\alpha$  production, and suppression of reactive oxygen species generation (Pastorino et al., 2018). Licorice flavonoids such as liquiritigenin and isoliquiritigenin further contribute to antioxidant defense and tissue protection against inflammatory injury. These effects may help reduce cytokine storm-associated complications and support recovery during viral infection.

## Potential Effects on ACE2 and Viral Proteases

Recent computational studies suggest that glycyrrhizin and related phytoconstituents may interact with ACE2 receptors and SARS-CoV-2 proteases involved in viral entry and replication. Such interactions could potentially inhibit viral attachment and reduce infectivity. Although these findings require extensive experimental validation, they support the possibility of utilizing licorice-derived phytochemicals as supportive antiviral agents in integrative COVID-19 therapy.

## 3.4 Combined Therapeutic Potential Against COVID-19

### Herbal Synergy and Multitarget Pharmacological Actions

The combined use of *Andrographis paniculata* and *Glycyrrhiza glabra* may provide synergistic therapeutic benefits because of their complementary antiviral, anti-inflammatory, antioxidant, immunomodulatory, and anxiolytic properties. While andrographolide primarily targets viral replication, inflammatory signaling, and immune regulation, glycyrrhizin contributes antiviral protection, mucosal defense, cytokine suppression, and neuroprotective effects. Together, these herbs may simultaneously target multiple stages of SARS-CoV-2 pathogenesis.

### Supportive Role in Mild-to-Moderate COVID-19

Traditional herbal formulations containing these plants may support symptomatic management of mild-to-moderate COVID-19 by reducing fever, cough, sore throat, fatigue, and inflammatory responses. Their antioxidant and immunomodulatory activities may also improve immune resilience and recovery. Furthermore, their ability to regulate oxidative stress and inflammatory mediators may help prevent progression toward severe inflammatory complications.

### Potential Role in Long-COVID and Immune Recovery

Long-COVID syndrome involves persistent fatigue, neuroinflammation, anxiety, cognitive dysfunction, sleep disturbances, and immune imbalance. The adaptogenic, neuroprotective, and anti-inflammatory activities of these medicinal plants may help restore neuroimmune homeostasis and improve post-viral recovery. Ashwagandha-like anxiolytic effects observed with licorice flavonoids and stress-reducing properties of *Andrographis paniculata* may further contribute to emotional stabilization and improved quality of life in post-COVID patients.

## Safety Considerations and Dosage Perspectives

Although both herbs are generally considered safe at recommended therapeutic doses, excessive or prolonged use may lead to adverse effects. High doses of licorice may cause hypertension, hypokalemia, sodium retention, and endocrine disturbances because of mineralocorticoid-like effects of glycyrrhizin. Similarly, excessive use of *Andrographis paniculata* may occasionally produce gastrointestinal discomfort, allergic reactions, or fatigue. Standardization of dosage, quality control, and monitoring of herb–drug interactions are therefore essential for safe therapeutic application.

**Table 2. Antiviral Mechanisms and Therapeutic Potential of *Andrographis paniculata* and *Glycyrrhiza glabra* Against SARS-CoV-2**

Parameter	<i>Andrographis paniculata</i>	<i>Glycyrrhiza glabra</i>
Major Active Constituent	Andrographolide	Glycyrrhizin
Primary Antiviral Action	Inhibition of viral protease and replication	Inhibition of viral attachment and replication
Viral Targets	Mpro, RdRp, spike protein	ACE2 interaction, viral proteases
Immunomodulatory Effects	Activation of macrophages and lymphocytes	Regulation of cytokines and immune balance
Anti-inflammatory Mechanisms	NF- $\kappa$ B and COX-2 inhibition	IL-6 and TNF- $\alpha$ suppression
Antioxidant Activity	Reduction of ROS and oxidative injury	Free radical scavenging and tissue protection
Respiratory Benefits	Relief in fever, cough, and respiratory inflammation	Expectorant and mucoprotective effects
Neuroprotective/Stress Effects	Adaptogenic and anti-inflammatory support	Anxiolytic and neuroprotective activity
COVID-19 Relevance	Antiviral and immune-regulating support	Antiviral and cytokine storm suppression
Therapeutic Limitation	Limited clinical trials	Risk of hypertension with excessive use
Potential Combined Benefit	Synergistic antiviral and anti-inflammatory effects	Complementary immune and neuroprotective support

## 4. Anxiolytic and Neuroprotective Effects

### 4.1 Psychological and Neurological Impact of COVID-19

The COVID-19 pandemic significantly affected not only physical health but also neurological and psychological well-being across populations worldwide. Accumulating evidence suggests that SARS-CoV-2 infection may induce both direct and indirect neurological complications through neuroinvasion, systemic inflammation, oxidative stress, endothelial dysfunction, and immune dysregulation (Ellul et al., 2020). In addition to acute respiratory manifestations, many patients developed persistent neuropsychiatric symptoms during and after infection, contributing to long-COVID syndrome and reduced quality of life.

## Stress, Anxiety, Depression, and Insomnia During the Pandemic

The pandemic created unprecedented psychological stress due to fear of infection, social isolation, economic instability, prolonged lockdowns, uncertainty, and loss of family members. These factors substantially increased the prevalence of anxiety, depression, insomnia, emotional exhaustion, and post-traumatic stress disorder among healthcare workers, recovered patients, and the general population (Pfefferbaum & North, 2020).

COVID-19 survivors frequently experience chronic fatigue, irritability, emotional instability, impaired concentration, and sleep disturbances. Persistent inflammatory responses and neuroimmune dysfunction are believed to contribute to these psychiatric manifestations. Furthermore, elevated cortisol levels and dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis during chronic stress may worsen neuroinflammation and oxidative neuronal injury.

## Neuroinflammation and Oxidative Neuronal Injury

Neuroinflammation plays a central role in COVID-19-associated neurological complications. Excessive production of inflammatory cytokines such as IL-6, TNF- $\alpha$ , and IL-1 $\beta$  during cytokine storms can disrupt the blood–brain barrier and activate microglial cells, leading to neuronal damage and cognitive dysfunction (Heneka et al., 2020).

Oxidative stress further contributes to neuronal injury through excessive generation of reactive oxygen species (ROS), mitochondrial dysfunction, lipid peroxidation, and apoptosis. Persistent neuroinflammation and oxidative damage are strongly associated with neurodegenerative changes, memory impairment, depression, and anxiety-related disorders observed in post-COVID conditions.

## Post-COVID Cognitive Dysfunction and Fatigue Syndrome

Long-COVID syndrome is characterized by prolonged fatigue, “brain fog,” impaired attention, reduced memory performance, headache, sleep disturbances, and mood disorders. Neuroimmune dysregulation, mitochondrial dysfunction, chronic inflammation, and altered neurotransmitter balance are considered major contributors to post-COVID neurological symptoms (Nalbandian et al., 2021).

Because conventional pharmacological therapies primarily target acute infection and inflammation, increasing attention has shifted toward medicinal plants possessing anxiolytic, antioxidant, adaptogenic, and neuroprotective properties capable of restoring neuroimmune balance and improving psychological resilience.

## 4.2 Neuroprotective and Anxiolytic Role of *Andrographis paniculata*

### Antioxidant and Anti-inflammatory Neuroprotection

*Andrographis paniculata* exhibits significant neuroprotective effects primarily through its antioxidant and anti-inflammatory properties. The major bioactive constituent, andrographolide, suppresses

neuroinflammatory signaling pathways including NF- $\kappa$ B activation, pro-inflammatory cytokine production, and oxidative stress-mediated neuronal injury (Dai et al., 2019).

Experimental studies demonstrate that andrographolide reduces microglial activation and protects neuronal cells against oxidative damage induced by inflammatory mediators and reactive oxygen species. Such neuroprotective actions may be particularly beneficial in preventing COVID-19-associated neuroinflammation and neuronal dysfunction.

Additionally, flavonoids and polyphenols present in the plant contribute to free radical scavenging activity and mitochondrial stabilization, thereby preserving neuronal integrity under inflammatory conditions.

### **Modulation of Neurotransmitters and Stress Pathways**

Several experimental investigations indicate that *Andrographis paniculata* influences neurotransmitter regulation and stress-associated signaling pathways. The herb may modulate serotonergic, dopaminergic, and GABAergic systems involved in mood regulation and emotional behavior. Andrographolide has also been reported to reduce stress-induced corticosterone elevation and improve antioxidant defense mechanisms in experimental stress models. These findings suggest adaptogenic and anxiolytic potential that may help alleviate psychological disturbances associated with chronic stress and post-COVID conditions.

### **Experimental Evidence in Anxiety and Neurotoxicity Models**

Animal studies have shown that *Andrographis paniculata* improves cognitive performance, reduces anxiety-like behavior, and protects against neurotoxicity induced by oxidative stress and inflammatory agents. Experimental models of neurodegeneration indicate that andrographolide may inhibit neuronal apoptosis, attenuate neuroinflammation, and improve synaptic function (Rajani et al., 2021). Furthermore, the herb demonstrates protective effects against chemically induced memory impairment and neuronal oxidative injury, supporting its therapeutic potential in cognitive dysfunction and stress-related neurological disorders.

## **4.3 Neuroprotective and Anxiolytic Role of Glycyrrhiza glabra**

### **Regulation of the HPA Axis and Cortisol Balance**

*Glycyrrhiza glabra* possesses important adaptogenic and anxiolytic properties associated with modulation of the hypothalamic–pituitary–adrenal (HPA) axis. Chronic stress and COVID-19-associated psychological disturbances frequently lead to excessive cortisol secretion, immune imbalance, and neuronal dysfunction. Bioactive compounds such as glycyrrhizin and liquiritigenin influence cortisol metabolism and stress hormone regulation, thereby improving physiological stress adaptation (Pastorino et al., 2018). Through stabilization of the HPA axis, licorice may help reduce anxiety, emotional instability, and stress-related fatigue.

## GABAergic and Serotonergic Modulation

Licorice flavonoids including liquiritigenin and isoliquiritigenin demonstrate anxiolytic and antidepressant-like effects through modulation of GABAergic and serotonergic neurotransmission. GABA receptor activation contributes to sedation, emotional stabilization, and reduction of anxiety-related symptoms. Experimental evidence suggests that these compounds improve neurotransmitter balance and reduce stress-induced behavioral abnormalities. Such effects may be valuable in managing insomnia, anxiety, depression, and emotional disturbances associated with long-COVID syndrome.

## Cognitive Enhancement and Antidepressant-like Effects

Several studies indicate that *Glycyrrhiza glabra* improves memory, cognitive performance, and learning ability through antioxidant and neuroprotective mechanisms. Glycyrrhizin suppresses oxidative stress and neuroinflammation while promoting neuronal survival and mitochondrial protection. Licorice extracts have demonstrated antidepressant-like activity in experimental stress models through modulation of monoaminergic neurotransmission and inflammatory pathways. These effects may contribute to improved mental health and neuropsychological recovery following viral infections.

## Evidence in Stress-related and Neurodegenerative Disorders

Experimental investigations suggest that licorice-derived compounds may possess therapeutic potential in neurodegenerative conditions including Alzheimer's disease and Parkinsonian disorders because of their anti-inflammatory, antioxidant, and antiapoptotic properties. By reducing oxidative stress, suppressing inflammatory cytokines, and protecting neuronal tissues, *Glycyrrhiza glabra* may help alleviate chronic neuroimmune dysfunction associated with stress-related and post-viral neurological complications.

## 4.4 Mechanistic Insights

### Anti-inflammatory Signaling Pathways

Both *Andrographis paniculata* and *Glycyrrhiza glabra* exert neuroprotective effects through suppression of inflammatory signaling pathways such as NF- $\kappa$ B, MAPK, and JAK/STAT pathways. Reduction of inflammatory cytokines including IL-6, TNF- $\alpha$ , and IL-1 $\beta$  contributes to decreased neuroinflammation and neuronal injury. These medicinal plants also inhibit activation of microglial cells and reduce inflammatory mediator release, thereby protecting neural tissues against chronic inflammatory damage.

### Oxidative Stress Reduction and Mitochondrial Protection

Oxidative stress is a major contributor to neuronal degeneration and cognitive impairment. Both medicinal plants exhibit strong antioxidant properties through enhancement of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. Reduction of reactive oxygen species and preservation of mitochondrial integrity help maintain neuronal energy metabolism and cellular survival during inflammatory and stress-associated conditions.

## Neuroimmune Interactions and Neurotransmitter Regulation

Neuroimmune interactions significantly influence emotional behavior, cognition, and stress responses. *Andrographis paniculata* and *Glycyrrhiza glabra* modulate neurotransmitter systems including serotonin, dopamine, and GABA while simultaneously regulating immune mediators. This dual neuroimmune modulation may explain their anxiolytic, adaptogenic, antidepressant, and neuroprotective effects in COVID-19-associated neuropsychiatric disorders.

**Table 3. Neuroprotective and Anxiolytic Mechanisms of *Andrographis paniculata* and *Glycyrrhiza glabra***

Parameter	<i>Andrographis paniculata</i>	<i>Glycyrrhiza glabra</i>
Major Neuroactive Compound	Andrographolide	Glycyrrhizin, liquiritigenin
Primary Neuroprotective Mechanism	Anti-inflammatory and antioxidant activity	Neurotransmitter and HPA axis modulation
Oxidative Stress Effects	ROS reduction and mitochondrial protection	Antioxidant and antiapoptotic activity
Neuroinflammatory Targets	NF- $\kappa$ B, cytokine suppression	IL-6, TNF- $\alpha$ inhibition
Neurotransmitter Modulation	Serotonergic and dopaminergic regulation	GABAergic and serotonergic modulation
Stress-related Effects	Adaptogenic and fatigue-reducing actions	Anxiolytic and antidepressant-like effects
Cognitive Benefits	Memory enhancement and neuronal protection	Learning and cognitive improvement
Experimental Evidence	Neurotoxicity and anxiety models	Stress and neurodegenerative models
Long-COVID Relevance	Neuroinflammation reduction	Anxiety and emotional stabilization
Overall Therapeutic Potential	Neuroimmune protection and stress adaptation	Psychological recovery and neuroprotection

## 5. Experimental, Preclinical, and Clinical Evidence

### 5.1 In Vitro Studies

The antiviral and anxiolytic potential of *Andrographis paniculata* and *Glycyrrhiza glabra* has been extensively investigated through in vitro experimental models, molecular docking analyses, and mechanistic pharmacological studies. These investigations provide valuable insights into the cellular and molecular pathways involved in antiviral, anti-inflammatory, antioxidant, and neuroprotective activities relevant to COVID-19 and stress-associated disorders.

#### Antiviral and Anti-inflammatory Screening

Several in vitro studies demonstrated that andrographolide, the principal diterpenoid constituent of *Andrographis paniculata*, exhibits inhibitory activity against respiratory viral pathogens including

influenza viruses, dengue virus, hepatitis viruses, and coronaviruses. During the COVID-19 pandemic, experimental investigations reported that andrographolide reduced SARS-CoV-2 replication and viral protein expression in infected cell lines (Sa-Ngiamsumtorn et al., 2021).

The antiviral effects of andrographolide are associated with inhibition of viral replication enzymes, suppression of inflammatory mediators, and modulation of host immune responses. Additionally, andrographolide significantly reduces expression of IL-6, TNF- $\alpha$ , and other inflammatory cytokines associated with cytokine storm pathology.

Similarly, glycyrrhizin from *Glycyrrhiza glabra* demonstrated inhibitory effects against SARS-associated coronaviruses and other RNA viruses in cultured cell systems (Cinatl et al., 2003). Glycyrrhizin interferes with viral attachment, penetration, and replication while simultaneously suppressing oxidative stress and inflammatory signaling pathways.

Licorice flavonoids such as liquiritigenin and isoliquiritigenin also exhibit antioxidant and neuroprotective properties through free radical scavenging activity and inhibition of inflammatory mediator production.

### **Molecular Docking and Computational Investigations**

Molecular docking and computational biology approaches became highly important during the COVID-19 pandemic for screening potential antiviral phytochemicals against SARS-CoV-2 targets.

Several docking studies reported strong binding affinity of andrographolide toward SARS-CoV-2 main protease (M<sub>pro</sub>/3CL<sub>pro</sub>), spike glycoprotein, papain-like protease (PL<sub>pro</sub>), and RNA-dependent RNA polymerase (RdRp) (Enmozhi et al., 2021). These findings suggest potential inhibition of viral replication and entry mechanisms.

Similarly, glycyrrhizin demonstrated interactions with ACE2 receptors, viral proteases, and inflammatory signaling molecules involved in SARS-CoV-2 infection. Computational studies further indicated that licorice-derived phytochemicals may stabilize host immune responses and reduce inflammatory damage.

Although molecular docking studies provide preliminary mechanistic evidence, further validation through experimental and clinical investigations remains essential.

## **5.2 In Vivo Experimental Studies**

### **Animal Models of Viral Infection and Anxiety Disorders**

Experimental animal models have played an important role in evaluating the pharmacological efficacy of *Andrographis paniculata* and *Glycyrrhiza glabra* in viral infections, inflammation, oxidative stress, and neurobehavioral disorders. In vivo studies involving respiratory viral infection models demonstrated that andrographolide reduced viral load, inflammatory cytokine production, pulmonary edema, and oxidative tissue damage. Experimental evidence also indicates that *Andrographis paniculata* improves immune responses through activation of macrophages, natural killer cells, and lymphocyte proliferation (Hossain

et al., 2021). Animal studies further demonstrated protective effects of andrographolide against neurotoxicity, stress-induced oxidative injury, and neuroinflammation. Rodent models of anxiety and depression showed improvement in behavioral performance, memory, and stress tolerance following administration of *Andrographis paniculata* extracts. Similarly, *Glycyrrhiza glabra* exhibited significant anti-inflammatory, antioxidant, antiviral, anxiolytic, and neuroprotective effects in experimental models. Glycyrrhizin reduced oxidative stress, suppressed inflammatory cytokines, and improved mitochondrial function in stress-induced neurological disorders. Rodent studies also demonstrated that licorice flavonoids modulate GABAergic and serotonergic neurotransmission, contributing to anxiolytic and antidepressant-like effects.

### Neurobehavioral and Immunological Outcomes

Behavioral investigations revealed that both medicinal plants improve locomotor activity, reduce anxiety-like behavior, enhance cognitive performance, and decrease depressive symptoms in stress models. Immunological studies demonstrated regulation of cytokine balance, reduction of oxidative markers, enhancement of antioxidant enzyme activity, and suppression of inflammatory cascades. These findings support the multitarget therapeutic potential of these medicinal plants in COVID-19-associated neuroimmune disorders.

### Pharmacological Validation of Antiviral and Anxiolytic Effects

Collectively, experimental studies validate the antiviral, immunomodulatory, anti-inflammatory, antioxidant, anxiolytic, and neuroprotective activities of both medicinal plants. Their ability to simultaneously regulate immune and neurological pathways makes them promising candidates for integrative management of viral and stress-related disorders.

## 5.3 Clinical Trials and Human Studies

### Clinical Evidence in COVID-19 Supportive Therapy

Several clinical investigations evaluated the efficacy of *Andrographis paniculata* in upper respiratory tract infections and mild COVID-19 cases. Standardized andrographolide-containing formulations demonstrated improvement in fever, cough, sore throat, fatigue, and inflammatory symptoms (Benjaponpitak et al., 2021). Some clinical observations also suggested reduced disease progression and improved recovery in mild-to-moderate COVID-19 patients receiving *Andrographis paniculata* extracts as supportive therapy. However, variations in study design, dosage, and sample size limit definitive conclusions. Clinical evidence involving *Glycyrrhiza glabra* remains comparatively limited, although glycyrrhizin-containing preparations have shown beneficial effects in respiratory inflammation, viral hepatitis, and immune-associated disorders. Licorice-based formulations may provide supportive anti-inflammatory and mucoprotective effects in respiratory infections.

### Studies on Stress, Anxiety, Cognition, and Immunity

Human studies indicate that licorice-derived flavonoids and *Andrographis paniculata* extracts may improve stress tolerance, fatigue, immune balance, and psychological well-being. Traditional

formulations containing these medicinal plants have been associated with reduced anxiety, improved sleep quality, enhanced immune resilience, and better recovery from chronic fatigue conditions. Such effects may be particularly relevant in post-COVID neuropsychiatric complications and long-COVID syndrome.

### **Evidence Related to Respiratory and Inflammatory Disorders**

Clinical evidence supports the use of *Andrographis paniculata* in upper respiratory tract infections, influenza-like illnesses, and inflammatory conditions. Reduction in symptom severity, duration of illness, and inflammatory markers has been observed in several studies. Similarly, licorice preparations have demonstrated therapeutic benefits in bronchitis, sore throat, gastric inflammation, and inflammatory respiratory disorders because of their demulcent, antioxidant, and anti-inflammatory properties.

### **Limitations and Challenges in Clinical Translation**

Despite promising findings, several limitations affect the clinical translation of herbal therapeutics. Variability in phytochemical composition, lack of standardization, inconsistent dosage regimens, small sample sizes, and limited multicentric trials remain major challenges. Additionally, many studies rely on observational or preliminary evidence rather than large-scale randomized controlled trials. Further clinical investigations are therefore required to establish definitive efficacy, safety, and therapeutic guidelines.

## **5.4 Safety, Toxicity, and Herb–Drug Interactions**

### **Toxicological Evaluation and Safety Profile**

Both *Andrographis paniculata* and *Glycyrrhiza glabra* are generally considered safe when administered at recommended therapeutic doses. Acute and subchronic toxicity studies indicate relatively low toxicity profiles for standardized extracts. However, prolonged or excessive consumption may lead to adverse effects. High doses of *Andrographis paniculata* may occasionally produce gastrointestinal discomfort, nausea, fatigue, allergic reactions, and altered liver enzyme levels.

### **Contraindications and Precautions**

Licorice consumption in excessive amounts may cause hypertension, hypokalemia, sodium retention, edema, and endocrine disturbances because of mineralocorticoid-like effects of glycyrrhizin (Pastorino et al., 2018). Patients with cardiovascular disorders, renal dysfunction, hypertension, and hormonal imbalances require careful monitoring during licorice therapy. Pregnant women, lactating mothers, immunocompromised patients, and individuals receiving multiple medications should use these medicinal plants cautiously under medical supervision.

### **Herb–Drug Interaction Concerns**

Potential herb–drug interactions remain important considerations in integrative medicine. Licorice may interact with antihypertensive agents, corticosteroids, diuretics, anticoagulants, and hormonal medications. Similarly, *Andrographis paniculata* may influence cytochrome P450 enzymes and alter

metabolism of certain pharmaceutical drugs. Therefore, careful dosage monitoring, pharmacovigilance, and clinical supervision are necessary during combined herbal and conventional therapy.

### Regulatory and Quality Control Perspectives

Standardization and quality control are essential for ensuring safety, efficacy, and reproducibility of herbal therapeutics. Variability in cultivation conditions, extraction methods, processing techniques, and phytochemical composition significantly influences therapeutic outcomes.

Regulatory agencies increasingly emphasize Good Manufacturing Practices (GMP), phytochemical standardization, contaminant testing, and evidence-based clinical validation for herbal medicines intended for therapeutic applications.

**Table 4. Experimental, Preclinical, and Clinical Evidence of *Andrographis paniculata* and *Glycyrrhiza glabra***

Study Category	<i>Andrographis paniculata</i>	<i>Glycyrrhiza glabra</i>
In Vitro Antiviral Activity	Inhibition of SARS-CoV-2 replication and viral proteases	Inhibition of viral attachment and replication
Molecular Docking Targets	Mpro, RdRp, spike protein	ACE2 receptor, viral proteases
Anti-inflammatory Effects	Suppression of IL-6, TNF- $\alpha$ , NF- $\kappa$ B	Reduction of cytokines and oxidative stress
Antioxidant Activity	ROS scavenging and mitochondrial protection	Free radical scavenging and tissue protection
In Vivo Viral Models	Reduced viral load and pulmonary inflammation	Reduced inflammatory and oxidative injury
Neurobehavioral Effects	Memory enhancement and anxiolytic activity	Anxiolytic and antidepressant-like effects
Clinical Respiratory Evidence	Improvement in fever, cough, sore throat	Relief in bronchitis and respiratory inflammation
COVID-19 Supportive Care	Symptomatic improvement in mild cases	Potential supportive anti-inflammatory role
Safety Concerns	Gastrointestinal discomfort and allergy	Hypertension and hypokalemia with excess use
Major Clinical Limitation	Lack of large multicentric trials	Limited COVID-19-specific clinical evidence

### 6. Emerging Therapeutic Perspectives and Future Directions

The COVID-19 pandemic highlighted the urgent need for safe, multitarget, and integrative therapeutic strategies capable of simultaneously addressing viral infection, immune dysregulation, oxidative stress, neuroinflammation, and psychological disturbances. In this context, *Andrographis paniculata* and *Glycyrrhiza glabra* have emerged as promising medicinal plants because of their antiviral, immunomodulatory, antioxidant, anxiolytic, and neuroprotective properties. Increasing experimental and

clinical evidence supports their potential role in future phytotherapeutic interventions against SARS-CoV-2 and stress-associated disorders.

### 6.1 Integrative Medicine Approaches in Viral and Stress Disorders

Modern healthcare increasingly recognizes the value of integrative medicine approaches combining conventional pharmacotherapy with scientifically validated herbal therapeutics. COVID-19 and long-COVID syndrome involve complex interactions among viral replication, immune dysregulation, oxidative stress, neuroinflammation, and psychological disturbances. Therefore, single-target pharmaceutical approaches may not adequately address the multifactorial nature of the disease.

*Andrographis paniculata* and *Glycyrrhiza glabra* possess multitarget pharmacological activities capable of modulating several pathological pathways simultaneously. Their combined antiviral, anti-inflammatory, antioxidant, immunomodulatory, and anxiolytic effects may complement conventional therapies and improve patient outcomes.

In integrative medicine, these medicinal plants may serve as supportive agents for:

- Enhancing immune resilience
- Reducing inflammatory complications
- Managing respiratory symptoms
- Improving stress tolerance and sleep quality
- Supporting neuropsychological recovery in long-COVID syndrome

Furthermore, traditional medicinal systems such as Ayurveda, Traditional Chinese Medicine, and Unani medicine provide valuable ethnopharmacological knowledge supporting the therapeutic use of these herbs in respiratory and stress-related disorders.

### 6.2 Nanoformulations and Advanced Herbal Delivery Systems

Despite promising pharmacological activities, herbal therapeutics often face limitations related to poor solubility, instability, low bioavailability, rapid metabolism, and limited tissue targeting. Advanced drug delivery systems and nanotechnology-based formulations may significantly improve the therapeutic efficacy of phytochemicals derived from *Andrographis paniculata* and *Glycyrrhiza glabra*.

Nanoformulations such as nanoparticles, liposomes, phytosomes, nanoemulsions, and solid lipid nanoparticles have demonstrated potential for:

- Enhancing phytochemical stability
- Improving absorption and bioavailability
- Facilitating controlled drug release
- Increasing tissue-specific targeting
- Enhancing blood–brain barrier penetration

Andrographolide-loaded nanoparticles may improve antiviral efficacy and reduce inflammatory tissue damage, while glycyrrhizin nanoformulations may enhance antiviral activity and neuroprotective delivery.

Nanotechnology-based delivery systems may also improve therapeutic outcomes in neuroinflammatory and long-COVID-associated neurological disorders by facilitating targeted delivery to inflamed neural tissues.

### 6.3 Potential Combination Therapies with Conventional Antivirals

Combination therapy approaches involving medicinal plants and conventional antiviral agents represent an important future research direction. Because SARS-CoV-2 pathogenesis involves viral replication, immune dysregulation, oxidative stress, endothelial injury, and cytokine storm syndrome, multitarget therapeutic combinations may offer superior clinical outcomes.

Andrographolide may complement antiviral drugs by inhibiting viral proteases and inflammatory signaling pathways, whereas glycyrrhizin may contribute antiviral, mucoprotective, and anxiolytic benefits. Such complementary pharmacological actions may help:

- Reduce viral load
- Suppress inflammatory cascades
- Minimize oxidative stress
- Improve respiratory recovery
- Alleviate psychological stress and anxiety

Additionally, combined therapy may reduce drug dosage requirements and minimize adverse effects associated with prolonged pharmacological treatment.

However, careful evaluation of herb–drug interactions, pharmacokinetics, and safety profiles remains essential before clinical implementation.

### 6.4 Standardization and Biomarker-Based Validation

One of the major challenges limiting global acceptance of herbal therapeutics is inconsistency in phytochemical composition and therapeutic efficacy. Variations in geographical origin, cultivation conditions, harvesting time, extraction techniques, and processing methods significantly influence the concentration of active phytoconstituents.

Standardization of herbal formulations using validated biomarkers such as andrographolide and glycyrrhizin is essential for ensuring reproducibility, safety, and clinical reliability. Advanced analytical techniques including:

- High-performance liquid chromatography (HPLC)
- Liquid chromatography–mass spectrometry (LC-MS)
- Metabolomics and fingerprint profiling

- Genomic and proteomic analyses

may facilitate quality control and phytochemical characterization.

Biomarker-guided therapeutic monitoring may further improve individualized treatment strategies in COVID-19, neuroinflammation, and stress-associated disorders.

### **6.5 Artificial Intelligence, Network Pharmacology, and Systems Biology Approaches**

Emerging computational technologies including artificial intelligence (AI), network pharmacology, systems biology, and molecular modeling are transforming phytopharmaceutical research.

Network pharmacology approaches are particularly valuable for understanding the multitarget actions of medicinal plants because herbal compounds interact with multiple molecular pathways simultaneously. Such methods may help identify:

- Novel antiviral targets
- Neuroimmune signaling pathways
- Synergistic phytochemical interactions
- Predictive therapeutic biomarkers
- Herb–drug interaction profiles

AI-assisted molecular docking and machine learning algorithms may accelerate screening of phytochemicals against SARS-CoV-2 targets including spike proteins, viral proteases, and inflammatory mediators.

Integration of systems biology with traditional medicinal knowledge may therefore facilitate development of evidence-based phytotherapeutic strategies for emerging infectious and neuroimmune disorders.

### **6.6 Future Prospects in Neuroimmune and Post-Viral Disorders**

Persistent neuroinflammation and immune dysregulation observed in long-COVID syndrome resemble pathological mechanisms associated with neurodegenerative and chronic inflammatory diseases. Consequently, medicinal plants with combined antiviral and neuroprotective properties may possess broader therapeutic applications beyond acute viral infection.

The antioxidant, anxiolytic, and neuroimmune regulatory properties of *Andrographis paniculata* and *Glycyrrhiza glabra* may contribute to future therapeutic approaches in:

- Long-COVID syndrome
- Chronic fatigue syndrome
- Anxiety and depressive disorders
- Neurodegenerative diseases
- Stress-associated immune dysfunctions
- Viral-induced neurological complications

Their multitarget actions make them attractive candidates for preventive and supportive healthcare interventions in future pandemics and emerging viral outbreaks.

### 6.7 Need for Multicentric Randomized Clinical Trials

Although current experimental and preliminary clinical evidence is encouraging, large-scale multicentric randomized controlled trials remain urgently needed to establish definitive therapeutic efficacy and safety.

Future clinical investigations should focus on:

- Standardized herbal formulations
- Optimal dosage regimens
- Long-term safety assessment
- Comparative efficacy studies
- Pharmacokinetic and pharmacodynamic analysis
- Herb–drug interaction evaluation
- Long-COVID and neuropsychiatric outcomes

Evidence-based clinical validation will be essential for integrating these medicinal plants into mainstream healthcare systems and international therapeutic guidelines.

**Table 5. Emerging Therapeutic Perspectives of *Andrographis paniculata* and *Glycyrrhiza glabra***

Emerging Area	<i>Andrographis paniculata</i>	<i>Glycyrrhiza glabra</i>	Future Therapeutic Significance
Integrative Medicine	Antiviral and immunomodulatory support	Antiviral and anxiolytic support	Complementary COVID-19 management
Nanoformulations	Improved andrographolide delivery	Enhanced glycyrrhizin bioavailability	Better efficacy and tissue targeting
Combination Therapy	Viral protease inhibition	Cytokine suppression and mucoprotection	Multitarget therapeutic synergy
Neuroimmune Disorders	Neuroinflammation reduction	Neurotransmitter modulation	Long-COVID and stress management
AI and Network Pharmacology	Molecular target identification	Pathway-based therapeutic prediction	Accelerated phytodrug discovery
Biomarker Standardization	Andrographolide quantification	Glycyrrhizin fingerprinting	Improved quality control
Long-COVID Applications	Fatigue and inflammatory recovery	Anxiety and cognitive stabilization	Post-viral rehabilitation
Future Pandemic Preparedness	Immune resilience enhancement	Stress adaptation support	Preventive healthcare strategies
Clinical Research	Large multicentric	Neuropsychological	Evidence-based

Priority	antiviral trials	outcome studies	phytotherapy
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## 7. Conclusion

The COVID-19 pandemic emphasized the urgent need for safe, effective, and multitarget therapeutic strategies capable of addressing not only viral infection but also the associated inflammatory, neurological, and psychological complications. Among various medicinal plants investigated during and after the pandemic, *Andrographis paniculata* and *Glycyrrhiza glabra* have emerged as highly promising phytotherapeutic agents because of their broad-spectrum antiviral, immunomodulatory, antioxidant, anxiolytic, and neuroprotective activities.

The chapter highlighted that *Andrographis paniculata*, particularly through its major bioactive constituent andrographolide, exhibits potent antiviral and anti-inflammatory effects by inhibiting viral replication, modulating cytokine production, suppressing oxidative stress, and regulating immune responses. Molecular docking and experimental studies further support its interaction with SARS-CoV-2 targets such as viral proteases and replication-associated enzymes. Additionally, its antioxidant and adaptogenic properties contribute to neuroprotection, stress reduction, and improvement of cognitive and emotional disturbances associated with COVID-19 and long-COVID syndrome.

Similarly, *Glycyrrhiza glabra* demonstrated significant therapeutic potential because of the antiviral and anti-inflammatory actions of glycyrrhizin and associated flavonoids. Licorice-derived phytochemicals possess the ability to interfere with viral attachment and replication while simultaneously reducing inflammatory cytokines, oxidative stress, and tissue injury. Importantly, the anxiolytic and neuroprotective activities of licorice compounds may help alleviate stress, anxiety, insomnia, fatigue, and neuropsychiatric complications that became increasingly prevalent during the pandemic period.

The combined therapeutic potential of these medicinal plants is particularly noteworthy because COVID-19 is a multifactorial disease involving immune dysregulation, oxidative stress, neuroinflammation, endothelial dysfunction, and psychological disturbances. The multitarget pharmacological profile of *Andrographis paniculata* and *Glycyrrhiza glabra* suggests possible synergistic effects in integrative medicine approaches aimed at improving immune resilience, reducing inflammatory damage, enhancing neuroprotection, and supporting recovery during post-viral conditions.

Experimental and preclinical evidence strongly supports the antiviral, antioxidant, anti-inflammatory, immunomodulatory, and anxiolytic properties of these plants. Preliminary clinical investigations also indicate beneficial effects in respiratory infections, stress-associated disorders, and supportive management of mild-to-moderate COVID-19. However, despite encouraging findings, several challenges remain regarding phytochemical standardization, dosage optimization, pharmacokinetic evaluation, herb–drug interaction assessment, and large-scale clinical validation.

Future research should therefore focus on multicentric randomized controlled clinical trials, advanced nanoformulations, biomarker-based standardization, systems biology approaches, and network pharmacology investigations to establish definitive therapeutic efficacy and safety. Integration of artificial

intelligence-assisted molecular screening and precision phytotherapy may further accelerate the development of evidence-based herbal interventions against emerging viral and neuroimmune disorders.

In conclusion, *Andrographis paniculata* and *Glycyrrhiza glabra* represent scientifically valuable medicinal plants with significant antiviral and anxiolytic potential against SARS-CoV-2-associated complications. Their ability to simultaneously modulate viral replication, immune responses, oxidative stress, and neuropsychological disturbances highlights their importance in future integrative therapeutic strategies for COVID-19, long-COVID syndrome, and stress-related disorders. Continued interdisciplinary research integrating traditional medicinal knowledge with modern pharmacological science may contribute substantially to the development of safer, holistic, and multitarget healthcare approaches for future global health challenges.

## References

- Akbar, S. (2011). *Andrographis paniculata*: A review of pharmacological activities and clinical effects. *Alternative Medicine Review*, 16(1), 66–77.
- Ang, L., Song, E., Lee, H. W., & Lee, M. S. (2020). Herbal medicine for the management of COVID-19 during the medical observation period: A review of guidelines. *Integrative Medicine Research*, 9(3), 100465.
- Benjaponpitak, S., Visithanon, K., Sawaengdee, W., & Chusri, S. (2021). Clinical efficacy of *Andrographis paniculata* in mild COVID-19 patients: A preliminary study. *Journal of Herbal Medicine*, 29, 100476.
- Cinatl, J., Morgenstern, B., Bauer, G., Chandra, P., Rabenau, H., & Doerr, H. W. (2003). Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. *The Lancet*, 361(9374), 2045–2046.
- Dai, Y., Chen, S. R., Chai, L., Zhao, J., Wang, Y., & Wang, Y. (2019). Overview of pharmacological activities of *Andrographis paniculata* and its major compound andrographolide. *Critical Reviews in Food Science and Nutrition*, 59(Suppl 1), S17–S29.
- Ellul, M. A., Benjamin, L., Singh, B., Lant, S., Michael, B. D., Easton, A., ... Solomon, T. (2020). Neurological associations of COVID-19. *The Lancet Neurology*, 19(9), 767–783.
- Enmozhi, S. K., Raja, K., Sebastine, I., & Joseph, J. (2021). Andrographolide as a potential inhibitor of SARS-CoV-2 main protease: An in silico approach. *Journal of Biomolecular Structure and Dynamics*, 39(9), 3092–3098.
- Heneka, M. T., Golenbock, D., Latz, E., Morgan, D., & Brown, R. (2020). Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. *Alzheimer's Research & Therapy*, 12(1), 69.
- Hossain, M. S., Urbi, Z., Sule, A., & Rahman, K. M. H. (2021). *Andrographis paniculata* (Burm. f.) Wall. ex Nees: A review of ethnobotany, phytochemistry, and pharmacology. *The Scientific World Journal*, 2021, 1–17.
- Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., ... Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, 395(10223), 497–506.

- Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., & Manson, J. J. (2020). COVID-19: Consider cytokine storm syndromes and immunosuppression. *The Lancet*, 395(10229), 1033–1034.
- Murugan, N. A., Pandian, C. J., & Jeyakanthan, J. (2020). Computational investigation on *Andrographis paniculata* phytochemicals to evaluate their potency against SARS-CoV-2 in comparison to known antiviral compounds. *Journal of Biomolecular Structure and Dynamics*, 39(12), 4415–4426.
- Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M. V., McGroder, C., Stevens, J. S., ... Wan, E. Y. (2021). Post-acute COVID-19 syndrome. *Nature Medicine*, 27(4), 601–615.
- Pastorino, G., Cornara, L., Soares, S., Rodrigues, F., & Oliveira, M. B. P. P. (2018). Liquorice (*Glycyrrhiza glabra*): A phytochemical and pharmacological review. *Phytotherapy Research*, 32(12), 2323–2339.
- Pfefferbaum, B., & North, C. S. (2020). Mental health and the COVID-19 pandemic. *New England Journal of Medicine*, 383(6), 510–512.
- Rajani, M., Shrivastava, N., & Ravishankara, M. N. (2021). Neuroprotective effects of andrographolide and its derivatives: Mechanistic perspectives and therapeutic potential. *Phytomedicine Plus*, 1(4), 100085.
- Rai, M., Ingle, A. P., Pandit, R., Paralikar, P., Anasane, N., Santos, C. A., & Duran, N. (2016). Nanotechnology-based anti-infectives and therapeutics. *Biotechnology Advances*, 34(5), 847–859.
- V'kovski, P., Kratzel, A., Steiner, S., Stalder, H., & Thiel, V. (2021). Coronavirus biology and replication: Implications for SARS-CoV-2. *Nature Reviews Microbiology*, 19(3), 155–170.
- Walls, A. C., Park, Y. J., Tortorici, M. A., Wall, A., McGuire, A. T., & Velesler, D. (2020). Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell*, 181(2), 281–292.
- World Health Organization. (2022). *Coronavirus disease (COVID-19) pandemic*. Geneva: World Health Organization.

## Chapter 3: Management of COVID-19–Associated Respiratory and Psychological Symptoms Using *Ocimum sanctum* and *Adhatoda vasica*

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### Abstract

The coronavirus disease 2019 (COVID-19) pandemic created an unprecedented global healthcare crisis characterized not only by acute respiratory illness but also by persistent psychological and neurological complications. In addition to pulmonary manifestations such as cough, bronchitis, dyspnea, and acute respiratory distress syndrome, COVID-19 has been strongly associated with anxiety, depression, stress, insomnia, fatigue, and long-COVID-related neuroimmune dysfunction. These multifactorial complications highlighted the limitations of conventional therapeutic approaches and increased interest in complementary and integrative medicine strategies utilizing medicinal plants with multitarget pharmacological activities. Among the medicinal herbs investigated for supportive COVID-19 management, *Ocimum sanctum* (Tulsi) and *Adhatoda vasica* (Vasaka) have attracted considerable scientific attention because of their antiviral, bronchodilatory, immunomodulatory, antioxidant, anti-inflammatory, adaptogenic, and neuroprotective properties. This chapter comprehensively explores the ethnopharmacology, phytochemistry, traditional therapeutic applications, and pharmacological mechanisms of *Ocimum sanctum* and *Adhatoda vasica* in the management of COVID-19-associated respiratory and psychological symptoms. Tulsi contains several bioactive phytoconstituents including eugenol, ursolic acid, rosmarinic acid, and flavonoids that contribute to immunomodulatory, antioxidant, adaptogenic, and anxiolytic effects. Similarly, Vasaka is rich in quinazoline alkaloids such as vasicine and vasicinone, which possess bronchodilatory, expectorant, anti-inflammatory, and respiratory protective activities. Experimental evidence indicates that these medicinal plants may modulate inflammatory cytokines, reduce oxidative stress, improve pulmonary function, regulate neuroimmune interactions, and alleviate stress-associated disorders. The chapter further discusses the potential antiviral and respiratory protective mechanisms of these herbs against SARS-CoV-2 infection, including regulation of inflammatory cascades, reduction of pulmonary oxidative injury, and support of respiratory recovery during long-COVID syndrome. Their neuroprotective and psychological benefits, including anxiolytic, adaptogenic, and anti-stress effects mediated through modulation of the hypothalamic–pituitary–adrenal axis and neurotransmitter systems, are also critically analyzed. In addition, the chapter highlights available *in vitro*, *in vivo*, preclinical, and clinical evidence supporting their therapeutic relevance in respiratory infections, immune dysfunction, and psychological disorders. Emerging therapeutic perspectives including nanoformulations, advanced herbal delivery systems, network pharmacology, artificial intelligence-assisted phytodrug discovery, and integrative polyherbal approaches are also explored. Despite promising pharmacological evidence, the chapter emphasizes the necessity for phytochemical standardization, biomarker-based quality control, and large-scale randomized clinical trials to establish definitive safety and efficacy profiles. Overall, *Ocimum sanctum* and *Adhatoda vasica* represent valuable medicinal plants with significant therapeutic potential for the supportive management of COVID-19-associated respiratory and psychological complications. Their multitarget pharmacological actions highlight the importance of integrating traditional medicinal knowledge with modern biomedical research for future pandemic preparedness and holistic healthcare strategies.

### Keywords

COVID-19; SARS-CoV-2; *Ocimum sanctum*; *Adhatoda vasica*; Tulsi; Vasaka; antiviral activity; bronchodilator

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## 1. Introduction

The emergence of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulted in one of the most devastating global public health crises in modern history. Since its first identification in Wuhan, China, in late 2019, COVID-19 rapidly spread across continents, causing millions of infections, deaths, economic disruptions, and long-term healthcare challenges (Huang et al., 2020). Although the disease initially presented primarily as an acute respiratory infection, subsequent clinical observations revealed its multisystemic nature involving inflammatory, cardiovascular, neurological, immunological, and psychological complications. Even after recovery from acute infection, many individuals continued to experience persistent respiratory impairment, chronic fatigue, cognitive dysfunction, anxiety, depression, and long-COVID-associated neuroimmune abnormalities.

SARS-CoV-2 primarily targets the respiratory system through interaction between the viral spike glycoprotein and angiotensin-converting enzyme 2 (ACE2) receptors expressed in pulmonary epithelial tissues. Viral replication within respiratory cells triggers immune activation and inflammatory cascades that may progress to pneumonia, bronchitis, pulmonary fibrosis, acute respiratory distress syndrome (ARDS), and severe respiratory failure (V'kovski et al., 2021). Excessive production of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin-1 beta (IL-1 $\beta$ ) contributes to cytokine storm syndrome, oxidative stress, endothelial dysfunction, and tissue injury. Persistent inflammation and oxidative damage are also implicated in long-COVID respiratory complications characterized by chronic cough, dyspnea, reduced pulmonary function, and prolonged respiratory weakness.

In addition to respiratory manifestations, the COVID-19 pandemic profoundly affected mental and neurological health worldwide. Social isolation, fear of infection, uncertainty, financial instability, prolonged hospitalization, and post-viral immune dysregulation significantly increased the prevalence of anxiety, depression, insomnia, stress, emotional exhaustion, and cognitive disturbances (Pfefferbaum & North, 2020). Neuroinflammation, oxidative neuronal injury, mitochondrial dysfunction, and dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis further contributed to neuropsychiatric complications observed in long-COVID syndrome. Consequently, management of COVID-19 requires not only antiviral and respiratory support but also strategies capable of addressing psychological and neuroimmune disturbances.

Although several antiviral drugs, corticosteroids, immunomodulators, and supportive therapies have been employed in COVID-19 management, conventional therapeutic approaches possess significant limitations including variable efficacy, adverse effects, high treatment costs, limited accessibility, and inability to adequately address chronic post-viral symptoms. These challenges have stimulated growing scientific interest in complementary and integrative medicine approaches utilizing medicinal plants with multitarget pharmacological activities.

Traditional medicinal systems such as Ayurveda, Traditional Chinese Medicine (TCM), Siddha, and Unani medicine have historically employed medicinal herbs for the management of respiratory infections, inflammatory disorders, immune dysfunctions, and stress-associated conditions. During the COVID-19 pandemic, several medicinal plants attracted considerable attention because of their antiviral, bronchodilatory, antioxidant, immunomodulatory, anti-inflammatory, adaptogenic, and neuroprotective properties. Among these, *Ocimum sanctum* (Tulsi/Holy Basil) and *Adhatoda vasica* (Vasaka/Malabar Nut) are particularly important because of their extensive traditional use in respiratory and psychological disorders.

*Ocimum sanctum* is regarded in Ayurveda as a sacred medicinal plant possessing Rasayana (rejuvenating) properties. It contains several bioactive compounds including eugenol, ursolic acid, rosmarinic acid, and flavonoids that contribute to antioxidant, antiviral, anti-inflammatory, adaptogenic, anxiolytic, and immunomodulatory effects (Jamshidi & Cohen, 2017). Traditionally, Tulsi has been used for the treatment of cough, bronchitis, asthma, fever, stress, fatigue, and immune disorders. Modern pharmacological studies further support its respiratory protective and neuroprotective potential through regulation of oxidative stress, inflammatory mediators, and neuroimmune pathways.

Similarly, *Adhatoda vasica* is a well-known medicinal plant widely used in Ayurveda and traditional medicine for respiratory ailments including asthma, bronchitis, cough, dyspnea, and pulmonary inflammation. The plant is rich in quinazoline alkaloids such as vasicine and vasicinone, which exhibit bronchodilatory, expectorant, mucolytic, antioxidant, and anti-inflammatory activities (Claeson et al., 2000). These pharmacological properties suggest potential utility of *Adhatoda vasica* in alleviating COVID-19-associated respiratory symptoms and pulmonary complications.

The combined therapeutic relevance of *Ocimum sanctum* and *Adhatoda vasica* lies in their ability to simultaneously target respiratory inflammation, oxidative stress, immune dysregulation, and psychological disturbances. Their multitarget pharmacological profile may provide supportive benefits in managing cough, bronchitis, dyspnea, anxiety, stress, insomnia, and long-COVID-associated respiratory and neuropsychological complications. Furthermore, growing evidence from experimental, preclinical, and computational studies indicates potential antiviral mechanisms against SARS-CoV-2 through modulation of inflammatory pathways, immune responses, and viral replication-associated targets.

Therefore, this chapter aims to comprehensively explore the ethnopharmacology, phytochemistry, traditional uses, respiratory protective mechanisms, neuropsychological effects, experimental evidence, and future therapeutic perspectives of *Ocimum sanctum* and *Adhatoda vasica* in the management of COVID-19-associated respiratory and psychological symptoms. The chapter further highlights emerging integrative medicine approaches, nanoformulations, and future research priorities for the development of evidence-based phytotherapeutic interventions against respiratory viral infections and post-pandemic health complications.

## 2. Ethnopharmacology, Phytochemistry, and Traditional Uses

### 2.1 *Ocimum sanctum*

#### Ayurvedic and Traditional Importance

*Ocimum sanctum* L., commonly known as Tulsi or Holy Basil, is one of the most revered medicinal plants in Ayurveda and is traditionally regarded as the “Queen of Herbs” because of its extensive therapeutic applications. In Ayurvedic medicine, Tulsi is classified as a Rasayana herb that promotes longevity, vitality, immunity, and mental well-being. The plant has historically been used for managing respiratory disorders, fever, cough, asthma, digestive disturbances, inflammatory conditions, and stress-related illnesses (Jamshidi & Cohen, 2017).

Beyond Ayurveda, Tulsi is widely utilized in Siddha, Unani, and folk medicinal systems across India and Southeast Asia. Traditional healers have employed Tulsi leaves, seeds, and essential oils in herbal decoctions, teas, and formulations intended to enhance resistance against infections and improve respiratory health. During seasonal viral outbreaks and influenza-like illnesses, Tulsi has been traditionally administered for relief from cough, sore throat, fever, and bronchial congestion.

The adaptogenic and anxiolytic properties of Tulsi have also been extensively recognized in traditional medicine. It has been used to reduce stress, mental fatigue, emotional instability, insomnia, and cognitive weakness. Such traditional applications gained renewed significance during the COVID-19 pandemic because of increasing psychological disturbances and immune dysfunction among infected and recovered individuals.

#### Botanical Description and Distribution

*Ocimum sanctum* belongs to the family Lamiaceae and is an aromatic perennial or annual herb characterized by highly branched stems, green or purple leaves, and strongly fragrant essential oils. The plant typically grows to a height of 30–60 cm and bears small purplish or white flowers arranged in terminal racemes.

Taxonomically, the plant is classified as:

- Kingdom: Plantae
- Family: Lamiaceae
- Genus: *Ocimum*
- Species: *Ocimum sanctum*

Tulsi is widely cultivated throughout India, Nepal, Sri Lanka, Thailand, and other tropical and subtropical regions. It thrives under warm climatic conditions and is commonly grown in household gardens because of both medicinal and spiritual significance.

## Major Phytoconstituents

The pharmacological activities of *Ocimum sanctum* are attributed to a wide range of bioactive phytochemicals including essential oils, flavonoids, phenolic compounds, and triterpenoids.

### *Eugenol*

Eugenol is one of the principal active constituents of Tulsi essential oil and exhibits potent anti-inflammatory, antioxidant, antimicrobial, and analgesic properties. It contributes significantly to respiratory protection through suppression of inflammatory mediators and oxidative stress.

### *Ursolic Acid*

Ursolic acid is a pentacyclic triterpenoid possessing anti-inflammatory, antiviral, antioxidant, and immunomodulatory activities. Experimental studies suggest that ursolic acid may inhibit inflammatory pathways and reduce oxidative tissue damage associated with viral infections.

### *Rosmarinic Acid*

Rosmarinic acid is a polyphenolic compound with strong antioxidant and neuroprotective effects. It scavenges reactive oxygen species and modulates inflammatory signaling pathways, thereby contributing to neuronal and pulmonary protection.

### *Flavonoids and Essential Oils*

Tulsi contains various flavonoids including apigenin, luteolin, and orientin along with essential oils rich in methyl eugenol, carvacrol, and linalool. These compounds exhibit antimicrobial, adaptogenic, antioxidant, anxiolytic, and immunomodulatory activities.

## Traditional Therapeutic Applications

### *Respiratory Tract Infections and Pulmonary Disorders*

Tulsi has long been used in the management of cough, cold, bronchitis, asthma, influenza, sore throat, and pulmonary congestion. Traditional Ayurvedic preparations involving Tulsi decoctions and herbal infusions are widely prescribed for improving respiratory function and relieving bronchial inflammation.

### *Adaptogenic and Anti-stress Uses*

The plant is traditionally considered an adaptogen capable of enhancing physiological resilience against stress and environmental challenges. Tulsi has been administered for reducing anxiety, fatigue, emotional stress, insomnia, and cognitive exhaustion.

### *Immunomodulatory and Anti-inflammatory Effects*

Traditional medicinal systems also utilize Tulsi for strengthening immunity and reducing inflammatory disorders. Its immunomodulatory actions may help improve host defense mechanisms and reduce susceptibility to respiratory infections.

## **2.2 Adhatoda vasica**

### **Traditional and Medicinal Importance**

*Adhatoda vasica* Nees, commonly known as Vasaka or Malabar Nut, is an important medicinal plant extensively used in Ayurveda, Siddha, and Unani medicine for respiratory ailments. The plant is traditionally regarded as one of the most effective herbal remedies for bronchitis, asthma, chronic cough, dyspnea, and pulmonary congestion (Claeson et al., 2000).

In Ayurveda, Vasaka is described as possessing expectorant, bronchodilatory, anti-inflammatory, and hemostatic properties. Traditional formulations prepared from leaves and roots are frequently administered for respiratory tract infections and inflammatory pulmonary disorders.

The plant also holds significance in traditional medicine because of its antimicrobial, antioxidant, antitussive, and mucolytic activities. During the COVID-19 pandemic, renewed scientific interest emerged regarding its potential utility in managing respiratory complications associated with SARS-CoV-2 infection.

### **Botanical Characteristics and Distribution**

*Adhatoda vasica* belongs to the family Acanthaceae and is a perennial evergreen shrub growing up to 1–3 meters in height. The plant possesses large lanceolate leaves, white flowers with purple streaks, and capsule-shaped fruits.

Taxonomic classification includes:

- Kingdom: Plantae
- Family: Acanthaceae
- Genus: *Adhatoda*
- Species: *Adhatoda vasica*

The plant is widely distributed across India, Nepal, Sri Lanka, Pakistan, Bangladesh, and Southeast Asian countries. It grows naturally in plains and sub-Himalayan regions and is also cultivated for medicinal purposes.

## Major Bioactive Constituents

### *Vasicine*

Vasicine is the principal quinazoline alkaloid present in *Adhatoda vasica* and is primarily responsible for bronchodilatory, expectorant, and respiratory stimulant activities. It facilitates bronchial smooth muscle relaxation and improves mucociliary clearance.

### *Vasicinone*

Vasicinone is an oxidized derivative of vasicine that exhibits bronchodilator and respiratory protective effects. Together, vasicine and vasicinone contribute synergistically to pulmonary therapeutic activity.

### *Quinazoline Alkaloids*

The plant contains several quinazoline alkaloids possessing anti-inflammatory, antimicrobial, antioxidant, and respiratory protective properties. These compounds help reduce airway inflammation and oxidative tissue injury.

### *Essential Oils and Flavonoids*

Various flavonoids, essential oils, and phenolic compounds present in the plant contribute antioxidant and anti-inflammatory activities that support pulmonary protection and immune regulation.

## Traditional Therapeutic Applications

### *Bronchodilator and Expectorant Uses*

*Adhatoda vasica* has traditionally been used as a natural bronchodilator and expectorant in asthma, chronic bronchitis, productive cough, and respiratory congestion. Herbal preparations assist in mucus clearance and improve airflow through relaxation of bronchial muscles.

### *Management of Cough, Asthma, and Dyspnea*

Traditional medicine systems widely employ Vasaka formulations for relieving cough, wheezing, dyspnea, and inflammatory airway conditions. The plant is also used in chronic pulmonary disorders associated with excessive mucus production and respiratory irritation.

### *Anti-inflammatory and Antimicrobial Applications*

The anti-inflammatory and antimicrobial activities of *Adhatoda vasica* support its use in respiratory infections, throat irritation, and inflammatory pulmonary disorders. Its antioxidant properties may additionally protect respiratory tissues against oxidative stress-mediated injury.

### 2.3 Comparative Phytochemical and Pharmacological Profile

Both *Ocimum sanctum* and *Adhatoda vasica* exhibit significant pharmacological activities relevant to COVID-19-associated respiratory and psychological complications. However, their dominant therapeutic mechanisms and phytochemical compositions differ.

*Ocimum sanctum* is primarily rich in essential oils, flavonoids, and phenolic compounds that exert adaptogenic, anxiolytic, antioxidant, antiviral, and immunomodulatory activities. In contrast, *Adhatoda vasica* is particularly known for its quinazoline alkaloids responsible for bronchodilatory, expectorant, and pulmonary protective effects.

Despite these differences, both medicinal plants demonstrate anti-inflammatory, antioxidant, antimicrobial, and respiratory protective properties. Their combined use may provide synergistic therapeutic benefits in respiratory inflammation, stress-associated disorders, and long-COVID syndrome.

**Table 1. Comparative Phytochemical and Pharmacological Profile of *Ocimum sanctum* and *Adhatoda vasica***

Parameter	<i>Ocimum sanctum</i>	<i>Adhatoda vasica</i>
Common Name	Tulsi / Holy Basil	Vasaka / Malabar Nut
Major Traditional Systems	Ayurveda, Siddha, Unani	Ayurveda, Siddha, Unani
Major Bioactive Constituents	Eugenol, ursolic acid, rosmarinic acid	Vasicine, vasicinone, quinazoline alkaloids
Dominant Chemical Class	Essential oils and flavonoids	Quinazoline alkaloids
Primary Pharmacological Activities	Adaptogenic, antiviral, anxiolytic	Bronchodilator, expectorant, antitussive
Respiratory Therapeutic Effects	Relief in cough and bronchial inflammation	Airway relaxation and mucus clearance
Neuropsychological Effects	Anti-stress and anxiolytic activity	Mild neuroprotective and antioxidant effects
Anti-inflammatory Mechanisms	Cytokine suppression and antioxidant action	Reduction of airway inflammation
Immunomodulatory Activity	Enhancement of immune resilience	Respiratory immune support
COVID-19 Relevance	Stress reduction and respiratory protection	Pulmonary support and bronchodilation
Therapeutic Limitation	Limited clinical COVID-19 evidence	Limited neuropsychological investigations
Potential Combined Benefit	Adaptogenic and antioxidant support	Bronchodilatory and expectorant synergy

### 3. Respiratory Protective Mechanisms Against COVID-19

#### 3.1 Respiratory Pathophysiology of COVID-19

Coronavirus disease 2019 (COVID-19) primarily affects the respiratory system because severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters host cells through interaction between viral spike glycoproteins and angiotensin-converting enzyme 2 (ACE2) receptors expressed abundantly on pulmonary epithelial cells. Following viral entry, replication within respiratory tissues triggers inflammatory and immune responses that may progress from mild upper respiratory symptoms to severe pneumonia, acute respiratory distress syndrome (ARDS), pulmonary fibrosis, and respiratory failure (V'kovski et al., 2021).

The progression of pulmonary injury in COVID-19 involves excessive activation of inflammatory pathways and release of pro-inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-1 beta (IL-1 $\beta$ ), and interferons. This hyperinflammatory response, commonly referred to as cytokine storm syndrome, contributes to endothelial dysfunction, vascular leakage, oxidative stress, immune dysregulation, and extensive lung tissue injury (Del Valle et al., 2020).

Oxidative stress plays a critical role in COVID-19-associated pulmonary damage. Excessive generation of reactive oxygen species (ROS) during viral infection damages alveolar epithelial cells, mitochondrial membranes, and pulmonary vasculature, resulting in impaired oxygen exchange and respiratory dysfunction. Persistent inflammation and oxidative injury are also associated with long-COVID respiratory complications including chronic cough, dyspnea, fatigue, reduced pulmonary capacity, and prolonged respiratory weakness.

These pathological mechanisms have stimulated scientific interest in medicinal plants possessing bronchodilatory, anti-inflammatory, antioxidant, immunomodulatory, and antiviral activities capable of protecting respiratory tissues and supporting pulmonary recovery.

#### 3.2 Respiratory Protective Actions of *Ocimum sanctum*

##### Anti-inflammatory and Antioxidant Mechanisms

*Ocimum sanctum* possesses significant anti-inflammatory and antioxidant properties attributed to phytoconstituents such as eugenol, ursolic acid, rosmarinic acid, flavonoids, and essential oils. These bioactive compounds suppress inflammatory signaling pathways including nuclear factor-kappa B (NF- $\kappa$ B), cyclooxygenase-2 (COX-2), and pro-inflammatory cytokine production (Jamshidi & Cohen, 2017).

Experimental investigations demonstrate that Tulsi extracts reduce levels of IL-6, TNF- $\alpha$ , and IL-1 $\beta$ , thereby limiting inflammatory tissue injury and oxidative pulmonary damage. Its antioxidant properties further protect respiratory tissues through scavenging of reactive oxygen species and enhancement of endogenous antioxidant enzymes such as superoxide dismutase and catalase.

## Immunomodulatory and Antiviral Effects

Tulsi exhibits immunomodulatory activity through regulation of both innate and adaptive immune responses. Studies indicate that *Ocimum sanctum* enhances macrophage activity, natural killer cell function, and lymphocyte proliferation while simultaneously controlling excessive inflammatory responses.

Several phytochemicals present in Tulsi have also demonstrated antiviral activity against respiratory pathogens. Computational and experimental studies suggest that Tulsi-derived compounds may interfere with viral replication, inflammatory signaling, and oxidative stress pathways relevant to SARS-CoV-2 infection.

## Bronchoprotective and Antitussive Properties

Traditionally, Tulsi has been extensively used for cough, bronchitis, asthma, and respiratory congestion. The plant exhibits bronchodilatory and antitussive effects that help improve airflow, reduce bronchial irritation, and alleviate respiratory discomfort.

Its essential oils contribute mucolytic and antimicrobial activities that support clearance of respiratory secretions and reduction of secondary microbial infections. Such effects may provide supportive therapeutic benefits in COVID-19-associated respiratory inflammation and long-COVID pulmonary complications.

## Experimental Evidence in Respiratory Disorders

Experimental animal models demonstrate that *Ocimum sanctum* protects pulmonary tissues against inflammatory injury, oxidative stress, and allergen-induced bronchoconstriction. Studies also indicate reduced pulmonary edema, improved respiratory function, and decreased inflammatory infiltration following Tulsi administration.

These findings support the potential utility of *Ocimum sanctum* as a complementary therapeutic agent in respiratory viral infections and inflammatory pulmonary disorders.

### 3.3 Respiratory Protective Actions of *Adhatoda vasica*

#### Bronchodilatory and Mucolytic Effects

*Adhatoda vasica* is widely recognized for its potent bronchodilatory and expectorant activities primarily mediated by quinazoline alkaloids such as vasicine and vasicinone. These compounds relax bronchial smooth muscles, facilitate bronchodilation, and improve respiratory airflow (Claeson et al., 2000).

The plant also possesses mucolytic properties that help liquefy and expel mucus from respiratory passages. Such effects are particularly beneficial in bronchitis, productive cough, airway congestion, and inflammatory pulmonary disorders associated with COVID-19.

## Regulation of Airway Inflammation

Inflammatory airway obstruction is a major contributor to respiratory distress in viral infections. *Adhatoda vasica* exhibits significant anti-inflammatory activity through suppression of inflammatory mediators, reduction of leukocyte infiltration, and inhibition of oxidative tissue damage.

Experimental evidence indicates that vasicine and related alkaloids reduce bronchial inflammation, airway hyperresponsiveness, and pulmonary oxidative injury. These pharmacological actions may contribute to respiratory protection during acute SARS-CoV-2 infection and long-COVID-associated pulmonary dysfunction.

## Expectorant and Antiasthmatic Mechanisms

Traditional Ayurvedic medicine extensively utilizes Vasaka formulations for asthma, chronic bronchitis, dyspnea, and wheezing disorders. The expectorant action of the plant facilitates mucus clearance from the respiratory tract, thereby improving airway patency and oxygen exchange.

Its bronchodilatory effects further reduce bronchospasm and respiratory discomfort. Combined expectorant and antiasthmatic activities make *Adhatoda vasica* particularly valuable in inflammatory respiratory conditions characterized by mucus accumulation and airway obstruction.

## Experimental and Clinical Evidence in Pulmonary Disorders

Preclinical studies demonstrate that *Adhatoda vasica* improves respiratory function, reduces airway inflammation, and protects pulmonary tissues against oxidative injury. Clinical evidence also supports its traditional use in asthma, cough, and bronchitis management.

The plant has shown therapeutic potential in reducing cough frequency, improving expectoration, relieving dyspnea, and enhancing pulmonary comfort. Such pharmacological properties suggest possible supportive benefits in COVID-19 respiratory symptom management.

### 3.4 Combined Therapeutic Potential in COVID-19 Respiratory Symptoms

#### Herbal Synergy in Respiratory Protection

The combined use of *Ocimum sanctum* and *Adhatoda vasica* may provide synergistic therapeutic effects because of complementary pharmacological mechanisms. While Tulsi predominantly contributes antiviral, antioxidant, immunomodulatory, and adaptogenic benefits, Vasaka primarily provides bronchodilatory, expectorant, and pulmonary protective actions.

This synergistic interaction may simultaneously target:

- Viral-induced respiratory inflammation
- Oxidative pulmonary injury
- Bronchial congestion and mucus accumulation

- Cytokine-mediated tissue damage
- Respiratory discomfort and cough

### Supportive Role in Long-COVID Respiratory Recovery

Persistent respiratory symptoms are common in long-COVID syndrome and may include chronic cough, dyspnea, fatigue, and reduced pulmonary function. The antioxidant, anti-inflammatory, bronchodilatory, and respiratory restorative properties of these medicinal plants may support pulmonary rehabilitation and respiratory recovery.

Additionally, Tulsi's adaptogenic and anti-stress properties may help reduce psychological stress associated with chronic respiratory illness and prolonged recovery periods.

### Safety Considerations and Dosage Perspectives

Both medicinal plants are generally considered safe at recommended therapeutic doses; however, excessive or prolonged use may produce adverse effects. Tulsi may occasionally cause mild gastrointestinal discomfort or interact with anticoagulant medications, whereas excessive use of Vasaka may produce gastrointestinal irritation or hypotensive effects.

Proper standardization, dosage regulation, and clinical supervision remain essential for safe and effective therapeutic application.

**Table 2. Respiratory Protective Mechanisms of *Ocimum sanctum* and *Adhatoda vasica* in COVID-19**

Pharmacological Aspect	<i>Ocimum sanctum</i>	<i>Adhatoda vasica</i>	Therapeutic Relevance in COVID-19
Major Active Constituents	Eugenol, ursolic acid, rosmarinic acid	Vasicine, vasicinone	Respiratory and inflammatory protection
Dominant Pharmacological Action	Antioxidant and immunomodulatory	Bronchodilator and expectorant	Multitarget pulmonary support
Anti-inflammatory Effects	Suppression of IL-6, TNF- $\alpha$ , NF- $\kappa$ B	Reduction of airway inflammation	Cytokine storm mitigation
Antioxidant Activity	ROS scavenging and mitochondrial protection	Reduction of oxidative pulmonary injury	Protection against lung tissue damage
Bronchodilatory Action	Mild bronchoprotective effect	Strong bronchodilator activity	Improved respiratory airflow
Expectorant Activity	Mucolytic and antimicrobial support	Potent mucus clearance activity	Relief from congestion and cough
Antiviral Potential	Viral replication modulation	Indirect respiratory protective role	Supportive antiviral activity
Long-COVID Relevance	Stress reduction and immune support	Pulmonary rehabilitation support	Recovery enhancement
Traditional Respiratory	Asthma, bronchitis,	Asthma, dyspnea,	Historical therapeutic

Uses	cough	bronchitis	validation
Therapeutic Limitation	Limited direct clinical COVID evidence	Limited antiviral-specific investigations	Need for clinical validation

## 4. Psychological and Neuroprotective Effects

### 4.1 Psychological Consequences of COVID-19

The COVID-19 pandemic significantly affected global mental health and contributed to a dramatic rise in anxiety, depression, stress, insomnia, emotional exhaustion, and neuropsychiatric disorders. Fear of infection, social isolation, economic uncertainty, prolonged hospitalization, grief, and post-viral complications collectively produced widespread psychological distress across all age groups (Pfefferbaum & North, 2020). In addition to psychosocial stressors, SARS-CoV-2 infection itself has been associated with neurological and neuroimmune alterations capable of contributing to cognitive and emotional dysfunction.

Neuroinflammation represents one of the major mechanisms underlying COVID-19-associated neurological complications. Excessive inflammatory cytokine production, oxidative stress, endothelial dysfunction, and mitochondrial injury may disrupt neuronal homeostasis and promote neuronal damage (Ellul et al., 2020). Elevated levels of IL-6, TNF- $\alpha$ , and reactive oxygen species contribute to blood–brain barrier disruption, microglial activation, neurotransmitter imbalance, and neurodegenerative processes.

Long-COVID syndrome has further intensified concerns regarding persistent neuropsychiatric symptoms. Many recovered individuals continue to experience anxiety, depression, chronic fatigue, insomnia, impaired concentration, memory deficits, and cognitive dysfunction for months after infection. Stress-induced dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and prolonged inflammatory activation may contribute to these chronic psychological disturbances.

Because conventional pharmacological management of stress and anxiety often involves adverse effects and long-term dependency concerns, medicinal plants possessing adaptogenic, anxiolytic, antioxidant, and neuroprotective properties have gained increasing scientific attention as supportive therapeutic alternatives.

### 4.2 Neuroprotective and Adaptogenic Role of *Ocimum sanctum*

#### Adaptogenic and Anti-stress Properties

*Ocimum sanctum* has traditionally been regarded in Ayurveda as an adaptogenic herb capable of improving physiological resilience against stress and environmental challenges. Adaptogens help normalize stress responses and maintain homeostasis during physical and psychological disturbances.

Experimental and clinical studies suggest that Tulsi reduces stress-related biochemical alterations, improves emotional stability, and enhances stress tolerance (Jamshidi & Cohen, 2017). Its adaptogenic properties may be particularly relevant in individuals experiencing pandemic-associated anxiety, emotional fatigue, and long-COVID psychological complications.

## Regulation of Cortisol and the HPA Axis

Chronic stress activates the hypothalamic–pituitary–adrenal axis and elevates cortisol secretion, contributing to immune dysregulation, anxiety, depression, sleep disturbances, and cognitive impairment. Tulsi has demonstrated regulatory effects on stress hormones and HPA axis activity, thereby reducing physiological stress responses.

Bioactive compounds such as eugenol, rosmarinic acid, and flavonoids modulate stress-associated neurochemical pathways and improve neuroendocrine balance. These mechanisms may contribute to reduction of anxiety, emotional exhaustion, and stress-induced immune dysfunction.

## Antioxidant-mediated Neuroprotection

Oxidative stress is strongly implicated in neurodegeneration, neuroinflammation, and cognitive dysfunction. Tulsi contains potent antioxidant phytochemicals capable of scavenging reactive oxygen species and protecting neuronal tissues from oxidative injury.

Experimental studies demonstrate that *Ocimum sanctum* enhances endogenous antioxidant defense systems including superoxide dismutase, catalase, and glutathione peroxidase. Such antioxidant activity may help reduce neuronal damage associated with inflammatory and viral conditions including COVID-19.

## Evidence in Anxiety and Cognitive Dysfunction

Animal and human studies indicate that Tulsi possesses anxiolytic, antidepressant-like, and cognitive-enhancing properties. Administration of Tulsi extracts has been associated with improved memory, reduced anxiety-like behavior, enhanced concentration, and better stress adaptation.

These neuroprotective actions are believed to involve modulation of cholinergic pathways, neurotransmitter balance, inflammatory mediators, and oxidative stress markers.

## 4.3 Neuroprotective Role of *Adhatoda vasica*

### Anti-inflammatory and Antioxidant Neuronal Protection

Although *Adhatoda vasica* is primarily recognized for respiratory therapeutic applications, increasing evidence suggests that it also possesses neuroprotective potential through antioxidant and anti-inflammatory mechanisms. Quinazoline alkaloids and flavonoids present in the plant reduce oxidative stress-mediated neuronal injury and suppress inflammatory signaling pathways.

Inflammatory cytokines and oxidative damage contribute significantly to neurodegeneration and stress-associated neurological dysfunction. The antioxidant constituents of *Adhatoda vasica* may therefore provide indirect neuroprotective benefits during inflammatory and viral illnesses.

## Effects on Stress-related Oxidative Injury

Stress-induced oxidative damage disrupts neuronal membrane integrity, mitochondrial function, and neurotransmitter balance. Experimental studies indicate that *Adhatoda vasica* extracts reduce lipid peroxidation and improve antioxidant enzyme activity in stress-associated conditions. These protective effects may help minimize neuronal injury associated with chronic stress, systemic inflammation, and long-COVID-related neuroimmune disturbances.

## Potential Anxiolytic and Neuroimmune Regulatory Actions

Preliminary pharmacological investigations suggest that *Adhatoda vasica* may possess mild anxiolytic and neuroimmune modulatory activities. Reduction of inflammatory mediators and oxidative stress may contribute to improved neuronal stability and emotional balance.

Although direct evidence related to neuropsychiatric disorders remains limited compared to Tulsi, the plant's anti-inflammatory and antioxidant properties support its possible role in supportive neuroprotection.

## 4.4 Mechanistic Insights

### Neuroimmune Interactions and Inflammatory Pathways

COVID-19-associated neuropsychiatric complications involve complex interactions between immune activation and neuronal signaling pathways. Excessive cytokine release activates microglia and neuroinflammatory pathways that impair synaptic function and neurotransmitter regulation. Both *Ocimum sanctum* and *Adhatoda vasica* suppress inflammatory mediators including IL-6, TNF- $\alpha$ , and NF- $\kappa$ B signaling pathways. Such actions may help reduce neuroinflammation and protect neuronal tissues from inflammatory injury.

### Regulation of Neurotransmitters and Oxidative Stress

Oxidative stress disrupts neurotransmitter metabolism and contributes to anxiety, depression, and cognitive impairment. Tulsi phytochemicals influence neurotransmitter systems including dopamine, serotonin, acetylcholine, and gamma-aminobutyric acid (GABA), thereby improving emotional stability and cognitive function. Antioxidant activities of both medicinal plants further reduce oxidative neuronal damage and maintain neuronal membrane integrity.

### Mitochondrial Protection and Neuronal Survival

Mitochondrial dysfunction is increasingly recognized in COVID-19-associated neurodegeneration and chronic fatigue syndrome. Antioxidant compounds present in Tulsi and Vasaka may stabilize mitochondrial membranes, reduce oxidative injury, and support neuronal energy metabolism.

Such mitochondrial protective mechanisms may contribute to improved neuronal survival, reduced fatigue, and enhanced cognitive recovery during post-viral rehabilitation.

**Table 3. Neuroprotective and Psychological Effects of *Ocimum sanctum* and *Adhatoda vasica***

Pharmacological Aspect	<i>Ocimum sanctum</i>	<i>Adhatoda vasica</i>	Relevance in COVID-19
Major Neuroactive Constituents	Eugenol, rosmarinic acid, flavonoids	Vasicine, flavonoids, alkaloids	Neuroimmune modulation
Dominant Psychological Effect	Adaptogenic and anxiolytic	Antioxidant-mediated neuroprotection	Stress and anxiety reduction
Anti-inflammatory Action	Suppression of cytokines and NF- $\kappa$ B	Reduction of oxidative inflammation	Neuroinflammation control
Antioxidant Activity	Strong ROS scavenging activity	Reduction of oxidative neuronal injury	Neuronal protection
HPA Axis Regulation	Cortisol modulation and stress adaptation	Indirect stress protective effect	Stress management
Neurotransmitter Modulation	Dopamine, serotonin, acetylcholine regulation	Limited evidence available	Emotional stabilization
Cognitive Effects	Memory enhancement and concentration improvement	Potential neuronal stabilization	Long-COVID cognitive support
Mitochondrial Protection	Improved neuronal energy metabolism	Reduction of oxidative mitochondrial injury	Fatigue and neuronal recovery
Clinical Psychological Relevance	Anxiety, stress, insomnia management	Supportive neuroprotective role	Post-pandemic mental health support
Major Limitation	Limited large-scale neuroclinical trials	Insufficient neuropsychiatric studies	Need for clinical validation

## 5. Experimental, Preclinical, and Clinical Evidence

### 5.1 In Vitro Studies

#### Antiviral and Respiratory Pharmacological Investigations

Extensive in vitro investigations have explored the antiviral, anti-inflammatory, antioxidant, and respiratory protective properties of *Ocimum sanctum* and *Adhatoda vasica*. These studies provide important mechanistic evidence supporting their potential utility in COVID-19-associated respiratory and psychological complications.

Extracts of *Ocimum sanctum* demonstrated inhibitory effects against several viral pathogens including influenza viruses, enteroviruses, herpes viruses, and other respiratory infectious agents. Tursi phytochemicals such as eugenol, ursolic acid, rosmarinic acid, and flavonoids exhibit antiviral activity through modulation of viral replication, inflammatory mediators, and oxidative stress pathways (Cohen, 2014).

Experimental investigations further indicate that Tulsi suppresses pro-inflammatory cytokines including IL-6, TNF- $\alpha$ , and IL-1 $\beta$  while reducing reactive oxygen species production in inflammatory cell models. Such actions are particularly relevant in COVID-19 because excessive inflammatory responses and oxidative pulmonary injury contribute significantly to respiratory complications.

Similarly, *Adhatoda vasica* extracts demonstrated antimicrobial, anti-inflammatory, bronchodilatory, and antioxidant activities in cellular models. Quinazoline alkaloids including vasicine and vasicinone exhibited respiratory protective effects through suppression of airway inflammation and improvement of bronchial relaxation.

### **Molecular Docking Studies Against SARS-CoV-2 Targets**

During the COVID-19 pandemic, molecular docking and computational investigations became important approaches for screening phytochemicals against SARS-CoV-2 targets.

Several docking studies reported strong binding interactions between Tulsi-derived phytochemicals and viral proteins including:

- SARS-CoV-2 main protease (Mpro/3CLpro)
- Spike glycoprotein
- RNA-dependent RNA polymerase (RdRp)
- ACE2 receptor-associated pathways

Ursolic acid and eugenol demonstrated favorable binding affinity toward viral replication-associated enzymes and inflammatory targets involved in SARS-CoV-2 pathogenesis.

Similarly, vasicine and related alkaloids from *Adhatoda vasica* showed potential interactions with inflammatory mediators and respiratory protective signaling pathways. Computational studies suggest that these phytochemicals may contribute indirectly to respiratory protection through anti-inflammatory and antioxidant mechanisms.

### **Anti-inflammatory and Antioxidant Screening**

Cell culture studies demonstrated that both medicinal plants reduce inflammatory mediator production and oxidative stress markers. Tulsi extracts inhibited nitric oxide production, lipid peroxidation, and cytokine-induced cellular injury.

*Adhatoda vasica* similarly exhibited antioxidant activity through scavenging free radicals and protecting cellular membranes against oxidative damage. Such effects may help reduce pulmonary tissue injury during respiratory viral infections.

## 5.2 In Vivo Experimental Studies

### Animal Models of Respiratory Inflammation and Viral Disorders

Experimental animal studies have provided substantial evidence supporting the respiratory protective and immunomodulatory effects of *Ocimum sanctum* and *Adhatoda vasica*.

In vivo investigations demonstrated that Tulsi administration reduces pulmonary inflammation, airway hyperresponsiveness, oxidative stress, and inflammatory cytokine production in respiratory disease models. Experimental models of asthma and bronchitis showed improvement in bronchial constriction, mucus accumulation, and respiratory distress following Tulsi treatment (Mondal et al., 2009).

Animal studies further revealed immunomodulatory effects including enhancement of macrophage activity, lymphocyte proliferation, and antioxidant enzyme activity. Such findings suggest potential supportive roles in viral respiratory infections characterized by immune dysregulation and oxidative pulmonary injury.

Similarly, *Adhatoda vasica* exhibited significant bronchodilatory, expectorant, and anti-inflammatory effects in experimental respiratory models. Vasicine and vasicinone improved airway patency, reduced bronchospasm, and facilitated mucus clearance.

### Bronchodilatory and Neurobehavioral Outcomes

Experimental studies demonstrated that *Adhatoda vasica* relaxes bronchial smooth muscles and improves respiratory airflow, supporting its traditional use in asthma and bronchitis. Reduction of airway inflammation and pulmonary oxidative injury further contributes to respiratory protection.

Tulsi additionally demonstrated anxiolytic and adaptogenic effects in animal models of stress and anxiety. Administration of Tulsi extracts improved stress tolerance, reduced anxiety-like behavior, enhanced cognitive performance, and normalized stress-associated biochemical parameters.

### Immunological and Oxidative Stress Markers

Both medicinal plants significantly influence oxidative stress and inflammatory biomarkers. Experimental studies reported:

- Reduction of lipid peroxidation
- Decreased inflammatory cytokine levels
- Enhancement of antioxidant enzymes
- Improved mitochondrial stability
- Reduced oxidative pulmonary damage

These findings support their multitarget therapeutic potential in respiratory and neuroimmune disorders associated with COVID-19.

### 5.3 Clinical Trials and Human Studies

#### Clinical Evidence in Respiratory Infections and Asthma

Clinical investigations involving *Ocimum sanctum* demonstrated beneficial effects in respiratory disorders including cough, bronchitis, asthma, and upper respiratory tract infections. Tulsi-containing formulations improved respiratory comfort, reduced cough severity, and enhanced immune resilience in several observational and clinical studies (Jamshidi & Cohen, 2017). Traditional Ayurvedic preparations containing Tulsi have also been used as supportive therapy for fever, sore throat, respiratory congestion, and influenza-like illnesses. During the COVID-19 pandemic, Tulsi was widely incorporated into preventive herbal formulations intended to support respiratory immunity and stress adaptation.

Similarly, *Adhatoda vasica* has shown clinical efficacy in chronic bronchitis, productive cough, asthma, and inflammatory airway disorders. Clinical observations indicate improvement in expectoration, airway clearance, respiratory discomfort, and bronchial congestion following Vasaka administration.

#### Studies Related to Stress, Immunity, and Psychological Symptoms

Several human studies suggest that Tulsi possesses adaptogenic, anxiolytic, and anti-stress properties. Tulsi supplementation has been associated with improved mood, reduced anxiety, enhanced cognitive performance, better sleep quality, and reduced stress-related symptoms. Because psychological stress and immune dysfunction became highly prevalent during the COVID-19 pandemic, these adaptogenic effects gained substantial therapeutic relevance. Although direct neuropsychological clinical evidence involving *Adhatoda vasica* remains limited, its antioxidant and anti-inflammatory properties may indirectly contribute to improved neuroimmune balance and stress-related symptom relief.

#### Potential Supportive Role in COVID-19 Management

During the pandemic, traditional herbal medicine systems incorporated Tulsi and Vasaka into supportive COVID-19 management protocols because of their respiratory protective and immunomodulatory activities.

Preliminary observational evidence suggested potential benefits in:

- Reduction of respiratory discomfort
- Relief from cough and congestion
- Improvement of stress tolerance
- Enhancement of immune resilience
- Supportive recovery during post-viral fatigue and long-COVID syndrome

However, definitive clinical evidence specifically targeting COVID-19 remains limited.

## Limitations and Challenges in Clinical Translation

Despite encouraging pharmacological evidence, several limitations restrict widespread clinical implementation:

- Lack of large multicentric randomized controlled trials
- Variability in phytochemical composition
- Inconsistent dosage standardization
- Limited pharmacokinetic studies
- Insufficient COVID-19-specific clinical evidence

Therefore, further evidence-based investigations are required for validation of therapeutic efficacy and safety

## 5.4 Safety, Toxicity, and Herb–Drug Interactions

### Toxicological Evaluation and Safety Profile

Both *Ocimum sanctum* and *Adhatoda vasica* are generally regarded as safe when used within recommended therapeutic dosages. Toxicological studies indicate relatively low acute toxicity profiles for standardized extracts. Tulsi is widely consumed as herbal tea and dietary supplement and is generally well tolerated. Similarly, Vasaka formulations have long histories of safe traditional use in respiratory medicine.

### Contraindications and Precautions

Although generally safe, excessive or prolonged consumption may produce adverse effects. Tulsi may occasionally cause mild gastrointestinal irritation, dizziness, or hypoglycemic effects in sensitive individuals. Excessive administration of *Adhatoda vasica* may produce gastrointestinal discomfort, nausea, or hypotensive effects because of its bronchodilatory alkaloids. Pregnant women should use Vasaka cautiously because high doses may possess uterotonic activity.

### Herb–Drug Interaction Considerations

Potential herb–drug interactions remain important considerations in integrative medicine practice. Tulsi may interact with:

- Anticoagulant medications
- Antidiabetic drugs
- Antihypertensive agents
- Immunomodulatory therapies

Similarly, Vasaka may influence respiratory medications and hypotensive agents.

Careful clinical supervision and dosage monitoring are therefore necessary during combined herbal and conventional therapeutic administration.

### Regulatory Perspectives and Quality Control

Standardization and quality assurance remain critical challenges in herbal medicine development. Variability in cultivation conditions, harvesting methods, extraction procedures, and phytochemical composition significantly affects therapeutic consistency.

Modern regulatory frameworks emphasize:

- Good Manufacturing Practices (GMP)
- Phytochemical standardization
- Contaminant testing
- Biomarker validation
- Clinical evidence generation

Such approaches are essential for integrating herbal therapeutics into evidence-based healthcare systems.

**Table 4. Experimental, Preclinical, and Clinical Evidence of *Ocimum sanctum* and *Adhatoda vasica***

Study Aspect	<i>Ocimum sanctum</i>	<i>Adhatoda vasica</i>	Therapeutic Significance
In Vitro Antiviral Activity	Inhibition of viral inflammatory pathways	Respiratory protective effects	Supportive antiviral potential
Molecular Docking Targets	Mpro, spike protein, RdRp	Inflammatory and respiratory targets	Mechanistic therapeutic evidence
Anti-inflammatory Effects	Reduction of IL-6, TNF- $\alpha$ , NF- $\kappa$ B	Suppression of airway inflammation	Cytokine regulation
Antioxidant Activity	ROS scavenging and mitochondrial protection	Reduction of oxidative pulmonary injury	Tissue protection
Bronchodilatory Action	Mild bronchoprotective effect	Strong bronchodilator and expectorant activity	Respiratory symptom relief
In Vivo Respiratory Evidence	Reduced airway inflammation and stress	Improved airflow and mucus clearance	Pulmonary protection
Neurobehavioral Effects	Adaptogenic and anxiolytic activity	Mild neuroprotective effects	Psychological support
Clinical Respiratory Evidence	Improvement in cough and respiratory comfort	Relief in bronchitis and asthma	Traditional therapeutic validation
COVID-19 Relevance	Immune resilience and stress reduction	Pulmonary supportive care	Long-COVID support
Major Safety Concern	Hypoglycemic and anticoagulant interaction risk	Uterotonic and hypotensive potential	Clinical monitoring required

Research Limitation	Limited COVID-specific clinical trials	Insufficient neuropsychological evidence	Need for multicentric trials
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## 6. Emerging Therapeutic Perspectives and Future Directions

The COVID-19 pandemic highlighted the importance of developing safe, multitarget, and integrative therapeutic approaches capable of simultaneously addressing respiratory inflammation, immune dysregulation, oxidative stress, and psychological disturbances. In this context, *Ocimum sanctum* and *Adhatoda vasica* have emerged as promising medicinal plants because of their combined antiviral, bronchodilatory, antioxidant, immunomodulatory, adaptogenic, and neuroprotective properties. Increasing pharmacological evidence supports their future potential in supportive management of COVID-19-associated respiratory and psychological complications.

### 6.1 Integrative Herbal Approaches in COVID-19 Management

Modern healthcare systems increasingly recognize the therapeutic value of integrative medicine approaches combining conventional pharmacotherapy with scientifically validated herbal therapeutics. COVID-19 and long-COVID syndrome involve complex interactions among viral infection, pulmonary inflammation, oxidative stress, immune dysregulation, neuroinflammation, and psychological distress. Consequently, single-target therapeutic interventions often fail to adequately address the multifactorial nature of the disease.

*Ocimum sanctum* and *Adhatoda vasica* possess complementary pharmacological properties capable of targeting several pathological pathways simultaneously. Tulsi primarily contributes immunomodulatory, antioxidant, antiviral, adaptogenic, and anxiolytic effects, whereas Vasaka provides bronchodilatory, expectorant, anti-inflammatory, and respiratory protective actions.

Integrative use of these medicinal plants may therefore support:

- Reduction of respiratory inflammation
- Improvement of airway function and mucus clearance
- Regulation of immune responses
- Reduction of oxidative stress
- Psychological stress management
- Enhancement of long-COVID recovery

Traditional systems such as Ayurveda and Siddha medicine have long utilized such polyherbal strategies for respiratory and stress-associated disorders, providing important ethnopharmacological foundations for modern phytotherapeutic research.

## 6.2 Advanced Herbal Formulations and Nanotechnology

One of the major limitations of herbal therapeutics involves poor bioavailability, instability, limited tissue targeting, and variability in phytochemical absorption. Nanotechnology-based delivery systems and advanced pharmaceutical formulations may significantly enhance therapeutic efficacy of medicinal plant-derived bioactive compounds.

Nanoformulations such as:

- Liposomes
- Phytosomes
- Nanoemulsions
- Polymeric nanoparticles
- Solid lipid nanoparticles
- Inhalable nanoformulations

have demonstrated considerable potential in improving pulmonary drug delivery and phytochemical stability.

Nanoencapsulation of eugenol, ursolic acid, vasicine, and flavonoids may:

- Improve bioavailability
- Enhance pulmonary tissue targeting
- Facilitate controlled release
- Increase blood–brain barrier penetration
- Reduce systemic toxicity

Inhalable herbal nanoformulations may be particularly useful for targeted respiratory delivery in pulmonary inflammatory disorders associated with COVID-19.

Additionally, nanotechnology-assisted delivery systems may improve neuroprotective efficacy by enhancing transport of antioxidant and adaptogenic phytochemicals into neural tissues affected by oxidative stress and neuroinflammation.

## 6.3 Combination Therapies and Polyherbal Approaches

Combination therapy involving medicinal plants and conventional pharmaceuticals represents an important future therapeutic strategy. SARS-CoV-2 pathogenesis involves multiple pathological mechanisms including viral replication, cytokine storm syndrome, pulmonary inflammation, oxidative stress, endothelial dysfunction, and neuroimmune disturbances. Therefore, multitarget therapeutic combinations may provide superior clinical outcomes.

The combination of *Ocimum sanctum* and *Adhatoda vasica* may offer synergistic respiratory and neuroprotective effects because of complementary pharmacological mechanisms:

- Tulsi reduces inflammatory cytokines and stress responses
- Vasaka improves bronchial airflow and mucus clearance
- Both plants contribute antioxidant and immunomodulatory activities

Such synergistic interactions may help reduce respiratory discomfort, improve psychological resilience, and support pulmonary rehabilitation during long-COVID recovery. Future polyherbal formulations incorporating additional antiviral and adaptogenic herbs may further enhance therapeutic effectiveness.

#### 6.4 Artificial Intelligence, Network Pharmacology, and Molecular Modeling

Emerging computational technologies such as artificial intelligence (AI), systems biology, molecular docking, and network pharmacology are transforming phytopharmaceutical research and drug discovery. Network pharmacology is particularly useful for understanding the multitarget actions of medicinal plants because phytochemicals interact with multiple molecular pathways simultaneously. Such approaches may help identify:

- Novel antiviral targets
- Neuroimmune signaling pathways
- Inflammatory mediators
- Synergistic phytochemical interactions
- Predictive biomarkers of therapeutic response

Molecular docking studies involving Tulsi and Vasaka phytochemicals have already demonstrated potential interactions with SARS-CoV-2 proteins including viral proteases and inflammatory targets.

AI-assisted screening and computational pharmacology may accelerate identification of novel phytochemical combinations for respiratory and neuroimmune disorders associated with emerging viral diseases.

#### 6.5 Standardization and Biomarker-Based Validation

One of the most significant challenges in herbal medicine development is variability in phytochemical composition resulting from differences in cultivation, geographical conditions, harvesting practices, processing techniques, and extraction procedures.

Standardization of *Ocimum sanctum* and *Adhatoda vasica* formulations using validated biomarkers such as:

- Eugenol
- Ursolic acid
- Rosmarinic acid
- Vasicine
- Vasicinone

is essential for ensuring reproducibility, therapeutic consistency, and safety.

Advanced analytical techniques including:

- High-performance liquid chromatography (HPLC)
- Gas chromatography–mass spectrometry (GC-MS)
- Metabolomics
- Proteomics
- Fingerprint profiling

may facilitate quality control and evidence-based phytopharmaceutical development.

### **6.6 Future Prospects in Long-COVID and Neuroimmune Disorders**

Persistent inflammation, oxidative stress, mitochondrial dysfunction, and immune dysregulation observed in long-COVID syndrome resemble pathological mechanisms associated with chronic respiratory and neurodegenerative diseases. Consequently, medicinal plants possessing combined respiratory and neuroprotective properties may have broader therapeutic applications beyond acute COVID-19 management.

The adaptogenic, antioxidant, and respiratory protective effects of Tulsi and Vasaka may provide future therapeutic potential in:

- Long-COVID syndrome
- Chronic respiratory inflammation
- Anxiety and depressive disorders
- Chronic fatigue syndrome
- Neuroimmune dysfunction
- Stress-associated pulmonary disorders

Their ability to simultaneously target respiratory and psychological complications highlights their importance in future integrative healthcare strategies.

### **6.7 Need for Multicentric Randomized Clinical Trials**

Although current experimental and preliminary clinical findings are encouraging, large-scale multicentric randomized controlled clinical trials remain necessary for definitive therapeutic validation.

Future investigations should focus on:

- Standardized herbal formulations
- Dose optimization
- Long-term safety evaluation
- Pharmacokinetic and pharmacodynamic studies
- Herb–drug interaction assessment
- COVID-19-specific clinical endpoints
- Long-COVID respiratory and neuropsychiatric outcomes

Evidence-based clinical validation will be essential for integrating medicinal plant therapeutics into mainstream healthcare systems and global pandemic preparedness strategies.

**Table 5. Emerging Therapeutic Perspectives of *Ocimum sanctum* and *Adhatoda vasica***

Emerging Area	<i>Ocimum sanctum</i>	<i>Adhatoda vasica</i>	Future Therapeutic Relevance
Integrative Medicine	Adaptogenic and immunomodulatory support	Bronchodilatory respiratory support	Complementary COVID-19 management
Nanoformulations	Enhanced delivery of eugenol and flavonoids	Improved vasicine bioavailability	Targeted pulmonary and neural protection
Polyherbal Therapy	Stress reduction and antioxidant support	Airway clearance and respiratory protection	Synergistic multitarget therapy
AI and Network Pharmacology	Viral and neuroimmune target identification	Respiratory signaling pathway analysis	Accelerated phytodrug discovery
Biomarker Standardization	Eugenol and ursolic acid profiling	Vasicine and vasicinone quantification	Improved quality control
Long-COVID Applications	Anxiety and fatigue management	Pulmonary rehabilitation support	Post-viral recovery enhancement
Neuroimmune Disorders	HPA axis regulation and neuroprotection	Oxidative stress reduction	Psychological recovery support
Advanced Delivery Systems	Phytosomes and nanoemulsions	Inhalable pulmonary formulations	Improved therapeutic efficacy
Clinical Research Priority	Stress and immunity-focused trials	Respiratory symptom-focused trials	Evidence-based therapeutic integration

## 7. Conclusion

The COVID-19 pandemic exposed the complex and multisystemic nature of viral diseases, emphasizing the urgent need for therapeutic approaches capable of simultaneously addressing respiratory inflammation, immune dysregulation, oxidative stress, and psychological disturbances. Beyond acute respiratory infection, SARS-CoV-2 infection has been associated with persistent pulmonary complications, neuroinflammation, chronic fatigue, anxiety, depression, insomnia, and long-COVID-associated neuroimmune dysfunction. These long-term health consequences highlighted important limitations of conventional therapeutic strategies and increased global interest in evidence-based complementary and integrative medicine approaches.

Among medicinal plants investigated for supportive COVID-19 management, *Ocimum sanctum* and *Adhatoda vasica* have demonstrated considerable therapeutic potential because of their multitarget pharmacological activities. Traditional medicinal systems including Ayurveda, Siddha, and Unani medicine have historically utilized these herbs for respiratory infections, inflammatory disorders, stress-related illnesses, and immune dysfunctions. Modern scientific investigations further support many of these traditional therapeutic claims through experimental, preclinical, and preliminary clinical evidence.

*Ocimum sanctum* possesses significant antioxidant, antiviral, anti-inflammatory, adaptogenic, immunomodulatory, anxiolytic, and neuroprotective properties largely attributed to bioactive constituents such as eugenol, ursolic acid, rosmarinic acid, and flavonoids. These phytochemicals contribute to suppression of inflammatory cytokines, regulation of oxidative stress, modulation of neuroimmune pathways, and enhancement of stress resilience. Such mechanisms may be highly beneficial in managing COVID-19-associated respiratory inflammation, immune imbalance, and psychological complications including anxiety, fatigue, insomnia, and cognitive dysfunction.

Similarly, *Adhatoda vasica* exhibits potent bronchodilatory, expectorant, antioxidant, anti-inflammatory, and pulmonary protective activities primarily mediated by quinazoline alkaloids including vasicine and vasicinone. These pharmacological actions support its traditional use in asthma, bronchitis, cough, dyspnea, and inflammatory airway disorders. The respiratory protective properties of Vasaka may provide important supportive benefits in COVID-19-associated pulmonary complications and long-COVID respiratory dysfunction characterized by chronic cough, airway inflammation, and reduced pulmonary function.

The combined therapeutic relevance of Tulsi and Vasaka lies in their complementary and synergistic pharmacological activities. While Tulsi contributes adaptogenic, immunomodulatory, antiviral, and anxiolytic effects, Vasaka provides bronchodilation, mucus clearance, and pulmonary protection. Together, these medicinal plants may simultaneously target inflammatory cascades, oxidative stress, respiratory dysfunction, neuroimmune disturbances, and stress-associated complications. Such multitarget therapeutic mechanisms are particularly valuable in complex disorders like COVID-19 and long-COVID syndrome where multiple pathological pathways interact simultaneously.

Experimental studies, molecular docking investigations, animal models, and preliminary clinical observations further support the therapeutic promise of these medicinal plants. Computational studies suggest potential interactions of Tulsi phytochemicals with SARS-CoV-2-associated molecular targets including viral proteases and inflammatory signaling pathways. In vivo studies demonstrate respiratory protective, antioxidant, anxiolytic, and immunomodulatory activities, whereas traditional clinical applications support their role in respiratory symptom relief and stress management. However, despite encouraging findings, substantial limitations remain regarding large-scale randomized clinical validation, phytochemical standardization, dosage optimization, and long-term safety evaluation.

Emerging therapeutic technologies including nanotechnology-based herbal formulations, network pharmacology, metabolomics, artificial intelligence-assisted phytodrug discovery, and advanced pulmonary delivery systems may significantly enhance the future clinical utility of *Ocimum sanctum* and *Adhatoda vasica*. Nanoformulations and targeted delivery systems may improve phytochemical bioavailability, pulmonary tissue targeting, and neuroprotective efficacy while reducing systemic toxicity. Similarly, biomarker-based standardization approaches may help ensure therapeutic consistency and regulatory acceptance of herbal medicines in evidence-based healthcare systems.

Future research should prioritize multicentric randomized controlled clinical trials investigating standardized formulations of Tulsi and Vasaka in COVID-19-associated respiratory and psychological disorders. Additional investigations are required to explore pharmacokinetics, herb–drug interactions,

molecular mechanisms, long-COVID outcomes, neuroimmune regulation, and personalized phytotherapeutic strategies. Integration of traditional medicinal knowledge with modern biomedical research may facilitate development of innovative, accessible, and holistic therapeutic approaches for future viral pandemics and chronic inflammatory diseases.

Overall, *Ocimum sanctum* and *Adhatoda vasica* represent promising medicinal plants with substantial therapeutic relevance in the supportive management of COVID-19-associated respiratory and psychological complications. Their combined respiratory protective, immunomodulatory, antioxidant, adaptogenic, and neuroprotective properties underscore the scientific importance of integrating traditional herbal medicine with modern therapeutic strategies for comprehensive healthcare and future pandemic preparedness.

## References

- Claeson, U. P., Malmfors, T., Wikman, G., & Bruhn, J. G. (2000). *Adhatoda vasica*: A critical review of ethnopharmacological and toxicological data. *Journal of Ethnopharmacology*, 72(1–2), 1–20.
- Cohen, M. M. (2014). Tulsi — *Ocimum sanctum*: A herb for all reasons. *Journal of Ayurveda and Integrative Medicine*, 5(4), 251–259.
- Del Valle, D. M., Kim-Schulze, S., Huang, H. H., Beckmann, N. D., Nirenberg, S., Wang, B., ... Gnjjatic, S. (2020). An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nature Medicine*, 26(10), 1636–1643.
- Ellul, M. A., Benjamin, L., Singh, B., Lant, S., Michael, B. D., Easton, A., ... Solomon, T. (2020). Neurological associations of COVID-19. *The Lancet Neurology*, 19(9), 767–783.
- Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., ... Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, 395(10223), 497–506.
- Jamshidi, N., & Cohen, M. M. (2017). The clinical efficacy and safety of Tulsi in humans: A systematic review of the literature. *Evidence-Based Complementary and Alternative Medicine*, 2017, 1–13.
- Mondal, S., Mirdha, B. R., & Mahapatra, S. C. (2009). The science behind sacredness of Tulsi (*Ocimum sanctum* Linn.). *Indian Journal of Physiology and Pharmacology*, 53(4), 291–306.
- Pfefferbaum, B., & North, C. S. (2020). Mental health and the COVID-19 pandemic. *New England Journal of Medicine*, 383(6), 510–512.
- Rai, M., Ingle, A. P., Pandit, R., Paralikar, P., Anasane, N., Santos, C. A., & Duran, N. (2016). Nanotechnology-based anti-infectives and therapeutics. *Biotechnology Advances*, 34(5), 847–859.
- Singh, S., & Sharma, B. (2013). Phytochemical and pharmacological profile of *Adhatoda vasica*. *International Journal of Pharmacy and Pharmaceutical Sciences*, 5(2), 1–6.
- Szcześniak, D., Gładka, A., Misiak, B., Cyran, A., & Rymaszewska, J. (2021). The SARS-CoV-2 and mental health: From biological mechanisms to social consequences. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 104, 110097.
- V'kovski, P., Kratzel, A., Steiner, S., Stalder, H., & Thiel, V. (2021). Coronavirus biology and replication: Implications for SARS-CoV-2. *Nature Reviews Microbiology*, 19(3), 155–170.

## Chapter 4: Regulation of Cytokine Storm and Neuroinflammation in COVID-19 by *Curcuma longa* and *Boswellia serrata*

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### Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is characterized not only by acute respiratory manifestations but also by severe systemic inflammatory responses and neurological complications. Among the major pathological features associated with severe COVID-19, cytokine storm syndrome and neuroinflammation have emerged as critical contributors to disease progression, multiorgan dysfunction, acute respiratory distress syndrome (ARDS), and long-COVID neurological complications. Excessive release of pro-inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-1 beta (IL-1 $\beta$ ), and interferon-gamma (IFN- $\gamma$ ) contributes to oxidative stress, endothelial injury, immune dysregulation, mitochondrial dysfunction, and neuronal damage. Persistent neuroinflammation has further been implicated in cognitive dysfunction, anxiety, depression, fatigue, brain fog, and neurodegenerative alterations observed during and after SARS-CoV-2 infection. These multifactorial pathological mechanisms have highlighted the urgent need for safe and multitarget therapeutic interventions capable of regulating inflammatory and neuroimmune pathways. In this context, medicinal plants possessing anti-inflammatory, antioxidant, immunomodulatory, and neuroprotective activities have attracted considerable scientific attention as complementary therapeutic agents. Among these, *Curcuma longa* (turmeric) and *Boswellia serrata* (Indian frankincense) are particularly important because of their long-standing traditional medicinal use and extensive pharmacological evidence supporting their anti-inflammatory and neuroprotective potential. *Curcuma longa* contains biologically active curcuminoids including curcumin, demethoxycurcumin, and bisdemethoxycurcumin, along with volatile oils and polyphenols that exhibit strong antioxidant, antiviral, anti-inflammatory, and neuroprotective activities. Curcumin has demonstrated the ability to modulate multiple inflammatory signaling pathways including nuclear factor-kappa B (NF- $\kappa$ B), Janus kinase/signal transducer and activator of transcription (JAK/STAT), mitogen-activated protein kinase (MAPK), and NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome pathways. These mechanisms contribute to suppression of cytokine release, reduction of oxidative stress, and protection against neuronal and pulmonary injury. Similarly, *Boswellia serrata* is rich in boswellic acids, particularly acetyl-11-keto- $\beta$ -boswellic acid (AKBA), which possess potent anti-inflammatory and immunomodulatory activities through inhibition of 5-lipoxygenase (5-LOX), leukotriene synthesis, and inflammatory mediator production. Boswellic acids further exhibit antioxidant and neuroprotective properties capable of reducing oxidative neuronal damage and regulating neuroimmune interactions. The respiratory protective and anti-inflammatory activities of *Boswellia serrata* may also help alleviate pulmonary inflammation and cytokine-mediated tissue injury associated with severe COVID-19. This chapter comprehensively explores the ethnopharmacology, phytochemistry, traditional therapeutic applications, anti-inflammatory mechanisms, neuroprotective effects, and therapeutic relevance of *Curcuma longa* and *Boswellia serrata* in regulating cytokine storm and neuroinflammation associated with COVID-19. Furthermore, the chapter discusses advanced therapeutic perspectives including nanoformulations, network pharmacology, biomarker-based standardization, artificial intelligence-assisted phytodrug discovery, and integrative herbal strategies for long-COVID management.

### Keywords

COVID-19; SARS-CoV-2; cytokine storm; neuroinflammation; *Curcuma longa*; turmeric; curcumin; *Boswellia serrata*; boswellic acids; immunomodulation; oxidative stress; NF- $\kappa$ B; NLRP3 inflammasome; JAK/STAT pathway

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## 1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged as an unprecedented global health emergency affecting millions of individuals worldwide. Although initially recognized primarily as an acute respiratory illness, subsequent clinical and molecular investigations revealed that COVID-19 is a complex multisystemic disorder involving severe inflammatory, immunological, cardiovascular, neurological, and metabolic complications (Huang et al., 2020). The pathological severity of SARS-CoV-2 infection is strongly associated with dysregulated immune responses, oxidative stress, endothelial dysfunction, and widespread inflammatory injury affecting multiple organs including the lungs, heart, kidneys, and central nervous system.

One of the most critical pathological features of severe COVID-19 is the development of cytokine storm syndrome, a hyperinflammatory condition characterized by uncontrolled release of pro-inflammatory cytokines and chemokines. Elevated levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-1 beta (IL-1 $\beta$ ), interferon-gamma (IFN- $\gamma$ ), and other inflammatory mediators contribute significantly to acute respiratory distress syndrome (ARDS), pulmonary edema, multiorgan dysfunction, coagulopathy, and increased mortality (Del Valle et al., 2020). Excessive cytokine production further activates oxidative stress pathways, inflammatory leukocyte infiltration, and endothelial injury, thereby amplifying tissue damage and systemic immune dysregulation.

In addition to respiratory complications, increasing evidence demonstrates that SARS-CoV-2 infection substantially affects the nervous system. Neurological manifestations observed in COVID-19 include headache, anosmia, encephalopathy, stroke, seizures, cognitive dysfunction, anxiety, depression, insomnia, and long-COVID-associated neuropsychiatric disorders (Ellul et al., 2020). Neuroinflammation is considered one of the major mechanisms underlying these neurological complications. Excessive cytokine release and systemic inflammation can disrupt the blood–brain barrier (BBB), activate microglial cells, induce oxidative neuronal injury, and impair neurotransmitter homeostasis. Such pathological alterations may contribute to chronic neuroimmune dysfunction, cognitive impairment, emotional instability, and neurodegenerative changes observed in post-COVID conditions.

Oxidative stress plays a central role in both cytokine storm syndrome and neuroinflammation during SARS-CoV-2 infection. Viral replication and inflammatory immune activation generate excessive reactive oxygen species (ROS), resulting in mitochondrial dysfunction, lipid peroxidation, protein oxidation, and DNA damage. Persistent oxidative stress not only aggravates pulmonary inflammation but also contributes to neuronal injury and blood–brain barrier disruption. Furthermore, inflammatory cytokines and oxidative mediators interact synergistically to sustain chronic neuroinflammatory processes associated with long-COVID syndrome.

Despite significant advances in antiviral drugs, corticosteroids, monoclonal antibodies, and immunosuppressive therapies, conventional treatment strategies for severe COVID-19 possess several limitations. Many anti-inflammatory and immunosuppressive agents are associated with adverse effects including secondary infections, hepatotoxicity, nephrotoxicity, metabolic disturbances, and immune suppression. In addition, single-target pharmacological interventions often fail to adequately address the multifactorial pathological mechanisms underlying cytokine storm, oxidative stress, neuroinflammation,

and post-viral complications. These limitations have stimulated growing interest in complementary and integrative therapeutic approaches involving medicinal plants with multitarget pharmacological properties.

Traditional medicinal systems such as Ayurveda, Traditional Chinese Medicine (TCM), Siddha, and Unani medicine have historically utilized medicinal plants for inflammatory disorders, respiratory diseases, immune dysfunction, and neurological conditions. Several medicinal herbs possess potent antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective activities capable of regulating inflammatory pathways and oxidative stress. Among these, *Curcuma longa* and *Boswellia serrata* have attracted considerable scientific attention because of their extensive traditional use and well-documented pharmacological activities.

*Curcuma longa* L., commonly known as turmeric, is a highly valued medicinal and culinary plant belonging to the family Zingiberaceae. The principal bioactive compound curcumin exhibits strong anti-inflammatory, antioxidant, antiviral, immunomodulatory, and neuroprotective effects through modulation of multiple signaling pathways including nuclear factor-kappa B (NF- $\kappa$ B), Janus kinase/signal transducer and activator of transcription (JAK/STAT), mitogen-activated protein kinase (MAPK), and NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome pathways (Hewlings & Kalman, 2017). Curcumin has also demonstrated the ability to suppress inflammatory cytokine production, reduce oxidative stress, stabilize mitochondrial function, and protect neuronal tissues from inflammatory injury.

Similarly, *Boswellia serrata* Roxb., commonly known as Indian frankincense or Shallaki, is widely recognized for its anti-inflammatory and immunomodulatory properties. Boswellic acids, particularly acetyl-11-keto- $\beta$ -boswellic acid (AKBA), inhibit 5-lipoxygenase (5-LOX) activity and leukotriene synthesis, thereby reducing inflammatory responses and oxidative tissue damage (Ammon, 2016). In addition to anti-inflammatory actions, *Boswellia serrata* possesses antioxidant, neuroprotective, anxiolytic, and respiratory protective properties that may be beneficial in regulating cytokine storm syndrome and neuroinflammation associated with COVID-19.

The combined therapeutic relevance of *Curcuma longa* and *Boswellia serrata* lies in their complementary multitarget pharmacological mechanisms. Both medicinal plants regulate inflammatory cytokines, suppress oxidative stress, modulate immune responses, and provide neuronal protection through distinct yet overlapping molecular pathways. Their synergistic therapeutic potential may therefore help reduce pulmonary inflammation, mitigate cytokine storm syndrome, protect neuronal tissues, and support recovery from long-COVID neuroimmune complications.

Therefore, this chapter aims to comprehensively explore the ethnopharmacology, phytochemistry, anti-inflammatory mechanisms, neuroprotective effects, experimental evidence, and therapeutic potential of *Curcuma longa* and *Boswellia serrata* in regulating cytokine storm and neuroinflammation associated with COVID-19. The chapter further discusses emerging therapeutic perspectives including nanotechnology-based formulations, network pharmacology, biomarker standardization, and future clinical applications of these medicinal plants in inflammatory and neuroimmune disorders.

## 2. Ethnopharmacology, Phytochemistry, and Traditional Uses

### 2.1 Curcuma longa

#### Ayurvedic and Traditional Importance

*Curcuma longa* L., commonly known as turmeric, is one of the most important medicinal plants in Ayurveda and traditional medicine systems worldwide. In Ayurveda, turmeric is referred to as “Haridra” and is classified as a Rasayana herb because of its rejuvenating, detoxifying, and disease-preventive properties. For centuries, turmeric has been extensively used for the management of inflammatory disorders, wound healing, respiratory illnesses, liver dysfunction, skin diseases, metabolic disorders, and neurological conditions (Hewlings & Kalman, 2017).

Traditional Ayurvedic literature describes turmeric as possessing anti-inflammatory, antimicrobial, antioxidant, blood-purifying, and immunomodulatory properties. It has historically been incorporated into herbal formulations for treatment of fever, cough, arthritis, edema, digestive disturbances, and chronic inflammatory diseases. In addition to Ayurveda, turmeric also holds significant importance in Traditional Chinese Medicine (TCM), Siddha, Unani, and Southeast Asian folk medicine.

The use of turmeric in wound healing and infection management is particularly well documented. Traditional preparations involving turmeric paste and decoctions have been applied to cuts, burns, ulcers, and inflammatory skin conditions because of their antiseptic and tissue-regenerative effects. Turmeric has also been utilized traditionally in neurological disorders including memory impairment, stress-related conditions, cognitive decline, and age-associated neurodegenerative diseases.

The COVID-19 pandemic renewed scientific interest in turmeric because of its ability to regulate inflammatory cytokines, oxidative stress, immune dysfunction, and neuroinflammatory processes associated with severe SARS-CoV-2 infection.

#### Botanical Description and Distribution

*Curcuma longa* belongs to the family Zingiberaceae and is a perennial rhizomatous herb widely cultivated in tropical and subtropical regions. The plant typically grows up to 1 meter in height and possesses large oblong leaves, yellow-orange rhizomes, and pale-yellow flowers arranged in spikes.

Taxonomically, the plant is classified as:

- Kingdom: Plantae
- Family: Zingiberaceae
- Genus: *Curcuma*
- Species: *Curcuma longa*

Turmeric is believed to have originated in South Asia, particularly India, where it has been cultivated for thousands of years. India remains the largest producer and exporter of turmeric globally. The plant is also cultivated extensively in China, Indonesia, Thailand, Sri Lanka, Bangladesh, and other tropical regions.

Turmeric thrives in warm and humid climatic conditions with well-drained fertile soil. The medicinally valuable portion of the plant is the underground rhizome, which is harvested, dried, and processed into powder or extracts for culinary and therapeutic purposes.

### **Major Phytoconstituents**

The therapeutic properties of *Curcuma longa* are primarily attributed to curcuminoids, volatile oils, and polyphenolic compounds.

#### ***Curcumin***

Curcumin is the principal bioactive polyphenolic compound present in turmeric and is responsible for its characteristic yellow color. It exhibits potent anti-inflammatory, antioxidant, antiviral, anticancer, immunomodulatory, and neuroprotective activities.

Curcumin regulates multiple molecular signaling pathways including:

- Nuclear factor-kappa B (NF- $\kappa$ B)
- Janus kinase/signal transducer and activator of transcription (JAK/STAT)
- Mitogen-activated protein kinase (MAPK)
- NLRP3 inflammasome pathways

These actions contribute to suppression of cytokine storm syndrome, oxidative stress, and neuroinflammation.

#### ***Demethoxycurcumin and Bisdemethoxycurcumin***

These curcuminoid derivatives possess antioxidant and anti-inflammatory properties similar to curcumin. They contribute synergistically to the pharmacological effects of turmeric and enhance free radical scavenging activity.

#### ***Turmerones and Essential Oils***

Turmeric essential oils contain  $\alpha$ -turmerone,  $\alpha$ -turmerone, and  $\beta$ -turmerone, which exhibit anti-inflammatory, antimicrobial, neuroprotective, and cognitive-enhancing properties. Turmerones may also improve curcumin bioavailability and facilitate neuroregenerative mechanisms.

#### ***Polyphenols and Flavonoids***

Various polyphenolic compounds and flavonoids present in turmeric contribute antioxidant and cytoprotective effects through reduction of oxidative stress and inflammatory tissue injury.

## Traditional Therapeutic Applications

### *Anti-inflammatory and Antioxidant Uses*

Turmeric has long been used in traditional medicine for inflammatory disorders including arthritis, edema, skin inflammation, gastrointestinal disorders, and chronic inflammatory diseases. Its antioxidant properties help neutralize reactive oxygen species and protect tissues from oxidative injury.

### *Respiratory and Immune-supportive Applications*

Traditional formulations containing turmeric have been administered for cough, bronchitis, sore throat, asthma, and respiratory infections. Turmeric milk and herbal decoctions are commonly utilized in Ayurveda for enhancing immunity and respiratory resilience. The immunomodulatory properties of turmeric became particularly important during the COVID-19 pandemic because of their potential role in regulating inflammatory cytokines and oxidative stress.

### *Neuroprotective and Cognitive Health Benefits*

Turmeric has historically been used to improve memory, concentration, and mental clarity. Modern studies support its neuroprotective potential in neurodegenerative diseases, cognitive dysfunction, depression, and stress-related disorders. Curcumin-mediated antioxidant and anti-inflammatory effects may help protect neurons from inflammatory injury and oxidative degeneration associated with neuroimmune disorders.

## 2.2 *Boswellia serrata*

### Traditional and Medicinal Importance

*Boswellia serrata* Roxb., commonly known as Indian frankincense or Shallaki, is a highly valued medicinal plant in Ayurveda and traditional medicine. The oleo-gum resin obtained from the bark of the plant has historically been used for inflammatory disorders, respiratory diseases, arthritis, wound healing, and neurological conditions (Ammon, 2016).

In Ayurveda, Shallaki is regarded as a potent anti-inflammatory and analgesic herb beneficial for disorders involving pain, swelling, and immune dysfunction. Traditional physicians have extensively utilized *Boswellia* formulations in rheumatoid arthritis, osteoarthritis, asthma, bronchitis, inflammatory bowel disease, and chronic respiratory inflammation.

The resin is also traditionally used in spiritual and medicinal fumigation practices because of its antimicrobial and purifying properties. During recent decades, *Boswellia* gained considerable scientific attention because of its ability to inhibit inflammatory enzymes and cytokine-mediated pathways involved in chronic inflammatory diseases.

## Botanical Characteristics and Distribution

*Boswellia serrata* belongs to the family Burseraceae and is a moderate-sized deciduous tree characterized by papery bark, pinnate leaves, and fragrant oleo-gum resin.

Taxonomic classification includes:

- Kingdom: Plantae
- Family: Burseraceae
- Genus: *Boswellia*
- Species: *Boswellia serrata*

The plant is primarily distributed across India, North Africa, and Middle Eastern regions. In India, it is commonly found in dry mountainous regions of Rajasthan, Madhya Pradesh, Gujarat, and parts of central and western India. The medicinally important resin is obtained through bark incisions and subsequently purified for therapeutic applications.

## Key Bioactive Compounds

### *Boswellic Acids*

Boswellic acids are the principal pharmacologically active triterpenoids present in *Boswellia* resin. These compounds possess potent anti-inflammatory, antioxidant, immunomodulatory, and neuroprotective properties.

Boswellic acids inhibit inflammatory enzymes and leukotriene synthesis pathways involved in chronic inflammatory disorders and cytokine-mediated tissue injury.

### *Acetyl-11-keto- $\beta$ -boswellic Acid (AKBA)*

AKBA is one of the most potent boswellic acid derivatives and exhibits strong inhibition of 5-lipoxygenase (5-LOX), a key enzyme involved in leukotriene-mediated inflammation.

AKBA also modulates:

- NF- $\kappa$ B signaling
- Cytokine release
- Oxidative stress pathways
- Microglial activation

These mechanisms are highly relevant in COVID-19-associated cytokine storm syndrome and neuroinflammation.

### ***Terpenoids and Volatile Oils***

Boswellia resin contains various terpenoids and volatile oils possessing antimicrobial, anti-inflammatory, antioxidant, and respiratory protective activities.

### ***Polysaccharides and Phenolic Compounds***

Polysaccharides and phenolic constituents contribute immunomodulatory and antioxidant effects that support tissue protection and inflammatory regulation.

### **Traditional Therapeutic Applications**

#### ***Arthritis and Inflammatory Disease Management***

Boswellia has traditionally been utilized for treatment of rheumatoid arthritis, osteoarthritis, inflammatory pain, and musculoskeletal disorders. Its anti-inflammatory properties help reduce swelling, stiffness, and tissue damage.

#### ***Respiratory Disorders and Immune Support***

Traditional medicine systems employ Boswellia resin in asthma, bronchitis, cough, and inflammatory respiratory disorders. The plant's respiratory protective properties may help alleviate airway inflammation and oxidative pulmonary injury.

#### ***Neuroprotective and Anti-stress Applications***

Boswellia has also been used traditionally for improving mental clarity, memory, emotional stability, and stress-related disorders. Emerging evidence suggests that boswellic acids may possess neuroprotective and anxiolytic activities through reduction of oxidative stress and neuroinflammation.

## **2.3 Comparative Phytochemical and Pharmacological Profile**

Both *Curcuma longa* and *Boswellia serrata* possess potent anti-inflammatory, antioxidant, immunomodulatory, and neuroprotective properties relevant to COVID-19-associated cytokine storm syndrome and neuroinflammation. However, their dominant phytochemical constituents and molecular mechanisms differ.

*Curcuma longa* primarily exerts pharmacological effects through curcuminoids and turmerones that regulate NF- $\kappa$ B, JAK/STAT, MAPK, and inflammasome signaling pathways. In contrast, *Boswellia serrata* predominantly acts through boswellic acids and AKBA-mediated inhibition of 5-lipoxygenase and leukotriene synthesis.

Despite mechanistic differences, both medicinal plants suppress inflammatory cytokines, reduce oxidative stress, stabilize mitochondrial function, and provide neuroprotective benefits. Their combined therapeutic

use may therefore provide synergistic multitarget regulation of cytokine storm syndrome, pulmonary inflammation, oxidative stress, and neuroimmune dysfunction associated with COVID-19.

**Table 1. Comparative Phytochemical and Pharmacological Profile of *Curcuma longa* and *Boswellia serrata***

Parameter	<i>Curcuma longa</i>	<i>Boswellia serrata</i>
Common Name	Turmeric	Indian Frankincense / Shallaki
Major Traditional Systems	Ayurveda, Siddha, TCM, Unani	Ayurveda, Unani
Principal Bioactive Compounds	Curcumin, turmerones, curcuminoids	Boswellic acids, AKBA
Dominant Chemical Class	Polyphenolic curcuminoids	Pentacyclic triterpenoids
Major Molecular Targets	NF- $\kappa$ B, JAK/STAT, MAPK, NLRP3	5-LOX, NF- $\kappa$ B, leukotriene pathways
Primary Pharmacological Effects	Anti-inflammatory and antioxidant	Anti-inflammatory and immunomodulatory
Neuroprotective Mechanisms	Reduction of oxidative neuronal injury	Suppression of neuroinflammatory mediators
Respiratory Protective Effects	Cytokine regulation and antioxidant support	Reduction of airway inflammation
Immune Regulatory Activity	Cytokine suppression and immune modulation	Leukotriene inhibition and inflammatory control
Traditional Clinical Uses	Arthritis, infections, cognitive disorders	Arthritis, asthma, inflammatory disorders
COVID-19 Relevance	Regulation of cytokine storm and oxidative stress	Pulmonary inflammation and immune modulation
Potential Synergistic Benefit	Antioxidant and cytokine suppression	Leukotriene and inflammatory pathway inhibition

### 3. Regulation of Cytokine Storm in COVID-19

#### 3.1 Cytokine Storm and Immune Dysregulation in COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection induces a complex immune response involving both innate and adaptive immune systems. Although controlled immune activation is essential for viral clearance, excessive and dysregulated inflammatory responses can lead to cytokine storm syndrome, a hyperinflammatory condition strongly associated with severe COVID-19, acute respiratory distress syndrome (ARDS), multiorgan dysfunction, and mortality (Del Valle et al., 2020).

The pathogenesis of cytokine storm syndrome begins with viral entry through interaction of the SARS-CoV-2 spike glycoprotein with angiotensin-converting enzyme 2 (ACE2) receptors expressed on respiratory epithelial cells, endothelial tissues, and immune cells. Following viral replication, activation of macrophages, dendritic cells, neutrophils, and T lymphocytes results in excessive release of pro-inflammatory cytokines and chemokines including:

- Interleukin-6 (IL-6)
- Tumor necrosis factor-alpha (TNF- $\alpha$ )
- Interleukin-1 beta (IL-1 $\beta$ )
- Interferon-gamma (IFN- $\gamma$ )
- Monocyte chemoattractant protein-1 (MCP-1)
- Granulocyte-macrophage colony-stimulating factor (GM-CSF)

These inflammatory mediators amplify pulmonary inflammation, vascular permeability, oxidative stress, and immune cell infiltration, leading to alveolar damage and respiratory failure.

The exaggerated inflammatory response further activates multiple intracellular signaling pathways including:

- Nuclear factor-kappa B (NF- $\kappa$ B)
- Janus kinase/signal transducer and activator of transcription (JAK/STAT)
- Mitogen-activated protein kinase (MAPK)
- NLRP3 inflammasome pathways

Activation of these pathways contributes to sustained cytokine production, oxidative tissue injury, mitochondrial dysfunction, endothelial damage, and coagulation abnormalities.

Oxidative stress is another major pathological factor associated with severe COVID-19. Excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) during inflammatory immune activation leads to lipid peroxidation, protein oxidation, DNA damage, and cellular apoptosis. Oxidative stress further enhances inflammatory signaling, thereby establishing a vicious cycle of inflammation and tissue injury.

In addition to pulmonary damage, systemic cytokine dysregulation contributes significantly to neuroinflammation and blood–brain barrier disruption. Elevated cytokine levels can activate microglial cells, induce neuronal oxidative injury, alter neurotransmitter homeostasis, and contribute to neurological manifestations including anxiety, depression, cognitive dysfunction, encephalopathy, and long-COVID neurological complications (Ellul et al., 2020).

Because cytokine storm syndrome involves multiple interconnected inflammatory pathways, multitarget therapeutic approaches possessing antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective properties are considered highly valuable in COVID-19 management. Medicinal plants such as *Curcuma longa* and *Boswellia serrata* have therefore attracted considerable scientific attention.

### 3.2 Anti-inflammatory and Immunomodulatory Actions of *Curcuma longa*

#### Curcumin-Mediated Regulation of Inflammatory Pathways

The anti-inflammatory properties of *Curcuma longa* are primarily attributed to curcumin, a polyphenolic curcuminoid capable of modulating multiple inflammatory signaling pathways involved in cytokine storm syndrome.

Curcumin suppresses activation of NF- $\kappa$ B, a central transcription factor regulating expression of pro-inflammatory cytokines including IL-6, TNF- $\alpha$ , IL-1 $\beta$ , and cyclooxygenase-2 (COX-2). By inhibiting NF- $\kappa$ B translocation and inflammatory gene transcription, curcumin significantly reduces cytokine-mediated tissue injury and inflammatory amplification (Hewlings & Kalman, 2017).

Curcumin also modulates:

- JAK/STAT signaling
- MAPK pathways
- NLRP3 inflammasome activation
- Toll-like receptor-mediated inflammatory responses

These multitarget effects contribute to regulation of excessive immune activation during severe SARS-CoV-2 infection.

### **Antioxidant and Cytoprotective Mechanisms**

Curcumin exhibits strong antioxidant activity through scavenging reactive oxygen species and enhancing endogenous antioxidant defense systems including:

- Superoxide dismutase (SOD)
- Catalase
- Glutathione peroxidase

Reduction of oxidative stress helps protect pulmonary tissues, endothelial cells, and neuronal structures from inflammatory injury.

Curcumin additionally activates the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which regulates antioxidant and cytoprotective gene expression. Nrf2 activation contributes to suppression of oxidative damage and restoration of cellular redox balance.

### **Experimental Evidence in Viral and Inflammatory Disorders**

Experimental studies demonstrate that curcumin suppresses inflammatory cytokines and improves survival in models of sepsis, viral infections, inflammatory lung injury, and neuroinflammation. Curcumin-mediated inhibition of inflammatory mediators has shown beneficial effects in reducing pulmonary edema, neutrophil infiltration, and oxidative tissue damage.

Several molecular docking investigations further suggest potential interactions between curcumin and SARS-CoV-2-associated molecular targets including:

- Main protease (M<sub>pro</sub>/3CL<sub>pro</sub>)
- Spike protein
- ACE2 receptor pathways
- Viral replication-associated enzymes

Although direct clinical evidence remains limited, these findings support the potential therapeutic relevance of curcumin in COVID-19-associated inflammatory disorders.

### **Neuroimmune Protective Actions**

Curcumin additionally exerts neuroprotective effects by reducing microglial activation, suppressing neuroinflammatory cytokines, and protecting neurons against oxidative stress. These mechanisms may help alleviate cognitive dysfunction, anxiety, depression, and long-COVID neuroimmune complications associated with SARS-CoV-2 infection.

### **3.3 Anti-inflammatory and Immunoregulatory Actions of *Boswellia serrata***

#### **Boswellic Acid-Mediated Inhibition of Inflammatory Cascades**

*Boswellia serrata* exerts potent anti-inflammatory effects primarily through boswellic acids, particularly acetyl-11-keto- $\beta$ -boswellic acid (AKBA). Unlike conventional nonsteroidal anti-inflammatory drugs (NSAIDs), boswellic acids selectively inhibit 5-lipoxygenase (5-LOX), a key enzyme involved in leukotriene biosynthesis (Ammon, 2016).

Leukotrienes play critical roles in:

- Pulmonary inflammation
- Bronchoconstriction
- Neutrophil recruitment
- Vascular permeability
- Cytokine-mediated tissue injury

Inhibition of leukotriene synthesis therefore contributes significantly to reduction of respiratory inflammation and cytokine storm severity.

#### **Regulation of Cytokines and Immune Cell Activation**

Boswellic acids suppress inflammatory cytokines including:

- IL-6
- TNF- $\alpha$
- IL-1 $\beta$
- IFN- $\gamma$

Additionally, AKBA modulates NF- $\kappa$ B signaling and reduces activation of inflammatory immune cells including macrophages and neutrophils. These mechanisms help limit excessive inflammatory amplification and pulmonary tissue injury.

### **Pulmonary Protective and Antioxidant Effects**

*Boswellia serrata* demonstrates significant respiratory protective effects through reduction of airway inflammation, pulmonary oxidative stress, mucus hypersecretion, and bronchial constriction. Such actions are highly relevant in COVID-19-associated respiratory complications characterized by inflammatory lung injury and impaired pulmonary function. Boswellic acids also possess antioxidant activity capable of reducing lipid peroxidation, mitochondrial dysfunction, and oxidative tissue injury.

### **Neuroprotective and Neuroimmune Regulatory Effects**

Emerging evidence suggests that boswellic acids may regulate neuroinflammatory pathways through suppression of microglial activation and inflammatory cytokine production within neural tissues. *Boswellia*-mediated antioxidant effects may further protect neurons against oxidative degeneration associated with chronic inflammation and long-COVID neurological complications.

### **3.4 Combined Therapeutic Potential in Severe COVID-19**

The combined use of *Curcuma longa* and *Boswellia serrata* may provide synergistic multitarget regulation of cytokine storm syndrome and neuroinflammation because of their complementary pharmacological mechanisms.

Curcumin predominantly regulates:

- NF- $\kappa$ B and JAK/STAT signaling
- Oxidative stress pathways
- Inflammasome activation
- Cytokine transcription

In contrast, boswellic acids primarily inhibit:

- 5-lipoxygenase activity
- Leukotriene synthesis
- Pulmonary inflammatory cascades
- Immune cell infiltration

Together, these medicinal plants may simultaneously:

- Reduce inflammatory cytokine production
- Suppress oxidative stress
- Improve pulmonary protection
- Stabilize endothelial function
- Regulate neuroimmune pathways
- Protect neuronal tissues

Such multitarget therapeutic actions are particularly valuable in severe COVID-19 where inflammation, oxidative stress, and neuroimmune dysfunction coexist.

### Potential Role in Long-COVID Syndrome

Persistent inflammatory and neuroimmune disturbances contribute significantly to long-COVID symptoms including fatigue, anxiety, depression, brain fog, chronic cough, and cognitive dysfunction. The antioxidant and neuroprotective effects of curcumin and boswellic acids may therefore support post-viral recovery and long-term neuroimmune stabilization.

### Safety and Therapeutic Considerations

Both *Curcuma longa* and *Boswellia serrata* are generally regarded as safe when used within recommended dosages. However, excessive consumption may lead to gastrointestinal discomfort, anticoagulant interactions, or hepatobiliary concerns in susceptible individuals. Further randomized clinical trials and standardized phytopharmaceutical formulations remain necessary for establishing definitive efficacy and dosage guidelines in COVID-19-associated inflammatory disorders.

**Table 2. Comparative Anti-inflammatory and Immunomodulatory Mechanisms of *Curcuma longa* and *Boswellia serrata* in COVID-19**

Parameter	<i>Curcuma longa</i>	<i>Boswellia serrata</i>	Therapeutic Relevance in COVID-19
Principal Bioactive Compound	Curcumin	Boswellic acids (AKBA)	Regulation of cytokine storm
Major Molecular Target	NF- $\kappa$ B, JAK/STAT, NLRP3	5-LOX and leukotriene pathways	Suppression of inflammation
Cytokine Regulation	IL-6, TNF- $\alpha$ , IL-1 $\beta$ inhibition	IL-6, TNF- $\alpha$ , leukotriene suppression	Reduced inflammatory injury
Antioxidant Activity	Strong ROS scavenging and Nrf2 activation	Reduction of lipid peroxidation	Protection against oxidative stress
Pulmonary Protective Effect	Reduction of inflammatory lung injury	Bronchoprotective and anti-inflammatory activity	Improved respiratory function
Neuroprotective Effect	Microglial inhibition and neuronal protection	Reduction of neuroinflammation	Long-COVID neurological support
Immune Modulation	Regulation of innate and adaptive immunity	Suppression of excessive immune activation	Immune homeostasis
Potential SARS-CoV-2 Interaction	Viral protease and spike protein modulation	Inflammatory pathway inhibition	Supportive antiviral relevance
Dominant Mechanistic Strength	Cytokine and inflammasome suppression	Leukotriene inhibition	Complementary therapeutic synergy

## 4. Neuroinflammation and Neuroprotective Effects

### 4.1 Neurological Manifestations of COVID-19

Although coronavirus disease 2019 (COVID-19) was initially recognized as a respiratory illness, increasing clinical evidence has demonstrated substantial neurological and neuropsychiatric involvement associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Neurological complications have been reported in both acute and post-COVID phases and include:

- Headache
- Dizziness
- Anosmia and ageusia
- Encephalopathy
- Stroke
- Seizures
- Anxiety and depression
- Cognitive dysfunction (“brain fog”)
- Sleep disturbances
- Chronic fatigue syndrome-like symptoms

These manifestations are particularly prevalent in patients experiencing severe inflammatory responses and long-COVID syndrome (Ellul et al., 2020).

Several mechanisms contribute to neurological injury during SARS-CoV-2 infection. Systemic cytokine storm syndrome induces widespread inflammatory signaling capable of disrupting blood–brain barrier (BBB) integrity, activating microglial cells, and promoting infiltration of inflammatory mediators into neural tissues. Elevated inflammatory cytokines including IL-6, TNF- $\alpha$ , IL-1 $\beta$ , and IFN- $\gamma$  contribute significantly to neuroinflammation, neuronal oxidative stress, mitochondrial dysfunction, and neurotransmitter imbalance.

Oxidative stress further aggravates neuronal injury through excessive generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Persistent oxidative damage contributes to lipid peroxidation, neuronal apoptosis, synaptic dysfunction, and neurodegenerative alterations. Neuroimmune dysregulation and chronic inflammation may therefore play major roles in the cognitive impairment, emotional instability, and neuropsychiatric symptoms observed in post-COVID conditions.

The hyperactivation of microglial cells and astrocytes also amplifies neuroinflammatory cascades through production of inflammatory cytokines, nitric oxide, and oxidative mediators. Such pathological changes are associated with neuronal degeneration, impaired synaptic plasticity, and altered neurochemical signaling.

Because neuroinflammation and oxidative neuronal injury are major contributors to COVID-19-associated neurological complications, medicinal plants possessing antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective properties have attracted significant attention as complementary

therapeutic agents. Among these, *Curcuma longa* and *Boswellia serrata* demonstrate promising neuroprotective potential through regulation of inflammatory signaling pathways and oxidative stress.

## 4.2 Neuroprotective Role of *Curcuma longa*

### Curcumin-Mediated Antioxidant and Neuroprotective Mechanisms

The neuroprotective effects of *Curcuma longa* are primarily attributed to curcumin, a multifunctional polyphenolic compound capable of modulating inflammatory, oxidative, and neurodegenerative pathways. Curcumin exerts strong antioxidant effects through scavenging reactive oxygen species and enhancing endogenous antioxidant defense systems including:

- Superoxide dismutase (SOD)
- Catalase
- Glutathione peroxidase

By reducing oxidative stress, curcumin protects neuronal membranes, mitochondria, proteins, and DNA from inflammatory injury.

Curcumin additionally activates the Nrf2 antioxidant signaling pathway, which regulates expression of cytoprotective and antioxidant enzymes. Nrf2 activation contributes to restoration of redox balance and neuronal survival under inflammatory conditions.

### Modulation of Neuroinflammatory Signaling Pathways

Curcumin suppresses activation of multiple neuroinflammatory pathways including:

- NF- $\kappa$ B signaling
- MAPK pathways
- JAK/STAT signaling
- NLRP3 inflammasome activation

These mechanisms reduce production of inflammatory cytokines and neurotoxic mediators within the central nervous system. Curcumin also inhibits microglial activation and suppresses astrocyte-mediated inflammatory responses, thereby limiting chronic neuroinflammation.

### Effects on Neurogenesis and Synaptic Plasticity

Experimental evidence suggests that curcumin enhances neurogenesis, neuronal differentiation, and synaptic plasticity. Curcumin has been shown to increase levels of brain-derived neurotrophic factor (BDNF), an important regulator of neuronal growth, cognitive function, and synaptic connectivity. The compound further improves mitochondrial function and neuronal energy metabolism, thereby supporting cognitive resilience and neuroprotection.

## Experimental Evidence in Neurodegenerative and Stress Models

Animal studies demonstrate that curcumin improves memory, learning behavior, and cognitive performance in models of:

- Alzheimer's disease
- Parkinson's disease
- Depression
- Chronic stress
- Neuroinflammation

Curcumin-mediated reduction of oxidative neuronal injury and inflammatory cytokine production contributes significantly to these neuroprotective effects.

### Antidepressant and Anxiolytic Effects

Curcumin also exhibits antidepressant-like and anxiolytic activities through modulation of serotonin, dopamine, and norepinephrine signaling pathways. These mechanisms may help alleviate anxiety, depression, emotional instability, and stress-associated disorders commonly observed during and after COVID-19 infection.

## 4.3 Neuroprotective Role of *Boswellia serrata*

### Boswellic Acids and Neuronal Anti-inflammatory Activity

*Boswellia serrata* possesses substantial neuroprotective potential primarily mediated by boswellic acids and acetyl-11-keto- $\beta$ -boswellic acid (AKBA). These compounds suppress inflammatory pathways involved in neuronal injury and neuroimmune dysfunction.

Boswellic acids inhibit:

- NF- $\kappa$ B activation
- Leukotriene synthesis
- Microglial inflammatory signaling
- Oxidative stress pathways

These mechanisms contribute to reduction of neuroinflammation and protection against inflammatory neuronal degeneration.

### Reduction of Oxidative Neuronal Injury

Boswellic acids possess antioxidant properties capable of reducing lipid peroxidation, mitochondrial dysfunction, and oxidative neuronal damage. Experimental studies demonstrate that *Boswellia* extracts improve antioxidant enzyme activity and protect neural tissues from oxidative stress-induced degeneration.

## Effects on Memory, Learning, and Cognitive Function

Traditional medicine systems have long utilized *Boswellia* preparations for improving memory and mental clarity. Modern experimental studies support these observations and indicate that *Boswellia* may enhance learning performance, synaptic plasticity, and neuronal connectivity. Animal studies suggest that *Boswellia* administration improves spatial memory and cognitive behavior through reduction of neuroinflammatory injury and enhancement of hippocampal neuronal integrity.

## Potential Anxiolytic and Anti-stress Effects

Emerging evidence indicates that *Boswellia* may exert anxiolytic and antidepressant-like effects through modulation of neuroimmune interactions and oxidative stress pathways. Reduction of inflammatory cytokines and neuronal oxidative injury may contribute to emotional stabilization and stress resilience.

## Experimental Evidence in Neurodegenerative Disorders

Experimental investigations demonstrate neuroprotective effects of *Boswellia* in models of:

- Alzheimer's disease
- Neuroinflammation
- Ischemic neuronal injury
- Oxidative stress-associated neurodegeneration

These findings suggest possible therapeutic relevance in COVID-19-associated neuroimmune complications and long-COVID neurological dysfunction.

## 4.4 Mechanistic Insights

### Regulation of Inflammatory Signaling Pathways

Both *Curcuma longa* and *Boswellia serrata* regulate multiple inflammatory signaling pathways involved in cytokine storm syndrome and neuroinflammation.

Curcumin predominantly inhibits:

- NF- $\kappa$ B signaling
- JAK/STAT pathways
- MAPK activation
- NLRP3 inflammasome signaling

Boswellic acids primarily suppress:

- 5-lipoxygenase (5-LOX) activity
- Leukotriene synthesis
- NF- $\kappa$ B-mediated inflammation

- Microglial inflammatory activation

The combined modulation of these pathways contributes to suppression of cytokine-mediated neuronal injury and neuroimmune dysregulation.

### Mitochondrial Protection and Oxidative Stress Reduction

Mitochondrial dysfunction is a major contributor to neuronal degeneration and long-COVID neurological complications. Both medicinal plants enhance mitochondrial stability, reduce oxidative stress, and improve cellular energy metabolism. Curcumin and boswellic acids further increase antioxidant enzyme activity and reduce free radical-mediated neuronal apoptosis.

### Neurotransmitter Regulation and Neuroimmune Interactions

Curcumin influences neurotransmitter homeostasis involving serotonin, dopamine, gamma-aminobutyric acid (GABA), and norepinephrine pathways. Boswellia may additionally modulate neuroimmune communication and inflammatory neurotransmitter alterations associated with chronic stress and neuroinflammation.

### Role in Neuroplasticity and Neuronal Survival

Both medicinal plants support neuroplasticity and neuronal survival through reduction of inflammatory injury and enhancement of neurotrophic signaling pathways. Increased expression of neuroprotective factors such as BDNF contributes to improved cognitive resilience and recovery from inflammatory neuronal damage.

The multitarget neuroprotective mechanisms of *Curcuma longa* and *Boswellia serrata* therefore highlight their potential therapeutic relevance in managing COVID-19-associated neurological complications and long-COVID neuroimmune disorders.

**Table 3. Neuroprotective and Anti-neuroinflammatory Mechanisms of *Curcuma longa* and *Boswellia serrata***

Parameter	<i>Curcuma longa</i>	<i>Boswellia serrata</i>	Neuroprotective Significance
Major Neuroprotective Compound	Curcumin	Boswellic acids (AKBA)	Regulation of neuroinflammation
Principal Molecular Targets	NF- $\kappa$ B, NLRP3, JAK/STAT	5-LOX, NF- $\kappa$ B, leukotriene pathways	Suppression of inflammatory injury
Antioxidant Activity	Strong ROS scavenging and Nrf2 activation	Reduction of oxidative neuronal damage	Neuronal protection
Microglial Regulation	Inhibition of microglial activation	Suppression of inflammatory signaling	Reduced neurotoxicity
Cognitive Effects	Improved memory and synaptic plasticity	Enhanced learning and neuronal integrity	Cognitive support

Neurotransmitter Effects	Serotonin and dopamine modulation	Neuroimmune stabilization	Emotional regulation
Mitochondrial Protection	Restoration of cellular redox balance	Reduction of mitochondrial oxidative stress	Prevention of neuronal apoptosis
Neurotrophic Activity	Increased BDNF expression	Improved neuronal connectivity	Neuroplasticity enhancement
Potential Long-COVID Benefit	Reduction of brain fog and depression	Neuroimmune recovery support	Long-term neurological protection

## 5. Experimental, Preclinical, and Clinical Evidence

### 5.1 In Vitro Studies

#### Anti-inflammatory and Antiviral Screening Studies

Extensive in vitro investigations have explored the anti-inflammatory, antioxidant, antiviral, and neuroprotective activities of *Curcuma longa* and *Boswellia serrata* in the context of inflammatory disorders and COVID-19-associated cytokine dysregulation. These studies provide mechanistic evidence supporting their therapeutic potential against cytokine storm syndrome and neuroinflammation.

Curcumin, the principal bioactive constituent of *Curcuma longa*, has demonstrated potent inhibitory effects on inflammatory cytokines and signaling mediators involved in severe SARS-CoV-2 infection. Cell culture studies revealed that curcumin suppresses production of IL-6, TNF- $\alpha$ , IL-1 $\beta$ , cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) through inhibition of NF- $\kappa$ B and JAK/STAT signaling pathways (Prasad et al., 2014).

Curcumin additionally reduces oxidative stress by scavenging reactive oxygen species (ROS), stabilizing mitochondrial function, and enhancing antioxidant enzyme activity. Such effects are particularly relevant in COVID-19 because oxidative stress and inflammatory cytokine amplification significantly contribute to pulmonary and neurological injury.

Similarly, boswellic acids derived from *Boswellia serrata* exhibit strong anti-inflammatory and immunomodulatory activities in cellular models. Acetyl-11-keto- $\beta$ -boswellic acid (AKBA) suppresses leukotriene synthesis through selective inhibition of 5-lipoxygenase (5-LOX), thereby reducing inflammatory signaling and immune cell activation (Ammon, 2016).

In vitro studies further demonstrate that *Boswellia* extracts inhibit:

- TNF- $\alpha$  release
- IL-6 production
- Nitric oxide generation
- Lipid peroxidation
- Microglial inflammatory activation

These effects support the potential role of Boswellia in regulating neuroinflammation and cytokine-mediated tissue injury.

### **Molecular Docking Against SARS-CoV-2 Targets**

During the COVID-19 pandemic, computational docking and molecular modeling studies became important tools for identifying phytochemicals capable of interacting with SARS-CoV-2-associated molecular targets.

Curcumin demonstrated favorable binding affinity toward several viral and inflammatory targets including:

- SARS-CoV-2 main protease (M<sub>pro</sub>/3CL<sub>pro</sub>)
- Spike glycoprotein
- RNA-dependent RNA polymerase (RdRp)
- ACE2 receptor-associated pathways

These interactions suggest possible antiviral and anti-inflammatory effects capable of interfering with viral replication and inflammatory amplification.

Boswellic acids also exhibited potential interactions with inflammatory signaling mediators and viral proteins associated with pulmonary inflammation and cytokine storm syndrome. Computational investigations suggest that AKBA may contribute to regulation of inflammatory pathways involved in severe COVID-19 progression.

### **Cytokine Suppression and Oxidative Stress Modulation**

Both medicinal plants significantly modulate inflammatory cytokine production and oxidative stress markers in experimental cell models.

Curcumin reduces:

- IL-6
- TNF- $\alpha$
- IL-1 $\beta$
- MCP-1
- ROS generation

Boswellic acids suppress:

- Leukotriene synthesis
- NF- $\kappa$ B activation
- Microglial inflammatory signaling
- Oxidative membrane damage

The combined antioxidant and anti-inflammatory effects of these phytochemicals support their multitarget therapeutic relevance in cytokine storm regulation and neuroprotection.

## 5.2 In Vivo Experimental Studies

### Animal Models of Cytokine Storm and Pulmonary Inflammation

Experimental animal studies have provided substantial evidence supporting the anti-inflammatory and neuroprotective activities of *Curcuma longa* and *Boswellia serrata*.

Curcumin administration significantly reduced inflammatory cytokine production, pulmonary edema, neutrophil infiltration, and oxidative tissue injury in animal models of inflammatory lung disease and systemic inflammation. Experimental investigations further demonstrated improvement in respiratory function, reduction of oxidative stress markers, and protection against inflammatory alveolar damage.

Animal models of acute lung injury revealed that curcumin suppresses NF- $\kappa$ B activation and inflammatory cytokine release while enhancing antioxidant enzyme activity. These mechanisms contribute to reduced pulmonary inflammation and improved tissue recovery.

Similarly, *Boswellia serrata* demonstrated potent anti-inflammatory effects in experimental respiratory and inflammatory disorders. Boswellic acids reduced leukocyte infiltration, airway inflammation, and pulmonary oxidative stress while improving bronchial function and tissue integrity.

### Neuroprotective and Cognitive Outcomes

Experimental studies involving neuroinflammation and neurodegenerative disease models demonstrated substantial neuroprotective effects of curcumin and boswellic acids.

Curcumin improved:

- Learning and memory performance
- Synaptic plasticity
- Neuronal survival
- Mitochondrial function
- Oxidative neuronal balance

Animal studies further revealed antidepressant-like and anxiolytic effects through modulation of serotonin, dopamine, and neurotrophic pathways.

*Boswellia* extracts similarly improved cognitive performance, spatial memory, and neuronal integrity in neuroinflammatory and oxidative stress models. Reduction of microglial activation and inflammatory cytokine production contributed significantly to these neuroprotective effects.

## Immunological and Oxidative Stress Biomarkers

Both medicinal plants significantly influence inflammatory and oxidative biomarkers associated with cytokine storm syndrome and neuroimmune dysfunction.

Experimental investigations reported:

- Reduction of IL-6 and TNF- $\alpha$  levels
- Suppression of NF- $\kappa$ B signaling
- Decreased lipid peroxidation
- Enhancement of glutathione activity
- Improved mitochondrial antioxidant defense
- Reduced neuronal oxidative injury

These findings support their therapeutic relevance in COVID-19-associated inflammatory and neurological complications.

### 5.3 Clinical Trials and Human Studies

#### Clinical Evidence in Inflammatory and Respiratory Disorders

Several clinical investigations have evaluated the anti-inflammatory and immunomodulatory effects of *Curcuma longa* and *Boswellia serrata* in inflammatory disorders, respiratory diseases, and neuroimmune conditions.

Curcumin supplementation demonstrated beneficial effects in:

- Chronic inflammatory diseases
- Arthritis
- Respiratory inflammation
- Oxidative stress-associated disorders
- Depression and anxiety

Clinical studies reported reductions in inflammatory cytokines, oxidative stress biomarkers, and pain severity following curcumin administration (Hewlings & Kalman, 2017).

Similarly, *Boswellia* formulations showed efficacy in inflammatory conditions including:

- Osteoarthritis
- Rheumatoid arthritis
- Bronchial asthma
- Inflammatory bowel disease

Reduction of inflammatory symptoms and improvement of respiratory function support the anti-inflammatory potential of *Boswellia* in pulmonary disorders.

## Human Studies Related to Cognition and Neuroinflammation

Curcumin has demonstrated promising neuroprotective effects in human studies involving cognitive impairment, depression, and stress-related disorders. Clinical evidence suggests that curcumin may improve:

- Mood and emotional stability
- Cognitive performance
- Memory function
- Anxiety symptoms
- Oxidative stress parameters

Boswellia supplementation has also shown beneficial effects on memory and cognitive performance in preliminary clinical studies. Reduction of neuroinflammatory and oxidative markers may contribute to these cognitive benefits.

## Potential Supportive Role in COVID-19 Management

During the COVID-19 pandemic, curcumin and Boswellia-containing herbal formulations were investigated as supportive therapeutic agents because of their anti-inflammatory and immunomodulatory properties.

Preliminary studies and observational evidence suggested potential benefits including:

- Reduction of inflammatory biomarkers
- Improvement of respiratory symptoms
- Decreased oxidative stress
- Modulation of cytokine responses
- Enhanced recovery during post-COVID conditions

Curcumin nanoformulations attracted particular attention because of improved bioavailability and enhanced anti-inflammatory activity. However, despite encouraging findings, definitive large-scale clinical validation remains limited.

## Limitations and Challenges in Clinical Translation

Several limitations restrict widespread clinical implementation of these medicinal plants:

- Limited multicentric randomized clinical trials
- Poor oral bioavailability of curcumin
- Variability in phytochemical composition
- Inconsistent dosage standardization
- Limited pharmacokinetic investigations
- Insufficient COVID-19-specific evidence

Advanced formulation strategies and standardized clinical protocols are therefore necessary for evidence-based therapeutic integration.

## 5.4 Safety, Toxicity, and Herb–Drug Interactions

### Toxicological Profile and Safety Considerations

Both *Curcuma longa* and *Boswellia serrata* are generally regarded as safe when used within recommended therapeutic doses. Traditional medicinal systems have utilized these plants for centuries with relatively low toxicity profiles. Curcumin is widely consumed as a dietary spice and herbal supplement. Clinical studies indicate good tolerability at moderate doses, although high doses may occasionally cause:

- Gastrointestinal discomfort
- Nausea
- Diarrhea
- Gastric irritation

*Boswellia* extracts are also generally well tolerated; however, excessive intake may produce mild gastrointestinal symptoms including nausea and abdominal discomfort.

### Contraindications and Precautions

Curcumin may interact with:

- Anticoagulant medications
- Antiplatelet drugs
- Antidiabetic agents
- Chemotherapeutic medications

Because curcumin may influence blood coagulation and glucose metabolism, caution is necessary in patients receiving anticoagulant or hypoglycemic therapy.

*Boswellia* may interact with anti-inflammatory medications and immunomodulatory therapies. Careful dosage monitoring is therefore recommended during combined herbal and conventional treatment.

### Regulatory and Standardization Perspectives

Standardization and quality control remain major challenges in phytopharmaceutical development. Variability in cultivation conditions, extraction procedures, phytochemical content, and manufacturing practices significantly affects therapeutic consistency.

Modern regulatory approaches emphasize:

- Good Manufacturing Practices (GMP)

- Biomarker standardization
- HPLC and chromatographic profiling
- Contaminant analysis
- Pharmacovigilance monitoring

Such measures are essential for ensuring safety, efficacy, and reproducibility of herbal therapeutic formulations.

**Table 4. Experimental, Preclinical, and Clinical Evidence of *Curcuma longa* and *Boswellia serrata***

Study Aspect	<i>Curcuma longa</i>	<i>Boswellia serrata</i>	Therapeutic Significance
Major Active Constituents	Curcumin, curcuminoids, turmerones	Boswellic acids, AKBA	Anti-inflammatory and neuroprotective effects
In Vitro Anti-inflammatory Activity	NF- $\kappa$ B and cytokine suppression	5-LOX and leukotriene inhibition	Regulation of cytokine storm
Molecular Docking Targets	Mpro, spike protein, ACE2 pathways	Inflammatory and pulmonary targets	Potential supportive antiviral action
Antioxidant Mechanisms	ROS scavenging and Nrf2 activation	Reduction of lipid peroxidation	Oxidative stress protection
Pulmonary Protective Effects	Reduced lung inflammation and edema	Bronchoprotective and anti-inflammatory activity	Respiratory support
Neuroprotective Effects	Cognitive enhancement and neuronal protection	Reduction of neuroinflammation	Long-COVID neurological support
Animal Model Evidence	Improved mitochondrial and immune function	Reduced inflammatory injury	Experimental therapeutic validation
Clinical Evidence	Arthritis, cognition, respiratory inflammation	Asthma and inflammatory disorders	Human therapeutic relevance
Main Limitation	Poor oral bioavailability	Limited COVID-specific trials	Need for advanced formulations
Safety Concerns	Anticoagulant interactions	Mild gastrointestinal irritation	Clinical monitoring required

## 6. Future Perspectives and Therapeutic Challenges

### 6.1 Emerging Role of Herbal Therapeutics in COVID-19 and Neuroimmune Disorders

The COVID-19 pandemic highlighted the urgent need for safe, multitarget, and accessible therapeutic interventions capable of regulating inflammatory, oxidative, immunological, and neurological complications. Conventional pharmacological approaches, including corticosteroids, antiviral drugs, monoclonal antibodies, and immunosuppressive therapies, demonstrated partial efficacy but were often

associated with adverse effects, limited accessibility, high treatment costs, and incomplete management of long-COVID complications.

In this context, medicinal plants possessing anti-inflammatory, antioxidant, immunomodulatory, and neuroprotective activities have gained substantial scientific attention as complementary therapeutic agents. *Curcuma longa* and *Boswellia serrata* represent particularly promising phytotherapeutic candidates because of their multitarget pharmacological mechanisms and long-standing traditional medicinal use.

Their therapeutic relevance extends beyond acute SARS-CoV-2 infection and may include:

- Long-COVID management
- Chronic neuroinflammation
- Post-viral fatigue syndrome
- Cognitive dysfunction
- Anxiety and depression
- Persistent respiratory inflammation
- Immune recovery support

The increasing integration of herbal medicine with modern biomedical research therefore represents an important future direction in neuroimmune healthcare and pandemic preparedness.

## 6.2 Nanotechnology-Based Herbal Drug Delivery Systems

### Limitations of Conventional Herbal Formulations

Despite promising pharmacological properties, clinical translation of curcumin and boswellic acids remains limited because of:

- Poor aqueous solubility
- Low oral bioavailability
- Rapid metabolism
- Limited systemic absorption
- Poor blood–brain barrier penetration

Curcumin, in particular, demonstrates extensive first-pass metabolism and low plasma stability, significantly reducing its therapeutic efficacy in conventional formulations.

### Nanoformulation Strategies

Nanotechnology-based drug delivery systems offer promising solutions for improving the pharmacokinetic and therapeutic properties of herbal phytoconstituents. Advanced formulations include:

- Liposomes
- Polymeric nanoparticles

- Solid lipid nanoparticles (SLNs)
- Nanoemulsions
- Phytosomes
- Micelles
- Nanostructured lipid carriers

Nanoformulated curcumin has demonstrated:

- Improved bioavailability
- Enhanced cellular uptake
- Better blood–brain barrier penetration
- Increased anti-inflammatory activity
- Sustained drug release
- Enhanced antioxidant effects

Similarly, nanoencapsulation of boswellic acids may improve pharmacokinetic stability and therapeutic targeting of inflammatory tissues.

### Neurotargeted Drug Delivery

Targeted nanocarrier systems capable of crossing the blood–brain barrier may enhance the neuroprotective efficacy of curcumin and boswellic acids in long-COVID neurological complications and neuroinflammatory disorders. Such strategies may facilitate:

- Reduced neuroinflammation
- Improved neuronal drug delivery
- Better cognitive outcomes
- Enhanced neuroimmune regulation

## 6.3 Network Pharmacology and Multi-Target Therapeutics

### Complexity of COVID-19 Pathogenesis

COVID-19-associated cytokine storm syndrome and neuroinflammation involve multiple interconnected molecular pathways rather than a single pathological target. Consequently, multitarget therapeutic approaches are increasingly considered superior to single-target pharmacological interventions.

Both *Curcuma longa* and *Boswellia serrata* contain multiple bioactive compounds capable of simultaneously modulating:

- NF- $\kappa$ B signaling
- JAK/STAT pathways
- MAPK cascades
- NLRP3 inflammasome activation
- Oxidative stress pathways

- Leukotriene biosynthesis
- Neuroimmune signaling

### **Role of Network Pharmacology**

Network pharmacology integrates systems biology, computational biology, molecular docking, and pharmacological data to understand complex interactions between phytochemicals, molecular targets, and disease pathways.

This approach may help:

- Identify synergistic phytochemical interactions
- Predict molecular targets
- Optimize herbal combinations
- Discover multitarget therapeutic mechanisms
- Improve phytopharmaceutical design

Artificial intelligence-assisted network pharmacology platforms may further accelerate identification of novel phytoconstituents with antiviral, anti-inflammatory, and neuroprotective properties.

## **6.4 Biomarker-Based Standardization and Personalized Herbal Medicine**

### **Challenges in Herbal Standardization**

One of the major obstacles in herbal medicine research is variability in phytochemical composition resulting from:

- Climatic conditions
- Soil composition
- Cultivation practices
- Harvesting time
- Extraction methods
- Storage conditions

Such variability significantly affects reproducibility and therapeutic efficacy.

### **Biomarker-Based Quality Control**

Future phytopharmaceutical development requires biomarker-based standardization using advanced analytical techniques including:

- High-performance liquid chromatography (HPLC)
- Liquid chromatography–mass spectrometry (LC-MS)
- Gas chromatography–mass spectrometry (GC-MS)
- Metabolomics profiling

- Fingerprint chromatographic analysis

Standardized quantification of:

- Curcumin
- Demethoxycurcumin
- Bisdemethoxycurcumin
- Boswellic acids
- AKBA

### **Personalized and Precision Herbal Medicine**

Emerging precision medicine approaches may enable individualized phytotherapeutic interventions based on:

- Genetic polymorphisms
- Immune biomarkers
- Inflammatory cytokine profiles
- Oxidative stress status
- Neuroimmune characteristics

Such strategies may optimize therapeutic outcomes in COVID-19-associated inflammatory and neurological disorders.

## **6.5 Clinical Translation and Evidence-Based Validation**

### **Need for Large-Scale Clinical Trials**

Although experimental and preliminary clinical findings are encouraging, robust evidence-based validation remains essential for wider clinical acceptance.

Future investigations should focus on:

- Multicentric randomized controlled trials
- Long-COVID patient populations
- Neuroinflammatory biomarkers
- Cytokine profiling
- Pharmacokinetic studies
- Comparative efficacy evaluations
- Long-term safety assessments

### **Integrative Medicine Approaches**

The integration of medicinal plants with conventional pharmacotherapy may provide synergistic therapeutic benefits in severe inflammatory and neuroimmune disorders.

Potential integrative applications include:

- Adjunctive therapy in cytokine storm syndrome
- Long-COVID rehabilitation support
- Neuroimmune recovery protocols
- Respiratory inflammatory management
- Stress-associated neurological disorders

Such approaches require interdisciplinary collaboration among:

- Pharmacologists
- Clinicians
- Neuroscientists
- Immunologists
- Ayurvedic researchers
- Pharmaceutical scientists

## 6.6 Regulatory, Ethical, and Safety Challenges

### Regulatory Considerations

Global regulatory frameworks for herbal medicines remain heterogeneous and often lack standardized evaluation protocols. Major challenges include:

- Variable product quality
- Inadequate pharmacovigilance systems
- Limited standardization guidelines
- Inconsistent clinical evidence requirements

Future regulatory strategies should emphasize:

- Evidence-based phytopharmaceutical approval
- GMP-compliant manufacturing
- Toxicological validation
- Quality assurance systems
- International harmonization standards

### Herb–Drug Interactions and Safety Monitoring

Curcumin and boswellic acids may interact with:

- Anticoagulants
- Antiplatelet drugs
- Anti-inflammatory medications
- Immunosuppressive agents

- Antidiabetic therapies

Therefore, systematic pharmacovigilance and safety monitoring are necessary during integrative therapeutic use.

### 6.7 Future Research Directions

Future scientific investigations should prioritize:

- Mechanistic neuroimmune studies
- Long-COVID therapeutic trials
- Blood–brain barrier transport studies
- Nanoformulation optimization
- AI-assisted phytodrug discovery
- Multi-omics and metabolomics approaches
- Combination phytotherapy investigations
- Clinical biomarker validation

Research should additionally explore the combined therapeutic potential of *Curcuma longa* and *Boswellia serrata* in regulating:

- Cytokine storm syndrome
- Neuroinflammation
- Oxidative stress
- Mitochondrial dysfunction
- Cognitive impairment
- Chronic inflammatory complications

The convergence of traditional medicine, molecular pharmacology, artificial intelligence, and nanotechnology may therefore significantly transform the future of herbal neuroimmune therapeutics.

**Table 5. Future Perspectives and Therapeutic Challenges of *Curcuma longa* and *Boswellia serrata***

Area	Current Challenges	Emerging Strategies	Future Therapeutic Significance
Bioavailability	Poor absorption and rapid metabolism	Nanoformulations and phytosomes	Improved systemic and brain delivery
Neuroinflammation	Limited targeted neurotherapies	BBB-targeted nanoparticles	Long-COVID neurological management
Cytokine Storm Regulation	Multifactorial inflammatory pathways	Multi-target phytotherapeutics	Better inflammatory control
Herbal Standardization	Variability in phytochemical composition	Biomarker-based quality control	Reproducible therapeutic efficacy

Clinical Validation	Limited multicentric trials	Evidence-based clinical protocols	Wider medical acceptance
Molecular Mechanisms	Incomplete pathway understanding	Network pharmacology and AI modeling	Advanced phytodrug discovery
Personalized Medicine	Variable patient responses	Biomarker-guided phytotherapy	Precision herbal therapeutics
Safety Monitoring	Herb–drug interaction concerns	Pharmacovigilance systems	Safer integrative medicine
Drug Delivery	Limited BBB penetration	Liposomes and nano-carriers	Enhanced neuroprotective efficacy
Regulatory Framework	Lack of harmonized standards	GMP and international guidelines	Improved phytopharmaceutical development

## 7. Conclusion

The coronavirus disease 2019 (COVID-19) pandemic highlighted the complex relationship between viral infection, immune dysregulation, oxidative stress, systemic inflammation, and neurological dysfunction. Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily affects the respiratory system, accumulating evidence demonstrates that excessive inflammatory responses and neuroimmune disturbances significantly contribute to disease severity, multiorgan complications, and long-COVID syndrome. Among the most critical pathological features associated with severe COVID-19 are cytokine storm syndrome, oxidative tissue injury, endothelial dysfunction, blood–brain barrier disruption, and persistent neuroinflammation.

Excessive release of pro-inflammatory cytokines including IL-6, TNF- $\alpha$ , IL-1 $\beta$ , and IFN- $\gamma$  contributes substantially to pulmonary inflammation, acute respiratory distress syndrome (ARDS), mitochondrial dysfunction, neuronal injury, and neuropsychiatric complications. Persistent neuroinflammation and oxidative stress further play important roles in the development of anxiety, depression, cognitive dysfunction, chronic fatigue, sleep disturbances, and long-COVID neurological manifestations. These multifactorial pathological mechanisms underscore the limitations of single-target therapeutic approaches and emphasize the need for safe, multitarget, and integrative treatment strategies.

In this context, medicinal plants possessing anti-inflammatory, antioxidant, immunomodulatory, and neuroprotective properties have emerged as promising complementary therapeutic agents. Among them, *Curcuma longa* and *Boswellia serrata* demonstrate substantial pharmacological potential in regulating cytokine storm syndrome and neuroinflammation associated with COVID-19.

*Curcuma longa*, rich in curcumin and related curcuminoids, exerts broad-spectrum anti-inflammatory and antioxidant effects through modulation of multiple signaling pathways including NF- $\kappa$ B, JAK/STAT, MAPK, and NLRP3 inflammasome pathways. Curcumin suppresses inflammatory cytokine production, scavenges reactive oxygen species, stabilizes mitochondrial function, and protects neuronal tissues from oxidative and inflammatory injury. Experimental and clinical studies further indicate its neuroprotective,

anxiolytic, antidepressant, and cognitive-enhancing activities, which may be highly relevant in long-COVID neurological complications and stress-associated disorders.

Similarly, *Boswellia serrata* possesses potent anti-inflammatory and immunomodulatory properties primarily mediated by boswellic acids and acetyl-11-keto- $\beta$ -boswellic acid (AKBA). Through selective inhibition of 5-lipoxygenase (5-LOX) and leukotriene biosynthesis, *Boswellia* effectively reduces inflammatory cascades, pulmonary inflammation, oxidative stress, and neuroimmune dysfunction. The plant additionally demonstrates neuroprotective, respiratory protective, and antioxidant activities that may support recovery from inflammatory and neurological complications associated with SARS-CoV-2 infection.

The complementary pharmacological mechanisms of *Curcuma longa* and *Boswellia serrata* provide a strong rationale for their combined therapeutic application in COVID-19-related cytokine storm syndrome and neuroinflammation. Curcumin predominantly regulates inflammatory transcription factors and oxidative stress pathways, whereas boswellic acids primarily inhibit leukotriene-mediated inflammatory cascades. Together, these medicinal plants may offer synergistic multitarget protection against pulmonary inflammation, neuronal injury, oxidative stress, immune dysregulation, and long-COVID neuroimmune complications.

Experimental investigations, molecular docking studies, animal models, and preliminary clinical evidence collectively support the therapeutic potential of these medicinal plants. Their ability to modulate inflammatory cytokines, reduce oxidative stress, improve mitochondrial stability, and regulate neuroimmune interactions highlights their importance in integrative medicine approaches targeting inflammatory and neurodegenerative disorders.

Despite encouraging findings, several limitations remain. Challenges associated with poor bioavailability, variability in phytochemical composition, inadequate standardization, limited pharmacokinetic studies, and insufficient multicentric clinical trials restrict definitive clinical implementation. Therefore, future research should prioritize:

- Large-scale randomized clinical trials
- Biomarker-based standardization
- Nanoformulation development
- Blood–brain barrier-targeted delivery systems
- Artificial intelligence-assisted phytodrug discovery
- Multi-omics and network pharmacology approaches
- Long-COVID-focused therapeutic investigations

Advances in nanotechnology, systems biology, and precision medicine may significantly improve the therapeutic applicability of curcumin and boswellic acids in neuroimmune and inflammatory disorders. Furthermore, evidence-based integration of traditional herbal medicine with modern biomedical therapeutics may contribute substantially to future pandemic preparedness and management of chronic inflammatory diseases.

Overall, *Curcuma longa* and *Boswellia serrata* represent promising multitarget medicinal plants with significant therapeutic relevance in regulating cytokine storm syndrome, neuroinflammation, oxidative stress, and neuroimmune dysfunction associated with COVID-19. Their broad-spectrum pharmacological properties support the scientific importance of integrating traditional medicinal knowledge with contemporary molecular and clinical research for the development of safer and more effective therapeutic strategies in inflammatory and neurological healthcare.

## References

- Aggarwal, B. B., Gupta, S. C., & Sung, B. (2013). Curcumin: An orally bioavailable blocker of TNF and other pro-inflammatory biomarkers. *British Journal of Pharmacology*, 169(8), 1672–1692.
- Ammon, H. P. T. (2016). Boswellic acids and their role in chronic inflammatory diseases. *Advances in Experimental Medicine and Biology*, 928, 291–327.
- Benzie, I. F. F., & Wachtel-Galor, S. (2011). *Herbal medicine: Biomolecular and clinical aspects* (2nd ed.). CRC Press.
- Bharadwaj, S., Lee, K. E., Dwivedi, V. D., Kang, S. G., & Tiwari, R. K. (2021). Medicinal plants and their bioactive compounds for the treatment of COVID-19. *Journal of Traditional and Complementary Medicine*, 11(5), 388–403.
- Chen, L., Liu, H. G., Liu, W., Liu, J., Liu, K., Shang, J., ... Wei, S. (2020). Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. *Zhonghua Jie He He Hu Xi Za Zhi*, 43(3), 203–208.
- Del Valle, D. M., Kim-Schulze, S., Huang, H. H., Beckmann, N. D., Nirenberg, S., Wang, B., ... Gnjjatic, S. (2020). An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nature Medicine*, 26(10), 1636–1643.
- Ellul, M. A., Benjamin, L., Singh, B., Lant, S., Michael, B. D., Easton, A., ... Solomon, T. (2020). Neurological associations of COVID-19. *The Lancet Neurology*, 19(9), 767–783.
- Gupta, S. C., Patchva, S., Koh, W., & Aggarwal, B. B. (2012). Discovery of curcumin, a component of golden spice, and its miraculous biological activities. *Clinical and Experimental Pharmacology and Physiology*, 39(3), 283–299.
- Hewlings, S. J., & Kalman, D. S. (2017). Curcumin: A review of its effects on human health. *Foods*, 6(10), 92.
- Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., ... Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, 395(10223), 497–506.
- Jiang, F., Deng, L., Zhang, L., Cai, Y., Cheung, C. W., & Xia, Z. (2020). Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). *Journal of General Internal Medicine*, 35(5), 1545–1549.
- Li, S., Chen, C., Zhang, H., Guo, H., Wang, H., Wang, L., ... Tan, X. (2005). Identification of natural compounds with antiviral activities against SARS-associated coronavirus. *Antiviral Research*, 67(1), 18–23.

- Liu, J., Manheimer, E., Shi, Y., & Gluud, C. (2004). Chinese herbal medicine for severe acute respiratory syndrome: A systematic review and meta-analysis. *Journal of Alternative and Complementary Medicine*, 10(6), 1041–1051.
- Prasad, S., Gupta, S. C., Tyagi, A. K., & Aggarwal, B. B. (2014). Curcumin, a component of golden spice: From bedside to bench and back. *Biotechnology Advances*, 32(6), 1053–1064.
- Rastogi, S., Pandey, M. M., & Rawat, A. K. S. (2016). Traditional herbs: A remedy for COVID-19? *Phytomedicine*, 85, 153300.
- Salehi, B., Mishra, A. P., Nigam, M., Sener, B., Kilic, M., Sharifi-Rad, M., ... Sharifi-Rad, J. (2018). Resveratrol: A double-edged sword in health benefits. *Biomedicines*, 6(3), 91.
- Sengupta, K., Alluri, K. V., Satish, A. R., Mishra, S., Golakoti, T., Sarma, K. V., ... Krishnaraju, A. V. (2011). A double blind, randomized, placebo controlled study of the efficacy and safety of 5-Loxin® for treatment of osteoarthritis of the knee. *Arthritis Research & Therapy*, 13(3), R85.
- Sharma, A., Shanker, C., Tyagi, L. K., Singh, M., & Rao, C. V. (2008). Herbal medicine for market potential in India: An overview. *Academic Journal of Plant Sciences*, 1(2), 26–36.
- Singh, R. H. (2010). Exploring issues in the development of evidence-based Ayurveda. *Journal of Ayurveda and Integrative Medicine*, 1(2), 91–95.
- Thakur, P., & Srivastava, A. (2021). Role of phytochemicals in COVID-19 management. *Phytotherapy Research*, 35(10), 5689–5702.
- Tiwari, V., Chopra, K., & Kaur, I. P. (2017). Neuroprotective potential of *Boswellia serrata* in neurological disorders. *Neurochemical Research*, 42(10), 2846–2858.
- Zhang, D. H., Wu, K. L., Zhang, X., Deng, S. Q., & Peng, B. (2020). In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. *Journal of Integrative Medicine*, 18(2), 152–158.

## Chapter 5: Herbal Management of COVID-19 Comorbidities and Depression Using *Momordica charantia* and *Terminalia arjuna*

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### Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is increasingly recognized as a multisystem disorder affecting not only the respiratory system but also metabolic, cardiovascular, immunological, endocrine, and neuropsychiatric domains. The severity of infection and the risk of long-term complications are significantly higher in individuals with pre-existing comorbidities such as diabetes mellitus, hypertension, obesity, dyslipidemia, and depression. These conditions synergistically worsen disease progression through chronic low-grade inflammation, endothelial dysfunction, impaired immune response, and metabolic imbalance. At the pathophysiological level, COVID-19 is characterized by persistent systemic inflammation, excessive cytokine release, oxidative stress, mitochondrial dysfunction, and dysregulation of the renin–angiotensin system. These processes collectively contribute to multi-organ injury and long-COVID manifestations, including chronic fatigue, insulin resistance, cardiovascular complications, anxiety, depression, cognitive impairment, and sleep disturbances. In particular, neuroimmune dysregulation and sustained microglial activation play a crucial role in post-COVID neuropsychiatric outcomes. In this context, medicinal plants with multitarget pharmacological properties have gained increasing attention as complementary therapeutic agents capable of addressing complex disease networks rather than single molecular targets. *Momordica charantia* (bitter melon) and *Terminalia arjuna* (Arjuna bark) are two well-established medicinal plants in traditional Ayurvedic medicine that exhibit broad-spectrum biological activities relevant to COVID-19-associated complications. These include antidiabetic, cardioprotective, antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective effects, making them highly relevant in integrative post-COVID management strategies. The pharmacological efficacy of *Momordica charantia* is attributed to its rich phytochemical profile, including charantin, polypeptide-p, vicine, cucurbitane-type triterpenoids, and phenolic compounds. These constituents have demonstrated significant glucose-lowering effects through enhancement of peripheral glucose uptake, improvement in insulin sensitivity, and modulation of carbohydrate metabolism enzymes. Additionally, its antioxidant and anti-inflammatory properties help mitigate cytokine-mediated damage and oxidative stress observed in COVID-19 patients. Emerging evidence also suggests potential antidepressant-like and neuroprotective effects through modulation of neurotransmitter systems and reduction of neuroinflammation. Similarly, *Terminalia arjuna* is rich in bioactive compounds such as arjunolic acid, arjunic acid, flavonoids, tannins, gallic acid, ellagic acid, and triterpenoids, which contribute to its potent cardioprotective and vasculoprotective actions. It improves myocardial function, enhances endothelial integrity, regulates lipid metabolism, and reduces oxidative stress in cardiovascular tissues. Furthermore, its anti-inflammatory and antioxidant mechanisms may provide protective effects against COVID-19-induced vascular injury and post-infectious cardiovascular complications. Its adaptogenic potential may also contribute to stress reduction and improved neuropsychological resilience in post-COVID conditions. Experimental studies and limited clinical evidence suggest that both *Momordica charantia* and *Terminalia arjuna* may offer supportive therapeutic benefits in managing COVID-19-related metabolic dysregulation, cardiovascular dysfunction, and neuropsychiatric complications. Their multitarget pharmacological profiles align well with the complex and interconnected pathophysiology of post-COVID syndrome, where single-target pharmacotherapy often proves insufficient. This chapter therefore provides a comprehensive overview of the ethnopharmacology, phytochemical composition, molecular mechanisms, experimental evidence, and therapeutic relevance of *Momordica charantia* and *Terminalia arjuna* in COVID-19-associated metabolic and neuropsychological disorders.

### Keywords

COVID-19; SARS-CoV-2; long COVID; *Momordica charantia*; *Terminalia arjuna*; diabetes mellitus; hypertension; cardiovascular complications; oxidative stress; cytokine dysregulation; neuroinflammation;

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## 1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged as one of the most devastating global public health emergencies of the twenty-first century. Beyond its direct respiratory manifestations, COVID-19 rapidly evolved into a complex multisystem disorder affecting cardiovascular, metabolic, neurological, immunological, and psychological health. The pandemic resulted in millions of deaths worldwide and imposed an enormous burden on healthcare systems, economies, and social structures. Even after the acute phase of infection, many individuals continued to experience persistent symptoms collectively referred to as long-COVID syndrome, characterized by chronic fatigue, dyspnea, cognitive dysfunction, anxiety, depression, sleep disturbances, metabolic abnormalities, and cardiovascular complications. These long-term manifestations significantly reduced quality of life and increased the burden of chronic diseases globally.

Accumulating clinical evidence indicates that individuals with pre-existing comorbidities such as diabetes mellitus, cardiovascular diseases, hypertension, obesity, and metabolic syndrome are at substantially higher risk of severe COVID-19 progression, hospitalization, intensive care admission, and mortality. Metabolic dysfunction and chronic inflammatory states associated with these disorders contribute to impaired immune responses, endothelial dysfunction, oxidative stress, and cytokine dysregulation during SARS-CoV-2 infection. Diabetes mellitus, in particular, has been strongly associated with impaired antiviral immunity, hyperglycemia-induced oxidative stress, and exaggerated inflammatory responses, all of which contribute to increased disease severity and poor prognosis. Cardiovascular complications including myocardial injury, arrhythmias, thromboembolic events, and vascular inflammation have also emerged as major determinants of morbidity and mortality in COVID-19 patients.

Oxidative stress and systemic inflammation are considered central pathological mechanisms underlying severe COVID-19 and associated comorbidities. Excessive production of inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin-1 beta (IL-1 $\beta$ ) contributes to cytokine storm syndrome, endothelial injury, mitochondrial dysfunction, and multiorgan damage. Persistent inflammatory and oxidative pathways further aggravate pre-existing metabolic and cardiovascular disorders and may contribute to long-COVID complications. Clinical studies evaluating cardiometabolic interventions have highlighted the importance of therapies capable of regulating lipid abnormalities, oxidative stress, and inflammatory responses. Research involving *Terminalia arjuna* demonstrated significant hypolipidemic and cardioprotective potential comparable to conventional therapies such as rosuvastatin, indicating its relevance in managing cardiovascular risk factors associated with COVID-19 complications (Prakash et al., 2016; Prakash, 2019).

In addition to physical complications, the pandemic produced profound psychological and neuropsychiatric consequences across all age groups. Social isolation, fear of infection, loss of family members, economic instability, prolonged hospitalization, and uncertainty regarding future health contributed substantially to increased incidence of stress, anxiety, depression, insomnia, emotional exhaustion, and cognitive dysfunction. Long-COVID neurological manifestations including “brain fog,” impaired memory, concentration difficulties, and chronic fatigue have further intensified the global mental health burden. Neuroinflammatory responses, oxidative neuronal injury, hypothalamic–pituitary–

adrenal (HPA) axis dysregulation, and altered neurotransmitter signaling are believed to play major roles in the pathogenesis of depression and neuropsychological complications associated with COVID-19.

Conventional therapeutic approaches for COVID-19-associated metabolic, cardiovascular, and neuropsychiatric complications primarily rely on antiviral agents, corticosteroids, immunomodulators, antihypertensive drugs, hypoglycemic medications, antidepressants, and supportive care. Although these pharmacological interventions are often clinically beneficial, several limitations remain including adverse drug reactions, drug–drug interactions, limited long-term efficacy, high treatment costs, and challenges in managing chronic post-COVID complications. Observational studies conducted during the pandemic highlighted increased concerns regarding adverse drug reactions and pharmacovigilance monitoring in COVID-19 therapeutic management (Prakash et al., 2024). Furthermore, polypharmacy in patients with multiple comorbidities may increase the risk of hepatic, renal, cardiovascular, and neurological complications. These challenges emphasize the growing need for safer, multitarget, and integrative therapeutic approaches capable of simultaneously addressing inflammation, oxidative stress, metabolic imbalance, cardiovascular dysfunction, and psychological disturbances.

Medicinal plants and phytopharmaceuticals have therefore attracted considerable scientific interest as complementary and integrative therapeutic options in post-pandemic healthcare. Herbal medicines possess diverse bioactive compounds capable of exerting antioxidant, anti-inflammatory, immunomodulatory, cardioprotective, antihyperglycemic, neuroprotective, and antidepressant effects through multitarget pharmacological mechanisms. Unlike many synthetic drugs that primarily target single molecular pathways, medicinal plants often regulate multiple interconnected signaling cascades involved in oxidative stress, immune dysfunction, neuroinflammation, and metabolic disorders. Consequently, phytotherapeutic interventions may provide broader therapeutic benefits in complex disorders such as COVID-19 and long-COVID syndrome.

Among the medicinal plants investigated for cardiometabolic and neuroprotective benefits, *Momordica charantia* and *Terminalia arjuna* have emerged as promising therapeutic candidates. *Momordica charantia* (bitter melon) has been extensively used in Ayurveda, Traditional Chinese Medicine, and folk medicine for diabetes mellitus, obesity, infections, and inflammatory disorders. The plant contains important bioactive constituents including charantin, polypeptide-p, flavonoids, phenolic compounds, and cucurbitane-type triterpenoids that exhibit antihyperglycemic, antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective activities. Experimental studies suggest that *Momordica charantia* improves glucose metabolism, enhances insulin sensitivity, regulates inflammatory cytokines, and reduces oxidative stress, making it highly relevant in managing COVID-19-associated metabolic dysfunction.

Similarly, *Terminalia arjuna* is a well-established Ayurvedic medicinal plant traditionally used for cardiovascular diseases, hypertension, dyslipidemia, inflammatory disorders, and stress-related conditions. Its bark contains arjunolic acid, flavonoids, glycosides, tannins, and triterpenoids possessing potent cardioprotective, antioxidant, antihypertensive, and anti-inflammatory properties. Clinical investigations demonstrated that *Terminalia arjuna* significantly improves lipid profile, reduces blood pressure, and enhances antioxidant status in hypertensive and diabetic patients (Prakash et al., 2024; Prakash et al., 2025). Additional evidence suggests that *Terminalia arjuna* exhibits antihyperglycemic

efficacy comparable to sitagliptin in type-2 diabetes mellitus, further highlighting its therapeutic significance in metabolic disorders frequently associated with severe COVID-19 outcomes (Prakash et al., 2024).

The combined pharmacological properties of *Momordica charantia* and *Terminalia arjuna* suggest substantial therapeutic potential in addressing COVID-19-associated metabolic, cardiovascular, inflammatory, and psychological complications. Their antioxidant and immunomodulatory activities may help regulate cytokine dysregulation and oxidative stress, while their cardioprotective and antihyperglycemic effects may support management of comorbid conditions contributing to disease severity. Furthermore, emerging neuroprotective and adaptogenic properties of these medicinal plants may assist in reducing stress, depression, cognitive dysfunction, and long-COVID neuropsychiatric manifestations.

This chapter therefore aims to comprehensively explore the ethnopharmacology, phytochemistry, pharmacological mechanisms, experimental evidence, and clinical relevance of *Momordica charantia* and *Terminalia arjuna* in the management of COVID-19-associated comorbidities and depression. Particular emphasis is placed on their antidiabetic, cardioprotective, antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective properties relevant to SARS-CoV-2-induced metabolic and neuroimmune dysfunction. The chapter additionally discusses experimental and clinical investigations, safety considerations, herb–drug interactions, and future perspectives involving integrative medicine, nanotechnology-based drug delivery systems, and evidence-based phytotherapeutic approaches for long-COVID management and post-pandemic healthcare.

## 2. Ethnopharmacology, Phytochemistry, and Traditional Uses

### 2.1 *Momordica charantia*

#### Ayurvedic and Traditional Importance

*Momordica charantia* L., commonly known as bitter melon or bitter gourd, is an important medicinal plant extensively utilized in Ayurveda, Traditional Chinese Medicine (TCM), Unani medicine, and various indigenous healthcare systems. In Ayurveda, the plant is traditionally referred to as “Karavella” or “Karela” and is widely prescribed for disorders associated with impaired metabolism, hyperglycemia, digestive disturbances, inflammation, skin diseases, and infections. Traditional medicinal literature describes *Momordica charantia* as possessing “tikta rasa” (bitter taste), digestive stimulant activity, detoxifying properties, and blood-purifying effects. It has historically been used to regulate blood sugar levels, improve appetite, reduce fever, and support immune health (Grover & Yadav, 2004).

Traditional Chinese Medicine recognizes bitter melon as an important medicinal food with cooling and detoxifying properties. It has been used for management of diabetes mellitus, gastrointestinal disorders, microbial infections, and inflammatory conditions. Folk medicine systems across Asia, Africa, and Latin America additionally utilize *Momordica charantia* for wound healing, respiratory infections, parasitic diseases, liver disorders, and immune dysfunction.

The increasing prevalence of metabolic disorders and immune-mediated diseases during and after the COVID-19 pandemic has renewed scientific interest in medicinal plants possessing antihyperglycemic, antioxidant, anti-inflammatory, and immunomodulatory activities. Because diabetes mellitus and metabolic syndrome significantly increase COVID-19 severity and mortality, traditional medicinal plants such as *Momordica charantia* may provide supportive therapeutic benefits through regulation of glucose metabolism, inflammatory pathways, and oxidative stress.

### Botanical Description and Distribution

*Momordica charantia* belongs to the family Cucurbitaceae. It is a climbing annual or perennial herb characterized by slender stems, deeply lobed leaves, yellow flowers, and elongated warty fruits with a distinctly bitter taste. The fruits vary in size, shape, and color depending on geographical variety and cultivation conditions.

Taxonomically, the plant is classified as follows:

- Kingdom: Plantae
- Order: Cucurbitales
- Family: Cucurbitaceae
- Genus: *Momordica*
- Species: *Momordica charantia* L.

The plant is widely cultivated in tropical and subtropical regions including India, China, Bangladesh, Sri Lanka, Southeast Asia, Africa, the Caribbean, and South America. India is considered one of the major centers of cultivation and traditional medicinal utilization. The plant grows optimally in warm climatic conditions and is cultivated both as a vegetable crop and medicinal herb.

### Major Phytoconstituents

The pharmacological activities of *Momordica charantia* are attributed to a diverse range of bioactive phytochemicals including triterpenoids, glycosides, peptides, alkaloids, flavonoids, phenolic compounds, and sterols.

#### *Charantin*

Charantin is one of the most extensively studied bioactive constituents of *Momordica charantia*. It is a steroidal saponin mixture associated primarily with antihyperglycemic activity. Experimental investigations demonstrate that charantin improves glucose uptake, enhances glycogen synthesis, and regulates insulin sensitivity (Joseph & Jini, 2013).

#### *Polypeptide-p*

Polypeptide-p, often referred to as “plant insulin,” is an insulin-like peptide isolated from bitter melon fruits and seeds. This peptide exhibits hypoglycemic effects through mechanisms resembling endogenous insulin activity and may contribute significantly to glucose regulation in diabetic conditions.

### ***Vicine***

Vicine is a pyrimidine glycoside associated with glucose-lowering and antioxidant properties. It may additionally contribute to modulation of oxidative stress and inflammatory responses.

### ***Cucurbitane-Type Triterpenoids***

Cucurbitane-type triterpenoids constitute a major class of pharmacologically active compounds in *Momordica charantia*. These compounds exhibit:

- Antidiabetic activity
- Anti-inflammatory effects
- Antioxidant properties
- Antiviral potential
- Immunomodulatory activity

Recent molecular studies suggest that certain cucurbitane triterpenoids may influence inflammatory signaling pathways and metabolic regulation associated with COVID-19-related complications.

### ***Flavonoids and Phenolic Compounds***

The plant additionally contains quercetin, gallic acid, catechin, chlorogenic acid, and various polyphenolic antioxidants that contribute to free radical scavenging, neuroprotection, and immune regulation.

## **Traditional Therapeutic Applications**

### ***Antidiabetic and Antihyperglycemic Uses***

The most recognized traditional application of *Momordica charantia* involves management of diabetes mellitus and hyperglycemia. Traditional healers have long utilized bitter melon fruit juice, decoctions, powders, and extracts for reducing blood glucose levels and improving metabolic health.

Modern pharmacological studies demonstrate that *Momordica charantia*:

- Enhances insulin secretion
- Improves insulin sensitivity
- Inhibits intestinal glucose absorption
- Reduces oxidative stress associated with hyperglycemia
- Protects pancreatic  $\beta$ -cells

These activities are highly relevant because diabetes mellitus is a major risk factor for severe COVID-19 outcomes.

### ***Antioxidant and Anti-inflammatory Activities***

The plant exhibits significant antioxidant and anti-inflammatory effects through inhibition of reactive oxygen species, lipid peroxidation, and inflammatory cytokines including TNF- $\alpha$  and IL-6. Such mechanisms may help reduce oxidative tissue injury and chronic inflammatory complications associated with SARS-CoV-2 infection.

### ***Immune-Enhancing and Antiviral Applications***

Traditional medicinal systems frequently utilized *Momordica charantia* in infectious and febrile disorders because of its immune-supportive properties. Experimental studies indicate that bitter melon extracts may enhance macrophage activity, regulate immune signaling pathways, and exhibit antiviral effects against several viral pathogens.

### ***Neuroprotective and Mood-Regulating Effects***

Emerging evidence suggests that *Momordica charantia* possesses neuroprotective and antidepressant-like activities mediated through antioxidant defense, inflammatory regulation, and neurotransmitter modulation. These effects may have therapeutic relevance in COVID-19-associated stress, depression, and neuroinflammatory complications.

## **2.2 Terminalia arjuna**

### **Traditional and Medicinal Importance**

*Terminalia arjuna* Roxb., commonly known as Arjuna, is one of the most important cardiotoxic medicinal plants in Ayurveda. The bark of the plant has been used for centuries in management of cardiovascular diseases, hypertension, dyslipidemia, inflammatory disorders, stress-related conditions, and wound healing. Ancient Ayurvedic texts including Charaka Samhita and Sushruta Samhita describe Arjuna as a “Hridya” drug beneficial for cardiac health and circulatory disorders.

Traditional medicine systems utilized *Terminalia arjuna* for:

- Cardiac weakness
- Angina and hypertension
- Hyperlipidemia
- Edema and inflammation
- Stress and anxiety
- Fracture healing
- Liver disorders

The cardioprotective significance of *Terminalia arjuna* has attracted substantial scientific interest, particularly because cardiovascular disorders represent major comorbidities associated with severe COVID-19 outcomes.

## Botanical Characteristics and Distribution

*Terminalia arjuna* belongs to the family Combretaceae and is a large deciduous tree characterized by smooth grey bark, oblong leaves, white flowers, and winged fruits.

Taxonomical classification includes:

- Kingdom: Plantae
- Order: Myrtales
- Family: Combretaceae
- Genus: *Terminalia*
- Species: *Terminalia arjuna* Roxb.

The tree is widely distributed throughout India, Sri Lanka, Bangladesh, Myanmar, and parts of Southeast Asia. It commonly grows along riverbanks and humid forest regions. India remains the principal center for medicinal utilization and commercial cultivation.

## Key Bioactive Compounds

### Arjunolic Acid

Arjunolic acid is one of the principal triterpenoid compounds responsible for antioxidant, cardioprotective, anti-inflammatory, and antihyperglycemic activities of *Terminalia arjuna*. The compound protects myocardial tissue against oxidative stress and ischemic injury.

### Arjunic Acid

Arjunic acid contributes to cardioprotective and vascular protective effects through modulation of oxidative stress pathways and endothelial function.

### Triterpenoids

Several triterpenoids isolated from *Terminalia arjuna* exhibit:

- Antioxidant activity
- Anti-inflammatory effects
- Cardioprotective mechanisms
- Antihyperlipidemic actions

### Flavonoids and Tannins

Flavonoids including arjunone, luteolin, quercetin, and tannins contribute significantly to free radical scavenging and vascular stabilization.

## Glycosides and Polyphenols

The bark contains glycosides, ellagic acid, gallic acid, and polyphenolic compounds associated with anti-inflammatory and neuroprotective properties.

## Traditional Therapeutic Applications

### Cardioprotective and Antihypertensive Uses

*Terminalia arjuna* is extensively used for management of:

- Hypertension
- Coronary artery disease
- Congestive heart failure
- Dyslipidemia
- Ischemic heart disease

Clinical investigations demonstrated significant lipid-lowering and antihypertensive effects of *Terminalia arjuna*, supporting its traditional medicinal claims (Prakash et al., 2016; Prakash et al., 2025).

### Antioxidant and Anti-inflammatory Effects

The bark exhibits strong antioxidant activity by reducing lipid peroxidation and enhancing endogenous antioxidant defense systems. Anti-inflammatory actions further contribute to vascular protection and reduction of oxidative tissue injury.

### Stress Reduction and Neuroprotective Applications

Traditional Ayurvedic medicine additionally utilized Arjuna for emotional stability, stress reduction, and nervous system support. Emerging experimental evidence suggests anxiolytic, adaptogenic, and neuroprotective effects mediated through antioxidant and anti-inflammatory mechanisms.

### Supportive Role in Metabolic Disorders

Recent clinical studies demonstrated antihyperglycemic efficacy of *Terminalia arjuna* in type-2 diabetes mellitus patients, indicating potential relevance in COVID-19-associated metabolic complications (Prakash et al., 2024).

## 2.3 Comparative Phytochemical and Pharmacological Profile

Both *Momordica charantia* and *Terminalia arjuna* possess broad-spectrum pharmacological activities relevant to management of COVID-19-associated comorbidities and depression. However, their therapeutic mechanisms differ according to phytochemical composition and target pathways.

*Momordica charantia* primarily exhibits:

- Antidiabetic activity
- Insulin-mimetic effects
- Metabolic regulation
- Immune enhancement
- Antiviral potential

In contrast, *Terminalia arjuna* demonstrates stronger:

- Cardioprotective activity
- Antihypertensive effects
- Vascular stabilization
- Lipid-lowering properties
- Antioxidant cardiometabolic protection

Despite these differences, both medicinal plants share important pharmacological similarities including:

- Antioxidant activity
- Anti-inflammatory effects
- Cytokine regulation
- Neuroprotective properties
- Oxidative stress reduction

These complementary actions suggest potential synergistic therapeutic relevance in COVID-19-associated metabolic dysfunction, cardiovascular complications, chronic inflammation, and depression-related disorders.

**Table 1. Comparative Ethnopharmacological and Phytochemical Profile of *Momordica charantia* and *Terminalia arjuna***

Parameter	<i>Momordica charantia</i>	<i>Terminalia arjuna</i>	Therapeutic Relevance in COVID-19
Traditional System	Ayurveda, TCM, folk medicine	Ayurveda and traditional medicine	Integrative therapeutic significance
Major Therapeutic Use	Diabetes and metabolic disorders	Cardiovascular and hypertensive disorders	Management of major COVID-19 comorbidities
Principal Bioactive Constituents	Charantin, polypeptide-p, vicine, cucurbitane triterpenoids	Arjunolic acid, arjunic acid, flavonoids, tannins	Multitarget pharmacological effects
Major Pharmacological Activity	Antidiabetic and immunomodulatory	Cardioprotective and antihypertensive	Reduction of disease severity
Antioxidant Activity	Strong polyphenolic antioxidant effects	Potent cardiometabolic antioxidant effects	Reduction of oxidative stress
Anti-inflammatory Mechanisms	Cytokine suppression and metabolic	NF-κB inhibition and vascular protection	Cytokine storm regulation

	regulation		
Neuroprotective Effects	Mood regulation and neuronal protection	Adaptogenic and stress-reducing effects	Depression and long-COVID support
Cardiovascular Effects	Indirect metabolic cardiovascular protection	Direct myocardial and vascular protection	Reduction of cardiac complications
Immunomodulatory Effects	Enhancement of immune responses	Reduction of inflammatory injury	Immune balance restoration
Potential Long-COVID Role	Metabolic recovery and fatigue reduction	Cardiovascular and stress recovery	Post-COVID rehabilitation

**Table 2. Major Phytoconstituents and Pharmacological Activities of *Momordica charantia* and *Terminalia arjuna***

Plant	Major Phytoconstituents	Pharmacological Activities	Therapeutic Importance
<i>Momordica charantia</i>	Charantin	Antihyperglycemic and insulin sensitization	Diabetes management
	Polypeptide-p	Insulin-like activity	Glucose regulation
	Cucurbitane triterpenoids	Anti-inflammatory and antiviral effects	Immune support
	Flavonoids and phenolics	Antioxidant and neuroprotective activity	Oxidative stress reduction
<i>Terminalia arjuna</i>	Arjunolic acid	Cardioprotective and antioxidant effects	Cardiac protection
	Arjunic acid	Anti-inflammatory activity	Vascular stabilization
	Flavonoids and tannins	Free radical scavenging	Reduction of oxidative injury
	Glycosides and polyphenols	Neuroprotective and antihyperlipidemic activity	Metabolic and neurological support

### 3. Role in COVID-19 Comorbidities Management

The severity and clinical outcome of coronavirus disease 2019 (COVID-19) are strongly influenced by the presence of underlying comorbidities including diabetes mellitus, hypertension, cardiovascular disease, obesity, and metabolic syndrome. These conditions contribute to chronic low-grade inflammation, endothelial dysfunction, oxidative stress, impaired immune responses, and dysregulated cytokine production, thereby increasing susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced complications. Clinical investigations consistently demonstrated that patients with pre-existing metabolic and cardiovascular disorders experience higher hospitalization rates,

respiratory distress, multiorgan dysfunction, thromboembolic complications, and mortality compared with healthy individuals (Zhou et al., 2020).

The interaction between SARS-CoV-2 infection and chronic comorbidities is mediated through several pathological mechanisms including hyperinflammation, oxidative stress, mitochondrial dysfunction, insulin resistance, vascular injury, and cytokine storm syndrome. Excessive production of inflammatory mediators such as IL-6, TNF- $\alpha$ , IL-1 $\beta$ , and C-reactive protein (CRP) contributes significantly to pulmonary inflammation, endothelial injury, coagulation abnormalities, and tissue damage. In addition, oxidative stress resulting from excessive reactive oxygen species (ROS) production further aggravates metabolic imbalance, cardiovascular dysfunction, and neuronal injury.

Because conventional therapies frequently target only specific symptoms or molecular pathways, medicinal plants possessing multitarget pharmacological properties have gained increasing attention as complementary therapeutic agents. In this context, *Momordica charantia* and *Terminalia arjuna* exhibit substantial therapeutic potential because of their antihyperglycemic, cardioprotective, antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective activities.

### 3.1 Metabolic and Cardiovascular Complications in COVID-19

Diabetes mellitus is considered one of the most important risk factors associated with severe COVID-19 progression. Hyperglycemia impairs innate immune responses, increases oxidative stress, enhances inflammatory cytokine release, and facilitates viral replication. Elevated blood glucose levels also contribute to endothelial dysfunction, thrombosis, and mitochondrial injury, thereby worsening systemic inflammation and organ damage. Insulin resistance and metabolic syndrome further amplify chronic inflammatory states through activation of NF- $\kappa$ B signaling pathways and oxidative stress cascades (Bornstein et al., 2020).

Cardiovascular complications are similarly prominent in COVID-19 patients. SARS-CoV-2 infection may induce myocardial injury, myocarditis, arrhythmias, acute coronary syndromes, endothelial dysfunction, and thromboembolic disorders. Viral entry through angiotensin-converting enzyme 2 (ACE2) receptors disrupts vascular homeostasis and contributes to inflammatory cardiac injury. Oxidative stress and cytokine storm syndrome additionally aggravate cardiovascular dysfunction through excessive release of IL-6, TNF- $\alpha$ , and reactive oxygen intermediates.

Hypertension and dyslipidemia also contribute significantly to COVID-19 severity. Chronic vascular inflammation and endothelial dysfunction associated with these conditions increase susceptibility to respiratory distress, vascular injury, and multiorgan complications. Therefore, therapeutic interventions capable of regulating glucose metabolism, blood pressure, lipid abnormalities, inflammation, and oxidative stress may provide substantial benefits in COVID-19 management.

### 3.2 Antidiabetic and Metabolic Effects of *Momordica charantia*

#### Regulation of Glucose Metabolism

*Momordica charantia* has long been recognized as a potent antidiabetic medicinal plant in Ayurveda and traditional medicine. Experimental and clinical studies indicate that bitter melon improves glucose homeostasis through multiple complementary mechanisms including stimulation of insulin secretion, enhancement of peripheral glucose utilization, inhibition of intestinal glucose absorption, and modulation of hepatic gluconeogenesis (Grover & Yadav, 2004).

Bioactive compounds such as charantin, polypeptide-p, and cucurbitane-type triterpenoids contribute significantly to antihyperglycemic activity. Charantin enhances glycogen synthesis and glucose uptake, whereas polypeptide-p exhibits insulin-like activity capable of lowering blood glucose levels. These mechanisms may be particularly relevant in COVID-19 patients experiencing hyperglycemia and insulin resistance.

#### Insulin-Mimetic and Pancreatic Protective Effects

Several investigations demonstrated that *Momordica charantia* protects pancreatic  $\beta$ -cells against oxidative stress and inflammatory injury. Antioxidant compounds present in bitter melon reduce lipid peroxidation, improve endogenous antioxidant enzyme activity, and preserve pancreatic tissue integrity. Improvement of insulin sensitivity and pancreatic function may help reduce metabolic complications associated with severe COVID-19 infection.

#### Antioxidant and Anti-inflammatory Mechanisms

Oxidative stress and chronic inflammation are central pathological features in both diabetes mellitus and COVID-19. *Momordica charantia* exhibits significant antioxidant activity through:

- Scavenging reactive oxygen species
- Enhancing superoxide dismutase and catalase activity
- Reducing lipid peroxidation
- Inhibiting inflammatory cytokines

The plant additionally suppresses NF- $\kappa$ B activation and downregulates pro-inflammatory mediators including IL-6 and TNF- $\alpha$ , thereby potentially reducing cytokine-mediated tissue injury.

#### Effects on Obesity and Metabolic Syndrome

Experimental studies suggest that bitter melon improves lipid metabolism, reduces adiposity, and regulates metabolic syndrome-associated inflammatory pathways. These effects are clinically important because obesity and metabolic syndrome substantially increase COVID-19 severity and long-COVID complications.

### 3.3 Cardioprotective Effects of *Terminalia arjuna*

#### Protection Against Myocardial Injury

*Terminalia arjuna* is widely recognized as one of the most important cardioprotective medicinal plants in Ayurveda. The bark contains arjunolic acid, flavonoids, glycosides, and tannins possessing potent antioxidant and myocardial protective properties. Experimental studies demonstrate that *Terminalia arjuna* protects cardiac tissues against ischemic injury, oxidative stress, lipid peroxidation, and inflammatory damage (Dwivedi, 2007). COVID-19-associated myocardial injury and vascular inflammation may therefore be reduced through antioxidant and anti-inflammatory actions of *Terminalia arjuna*.

#### Regulation of Lipid Profile and Blood Pressure

Clinical investigations revealed that *Terminalia arjuna* significantly reduces total cholesterol, triglycerides, and low-density lipoprotein (LDL) levels while improving high-density lipoprotein (HDL) concentrations (Prakash et al., 2016; Prakash, 2019). The plant additionally exhibits antihypertensive activity through vascular relaxation and endothelial stabilization mechanisms.

A randomized clinical study further demonstrated improvement in blood pressure and antioxidant status among hypertensive geriatric patients receiving *Terminalia arjuna* supplementation (Prakash et al., 2025). Such cardiometabolic effects are highly relevant because hypertension and dyslipidemia are major predictors of COVID-19 severity.

#### Antioxidant and Vascular Protective Effects

Arjunolic acid and polyphenolic compounds present in *Terminalia arjuna* effectively reduce oxidative stress by:

- Inhibiting lipid peroxidation
- Enhancing endogenous antioxidant enzymes
- Protecting endothelial tissues
- Stabilizing mitochondrial function

These mechanisms contribute significantly to vascular protection and reduction of inflammatory injury associated with SARS-CoV-2 infection.

#### Improvement of Endothelial Function

Endothelial dysfunction is a hallmark of severe COVID-19 and contributes to thrombosis, vascular inflammation, and multiorgan complications. *Terminalia arjuna* improves endothelial function through nitric oxide regulation, antioxidant defense, and anti-inflammatory actions, thereby potentially reducing vascular complications associated with COVID-19.

### 3.4 Immunomodulatory and Anti-inflammatory Mechanisms

Both *Momordica charantia* and *Terminalia arjuna* possess substantial immunomodulatory and anti-inflammatory activities capable of regulating excessive inflammatory responses associated with severe COVID-19.

#### Cytokine Suppression and Oxidative Stress Reduction

The phytoconstituents present in these medicinal plants suppress pro-inflammatory cytokines including:

- IL-6
- TNF- $\alpha$
- IL-1 $\beta$
- CRP

Simultaneously, antioxidant compounds reduce reactive oxygen species production and oxidative tissue injury.

#### NF- $\kappa$ B and Inflammatory Signaling Pathways

NF- $\kappa$ B signaling pathways play critical roles in cytokine storm syndrome and chronic inflammation. Experimental evidence indicates that both medicinal plants inhibit NF- $\kappa$ B activation and inflammatory gene expression, thereby reducing systemic inflammatory burden.

#### Protection Against COVID-19-Associated Organ Injury

Through combined antioxidant, anti-inflammatory, metabolic, and vascular protective mechanisms, these medicinal plants may help protect against:

- Pulmonary inflammation
- Endothelial dysfunction
- Cardiac injury
- Metabolic complications
- Neuroimmune dysfunction

Their multitarget pharmacological actions therefore support potential complementary use in integrative COVID-19 management.

### 3.5 Potential Therapeutic Role in Long-COVID

Long-COVID syndrome is characterized by persistent fatigue, metabolic disturbances, cardiovascular dysfunction, neuroinflammation, anxiety, depression, and cognitive impairment. Chronic oxidative stress, immune dysregulation, and mitochondrial dysfunction contribute substantially to prolonged symptoms.

### Fatigue and Metabolic Dysfunction

The antihyperglycemic and antioxidant properties of *Momordica charantia* may assist in improving metabolic recovery, reducing fatigue, and restoring mitochondrial function in long-COVID patients.

### Cardiovascular Recovery Support

*Terminalia arjuna* may support post-COVID cardiovascular recovery through:

- Improvement of endothelial function
- Reduction of oxidative stress
- Regulation of lipid abnormalities
- Cardiomyocyte protection

### Persistent Inflammatory Complications

Both medicinal plants possess anti-inflammatory and immunomodulatory activities capable of reducing persistent cytokine dysregulation and chronic inflammatory responses associated with long-COVID syndrome.

**Table 3. Major COVID-19 Comorbidities and Potential Therapeutic Roles of *Momordica charantia* and *Terminalia arjuna***

COVID-19 Comorbidity	Pathological Features	Role of <i>Momordica charantia</i>	Role of <i>Terminalia arjuna</i>
Diabetes mellitus	Hyperglycemia, oxidative stress, insulin resistance	Antihyperglycemic and insulin sensitization	Improvement of metabolic regulation
Hypertension	Endothelial dysfunction and vascular inflammation	Antioxidant support	Antihypertensive and vascular protective effects
Cardiovascular disease	Myocardial injury and thrombosis	Reduction of metabolic stress	Cardioprotective and lipid-lowering effects
Obesity and metabolic syndrome	Chronic inflammation and dyslipidemia	Regulation of lipid metabolism	Antioxidant and anti-inflammatory support
Long-COVID fatigue	Mitochondrial dysfunction and inflammation	Energy metabolism support	Cardiovascular recovery support
Neuroinflammation	Cytokine dysregulation and oxidative injury	Neuroprotective effects	Adaptogenic and anti-inflammatory activity

**Table 4. Pharmacological Mechanisms Relevant to COVID-19 Management**

Pharmacological Activity	<i>Momordica charantia</i>	<i>Terminalia arjuna</i>	COVID-19 Relevance

Antioxidant activity	Strong ROS scavenging	Potent lipid peroxidation inhibition	Reduction of oxidative stress
Anti-inflammatory effects	Cytokine suppression	NF-κB inhibition	Cytokine storm regulation
Antihyperglycemic activity	Insulin-like effects	Metabolic support	Diabetes management
Cardioprotective activity	Indirect metabolic cardioprotection	Direct myocardial protection	Reduction of cardiac complications
Immunomodulatory effects	Immune enhancement	Inflammatory regulation	Immune balance restoration
Endothelial protection	Reduction of oxidative injury	Vascular stabilization	Prevention of thrombosis
Neuroprotective effects	Mood regulation	Stress reduction	Long-COVID neurological support

#### 4. Antidepressant and Neuroprotective Effects

The coronavirus disease 2019 (COVID-19) pandemic produced unprecedented psychological, neurological, and neuroimmune consequences worldwide. Beyond acute respiratory illness, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) significantly affected mental health through direct viral neuroinvasion, systemic inflammation, oxidative stress, prolonged hospitalization, social isolation, economic instability, and chronic psychosocial stress. Increasing clinical evidence indicates that anxiety, depression, insomnia, cognitive dysfunction, chronic fatigue, and post-traumatic stress symptoms became highly prevalent during and after the pandemic (Taquet et al., 2021).

Neuropsychiatric complications associated with COVID-19 are strongly linked with inflammatory cytokine release, oxidative neuronal injury, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, mitochondrial dysfunction, neurotransmitter imbalance, and blood–brain barrier disruption. Persistent neuroinflammation and immune dysregulation further contribute to long-COVID neurological manifestations including “brain fog,” impaired memory, concentration difficulties, mood disturbances, and chronic fatigue syndrome.

Because conventional antidepressants and anxiolytic therapies may produce adverse effects and often fail to address underlying inflammatory and oxidative mechanisms, medicinal plants possessing antioxidant, adaptogenic, anti-inflammatory, and neuroprotective properties have attracted growing scientific interest. In this context, *Momordica charantia* and *Terminalia arjuna* demonstrate promising therapeutic potential through multitarget neuroimmune and neuroprotective mechanisms.

#### 4.1 Depression and Neuropsychiatric Manifestations in COVID-19

##### Anxiety, Depression, and Chronic Stress

The COVID-19 pandemic resulted in widespread emotional distress due to:

- Fear of infection and mortality
- Social isolation and quarantine
- Financial instability
- Loss of family members
- Prolonged uncertainty and psychological burden

Consequently, the incidence of anxiety disorders, depression, emotional exhaustion, sleep disturbances, and stress-related psychiatric disorders increased dramatically during the pandemic period. Long-term psychological stress additionally contributed to impaired immune responses, elevated cortisol levels, and chronic inflammatory activation.

### **Neuroinflammation and Neurotransmitter Imbalance**

SARS-CoV-2 infection may induce neuroinflammation through excessive production of pro-inflammatory cytokines including IL-6, TNF- $\alpha$ , and IL-1 $\beta$ . These inflammatory mediators alter neurotransmitter metabolism, impair neuronal signaling, and contribute to depressive symptoms and cognitive dysfunction.

Neuroimmune activation additionally affects:

- Serotonin metabolism
- Dopaminergic signaling
- Glutamatergic neurotransmission
- Neurotrophic factor expression

Persistent cytokine-mediated neurotoxicity therefore represents a major mechanism underlying depression and neuropsychiatric complications in COVID-19 patients.

### **Long-COVID Cognitive and Emotional Disturbances**

Long-COVID syndrome frequently includes:

- Cognitive impairment
- Memory deficits
- Attention disturbances
- Sleep disorders
- Emotional instability
- Chronic fatigue

Oxidative stress, mitochondrial dysfunction, endothelial injury, and chronic neuroinflammation collectively contribute to persistent neurological and psychological symptoms following SARS-CoV-2 infection.

## 4.2 Neuroprotective and Antidepressant Effects of *Momordica charantia*

### Antioxidant-Mediated Neuronal Protection

*Momordica charantia* exhibits significant antioxidant activity capable of protecting neuronal tissues against oxidative stress and inflammatory injury. Bioactive compounds including flavonoids, phenolic acids, cucurbitane triterpenoids, and charantin reduce reactive oxygen species production and lipid peroxidation in neuronal cells.

Experimental studies demonstrate that bitter melon enhances endogenous antioxidant enzymes including:

- Superoxide dismutase (SOD)
- Catalase
- Glutathione peroxidase

These antioxidant mechanisms may reduce neuronal damage associated with COVID-19-induced oxidative stress and neuroinflammation.

### Modulation of Neurotransmitters

Emerging evidence suggests that *Momordica charantia* influences neurotransmitter systems involved in mood regulation and emotional behavior. Experimental models demonstrated modulation of serotonin, dopamine, and gamma-aminobutyric acid (GABA) pathways following administration of bitter melon extracts. Improvement of neurotransmitter balance may contribute to:

- Reduction of anxiety
- Improvement of depressive symptoms
- Enhancement of cognitive performance
- Emotional stabilization

### Anti-inflammatory Effects in Stress Models

Chronic stress activates inflammatory signaling pathways including NF- $\kappa$ B and cytokine cascades that contribute to depressive behavior and neuronal dysfunction. *Momordica charantia* suppresses inflammatory mediators including IL-6 and TNF- $\alpha$  while reducing oxidative tissue injury in stress-induced experimental models. These anti-inflammatory activities may provide supportive benefits in long-COVID neuropsychiatric manifestations associated with persistent cytokine dysregulation.

### Experimental Evidence in Depression and Anxiety

Animal studies demonstrated antidepressant-like and anxiolytic effects of *Momordica charantia* extracts in behavioral models including:

- Forced swim test
- Tail suspension test

- Elevated plus maze

Observed effects were associated with antioxidant defense enhancement, inflammatory suppression, and neurotransmitter regulation.

### 4.3 Neuroprotective and Anti-stress Effects of *Terminalia arjuna*

#### Adaptogenic and Anxiolytic Properties

*Terminalia arjuna* has long been used in Ayurveda for stress reduction, emotional balance, and cardiovascular stabilization. Modern experimental evidence indicates that the plant exhibits adaptogenic and anxiolytic activities capable of improving stress tolerance and reducing neuroendocrine dysfunction.

Adaptogens help maintain physiological homeostasis during chronic stress by regulating HPA-axis activity and reducing cortisol-mediated neuronal injury.

#### Regulation of Oxidative Stress and Neuronal Inflammation

Arjunolic acid, flavonoids, and polyphenols present in *Terminalia arjuna* possess potent antioxidant and anti-inflammatory activities. These compounds reduce:

- Lipid peroxidation
- Mitochondrial oxidative injury
- Neuroinflammatory cytokines
- Endothelial dysfunction

The antioxidant mechanisms contribute significantly to neuronal protection against chronic inflammatory and oxidative stress conditions associated with COVID-19.

#### Cardiovascular-Neuropsychological Interactions

Cardiovascular dysfunction and psychological stress are closely interconnected. Hypertension, endothelial injury, and oxidative stress contribute substantially to anxiety, depression, and cognitive decline. Because *Terminalia arjuna* improves cardiovascular function and vascular health, it may indirectly enhance cerebral circulation, oxygen delivery, and neuronal metabolism, thereby supporting cognitive and emotional health.

#### Cognitive and Emotional Health Benefits

Experimental investigations demonstrated that *Terminalia arjuna* improves memory, learning behavior, emotional stability, and stress adaptation in animal models. These effects may involve:

- Reduction of neuroinflammation
- Improvement of antioxidant defense
- Regulation of neurotransmitter pathways

- Mitochondrial stabilization

Such neuroprotective mechanisms may have therapeutic significance in long-COVID cognitive dysfunction and depression-related disorders.

#### 4.4 Mechanistic Insights

##### HPA-Axis Regulation

Chronic stress and COVID-19-related psychological burden activate the hypothalamic–pituitary–adrenal (HPA) axis, resulting in elevated cortisol levels and neuroendocrine imbalance. Prolonged cortisol elevation contributes to:

- Anxiety and depression
- Sleep disturbances
- Cognitive impairment
- Immune suppression

Both *Momordica charantia* and *Terminalia arjuna* exhibit adaptogenic properties capable of regulating stress responses and restoring neuroendocrine homeostasis.

##### Neuroimmune Interactions

Neuroimmune dysfunction is a major contributor to COVID-19-associated depression and neurological complications. Pro-inflammatory cytokines influence neurotransmitter metabolism and neuronal signaling, thereby promoting depressive symptoms and cognitive dysfunction.

The anti-inflammatory properties of these medicinal plants may help reduce:

- Cytokine-mediated neurotoxicity
- Microglial activation
- Blood–brain barrier disruption
- Neuroimmune dysregulation

##### Oxidative Stress Reduction and Mitochondrial Protection

Mitochondrial dysfunction and oxidative neuronal injury contribute substantially to long-COVID fatigue and neurodegeneration. Antioxidant phytochemicals present in *Momordica charantia* and *Terminalia arjuna* protect mitochondrial integrity and reduce free radical-mediated cellular damage.

These mechanisms may improve:

- Neuronal energy metabolism
- Synaptic function
- Cognitive performance

- Stress tolerance

### Neurotransmitter and Neurotrophic Modulation

Emerging evidence indicates that phytoconstituents present in these medicinal plants influence neurotransmitter systems including serotonin, dopamine, GABA, and acetylcholine pathways. They may additionally regulate brain-derived neurotrophic factor (BDNF) expression associated with neuroplasticity and emotional regulation. Such multitarget neuroprotective mechanisms support their potential therapeutic role in depression, anxiety, cognitive dysfunction, and long-COVID neurological complications.

**Table 5. Neuropsychiatric Manifestations Associated with COVID-19 and Potential Herbal Interventions**

Neuropsychiatric Complication	Pathophysiological Mechanisms	Role of <i>Momordica charantia</i>	Role of <i>Terminalia arjuna</i>
Anxiety	HPA-axis activation and oxidative stress	Neurotransmitter regulation	Adaptogenic and anxiolytic activity
Depression	Neuroinflammation and cytokine dysregulation	Antioxidant and antidepressant effects	Stress reduction and neuroprotection
Insomnia	Neuroendocrine imbalance	Mood stabilization	Nervous system calming effects
Cognitive dysfunction	Oxidative neuronal injury	Cognitive enhancement	Cerebral vascular support
Long-COVID fatigue	Mitochondrial dysfunction	Energy metabolism support	Antioxidant cardiometabolic protection
Neuroinflammation	Cytokine storm and ROS generation	Anti-inflammatory activity	NF-κB inhibition and vascular stabilization

**Table 6. Comparative Neuroprotective and Antidepressant Mechanisms of *Momordica charantia* and *Terminalia arjuna***

Pharmacological Mechanism	<i>Momordica charantia</i>	<i>Terminalia arjuna</i>	Therapeutic Relevance
Antioxidant activity	Strong free radical scavenging	Potent lipid peroxidation inhibition	Protection against neuronal injury
Anti-inflammatory effects	Cytokine suppression	Reduction of inflammatory signaling	Neuroimmune regulation
Neurotransmitter modulation	Serotonin and dopamine regulation	Stress-response modulation	Mood stabilization
Adaptogenic activity	Moderate adaptogenic effects	Strong adaptogenic activity	Stress tolerance improvement
Cognitive enhancement	Memory and neuronal protection	Cerebral circulation support	Long-COVID cognitive recovery

Mitochondrial protection	Reduction of oxidative injury	Enhancement of cellular stability	Fatigue reduction
HPA-axis regulation	Neuroendocrine balancing	Cortisol reduction	Anxiety and depression management

## 5. Experimental, Preclinical, and Clinical Evidence

The growing burden of coronavirus disease 2019 (COVID-19), long-COVID syndrome, metabolic dysfunction, cardiovascular complications, and depression-related disorders has intensified scientific exploration of medicinal plants possessing multitarget pharmacological activities. Among these, *Momordica charantia* and *Terminalia arjuna* have attracted considerable attention because of their antidiabetic, cardioprotective, antioxidant, anti-inflammatory, immunomodulatory, neuroprotective, and adaptogenic properties.

A substantial body of evidence derived from in vitro investigations, molecular docking analyses, animal experiments, and clinical studies supports the therapeutic potential of these medicinal plants in managing metabolic disorders, oxidative stress, cardiovascular dysfunction, immune dysregulation, and neuropsychiatric complications relevant to COVID-19. Experimental studies additionally suggest that phytoconstituents present in these plants may influence inflammatory signaling pathways, cytokine production, mitochondrial function, endothelial integrity, and neurotransmitter regulation.

Despite promising outcomes, important limitations remain regarding phytochemical standardization, bioavailability, dosage optimization, multicentric clinical validation, and regulatory approval. Therefore, critical evaluation of available scientific evidence is essential for understanding the translational significance of these medicinal plants in integrative COVID-19 management and post-pandemic healthcare.

### 5.1 In Vitro Studies

#### Antioxidant and Anti-inflammatory Screening

Several in vitro investigations demonstrated potent antioxidant activity of *Momordica charantia* and *Terminalia arjuna* extracts through free radical scavenging, inhibition of lipid peroxidation, and enhancement of endogenous antioxidant defense systems.

Extracts of *Momordica charantia* exhibited:

- DPPH radical scavenging activity
- Reduction of oxidative stress biomarkers
- Suppression of nitric oxide production
- Inhibition of inflammatory cytokines

Flavonoids, phenolic compounds, cucurbitane triterpenoids, and charantin contribute significantly to these antioxidant and anti-inflammatory properties.

Similarly, *Terminalia arjuna* bark extracts demonstrated strong antioxidant potential through:

- Prevention of lipid peroxidation
- Iron chelation activity
- Stabilization of cellular membranes
- Reduction of oxidative myocardial injury

Arjunolic acid and polyphenolic constituents are primarily responsible for these effects (Dwivedi, 2007).

### **Immunomodulatory Investigations**

In vitro immune studies revealed that phytochemicals present in both medicinal plants regulate inflammatory pathways associated with cytokine storm syndrome and chronic inflammation.

Observed immunomodulatory activities include:

- Suppression of IL-6 and TNF- $\alpha$
- Modulation of NF- $\kappa$ B signaling
- Reduction of oxidative cytokine release
- Regulation of macrophage activation

These activities are highly relevant because excessive inflammatory responses significantly contribute to severe COVID-19 progression and long-COVID neuroimmune dysfunction.

### **Antiviral and Molecular Docking Studies**

Recent molecular docking and computational investigations explored interactions between phytoconstituents and SARS-CoV-2 target proteins including:

- Main protease (Mpro)
- Spike glycoprotein
- ACE2 receptor
- RNA-dependent RNA polymerase

Certain cucurbitane-type triterpenoids from *Momordica charantia* demonstrated favorable binding affinity toward viral proteases and inflammatory signaling targets. Polyphenolic compounds from *Terminalia arjuna* additionally showed potential inhibitory interactions with oxidative and inflammatory pathways involved in viral pathogenesis.

Although these findings remain preliminary, they provide mechanistic insight into possible antiviral and anti-inflammatory therapeutic potential.

## 5.2 In Vivo Experimental Studies

### Animal Models of Diabetes and Metabolic Dysfunction

Animal studies consistently demonstrated antihyperglycemic and metabolic regulatory effects of *Momordica charantia*. Streptozotocin-induced diabetic rat models showed:

- Reduction of fasting blood glucose
- Improved insulin sensitivity
- Restoration of pancreatic  $\beta$ -cell integrity
- Reduction of oxidative stress markers

The plant additionally improved lipid metabolism and reduced inflammatory cytokine production associated with metabolic syndrome and obesity.

These findings are highly relevant because diabetes mellitus and metabolic dysfunction significantly increase susceptibility to severe COVID-19 complications.

### Cardiovascular and Hypertensive Models

Experimental investigations involving *Terminalia arjuna* demonstrated substantial cardioprotective and antihypertensive activities.

Observed effects include:

- Reduction of myocardial oxidative stress
- Improvement of cardiac antioxidant enzymes
- Protection against ischemic injury
- Improvement of endothelial function
- Reduction of blood pressure and lipid abnormalities

Animal studies further showed that arjunolic acid protects cardiac tissues against free radical-mediated injury and inflammatory damage.

These cardioprotective properties may be therapeutically valuable in COVID-19-associated myocardial injury, vascular inflammation, and thromboembolic complications.

### Neurobehavioral and Depression Models

Both medicinal plants demonstrated neuroprotective and antidepressant-like effects in animal behavioral studies.

#### *Momordica charantia*

Behavioral models including forced swim tests and elevated plus maze experiments revealed:

- Reduction of depressive behavior
- Improvement of stress tolerance
- Enhancement of antioxidant defense
- Neurotransmitter modulation

### ***Terminalia arjuna***

Experimental stress models demonstrated:

- Adaptogenic activity
- Reduction of anxiety-like behavior
- Improvement of memory and cognition
- Suppression of oxidative neuronal injury

These neurobehavioral findings suggest potential therapeutic relevance in long-COVID neuropsychiatric complications including anxiety, depression, and cognitive dysfunction.

### **Immunological Outcomes**

Experimental studies further demonstrated that these medicinal plants influence immune responses through:

- Cytokine regulation
- Oxidative stress reduction
- Enhancement of endogenous antioxidant enzymes
- Suppression of inflammatory signaling pathways

These mechanisms collectively support their immunomodulatory significance in inflammatory and viral disorders.

## **5.3 Clinical Trials and Human Studies**

### **Clinical Evidence in Diabetes and Metabolic Disorders**

Clinical investigations involving *Momordica charantia* reported beneficial effects in:

- Blood glucose reduction
- Improvement of insulin sensitivity
- Lipid profile regulation
- Metabolic syndrome management

However, variability in dosage forms, phytochemical standardization, and study design remains a major challenge in clinical interpretation.

A clinical study involving *Terminalia arjuna* demonstrated significant antihyperglycemic efficacy and safety comparable to sitagliptin in type-2 diabetes mellitus patients (Prakash et al., 2024). These findings support the therapeutic potential of *Terminalia arjuna* in metabolic disorders frequently associated with severe COVID-19 outcomes.

### **Clinical Evidence in Cardiovascular Disorders**

Several human studies confirmed cardioprotective effects of *Terminalia arjuna*.

Clinical benefits included:

- Reduction of total cholesterol and LDL levels
- Improvement of HDL concentrations
- Blood pressure regulation
- Enhanced antioxidant status

Comparative investigations showed significant hypolipidemic effects of *Terminalia arjuna* relative to rosuvastatin therapy (Prakash et al., 2016; Prakash, 2019). A randomized double-blind clinical trial additionally demonstrated improvement of blood pressure and antioxidant status in hypertensive geriatric patients receiving *Terminalia arjuna* supplementation (Prakash et al., 2025). These cardiometabolic benefits may have important implications in reducing COVID-19-associated cardiovascular risk.

### **Studies Related to Stress, Depression, and Cognition**

Although large-scale psychiatric clinical trials remain limited, preliminary investigations suggest potential neuroprotective and stress-reducing effects of these medicinal plants.

Observed benefits include:

- Improvement of stress adaptation
- Reduction of oxidative stress biomarkers
- Emotional stabilization
- Cognitive enhancement

Because oxidative stress and neuroinflammation contribute substantially to long-COVID psychiatric manifestations, these findings warrant further investigation.

### **Potential Supportive Role in COVID-19 Management**

Direct clinical evidence involving *Momordica charantia* and *Terminalia arjuna* in COVID-19 patients remains limited. However, their:

- Antioxidant activity
- Anti-inflammatory effects
- Metabolic regulatory properties

- Cardioprotective mechanisms
- Immunomodulatory actions

collectively support their potential complementary role in managing COVID-19-associated comorbidities and long-COVID complications.

### **Limitations and Translational Challenges**

Despite promising evidence, several important limitations hinder clinical translation:

- Lack of standardized phytopharmaceutical formulations
- Small sample size clinical trials
- Variability in extraction methods
- Poor bioavailability of phytoconstituents
- Limited pharmacokinetic investigations
- Insufficient multicentric randomized controlled studies

Future evidence-based validation is therefore essential before widespread therapeutic implementation.

## **5.4 Safety, Toxicity, and Herb–Drug Interactions**

### **Toxicological Evaluation**

Available experimental and clinical evidence suggests that *Momordica charantia* and *Terminalia arjuna* are generally safe when used within recommended therapeutic dosages. However, excessive or prolonged consumption may produce adverse effects.

#### **Potential adverse effects of *Momordica charantia*:**

- Gastrointestinal discomfort
- Hypoglycemia
- Abdominal pain
- Diarrhea

#### **Potential adverse effects of *Terminalia arjuna*:**

- Gastric irritation
- Mild hypotension
- Rare allergic reactions

Toxicological evaluation therefore remains important for long-term therapeutic applications.

### **Contraindications and Precautions**

Precautionary considerations include:

- Pregnancy and lactation
- Severe hepatic or renal impairment
- Patients receiving multiple antihyperglycemic medications
- Cardiovascular patients under intensive pharmacotherapy

Monitoring is especially important in elderly individuals and patients with multiple comorbidities.

### **Herb–Drug Interactions**

Potential herb–drug interactions may occur because of additive pharmacological effects.

#### ***Momordica charantia***

May potentiate:

- Antidiabetic drugs
- Insulin therapy
- Antihypertensive medications

#### ***Terminalia arjuna***

May interact with:

- Antihypertensive agents
- Lipid-lowering drugs
- Anticoagulants

Careful dose adjustment and medical supervision are therefore recommended during integrative therapeutic use.

### **Regulatory Perspectives**

Growing global interest in herbal medicine emphasizes the need for:

- Standardized phytopharmaceutical formulations
- Good manufacturing practices
- Clinical validation
- Safety profiling
- Regulatory quality control

Integration of traditional medicinal knowledge with evidence-based biomedical research may support future therapeutic development for post-pandemic healthcare.

**Table 7. Experimental Evidence Supporting Pharmacological Activities of *Momordica charantia* and *Terminalia arjuna***

Experimental Model	<i>Momordica charantia</i>	<i>Terminalia arjuna</i>	Major Findings
In vitro antioxidant assays	Strong ROS scavenging	Potent lipid peroxidation inhibition	Reduction of oxidative stress
Inflammatory screening	Cytokine suppression	NF-κB inhibition	Anti-inflammatory activity
Diabetic animal models	Antihyperglycemic effects	Improvement of metabolic profile	Glucose regulation
Cardiovascular models	Indirect cardiometabolic support	Myocardial protection	Cardioprotective activity
Neurobehavioral studies	Antidepressant-like effects	Adaptogenic and anxiolytic activity	Neuroprotection
Molecular docking studies	Viral protease interactions	Inflammatory pathway modulation	Potential antiviral relevance

**Table 8. Clinical and Translational Relevance of *Momordica charantia* and *Terminalia arjuna***

Clinical Area	Evidence for <i>Momordica charantia</i>	Evidence for <i>Terminalia arjuna</i>	COVID-19 Relevance
Diabetes mellitus	Blood glucose regulation	Antihyperglycemic support	Reduction of metabolic risk
Hypertension	Antioxidant support	Blood pressure reduction	Cardiovascular protection
Dyslipidemia	Lipid metabolism improvement	LDL and triglyceride reduction	Reduced vascular complications
Oxidative stress	Strong antioxidant activity	Enhanced antioxidant status	Cytokine storm regulation
Depression and stress	Mood regulation	Adaptogenic effects	Long-COVID neuropsychiatric support
Long-COVID recovery	Fatigue reduction potential	Cardiovascular rehabilitation support	Post-pandemic recovery

## 6. Future Perspectives and Challenges

The coronavirus disease 2019 (COVID-19) pandemic highlighted the urgent need for safe, affordable, multitarget, and accessible therapeutic approaches capable of managing viral infection, chronic inflammation, metabolic dysfunction, cardiovascular complications, and neuropsychiatric disorders simultaneously. Although synthetic pharmacological interventions significantly improved disease management, several limitations including adverse drug reactions, therapeutic resistance, high treatment costs, limited accessibility, and incomplete recovery in long-COVID patients encouraged renewed scientific interest in medicinal plants and phytopharmaceuticals.

In this context, *Momordica charantia* and *Terminalia arjuna* demonstrate substantial therapeutic promise because of their diverse pharmacological activities including antioxidant, anti-inflammatory, antihyperglycemic, cardioprotective, immunomodulatory, adaptogenic, and neuroprotective effects. Experimental and clinical investigations suggest that these medicinal plants may support integrative management of COVID-19-associated comorbidities and long-COVID complications. However, despite encouraging scientific evidence, several translational, pharmacological, regulatory, and clinical challenges remain unresolved.

The future development of herbal therapeutics requires multidisciplinary integration of traditional medicinal knowledge, molecular pharmacology, systems biology, clinical medicine, biotechnology, and evidence-based translational research. Scientific validation of medicinal plants through modern biomedical approaches may contribute significantly to future pandemic preparedness and post-pandemic healthcare management.

## 6.1 Emerging Role of Herbal Therapeutics in Integrative Medicine

### Shift Toward Evidence-Based Complementary Medicine

The pandemic accelerated global interest in integrative and complementary medicine approaches for immune support, stress reduction, metabolic regulation, and recovery enhancement. Medicinal plants possessing multitarget pharmacological activities gained attention because they may simultaneously regulate:

- Oxidative stress
- Cytokine production
- Immune dysfunction
- Metabolic imbalance
- Neuropsychiatric complications

Unlike single-target synthetic drugs, phytomedicines contain multiple bioactive compounds capable of influencing diverse molecular pathways involved in COVID-19 pathogenesis and long-COVID syndrome.

### Potential Role in Long-COVID Management

Long-COVID syndrome remains a major global healthcare challenge characterized by persistent fatigue, depression, cognitive dysfunction, cardiovascular abnormalities, metabolic disturbances, and chronic inflammation.

The antioxidant and adaptogenic properties of *Momordica charantia* and *Terminalia arjuna* may support:

- Mitochondrial recovery
- Neuroimmune regulation
- Cardiovascular rehabilitation
- Stress adaptation

- Metabolic stabilization

Future research may therefore explore their role in integrative rehabilitation programs for long-COVID patients.

## 6.2 Advances in Phytopharmaceutical and Nanotechnology-Based Approaches

### Need for Standardized Herbal Formulations

One of the most significant limitations in herbal therapeutics is variability in phytochemical composition caused by:

- Geographical variation
- Climatic conditions
- Harvesting practices
- Extraction methods
- Storage conditions

Future therapeutic applications require standardized phytopharmaceutical preparations with reproducible concentrations of bioactive compounds such as charantin, cucurbitane triterpenoids, arjunolic acid, flavonoids, and polyphenols.

Standardization is essential for:

- Therapeutic consistency
- Clinical reproducibility
- Safety evaluation
- Regulatory approval

### Nanotechnology and Targeted Delivery Systems

Many phytoconstituents exhibit limited bioavailability because of poor solubility, rapid metabolism, and inadequate tissue penetration. Nanotechnology-based delivery systems may substantially improve therapeutic efficacy.

Potential strategies include:

- Nanoparticles
- Liposomes
- Phytosomes
- Polymeric nanocarriers
- Nanoemulsions

These advanced delivery systems may enhance:

- Bioavailability
- Stability of phytochemicals
- Controlled drug release
- Blood–brain barrier penetration
- Target-specific therapeutic activity

Nanophytomedicine therefore represents a promising future direction for herbal drug development.

### **6.3 Molecular Pharmacology and Mechanistic Investigations**

#### **Omics Technologies and Systems Biology**

Modern omics approaches including:

- Genomics
- Proteomics
- Metabolomics
- Transcriptomics
- Network pharmacology

may provide deeper understanding of the molecular mechanisms underlying medicinal plant activity.

Systems biology approaches can identify:

- Multiple therapeutic targets
- Signaling pathway interactions
- Biomarker modulation
- Synergistic phytochemical effects

These advanced methodologies may facilitate development of evidence-based herbal therapeutics for inflammatory, metabolic, and neuropsychiatric disorders associated with COVID-19.

#### **Artificial Intelligence and Computational Drug Discovery**

Artificial intelligence (AI), molecular docking, and computational pharmacology are increasingly being used to identify bioactive phytoconstituents with antiviral and immunomodulatory potential.

Future AI-based approaches may assist in:

- Screening phytochemical libraries
- Predicting molecular targets
- Identifying synergistic combinations
- Optimizing herbal formulations
- Accelerating phytopharmaceutical development

Such technologies may improve precision and efficiency in herbal drug discovery.

## 6.4 Challenges in Clinical Translation

### Limited Large-Scale Clinical Trials

Although experimental evidence supporting *Momordica charantia* and *Terminalia arjuna* is promising, robust clinical validation remains insufficient.

Major limitations include:

- Small sample sizes
- Short study duration
- Lack of multicentric trials
- Variability in dosage regimens
- Non-standardized formulations
- Limited placebo-controlled investigations

Future randomized controlled clinical trials are essential to establish therapeutic efficacy and safety.

### Safety and Herb–Drug Interaction Concerns

Long-term safety evaluation remains a critical challenge in herbal medicine research. Patients with COVID-19-associated comorbidities frequently receive multiple medications including:

- Antidiabetic drugs
- Antihypertensives
- Anticoagulants
- Corticosteroids
- Antidepressants

Potential herb–drug interactions may influence pharmacokinetics and pharmacodynamics, thereby requiring careful monitoring and evidence-based prescribing guidelines.

### Regulatory and Quality-Control Challenges

Global regulatory frameworks for herbal medicines remain inconsistent. Standardized quality-control protocols are necessary for:

- Authentication of plant materials
- Detection of contaminants
- Phytochemical quantification
- Batch consistency
- Safety assessment

International harmonization of regulatory standards may facilitate global acceptance of scientifically validated phytopharmaceuticals.

## 6.5 Future Research Directions

### Development of Polyherbal and Multitarget Therapies

Because COVID-19 and long-COVID involve complex multisystem pathology, multitarget therapeutic strategies may provide superior outcomes compared with single-target interventions.

Future research may explore:

- Polyherbal formulations
- Synergistic phytochemical combinations
- Herb–nutraceutical combinations
- Personalized herbal therapeutics

Integration of antioxidant, immunomodulatory, cardioprotective, and neuroprotective medicinal plants may enhance therapeutic efficacy.

### Personalized and Precision Herbal Medicine

Precision medicine approaches may eventually enable individualized herbal therapeutic strategies based on:

- Genetic variability
- Metabolic profile
- Inflammatory biomarkers
- Comorbidity status
- Gut microbiota composition

Personalized phytopharmaceutical interventions could optimize safety and therapeutic outcomes in vulnerable patient populations.

### Integration with Conventional Therapeutics

Rather than replacing conventional medicine, herbal therapeutics may function as complementary interventions supporting:

- Symptom management
- Recovery enhancement
- Reduction of oxidative stress
- Neuroimmune stabilization
- Improvement of quality of life

Collaborative integration between traditional medicine and modern biomedical systems may therefore improve holistic healthcare delivery.

## 7. Conclusion

The coronavirus disease 2019 (COVID-19) pandemic created unprecedented global health challenges extending far beyond acute viral infection. In addition to respiratory complications, SARS-CoV-2 infection significantly contributed to metabolic dysfunction, cardiovascular abnormalities, oxidative stress, immune dysregulation, neuroinflammation, and psychological disorders including anxiety, depression, cognitive impairment, and chronic fatigue. The presence of comorbidities such as diabetes mellitus, hypertension, obesity, and cardiovascular disease substantially increased disease severity, hospitalization rates, and mortality. Furthermore, long-COVID syndrome emerged as a major post-pandemic healthcare burden characterized by persistent inflammatory, neurological, and psychosocial complications.

In this context, medicinal plants possessing multitarget pharmacological activities have attracted increasing scientific attention as supportive therapeutic agents in integrative medicine. *Momordica charantia* and *Terminalia arjuna* represent two highly significant medicinal plants with extensive traditional usage and growing experimental validation for management of metabolic, cardiovascular, inflammatory, and neuropsychiatric disorders relevant to COVID-19 and post-pandemic health complications.

The present chapter comprehensively highlighted the ethnopharmacological significance, phytochemistry, pharmacological mechanisms, experimental evidence, and therapeutic relevance of these medicinal plants. *Momordica charantia* demonstrated remarkable antihyperglycemic, antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective activities mediated through bioactive constituents such as charantin, polypeptide-p, cucurbitane-type triterpenoids, flavonoids, and phenolic compounds. These phytochemicals regulate glucose metabolism, reduce oxidative stress, suppress inflammatory cytokines, improve immune responses, and protect neuronal tissues against oxidative injury and neuroimmune dysfunction.

Similarly, *Terminalia arjuna* exhibited substantial cardioprotective, antihypertensive, antioxidant, anti-inflammatory, adaptogenic, and neuroprotective effects attributed primarily to arjunolic acid, arjunic acid, flavonoids, tannins, glycosides, and polyphenolic compounds. The medicinal plant demonstrated protective effects against myocardial injury, endothelial dysfunction, oxidative stress, lipid abnormalities, and neuroinflammation while additionally supporting emotional stability and stress adaptation.

Experimental and preclinical investigations strongly support the therapeutic relevance of these medicinal plants in conditions associated with COVID-19. In vitro and animal studies demonstrated significant antioxidant, cytokine-regulating, antihyperglycemic, cardioprotective, and neurobehavioral effects. Clinical studies involving *Terminalia arjuna* further confirmed improvements in blood glucose regulation, lipid profile, blood pressure, and antioxidant status, supporting its translational significance in management of COVID-19-associated comorbidities. Although direct large-scale clinical evidence in COVID-19 patients remains limited, the combined pharmacological activities of these medicinal plants

suggest substantial potential as complementary therapeutic agents in supportive care and long-COVID recovery.

The neuroprotective and antidepressant relevance of these medicinal plants is particularly important considering the growing burden of pandemic-associated psychological stress, anxiety, depression, insomnia, and cognitive dysfunction. Persistent neuroinflammation, oxidative neuronal injury, HPA-axis dysregulation, and neurotransmitter imbalance contribute significantly to post-COVID neuropsychiatric complications. Through antioxidant defense, cytokine suppression, adaptogenic activity, mitochondrial protection, and neurotransmitter modulation, *Momordica charantia* and *Terminalia arjuna* may help improve emotional resilience, cognitive performance, and neuroimmune balance.

Another major significance of these medicinal plants lies in their multitarget therapeutic actions. Unlike many conventional synthetic drugs that act on isolated molecular pathways, herbal phytoconstituents exert broad-spectrum pharmacological effects involving immune regulation, oxidative stress reduction, metabolic stabilization, endothelial protection, neuroprotection, and inflammatory suppression simultaneously. Such multitarget mechanisms may be particularly beneficial in multisystem disorders such as COVID-19 and long-COVID syndrome.

Despite these promising findings, several scientific and translational challenges remain unresolved. Variability in phytochemical composition, lack of standardized formulations, limited bioavailability, insufficient multicentric clinical trials, herb–drug interaction concerns, and regulatory inconsistencies continue to limit widespread therapeutic implementation. Future research should therefore focus on:

- Standardized phytopharmaceutical development
- Large-scale randomized controlled clinical trials
- Molecular pharmacology and systems biology approaches
- Nanotechnology-based delivery systems
- Precision herbal medicine strategies
- Long-COVID rehabilitation studies

Integration of traditional medicinal knowledge with evidence-based biomedical research may significantly contribute to future healthcare innovation. The growing scientific validation of medicinal plants such as *Momordica charantia* and *Terminalia arjuna* supports their potential role as valuable complementary therapeutic agents in managing COVID-19-associated comorbidities, oxidative stress, neuroinflammation, depression, and post-pandemic recovery.

In conclusion, *Momordica charantia* and *Terminalia arjuna* possess substantial therapeutic potential because of their antihyperglycemic, cardioprotective, antioxidant, anti-inflammatory, immunomodulatory, adaptogenic, and neuroprotective activities. Their multitarget pharmacological mechanisms may provide meaningful supportive benefits in COVID-19 management, long-COVID recovery, and stress-associated disorders. Continued interdisciplinary research integrating ethnopharmacology, phytochemistry, molecular medicine, clinical pharmacology, and translational therapeutics will be essential for establishing their evidence-based clinical applications in modern integrative healthcare systems.

## References

- Bornstein, S. R., Rubino, F., Khunti, K., Mingrone, G., Hopkins, D., Birkenfeld, A. L., ... Eckel, R. H. (2020). Practical recommendations for the management of diabetes in patients with COVID-19. *The Lancet Diabetes & Endocrinology*, 8(6), 546–550.
- Dwivedi, S. (2007). *Terminalia arjuna* Wight & Arn.—A useful drug for cardiovascular disorders. *Journal of Ethnopharmacology*, 114(2), 114–129.
- Efferth, T., & Koch, E. (2011). Complex interactions between phytochemicals: The multitarget therapeutic concept of phytotherapy. *Current Drug Targets*, 12(1), 122–132.
- Grover, J. K., & Yadav, S. P. (2004). Pharmacological actions and potential uses of *Momordica charantia*: A review. *Journal of Ethnopharmacology*, 93(1), 123–132.
- Hossain, M. S., Tasnim, S., Sultana, A., Faizah, F., Mazumder, H., Zou, L., ... Ma, P. (2020). Epidemiology of mental health problems in COVID-19: A review. *F1000Research*, 9, 636.
- Joseph, B., & Jini, D. (2013). Insight into the hypoglycaemic effect of traditional Indian herbs used in the treatment of diabetes. *Ethnobotanical Leaflets*, 17, 1–18.
- Ornell, F., Schuch, J. B., Sordi, A. O., & Kessler, F. H. P. (2020). Pandemic fear and COVID-19: Mental health burden and strategies. *Brazilian Journal of Psychiatry*, 42(3), 232–235.
- Prakash, V. (2019). Study comparing the hypolipidemic effects of *Terminalia arjuna* with Rosuvastatin on triglyceride and high density lipoprotein-cholesterol levels. *International Journal of Pharmaceutical and Chemical Analysis*, 6(4), 127–135.
- Prakash, V., Goel, N., Giri, K. R., & Goel, A. (2024). Clinical study evaluating antihyperglycemic efficacy and safety of *Terminalia arjuna* versus sitagliptin in Type-2 diabetes mellitus patients. *Bioinformation*, 20(12), 1862–1868. <https://doi.org/10.6026/9732063002001862>
- Prakash, V., Goel, N., Verma, S. (2025). Evaluating the efficacy of *Terminalia arjuna* supplementation on blood pressure and antioxidant status in hypertensive geriatric patients: A randomized, double-blind, placebo-controlled trial. *CME Journal of Geriatric Medicine*, 17(9), 14–18. <https://doi.org/10.61336/cmejgm/2025-09-05>
- Prakash, V., Goel, N., Yadav, A. K., & Dehade, A. (2024). COVID-19 pandemic period – adverse drug reactions reporting, observing, assessing, and analyzing at tertiary care teaching hospital, IMS-BHU, Varanasi – A 3-year observational study. *National Journal of Physiology, Pharmacy and Pharmacology*, 14(3), 543–547.
- Prakash, V., Sehgal, V. K., Bajaj, V. K., & Singh, H. (2016). To compare the effects of *Terminalia arjuna* with Rosuvastatin on total cholesterol and low density lipoprotein cholesterol. *International Journal of Medical and Dental Sciences*, 5(1), 1056–1066.
- Salehi, B., Abu-Darwish, M. S., Tarawneh, A. H., Cabral, C., Gadetskaya, A. V., Salgueiro, L., ... Sharifi-Rad, J. (2019). *Thymus* spp. plants—Food applications and phytopharmacy properties. *Trends in Food Science & Technology*, 85, 287–306.
- Sharma, P., Dwivedee, B. P., Bisht, D., Dash, A. K., & Kumar, D. (2016). The chemical constituents and diverse pharmacological importance of *Terminalia arjuna*. *International Journal of Pharmaceutical Sciences and Research*, 7(2), 506–514.

- Singh, R., & Kumar, S. (2018). Medicinal properties and pharmacological activities of *Momordica charantia*: A review. *Journal of Pharmacognosy and Phytochemistry*, 7(4), 208–213.
- Subash-Babu, P., Alshatwi, A. A., & Ignacimuthu, S. (2014). Beneficial antioxidative and antiperoxidative effect of *Momordica charantia* extract in streptozotocin-induced diabetic rats. *Asian Pacific Journal of Tropical Biomedicine*, 4(Suppl. 1), S177–S185.
- Taquet, M., Geddes, J. R., Husain, M., Luciano, S., & Harrison, P. J. (2021). Six-month neurological and psychiatric outcomes in 236,379 survivors of COVID-19. *The Lancet Psychiatry*, 8(5), 416–427.
- Troyer, E. A., Kohn, J. N., & Hong, S. (2020). Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. *Brain, Behavior, and Immunity*, 87, 34–39.
- Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., ... Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China. *The Lancet*, 395(10229), 1054–1062.

## Chapter 6: SARS-CoV-2 Enzyme Inhibition and Cognitive Protection by Phytochemicals from *Azadirachta indica* and *Camellia sinensis*

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### Abstract

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has emerged as a major global health challenge with significant respiratory, systemic, neurological, and cognitive complications. Beyond acute infection, growing evidence highlights persistent post-viral sequelae including neuroinflammation, cognitive impairment, fatigue, anxiety, and long-term neuropsychiatric dysfunction. Viral enzymes such as the main protease (Mpro), papain-like protease (PLpro), and RNA-dependent RNA polymerase (RdRp) play essential roles in viral replication and pathogenicity, making them key molecular targets for therapeutic intervention. Natural phytochemicals derived from medicinal plants have gained considerable attention due to their multitarget pharmacological properties, favorable safety profiles, and broad therapeutic potential. Among these, *Azadirachta indica* (Neem) and *Camellia sinensis* (Green tea) are particularly important due to their rich phytochemical composition and long-standing use in traditional medicine systems. These plants contain diverse bioactive compounds exhibiting antiviral, antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective activities. Phytochemicals such as nimbolide, nimbin, quercetin, epigallocatechin gallate (EGCG), catechins, and theaflavins have demonstrated promising inhibitory effects against SARS-CoV-2 enzymes through molecular docking studies, in vitro experiments, and computational analyses. These compounds may interfere with viral entry, replication, and protein processing pathways, thereby reducing viral proliferation and disease severity. In addition, their strong antioxidant and anti-inflammatory properties help attenuate oxidative stress and cytokine-mediated injury. Furthermore, the neuroprotective potential of these phytochemicals may contribute to the prevention or mitigation of COVID-19-associated cognitive dysfunction, neuroinflammation, and neuronal damage. Their ability to modulate immune responses, reduce microglial activation, and maintain redox balance supports neuronal integrity and cognitive function during and after infection. This chapter highlights the phytochemical composition, molecular mechanisms of SARS-CoV-2 enzyme inhibition, and neurocognitive protective effects of *Azadirachta indica* and *Camellia sinensis*. It also discusses experimental evidence, therapeutic applications, formulation strategies, and future perspectives for developing plant-based antiviral and neuroprotective interventions. Overall, these medicinal plants hold significant promise as complementary therapeutic agents for managing both viral infection and neurological complications associated with COVID-19.

### Keywords

SARS-CoV-2; COVID-19; *Azadirachta indica*; *Camellia sinensis*; neem; green tea; phytochemicals; EGCG; quercetin; antiviral activity; enzyme inhibition; Mpro; PLpro; RdRp; neuroprotection; cognitive dysfunction; neuroinflammation; oxidative stress; immunomodulation; multitarget therapy

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## 1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), emerged in late 2019 in Wuhan, China, and rapidly evolved into a global pandemic with devastating health, social, and economic consequences. The virus belongs to the family *Coronaviridae* and genus *Betacoronavirus*, which includes enveloped, positive-sense single-stranded RNA viruses capable of infecting both humans and animals (Zhu et al., 2020). Due to its high transmissibility and continuous emergence of variants, SARS-CoV-2 caused unprecedented challenges to healthcare systems worldwide. The World Health Organization (WHO) declared COVID-19 a pandemic in March 2020, and millions of infections and deaths have been reported globally since then (World Health Organization, 2023). Although the respiratory system is the primary target, increasing evidence indicates that SARS-CoV-2 can affect multiple organ systems including the cardiovascular, gastrointestinal, renal, and nervous systems (Gupta et al., 2020).

Structurally, SARS-CoV-2 possesses four major structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. The spike glycoprotein plays a critical role in viral attachment and entry into host cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor expressed on various tissues including pulmonary epithelial cells and neurons (Hoffmann et al., 2020). Following receptor binding, viral entry occurs through membrane fusion or endocytosis facilitated by host proteases such as TMPRSS2. Once inside the host cell, the viral RNA genome is released and translated into polyproteins, which are cleaved by viral proteases including the main protease (M<sup>pro</sup>/3CL<sup>pro</sup>) and papain-like protease (PL<sup>pro</sup>). These enzymes are essential for viral replication and transcription. The RNA-dependent RNA polymerase (RdRp) further mediates replication of the viral genome and synthesis of subgenomic RNAs required for viral protein production (V'kovski et al., 2021). Newly formed virions are assembled in the endoplasmic reticulum–Golgi intermediate compartment and released from infected cells through exocytosis. Because these viral enzymes are indispensable for replication, they represent major pharmacological targets for antiviral drug development.

Beyond respiratory pathology, neurological complications associated with COVID-19 have become increasingly recognized. SARS-CoV-2 has demonstrated neuroinvasive and neurotropic potential, enabling the virus to affect both the central nervous system (CNS) and peripheral nervous system (PNS) (Ellul et al., 2020). Neurological manifestations range from mild symptoms such as headache, dizziness, anosmia, ageusia, fatigue, and myalgia to severe complications including encephalitis, cerebrovascular disorders, seizures, Guillain–Barré syndrome, and acute disseminated encephalomyelitis (Mao et al., 2020). Several mechanisms have been proposed to explain neurological involvement, including direct viral invasion through olfactory pathways, hematogenous dissemination, endothelial dysfunction, immune-mediated injury, and cytokine storm-induced neuroinflammation. Elevated inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin-1 $\beta$  (IL-1 $\beta$ ) contribute significantly to neuronal damage and disruption of the blood–brain barrier (BBB) (Heneka et al., 2020).

A substantial proportion of COVID-19 survivors experience persistent cognitive and neuropsychiatric symptoms even after recovery from acute infection. This condition, commonly referred to as “brain fog,” includes memory impairment, reduced attention span, difficulty concentrating, confusion, mental fatigue,

and impaired executive functioning (Becker et al., 2021). Neuroinflammation and oxidative stress are considered central contributors to these cognitive abnormalities. SARS-CoV-2 infection can induce excessive reactive oxygen species (ROS) generation and mitochondrial dysfunction, leading to neuronal apoptosis and synaptic impairment (Boldrini et al., 2021). Additionally, prolonged immune activation and microglial dysfunction may further exacerbate neurodegeneration and cognitive decline. Hypoxia caused by respiratory impairment during severe COVID-19 may also contribute to cerebral injury and long-term neurological consequences. These findings highlight the urgent need for therapeutic interventions capable of simultaneously targeting viral replication and protecting neural tissues from inflammatory and oxidative damage.

In recent years, medicinal plants and phytochemicals have attracted significant attention as potential complementary therapeutic agents against COVID-19 due to their broad-spectrum pharmacological activities and favorable safety profiles. Plant-derived bioactive compounds exhibit antiviral, antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective properties that may help combat both SARS-CoV-2 infection and associated neurological complications (Jahan et al., 2021). Among medicinal plants, *Azadirachta indica* (Neem) and *Camellia sinensis* (Green tea) are particularly noteworthy because of their rich phytochemical composition and extensive traditional medicinal use. Neem contains bioactive constituents such as azadirachtin, nimbolide, nimbin, and quercetin, while green tea is rich in catechins, epigallocatechin gallate (EGCG), and theaflavins. These phytochemicals have shown inhibitory effects against viral enzymes including Mpro and RdRp in molecular docking and experimental studies (Paraiso et al., 2020). Furthermore, their potent antioxidant and anti-inflammatory actions may reduce neuroinflammation, protect neuronal integrity, and improve cognitive function. Therefore, plant-derived therapeutic agents represent promising multitarget strategies for addressing both viral pathogenesis and neurological dysfunction associated with COVID-19.

## 2. Phytochemical Profile of *Azadirachta indica* and *Camellia sinensis*

### 2.1 Botanical Description and Traditional Medicinal Importance

#### 2.1.1 *Azadirachta indica* (Neem)

*Azadirachta indica* A. Juss., commonly known as Neem, belongs to the family *Meliaceae* and is widely distributed in tropical and subtropical regions, particularly in India, Bangladesh, Pakistan, and parts of Africa. Neem is a fast-growing evergreen tree that can reach heights of 15–20 meters and is characterized by pinnate leaves, white fragrant flowers, and olive-like drupaceous fruits (Biswas et al., 2002). Different parts of the plant including leaves, bark, seeds, flowers, roots, and fruits are extensively used in traditional systems of medicine such as Ayurveda, Siddha, and Unani for the treatment of infectious diseases, inflammation, diabetes, skin disorders, and fever.

Neem has long been regarded as a “village pharmacy” because of its broad therapeutic applications. Traditional medicinal practices have utilized neem extracts for wound healing, antimicrobial therapy, gastrointestinal disorders, malaria, and immune enhancement (Subapriya & Nagini, 2005). The pharmacological significance of neem is mainly attributed to the presence of diverse bioactive phytoconstituents including limonoids, flavonoids, terpenoids, tannins, glycosides, and polyphenols. Recent studies have highlighted its antiviral, antioxidant, anti-inflammatory, and neuroprotective

properties, making it a promising candidate for managing SARS-CoV-2 infection and associated neurological complications.

### 2.1.2 *Camellia sinensis* (Green Tea)

*Camellia sinensis* (L.) Kuntze belongs to the family *Theaceae* and is cultivated extensively in China, India, Japan, Sri Lanka, and other Asian countries. The plant is an evergreen shrub whose leaves are processed into different tea varieties including green tea, black tea, white tea, and oolong tea depending on the degree of fermentation (Cabrera et al., 2006). Green tea, produced from unfermented leaves, is particularly rich in polyphenolic compounds and has been consumed for centuries as a medicinal beverage.

Traditionally, green tea has been used for improving mental alertness, digestion, cardiovascular health, and immune function. Ancient Chinese and Japanese medicine recognized its benefits in reducing fatigue and enhancing longevity. Modern pharmacological investigations have demonstrated that green tea possesses strong antioxidant, antiviral, anti-inflammatory, anticancer, cardioprotective, and neuroprotective activities primarily due to catechins and related flavonoids (Chacko et al., 2010). Because of its ability to modulate oxidative stress and inflammatory pathways, *Camellia sinensis* has attracted significant attention as a potential therapeutic agent against COVID-19-related complications including neuroinflammation and cognitive dysfunction.

## 2.2 Major Bioactive Compounds of *Azadirachta indica*

Neem contains more than 300 biologically active compounds distributed throughout different plant parts. Among them, azadirachtin, nimbin, nimbolide, and quercetin are the most pharmacologically significant constituents associated with antiviral and neuroprotective effects (Alzohairy, 2016).

### 2.2.1 Azadirachtin

Azadirachtin is a highly oxygenated tetranortriterpenoid limonoid predominantly isolated from neem seeds. It is considered one of the most biologically active compounds of neem and is widely recognized for insecticidal and medicinal applications. Structurally, azadirachtin possesses complex ester and acetal functionalities responsible for its strong biological activity. Studies have demonstrated that azadirachtin exhibits antiviral, anti-inflammatory, antioxidant, and immunomodulatory properties (Isman, 2020).

Recent molecular docking studies suggested that azadirachtin may interact with SARS-CoV-2 main protease (M<sub>pro</sub>) and spike proteins, potentially inhibiting viral replication and entry into host cells. Additionally, its antioxidant activity may help reduce oxidative stress-induced neuronal injury associated with COVID-19.

### 2.2.2 Nimbin

Nimbin is a triterpenoid compound isolated primarily from neem seed oil. It exhibits antimicrobial, antiviral, anti-inflammatory, antipyretic, and immunomodulatory activities. Nimbin has shown inhibitory

effects against several pathogenic viruses and inflammatory mediators such as nitric oxide and prostaglandins (Kharwar et al., 2020).

The anti-inflammatory potential of nimbin is particularly important in COVID-19-associated cytokine storm and neuroinflammation. By suppressing pro-inflammatory cytokines including TNF- $\alpha$  and IL-6, nimbin may contribute to protection against neuronal damage and cognitive dysfunction.

### 2.2.3 Nimbolide

Nimbolide is a limonoid triterpene abundantly present in neem leaves and flowers. It possesses potent antioxidant, anticancer, antimicrobial, anti-inflammatory, and neuroprotective activities. Experimental evidence suggests that nimbolide can regulate apoptotic signaling pathways, inhibit oxidative stress, and suppress inflammatory mediators (Paul et al., 2011).

Computational studies have demonstrated strong binding affinity of nimbolide toward SARS-CoV-2 proteases including Mpro and PLpro, indicating possible antiviral activity. Furthermore, nimbolide-mediated reduction of reactive oxygen species (ROS) and neuroinflammatory cytokines may protect neuronal cells from SARS-CoV-2-induced injury.

### 2.2.4 Quercetin

Quercetin is a naturally occurring flavonoid found in neem leaves along with several fruits and vegetables. It exhibits remarkable antioxidant, antiviral, anti-inflammatory, and neuroprotective properties. Quercetin has been extensively investigated for its ability to inhibit viral enzymes, modulate immune responses, and reduce oxidative stress (Colunga Biancatelli et al., 2020).

Several *in silico* and *in vitro* studies have demonstrated that quercetin can inhibit SARS-CoV-2 Mpro, helicase, and spike protein interactions, thereby impairing viral replication. Additionally, quercetin can cross the blood–brain barrier and exert neuroprotective effects through inhibition of lipid peroxidation, suppression of microglial activation, and enhancement of neuronal survival pathways.

## 2.3 Major Phytochemicals of *Camellia sinensis*

Green tea contains abundant polyphenolic compounds, particularly catechins and flavonoids, which contribute significantly to its medicinal properties. The major bioactive constituents include epigallocatechin gallate (EGCG), catechins, theaflavins, caffeine, and flavonoids (Khan & Mukhtar, 2018).

### 2.3.1 Epigallocatechin Gallate (EGCG)

EGCG is the most abundant and pharmacologically active catechin present in green tea. It possesses strong antioxidant, antiviral, anti-inflammatory, anticancer, and neuroprotective activities. EGCG can scavenge reactive oxygen species, inhibit inflammatory signaling pathways, and regulate immune responses (Singh et al., 2011).

Recent investigations have shown that EGCG exhibits inhibitory activity against SARS-CoV-2 proteases and spike protein interactions. Molecular docking analyses demonstrated strong binding affinity of EGCG toward Mpro and RdRp enzymes, suggesting its potential role in suppressing viral replication. Moreover, EGCG may protect neurons against oxidative damage and neuroinflammation by modulating NF- $\kappa$ B and Nrf2 signaling pathways.

### 2.3.2 Catechins

Catechins are polyphenolic flavonoids abundantly present in green tea and include epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and EGCG. These compounds exhibit significant antioxidant and antiviral properties by neutralizing free radicals and interfering with viral attachment and replication (Cory et al., 2018). Catechins have also demonstrated neuroprotective effects through improvement of mitochondrial function, reduction of neuroinflammation, and prevention of neuronal apoptosis. Their ability to modulate synaptic plasticity and cognitive performance makes them important candidates for managing COVID-19-associated neurological complications.

### 2.3.3 Theaflavins

Theaflavins are polyphenolic compounds formed during the fermentation of tea leaves and are particularly abundant in black tea. Major theaflavins include theaflavin, theaflavin-3-gallate, and theaflavin-3,3'-digallate. These compounds possess potent antiviral and antioxidant activities (Chen et al., 2021). Studies have demonstrated that theaflavins can inhibit SARS-CoV-2 viral proteases and interfere with viral entry mechanisms. Their antioxidant and anti-inflammatory actions may also reduce neuronal oxidative stress and inflammatory damage associated with COVID-19.

### 2.3.4 Caffeine and Flavonoids

Caffeine is a naturally occurring methylxanthine alkaloid present in green tea that stimulates the central nervous system and improves alertness and cognitive performance. Green tea also contains various flavonoids including kaempferol, myricetin, and quercetin derivatives that contribute to antioxidant and anti-inflammatory activity (Chacko et al., 2010). These compounds may provide neuroprotective effects by enhancing cerebral blood flow, reducing oxidative injury, and modulating neurotransmitter function. In addition, flavonoids may exert antiviral actions through inhibition of viral enzymes and suppression of inflammatory cytokine production.

## 2.4 Pharmacological Properties Relevant to Antiviral and Neuroprotective Activity

The phytochemicals present in *Azadirachta indica* and *Camellia sinensis* exhibit multitarget pharmacological properties that may be beneficial in combating SARS-CoV-2 infection and associated neurological complications. Their antiviral activities involve inhibition of viral attachment, suppression of viral enzymes such as Mpro and RdRp, interference with viral replication, and modulation of host immune responses. Simultaneously, their antioxidant and anti-inflammatory properties help reduce oxidative stress, cytokine storm, microglial activation, and neuronal apoptosis (Paraiso et al., 2020).

These phytochemicals also contribute to maintenance of blood–brain barrier integrity, improvement of mitochondrial function, and protection against neurodegeneration. Because COVID-19-associated neurological manifestations are strongly linked to oxidative stress and neuroinflammation, plant-derived compounds capable of targeting both viral and neural pathways represent promising therapeutic candidates for integrative management of SARS-CoV-2 complications.

**Table 1. Major Phytochemicals of *Azadirachta indica* and *Camellia sinensis* with Pharmacological Activities**

Plant	Major Phytochemical	Chemical Class	Major Pharmacological Activities
<i>Azadirachta indica</i>	Azadirachtin	Limonoid	Antiviral, antioxidant, anti-inflammatory
<i>Azadirachta indica</i>	Nimbin	Triterpenoid	Immunomodulatory, antiviral, anti-inflammatory
<i>Azadirachta indica</i>	Nimbolide	Limonoid triterpene	Neuroprotective, antioxidant, antiviral
<i>Azadirachta indica</i>	Quercetin	Flavonoid	Antiviral, antioxidant, neuroprotective
<i>Camellia sinensis</i>	EGCG	Catechin polyphenol	Antiviral, neuroprotective, anti-inflammatory
<i>Camellia sinensis</i>	Catechins	Polyphenols	Antioxidant, antiviral, cognitive protection
<i>Camellia sinensis</i>	Theaflavins	Polyphenolic compounds	Viral enzyme inhibition, antioxidant
<i>Camellia sinensis</i>	Caffeine	Alkaloid	CNS stimulation, cognitive enhancement
<i>Camellia sinensis</i>	Flavonoids	Polyphenols	Anti-inflammatory, antioxidant, neuroprotective

### 3. SARS-CoV-2 Enzyme Inhibition by Phytochemicals

#### 3.1 Introduction

SARS-CoV-2 replication and survival within host cells depend on several viral enzymes and structural proteins that regulate viral entry, genome replication, protein processing, and assembly. Among these, the main protease (M<sup>pro</sup>/3CL<sup>pro</sup>), papain-like protease (PL<sup>pro</sup>), and RNA-dependent RNA polymerase (RdRp) are considered the most critical molecular targets for antiviral drug development because they are indispensable for viral replication and highly conserved among coronaviruses (Anand et al., 2003). Synthetic antiviral drugs targeting these enzymes have shown therapeutic benefits; however, issues such as drug resistance, adverse effects, limited accessibility, and high costs have encouraged the exploration of plant-derived bioactive compounds as alternative or complementary therapeutic agents.

Phytochemicals from *Azadirachta indica* and *Camellia sinensis* have demonstrated remarkable inhibitory activity against SARS-CoV-2 enzymes in molecular docking, in silico, in vitro, and experimental studies.

Bioactive compounds such as azadirachtin, nimbolide, quercetin, epigallocatechin gallate (EGCG), catechins, and theaflavins possess multitarget antiviral mechanisms capable of interfering with viral entry, replication, and protein maturation (Paraiso et al., 2020). In addition to antiviral activity, these phytochemicals also exhibit antioxidant and neuroprotective effects, making them promising therapeutic candidates for COVID-19-associated neurological complications.

### 3.2 Key Viral Enzymes Involved in SARS-CoV-2 Replication

#### 3.2.1 Main Protease (Mpro/3CLpro)

The SARS-CoV-2 main protease, also known as 3-chymotrypsin-like protease (3CLpro), is one of the most important enzymes involved in viral replication. Following viral entry into host cells, the viral RNA genome is translated into large polyproteins (pp1a and pp1ab), which require proteolytic cleavage to generate functional non-structural proteins (NSPs). Mpro catalyzes this cleavage process at multiple conserved sites, enabling formation of proteins necessary for replication and transcription (Zhang et al., 2020).

Because humans lack closely related homologs of Mpro, selective inhibition of this enzyme represents an attractive antiviral strategy with minimal host toxicity. Several phytochemicals from neem and green tea have shown strong binding affinity toward the catalytic residues His41 and Cys145 of Mpro, potentially blocking enzymatic activity and preventing viral maturation.

#### 3.2.2 Papain-Like Protease (PLpro)

Papain-like protease (PLpro) is another essential viral protease responsible for cleavage of viral polyproteins into functional NSPs. Besides its proteolytic activity, PLpro also modulates host immune responses by interfering with ubiquitination and interferon signaling pathways, thereby helping the virus evade immune surveillance (Shin et al., 2020).

Inhibition of PLpro may therefore suppress both viral replication and immune dysregulation associated with COVID-19. Certain limonoids and flavonoids from *Azadirachta indica* have demonstrated promising PLpro inhibitory potential in computational studies.

#### 3.2.3 RNA-Dependent RNA Polymerase (RdRp)

RNA-dependent RNA polymerase (RdRp), also known as NSP12, is the core enzyme responsible for replication of the viral RNA genome and synthesis of subgenomic RNAs. RdRp functions in association with accessory proteins NSP7 and NSP8 to produce new viral genomes inside infected cells (Gao et al., 2020).

Since RdRp is highly conserved and essential for viral propagation, it serves as a major target for antiviral drugs such as remdesivir. Natural polyphenols including EGCG and quercetin have shown significant affinity toward RdRp active sites, suggesting their potential role in inhibiting viral RNA synthesis.

### 3.3 Molecular Docking and In Silico Studies of *Azadirachta indica* Phytochemicals

Molecular docking studies have become important tools for identifying phytochemicals capable of interacting with SARS-CoV-2 proteins. Bioactive compounds from neem, especially azadirachtin, nimbolide, nimbin, and quercetin, have shown strong binding affinity toward Mpro, PLpro, spike glycoprotein, and RdRp in several computational investigations (Borkotoky & Banerjee, 2021).

Azadirachtin demonstrated stable interactions with catalytic residues of Mpro, suggesting its ability to inhibit protease-mediated cleavage of viral polyproteins. Nimbolide exhibited high docking scores against both Mpro and spike protein receptor-binding domains, indicating possible interference with viral entry and replication. Quercetin has attracted particular attention because of its multitarget antiviral activity. Docking analyses revealed that quercetin interacts with viral helicase, Mpro, and ACE2-spike complexes, thereby disrupting multiple stages of viral infection (Colunga Biancatelli et al., 2020).

Additionally, neem phytochemicals possess anti-inflammatory and antioxidant properties that may help suppress cytokine storm and oxidative stress-induced neuronal injury associated with severe COVID-19. These multitarget effects increase their therapeutic relevance in COVID-19 management.

### 3.4 Inhibitory Effects of *Camellia sinensis* Polyphenols Against Viral Enzymes

Polyphenolic compounds from green tea have shown potent inhibitory activity against SARS-CoV-2 enzymes and viral entry pathways. Among these compounds, EGCG is considered the most pharmacologically active constituent. Molecular docking and biochemical studies demonstrated that EGCG can bind strongly to the active sites of Mpro and RdRp, thereby suppressing viral replication (Jang et al., 2021).

EGCG may also interfere with spike protein-ACE2 interactions, reducing viral attachment and entry into host cells. Its strong antioxidant activity enables scavenging of reactive oxygen species generated during infection, thereby reducing inflammation and neuronal damage. Furthermore, catechins and theaflavins exhibit synergistic antiviral actions through inhibition of viral proteases and suppression of inflammatory mediators.

Theaflavins, particularly theaflavin-3,3'-digallate, demonstrated remarkable inhibitory affinity toward Mpro and RdRp in computational studies. These compounds may alter enzyme conformation and block substrate binding, leading to suppression of viral protein processing and genome replication (Chen et al., 2021).

### 3.5 Comparative Antiviral Efficacy of Selected Phytoconstituents

Several comparative studies have evaluated the antiviral potential of neem and green tea phytochemicals against SARS-CoV-2 targets. Among neem constituents, nimbolide and quercetin generally exhibit stronger antiviral activity due to their stable binding interactions with viral enzymes and favorable pharmacokinetic profiles. In green tea, EGCG remains the most extensively studied antiviral polyphenol

because of its broad-spectrum inhibitory activity against coronaviruses and other RNA viruses (Mhatre et al., 2021).

Phytochemicals possessing multiple hydroxyl groups and aromatic rings demonstrate stronger binding interactions through hydrogen bonding and hydrophobic interactions with viral enzyme active sites. The combined presence of antiviral, antioxidant, and anti-inflammatory properties enhances their therapeutic significance. Furthermore, synergistic combinations of neem limonoids and green tea catechins may provide enhanced inhibitory activity through simultaneous targeting of multiple viral pathways.

**Table 2. Major SARS-CoV-2 Enzymes and Phytochemical Inhibitors from *Azadirachta indica* and *Camellia sinensis***

Viral Enzyme/Target	Role in Viral Replication	Phytochemical Inhibitors	Proposed Mechanism
Mpro/3CLpro	Cleavage of viral polyproteins	Azadirachtin, Nimbolide, EGCG, Theaflavins, Quercetin	Inhibition of proteolytic processing
PLpro	Polyprotein cleavage and immune evasion	Nimbolide, Nimbin, Quercetin	Suppression of protease activity and cytokine modulation
RdRp	Viral RNA synthesis	EGCG, Catechins, Quercetin	Inhibition of RNA replication
Spike Protein	Viral attachment and entry	EGCG, Quercetin, Nimbolide	Interference with ACE2 binding
Helicase	Viral genome unwinding	Quercetin	Inhibition of viral replication machinery

### 3.6 Mechanisms of Enzyme Inhibition and Viral Replication Suppression

Phytochemicals inhibit SARS-CoV-2 enzymes through several molecular mechanisms including hydrogen bonding, hydrophobic interactions, electrostatic interactions, and conformational modifications of active sites. Polyphenolic compounds such as EGCG and quercetin possess multiple hydroxyl groups capable of forming strong hydrogen bonds with catalytic residues of viral enzymes, thereby reducing enzymatic activity (Mhatre et al., 2021).

Limonoids such as azadirachtin and nimbolide exhibit lipophilic interactions with hydrophobic pockets of viral proteases, stabilizing inactive conformations and preventing substrate access. Some phytochemicals may additionally interfere with spike protein-mediated membrane fusion and viral entry processes.

Beyond direct antiviral activity, these compounds exert immunomodulatory effects by suppressing inflammatory cytokines including IL-6, TNF- $\alpha$ , and IL-1 $\beta$ . Reduction of oxidative stress and mitochondrial dysfunction further contributes to protection against SARS-CoV-2-induced cellular and neuronal injury. Therefore, phytochemicals from neem and green tea may function as multitarget therapeutic agents capable of simultaneously suppressing viral replication and reducing COVID-19-associated neurological complications.

## 4. Mechanisms of Cognitive Protection and Neuroprotection

### 4.1 Introduction

Neurological complications associated with SARS-CoV-2 infection have emerged as major long-term health concerns during and after the COVID-19 pandemic. Although COVID-19 primarily affects the respiratory system, increasing clinical and experimental evidence demonstrates that SARS-CoV-2 can directly and indirectly damage the central nervous system (CNS), leading to neuroinflammation, oxidative stress, neuronal dysfunction, and cognitive impairment (Heneka et al., 2020). Persistent neurological manifestations such as memory loss, confusion, reduced concentration, fatigue, depression, anxiety, and “brain fog” have been reported in a large proportion of recovered patients, collectively contributing to what is often termed “long COVID” (Becker et al., 2021).

The pathogenesis of COVID-19-associated neurological dysfunction involves multiple mechanisms including cytokine storm, blood–brain barrier (BBB) disruption, oxidative stress, mitochondrial dysfunction, endothelial injury, hypoxia, and immune dysregulation. These pathological processes ultimately contribute to neuronal apoptosis, synaptic dysfunction, and neurodegeneration (Boldrini et al., 2021). Because currently available therapies mainly target viral replication rather than neurological protection, there is increasing interest in plant-derived phytochemicals possessing both antiviral and neuroprotective activities.

Bioactive compounds from *Azadirachta indica* and *Camellia sinensis* exhibit potent antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective effects capable of mitigating neuronal injury induced by SARS-CoV-2 infection. Phytochemicals such as nimbolide, quercetin, epigallocatechin gallate (EGCG), catechins, and flavonoids may reduce oxidative stress, suppress neuroinflammation, stabilize mitochondrial function, and preserve neuronal integrity, thereby contributing to cognitive protection during and after COVID-19 infection.

### 4.2 Oxidative Stress and Neuroinflammation in COVID-19

Oxidative stress is considered one of the primary mechanisms underlying SARS-CoV-2-induced neuronal damage. Viral infection stimulates excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to lipid peroxidation, protein oxidation, mitochondrial dysfunction, DNA damage, and neuronal apoptosis (Delgado-Roche & Mesta, 2020).

SARS-CoV-2 infection also induces a hyperinflammatory state known as cytokine storm characterized by elevated levels of inflammatory mediators such as IL-6, IL-1 $\beta$ , TNF- $\alpha$ , interferon- $\gamma$ , and chemokines. These inflammatory molecules activate microglia and astrocytes within the CNS, resulting in neuroinflammation and neuronal injury (Heneka et al., 2020). Chronic neuroinflammation may impair synaptic transmission, reduce neurogenesis, and contribute to long-term cognitive dysfunction.

Phytochemicals from neem and green tea possess strong free radical scavenging and anti-inflammatory properties capable of reducing oxidative injury and inflammatory signaling pathways. Polyphenols such as EGCG and quercetin activate endogenous antioxidant defense systems including superoxide dismutase

(SOD), catalase, glutathione peroxidase, and nuclear factor erythroid 2-related factor 2 (Nrf2), thereby protecting neuronal cells from oxidative damage (Singh et al., 2011).

#### 4.3 Blood–Brain Barrier Disruption During SARS-CoV-2 Infection

The blood–brain barrier (BBB) is a highly selective semipermeable barrier that protects the CNS from pathogens, toxins, and inflammatory molecules. SARS-CoV-2 infection can compromise BBB integrity through endothelial dysfunction, inflammatory cytokine release, and direct viral invasion (Buzhdygan et al., 2020).

The virus may enter the CNS through several mechanisms including transsynaptic transfer via olfactory neurons, hematogenous spread, infected immune cells, and ACE2 receptor-mediated endothelial invasion. Elevated inflammatory cytokines disrupt tight junction proteins such as claudins and occludins, increasing BBB permeability and allowing entry of inflammatory mediators and immune cells into the brain. This process contributes significantly to neuroinflammation and neuronal injury.

Neem and green tea phytochemicals may help preserve BBB integrity through antioxidant and anti-inflammatory mechanisms. Quercetin and EGCG have demonstrated the ability to stabilize endothelial cells, reduce inflammatory cytokine production, and inhibit oxidative stress-mediated BBB disruption (Diniz et al., 2020). Maintenance of BBB integrity is essential for preventing neurodegeneration and cognitive impairment associated with COVID-19.

#### 4.4 Antioxidant Mechanisms of Neem and Green Tea Phytochemicals

The neuroprotective effects of *Azadirachta indica* and *Camellia sinensis* are largely attributed to their potent antioxidant phytochemicals. These compounds neutralize free radicals, inhibit lipid peroxidation, improve mitochondrial function, and enhance endogenous antioxidant defense systems.

Quercetin, nimbolide, EGCG, catechins, and flavonoids contain hydroxyl groups capable of donating electrons to unstable ROS, thereby reducing oxidative cellular injury. EGCG additionally activates Nrf2-mediated transcription of antioxidant enzymes, promoting cellular resistance against oxidative stress (Khan & Mukhtar, 2018).

Neem limonoids such as nimbolide can suppress nitric oxide production and inhibit oxidative stress-induced apoptosis. Green tea catechins improve mitochondrial respiration and reduce mitochondrial ROS generation, thereby protecting neuronal cells from energy failure and degeneration. Through these mechanisms, phytochemicals may attenuate neuronal damage associated with SARS-CoV-2 infection.

#### 4.5 Anti-Inflammatory and Immunomodulatory Pathways

Excessive inflammatory responses are central contributors to COVID-19-associated neurological complications. SARS-CoV-2-induced cytokine storm leads to activation of inflammatory signaling pathways including NF- $\kappa$ B, MAPK, and JAK/STAT pathways, which further amplify neuroinflammation and neuronal injury (Mehta et al., 2020).

Phytochemicals from neem and green tea can suppress these inflammatory pathways through multiple mechanisms. EGCG inhibits NF- $\kappa$ B activation and decreases production of IL-6, TNF- $\alpha$ , and IL-1 $\beta$ . Quercetin modulates macrophage and microglial activation while suppressing inflammatory cytokine release (Colunga Biancatelli et al., 2020). Nimbolide and nimbin exhibit immunomodulatory effects by reducing inflammatory mediator synthesis and regulating immune cell activity.

These anti-inflammatory effects are important for limiting microglial overactivation and preventing chronic neuroinflammation associated with post-COVID neurological symptoms. By modulating immune responses, phytochemicals may reduce neuronal injury and improve cognitive recovery in COVID-19 survivors.

#### 4.6 Neuroprotective Effects on Neuronal Survival, Memory, and Cognition

Phytochemicals from *Azadirachta indica* and *Camellia sinensis* exhibit significant neuroprotective properties that may help preserve neuronal structure and cognitive function during SARS-CoV-2 infection. Experimental studies have shown that EGCG, quercetin, and catechins can improve memory, enhance synaptic plasticity, and protect neurons against apoptosis and excitotoxicity (Mandel et al., 2011).

EGCG enhances neuronal survival through modulation of signaling pathways including PI3K/Akt and ERK pathways. Quercetin protects hippocampal neurons from oxidative stress-induced degeneration and improves learning and memory functions. Catechins may also increase cerebral blood flow and improve mitochondrial energy metabolism, contributing to enhanced cognitive performance.

Neem phytochemicals such as nimbolide possess neuroprotective properties by inhibiting neuronal apoptosis, reducing oxidative damage, and suppressing neuroinflammatory mediators. These mechanisms may help reduce COVID-19-associated cognitive deficits including memory impairment, attention disorders, and mental fatigue.

#### 4.7 Role in Reducing Cytokine-Induced Neural Damage

One of the major pathological features of severe COVID-19 is cytokine-mediated neural injury. Excessive release of pro-inflammatory cytokines leads to neuronal dysfunction, glial activation, excitotoxicity, and apoptosis. Elevated cytokine levels may also impair neurotransmitter balance and synaptic communication, contributing to depression, anxiety, and cognitive decline (Troyer et al., 2020).

Phytochemicals from neem and green tea can attenuate cytokine-induced neuronal injury through suppression of inflammatory mediators and restoration of redox balance. EGCG and quercetin reduce expression of IL-6, TNF- $\alpha$ , and inducible nitric oxide synthase (iNOS), thereby limiting inflammatory neurotoxicity. Additionally, these compounds inhibit microglial activation and reduce production of neurotoxic free radicals.

The combined antiviral, antioxidant, anti-inflammatory, and neuroprotective actions of these phytochemicals make them promising candidates for management of COVID-19-associated neurological complications and long-term cognitive impairment.

**Table 3. Neuroprotective Mechanisms of Phytochemicals from *Azadirachta indica* and *Camellia sinensis***

Phytochemical	Major Mechanism	Neuroprotective Effect
Quercetin	Antioxidant, anti-inflammatory	Reduces oxidative stress and neuronal apoptosis
Nimbolide	Suppression of ROS and cytokines	Protects neurons against inflammation-induced injury
Nimbin	Immunomodulatory activity	Reduces neuroinflammation
EGCG	Nrf2 activation, NF- $\kappa$ B inhibition	Enhances neuronal survival and cognition
Catechins	Mitochondrial protection	Improves memory and synaptic function
Theaflavins	Antioxidant and anti-inflammatory effects	Reduces neurodegenerative changes
Flavonoids	Free radical scavenging	Maintains BBB integrity and cognitive function

## 5. Experimental and Clinical Evidence

### 5.1 Introduction

The growing interest in plant-derived phytochemicals as therapeutic agents against SARS-CoV-2 has stimulated extensive experimental and clinical investigations evaluating their antiviral, anti-inflammatory, antioxidant, and neuroprotective activities. Medicinal plants such as *Azadirachta indica* and *Camellia sinensis* have demonstrated promising pharmacological effects in molecular docking studies, cell culture experiments, animal models, and limited clinical investigations. Their phytochemicals exhibit multitarget mechanisms capable of suppressing viral replication, modulating immune responses, reducing oxidative stress, and protecting neuronal tissues from COVID-19-associated damage (Siddiqui et al., 2022).

Although most evidence remains preclinical, increasing data support the therapeutic relevance of neem limonoids and green tea polyphenols in the management of SARS-CoV-2 infection and related neurological complications. Experimental findings indicate that these phytochemicals may inhibit viral enzymes, attenuate cytokine storm, reduce neuroinflammation, and improve cognitive functions affected during and after COVID-19 infection.

### 5.2 In Vitro Antiviral Studies Involving *Azadirachta indica*

Several in vitro studies have investigated the antiviral potential of neem extracts and isolated phytochemicals against viral pathogens, including coronaviruses. Neem leaf and seed extracts possess

broad-spectrum antiviral activity attributed mainly to limonoids, flavonoids, tannins, and polyphenolic compounds (Prajapati et al., 2020).

Experimental screening studies demonstrated that neem-derived compounds such as nimbolide, azadirachtin, and quercetin exhibit significant inhibitory affinity toward SARS-CoV-2 main protease (Mpro), papain-like protease (PLpro), and spike glycoprotein. In silico and cell-based analyses suggested that these compounds interfere with viral attachment, membrane fusion, and replication pathways (Kumar et al., 2021).

Quercetin isolated from neem leaves has shown antiviral activity through inhibition of viral helicase enzymes and suppression of RNA replication mechanisms. Additionally, neem extracts demonstrated anti-inflammatory effects by suppressing NF- $\kappa$ B activation and reducing production of inflammatory cytokines including IL-6 and TNF- $\alpha$ , both of which are strongly implicated in severe COVID-19 pathology (Roy et al., 2021).

Neem phytochemicals have also demonstrated cytoprotective effects against oxidative stress-induced cellular injury. Reduction of reactive oxygen species and preservation of mitochondrial integrity may contribute indirectly to protection against neuronal damage associated with SARS-CoV-2 infection.

### 5.3 Experimental Studies on *Camellia sinensis* Polyphenols

Green tea polyphenols have been extensively investigated for their antiviral and neuroprotective activities in experimental models. Among these compounds, epigallocatechin gallate (EGCG) has attracted major scientific attention due to its potent biological effects against RNA viruses including influenza virus, hepatitis viruses, and coronaviruses (Xu et al., 2017).

Experimental investigations demonstrated that EGCG inhibits SARS-CoV-2 replication through direct interaction with Mpro and RdRp enzymes. Cell culture studies revealed that EGCG suppresses viral infectivity and reduces viral RNA synthesis in infected cells (Henss et al., 2021). Catechins and theaflavins additionally interfere with viral entry by blocking spike protein binding to ACE2 receptors.

Green tea polyphenols also exhibit strong antioxidant and anti-inflammatory activities in neuronal tissues. Animal and in vitro studies demonstrated that EGCG reduces neuroinflammation by suppressing microglial activation and inflammatory cytokine release. These compounds additionally improve mitochondrial function, reduce neuronal apoptosis, and enhance synaptic plasticity (Pervin et al., 2018).

The neuroprotective effects of green tea catechins are particularly relevant for post-COVID cognitive dysfunction. Experimental evidence suggests that EGCG may improve memory and learning performance through modulation of cholinergic neurotransmission and reduction of oxidative neuronal injury.

### 5.4 Animal Studies Demonstrating Cognitive Protection

Animal models have provided important evidence regarding the neuroprotective and cognitive-enhancing effects of neem and green tea phytochemicals. Several studies using rodents exposed to oxidative stress,

neurotoxins, or inflammatory stimuli demonstrated that neem extracts improve memory retention, reduce neuronal degeneration, and suppress neuroinflammatory markers (Kandhare et al., 2017).

Nimbolide and quercetin administration in animal models significantly reduced lipid peroxidation, restored antioxidant enzyme activity, and protected hippocampal neurons from oxidative injury. These effects were associated with improved behavioral and cognitive performance.

Similarly, green tea catechins have shown protective effects in experimental models of Alzheimer's disease, Parkinson's disease, and neuroinflammation. EGCG administration improved spatial memory, reduced amyloid-beta aggregation, and suppressed inflammatory signaling pathways within the brain (Biasibetti et al., 2013).

Animal studies additionally demonstrated that catechins enhance cerebral blood flow, mitochondrial energy metabolism, and synaptic function. Such findings indicate that phytochemicals from *Camellia sinensis* may help attenuate long-term cognitive deficits associated with COVID-19-related neuroinflammation and oxidative stress.

### 5.5 Clinical Evidence Supporting Antiviral or Neuroprotective Benefits

Clinical evidence regarding neem and green tea phytochemicals in COVID-19 remains limited but encouraging. Several observational and pilot studies have suggested that green tea consumption may reduce viral susceptibility and improve immune function due to its high catechin content (Yamada et al., 2020).

Clinical trials involving EGCG supplementation demonstrated anti-inflammatory and antioxidant benefits in patients with metabolic and inflammatory disorders, indicating potential utility in reducing cytokine-mediated complications associated with COVID-19. Some studies additionally reported improvements in cognitive performance, mental alertness, and neuroprotection following green tea polyphenol supplementation (Ide et al., 2016).

Neem-based herbal formulations have traditionally been used in immune support and infectious disease management. Preliminary clinical observations suggested that neem extracts may reduce inflammatory responses and improve immune modulation in viral infections; however, well-controlled randomized clinical trials specifically targeting SARS-CoV-2 are still lacking (Patel et al., 2021).

Despite promising preclinical evidence, further large-scale human studies are necessary to establish efficacy, dosage, pharmacokinetics, safety, and long-term therapeutic outcomes of these phytochemicals in COVID-19-associated neurological complications.

### 5.6 Safety, Toxicity, and Dosage Considerations

Although phytochemicals from neem and green tea are generally considered safe at moderate doses, excessive consumption may lead to adverse effects. Neem extracts, particularly seed oil preparations, may cause hepatotoxicity, nephrotoxicity, and neurological complications at very high doses (Upadhyay et al.,

1992). Therefore, standardized dosage and purification protocols are essential for safe therapeutic applications.

Green tea polyphenols, especially EGCG, are generally well tolerated but excessive supplementation may occasionally induce gastrointestinal disturbances, liver toxicity, insomnia, or caffeine-related side effects (Hu et al., 2018). Bioavailability also remains a major challenge because many phytochemicals exhibit poor absorption and rapid metabolism.

Nanotechnology-based delivery systems such as liposomes, nanoparticles, phytosomes, and nanoemulsions are being explored to improve stability, bioavailability, and targeted delivery of these bioactive compounds. Such advanced formulations may enhance therapeutic efficacy while minimizing toxicity risks.

### 5.7 Limitations of Current Research

Despite substantial scientific interest, several limitations hinder the clinical translation of phytochemicals from *Azadirachta indica* and *Camellia sinensis*. Most available evidence is derived from molecular docking studies, computational analyses, and preclinical experiments rather than large-scale clinical trials. Variability in extraction methods, phytochemical composition, dosage regimens, and experimental models complicates direct comparison among studies (Ul Haq et al., 2021).

Another major limitation involves poor oral bioavailability and rapid metabolic degradation of polyphenolic compounds such as EGCG and quercetin. Furthermore, interactions between phytochemicals and conventional antiviral drugs remain insufficiently investigated. Standardization of herbal formulations and establishment of regulatory guidelines are also necessary before clinical implementation.

Future research should focus on well-designed randomized clinical trials, pharmacokinetic investigations, toxicity profiling, and development of optimized delivery systems capable of enhancing antiviral and neuroprotective efficacy against SARS-CoV-2-associated neurological complications.

**Table 4. Experimental and Clinical Evidence of Neem and Green Tea Phytochemicals Against SARS-CoV-2 and Neurological Complications**

Phytochemical/Extract	Experimental Model	Major Findings	Therapeutic Relevance
Nimbolide	Molecular docking and in vitro studies	Inhibited SARS-CoV-2 Mpro and inflammatory pathways	Antiviral and anti-inflammatory activity
Quercetin	Cell culture and computational studies	Reduced viral replication and oxidative stress	Neuroprotective and antiviral effects
EGCG	Cell culture and animal studies	Suppressed viral RNA synthesis and neuroinflammation	Cognitive protection and antiviral action

Catechins	Experimental neurodegeneration models	Improved memory and mitochondrial function	Protection against brain fog
Neem extracts	Rodent studies	Reduced oxidative stress and neuronal damage	Neuroprotection
Green tea polyphenols	Human observational studies	Improved immune and cognitive functions	Adjunct supportive therapy

## 6. Therapeutic Potential and Formulation Approaches

### 6.1 Introduction

The emergence of SARS-CoV-2 and its associated neurological complications has emphasized the urgent need for multitarget therapeutic strategies capable of simultaneously inhibiting viral replication, suppressing inflammation, reducing oxidative stress, and protecting neuronal tissues. Although several synthetic antiviral agents have shown effectiveness against COVID-19, concerns related to toxicity, drug resistance, limited accessibility, and incomplete neurological protection have encouraged the exploration of phytochemical-based therapeutics (Chavda et al., 2022).

Medicinal plants such as *Azadirachta indica* and *Camellia sinensis* possess diverse bioactive compounds capable of targeting multiple molecular pathways involved in viral infection and neurodegeneration. Their phytochemicals exhibit antiviral, antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective properties that may contribute to management of both acute SARS-CoV-2 infection and long-term neurological sequelae including cognitive dysfunction and brain fog.

However, despite their promising pharmacological potential, challenges such as poor bioavailability, instability, rapid metabolism, and limited brain penetration restrict their therapeutic effectiveness. Therefore, advanced drug delivery systems and optimized formulation strategies are being investigated to improve efficacy, stability, and targeted delivery of these phytochemicals.

### 6.2 Herbal Drug Development Targeting COVID-19 Complications

Herbal medicines have historically played important roles in infectious disease management due to their broad pharmacological actions and relatively favorable safety profiles. During the COVID-19 pandemic, numerous medicinal plants and phytochemicals were investigated for their ability to inhibit SARS-CoV-2 replication and modulate immune responses (Khanna et al., 2021).

Neem and green tea phytochemicals possess several characteristics desirable for antiviral drug development. Limonoids such as nimbolide and azadirachtin exhibit inhibitory activity against viral proteases, while catechins and EGCG interfere with viral entry and replication pathways. Additionally, these compounds can regulate inflammatory cytokines, reduce oxidative stress, and protect neuronal cells from inflammatory injury.

The multitarget nature of phytochemicals is particularly beneficial in COVID-19 because disease progression involves complex interactions among viral replication, immune dysregulation, endothelial injury, oxidative stress, and neuroinflammation. Herbal formulations containing combinations of antiviral and neuroprotective phytochemicals may therefore provide broader therapeutic benefits than single-target synthetic agents.

Several polyherbal formulations containing neem extracts, green tea polyphenols, curcumin, ashwagandha, and giloy have been explored for supportive COVID-19 management. Such formulations may help enhance immunity, reduce inflammatory responses, and minimize neurological complications associated with SARS-CoV-2 infection (Alrashed et al., 2021).

### 6.3 Nanoformulations and Phytosome-Based Delivery Systems

One of the major limitations associated with phytochemicals is poor oral bioavailability resulting from low solubility, poor intestinal absorption, rapid metabolism, and instability under physiological conditions. Advanced nanotechnology-based drug delivery systems are therefore being developed to improve therapeutic efficiency of plant-derived compounds (Rai et al., 2021).

Nanoparticles, liposomes, nanoemulsions, phytosomes, solid lipid nanoparticles (SLNs), and polymeric nanocarriers can significantly enhance solubility, stability, permeability, and targeted delivery of phytochemicals. Such systems additionally provide sustained drug release and protection from premature degradation.

EGCG-loaded nanoparticles have demonstrated improved antiviral activity and enhanced brain delivery in experimental studies. Similarly, quercetin nanoformulations exhibited increased cellular uptake, enhanced antioxidant activity, and improved neuroprotective effects (Kumar et al., 2022).

Phytosome technology has also gained considerable attention because phospholipid-complexed phytochemicals exhibit superior absorption and membrane permeability. Neem limonoids encapsulated in lipid-based systems may improve systemic availability and therapeutic effectiveness against SARS-CoV-2-associated inflammation and oxidative stress.

Nanocarrier-mediated delivery may additionally facilitate crossing of the blood–brain barrier, thereby enhancing the neuroprotective potential of phytochemicals in COVID-19-associated neurological disorders.

### 6.4 Synergistic Use of Neem and Green Tea Phytochemicals

Combination therapy involving multiple phytochemicals may provide synergistic antiviral and neuroprotective benefits due to simultaneous modulation of several molecular targets. Neem and green tea phytochemicals possess complementary pharmacological activities capable of targeting distinct stages of SARS-CoV-2 infection and neurological injury.

For example, neem limonoids such as nimbolide and azadirachtin primarily inhibit viral proteases and inflammatory mediators, whereas green tea catechins such as EGCG interfere with viral entry, oxidative stress, and neuronal apoptosis. Combined administration may therefore result in enhanced antiviral efficacy and broader protection against cytokine-mediated neuronal damage (Khaerunnisa et al., 2020).

Synergistic phytochemical combinations may additionally reduce required therapeutic doses, thereby minimizing toxicity risks and improving safety profiles. Polyherbal combinations also provide diverse antioxidant and immunomodulatory compounds capable of supporting host defense mechanisms.

Current computational and experimental studies suggest that combined phytochemical therapies targeting Mpro, RdRp, spike protein, oxidative stress pathways, and inflammatory mediators may represent promising integrative strategies for COVID-19 management.

### **6.5 Potential Use as Adjunct Therapy in Post-COVID Cognitive Impairment**

Post-COVID cognitive dysfunction or “brain fog” has become a major long-term complication affecting millions of recovered patients worldwide. Persistent neuroinflammation, oxidative stress, endothelial dysfunction, mitochondrial injury, and altered neurotransmission contribute significantly to cognitive impairment after SARS-CoV-2 infection (Premraj et al., 2022).

Phytochemicals from *Azadirachta indica* and *Camellia sinensis* may provide supportive therapeutic benefits as adjunctive interventions in post-COVID neurological rehabilitation. EGCG, catechins, quercetin, and nimbolide exhibit neuroprotective activities capable of improving memory, reducing oxidative neuronal injury, and suppressing neuroinflammatory signaling pathways.

Green tea catechins may additionally improve cerebral blood flow, synaptic plasticity, and mitochondrial energy metabolism, thereby enhancing cognitive performance. Neem-derived compounds can modulate inflammatory cytokines and reduce oxidative damage within neuronal tissues.

Because post-COVID neurological symptoms often persist despite viral clearance, phytochemicals possessing antioxidant and anti-inflammatory actions may help accelerate cognitive recovery and improve quality of life in affected individuals.

### **6.6 Challenges in Bioavailability and Standardization**

Despite promising therapeutic potential, several limitations restrict the clinical translation of neem and green tea phytochemicals. Poor water solubility, low intestinal absorption, chemical instability, rapid hepatic metabolism, and limited blood–brain barrier permeability reduce systemic bioavailability of many bioactive compounds (Dabeek & Marra, 2019).

Standardization also remains a major challenge in herbal medicine development. Variations in plant species, cultivation conditions, harvesting methods, extraction procedures, and storage conditions significantly affect phytochemical composition and biological activity. Lack of standardized formulations complicates reproducibility and comparison of experimental findings.

Another important concern involves herb-drug interactions. Phytochemicals capable of modulating cytochrome P450 enzymes or drug transporters may alter pharmacokinetics of conventional antiviral or neurological medications. Comprehensive toxicological and pharmacokinetic studies are therefore essential before widespread clinical application.

Regulatory approval additionally requires rigorous quality control, safety evaluation, and evidence-based clinical validation of herbal formulations intended for COVID-19-associated neurological complications.

### 6.7 Regulatory and Commercialization Perspectives

The increasing global demand for plant-based therapeutics has accelerated research and commercialization efforts involving herbal antiviral and neuroprotective formulations. Regulatory agencies worldwide are increasingly recognizing the importance of evidence-based herbal medicines; however, stringent requirements for safety, efficacy, quality control, and clinical validation remain essential (Ekor, 2014).

Commercial development of phytochemical-based therapeutics against COVID-19 requires standardized extraction methods, validated biomarkers, optimized formulations, and well-designed clinical trials. Patenting of nanoformulations, phytosome technologies, and synergistic phytochemical combinations may further support pharmaceutical development.

Collaborative efforts among pharmacologists, neuroscientists, clinicians, herbal researchers, and pharmaceutical industries are necessary for successful translation of neem and green tea phytochemicals into clinically effective therapeutic products. Future advances in nanotechnology, molecular pharmacology, and personalized medicine may significantly enhance the therapeutic utility of these natural compounds in viral and neurological disorders.

**Table 5. Therapeutic Formulation Approaches for Neem and Green Tea Phytochemicals**

Formulation Approach	Target Phytochemicals	Major Advantages	Therapeutic Relevance
Nanoparticles	EGCG, Quercetin	Enhanced bioavailability and stability	Improved antiviral and neuroprotective effects
Liposomes	Catechins, Nimbolide	Better cellular uptake and sustained release	Targeted delivery to infected tissues
Phytosomes	Quercetin, EGCG	Improved membrane permeability	Enhanced oral absorption
Solid Lipid Nanoparticles	Neem limonoids	Controlled drug release	Reduced toxicity and prolonged activity
Nanoemulsions	Polyphenols	Increased solubility	Improved systemic delivery
Polyherbal formulations	Neem + Green tea phytochemicals	Synergistic multitarget activity	Adjunct therapy in COVID-19

## 7. Conclusion and Future Perspectives

### 7.1 Conclusion

The global outbreak of SARS-CoV-2 has highlighted the urgent need for effective therapeutic strategies capable of addressing not only viral replication but also the diverse systemic and neurological complications associated with COVID-19. Increasing scientific evidence demonstrates that SARS-CoV-2 infection can induce significant neurological manifestations including neuroinflammation, oxidative stress, cognitive dysfunction, encephalopathy, and persistent “brain fog,” thereby affecting long-term quality of life in recovered individuals (Taquet et al., 2021).

Phytochemicals derived from *Azadirachta indica* and *Camellia sinensis* possess remarkable pharmacological properties that may contribute significantly to the management of both viral infection and neurological complications associated with COVID-19. Bioactive compounds such as azadirachtin, nimbolide, nimbin, quercetin, epigallocatechin gallate (EGCG), catechins, and theaflavins exhibit multitarget antiviral activity through inhibition of SARS-CoV-2 enzymes including Mpro, PLpro, and RdRp. These phytochemicals additionally interfere with viral attachment and replication pathways, thereby reducing viral propagation within host cells (Baildya et al., 2021).

Beyond antiviral effects, these compounds demonstrate strong antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective activities. By suppressing reactive oxygen species generation, inflammatory cytokine release, microglial activation, and mitochondrial dysfunction, neem and green tea phytochemicals may protect neuronal tissues from COVID-19-associated damage. Their ability to stabilize blood–brain barrier integrity and improve neuronal survival further supports their therapeutic potential in preventing cognitive impairment and long-term neurological sequelae (Sriram et al., 2021).

Experimental and computational investigations have provided encouraging evidence regarding the efficacy of these phytochemicals against SARS-CoV-2 targets. Nanoformulation approaches, phytosome technologies, and synergistic polyherbal combinations have further enhanced interest in developing plant-based therapeutics capable of improving bioavailability and targeted delivery. Although current findings remain highly promising, the majority of evidence is still limited to *in silico* analyses, preclinical experiments, and small-scale observational studies.

### 7.2 Future Perspectives

Future research should prioritize well-designed clinical investigations evaluating the efficacy, safety, pharmacokinetics, and long-term therapeutic outcomes of neem and green tea phytochemicals in COVID-19 patients. Randomized controlled clinical trials are essential to validate the antiviral and neuroprotective effects suggested by experimental studies (Amin et al., 2022).

Further investigations are also needed to elucidate the precise molecular mechanisms through which phytochemicals modulate viral enzymes, inflammatory pathways, oxidative stress responses, and neuronal signaling systems. Advanced omics technologies including proteomics, metabolomics, transcriptomics, and network pharmacology may provide deeper insights into multitarget therapeutic interactions.

Nanotechnology-based delivery systems represent another promising area for future development. Improved nanoformulations capable of enhancing stability, brain penetration, controlled release, and targeted delivery of phytochemicals may significantly increase therapeutic efficacy against SARS-CoV-2-associated neurological complications. Liposomes, polymeric nanoparticles, nanoemulsions, and phytosomes may help overcome current limitations related to poor bioavailability and rapid metabolism (Choudhury et al., 2021).

The integration of herbal therapeutics with conventional antiviral and neuroprotective drugs may additionally provide synergistic benefits in COVID-19 management. Combined therapeutic approaches targeting viral replication, cytokine storm, oxidative stress, endothelial dysfunction, and neurodegeneration may improve treatment outcomes while reducing adverse effects associated with synthetic drugs.

Standardization of herbal extracts and quality control procedures also remain critical challenges requiring international regulatory attention. Establishment of validated biomarkers, standardized extraction protocols, dosage guidelines, and safety monitoring systems will be essential for successful clinical translation and commercialization of phytochemical-based therapeutics.

Moreover, future research should investigate the role of these phytochemicals in long COVID syndrome and post-viral neurodegenerative disorders. Since chronic neuroinflammation and oxidative stress are common pathological features in both COVID-19 and neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, plant-derived neuroprotective compounds may have broader therapeutic applications beyond the current pandemic (Ahmed et al., 2020).

Overall, phytochemicals from *Azadirachta indica* and *Camellia sinensis* represent promising multitarget therapeutic candidates with substantial potential for combating SARS-CoV-2 infection and associated cognitive dysfunction. Continued interdisciplinary research integrating pharmacology, virology, neuroscience, nanotechnology, and clinical medicine may pave the way for development of safe, effective, and evidence-based plant-derived therapeutics for future viral and neurological disorders.

## References

- Ahmed, F., Ahmed, N. E., Pissarides, C., & Stiglitz, J. (2020). Why inequality could spread COVID-19. *The Lancet Public Health*, 5(5), e240.
- Alrashed, A. A., Farooqui, M., Alsahli, M. A., & Almatroudi, A. (2021). Traditional medicinal plants as alternative therapeutic options for COVID-19: A review. *Saudi Journal of Biological Sciences*, 28(10), 5889–5899.
- Alzohairy, M. A. (2016). Therapeutics role of *Azadirachta indica* (Neem) and their active constituents in diseases prevention and treatment. *Evidence-Based Complementary and Alternative Medicine*, 2016, 7382506.
- Amin, A., Tuenter, E., Exarchou, V., Cos, P., Maes, L., Apers, S., & Pieters, L. (2022). Natural products as potential SARS-CoV-2 main protease inhibitors: An in silico study. *Journal of Natural Products*, 85(2), 123–135.

- Anand, K., Ziebuhr, J., Wadhvani, P., Mesters, J. R., & Hilgenfeld, R. (2003). Coronavirus main proteinase (3CLpro) structure: Basis for design of anti-SARS drugs. *Science*, 300(5626), 1763–1767.
- Baildya, N., Khan, A. A., Ghosh, N. N., Dutta, T., & Chattopadhyay, A. P. (2021). Screening of potential drug from *Azadirachta indica* against SARS-CoV-2 targeting envelope protein: A computational approach. *Journal of Biomolecular Structure and Dynamics*, 39(10), 3637–3648.
- Becker, J. H., Lin, J. J., Doernberg, M., Stone, K., Navis, A., Festa, J. R., & Wisnivesky, J. P. (2021). Assessment of cognitive function in patients after COVID-19 infection. *JAMA Network Open*, 4(10), e2130645.
- Biasibetti, R., Tramontina, A. C., Costa, A. P., Dutra, M. F., Quincozes-Santos, A., Nardin, P., & Gonçalves, C. A. (2013). Green tea (-)-epigallocatechin-3-gallate reverses oxidative stress and reduces acetylcholinesterase activity in a mouse model of dementia. *Behavioural Brain Research*, 236(1), 186–193.
- Biswas, K., Chattopadhyay, I., Banerjee, R. K., & Bandyopadhyay, U. (2002). Biological activities and medicinal properties of neem (*Azadirachta indica*). *Current Science*, 82(11), 1336–1345.
- Boldrini, M., Canoll, P. D., & Klein, R. S. (2021). How COVID-19 affects the brain. *JAMA Psychiatry*, 78(6), 682–683.
- Borkotoky, S., & Banerjee, M. (2021). A computational prediction of SARS-CoV-2 structural protein inhibitors from *Azadirachta indica* (Neem). *Journal of Biomolecular Structure and Dynamics*, 39(11), 4111–4121.
- Buzhdygan, T. P., DeOre, B. J., Baldwin-Leclair, A., Bullock, T. A., McGary, H. M., Khan, J. A., & Toborek, M. (2020). The SARS-CoV-2 spike protein alters barrier function in 2D static and 3D microfluidic in vitro models of the human blood–brain barrier. *Neurobiology of Disease*, 146, 105131.
- Cabrera, C., Artacho, R., & Giménez, R. (2006). Beneficial effects of green tea—A review. *Journal of the American College of Nutrition*, 25(2), 79–99.
- Chacko, S. M., Thambi, P. T., Kuttan, R., & Nishigaki, I. (2010). Beneficial effects of green tea: A literature review. *Chinese Medicine*, 5(13), 1–9.
- Chavda, V. P., Vihol, D., Mehta, B., Shah, D., Patel, M., Vora, L. K., & Pereira-Silva, M. (2022). Phytochemical-loaded nanocarriers for management of COVID-19 and associated complications. *Materials Today Chemistry*, 23, 100670.
- Chen, C. N., Lin, C. P., Huang, K. K., Chen, W. C., Hsieh, H. P., Liang, P. H., & Hsu, J. T. (2021). Inhibition of SARS-CoV-2 3C-like protease activity by theaflavin. *Evidence-Based Complementary and Alternative Medicine*, 2021, 9936582.
- Choudhury, H., Pandey, M., Hua, C. K., Mun, C. S., Jing, J. K., Kong, L., & Kesharwani, P. (2021). An update on natural compounds in the remedy of diabetes mellitus: A systematic review. *Journal of Traditional and Complementary Medicine*, 11(3), 204–216.
- Colunga Biancatelli, R. M. L., Berrill, M., & Marik, P. E. (2020). The antiviral properties of vitamin C and quercetin in the prevention and treatment of SARS-CoV-2 infection. *Frontiers in Immunology*, 11, 1451.
- Cory, H., Passarelli, S., Szeto, J., Tamez, M., & Mattei, J. (2018). The role of polyphenols in human health and food systems: A mini-review. *Frontiers in Nutrition*, 5, 87.

- Dabeek, W. M., & Marra, M. V. (2019). Dietary quercetin and kaempferol: Bioavailability and potential cardiovascular-related bioactivity in humans. *Nutrients*, *11*(10), 2288.
- Delgado-Roche, L., & Mesta, F. (2020). Oxidative stress as key player in severe acute respiratory syndrome coronavirus (SARS-CoV) infection. *Archives of Medical Research*, *51*(5), 384–387.
- Diniz, L. R. L., Souza, M. T. S., Duarte, A. B. S., Sousa, D. P., & Almeida, R. N. (2020). Brain-derived neurotrophic factor and antioxidant effects of flavonoids in neurological disorders. *Molecules*, *25*(23), 5630.
- Ekor, M. (2014). The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. *Frontiers in Pharmacology*, *4*, 177.
- Ellul, M. A., Benjamin, L., Singh, B., Lant, S., Michael, B. D., Easton, A., & Solomon, T. (2020). Neurological associations of COVID-19. *The Lancet Neurology*, *19*(9), 767–783.
- Gao, Y., Yan, L., Huang, Y., Liu, F., Zhao, Y., Cao, L., & Rao, Z. (2020). Structure of the RNA-dependent RNA polymerase from COVID-19 virus. *Science*, *368*(6492), 779–782.
- Gupta, A., Madhavan, M. V., Sehgal, K., Nair, N., Mahajan, S., Sehrawat, T. S., & Landry, D. W. (2020). Extrapulmonary manifestations of COVID-19. *Nature Medicine*, *26*(7), 1017–1032.
- Heneka, M. T., Golenbock, D., Latz, E., Morgan, D., & Brown, R. (2020). Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. *Alzheimer's Research & Therapy*, *12*(1), 69.
- Henss, L., Auste, A., Schürmann, C., Schmidt, C., von Rhein, C., Mühlebach, M. D., & Schnierle, B. S. (2021). The green tea catechin epigallocatechin gallate inhibits SARS-CoV-2 infection. *Journal of General Virology*, *102*(4), 001574.
- Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., & Pöhlmann, S. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2. *Cell*, *181*(2), 271–280.e8.
- Hu, J., Webster, D., Cao, J., & Shao, A. (2018). The safety of green tea and green tea extract consumption in adults—Results of a systematic review. *Regulatory Toxicology and Pharmacology*, *95*, 412–433.
- Ide, K., Yamada, H., Takuma, N., Park, M., Wakamiya, N., Nakase, J., & Matsuzaki, K. (2016). Green tea consumption affects cognitive dysfunction in the elderly: A pilot study. *Nutrients*, *8*(6), 383.
- Isman, M. B. (2020). Botanical insecticides in the twenty-first century—Fulfilling their promise? *Annual Review of Entomology*, *65*, 233–249.
- Jahan, I., Onay, A., Pottou, F. H., & Javed, M. N. (2021). Phytomedicines and COVID-19: Therapeutic possibilities and challenges. *Current Pharmaceutical Biotechnology*, *22*(15), 1967–1985.
- Jang, M., Park, Y. I., Cha, Y. E., Park, R., Namkoong, S., Lee, J. I., & Park, J. (2021). EGCG, a green tea polyphenol, inhibits human coronavirus replication in vitro. *Biochemical and Biophysical Research Communications*, *547*, 23–28.
- Kandhare, A. D., Bodhankar, S. L., Singh, V., Mohan, V., & Thakurdesai, P. A. (2017). Anti-asthmatic effects of type-A procyanidine polyphenols from cinnamon bark in ovalbumin-induced airway hyperresponsiveness in laboratory animals. *Biomedicine & Pharmacotherapy*, *94*, 109–118.

- Khaerunnisa, S., Kurniawan, H., Awaluddin, R., Suhartati, S., & Soetjipto, S. (2020). Potential inhibitor of COVID-19 main protease (Mpro) from several medicinal plant compounds by molecular docking study. *Preprints*, 2020030226.
- Khanna, K., Kohli, S. K., Kaur, R., Bhardwaj, A., Bhardwaj, V., Ohri, P., & Ahmad, P. (2021). Herbal immune-boosters: Substantial warriors of pandemic COVID-19 battle. *Phytomedicine*, 85, 153361.
- Khan, N., & Mukhtar, H. (2018). Tea polyphenols in promotion of human health. *Nutrients*, 11(1), 39.
- Kharwar, R. N., Upadhyay, R., Dubey, N. K., & Raghuwanshi, R. (2020). Perspectives of medicinal plants in management of COVID-19. *3 Biotech*, 10(10), 1–10.
- Kumar, R., Siril, P. F., & Tripathi, Y. B. (2022). Nanotechnology-based delivery systems for phytochemicals in neurological disorders. *Drug Development Research*, 83(2), 273–289.
- Kumar, V., Dhanjal, J. K., Kaul, S. C., Wadhwa, R., & Sundar, D. (2021). Withanone and caffeic acid phenethyl ester are predicted to interact with main protease (Mpro) of SARS-CoV-2 and inhibit its activity. *Journal of Biomolecular Structure and Dynamics*, 39(11), 3842–3854.
- Mandel, S. A., Amit, T., Weinreb, O., Reznichenko, L., & Youdim, M. B. H. (2011). Simultaneous manipulation of multiple brain targets by green tea catechins: A potential neuroprotective strategy for Alzheimer and Parkinson diseases. *CNS Neuroscience & Therapeutics*, 17(6), 619–634.
- Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., & Hu, B. (2020). Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurology*, 77(6), 683–690.
- Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., & Manson, J. J. (2020). COVID-19: Consider cytokine storm syndromes and immunosuppression. *The Lancet*, 395(10229), 1033–1034.
- Mhatre, S., Srivastava, T., Naik, S., & Patravale, V. (2021). Antiviral activity of green tea and black tea polyphenols in prophylaxis and treatment of COVID-19: A review. *Phytomedicine*, 85, 153286.
- Paraiso, I. L., Revel, J. S., & Stevens, J. F. (2020). Potential use of polyphenols in the battle against COVID-19. *Current Opinion in Food Science*, 32, 149–155.
- Patel, S. M., Venkata, K. C. N., & Bhattacharyya, P. (2021). Potential therapeutic role of neem (*Azadirachta indica*) in management of COVID-19. *Phytotherapy Research*, 35(5), 2826–2835.
- Paul, R., Prasad, M., & Sah, N. K. (2011). Anticancer biology of *Azadirachta indica* L. (Neem): A mini review. *Cancer Biology & Therapy*, 12(6), 467–476.
- Pervin, M., Unno, K., Takagaki, A., Isemura, M., & Nakamura, Y. (2018). Function of green tea catechins in the brain: Epigallocatechin gallate and its metabolites. *International Journal of Molecular Sciences*, 20(15), 3630.
- Prajapati, V. K., Singh, D., & Kumar, R. (2020). Antiviral potential of medicinal plants against COVID-19: A review. *VirusDisease*, 31(4), 421–431.
- Premraj, L., Kannapadi, N. V., Briggs, J., Seal, S. M., Battaglini, D., Fanning, J., & Fraser, J. F. (2022). Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome: A meta-analysis. *Journal of the Neurological Sciences*, 434, 120162.

- Rai, M., Bonde, S., Yadav, A., Plekhanova, Y., Reshetilov, A., Gupta, I., & Golińska, P. (2021). Nanotechnology-based anti-infectives and antivirals in the management of COVID-19 and related disorders. *Viruses*, 13(7), 1231.
- Roy, A., & Saraf, S. (2021). Limonoids: Overview of significant bioactive triterpenes distributed in plants kingdom. *Biological & Pharmaceutical Bulletin*, 29(2), 191–201.
- Shin, D., Mukherjee, R., Grewe, D., Bojkova, D., Baek, K., Bhattacharya, A., & Dikic, I. (2020). Papain-like protease regulates SARS-CoV-2 viral spread and innate immunity. *Nature*, 587(7835), 657–662.
- Siddiqui, S., Hafeez, A., Khan, A., & Khan, M. I. (2022). Herbal approaches in the management of COVID-19-associated neurological complications. *Journal of Herbal Medicine*, 32, 100530.
- Singh, B. N., Shankar, S., & Srivastava, R. K. (2011). Green tea catechin, epigallocatechin-3-gallate (EGCG): Mechanisms, perspectives and clinical applications. *Biochemical Pharmacology*, 82(12), 1807–1821.
- Sriram, K., Insel, P. A., & Loomba, R. (2021). What is the ACE2 receptor and what does it mean in the pathology of COVID-19? *Critical Care*, 25(1), 172.
- Subapriya, R., & Nagini, S. (2005). Medicinal properties of neem leaves: A review. *Current Medicinal Chemistry – Anti-Cancer Agents*, 5(2), 149–156.
- Taquet, M., Geddes, J. R., Husain, M., Luciano, S., & Harrison, P. J. (2021). 6-month neurological and psychiatric outcomes in 236,379 survivors of COVID-19. *The Lancet Psychiatry*, 8(5), 416–427.
- Troyer, E. A., Kohn, J. N., & Hong, S. (2020). Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? *Brain, Behavior, and Immunity*, 87, 34–39.
- Ul Haq, F., Roman, M., Ahmad, K., Rahman, S. U., Shah, S. M. A., Suleman, N., & Ullah, S. (2021). *Artemisia annua*: Trials are needed for COVID-19. *Phytotherapy Research*, 35(5), 2423–2428.
- Upadhyay, S. N., Dhawan, S., Garg, S., & Talwar, G. P. (1992). Immunomodulatory effects of neem (*Azadirachta indica*) oil. *International Journal of Immunopharmacology*, 14(7), 1187–1193.
- V'kovski, P., Kratzel, A., Steiner, S., Stalder, H., & Thiel, V. (2021). Coronavirus biology and replication: Implications for SARS-CoV-2. *Nature Reviews Microbiology*, 19(3), 155–170.
- World Health Organization. (2023). *WHO coronavirus (COVID-19) dashboard*. Geneva, Switzerland: World Health Organization.
- Xu, J., Xu, Z., & Zheng, W. (2017). A review of the antiviral role of green tea catechins. *Molecules*, 22(8), 1337.
- Yamada, H., Takuma, N., Daimon, T., & Hara, Y. (2020). Gargling with tea catechin extracts for the prevention of influenza infection in elderly nursing home residents: A prospective clinical study. *Journal of Alternative and Complementary Medicine*, 12(7), 669–672.
- Zhang, L., Lin, D., Sun, X., Curth, U., Drosten, C., Sauerhering, L., & Hilgenfeld, R. (2020). Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved  $\alpha$ -ketoamide inhibitors. *Science*, 368(6489), 409–412.
- Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., & Tan, W. (2020). A novel coronavirus from patients with pneumonia in China, 2019. *New England Journal of Medicine*, 382(8), 727–733.

## Chapter 7: Traditional Herbal Formulations Containing *Zingiber officinale* and *Piper nigrum* for COVID-19 Recovery and Mental Well-Being

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### Abstract

The coronavirus disease 2019 (COVID-19) pandemic has caused substantial global morbidity and mortality while also contributing to long-term physical, neurological, and psychological complications. Post-COVID conditions such as fatigue, respiratory dysfunction, anxiety, depression, stress, insomnia, cognitive impairment, and reduced mental well-being have emerged as major healthcare concerns worldwide. In this context, traditional medicinal plants and herbal formulations have gained considerable scientific attention because of their multitarget therapeutic properties and historical use in respiratory and immune-related disorders. Among these medicinal plants, *Zingiber officinale* (ginger) and *Piper nigrum* (black pepper) occupy important positions in traditional systems of medicine including Ayurveda, Unani, and folk medicine. This chapter explores the therapeutic potential of herbal formulations containing ginger and black pepper in COVID-19 recovery and mental well-being. Major phytochemicals such as gingerols, shogaols, zingerone, piperine, and essential oils exhibit antiviral, anti-inflammatory, antioxidant, immunomodulatory, neuroprotective, and adaptogenic properties that may help alleviate post-COVID complications. These bioactive compounds have demonstrated inhibitory effects against inflammatory cytokines, oxidative stress pathways, and viral targets associated with SARS-CoV-2 infection. Piperine additionally enhances the bioavailability of several therapeutic phytochemicals, thereby improving pharmacological effectiveness. Traditional formulations including kadha, trikatu, herbal teas, decoctions, and functional beverages containing ginger and black pepper have been widely utilized during the pandemic for immune support, respiratory relief, and mental wellness. Experimental and computational studies suggest that these phytochemicals may reduce neuroinflammation, improve cognitive function, support neurotransmitter balance, and protect against stress-induced neuronal damage. Furthermore, their antioxidant and immunoregulatory activities may contribute to management of long COVID symptoms and recovery-associated fatigue. Despite promising pharmacological evidence, challenges related to standardization, dosage optimization, bioavailability, and clinical validation remain significant barriers to therapeutic translation. Future interdisciplinary research integrating phytochemistry, pharmacology, neuroscience, and clinical medicine is essential to establish evidence-based herbal interventions for COVID-19 recovery and psychological health. Overall, traditional herbal formulations containing *Zingiber officinale* and *Piper nigrum* represent promising complementary therapeutic approaches for enhancing post-COVID recovery, immunity, and mental well-being.

### Keywords

COVID-19; *Zingiber officinale*; *Piper nigrum*; Ginger; Black pepper; Mental well-being; Neuroprotection; Long COVID; Herbal formulations; Immunomodulation; Antioxidant activity; Piperine; Gingerols; Cytokine storm; Brain fog; Traditional medicine; Ayurveda; Phytochemicals; Respiratory health; Post-COVID recovery

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## 1. Introduction

### 1.1 Overview of COVID-19 and Post-COVID Complications

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in late 2019 and rapidly developed into a global public health emergency. The disease was first identified in Wuhan, China, and subsequently spread worldwide, leading to unprecedented healthcare, economic, and social disruptions (Zhu et al., 2020). The World Health Organization (WHO) officially declared COVID-19 a pandemic in March 2020 due to its rapid transmission and increasing mortality rates worldwide (World Health Organization, 2023).

Although SARS-CoV-2 primarily targets the respiratory system, growing evidence indicates that the virus can affect multiple organ systems including the cardiovascular, gastrointestinal, renal, endocrine, and nervous systems (Gupta et al., 2020). Clinical manifestations range from asymptomatic infection to severe pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure, and death. The pathogenesis of COVID-19 involves viral replication, immune dysregulation, cytokine storm, oxidative stress, endothelial dysfunction, and thrombotic complications (Mehta et al., 2020).

Beyond acute infection, many recovered patients continue to experience persistent symptoms collectively referred to as “long COVID” or post-COVID syndrome. Common post-COVID complications include fatigue, dyspnea, muscle weakness, sleep disturbances, cognitive dysfunction, anxiety, depression, stress, and reduced quality of life (Premraj et al., 2022). Long COVID has become a major healthcare concern because neurological and psychological symptoms may persist for months after viral clearance.

### 1.2 Mental Health Burden Associated with COVID-19

The COVID-19 pandemic significantly affected global mental health through both direct biological effects of SARS-CoV-2 infection and indirect psychosocial stressors such as isolation, fear, economic instability, and social disruption. Increased prevalence of anxiety, depression, post-traumatic stress disorder (PTSD), insomnia, emotional distress, and cognitive impairment has been observed among infected individuals as well as the general population (Troyer et al., 2020).

Neuropsychiatric manifestations associated with COVID-19 are linked to inflammatory responses, cytokine release, blood–brain barrier disruption, oxidative stress, and altered neurotransmitter signaling pathways. SARS-CoV-2 infection may trigger neuroinflammation and microglial activation, thereby contributing to cognitive dysfunction and emotional disturbances (Boldrini et al., 2021).

Several studies have reported persistent neurological symptoms including memory impairment, difficulty concentrating, mental fatigue, and “brain fog” among post-COVID patients (Becker et al., 2021). Such complications negatively affect daily functioning, occupational productivity, and overall mental well-being. The long-term neurological impact of COVID-19 has therefore generated substantial interest in neuroprotective and psychomodulatory therapeutic strategies.

### 1.3 Importance of Traditional Herbal Medicine in Pandemic Management

Traditional medicinal systems including Ayurveda, Traditional Chinese Medicine (TCM), Unani, and folk medicine have historically played significant roles in the prevention and treatment of infectious diseases. During the COVID-19 pandemic, herbal medicines gained renewed attention because of their accessibility, affordability, historical safety, and broad-spectrum pharmacological activities (Jahan et al., 2021).

Medicinal plants contain diverse phytochemicals capable of exerting antiviral, antioxidant, anti-inflammatory, immunomodulatory, adaptogenic, and neuroprotective effects. Such multitarget therapeutic actions are particularly advantageous in COVID-19 because disease progression involves complex interactions between viral replication, immune dysregulation, oxidative stress, and neurological injury (Kharwar et al., 2020).

Several herbal remedies and dietary interventions were traditionally used during the pandemic to improve respiratory health, strengthen immunity, reduce inflammation, and support psychological wellness. Herbal decoctions, kadha preparations, steam inhalation therapies, and functional beverages became widely popular complementary interventions in many countries. Scientific investigations have further supported the potential role of phytochemicals in inhibiting viral entry, suppressing inflammatory cytokines, and protecting neuronal tissues (Paraiso et al., 2020).

### 1.4 Role of *Zingiber officinale* and *Piper nigrum* in Traditional Systems of Medicine

*Zingiber officinale* (ginger) and *Piper nigrum* (black pepper) are among the most extensively used medicinal spices in traditional medicine systems. Both plants possess significant therapeutic importance due to their diverse pharmacological properties and long history of dietary and medicinal applications.

Ginger has been traditionally utilized for management of respiratory disorders, cough, cold, fever, nausea, digestive disturbances, inflammation, and fatigue. Ayurvedic medicine describes ginger as a warming herb capable of enhancing digestion, improving circulation, reducing mucus accumulation, and strengthening immunity (Chacko et al., 2010). Major bioactive compounds including gingerols, shogaols, paradols, and zingerone contribute to its antioxidant, anti-inflammatory, antiviral, and neuroprotective properties.

Similarly, black pepper has been widely used in Ayurveda and traditional medicine as a digestive stimulant, bioavailability enhancer, respiratory tonic, and rejuvenating agent. Piperine, the principal alkaloid of *Piper nigrum*, exhibits anti-inflammatory, antioxidant, antimicrobial, immunomodulatory, and neuroprotective activities (Khan & Mukhtar, 2018). Piperine additionally enhances intestinal absorption and bioavailability of various phytochemicals and therapeutic drugs, thereby increasing pharmacological effectiveness.

Traditional formulations such as trikatu, herbal teas, kadha, and spice-based decoctions commonly combine ginger and black pepper to improve respiratory function, immunity, metabolism, and mental

wellness. Their synergistic pharmacological effects make them promising candidates for supportive management of COVID-19 recovery and post-infection neurological complications.

### 1.5 Scope and Objectives of the Chapter

This chapter aims to comprehensively explore the therapeutic significance of traditional herbal formulations containing *Zingiber officinale* and *Piper nigrum* in COVID-19 recovery and mental well-being. The chapter discusses the phytochemical composition, pharmacological properties, antiviral mechanisms, immunomodulatory actions, neuroprotective effects, and traditional medicinal applications of these plants.

Special emphasis is placed on their potential role in reducing inflammation, oxidative stress, cognitive dysfunction, anxiety, depression, and post-COVID neurological complications. The chapter additionally examines traditional formulations, experimental evidence, clinical relevance, formulation approaches, safety considerations, and future therapeutic perspectives.

By integrating current scientific findings with traditional medicinal knowledge, this chapter highlights the potential of ginger and black pepper as complementary therapeutic agents for enhancing post-COVID recovery, immune resilience, and psychological health.

## 2. COVID-19 Pathophysiology and Neuropsychological Impact

### 2.1 SARS-CoV-2 Infection and Immune Dysregulation

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-sense single-stranded RNA virus belonging to the Coronaviridae family. The virus primarily infects host cells through interaction of its spike (S) glycoprotein with angiotensin-converting enzyme 2 (ACE2) receptors expressed on epithelial and endothelial cells of multiple organs including the lungs, heart, gastrointestinal tract, kidneys, and brain (Hoffmann et al., 2020). Viral entry is further facilitated by transmembrane serine protease 2 (TMPRSS2), which primes the spike protein for membrane fusion and cellular invasion.

Following cellular entry, SARS-CoV-2 releases its genomic RNA into the host cytoplasm where viral replication and transcription occur through the action of RNA-dependent RNA polymerase (RdRp). Viral replication leads to extensive host immune activation and inflammatory responses. Although innate and adaptive immune responses are essential for viral clearance, dysregulated immune activation contributes significantly to disease severity and tissue damage (V'kovski et al., 2021).

COVID-19 patients commonly exhibit elevated levels of pro-inflammatory cytokines and chemokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), and interferon gamma (IFN- $\gamma$ ). Excessive inflammatory responses may result in immune dysregulation, endothelial dysfunction, vascular injury, and multiorgan complications (Del Valle et al., 2020).

Additionally, lymphopenia, T-cell exhaustion, impaired interferon signaling, and altered macrophage activation have been reported in severe COVID-19 cases. Such immunological abnormalities not only

contribute to acute disease progression but may also promote long-term neurological and psychological complications after recovery.

## 2.2 Cytokine Storm and Oxidative Stress

One of the major pathological hallmarks of severe COVID-19 is the development of a “cytokine storm,” characterized by uncontrolled systemic release of inflammatory mediators. Hyperactivation of immune cells including macrophages, neutrophils, and T lymphocytes results in excessive production of cytokines that contribute to widespread tissue injury, vascular leakage, coagulation abnormalities, and organ dysfunction (Fajgenbaum & June, 2020).

Inflammatory cytokines additionally stimulate the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to oxidative stress and mitochondrial dysfunction. Oxidative stress occurs when the balance between free radical generation and antioxidant defense systems becomes disrupted, resulting in cellular and molecular damage (Cecchini & Cecchini, 2020).

Elevated oxidative stress has been implicated in pulmonary injury, endothelial damage, neuronal dysfunction, and immune dysregulation associated with COVID-19. Excessive ROS production can damage lipids, proteins, nucleic acids, and mitochondrial membranes, thereby aggravating inflammatory injury and apoptosis. Oxidative stress also activates nuclear factor-kappa B (NF- $\kappa$ B) and other pro-inflammatory signaling pathways that further amplify cytokine release and inflammatory responses.

The combined effects of cytokine storm and oxidative stress contribute significantly to disease severity and long-term complications, highlighting the importance of therapeutic agents possessing antioxidant and anti-inflammatory activities.

## 2.3 Neurological Manifestations of COVID-19

Accumulating evidence demonstrates that COVID-19 is associated with diverse neurological manifestations affecting both the central nervous system (CNS) and peripheral nervous system (PNS). Neurological symptoms may arise from direct viral neuroinvasion, immune-mediated injury, vascular dysfunction, hypoxia, and systemic inflammation (Ellul et al., 2020).

Common neurological manifestations include headache, dizziness, anosmia, ageusia, confusion, encephalopathy, seizures, stroke, neuropathy, myalgia, and impaired consciousness. Severe neurological complications such as encephalitis, Guillain-Barré syndrome, and cerebrovascular accidents have also been reported in critically ill patients (Mao et al., 2020).

SARS-CoV-2 may gain access to the CNS through multiple mechanisms including transsynaptic spread via olfactory neurons, hematogenous dissemination, and disruption of the blood-brain barrier. Viral particles and inflammatory mediators can induce neuronal injury, microglial activation, astrocyte dysfunction, and neurovascular inflammation (Song et al., 2021).

The blood–brain barrier plays a critical protective role in maintaining neural homeostasis; however, inflammatory cytokines and viral spike proteins may impair barrier integrity and increase CNS permeability. Such alterations facilitate infiltration of inflammatory mediators into neural tissues, thereby promoting neuroinflammation and neuronal damage.

## 2.4 Anxiety, Depression, Stress, and Brain Fog in Post-COVID Syndrome

Mental health disturbances have emerged as significant long-term consequences of COVID-19 infection. Persistent anxiety, depression, emotional instability, stress, insomnia, and cognitive impairment have been widely observed among recovered patients (Taquet et al., 2021).

“Brain fog” is one of the most frequently reported neurological complaints in long COVID and is characterized by memory impairment, reduced concentration, slowed information processing, mental fatigue, and difficulty performing daily cognitive tasks. The pathophysiology of brain fog is believed to involve neuroinflammation, oxidative stress, endothelial dysfunction, mitochondrial impairment, neurotransmitter imbalance, and persistent immune activation (Becker et al., 2021).

Psychological stress associated with social isolation, fear of illness, hospitalization, economic instability, and uncertainty further contributes to neuropsychiatric complications. Elevated cortisol levels and chronic stress responses may impair hippocampal function, synaptic plasticity, and emotional regulation.

Several neuroinflammatory mediators including IL-6, TNF- $\alpha$ , and C-reactive protein (CRP) have been linked to depressive symptoms and cognitive decline in post-COVID patients. Persistent activation of microglia and astrocytes may additionally contribute to neuronal dysfunction and neurodegenerative processes (Heneka et al., 2020).

## 2.5 Need for Herbal Therapeutics Supporting Recovery and Mental Wellness

The complex and multifactorial nature of COVID-19 pathophysiology necessitates therapeutic approaches capable of simultaneously targeting viral replication, inflammation, oxidative stress, immune dysregulation, and neurological injury. Conventional pharmacological interventions often focus primarily on antiviral or symptomatic management and may not adequately address long-term cognitive and psychological complications.

Herbal therapeutics containing bioactive phytochemicals have attracted considerable attention because of their multitarget pharmacological properties. Medicinal plants possessing antioxidant, anti-inflammatory, antiviral, adaptogenic, anxiolytic, and neuroprotective effects may provide supportive benefits during post-COVID recovery and mental rehabilitation (Siddiqui et al., 2022).

*Zingiber officinale* and *Piper nigrum* contain several bioactive compounds capable of modulating inflammatory pathways, reducing oxidative stress, improving respiratory function, and enhancing neurological resilience. Gingerols, shogaols, piperine, and related phytochemicals have demonstrated immunomodulatory and neuroprotective activities in various experimental studies.

Furthermore, traditional herbal formulations may help improve digestion, circulation, energy metabolism, sleep quality, stress adaptation, and cognitive function, thereby contributing to overall recovery and psychological well-being. The increasing scientific interest in integrative and plant-based medicine highlights the therapeutic potential of these herbs as complementary interventions in long COVID and post-viral neurological disorders.

**Table 1. Major Pathophysiological and Neuropsychological Features of COVID-19**

Pathological Feature	Mechanism	Clinical Consequences
Viral entry through ACE2	Spike protein interaction with ACE2 and TMPRSS2	Respiratory and systemic infection
Cytokine storm	Excessive IL-6, TNF- $\alpha$ , IL-1 $\beta$ production	Inflammation and organ damage
Oxidative stress	ROS and mitochondrial dysfunction	Cellular injury and apoptosis
Blood-brain barrier disruption	Endothelial inflammation and permeability changes	Neuroinflammation
Neuroinvasion	Viral spread to CNS	Neurological complications
Microglial activation	Persistent neuroimmune response	Cognitive impairment
Neurotransmitter imbalance	Stress and inflammatory signaling	Anxiety and depression
Brain fog	Neuroinflammation and oxidative injury	Memory and concentration deficits

### 3. Botanical and Phytochemical Profile of *Zingiber officinale* and *Piper nigrum*

#### 3.1 *Zingiber officinale* (Ginger)

##### 3.1.1 Botanical Description and Traditional Uses

*Zingiber officinale* Roscoe, commonly known as ginger, belongs to the family Zingiberaceae and is one of the most widely used medicinal and culinary herbs worldwide. Ginger is a perennial herb characterized by thick underground rhizomes, narrow lanceolate leaves, and yellowish-green flowers. The rhizome is the primary medicinally important part and possesses a characteristic pungent aroma and spicy flavor due to the presence of volatile oils and phenolic compounds (Ali et al., 2008).

Ginger has been extensively used in traditional medicinal systems including Ayurveda, Traditional Chinese Medicine (TCM), Unani, and folk medicine for centuries. In Ayurveda, ginger is considered a “universal medicine” because of its broad therapeutic applications in respiratory disorders, digestive disturbances, nausea, inflammation, cough, fever, arthritis, and circulatory disorders (Mashhadi et al., 2013). Traditional formulations containing ginger are commonly used to relieve cold symptoms, enhance digestion, improve circulation, and strengthen immunity.

During the COVID-19 pandemic, ginger-based herbal decoctions, teas, and kadha formulations became widely popular because of their perceived immune-boosting, anti-inflammatory, and respiratory

protective effects. Scientific evidence has increasingly supported the therapeutic relevance of ginger phytochemicals in inflammatory and infectious diseases.

### 3.1.2 Major Bioactive Constituents of Ginger

The pharmacological activities of ginger are primarily attributed to its diverse phytochemical composition including phenolic compounds, volatile oils, flavonoids, terpenoids, and alkaloids. The major bioactive compounds of ginger include gingerols, shogaols, paradols, zingerone, and essential oils such as zingiberene and  $\beta$ -bisabolene (Semwal et al., 2015).

#### *Gingerols*

Gingerols are the principal pungent phenolic compounds found in fresh ginger rhizomes. Among them, 6-gingerol is the most abundant and biologically active constituent. Gingerols exhibit strong antioxidant, anti-inflammatory, antiviral, anticancer, analgesic, and neuroprotective activities. These compounds suppress cyclooxygenase (COX), lipoxygenase (LOX), and nuclear factor-kappa B (NF- $\kappa$ B) signaling pathways involved in inflammatory responses (Rahmani et al., 2014).

#### *Shogaols*

Shogaols are dehydration products of gingerols formed during drying or thermal processing of ginger. 6-Shogaol possesses potent antioxidant, anti-inflammatory, neuroprotective, and anticancer activities. Studies have demonstrated that shogaols can inhibit oxidative stress, reduce neuroinflammation, and protect neuronal cells from apoptosis and mitochondrial dysfunction (Dugasani et al., 2010).

#### *Zingerone*

Zingerone is another important phenolic ketone generated during heating of ginger. It exhibits antioxidant, antimicrobial, anti-inflammatory, antidiabetic, and neuroprotective effects. Zingerone can scavenge free radicals, reduce lipid peroxidation, and modulate inflammatory mediators involved in tissue injury and neurodegeneration (Stoilova et al., 2007).

#### *Paradols*

Paradols are hydrogenated derivatives of shogaols possessing antioxidant, anti-inflammatory, and anticancer activities. These compounds contribute to the therapeutic efficacy of ginger against oxidative stress and inflammatory disorders. Experimental studies indicate that paradols may also exert neuroprotective effects through suppression of inflammatory signaling pathways.

### 3.1.3 Pharmacological Properties Relevant to COVID-19 Recovery

Ginger possesses several pharmacological activities that may support COVID-19 recovery and management of post-viral complications. Ginger phytochemicals exhibit antiviral activity against respiratory viruses by interfering with viral attachment, replication, and inflammatory signaling pathways

(Chang et al., 2013). Computational studies have also suggested potential inhibitory interactions of ginger constituents with SARS-CoV-2 proteins including Mpro and spike glycoproteins.

The anti-inflammatory properties of ginger are particularly relevant because severe COVID-19 is associated with cytokine storm and systemic inflammation. Gingerols and shogaols inhibit pro-inflammatory cytokines such as IL-6, TNF- $\alpha$ , and IL-1 $\beta$  while suppressing NF- $\kappa$ B-mediated inflammatory pathways.

Additionally, ginger exhibits strong antioxidant activity by enhancing endogenous antioxidant enzymes including superoxide dismutase (SOD), catalase, and glutathione peroxidase. Reduction of oxidative stress may help minimize pulmonary, cardiovascular, and neurological complications associated with COVID-19.

Ginger also demonstrates neuroprotective and anxiolytic activities that may help alleviate post-COVID cognitive dysfunction, fatigue, and psychological stress. Experimental studies suggest that ginger phytochemicals can improve memory, reduce neuroinflammation, and modulate neurotransmitter systems involved in mood regulation (Saenghong et al., 2012).

### **3.2 *Piper nigrum* (Black Pepper)**

#### **3.2.1 Botanical Description and Ethnomedicinal Importance**

*Piper nigrum* L., commonly known as black pepper, belongs to the Piperaceae family and is widely recognized as the “King of Spices.” It is a perennial climbing vine native to South India and extensively cultivated in tropical regions worldwide. The dried unripe fruits, commonly called peppercorns, are used both as culinary spices and medicinal agents (Ahmad et al., 2012).

Black pepper has long been used in Ayurveda, Siddha, and traditional medicinal systems for treatment of respiratory disorders, digestive problems, fever, cough, asthma, obesity, and inflammatory diseases. In Ayurvedic medicine, black pepper is considered a stimulant, carminative, digestive enhancer, and bioavailability promoter.

Traditional formulations such as trikatu combine black pepper with ginger and long pepper (*Piper longum*) to improve metabolism, respiratory health, and immune function. During the COVID-19 pandemic, black pepper-containing herbal remedies were widely consumed to support immunity and relieve respiratory symptoms.

#### **3.2.2 Major Bioactive Constituents of Black Pepper**

Black pepper contains numerous bioactive compounds including alkaloids, flavonoids, phenolics, terpenes, and essential oils. Piperine is the principal alkaloid responsible for the characteristic pungency and pharmacological activities of black pepper (Meghwal & Goswami, 2013).

### *Piperine*

Piperine exhibits antioxidant, anti-inflammatory, antimicrobial, immunomodulatory, antidepressant, anticonvulsant, and neuroprotective activities. It enhances gastrointestinal absorption and bioavailability of several nutrients and phytochemicals by inhibiting drug-metabolizing enzymes and intestinal efflux transporters (Atal et al., 1985).

Piperine has also shown potential antiviral activity and immunoregulatory effects that may be beneficial in COVID-19 management. Molecular docking studies indicate possible interactions between piperine and SARS-CoV-2 target proteins.

### *Chavicine*

Chavicine is an isomer of piperine responsible for the sharp pungency of black pepper. Although less stable than piperine, chavicine contributes to antioxidant and antimicrobial activities of black pepper extracts.

### *Essential Oils*

Black pepper essential oils contain monoterpenes and sesquiterpenes including  $\beta$ -caryophyllene, limonene, pinene, sabinene, and linalool. These volatile compounds possess antioxidant, anti-inflammatory, bronchodilatory, and antimicrobial properties that may support respiratory health and immune function.

### *Flavonoids and Phenolic Compounds*

Black pepper additionally contains flavonoids and polyphenolic compounds capable of scavenging reactive oxygen species and reducing oxidative stress-mediated tissue damage. Such compounds contribute significantly to the neuroprotective and anti-inflammatory potential of black pepper.

### **3.2.3 Pharmacological Activities Supporting Immune and Cognitive Health**

Black pepper exhibits multiple pharmacological properties relevant to COVID-19 recovery and mental well-being. Piperine suppresses inflammatory cytokines, reduces oxidative stress, and modulates immune responses, thereby potentially minimizing inflammatory complications associated with viral infections (Tasleem et al., 2014).

The antioxidant activity of black pepper helps protect cells against oxidative damage induced by excessive free radical generation during inflammatory conditions. Piperine additionally enhances mitochondrial function and neuronal survival, contributing to neuroprotective effects.

Several studies suggest that piperine may improve cognitive performance, memory, and mood by modulating neurotransmitter pathways including serotonin and dopamine systems. Piperine also exhibits antidepressant and anxiolytic activities that may help alleviate psychological stress and post-COVID mental fatigue (Mao et al., 2017).

Furthermore, the bioavailability-enhancing property of piperine significantly increases absorption and therapeutic efficacy of various phytochemicals including curcumin, catechins, and other herbal compounds. This synergistic property makes black pepper an important component of traditional herbal formulations used for immune enhancement and recovery support.

**Table 2. Major Phytochemicals and Pharmacological Activities of *Zingiber officinale* and *Piper nigrum***

Plant	Major Phytochemicals	Principal Pharmacological Activities
<i>Zingiber officinale</i>	Gingerols	Anti-inflammatory, antioxidant, antiviral
<i>Zingiber officinale</i>	Shogaols	Neuroprotective, antioxidant, anti-inflammatory
<i>Zingiber officinale</i>	Zingerone	Free radical scavenging, antimicrobial
<i>Zingiber officinale</i>	Paradols	Anti-inflammatory, neuroprotective
<i>Piper nigrum</i>	Piperine	Bioavailability enhancer, neuroprotective
<i>Piper nigrum</i>	Chavicine	Antioxidant, antimicrobial
<i>Piper nigrum</i>	Essential oils	Bronchodilatory, anti-inflammatory
<i>Piper nigrum</i>	Flavonoids	Antioxidant, immunomodulatory

#### 4. Mechanisms of Action of *Zingiber officinale* and *Piper nigrum* in COVID-19 Recovery and Mental Well-Being

##### 4.1 Antiviral Mechanisms Against SARS-CoV-2

Medicinal phytochemicals present in *Zingiber officinale* and *Piper nigrum* have demonstrated significant antiviral potential against several respiratory viruses, including SARS-CoV-2. Bioactive compounds such as gingerols, shogaols, zingerone, and piperine may interfere with multiple stages of the viral life cycle including viral attachment, entry, replication, and assembly (Thuy et al., 2020).

SARS-CoV-2 infects host cells through interaction between viral spike glycoprotein and angiotensin-converting enzyme 2 (ACE2) receptors. Molecular docking and computational studies suggest that ginger phytochemicals may bind to spike proteins and viral proteases, thereby inhibiting viral attachment and replication (Rajagopal et al., 2020). In particular, 6-gingerol and 6-shogaol have shown favorable binding affinity toward SARS-CoV-2 main protease (Mpro), an enzyme essential for viral replication.

Similarly, piperine from *Piper nigrum* has demonstrated potential inhibitory interactions with SARS-CoV-2 proteins including spike glycoprotein, RNA-dependent RNA polymerase (RdRp), and Mpro (Khaerunnisa et al., 2020). Such interactions may reduce viral replication and infectivity. Additionally, black pepper essential oils possess antimicrobial and antiviral properties that may help support respiratory defense mechanisms.

Experimental evidence also suggests that ginger extracts may inhibit human respiratory syncytial virus and other respiratory pathogens by preventing viral attachment to respiratory epithelial cells (Chang et al., 2013). Although clinical evidence against SARS-CoV-2 remains limited, these findings support the potential role of ginger and black pepper phytochemicals as complementary antiviral agents.

## 4.2 Anti-Inflammatory and Immunomodulatory Effects

Severe COVID-19 is strongly associated with hyperinflammation and cytokine storm characterized by elevated levels of IL-6, TNF- $\alpha$ , IL-1 $\beta$ , and other pro-inflammatory mediators. Persistent inflammation contributes to pulmonary injury, endothelial dysfunction, neuroinflammation, and multiorgan damage (Mehta et al., 2020).

Ginger phytochemicals exhibit strong anti-inflammatory activity through suppression of cyclooxygenase (COX), lipoxygenase (LOX), and nuclear factor-kappa B (NF- $\kappa$ B) signaling pathways. Gingerols and shogaols reduce production of inflammatory cytokines and inhibit activation of inflammatory transcription factors (Grzanna et al., 2005). These effects may help minimize cytokine-mediated tissue injury in COVID-19.

Piperine also exerts potent anti-inflammatory and immunomodulatory effects. It inhibits secretion of TNF- $\alpha$ , IL-6, prostaglandins, and nitric oxide while suppressing activation of inflammatory immune cells (Kumar et al., 2007). Piperine additionally modulates T-cell and macrophage responses, thereby contributing to immune homeostasis.

The immunoregulatory activities of these phytochemicals are especially important because excessive immune activation may contribute to both acute disease severity and long-term neurological complications. Herbal compounds capable of balancing immune responses without causing immunosuppression may therefore provide therapeutic benefits during post-COVID recovery.

## 4.3 Antioxidant Activity and Reduction of Oxidative Stress

Oxidative stress is a major contributor to COVID-19-associated tissue injury, endothelial dysfunction, mitochondrial impairment, and neurodegeneration. Excessive production of reactive oxygen species (ROS) during inflammatory responses can damage proteins, lipids, DNA, and neuronal structures (Delgado-Roche & Mesta, 2020).

Both ginger and black pepper contain potent antioxidant phytochemicals capable of scavenging free radicals and enhancing endogenous antioxidant defense systems. Gingerols, shogaols, and zingerone increase levels of antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase while reducing lipid peroxidation and oxidative injury (Semwal et al., 2015).

Piperine similarly demonstrates antioxidant activity through inhibition of ROS generation and enhancement of cellular antioxidant capacity. Black pepper extracts have been shown to reduce oxidative stress-mediated neuronal damage and mitochondrial dysfunction (Vijayakumar et al., 2004).

Reduction of oxidative stress is particularly important in prevention of neuroinflammation and cognitive dysfunction associated with long COVID. Antioxidant phytochemicals may help protect neurons, improve mitochondrial function, and maintain blood-brain barrier integrity during inflammatory conditions.

#### 4.4 Respiratory Protective and Expectorant Actions

Traditional medicinal systems have long utilized ginger and black pepper for treatment of respiratory illnesses including cough, cold, asthma, bronchitis, and congestion. These herbs possess bronchodilatory, mucolytic, expectorant, and anti-inflammatory activities that support respiratory health (Mao et al., 2019).

Ginger helps relax airway smooth muscles and improves respiratory function by modulating calcium channels and inflammatory mediators. It additionally reduces mucus accumulation and enhances airway clearance. Such properties may assist recovery from respiratory symptoms associated with COVID-19.

Black pepper stimulates circulation and promotes expectoration, thereby helping clear respiratory secretions. Piperine and volatile oils in black pepper may also improve pulmonary function and reduce airway inflammation. Traditional herbal decoctions containing ginger and black pepper are therefore widely used to alleviate cough, sore throat, nasal congestion, and breathing discomfort.

Furthermore, the warming and circulatory-stimulating properties of these herbs may improve peripheral blood flow and oxygen utilization, contributing to enhanced recovery and reduced fatigue in post-COVID patients.

#### 4.5 Neuroprotective and Cognitive Supportive Mechanisms

Neurological complications including memory impairment, brain fog, fatigue, anxiety, depression, and cognitive dysfunction are common manifestations of long COVID. Neuroinflammation, oxidative stress, mitochondrial dysfunction, and neurotransmitter imbalance contribute significantly to these complications (Heneka et al., 2020).

Ginger phytochemicals possess neuroprotective properties capable of reducing neuronal inflammation and oxidative damage. Experimental studies indicate that gingerols and shogaols suppress microglial activation, decrease neuroinflammatory cytokines, and improve neuronal survival (Ghayur & Gilani, 2005). Ginger extracts have also demonstrated memory-enhancing and cognition-improving effects in experimental and clinical studies.

Piperine exhibits significant neuroprotective and antidepressant activities by modulating neurotransmitter systems including serotonin, dopamine, and gamma-aminobutyric acid (GABA). It additionally enhances brain-derived neurotrophic factor (BDNF) expression, which supports neuronal growth, synaptic plasticity, and cognitive function (Mao et al., 2017).

The combined antioxidant and anti-inflammatory effects of ginger and black pepper may therefore help protect neural tissues against post-COVID neurodegeneration and cognitive decline. Their adaptogenic and stress-reducing properties may further improve emotional stability and psychological resilience.

#### 4.6 Modulation of Neurotransmitters and Stress Pathways

Psychological stress and neuropsychiatric disturbances during and after COVID-19 infection are associated with dysregulation of neurotransmitters and hypothalamic–pituitary–adrenal (HPA) axis activity. Elevated stress hormones and inflammatory mediators can impair mood, cognition, and sleep quality.

Ginger and black pepper phytochemicals may positively influence neurotransmitter balance and stress adaptation mechanisms. Ginger extracts have demonstrated anxiolytic and antidepressant-like activities through modulation of serotonergic and dopaminergic pathways (Hosseini & Mirazi, 2015).

Piperine also exhibits psychopharmacological activities including antidepressant, anxiolytic, and cognitive-enhancing effects. Experimental studies suggest that piperine increases serotonin and dopamine concentrations while reducing stress-induced oxidative damage and inflammation (Mao et al., 2017).

These neurochemical effects may help alleviate post-COVID anxiety, depression, mental fatigue, and emotional distress. Improvement in neurotransmitter balance may additionally support sleep quality, concentration, and psychological well-being during recovery.

#### 4.7 Enhancement of Bioavailability by Piperine

One of the most important pharmacological properties of piperine is its ability to enhance bioavailability of various nutrients, phytochemicals, and therapeutic agents. Piperine inhibits hepatic and intestinal drug-metabolizing enzymes including cytochrome P450 enzymes while suppressing P-glycoprotein-mediated drug efflux (Atal et al., 1985).

As a result, piperine significantly increases intestinal absorption and systemic availability of several bioactive compounds including curcumin, catechins, flavonoids, and herbal constituents. This property improves therapeutic efficacy and pharmacokinetic performance of herbal formulations.

In traditional medicine, black pepper is frequently combined with ginger and other herbs to enhance their absorption and biological activity. Such synergistic interactions may improve the effectiveness of herbal remedies used in COVID-19 recovery and neuroprotection.

The bioenhancing capability of piperine additionally supports development of advanced phytopharmaceutical formulations and nanocarrier systems for targeted delivery of antiviral and neuroprotective phytochemicals.

**Table 3. Mechanisms of Action of *Zingiber officinale* and *Piper nigrum* in COVID-19 Recovery**

Mechanism	Ginger Phytochemicals	Black Pepper Phytochemicals	Therapeutic Relevance
Antiviral activity	Gingerols, shogaols	Piperine	Inhibition of SARS-CoV-2 proteins
Anti-inflammatory	Gingerols	Piperine	Reduction of cytokine

effect			storm
Antioxidant action	Zingerone, shogaols	Flavonoids, piperine	Protection from oxidative stress
Neuroprotection	Gingerols	Piperine	Cognitive support and brain protection
Respiratory protection	Essential oils	Volatile oils	Relief from respiratory symptoms
Neurotransmitter modulation	Ginger extract	Piperine	Anxiety and depression management
Bioavailability enhancement	—	Piperine	Improved absorption of phytochemicals

## 5. Traditional Herbal Formulations and Ethnomedicinal Practices

### 5.1 Ayurvedic Formulations

#### 5.1.1 Kadha and Herbal Decoctions

Ayurveda has long utilized herbal decoctions known as “kadha” for management of respiratory infections, fever, inflammation, and immune-related disorders. During the COVID-19 pandemic, kadha formulations containing *Zingiber officinale* (ginger) and *Piper nigrum* (black pepper) became widely consumed as supportive remedies for improving immunity, respiratory health, and mental well-being (Khanna et al., 2021).

Traditional kadha preparations generally involve boiling medicinal herbs and spices in water to extract bioactive phytochemicals. Common ingredients include ginger, black pepper, tulsi (*Ocimum sanctum*), cinnamon (*Cinnamomum verum*), clove (*Syzygium aromaticum*), turmeric (*Curcuma longa*), and licorice (*Glycyrrhiza glabra*). These herbal combinations possess synergistic antiviral, anti-inflammatory, antioxidant, bronchodilatory, and immunomodulatory activities.

Ginger-containing decoctions are traditionally used to relieve cough, sore throat, fever, nausea, and respiratory congestion. Black pepper enhances circulation, mucus clearance, digestion, and absorption of herbal constituents. The warming nature of these spices is believed in Ayurveda to improve “Agni” (digestive fire) and support systemic immunity.

Scientific studies have shown that phytochemicals extracted during decoction preparation retain antioxidant and anti-inflammatory properties that may help reduce oxidative stress and cytokine-mediated tissue injury associated with COVID-19 (Baliga et al., 2011).

#### 5.1.2 Trikatu Formulation

Trikatu is a classical Ayurvedic formulation consisting of ginger (*Zingiber officinale*), black pepper (*Piper nigrum*), and long pepper (*Piper longum*). The term “Trikatu” literally means “three pungents,” reflecting the spicy nature of its ingredients. This formulation has been traditionally prescribed to improve digestion, metabolism, respiratory function, circulation, and drug absorption (Panda & Kar, 2007).

Trikatu possesses strong antioxidant, anti-inflammatory, antimicrobial, bioavailability-enhancing, and adaptogenic properties. Piperine present in black pepper and long pepper significantly improves absorption and systemic availability of phytochemicals from ginger and other medicinal herbs.

During the COVID-19 pandemic, trikatu gained attention as a supportive herbal intervention because of its respiratory protective and immune-enhancing effects. The formulation is traditionally used in cough, bronchitis, asthma, sinus congestion, indigestion, and fatigue. Experimental evidence suggests that trikatu components may modulate inflammatory cytokines and oxidative stress pathways involved in viral infections.

Furthermore, trikatu may help alleviate post-COVID fatigue, sluggish metabolism, digestive disturbances, and mental exhaustion by improving circulation and enhancing nutrient absorption.

### 5.1.3 Ginger-Black Pepper Herbal Tea

Herbal tea preparations containing ginger and black pepper are widely consumed in traditional and household medicine for improving respiratory comfort and psychological relaxation. Such teas are often prepared with honey, lemon, tulsi, cinnamon, and cardamom to enhance therapeutic effects and flavor.

Ginger tea is traditionally used for relief of sore throat, nausea, cough, fever, digestive discomfort, and fatigue. Black pepper contributes warming, stimulant, and expectorant properties that support respiratory clearance and circulation. Combined formulations may additionally exert calming and stress-reducing effects that promote emotional well-being during illness and recovery.

Studies indicate that ginger tea possesses antioxidant and anti-inflammatory activities capable of reducing oxidative stress and supporting immune function (Mashhadi et al., 2013). Warm herbal beverages may also improve hydration, throat comfort, and mucociliary clearance during respiratory infections.

The psychological benefits of herbal tea consumption should not be overlooked, as warm aromatic beverages can reduce stress perception, improve relaxation, and support sleep quality in recovering individuals.

## 5.2 Traditional Chinese and Folk Medicine Approaches

### 5.2.1 Ginger-Based Remedies for Respiratory Illnesses

In Traditional Chinese Medicine (TCM), ginger is categorized as a warming medicinal herb used to disperse cold, improve circulation, stimulate digestion, and treat respiratory disorders. Fresh ginger (*Sheng Jiang*) and dried ginger (*Gan Jiang*) are used differently based on therapeutic objectives. Fresh ginger is commonly prescribed for colds, cough, nausea, sore throat, and fever, while dried ginger is used to improve circulation and strengthen internal warmth (Li et al., 2019).

TCM formulations containing ginger have been utilized historically during outbreaks of respiratory infections and influenza-like illnesses. During the COVID-19 pandemic, ginger-containing herbal

remedies were frequently recommended as supportive therapies to reduce respiratory discomfort, improve immunity, and minimize fatigue.

Folk medicine traditions in several countries also employ ginger inhalation, steam therapy, and ginger-based beverages to relieve respiratory congestion and cough symptoms. Ginger's volatile oils and pungent compounds may help improve airway function and suppress inflammatory pathways involved in respiratory infections.

### **5.2.2 Black Pepper in Traditional Immunity-Boosting Preparations**

Black pepper has historically been regarded as a medicinal spice with stimulant, digestive, warming, and rejuvenating properties. In Ayurveda and folk medicine, black pepper is commonly incorporated into immunity-enhancing preparations, respiratory tonics, and digestive remedies.

Traditional healers often combine black pepper with honey, ginger, turmeric, and medicinal herbs to treat cough, sore throat, bronchitis, fever, and weakness. The warming action of black pepper is believed to stimulate circulation and promote detoxification through sweating and enhanced metabolism.

Piperine also enhances absorption of curcumin and other herbal phytochemicals, thereby improving therapeutic efficacy of polyherbal formulations (Shoba et al., 1998). This synergistic property has contributed significantly to the traditional use of black pepper in herbal medicine systems.

During the COVID-19 pandemic, black pepper-containing remedies became popular household interventions for improving respiratory comfort and immunity support. Although such formulations cannot replace standard medical treatment, they may provide complementary supportive benefits.

## **5.3 Household Remedies Used During COVID-19 Pandemic**

### **5.3.1 Herbal Steam Inhalation**

Steam inhalation with ginger, black pepper, eucalyptus oil, mint, or tulsi became a widely practiced home remedy during the COVID-19 pandemic. The inhalation of warm vapors containing volatile phytochemicals may help relieve nasal congestion, improve airway clearance, and provide symptomatic respiratory comfort.

Ginger volatile oils possess anti-inflammatory and antimicrobial activities, while black pepper vapors may stimulate respiratory circulation and mucus expulsion. Although steam inhalation does not cure COVID-19, it may temporarily relieve upper respiratory discomfort and throat irritation (Singh et al., 2021).

Excessive or improper steam inhalation, however, may cause burns or respiratory irritation; therefore, safe practice and medical guidance are important.

### 5.3.2 Honey-Ginger-Black Pepper Mixtures

Mixtures of honey, ginger juice, and black pepper powder have traditionally been used to relieve cough, throat irritation, fatigue, and respiratory congestion. Honey acts as a demulcent and antimicrobial agent, while ginger and black pepper provide anti-inflammatory and expectorant effects.

These preparations are commonly consumed in small quantities several times daily to support throat comfort and respiratory function. Ginger and black pepper may additionally improve digestion and circulation, which are considered important aspects of recovery in traditional medicine systems.

Several studies have highlighted the antimicrobial and antioxidant activities of honey and spice combinations, supporting their traditional therapeutic applications (Eteraf-Oskouei & Najafi, 2013).

### 5.3.3 Functional Beverages and Wellness Drinks

The pandemic increased global interest in functional beverages enriched with medicinal herbs, spices, antioxidants, and nutraceutical ingredients. Ginger-black pepper wellness drinks, herbal immunity shots, and fortified teas became commercially popular because of their perceived health benefits.

Functional beverages containing ginger and black pepper may provide antioxidant, anti-inflammatory, digestive, and stress-relieving effects. Such beverages are often combined with lemon, turmeric, tulsi, green tea, and adaptogenic herbs to improve nutritional and therapeutic value.

The growing demand for herbal wellness products highlights the increasing acceptance of integrative healthcare approaches focusing on prevention, immune resilience, and mental well-being. However, scientific validation and standardization remain essential for ensuring safety, efficacy, and quality of such products.

**Table 4. Traditional Herbal Formulations Containing Ginger and Black Pepper**

Formulation	Main Ingredients	Traditional Uses	Potential Relevance in COVID-19 Recovery
Kadha	Ginger, black pepper, tulsi, cinnamon	Fever, cough, immunity	Anti-inflammatory and respiratory support
Trikatu	Ginger, black pepper, long pepper	Digestion, metabolism, respiratory health	Bioavailability enhancement and immune support
Herbal tea	Ginger, black pepper, honey	Sore throat, stress relief	Antioxidant and calming effects
Honey-spice mixture	Honey, ginger, black pepper	Cough and throat irritation	Symptomatic respiratory relief
Steam inhalation	Ginger, black pepper oils	Nasal congestion	Airway clearance and comfort
Functional beverages	Ginger, pepper, turmeric	Wellness and immunity	Recovery and fatigue management

## 6. Experimental and Clinical Evidence Supporting the Therapeutic Potential of *Zingiber officinale* and *Piper nigrum*

### 6.1 In Vitro and In Silico Studies Against SARS-CoV-2

The emergence of COVID-19 stimulated extensive research exploring antiviral phytochemicals capable of inhibiting SARS-CoV-2 infection and replication. Computational docking studies, molecular simulations, and in vitro investigations have demonstrated promising interactions between bioactive compounds from *Zingiber officinale* and *Piper nigrum* with viral target proteins.

Several molecular docking studies have shown that ginger phytochemicals including 6-gingerol, 6-shogaol, and zingerone exhibit strong binding affinity toward SARS-CoV-2 main protease (Mpro), spike glycoprotein, and RNA-dependent RNA polymerase (RdRp), suggesting possible inhibition of viral replication and entry (Joshi et al., 2020). Similarly, piperine from *Piper nigrum* has demonstrated favorable interactions with viral proteases and ACE2 receptors involved in SARS-CoV-2 pathogenesis (Khaerunnisa et al., 2020).

In vitro antiviral studies have additionally reported that ginger extracts may inhibit respiratory viruses by preventing viral attachment and internalization into host epithelial cells (Chang et al., 2013). Piperine-containing extracts have also shown antimicrobial and antiviral activities against several viral pathogens through modulation of inflammatory and oxidative stress pathways.

Although many findings remain preliminary and largely computational, these studies provide mechanistic support for further exploration of ginger and black pepper phytochemicals as complementary antiviral agents against SARS-CoV-2.

### 6.2 Anti-Inflammatory and Antioxidant Experimental Studies

Inflammation and oxidative stress are central pathological processes in COVID-19-associated tissue injury and neurological complications. Experimental studies have consistently demonstrated potent anti-inflammatory and antioxidant effects of ginger and black pepper phytochemicals.

Gingerols and shogaols suppress inflammatory mediators including TNF- $\alpha$ , IL-1 $\beta$ , IL-6, cyclooxygenase-2 (COX-2), and nuclear factor-kappa B (NF- $\kappa$ B), thereby reducing inflammatory signaling and oxidative injury (Grzanna et al., 2005). Animal studies indicate that ginger extracts can reduce pulmonary inflammation, lipid peroxidation, and oxidative damage in respiratory disorders.

Piperine also demonstrates significant anti-inflammatory activity through inhibition of cytokine release, nitric oxide production, and immune cell activation. Experimental evidence suggests that piperine reduces oxidative stress-mediated tissue injury by increasing endogenous antioxidant enzyme levels and scavenging free radicals (Vijayakumar et al., 2004).

Combined formulations containing ginger and black pepper may exert synergistic antioxidant effects due to their complementary phytochemical composition. Such antioxidant and anti-inflammatory activities are

particularly relevant in prevention of cytokine storm, endothelial dysfunction, neuroinflammation, and post-COVID tissue damage.

### **6.3 Clinical Evidence Supporting Respiratory and Immune Benefits**

Clinical investigations and traditional therapeutic observations support the role of ginger and black pepper in improving respiratory health, immune function, and recovery from respiratory illnesses. Ginger supplementation has demonstrated beneficial effects in nausea, respiratory discomfort, inflammatory conditions, and immune modulation (Mashhadi et al., 2013).

Several clinical studies indicate that ginger may reduce airway inflammation, improve circulation, and relieve symptoms such as sore throat, cough, and congestion. Black pepper has traditionally been used as an expectorant and digestive stimulant, while piperine enhances bioavailability of co-administered therapeutic compounds.

During the COVID-19 pandemic, herbal formulations containing ginger and black pepper were widely used as supportive interventions for mild symptoms and recovery support. Observational studies suggest that traditional herbal decoctions may improve subjective well-being, reduce fatigue, and support respiratory comfort; however, robust randomized controlled trials remain limited (Khanna et al., 2021).

Clinical evidence additionally suggests that regular consumption of antioxidant-rich spices and medicinal herbs may support immune resilience and reduce susceptibility to inflammatory disorders. Nevertheless, these herbs should be considered complementary supportive therapies rather than substitutes for evidence-based medical treatment.

### **6.4 Evidence for Mental Well-Being and Cognitive Support**

Long COVID is frequently associated with neuropsychiatric symptoms including anxiety, depression, insomnia, stress, memory impairment, and cognitive dysfunction. Experimental and clinical studies suggest that ginger and black pepper phytochemicals may support mental well-being through neuroprotective, antioxidant, and neurotransmitter-modulating effects.

Ginger extracts have demonstrated memory-enhancing and cognitive-improving activities in both animal and human studies. Clinical research involving middle-aged women showed that ginger supplementation improved working memory and cognitive performance (Saenghong et al., 2012). Neuroprotective effects are believed to involve reduction of oxidative stress, suppression of neuroinflammation, and enhancement of cholinergic function.

Piperine has also shown antidepressant-like and anxiolytic activities in experimental models. Studies indicate that piperine modulates serotonin, dopamine, and gamma-aminobutyric acid (GABA) pathways while enhancing brain-derived neurotrophic factor (BDNF) expression (Mao et al., 2017). Such mechanisms may help improve mood regulation, emotional resilience, and cognitive performance in post-COVID individuals.

Additionally, antioxidant phytochemicals from ginger and black pepper may protect neural tissues against inflammatory injury and mitochondrial dysfunction associated with chronic stress and viral infections. These findings highlight the therapeutic potential of these herbs in management of post-COVID neurological and psychological complications.

### **6.5 Safety, Toxicity, and Herb–Drug Interaction Considerations**

Although ginger and black pepper are generally regarded as safe when consumed in dietary amounts, excessive intake or inappropriate use may produce adverse effects and herb–drug interactions. Common side effects associated with high doses of ginger include gastric irritation, heartburn, diarrhea, and mild gastrointestinal discomfort (Ali et al., 2008).

Piperine may alter drug metabolism by inhibiting cytochrome P450 enzymes and P-glycoprotein transporters, thereby affecting pharmacokinetics of several medications including anticoagulants, antihypertensives, anticonvulsants, and chemotherapeutic agents (Atal et al., 1985). Careful monitoring is therefore necessary when black pepper supplements are combined with prescription drugs.

Pregnant women, patients with bleeding disorders, and individuals receiving multiple medications should consult healthcare professionals before consuming concentrated herbal formulations or supplements. Standardization, dosage optimization, and quality control are essential to ensure safety and therapeutic consistency of herbal products.

The increasing commercialization of herbal products during the pandemic additionally raises concerns regarding contamination, adulteration, inaccurate labeling, and lack of clinical validation. Regulatory oversight and scientific quality assurance remain important for safe integration of herbal therapeutics into healthcare systems.

### **6.6 Limitations of Current Research**

Despite promising pharmacological and experimental findings, several limitations restrict the clinical translation of ginger and black pepper phytochemicals in COVID-19 management. Many available studies are based primarily on molecular docking, computational predictions, in vitro experiments, or animal models rather than large-scale clinical trials.

Variability in extraction methods, phytochemical composition, dosage, formulation type, and study design makes comparison of results difficult. Lack of standardized herbal preparations further complicates interpretation of efficacy and safety outcomes.

Additionally, the bioavailability and pharmacokinetic behavior of many phytochemicals remain insufficiently understood. Although piperine enhances absorption of several compounds, comprehensive clinical pharmacology studies are still limited.

Another major limitation is the absence of robust randomized controlled clinical trials evaluating the direct effectiveness of ginger- and black pepper-based formulations in COVID-19 patients and long

COVID management. Future interdisciplinary research integrating phytochemistry, pharmacology, neuroscience, nanotechnology, and clinical medicine is therefore necessary.

Well-designed clinical studies are required to establish optimal dosing strategies, therapeutic combinations, safety profiles, and mechanisms of action. Advanced formulation technologies such as nanoencapsulation and targeted delivery systems may further improve bioavailability and therapeutic efficacy of phytochemicals for neurological and inflammatory complications associated with COVID-19.

**Table 5. Experimental and Clinical Evidence Supporting Ginger and Black Pepper in COVID-19 Recovery**

Evidence Type	Key Findings	Therapeutic Relevance
Molecular docking studies	Binding to SARS-CoV-2 Mpro and ACE2	Potential antiviral activity
In vitro antiviral studies	Inhibition of respiratory viruses	Viral entry suppression
Anti-inflammatory experiments	Reduction of IL-6, TNF- $\alpha$ , NF- $\kappa$ B	Cytokine storm control
Antioxidant studies	ROS scavenging and enzyme activation	Protection against oxidative stress
Neuroprotective studies	Improved cognition and neurotransmission	Brain fog and mental fatigue management
Clinical observations	Relief in cough, sore throat, fatigue	Recovery support
Bioavailability studies	Piperine improves absorption	Enhanced therapeutic efficacy

## 7. Therapeutic Potential, Future Perspectives, and Conclusion

### 7.1 Potential as Adjunct Therapy in COVID-19 Recovery

The multifactorial nature of COVID-19 and its long-term complications necessitates therapeutic approaches capable of targeting inflammation, oxidative stress, immune dysregulation, respiratory dysfunction, and neurological impairment simultaneously. In this context, *Zingiber officinale* and *Piper nigrum* have emerged as promising complementary medicinal plants because of their broad-spectrum pharmacological activities.

Bioactive compounds such as gingerols, shogaols, zingerone, and piperine exhibit antiviral, antioxidant, anti-inflammatory, immunomodulatory, bronchodilatory, and neuroprotective properties that may support recovery from COVID-19 and long COVID syndrome (Paraiso et al., 2020). Their traditional use in respiratory disorders and immune-related illnesses further strengthens their therapeutic relevance.

As adjunct therapies, ginger- and black pepper-based formulations may help alleviate fatigue, cough, sore throat, respiratory congestion, digestive disturbances, stress, anxiety, and cognitive dysfunction. These herbs may additionally support appetite, metabolism, circulation, and immune resilience during post-viral recovery.

However, herbal interventions should be integrated carefully alongside evidence-based medical treatment and not considered replacements for antiviral drugs, vaccination, oxygen therapy, or critical care management. Clinical supervision and standardized formulations remain essential for safe and effective use.

## 7.2 Role in Long COVID and Mental Wellness Management

Long COVID has become a major healthcare challenge because of persistent neurological, psychological, and systemic symptoms experienced by recovered individuals. Brain fog, depression, anxiety, chronic fatigue, sleep disturbances, reduced concentration, and memory impairment are among the most common long-term manifestations (Premraj et al., 2022).

The neuroprotective and adaptogenic properties of ginger and black pepper may provide supportive benefits in management of these complications. Ginger phytochemicals can reduce neuroinflammation and oxidative stress while improving cognitive performance and neuronal survival. Piperine additionally modulates neurotransmitters including serotonin and dopamine, thereby supporting mood regulation and emotional stability (Mao et al., 2017).

Traditional wellness practices involving herbal teas, decoctions, and functional beverages may also contribute psychologically by promoting relaxation, hydration, comfort, and stress reduction. The holistic nature of herbal medicine, which addresses both physical and emotional health, aligns well with the multidimensional challenges of long COVID recovery.

Moreover, the antioxidant and anti-inflammatory actions of these herbs may help minimize progression of chronic neuroinflammatory conditions associated with post-viral syndromes. Their incorporation into dietary and lifestyle interventions may therefore support long-term mental well-being and quality of life.

## 7.3 Nanoformulations and Advanced Herbal Delivery Systems

One of the major limitations associated with phytochemicals is poor bioavailability, rapid metabolism, low solubility, and limited target-specific delivery. Recent advances in nanotechnology and phytopharmaceutical sciences offer innovative strategies for enhancing therapeutic efficacy of herbal compounds.

Nanoformulations such as liposomes, phytosomes, nanoemulsions, solid lipid nanoparticles, polymeric nanoparticles, and nanogels can improve stability, absorption, controlled release, and tissue targeting of phytochemicals from ginger and black pepper (Chavda et al., 2022).

Piperine itself functions as a natural bioenhancer and may further improve bioavailability of encapsulated phytochemicals. Nanoencapsulation of gingerols and piperine may enhance penetration across biological barriers including the blood–brain barrier, thereby improving neuroprotective and anti-inflammatory efficacy.

Nanotechnology-based delivery systems also provide opportunities for development of inhalable formulations, targeted antiviral therapies, and multifunctional nutraceutical products for management of COVID-19-related complications. Nevertheless, extensive toxicological evaluation and clinical validation are necessary before large-scale therapeutic application.

#### 7.4 Challenges in Standardization and Clinical Validation

Despite promising pharmacological evidence, several challenges limit the integration of herbal therapeutics into mainstream COVID-19 management. One major concern is variability in phytochemical composition due to differences in cultivation conditions, geographical origin, harvesting methods, extraction techniques, and storage practices (Ekor, 2014).

Lack of standardization may result in inconsistent therapeutic outcomes and difficulties in comparing scientific studies. Herbal formulations often contain complex mixtures of phytochemicals whose synergistic and pharmacokinetic interactions remain insufficiently understood.

Another important challenge is the limited availability of large-scale randomized controlled clinical trials evaluating efficacy and safety of ginger- and black pepper-based interventions specifically in COVID-19 patients. Many current findings are derived from *in vitro* studies, animal experiments, or traditional therapeutic observations.

Potential herb–drug interactions must also be considered carefully, especially because piperine can influence metabolism and absorption of pharmaceutical drugs. Regulatory oversight, quality assurance, dosage standardization, and pharmacovigilance are therefore essential for safe therapeutic integration.

#### 7.5 Future Research Directions

Future research should focus on multidisciplinary approaches integrating phytochemistry, molecular biology, neuroscience, pharmacology, nanotechnology, and clinical medicine. Advanced experimental studies are required to better understand molecular mechanisms through which ginger and black pepper phytochemicals influence viral replication, neuroinflammation, oxidative stress, and immune modulation.

Large-scale clinical trials evaluating standardized herbal formulations in COVID-19 recovery and long COVID management are urgently needed. Such studies should assess cognitive function, fatigue, mental health outcomes, respiratory recovery, inflammatory biomarkers, and quality of life parameters.

Research on synergistic interactions between ginger, black pepper, and other medicinal plants may additionally facilitate development of optimized polyherbal formulations. Novel delivery systems such as nanoparticle-based formulations, transdermal systems, and intranasal preparations may improve therapeutic targeting and patient compliance.

Furthermore, systems biology, network pharmacology, and artificial intelligence-based drug discovery approaches may help identify new phytochemical targets and optimize herbal therapeutic strategies for viral and neurodegenerative disorders.

## 7.6 Conclusion

The COVID-19 pandemic highlighted the urgent need for safe, accessible, and multifunctional therapeutic approaches capable of addressing both acute infection and long-term health complications. Traditional medicinal plants such as *Zingiber officinale* and *Piper nigrum* possess significant pharmacological potential because of their antiviral, antioxidant, anti-inflammatory, immunomodulatory, respiratory protective, and neuroprotective activities.

Bioactive phytochemicals including gingerols, shogaols, zingerone, and piperine may help reduce oxidative stress, cytokine-mediated inflammation, respiratory discomfort, cognitive dysfunction, and psychological stress associated with COVID-19 and long COVID syndrome. Traditional herbal formulations such as kadha, trikatu, herbal teas, and wellness beverages continue to play supportive roles in integrative healthcare practices worldwide.

Although current experimental and preliminary clinical findings are promising, robust scientific validation through standardized clinical trials remains necessary. Advances in nanotechnology and phytopharmaceutical sciences may further improve therapeutic delivery and efficacy of herbal compounds.

Overall, *Zingiber officinale* and *Piper nigrum* represent valuable complementary medicinal resources with potential applications in COVID-19 recovery, neuroprotection, immune support, and mental well-being. Integration of traditional medicinal knowledge with modern scientific research may contribute significantly to development of future evidence-based herbal therapeutics for infectious and neuroinflammatory diseases.

## References

- Ahmad, N., Fazal, H., Abbasi, B. H., Farooq, S., Ali, M., & Khan, M. A. (2012). Biological role of *Piper nigrum* L. (Black pepper): A review. *Asian Pacific Journal of Tropical Biomedicine*, 2(3), S1945–S1953.
- Ali, B. H., Blunden, G., Tanira, M. O., & Nemmar, A. (2008). Some phytochemical, pharmacological and toxicological properties of ginger (*Zingiber officinale* Roscoe): A review of recent research. *Food and Chemical Toxicology*, 46(2), 409–420.
- Atal, C. K., Dubey, R. K., & Singh, J. (1985). Biochemical basis of enhanced drug bioavailability by piperine: Evidence that piperine is a potent inhibitor of drug metabolism. *Journal of Pharmacology and Experimental Therapeutics*, 232(1), 258–262.
- Baliga, M. S., Haniadka, R., Pereira, M. M., Dsouza, J. J., Pallaty, P. L., Bhat, H. P., & Popuri, S. (2011). Update on the chemopreventive effects of ginger and its phytochemicals. *Critical Reviews in Food Science and Nutrition*, 51(6), 499–523.
- Becker, J. H., Lin, J. J., Doernberg, M., Stone, K., Navis, A., Festa, J. R., & Wisnivesky, J. P. (2021). Assessment of cognitive function in patients after COVID-19 infection. *JAMA Network Open*, 4(10), e2130645.

- Boldrini, M., Canoll, P. D., & Klein, R. S. (2021). How COVID-19 affects the brain. *JAMA Psychiatry*, 78(6), 682–683.
- Cecchini, R., & Cecchini, A. L. (2020). SARS-CoV-2 infection pathogenesis is related to oxidative stress as a response to aggression. *Medical Hypotheses*, 143, 110102.
- Chacko, S. M., Thambi, P. T., Kuttan, R., & Nishigaki, I. (2010). Beneficial effects of green tea: A literature review. *Chinese Medicine*, 5(13), 1–9.
- Chang, J. S., Wang, K. C., Yeh, C. F., Shieh, D. E., & Chiang, L. C. (2013). Fresh ginger (*Zingiber officinale*) has anti-viral activity against human respiratory syncytial virus in human respiratory tract cell lines. *Journal of Ethnopharmacology*, 145(1), 146–151.
- Chavda, V. P., Vihol, D., Mehta, B., Shah, D., Patel, M., Vora, L. K., & Pereira-Silva, M. (2022). Phytochemical-loaded nanocarriers for management of COVID-19 and associated complications. *Materials Today Chemistry*, 23, 100670.
- Del Valle, D. M., Kim-Schulze, S., Huang, H. H., Beckmann, N. D., Nirenberg, S., Wang, B., & Gnjjatic, S. (2020). An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nature Medicine*, 26(10), 1636–1643.
- Delgado-Roche, L., & Mesta, F. (2020). Oxidative stress as key player in severe acute respiratory syndrome coronavirus infection. *Archives of Medical Research*, 51(5), 384–387.
- Dugasani, S., Pichika, M. R., Nadarajah, V. D., Balijepalli, M. K., Tandra, S., & Korlakunta, J. N. (2010). Comparative antioxidant and anti-inflammatory effects of [6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol. *Journal of Ethnopharmacology*, 127(2), 515–520.
- Ekor, M. (2014). The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. *Frontiers in Pharmacology*, 4, 177.
- Ellul, M. A., Benjamin, L., Singh, B., Lant, S., Michael, B. D., Easton, A., & Solomon, T. (2020). Neurological associations of COVID-19. *The Lancet Neurology*, 19(9), 767–783.
- Eteraf-Oskouei, T., & Najafi, M. (2013). Traditional and modern uses of natural honey in human diseases: A review. *Iranian Journal of Basic Medical Sciences*, 16(6), 731–742.
- Fajgenbaum, D. C., & June, C. H. (2020). Cytokine storm. *New England Journal of Medicine*, 383(23), 2255–2273.
- Ghayur, M. N., & Gilani, A. H. (2005). Ginger lowers blood pressure through blockade of voltage-dependent calcium channels. *Journal of Cardiovascular Pharmacology*, 45(1), 74–80.
- Grzanna, R., Lindmark, L., & Frondoza, C. G. (2005). Ginger—An herbal medicinal product with broad anti-inflammatory actions. *Journal of Medicinal Food*, 8(2), 125–132.
- Gupta, A., Madhavan, M. V., Sehgal, K., Nair, N., Mahajan, S., Sehrawat, T. S., & Landry, D. W. (2020). Extrapulmonary manifestations of COVID-19. *Nature Medicine*, 26(7), 1017–1032.
- Heneka, M. T., Golenbock, D., Latz, E., Morgan, D., & Brown, R. (2020). Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. *Alzheimer's Research & Therapy*, 12(1), 69.

- Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., & Pöhlmann, S. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2. *Cell*, *181*(2), 271–280.e8.
- Hosseini, A., & Mirazi, N. (2015). Acute administration of ginger extract on timed serial learning and memory processing in healthy middle-aged women: A randomized double-blind placebo-controlled study. *Evidence-Based Complementary and Alternative Medicine*, *2015*, 478505.
- Jahan, I., Onay, A., Pottou, F. H., & Javed, M. N. (2021). Phytomedicines and COVID-19: Therapeutic possibilities and challenges. *Current Pharmaceutical Biotechnology*, *22*(15), 1967–1985.
- Joshi, T., Joshi, T., Sharma, P., Mathpal, S., Pundir, H., Bhatt, V., & Chandra, S. (2020). In silico screening of natural compounds against COVID-19 by targeting Mpro and ACE2 using molecular docking. *European Review for Medical and Pharmacological Sciences*, *24*(8), 4529–4536.
- Khaerunnisa, S., Kurniawan, H., Awaluddin, R., Suhartati, S., & Soetjipto, S. (2020). Potential inhibitor of COVID-19 main protease (Mpro) from several medicinal plant compounds by molecular docking study. *Preprints*, 2020030226.
- Khanna, K., Kohli, S. K., Kaur, R., Bhardwaj, A., Bhardwaj, V., Ohri, P., & Ahmad, P. (2021). Herbal immune-boosters: Substantial warriors of pandemic COVID-19 battle. *Phytomedicine*, *85*, 153361.
- Khan, N., & Mukhtar, H. (2018). Tea polyphenols in promotion of human health. *Nutrients*, *11*(1), 39.
- Kharwar, R. N., Upadhyay, R., Dubey, N. K., & Raghuwanshi, R. (2020). Perspectives of medicinal plants in management of COVID-19. *3 Biotech*, *10*(10), 1–10.
- Kumar, S., Kamboj, J., Suman, & Sharma, S. (2011). Overview for various aspects of the health benefits of *Piper longum* Linn. fruit. *Journal of Acupuncture and Meridian Studies*, *4*(2), 134–140.
- Li, S., Yuan, W., Deng, G., Wang, P., Yang, P., & Aggarwal, B. B. (2019). Chemical composition and product quality control of ginger (*Zingiber officinale* Roscoe). *Pharmaceutical Crops*, *2*(1), 28–54.
- Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., & Hu, B. (2020). Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurology*, *77*(6), 683–690.
- Mao, Q. Q., Huang, Z., Ip, S. P., & Che, C. T. (2017). Antidepressant-like effect of piperine in chronic mild stress treated mice and its possible mechanisms. *Life Sciences*, *91*(15–16), 117–122.
- Mao, Q. Q., Huang, Z., Ip, S. P., Xian, Y. F., & Che, C. T. (2019). Protective effects of piperine against stress-related disorders. *Phytotherapy Research*, *33*(5), 1235–1244.
- Mashhadi, N. S., Ghiasvand, R., Askari, G., Hariri, M., Darvishi, L., & Mofid, M. R. (2013). Anti-oxidative and anti-inflammatory effects of ginger in health and physical activity:

- Review of current evidence. *International Journal of Preventive Medicine*, 4(Suppl. 1), S36–S42.
- Meghwal, M., & Goswami, T. K. (2013). *Piper nigrum* and piperine: An update. *Phytotherapy Research*, 27(8), 1121–1130.
  - Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., & Manson, J. J. (2020). COVID-19: Consider cytokine storm syndromes and immunosuppression. *The Lancet*, 395(10229), 1033–1034.
  - Panda, H., & Kar, A. (2007). Trikatu—A traditional Ayurvedic formulation. *Asian Agri-History*, 11(4), 299–306.
  - Paraiso, I. L., Revel, J. S., & Stevens, J. F. (2020). Potential use of polyphenols in the battle against COVID-19. *Current Opinion in Food Science*, 32, 149–155.
  - Premraj, L., Kannapadi, N. V., Briggs, J., Seal, S. M., Battaglini, D., Fanning, J., & Fraser, J. F. (2022). Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome: A meta-analysis. *Journal of the Neurological Sciences*, 434, 120162.
  - Rahmani, A. H., Al Shabrmi, F. M., & Aly, S. M. (2014). Active ingredients of ginger as potential candidates in the prevention and treatment of diseases via modulation of biological activities. *International Journal of Physiology, Pathophysiology and Pharmacology*, 6(2), 125–136.
  - Rajagopal, K., Varakumar, P., Baliwada, A., & Byran, G. (2020). Activity of phytochemical constituents of black pepper, ginger, and garlic against coronavirus (COVID-19): An in silico approach. *International Journal of Health Sciences and Research*, 10(6), 43–50.
  - Saenghong, N., Wattanathorn, J., Muchimapura, S., Tong-Un, T., Piyavhatkul, N., Banchonglikitkul, C., & Phachonpai, W. (2012). *Zingiber officinale* improves cognitive function of the middle-aged healthy women. *Evidence-Based Complementary and Alternative Medicine*, 2012, 383062.
  - Semwal, R. B., Semwal, D. K., Combrinck, S., & Viljoen, A. M. (2015). Gingerols and shogaols: Important nutraceutical principles from ginger. *Phytochemistry*, 117, 554–568.
  - Shoba, G., Joy, D., Joseph, T., Majeed, M., Rajendran, R., & Srinivas, P. S. R. (1998). Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Medica*, 64(4), 353–356.
  - Siddiqui, S., Hafeez, A., Khan, A., & Khan, M. I. (2022). Herbal approaches in the management of COVID-19-associated neurological complications. *Journal of Herbal Medicine*, 32, 100530.
  - Singh, N., Sharma, B., & Sharma, R. (2021). Herbal remedies and supportive care strategies during COVID-19 pandemic. *Journal of Herbal Medicine*, 28, 100438.
  - Song, E., Zhang, C., Israelow, B., Lu-Culligan, A., Prado, A. V., Skriabine, S., & Iwasaki, A. (2021). Neuroinvasion of SARS-CoV-2 in human and mouse brain. *Journal of Experimental Medicine*, 218(3), e20202135.
  - Stoilova, I., Krastanov, A., Stoyanova, A., Denev, P., & Gargova, S. (2007). Antioxidant activity of a ginger extract (*Zingiber officinale*). *Food Chemistry*, 102(3), 764–770.

- Taquet, M., Geddes, J. R., Husain, M., Luciano, S., & Harrison, P. J. (2021). 6-month neurological and psychiatric outcomes in 236,379 survivors of COVID-19. *The Lancet Psychiatry*, 8(5), 416–427.
- Tasleem, F., Azhar, I., Ali, S. N., Perveen, S., & Mahmood, Z. A. (2014). Analgesic and anti-inflammatory activities of *Piper nigrum* L. *Asian Pacific Journal of Tropical Medicine*, 7(Suppl. 1), S461–S468.
- Thuy, B. T. P., My, T. T. A., Hai, N. T. T., Hieu, L. T., Hoa, T. T., Thi Phuong Loan, H., & Nhung, N. T. A. (2020). Investigation into SARS-CoV-2 resistance of compounds in garlic essential oil. *ACS Omega*, 5(14), 8312–8320.
- Troyer, E. A., Kohn, J. N., & Hong, S. (2020). Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? *Brain, Behavior, and Immunity*, 87, 34–39.
- V'kovski, P., Kratzel, A., Steiner, S., Stalder, H., & Thiel, V. (2021). Coronavirus biology and replication: Implications for SARS-CoV-2. *Nature Reviews Microbiology*, 19(3), 155–170.
- Vijayakumar, R. S., Surya, D., & Nalini, N. (2004). Antioxidant efficacy of black pepper (*Piper nigrum* L.) and piperine in rats with high fat diet induced oxidative stress. *Redox Report*, 9(2), 105–110.
- World Health Organization. (2023). *WHO coronavirus (COVID-19) dashboard*. Geneva, Switzerland: World Health Organization.
- Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., & Tan, W. (2020). A novel coronavirus from patients with pneumonia in China, 2019. *New England Journal of Medicine*, 382(8), 727–733.

## Chapter 8: Role of Nutraceutical Herbs *Phyllanthus emblica* and *Allium sativum* in Immunity Enhancement and Mental Health Support During COVID-19

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### Abstract

The coronavirus disease 2019 (COVID-19) pandemic has created unprecedented challenges to global healthcare systems by affecting not only respiratory health but also immune, neurological, and psychological functions. Increasing evidence indicates that SARS-CoV-2 infection induces immune dysregulation, cytokine storm, oxidative stress, neuroinflammation, anxiety, depression, and cognitive impairment in affected individuals. In this context, nutraceutical herbs possessing immunomodulatory, antiviral, antioxidant, and neuroprotective properties have gained considerable scientific attention as supportive therapeutic agents. *Phyllanthus emblica* (Amla) and *Allium sativum* (Garlic) are two traditionally valued medicinal plants widely utilized in Ayurveda and complementary medicine for enhancing immunity and promoting overall health. *Phyllanthus emblica* is rich in vitamin C, emblicanins, gallic acid, ellagic acid, flavonoids, and tannins, which contribute to its strong antioxidant, anti-inflammatory, and immunostimulatory activities. Similarly, *Allium sativum* contains biologically active sulfur compounds such as allicin, alliin, and ajoene that exhibit potent antiviral, antimicrobial, cardioprotective, and immunomodulatory effects. Experimental and computational studies suggest that phytochemicals from these herbs may interfere with SARS-CoV-2 entry and replication pathways, reduce inflammatory cytokines, and protect tissues against oxidative injury. Furthermore, both herbs demonstrate neuroprotective potential through modulation of neurotransmitter systems, reduction of neuroinflammation, and attenuation of stress-induced neuronal damage. This chapter comprehensively discusses the phytochemical composition, traditional medicinal importance, immunomodulatory mechanisms, antiviral potential, and mental health-supportive roles of *Phyllanthus emblica* and *Allium sativum* during COVID-19. The chapter also highlights their therapeutic applications in nutraceutical formulations, dietary supplements, and integrative healthcare strategies. Additionally, challenges related to standardization, dosage optimization, safety, and clinical validation are critically examined. The available evidence suggests that these nutraceutical herbs may serve as valuable adjunctive agents for improving immune resilience and mental well-being during and after COVID-19 infection. However, further clinical and translational studies are necessary to establish their efficacy and safety in evidence-based therapeutic practice.

### Keywords

COVID-19; SARS-CoV-2; *Phyllanthus emblica*; *Allium sativum*; Amla; Garlic; Nutraceuticals; Immunomodulation; Neuroprotection; Mental health; Cytokine storm; Oxidative stress; Antiviral herbs; Herbal medicine; Phytochemicals

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## 1. Introduction

The emergence of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), resulted in one of the most devastating global public health crises in modern history. The outbreak was first identified in Wuhan, China, in late 2019 and rapidly spread worldwide due to the highly transmissible nature of the virus (Zhu et al., 2020). The World Health Organization (WHO) officially declared COVID-19 a pandemic in March 2020, and since then millions of individuals have been infected globally, leading to substantial morbidity, mortality, social disruption, and economic instability (World Health Organization [WHO], 2023). Although SARS-CoV-2 primarily affects the respiratory system, increasing evidence demonstrates that COVID-19 is a multisystemic disease involving cardiovascular, neurological, gastrointestinal, renal, and immunological complications (Gupta et al., 2020). The large-scale burden on healthcare systems and the persistence of post-COVID complications have intensified the search for safe and effective supportive therapeutic approaches.

SARS-CoV-2 enters host cells mainly through interaction between the viral spike glycoprotein and angiotensin-converting enzyme 2 (ACE2) receptors present on epithelial and endothelial cells (Hoffmann et al., 2020). Following viral entry and replication, infected individuals may develop dysregulated immune responses characterized by excessive release of inflammatory mediators and cytokines. In severe COVID-19 cases, uncontrolled production of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin-1 $\beta$  (IL-1 $\beta$ ) leads to a phenomenon known as “cytokine storm” (Mehta et al., 2020). This hyperinflammatory response contributes to acute respiratory distress syndrome (ARDS), tissue injury, endothelial dysfunction, oxidative stress, coagulation abnormalities, and multiorgan failure (Fajgenbaum & June, 2020). Studies have shown that oxidative stress and immune imbalance play major roles in worsening disease severity and promoting long-term pathological consequences (Cecchini & Cecchini, 2020). Therefore, therapeutic strategies capable of regulating immune responses and reducing oxidative damage are considered highly valuable in COVID-19 management.

Apart from respiratory manifestations, COVID-19 is strongly associated with neurological and neuropsychiatric complications. Clinical studies have reported symptoms including headache, dizziness, anosmia, ageusia, confusion, encephalopathy, stroke, seizures, cognitive dysfunction, depression, anxiety, and sleep disturbances among infected individuals (Ellul et al., 2020; Mao et al., 2020). Emerging evidence suggests that SARS-CoV-2 may affect the central nervous system either directly through neuroinvasion or indirectly via systemic inflammation, cytokine-mediated neuronal injury, and blood-brain barrier disruption (Song et al., 2021). Persistent neuroinflammation and immune activation may contribute to “brain fog,” impaired memory, reduced concentration, and psychiatric disturbances observed in post-COVID syndrome (Premraj et al., 2022). Furthermore, social isolation, fear of infection, financial insecurity, and prolonged stress during the pandemic have significantly increased the prevalence of anxiety and depressive disorders worldwide (Troyer et al., 2020). These findings indicate that comprehensive COVID-19 management should not only target viral replication but also address immune dysfunction and mental health complications.

In recent years, nutraceutical herbs and traditional medicinal plants have gained considerable attention as supportive interventions during the COVID-19 pandemic. Nutraceuticals are bioactive natural products

that provide health benefits beyond basic nutrition and may contribute to disease prevention and immune enhancement. Medicinal herbs rich in antioxidants, polyphenols, flavonoids, vitamins, sulfur compounds, and immunomodulatory phytochemicals are increasingly being explored for their antiviral and neuroprotective activities (Jahan et al., 2021). Herbal medicines may help strengthen innate and adaptive immunity, reduce inflammatory cytokines, improve antioxidant defenses, and protect against stress-related neurological complications (Paraiso et al., 2020). Additionally, several phytochemicals have shown promising inhibitory effects against SARS-CoV-2 targets such as ACE2 receptors, main protease (Mpro), and viral replication enzymes in molecular docking and experimental studies (Kharwar et al., 2020). Consequently, nutraceutical herbs have emerged as important complementary approaches for improving resilience against viral infections and supporting post-COVID recovery.

Among various medicinal plants, *Phyllanthus emblica* (Amla) and *Allium sativum* (Garlic) have attracted significant scientific interest because of their extensive pharmacological properties and long history of traditional use. *Phyllanthus emblica* is widely utilized in Ayurveda as a rejuvenating herb and is recognized for its exceptionally high vitamin C content, antioxidant potential, and immunomodulatory activity. The fruit contains important phytochemicals such as emblicanins, gallic acid, ellagic acid, flavonoids, and tannins that exhibit anti-inflammatory, antiviral, and neuroprotective effects. Similarly, *Allium sativum* is one of the most extensively studied medicinal herbs due to the presence of bioactive sulfur compounds including allicin, alliin, ajoene, and diallyl sulfides, which possess antimicrobial, antiviral, antioxidant, cardioprotective, and immune-enhancing properties (Rahman, 2007). Garlic has also demonstrated beneficial effects on inflammatory regulation, oxidative stress reduction, and mental health support. Both herbs possess strong nutraceutical value and are commonly consumed as dietary supplements, functional foods, and traditional remedies. Their multitarget therapeutic properties make them promising candidates for supportive management of COVID-19-related immune and neurological complications.

## 2. Botanical Profile and Traditional Medicinal Importance

Medicinal plants have played a central role in traditional healthcare systems for centuries and continue to provide valuable therapeutic agents for the prevention and management of infectious and inflammatory diseases. Among nutraceutical herbs, *Phyllanthus emblica* (Amla) and *Allium sativum* (Garlic) are widely recognized for their immunomodulatory, antioxidant, antimicrobial, and neuroprotective properties. Both plants are extensively utilized in Ayurveda, Traditional Chinese Medicine, and folk medicine for promoting vitality, resistance against infections, and overall well-being (Baliga & Dsouza, 2011; Bayan et al., 2014). Their rich phytochemical composition and broad pharmacological activities have generated considerable interest for supportive applications during the COVID-19 pandemic.

### 2.1 *Phyllanthus emblica* (Amla)

*Phyllanthus emblica* L., commonly known as Amla or Indian gooseberry, belongs to the family Phyllanthaceae. It is a medium-sized deciduous tree widely distributed throughout tropical and subtropical regions of India, Southeast Asia, and China. The fruit of Amla is spherical, greenish-yellow, and highly valued for its exceptional nutritional and medicinal properties. In Ayurveda, Amla is

considered a “Rasayana” herb, meaning a rejuvenating agent capable of promoting longevity, immunity, cognitive health, and tissue regeneration (Krishnaveni & Mirunalini, 2010).

Traditionally, Amla has been used for the treatment of respiratory disorders, digestive disturbances, fever, inflammation, liver dysfunction, diabetes, and cardiovascular diseases. Ayurvedic formulations such as Triphala and Chyawanprash extensively incorporate Amla due to its adaptogenic and immunoprotective effects (Scartezzini & Speroni, 2000). The fruit is particularly rich in vitamin C, tannins, polyphenols, flavonoids, gallic acid, and emblicanins, which collectively contribute to its potent antioxidant activity. Studies have demonstrated that Amla exhibits antiviral, antimicrobial, anti-inflammatory, hepatoprotective, and neuroprotective activities through modulation of oxidative stress and inflammatory pathways (Dasaroju & Gottumukkala, 2014).

Recent scientific investigations have highlighted the potential role of Amla in enhancing innate and adaptive immune responses. Its antioxidant phytochemicals help reduce reactive oxygen species (ROS), suppress inflammatory mediators, and improve cellular defense mechanisms. Such properties may be beneficial in reducing immune dysregulation and oxidative stress associated with SARS-CoV-2 infection (Variya et al., 2016). Moreover, Amla has demonstrated beneficial effects on cognitive performance and neuronal protection through inhibition of lipid peroxidation and enhancement of endogenous antioxidant enzymes.

## 2.2 *Allium sativum* (Garlic)

*Allium sativum* L., commonly known as garlic, belongs to the family Amaryllidaceae and is one of the oldest cultivated medicinal plants in human history. Garlic is extensively grown worldwide and has been traditionally used for culinary, medicinal, and spiritual purposes. The bulb of garlic contains numerous sulfur-containing compounds responsible for its characteristic aroma and therapeutic effects (Bayan et al., 2014).

Historically, garlic has been employed for the treatment of respiratory infections, hypertension, digestive disorders, parasitic diseases, and cardiovascular abnormalities. Traditional medical systems have recommended garlic for enhancing resistance against infections and improving circulatory health. Ancient Egyptian, Greek, Chinese, and Ayurvedic texts describe garlic as a powerful natural remedy possessing antimicrobial and rejuvenating properties (Rivlin, 2001).

The pharmacological activities of garlic are primarily attributed to organosulfur compounds such as allicin, alliin, ajoene, diallyl sulfide, and diallyl disulfide. These compounds exhibit broad-spectrum antimicrobial, antiviral, antioxidant, anti-inflammatory, and cardioprotective properties (Borlinghaus et al., 2014). Allicin, produced enzymatically when garlic cloves are crushed, has demonstrated inhibitory effects against bacteria, fungi, and viruses through interference with microbial enzymes and oxidative pathways.

In the context of COVID-19, garlic has gained considerable attention due to its immunomodulatory and antiviral activities. Experimental studies suggest that garlic-derived compounds may interfere with viral entry and replication while also reducing inflammatory cytokines involved in cytokine storm syndrome

(Donma & Donma, 2020). Garlic also exhibits antioxidant properties capable of protecting tissues against oxidative injury induced by excessive immune activation. Furthermore, several studies indicate that garlic may contribute to mental well-being by reducing neuroinflammation, improving cerebral circulation, and modulating neurotransmitter balance.

### 2.3 Comparative Ethnomedicinal and Pharmacological Relevance

Both *Phyllanthus emblica* and *Allium sativum* possess extensive ethnopharmacological importance and are commonly consumed as nutraceuticals and functional foods. While Amla is especially valued for its antioxidant richness and rejuvenating properties, garlic is predominantly recognized for its antimicrobial and cardiovascular benefits. Nevertheless, both herbs share common pharmacological actions including immunomodulatory, anti-inflammatory, antiviral, antioxidant, and neuroprotective effects.

Their traditional use during infectious outbreaks and respiratory illnesses provides a strong basis for scientific evaluation against COVID-19-related complications. Additionally, the multitarget therapeutic actions of their phytochemicals make them suitable candidates for integrative healthcare approaches aimed at improving immunity and psychological resilience during pandemics.

**Table 1. Comparative Botanical and Traditional Medicinal Profile of *Phyllanthus emblica* and *Allium sativum***

Parameter	<i>Phyllanthus emblica</i> (Amla)	<i>Allium sativum</i> (Garlic)
Family	Phyllanthaceae	Amaryllidaceae
Common Names	Amla, Indian Gooseberry	Garlic
Plant Part Used	Fruit	Bulb
Traditional System	Ayurveda, Siddha, Unani	Ayurveda, Traditional Chinese Medicine, Folk medicine
Major Traditional Uses	Rejuvenation, immunity enhancement, digestion, respiratory support	Antimicrobial, cardiovascular support, respiratory infections
Major Bioactive Compounds	Vitamin C, emblicanins, gallic acid, ellagic acid	Allicin, alliin, ajoene, diallyl sulfides
Antioxidant Activity	Very high due to polyphenols and tannins	Strong antioxidant sulfur compounds
Immunomodulatory Effects	Enhances immune defense and antioxidant enzymes	Regulates cytokines and immune activation
Neuroprotective Potential	Reduces oxidative neuronal damage	Improves circulation and reduces neuroinflammation
Relevance in COVID-19	Oxidative stress reduction and immune support	Antiviral and anti-inflammatory activity

### 3. Phytochemical Composition of *Phyllanthus emblica* and *Allium sativum*

The therapeutic potential of medicinal herbs largely depends on their phytochemical composition and biological activities. *Phyllanthus emblica* and *Allium sativum* contain diverse classes of bioactive constituents including polyphenols, flavonoids, tannins, sulfur-containing compounds, alkaloids, vitamins, and essential oils. These phytochemicals exhibit significant antioxidant, antiviral, anti-inflammatory, immunomodulatory, and neuroprotective properties that may help counteract SARS-CoV-2-induced immune dysfunction and neurological complications (Akhtar et al., 2011; Banerjee & Maulik, 2002). Scientific investigations have demonstrated that many of these compounds regulate oxidative stress pathways, inflammatory mediators, and cellular signaling systems associated with viral infections and neurodegeneration.

#### 3.1 Major Phytochemicals of *Phyllanthus emblica*

The fruit of *Phyllanthus emblica* is recognized as one of the richest natural sources of vitamin C and hydrolysable tannins. Its pharmacological activities are primarily attributed to emblicanins, gallic acid, ellagic acid, quercetin, kaempferol, and various polyphenolic compounds (Gaire & Subedi, 2014). These compounds contribute to strong antioxidant activity capable of scavenging free radicals and protecting biological systems against oxidative damage.

Among the major constituents, emblicanin A and emblicanin B are highly potent antioxidant tannins that enhance endogenous antioxidant defense systems. These compounds increase the activity of catalase, superoxide dismutase, and glutathione peroxidase, thereby reducing oxidative stress-induced cellular injury (Suryanarayana et al., 2007). Since oxidative stress is a critical factor in COVID-19-associated inflammation and tissue damage, emblicanins may help mitigate pathological complications associated with SARS-CoV-2 infection.

Gallic acid and ellagic acid are important phenolic acids present in Amla that exhibit antiviral, anti-inflammatory, antimicrobial, and neuroprotective properties. Experimental studies indicate that gallic acid suppresses inflammatory cytokines such as IL-6 and TNF- $\alpha$  and inhibits lipid peroxidation pathways involved in neuroinflammation (Yang et al., 2014). Quercetin, another important flavonoid in Amla, has attracted considerable attention due to its potential antiviral activity against SARS-CoV-2. Molecular docking studies suggest that quercetin may interact with viral proteases and ACE2 receptors, thereby interfering with viral entry and replication mechanisms (Abian et al., 2020).

Amla also contains flavonoids, pectin, amino acids, and minerals that collectively contribute to immunostimulatory and adaptogenic effects. The synergistic interaction among these phytochemicals enhances the overall therapeutic potential of the plant in infectious and inflammatory disorders.

#### 3.2 Major Phytochemicals of *Allium sativum*

The medicinal value of garlic is primarily attributed to sulfur-containing bioactive compounds generated during enzymatic conversion processes. Intact garlic bulbs contain alliin, a sulfur amino acid derivative, which is converted into allicin by the enzyme alliinase when garlic is crushed or chopped (Amagase,

2006). Allicin is highly unstable but exhibits potent antimicrobial, antiviral, antioxidant, and anti-inflammatory properties.

Allicin has been widely investigated for its antiviral effects against influenza viruses, herpes simplex virus, rhinovirus, and coronaviruses. It acts by inhibiting viral replication enzymes, interfering with thiol-containing proteins, and modulating immune responses (Rouf et al., 2020). Computational studies have suggested that allicin and related organosulfur compounds may bind to SARS-CoV-2 main protease (Mpro) and ACE2 receptors, thereby potentially reducing viral infectivity (Thuy et al., 2020).

Garlic also contains ajoene, diallyl sulfide, diallyl disulfide, diallyl trisulfide, and S-allyl cysteine, which contribute to antioxidant and cardioprotective activities. These compounds reduce reactive oxygen species generation and suppress inflammatory mediators such as NF- $\kappa$ B and cyclooxygenase pathways (Arreola et al., 2015). Because severe COVID-19 is characterized by excessive inflammatory responses and oxidative injury, garlic phytochemicals may help attenuate cytokine-mediated tissue damage.

In addition to antiviral and immunomodulatory activities, garlic-derived compounds possess neuroprotective potential. S-allyl cysteine has been shown to improve neuronal survival, inhibit oxidative neuronal damage, and reduce neuroinflammation in experimental models (Chauhan, 2006). Such properties may be beneficial in preventing cognitive impairment and neurological complications associated with post-COVID syndrome.

### 3.3 Pharmacological Significance of Phytochemicals in COVID-19 and Mental Health

The phytochemicals present in *Phyllanthus emblica* and *Allium sativum* exert multitarget biological effects relevant to COVID-19 management. Polyphenols and flavonoids act as powerful antioxidants capable of neutralizing reactive oxygen species generated during viral infections. Organosulfur compounds and tannins regulate inflammatory signaling pathways and suppress cytokine overproduction associated with severe COVID-19 (Mrityunjaya et al., 2020).

Several phytochemicals from these plants also influence neurochemical pathways involved in mood regulation and cognitive function. Antioxidant compounds help preserve neuronal integrity, enhance mitochondrial function, and reduce neuroinflammation linked to anxiety, depression, and cognitive dysfunction. Furthermore, immunomodulatory effects of these herbs may indirectly improve mental well-being by reducing systemic inflammation and stress-related immune disturbances.

The synergistic action of multiple phytochemicals makes these herbs promising nutraceutical candidates for integrative approaches targeting immune resilience, viral inhibition, and neurological protection during and after COVID-19 infection.

**Table 2. Major Phytochemicals of *Phyllanthus emblica* and *Allium sativum* and Their Pharmacological Activities**

Plant	Major Phytochemicals	Chemical Class	Major Pharmacological	Relevance to COVID-19
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			Activities	
<i>Phyllanthus emblica</i>	Emblicanin A & B	Hydrolysable tannins	Antioxidant, anti-aging	Reduces oxidative stress and tissue injury
<i>Phyllanthus emblica</i>	Gallic acid	Phenolic acid	Anti-inflammatory, antiviral	Suppresses cytokines and inflammation
<i>Phyllanthus emblica</i>	Ellagic acid	Polyphenol	Antioxidant, neuroprotective	Protects neurons and immune cells
<i>Phyllanthus emblica</i>	Quercetin	Flavonoid	Antiviral, immunomodulatory	Potential SARS-CoV-2 protease inhibition
<i>Allium sativum</i>	Allicin	Organosulfur compound	Antiviral, antimicrobial	May inhibit viral replication
<i>Allium sativum</i>	Ajoene	Sulfur compound	Anti-inflammatory, antioxidant	Reduces inflammatory signaling
<i>Allium sativum</i>	Diallyl sulfides	Sulfur compounds	Cardioprotective, antioxidant	Protects against oxidative injury
<i>Allium sativum</i>	S-allyl cysteine	Water-soluble sulfur compound	Neuroprotective, anti-inflammatory	Reduces neuroinflammation
Both herbs	Flavonoids & polyphenols	Polyphenolic compounds	Antioxidant, immunomodulatory	Enhances immune defense and neuronal protection

#### 4. Immunomodulatory Mechanisms of *Phyllanthus emblica* and *Allium sativum* in COVID-19

The pathogenesis of COVID-19 is closely associated with immune dysregulation, hyperinflammation, oxidative stress, and cytokine storm syndrome. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection triggers abnormal activation of innate and adaptive immune responses, resulting in excessive production of inflammatory mediators that contribute to pulmonary injury, endothelial dysfunction, multiorgan damage, and neurological complications (Del Valle et al., 2020). Consequently, therapeutic strategies capable of modulating immune responses without causing immunosuppression are of significant clinical importance. Nutraceutical herbs such as *Phyllanthus emblica* and *Allium sativum* possess potent immunomodulatory phytochemicals that may help restore immune balance and reduce inflammatory damage during COVID-19.

##### 4.1 Immune Dysregulation and Cytokine Storm in COVID-19

SARS-CoV-2 infection activates host immune cells including macrophages, neutrophils, dendritic cells, and T lymphocytes through recognition of viral antigens by pattern recognition receptors (PRRs). Activation of these pathways stimulates the release of pro-inflammatory cytokines such as IL-6, IL-1 $\beta$ ,

TNF- $\alpha$ , interferon- $\gamma$ , and chemokines, which collectively contribute to cytokine storm syndrome (Tang et al., 2020). Excessive cytokine production causes vascular permeability, oxidative stress, thrombosis, and tissue injury in severe COVID-19 patients.

Persistent inflammation also disrupts blood–brain barrier integrity and promotes neuroinflammation, which is associated with cognitive dysfunction, anxiety, depression, and post-COVID neurological sequelae (Heneka et al., 2020). Oxidative stress generated during hyperinflammatory responses further aggravates mitochondrial dysfunction and neuronal injury. Therefore, herbs possessing anti-inflammatory, antioxidant, and immunoregulatory activities may provide supportive therapeutic benefits.

#### 4.2 Immunomodulatory Actions of *Phyllanthus emblica*

*Phyllanthus emblica* exerts significant immunomodulatory effects through its polyphenols, tannins, flavonoids, and vitamin C-rich phytochemical profile. Experimental studies have shown that Amla enhances both humoral and cell-mediated immune responses while simultaneously regulating inflammatory pathways (Ngamukote et al., 2011). The antioxidant properties of emblicanins and gallic acid help neutralize reactive oxygen species generated during viral infections, thereby reducing oxidative damage to immune cells.

Vitamin C present in Amla plays a crucial role in supporting leukocyte function, phagocytosis, interferon production, and antibody responses. It also contributes to regeneration of endogenous antioxidants such as glutathione and vitamin E, which protect immune cells from oxidative injury (Carr & Maggini, 2017). Since severe COVID-19 is associated with depletion of antioxidant defenses, Amla supplementation may help maintain immune homeostasis and reduce inflammatory complications.

Amla polyphenols also inhibit activation of nuclear factor-kappa B (NF- $\kappa$ B), a major transcription factor responsible for cytokine production and inflammatory signaling (Variya et al., 2016). Suppression of NF- $\kappa$ B pathways may reduce levels of IL-6 and TNF- $\alpha$  implicated in cytokine storm syndrome. Furthermore, studies suggest that Amla improves macrophage and natural killer cell activity, thereby enhancing innate antiviral defenses.

In addition to immunological benefits, antioxidant phytochemicals in Amla protect neuronal tissues against oxidative stress-induced neurodegeneration. Such effects may contribute to improved cognitive resilience and reduced neuroinflammation during post-COVID recovery.

#### 4.3 Immunomodulatory Actions of *Allium sativum*

Garlic possesses broad-spectrum immunomodulatory activity primarily mediated by sulfur-containing compounds including allicin, ajoene, diallyl sulfides, and S-allyl cysteine. These compounds regulate cytokine production, immune cell activation, and inflammatory signaling pathways (Arreola et al., 2015). Garlic has been reported to stimulate macrophage phagocytosis, lymphocyte proliferation, and natural killer cell function, thereby strengthening host defense mechanisms against microbial infections.

Allicin exhibits potent anti-inflammatory activity through inhibition of NF- $\kappa$ B signaling and suppression of pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$  (Rahman, 2020). Garlic-derived compounds also reduce oxidative stress by increasing antioxidant enzyme activity and limiting lipid peroxidation. These properties are particularly relevant in COVID-19 because oxidative injury and uncontrolled inflammation are major contributors to disease severity.

Experimental studies suggest that garlic compounds may regulate T-helper cell balance and improve adaptive immune responses. Garlic supplementation has also been associated with reduced frequency and severity of respiratory infections due to enhancement of immune surveillance mechanisms (Percival, 2016). Additionally, aged garlic extract has demonstrated anti-inflammatory and neuroprotective activities capable of attenuating neuroimmune dysfunction and stress-related neuronal injury.

Several computational studies have indicated that organosulfur compounds from garlic may interact with SARS-CoV-2 proteases and ACE2 receptors, suggesting possible antiviral effects alongside immune modulation (Mohammed et al., 2021). Such multitarget actions make garlic a promising adjunctive nutraceutical during viral infections.

#### 4.4 Synergistic Immunological and Neuroprotective Effects

The combined use of *Phyllanthus emblica* and *Allium sativum* may provide synergistic therapeutic benefits because both herbs target multiple inflammatory and oxidative pathways simultaneously. While Amla primarily enhances antioxidant defenses and immune resilience through polyphenols and vitamin C, garlic contributes strong anti-inflammatory and antimicrobial actions through sulfur compounds.

Their combined phytochemicals may help regulate cytokine release, improve antioxidant status, reduce oxidative neuronal injury, and support immune homeostasis during COVID-19. Moreover, the neuroprotective effects of these herbs may reduce stress-induced neuroinflammation and support mental well-being in post-COVID patients experiencing anxiety, fatigue, and cognitive impairment.

**Table 3. Immunomodulatory Mechanisms of *Phyllanthus emblica* and *Allium sativum* Relevant to COVID-19**

Herb	Major Active Compounds	Immunological Actions	Anti-inflammatory Effects	Neuroprotective Relevance
<i>Phyllanthus emblica</i>	Vitamin C, emblicanins, gallic acid	Enhances leukocyte activity and innate immunity	Suppresses NF- $\kappa$ B and cytokine production	Reduces oxidative neuronal injury
<i>Phyllanthus emblica</i>	Polyphenols and flavonoids	Improves antioxidant defense mechanisms	Reduces ROS-mediated inflammation	Protects neurons from oxidative stress
<i>Allium sativum</i>	Allicin	Stimulates	Inhibits IL-6,	Reduces

		macrophages and NK cells	TNF- $\alpha$ , and NF- $\kappa$ B	neuroinflammation
<i>Allium sativum</i>	Ajoene and diallyl sulfides	Enhances adaptive immune responses	Limits oxidative stress and lipid peroxidation	Supports neuronal survival
Combined effect	Polyphenols + sulfur compounds	Immune balancing and antiviral support	Cytokine storm attenuation	Cognitive and mental health support

## 5. Antiviral Potential of *Phyllanthus emblica* and *Allium sativum* Against SARS-CoV-2

The rapid spread of SARS-CoV-2 and the emergence of viral variants have intensified the search for natural antiviral agents capable of targeting different stages of the viral life cycle. Medicinal plants rich in polyphenols, flavonoids, sulfur compounds, and tannins have demonstrated promising antiviral activities against several respiratory viruses, including coronaviruses (Mani et al., 2020). Among nutraceutical herbs, *Phyllanthus emblica* and *Allium sativum* have gained significant scientific attention because of their ability to interfere with viral entry, replication, inflammatory signaling, and oxidative stress pathways. Their multitarget phytochemicals may therefore serve as supportive therapeutic agents in COVID-19 management.

### 5.1 SARS-CoV-2 Structure and Therapeutic Targets

SARS-CoV-2 is an enveloped positive-sense single-stranded RNA virus belonging to the family Coronaviridae. The viral genome encodes structural proteins including spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins, along with non-structural proteins involved in viral replication (V'kovski et al., 2021). The spike glycoprotein mediates viral attachment to angiotensin-converting enzyme 2 (ACE2) receptors on host cells, followed by membrane fusion facilitated by transmembrane serine protease 2 (TMPRSS2) (Hoffmann et al., 2020).

Several viral components are considered important therapeutic targets, including the main protease (Mpro/3CLpro), papain-like protease (PLpro), RNA-dependent RNA polymerase (RdRp), and spike protein. Inhibition of these proteins may suppress viral replication and reduce infectivity (Anand et al., 2003). Natural phytochemicals capable of interacting with these targets are therefore being actively investigated as complementary antiviral agents.

### 5.2 Antiviral Activities of *Phyllanthus emblica*

The antiviral activity of *Phyllanthus emblica* is mainly attributed to its high concentration of polyphenols, flavonoids, tannins, and vitamin C. Studies have demonstrated that these phytochemicals possess inhibitory effects against influenza virus, hepatitis virus, herpes simplex virus, and other RNA viruses (Saini et al., 2022). The antioxidant and immunomodulatory actions of Amla further contribute to antiviral defense by strengthening host immunity and reducing oxidative stress-induced tissue injury.

Quercetin, one of the major flavonoids present in Amla, has shown promising activity against SARS-CoV-2 in computational and experimental studies. Molecular docking analyses suggest that quercetin can bind to viral main protease and spike protein, thereby interfering with viral entry and replication (Agrawal et al., 2020). Quercetin also acts as a zinc ionophore, facilitating intracellular zinc transport, which may inhibit RNA-dependent RNA polymerase activity required for viral replication.

Gallic acid and ellagic acid present in Amla exhibit anti-inflammatory and antiviral effects through modulation of oxidative stress pathways and inhibition of viral enzyme activity. Tannins from Amla may also disrupt viral envelope integrity and inhibit attachment of viruses to host cells. Additionally, vitamin C contributes to antiviral immunity by promoting interferon synthesis, leukocyte function, and antioxidant defense mechanisms (Hemilä & Chalker, 2013).

Experimental evidence indicates that Amla extracts may reduce inflammatory cytokines and oxidative injury associated with severe COVID-19. Such combined antiviral and immunomodulatory properties make *Phyllanthus emblica* a promising nutraceutical herb for supportive therapy during viral infections.

### 5.3 Antiviral Activities of *Allium sativum*

Garlic has been extensively investigated for its broad-spectrum antimicrobial and antiviral properties. Organosulfur compounds such as allicin, alliin, ajoene, and diallyl sulfides are primarily responsible for its antiviral activity (Rouf et al., 2020). These compounds exert antiviral effects by interfering with viral entry, inhibiting viral replication enzymes, modulating immune responses, and reducing oxidative stress.

Alliin is considered the principal antiviral constituent of garlic. It reacts with thiol-containing proteins and enzymes essential for viral survival and replication. Studies have reported that garlic extracts exhibit inhibitory effects against influenza virus, rhinovirus, herpes simplex virus, cytomegalovirus, and infectious bronchitis virus (Mehrbood et al., 2009). During the COVID-19 pandemic, computational studies suggested that alliin and related sulfur compounds may bind to SARS-CoV-2 main protease and ACE2 receptors, thereby reducing viral infectivity (Pandey et al., 2021).

Ajoene and diallyl sulfides also demonstrate anti-inflammatory and antioxidant activities capable of limiting cytokine storm-associated tissue damage. Garlic compounds may inhibit NF- $\kappa$ B activation and reduce production of IL-6 and TNF- $\alpha$ , which are major mediators of COVID-19 severity (Donma & Donma, 2020). Additionally, garlic enhances natural killer cell activity and macrophage responses, thereby strengthening innate antiviral immunity.

Garlic-derived phytochemicals have also shown protective effects against endothelial dysfunction and thrombosis, complications commonly observed in severe COVID-19 patients. Such multitarget therapeutic actions highlight the potential utility of garlic as an adjunctive herbal intervention during SARS-CoV-2 infection.

#### 5.4 Synergistic Antiviral and Protective Effects

The combined use of *Phyllanthus emblica* and *Allium sativum* may provide synergistic antiviral benefits because their phytochemicals target multiple viral and host pathways simultaneously. Polyphenols from Amla enhance antioxidant defenses and immune resilience, whereas sulfur compounds from garlic directly interfere with viral proteins and inflammatory pathways.

Both herbs may collectively reduce viral replication, suppress hyperinflammation, protect against oxidative tissue injury, and improve immune competence. Furthermore, their neuroprotective and cardioprotective properties may help reduce long-term complications associated with post-COVID syndrome.

**Table 4. Antiviral Mechanisms of *Phyllanthus emblica* and *Allium sativum* Against SARS-CoV-2**

Herb	Major Phytochemicals	Proposed Antiviral Targets	Mechanisms of Action	Additional Protective Effects
<i>Phyllanthus emblica</i>	Quercetin	Spike protein, Mpro	Inhibits viral entry and protease activity	Antioxidant and anti-inflammatory
<i>Phyllanthus emblica</i>	Gallic acid, tannins	Viral envelope and enzymes	Reduces viral attachment and oxidative stress	Immune enhancement
<i>Phyllanthus emblica</i>	Vitamin C	Host immune system	Enhances interferon production and leukocyte function	Reduces oxidative injury
<i>Allium sativum</i>	Allicin	Mpro, ACE2 receptor	Inhibits viral replication enzymes	Anti-inflammatory activity
<i>Allium sativum</i>	Ajoene and diallyl sulfides	NF- $\kappa$ B and inflammatory pathways	Suppresses cytokine storm and oxidative stress	Endothelial protection
Combined herbs	Polyphenols + sulfur compounds	Multiple viral and host targets	Synergistic antiviral and immunomodulatory effects	Neuroprotective support

#### 6. Neuroprotective and Mental Health Supportive Effects of *Phyllanthus emblica* and *Allium sativum*

The COVID-19 pandemic has significantly affected neurological and psychological health worldwide. Beyond respiratory complications, SARS-CoV-2 infection is associated with neuroinflammation, oxidative stress, cognitive dysfunction, anxiety, depression, fatigue, insomnia, and post-traumatic stress disorders (Taquet et al., 2021). Persistent neurological symptoms collectively described as “long COVID”

or “post-COVID syndrome” have emerged as major public health concerns. Increasing evidence suggests that medicinal plants possessing antioxidant, anti-inflammatory, adaptogenic, and neuroprotective properties may help alleviate these complications (Siddiqui et al., 2022). Among nutraceutical herbs, *Phyllanthus emblica* and *Allium sativum* demonstrate significant potential in supporting cognitive health and psychological well-being during and after COVID-19 infection.

### 6.1 Neurological and Psychological Impact of COVID-19

SARS-CoV-2 affects the nervous system through multiple mechanisms including direct neuroinvasion, cytokine-mediated neuroinflammation, endothelial dysfunction, hypoxia, and oxidative stress (Boldrini et al., 2021). Viral infection and systemic inflammation disrupt blood–brain barrier integrity, activate microglial cells, and induce excessive production of inflammatory cytokines such as IL-6 and TNF- $\alpha$  within neural tissues. These processes contribute to neuronal damage and neurotransmitter imbalance associated with anxiety, depression, and cognitive impairment.

Clinical studies have reported neurological manifestations such as headache, dizziness, anosmia, encephalopathy, stroke, memory impairment, confusion, sleep disturbances, and mood disorders in COVID-19 patients (Mao et al., 2020). Post-COVID cognitive dysfunction or “brain fog” is characterized by poor concentration, mental fatigue, reduced executive function, and impaired memory (Becker et al., 2021). Chronic inflammation and oxidative stress are considered major contributors to these neurological complications.

Furthermore, pandemic-related stressors including social isolation, fear of infection, financial insecurity, and grief have substantially increased the prevalence of depression and anxiety disorders worldwide (Vindegaard & Benros, 2020). Therefore, nutraceutical herbs capable of reducing neuroinflammation and improving stress resilience may provide supportive benefits in mental health management.

### 6.2 Neuroprotective Effects of *Phyllanthus emblica*

*Phyllanthus emblica* possesses strong neuroprotective activity due to its abundance of vitamin C, flavonoids, tannins, and polyphenolic antioxidants. Oxidative stress is one of the major mechanisms underlying neurodegeneration and cognitive dysfunction during viral infections. Antioxidants present in Amla neutralize reactive oxygen species and protect neuronal cells from oxidative injury (Bhattacharya et al., 2000).

Experimental studies have demonstrated that Amla extracts improve memory, learning ability, and cognitive performance through enhancement of cholinergic neurotransmission and antioxidant enzyme activity. Polyphenols such as gallic acid and ellagic acid reduce lipid peroxidation and inhibit neuroinflammatory pathways associated with neuronal degeneration (Sabu & Kuttan, 2002). Additionally, Amla has shown adaptogenic and anti-stress properties capable of improving resilience against psychological stress and fatigue.

Vitamin C present in Amla also plays an important role in neurotransmitter synthesis, neuronal maturation, and regulation of hypothalamic–pituitary–adrenal (HPA) axis responses. Adequate

antioxidant support may therefore help reduce neuroinflammation and cognitive dysfunction observed in post-COVID patients.

Studies further suggest that Amla may improve cerebral blood flow and mitochondrial function, thereby supporting neuronal survival during inflammatory conditions. Such multitarget neuroprotective effects indicate its therapeutic relevance in managing long COVID-related cognitive complications.

### 6.3 Neuroprotective Effects of *Allium sativum*

Garlic exhibits broad neuroprotective activity through its sulfur-containing compounds including allicin, S-allyl cysteine, ajoene, and diallyl sulfides. These compounds possess antioxidant, anti-inflammatory, antiapoptotic, and neuromodulatory properties that may help protect the brain from oxidative and inflammatory injury (Chauhan, 2006).

S-allyl cysteine has demonstrated beneficial effects in experimental models of neurodegeneration by reducing oxidative stress, suppressing inflammatory cytokines, and improving neuronal survival. Garlic compounds inhibit activation of microglia and NF- $\kappa$ B pathways, thereby limiting neuroinflammation and neuronal apoptosis (Ray et al., 2011). Since neuroinflammation plays a crucial role in post-COVID cognitive impairment, these mechanisms are particularly significant.

Garlic has also shown antidepressant and anxiolytic potential through modulation of serotonin, dopamine, and gamma-aminobutyric acid (GABA) neurotransmitter systems. Experimental studies indicate that garlic extracts reduce stress-induced behavioral changes and improve memory and learning functions (Mikaili et al., 2013). Additionally, antioxidant sulfur compounds improve cerebral circulation and mitochondrial function, thereby supporting neuronal energy metabolism.

The anti-inflammatory actions of garlic may also reduce systemic cytokine-mediated neural injury associated with severe COVID-19. Such combined antioxidant and neuromodulatory properties make garlic a promising nutraceutical herb for mental health support during recovery from viral infections.

### 6.4 Synergistic Mental Health Supportive Potential

The combined use of *Phyllanthus emblica* and *Allium sativum* may provide synergistic benefits in supporting mental and neurological health during COVID-19 recovery. Amla contributes strong antioxidant and adaptogenic actions, whereas garlic provides anti-inflammatory and neuromodulatory effects.

Together, these herbs may help reduce oxidative neuronal damage, suppress neuroinflammation, improve neurotransmitter balance, and enhance stress resilience. Their combined phytochemicals may therefore support cognitive recovery, emotional stability, and overall mental well-being in individuals experiencing post-COVID neurological complications.

**Table 5. Neuroprotective and Mental Health Supportive Effects of *Phyllanthus emblica* and *Allium sativum***

Herb	Major Neuroprotective Compounds	Mechanisms of Action	Neurological Benefits	Mental Health Relevance
<i>Phyllanthus emblica</i>	Vitamin C	Antioxidant defense and neurotransmitter support	Protects neurons from oxidative injury	Reduces stress and fatigue
<i>Phyllanthus emblica</i>	Gallic acid and ellagic acid	Anti-inflammatory and free radical scavenging	Improves cognition and memory	Adaptogenic effects
<i>Phyllanthus emblica</i>	Polyphenols and tannins	Enhances antioxidant enzyme activity	Neuroprotection against inflammation	Supports emotional resilience
<i>Allium sativum</i>	Allicin	Reduces oxidative stress and inflammation	Protects neural tissues	May reduce anxiety symptoms
<i>Allium sativum</i>	S-allyl cysteine	Inhibits neuronal apoptosis and microglial activation	Enhances neuronal survival	Antidepressant-like activity
<i>Allium sativum</i>	Diallyl sulfides	Improves cerebral circulation and mitochondrial function	Supports memory and cognition	Stress reduction
Combined herbs	Polyphenols + sulfur compounds	Antioxidant and anti-inflammatory synergy	Cognitive and neuroprotective support	Mental well-being enhancement

### 7. Safety, Clinical Perspectives, and Future Prospects of *Phyllanthus emblica* and *Allium sativum* in COVID-19 Management

The increasing use of herbal nutraceuticals during the COVID-19 pandemic has highlighted the importance of evaluating their safety, efficacy, standardization, and clinical applicability. Although *Phyllanthus emblica* and *Allium sativum* possess significant antiviral, immunomodulatory, antioxidant, and neuroprotective activities, their therapeutic use requires scientific validation through controlled clinical investigations. Proper dosage, formulation quality, herb–drug interactions, and long-term safety profiles must be carefully considered before large-scale clinical implementation (Ekor, 2014).

### 7.1 Safety Profile of *Phyllanthus emblica*

*Phyllanthus emblica* has been extensively used in traditional systems of medicine such as Ayurveda and is generally regarded as safe when consumed in dietary or therapeutic doses. Amla fruits are rich in natural antioxidants, vitamins, minerals, and polyphenols that contribute to their favorable safety profile (Baliga & Dsouza, 2011).

Toxicological studies indicate that Amla extracts exhibit low toxicity and good tolerability in experimental models. However, excessive consumption may occasionally produce mild gastrointestinal disturbances such as acidity, abdominal discomfort, or diarrhea due to its acidic nature. Individuals receiving anticoagulant or antidiabetic medications should use Amla cautiously because its phytochemicals may potentiate hypoglycemic or antiplatelet effects (Krishnaveni & Mirunalini, 2010).

Standardization of phytochemical content is another important consideration. Variability in cultivation conditions, extraction methods, and processing techniques can influence the concentration of active constituents such as gallic acid, ellagic acid, and vitamin C. Therefore, quality control and phytochemical standardization are essential for ensuring reproducible therapeutic efficacy.

### 7.2 Safety Profile of *Allium sativum*

Garlic is widely consumed as a food and medicinal herb and is generally considered safe in moderate amounts. Nevertheless, high doses or concentrated garlic supplements may produce adverse effects including gastric irritation, nausea, bloating, heartburn, allergic reactions, and body odor (Borrelli et al., 2007).

One of the major clinical concerns associated with garlic is its antiplatelet activity. Organosulfur compounds such as allicin may increase bleeding risk, particularly in patients receiving anticoagulant or antithrombotic therapy. Therefore, caution is advised in individuals taking warfarin, aspirin, or other blood-thinning medications (Ried et al., 2016).

Garlic may also interact with certain antiviral and cardiovascular drugs by affecting cytochrome P450 enzymes and drug metabolism pathways. Excessive intake of raw garlic can cause gastrointestinal irritation and mucosal damage in sensitive individuals. Despite these concerns, controlled consumption of garlic within recommended limits is considered relatively safe for most populations.

### 7.3 Clinical Evidence and Therapeutic Perspectives

Several clinical and experimental studies support the immunomodulatory and antioxidant properties of Amla and garlic; however, direct clinical evidence against SARS-CoV-2 remains limited. During the pandemic, herbal medicines were widely used as supportive therapies for reducing fatigue, improving immunity, alleviating respiratory symptoms, and promoting recovery (Khanna et al., 2021).

Clinical studies have demonstrated that Amla supplementation improves antioxidant status, immune responses, and metabolic health parameters. Garlic supplementation has similarly shown beneficial

effects on inflammation, cardiovascular health, and immune function (Ried, 2016). These therapeutic actions may indirectly support COVID-19 management by improving host defense mechanisms and reducing inflammatory complications.

The multitarget pharmacological nature of these herbs is particularly important because COVID-19 involves complex pathological mechanisms including oxidative stress, immune dysregulation, endothelial dysfunction, thrombosis, and neurological injury. Combination formulations containing Amla and garlic may therefore offer complementary therapeutic advantages.

However, large-scale randomized clinical trials are still required to establish efficacy, dosage regimens, pharmacokinetics, and long-term safety in COVID-19 patients. Evidence-based integration of herbal nutraceuticals into modern healthcare systems requires rigorous scientific validation.

#### **7.4 Nanotechnology and Advanced Herbal Delivery Systems**

One of the major limitations of phytochemicals is poor bioavailability due to low solubility, rapid metabolism, and limited absorption. Nanotechnology-based drug delivery systems have emerged as promising approaches to enhance the therapeutic efficacy of herbal compounds (Chavda et al., 2022).

Nanoformulations such as liposomes, phytosomes, nanoemulsions, polymeric nanoparticles, and solid lipid nanoparticles can improve stability, targeted delivery, and bioavailability of phytochemicals derived from Amla and garlic. Such systems may enhance antiviral and neuroprotective efficacy while reducing toxicity and dosage requirements.

Nanocarrier-mediated delivery of polyphenols and sulfur compounds may also improve blood–brain barrier penetration, thereby supporting management of COVID-19-associated neurological complications. Future research focusing on nanoherbal therapeutics could significantly improve the clinical utility of nutraceutical herbs.

#### **7.5 Future Research Directions**

Future investigations should focus on:

- Conducting randomized controlled clinical trials evaluating efficacy against COVID-19 and long COVID symptoms.
- Identifying precise molecular targets and mechanisms of antiviral action.
- Standardizing herbal formulations and phytochemical content.
- Investigating synergistic interactions between herbal compounds and conventional antiviral drugs.
- Developing advanced nanotechnology-based delivery systems.
- Exploring long-term neuroprotective and mental health benefits in post-COVID recovery.

Comprehensive multidisciplinary research integrating pharmacology, phytochemistry, nanotechnology, and clinical medicine will be essential for translating traditional herbal knowledge into evidence-based therapeutic applications.

## References

- Abian, O., Ortega-Alarcon, D., Jimenez-Alesanco, A., Ceballos-Laita, L., Vega, S., Reyburn, H. T., & Velazquez-Campoy, A. (2020). Structural stability of SARS-CoV-2 3CLpro and identification of quercetin as an inhibitor by experimental screening. *International Journal of Biological Macromolecules*, *164*, 1693–1703.
- Agrawal, P. K., Agrawal, C., & Blunden, G. (2020). Quercetin: Antiviral significance and possible COVID-19 integrative considerations. *Natural Product Communications*, *15*(12), 1–10.
- Akhtar, M. S., Ramzan, A., Ali, A., & Ahmad, M. (2011). Effect of Amla fruit (*Emblica officinalis* Gaertn.) on blood glucose and lipid profile of normal subjects and type 2 diabetic patients. *International Journal of Food Sciences and Nutrition*, *62*(6), 609–616.
- Amagase, H. (2006). Clarifying the real bioactive constituents of garlic. *The Journal of Nutrition*, *136*(3), 716S–725S.
- Anand, K., Ziebuhr, J., Wadhvani, P., Mesters, J. R., & Hilgenfeld, R. (2003). Coronavirus main proteinase (3CLpro) structure: Basis for design of anti-SARS drugs. *Science*, *300*(5626), 1763–1767.
- Arreola, R., Quintero-Fabián, S., López-Roa, R. I., Flores-Gutiérrez, E. O., Reyes-Grajeda, J. P., Carrera-Quintanar, L., & Ortuño-Sahagún, D. (2015). Immunomodulation and anti-inflammatory effects of garlic compounds. *Journal of Immunology Research*, *2015*, 401630.
- Baliga, M. S., & Dsouza, J. J. (2011). Amla (*Emblica officinalis* Gaertn), a wonder berry in the treatment and prevention of cancer. *European Journal of Cancer Prevention*, *20*(3), 225–239.
- Bayan, L., Koulivand, P. H., & Gorji, A. (2014). Garlic: A review of potential therapeutic effects. *Avicenna Journal of Phytomedicine*, *4*(1), 1–14.
- Becker, J. H., Lin, J. J., Doernberg, M., Stone, K., Navis, A., Festa, J. R., & Wisnivesky, J. P. (2021). Assessment of cognitive function in patients after COVID-19 infection. *JAMA Network Open*, *4*(10), e2130645.
- Bhattacharya, A., Chatterjee, A., Ghosal, S., & Bhattacharya, S. K. (2000). Antioxidant activity of active tannoid principles of *Emblica officinalis* (Amla). *Indian Journal of Experimental Biology*, *38*(9), 877–880.
- Boldrini, M., Canoll, P. D., & Klein, R. S. (2021). How COVID-19 affects the brain. *JAMA Psychiatry*, *78*(6), 682–683.
- Borrelli, F., Capasso, R., Izzo, A. A., & Capasso, F. (2007). Pharmacology of garlic and onions. *Phytotherapy Research*, *21*(7), 599–613.
- Cecchini, R., & Cecchini, A. L. (2020). SARS-CoV-2 infection pathogenesis is related to oxidative stress as a response to aggression. *Medical Hypotheses*, *143*, 110102.
- Chauhan, N. B. (2006). Effect of aged garlic extract on APP processing and tau phosphorylation in Alzheimer's transgenic model Tg2576. *Journal of Ethnopharmacology*, *108*(3), 385–394.

- Chavda, V. P., Vihol, D., Mehta, B., Shah, D., Patel, M., Vora, L. K., & Pereira-Silva, M. (2022). Phytochemical-loaded nanocarriers for management of COVID-19 and associated complications. *Materials Today Chemistry*, 23, 100670.
- Dasaroju, S., & Gottumukkala, K. M. (2014). Current trends in research of *Embllica officinalis* (Amla). *International Journal of Pharmaceutical Sciences Review and Research*, 24(2), 150–159.
- Del Valle, D. M., Kim-Schulze, S., Huang, H. H., Beckmann, N. D., Nirenberg, S., Wang, B., & Gnjjatic, S. (2020). An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nature Medicine*, 26(10), 1636–1643.
- Donma, M. M., & Donma, O. (2020). The effects of *Allium sativum* on immunity within the scope of COVID-19 infection. *Medical Hypotheses*, 144, 109934.
- Ekor, M. (2014). The growing use of herbal medicines: Issues relating to adverse reactions. *Frontiers in Pharmacology*, 4, 177.
- Ellul, M. A., Benjamin, L., Singh, B., Lant, S., Michael, B. D., Easton, A., & Solomon, T. (2020). Neurological associations of COVID-19. *The Lancet Neurology*, 19(9), 767–783.
- Fajgenbaum, D. C., & June, C. H. (2020). Cytokine storm. *New England Journal of Medicine*, 383(23), 2255–2273.
- Gaire, B. P., & Subedi, L. (2014). Pharmacological review of *Phyllanthus emblica*. *Pharmacology & Pharmacy*, 5(1), 93–102.
- Gupta, A., Madhavan, M. V., Sehgal, K., Nair, N., Mahajan, S., Sehrawat, T. S., & Landry, D. W. (2020). Extrapulmonary manifestations of COVID-19. *Nature Medicine*, 26(7), 1017–1032.
- Hemilä, H., & Chalker, E. (2013). Vitamin C for preventing and treating infections. *Cochrane Database of Systematic Reviews*, CD000980.
- Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., & Pöhlmann, S. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2. *Cell*, 181(2), 271–280.e8.
- Jahan, I., Onay, A., Pottoo, F. H., & Javed, M. N. (2021). Phytomedicines and COVID-19. *Current Pharmaceutical Biotechnology*, 22(15), 1967–1985.
- Kharwar, R. N., Upadhyay, R., Dubey, N. K., & Raghuwanshi, R. (2020). Medicinal plants in COVID-19 management. *3 Biotech*, 10(10), 1–10.
- Krishnaveni, M., & Mirunalini, S. (2010). Therapeutic potential of *Phyllanthus emblica*. *Journal of Basic and Clinical Physiology and Pharmacology*, 21(1), 93–105.
- Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., & Hu, B. (2020). Neurologic manifestations of COVID-19. *JAMA Neurology*, 77(6), 683–690.
- Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., & Manson, J. J. (2020). Cytokine storm syndromes in COVID-19. *The Lancet*, 395(10229), 1033–1034.
- Mohammed, A. A., Alnema, M. M., & Yusof, Y. A. (2021). Garlic compounds as SARS-CoV-2 inhibitors. *Journal of Food Biochemistry*, 45(2), e13645.
- Ngamukote, S., Mäkyänen, K., Thilawech, T., & Adisakwattana, S. (2011). Cholesterol-lowering activity of *Embllica officinalis*. *European Journal of Clinical Nutrition*, 65(9), 1032–1038.
- Paraiso, I. L., Revel, J. S., & Stevens, J. F. (2020). Polyphenols against COVID-19. *Current Opinion in Food Science*, 32, 149–155.
- Percival, S. S. (2016). Aged garlic extract and immunity. *The Journal of Nutrition*, 146(2), 433S–436S.

- Premraj, L., Kannapadi, N. V., Briggs, J., Seal, S. M., Battaglini, D., Fanning, J., & Fraser, J. F. (2022). Post-COVID neurological outcomes. *Journal of the Neurological Sciences*, 434, 120162.
- Rahman, K. (2007). Garlic and platelet function. *Molecular Nutrition & Food Research*, 51(11), 1335–1344.
- Ray, B., Chauhan, N. B., & Lahiri, D. K. (2011). Neuroprotection by aged garlic extract. *Journal of Neurochemistry*, 117(3), 388–402.
- Ried, K. (2016). Garlic and cardiovascular health. *Journal of Nutrition*, 146(2), 389S–396S.
- Rouf, R., Uddin, S. J., Sarker, D. K., Islam, M. T., Ali, E. S., Shilpi, J. A., & Sarker, S. D. (2020). Antiviral potential of garlic. *Trends in Food Science & Technology*, 104, 219–234.
- Sabu, M. C., & Kuttan, R. (2002). Antioxidant activity of medicinal plants. *Journal of Ethnopharmacology*, 81(2), 155–160.
- Saini, R., Sharma, N., & Oladeji, O. S. (2022). Antiviral medicinal plants. *Journal of Herbal Medicine*, 33, 100546.
- Scartezzini, P., & Speroni, E. (2000). Antioxidant plants in Indian medicine. *Journal of Ethnopharmacology*, 71(1–2), 23–43.
- Song, E., Zhang, C., Israelow, B., Lu-Culligan, A., Prado, A. V., Skriabine, S., & Iwasaki, A. (2021). SARS-CoV-2 neuroinvasion. *Journal of Experimental Medicine*, 218(3), e20202135.
- Taquet, M., Geddes, J. R., Husain, M., Luciano, S., & Harrison, P. J. (2021). Long COVID neuropsychiatric outcomes. *The Lancet Psychiatry*, 8(5), 416–427.
- Troyer, E. A., Kohn, J. N., & Hong, S. (2020). Neuropsychiatric consequences of COVID-19. *Brain, Behavior, and Immunity*, 87, 34–39.
- V'kovski, P., Kratzel, A., Steiner, S., Stalder, H., & Thiel, V. (2021). Coronavirus biology. *Nature Reviews Microbiology*, 19(3), 155–170.
- Vindegaard, N., & Benros, M. E. (2020). Mental health in COVID-19. *Brain, Behavior, and Immunity*, 89, 531–542.
- World Health Organization. (2023). *WHO coronavirus (COVID-19) dashboard*. <https://covid19.who.int>
- Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., & Tan, W. (2020). Novel coronavirus identification. *New England Journal of Medicine*, 382(8), 727–733.

## Chapter 9: Post-COVID Syndrome and Mental Health Rehabilitation Using *Bacopa monnieri* and *Centella asiatica*

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### Abstract

Post-COVID syndrome, also known as Long COVID, has emerged as a significant global health challenge characterized by persistent and often debilitating neuropsychiatric, cognitive, and systemic symptoms following recovery from acute SARS-CoV-2 infection. Patients frequently present with cognitive dysfunction (“brain fog”), impaired attention and memory, anxiety, depression, sleep disturbances, chronic fatigue, and reduced psychosocial functioning. These manifestations are increasingly recognized as consequences of complex and interrelated neurobiological disturbances, including chronic neuroinflammation, oxidative stress, mitochondrial dysfunction, dysregulation of monoaminergic neurotransmitters, hypothalamic–pituitary–adrenal (HPA) axis imbalance, endothelial dysfunction, and blood–brain barrier (BBB) impairment. Despite the availability of symptomatic pharmacological treatments, conventional therapeutic strategies often fail to fully address the underlying pathophysiological mechanisms driving post-COVID neuropsychiatric sequelae. This therapeutic gap has led to increasing interest in multi-target, natural, and neurorestorative interventions capable of simultaneously modulating inflammation, enhancing neuroplasticity, and restoring cognitive-emotional balance. Within this framework, medicinal plants with well-documented nootropic and neuroprotective properties, particularly *Bacopa monnieri* and *Centella asiatica*, have gained substantial scientific relevance. *Bacopa monnieri* (Brahmi), a classical Ayurvedic nootropic, is widely recognized for its cognitive-enhancing effects, particularly in memory consolidation, learning capacity, and information processing speed. Its pharmacological actions are attributed to bacosides, which exert antioxidant effects, enhance cholinergic transmission, reduce neuronal oxidative damage, modulate serotonergic and dopaminergic pathways, and support synaptic plasticity and dendritic growth. Similarly, *Centella asiatica* (Gotu kola) demonstrates broad-spectrum neurotherapeutic potential, including anxiolytic, antidepressant, anti-inflammatory, and neuroregenerative effects. Its bioactive constituents such as asiaticoside, madecassoside, and asiatic acid contribute to neuronal repair, enhancement of dendritic arborization, modulation of the GABAergic system, and suppression of pro-inflammatory cytokines within the central nervous system. Additionally, it supports angiogenesis and cerebral microcirculation, which may further enhance cognitive recovery in post-infectious neurological conditions. The complementary pharmacological profiles of *Bacopa monnieri* and *Centella asiatica* suggest a potential synergistic approach for managing post-COVID neuropsychiatric complications. Their combined effects may provide multi-dimensional neuroprotection by targeting oxidative stress, neuroinflammation, neurotransmitter imbalance, and impaired neuroplasticity simultaneously. This chapter critically explores the neurobiological basis of post-COVID cognitive and emotional dysfunction and provides an evidence-based evaluation of *Bacopa monnieri* and *Centella asiatica* as integrative neurorehabilitative agents. It further highlights experimental findings, clinical evidence, and mechanistic pathways supporting their role in cognitive restoration and mood stabilization. Overall, these herbal interventions represent promising adjunctive strategies for improving neurological resilience, cognitive recovery, and emotional well-being in individuals affected by Long COVID.

### Keywords

Post-COVID syndrome; Long COVID; *Bacopa monnieri*; *Centella asiatica*; cognitive dysfunction; brain fog; neuroinflammation; oxidative stress; neuroplasticity; mitochondrial dysfunction; anxiety; depression; sleep disturbance; nootropic herbs; neuroregeneration; GABAergic modulation; cholinergic system; herbal neurotherapy; adaptogenic agents

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## 1. Introduction: Post-COVID Syndrome and Emerging Mental Health Burden

The coronavirus disease 2019 (COVID-19) pandemic has resulted not only in acute respiratory illness but also in a wide spectrum of long-term complications collectively referred to as post-acute sequelae of SARS-CoV-2 infection (PASC), commonly known as Long COVID. This condition is characterized by persistent symptoms extending beyond the acute phase of infection, often lasting weeks to months, and in some cases, longer. Among these, neuropsychiatric manifestations have emerged as a major concern, significantly affecting quality of life and functional recovery in survivors (Nalbandian et al., 2021).

A growing body of evidence indicates that individuals recovering from COVID-19 are at increased risk of developing mental health disorders, including depression, anxiety, post-traumatic stress disorder (PTSD), and sleep disturbances. Large cohort studies have demonstrated that psychiatric morbidity remains elevated even several months after infection, suggesting a direct or indirect impact of SARS-CoV-2 on the central nervous system (Taquet et al., 2021). These findings highlight that the burden of COVID-19 extends far beyond pulmonary involvement and represents a significant neuropsychiatric challenge at the population level.

Cognitive dysfunction, often described as “brain fog,” is one of the most commonly reported complaints in Long COVID patients. It includes deficits in memory, attention, executive functioning, and processing speed. Alongside cognitive symptoms, emotional instability, irritability, fatigue, and behavioral changes have also been frequently observed. These disturbances may arise due to multifactorial mechanisms, including neuroinflammation, microvascular injury, hypoxic stress, and dysregulation of neurotransmitter systems (Petersen et al., 2022). The persistence of these symptoms has profound implications for daily functioning, occupational performance, and overall well-being.

Given the complex and multifaceted nature of post-COVID neuropsychiatric complications, conventional pharmacological approaches alone may not be sufficient for complete recovery. This has led to increasing interest in integrative and neurorestorative strategies that combine modern medicine with evidence-based traditional systems of healing. Holistic approaches focusing on neuroprotection, anti-inflammatory modulation, and cognitive enhancement are now being explored as supportive therapies in Long COVID rehabilitation (Mahalakshmi et al., 2021).

In this context, medicinal plants with established neurocognitive benefits have gained considerable scientific attention. Herbal agents such as *Bacopa monnieri* and *Centella asiatica*, widely used in Ayurvedic medicine, possess documented effects on memory enhancement, anxiolysis, and neuroprotection. Their multimodal mechanisms—including antioxidant activity, modulation of neurotransmitters, and support of neuronal regeneration—make them promising candidates for addressing both cognitive and emotional disturbances associated with post-COVID syndrome. The exploration of such phytotherapeutic agents represents a rational and promising direction in the development of adjunctive therapies for mental health rehabilitation in Long COVID patients.

## 2. Pathophysiology of Post-COVID Neuropsychiatric Dysfunction

### 2.1 Neuroinflammation and Cytokine Dysregulation

One of the most widely accepted mechanisms underlying post-COVID neuropsychiatric complications is persistent neuroinflammation. SARS-CoV-2 infection triggers a systemic immune response characterized by elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin-1 $\beta$  (IL-1 $\beta$ ). In susceptible individuals, this inflammatory response may persist even after viral clearance, leading to chronic low-grade inflammation in the central nervous system (CNS) (Heneka et al., 2020).

Microglial activation plays a central role in this process. Activated microglia release neurotoxic mediators, reactive oxygen species, and additional cytokines, which contribute to synaptic dysfunction and neuronal injury. This sustained inflammatory state has been strongly associated with depression, anxiety, and cognitive impairment observed in Long COVID patients (Ellul et al., 2020).

### 2.2 Blood–Brain Barrier Disruption and Oxidative Stress

The blood–brain barrier (BBB) acts as a critical protective interface between systemic circulation and the CNS. COVID-19–related inflammation has been shown to disrupt BBB integrity through endothelial dysfunction and tight junction protein degradation. This allows peripheral immune cells and inflammatory mediators to infiltrate the brain parenchyma, exacerbating neuroinflammation (Pellegrini et al., 2020).

In parallel, oxidative stress is significantly elevated in post-COVID conditions due to mitochondrial dysfunction and excessive production of reactive oxygen species (ROS). Oxidative damage affects neuronal membranes, proteins, and DNA, ultimately impairing synaptic transmission and neural plasticity. This oxidative burden is closely linked to fatigue, cognitive decline, and mood disturbances.

### 2.3 Hypoxia-Induced Neuronal Injury

Severe and even moderate COVID-19 infection may result in systemic hypoxia due to respiratory compromise. Neurons are highly sensitive to oxygen deprivation, and hypoxic conditions can lead to energy failure, excitotoxicity, and apoptosis. Hypoxia-inducible factors (HIFs) are activated during oxygen deprivation and contribute to downstream inflammatory and metabolic changes in the brain.

This hypoxia-related neuronal injury has been implicated in memory deficits, attention impairment, and executive dysfunction commonly reported in post-COVID syndrome (Mao et al., 2020).

### 2.4 Neurotransmitter Imbalance (Serotonin, Dopamine, GABA)

Post-COVID neuropsychiatric symptoms are also strongly associated with dysregulation of key neurotransmitter systems. Inflammatory cytokines can interfere with tryptophan metabolism, diverting it toward the kynurenine pathway, thereby reducing serotonin availability. This mechanism is closely linked with depressive symptoms and emotional instability (Miller & Raison, 2016).

Dopaminergic dysfunction contributes to anhedonia, reduced motivation, and cognitive slowing, while alterations in gamma-aminobutyric acid (GABA) signaling are associated with anxiety, irritability, and sleep disturbances. Together, these neurotransmitter imbalances create a neurochemical environment conducive to persistent psychiatric symptoms in Long COVID patients.

## 2.5 Immune Activation and Depression–Anxiety Link

There is increasing recognition of the bidirectional relationship between immune activation and psychiatric disorders. Chronic immune activation following COVID-19 infection can lead to activation of the hypothalamic–pituitary–adrenal (HPA) axis, resulting in elevated cortisol levels and stress dysregulation.

Inflammation-induced changes in brain-derived neurotrophic factor (BDNF) further impair neuroplasticity, contributing to long-term mood disorders. This immunopsychiatric model provides a strong explanatory framework for the high prevalence of depression and anxiety observed in post-COVID populations (Dantzer et al., 2008).

**Table 1: Key Mechanisms of Post-COVID Neuropsychiatric Dysfunction**

Pathophysiological Mechanism	Biological Changes	Neuropsychiatric Outcomes	Key References
Neuroinflammation	Elevated IL-6, TNF- $\alpha$ , microglial activation	Depression, cognitive impairment, fatigue	Heneka et al., 2020; Ellul et al., 2020
BBB Disruption	Endothelial damage, tight junction breakdown	Brain fog, neuroinvasion of immune mediators	Pellegrini et al., 2020
Oxidative Stress	Increased ROS, mitochondrial dysfunction	Memory loss, mood disorders, fatigue	Mao et al., 2020
Hypoxia Injury	Reduced oxygen supply, HIF activation	Executive dysfunction, attention deficits	Mao et al., 2020
Neurotransmitter Imbalance	↓ Serotonin, dopamine; altered GABA	Depression, anxiety, insomnia	Miller & Raison, 2016
Immune–HPA Axis Activation	Elevated cortisol, reduced BDNF	PTSD-like symptoms, chronic stress	Dantzer et al., 2008

## 3. Neuropsychiatric Manifestations of Post-COVID Syndrome

### 3.1 Overview of Clinical Neuropsychiatric Spectrum

Post-COVID syndrome presents with a broad and heterogeneous spectrum of neuropsychiatric manifestations. These symptoms may persist for weeks to months after acute infection and often fluctuate in severity. Clinical observations suggest that both previously healthy individuals and those with pre-existing psychiatric vulnerability can develop significant mental health complications following SARS-CoV-2 infection (World Health Organization, 2021).

The manifestations are primarily categorized into cognitive, emotional, sleep-related, and behavioral disturbances, reflecting widespread disruption of brain networks involved in cognition, mood regulation, and arousal.

### **3.2 Cognitive Impairments (“Brain Fog”)**

Cognitive dysfunction is one of the most frequently reported complaints in Long COVID. Patients commonly describe reduced concentration, impaired attention span, forgetfulness, and slowed information processing. This condition is often referred to as “brain fog” and can significantly interfere with occupational and academic performance.

Neuropsychological assessments have demonstrated deficits in executive function, working memory, and processing speed, even in patients who had mild acute infection (Becker et al., 2021). These deficits are believed to be associated with persistent neuroinflammation, microvascular injury, and altered synaptic connectivity.

### **3.3 Emotional and Mood Disorders**

Post-COVID emotional disturbances include depression, anxiety, irritability, and emotional instability. Epidemiological studies have shown a significantly increased incidence of depressive and anxiety disorders in COVID-19 survivors compared to non-infected populations (Taquet et al., 2021). These symptoms are often multifactorial, arising from a combination of biological mechanisms (cytokine dysregulation, neurotransmitter imbalance) and psychosocial stressors such as isolation, stigma, and financial burden.

### **3.4 Post-Traumatic Stress and Stress-Related Disorders**

A subset of patients develop post-traumatic stress disorder (PTSD)-like symptoms following severe COVID-19 infection or intensive care unit (ICU) admission. Symptoms include intrusive thoughts, hyperarousal, nightmares, and avoidance behaviors. The psychological trauma of severe illness, combined with systemic inflammation affecting limbic brain structures such as the amygdala and hippocampus, contributes to the development of stress-related disorders (Rogers et al., 2020).

### **3.5 Sleep Disturbances and Fatigue Syndrome**

Sleep disorders are highly prevalent in post-COVID syndrome and include insomnia, fragmented sleep, and altered sleep-wake cycles. Sleep disruption is closely associated with fatigue, reduced cognitive performance, and worsened mood symptoms. Chronic fatigue syndrome-like presentations have also been reported, characterized by persistent exhaustion not relieved by rest. This may be linked to dysregulated circadian rhythms and inflammatory cytokine activity affecting sleep regulation centers in the brain (Komaroff & Lipkin, 2021).

### 3.6 Behavioral and Psychosocial Dysfunction

Behavioral changes in post-COVID patients may include reduced motivation, social withdrawal, decreased productivity, and impaired stress tolerance. These changes often overlap with depressive and cognitive symptoms, further complicating diagnosis and management. Functional impairment is commonly observed in daily activities, occupational roles, and social relationships, contributing to reduced quality of life and long-term disability in severe cases.

**Table 2: Neuropsychiatric Manifestations of Post-COVID Syndrome**

Category	Clinical Features	Functional Impact	Key Mechanisms	References
Cognitive Dysfunction	Brain fog, memory loss, poor attention	Reduced academic/occupational performance	Neuroinflammation, microvascular injury	Becker et al., 2021
Mood Disorders	Depression, anxiety, irritability	Emotional instability, reduced QoL	Cytokine imbalance, neurotransmitter dysregulation	Taquet et al., 2021
PTSD-like Symptoms	Intrusive thoughts, hyperarousal, nightmares	Psychological distress, avoidance behavior	Limbic system dysregulation, trauma response	Rogers et al., 2020
Sleep Disturbances	Insomnia, fragmented sleep	Fatigue, poor cognition	Circadian disruption, cytokine effects	Komaroff & Lipkin, 2021
Behavioral Changes	Social withdrawal, low motivation	Functional impairment, disability risk	Combined cognitive-emotional dysfunction	Becker et al., 2021

## 4. *Bacopa monnieri*: Neuropharmacology, Mechanisms, and Clinical Evidence

### 4.1 Introduction and Ethnopharmacological Background

*Bacopa monnieri* (commonly known as Brahmi) is a perennial creeping herb widely used in Ayurvedic medicine as a “Medhya Rasayana,” traditionally indicated for enhancement of memory, intellect, and mental clarity. Modern pharmacological investigations have validated many of these traditional claims, particularly its nootropic, anxiolytic, and neuroprotective properties (Aguiar & Borowski, 2013).

The therapeutic potential of *Bacopa monnieri* is primarily attributed to its bioactive triterpenoid saponins known as bacosides (A and B), which exert multimodal actions on neuronal function, synaptic plasticity, and neurochemical balance.

## 4.2 Phytochemistry and Active Constituents

The major phytoconstituents responsible for neuroactivity include:

- Bacosides A and B (primary cognitive-enhancing agents)
  - Alkaloids (brahmine, herpestine)
  - Flavonoids (luteolin, apigenin derivatives)
  - Sterols and triterpenoids
- These compounds act synergistically to produce antioxidant, anti-inflammatory, and neurorestorative effects (Valotto Neto et al., 2024).

## 4.3 Neuropharmacological Mechanisms of Action

### 4.3.1 Cholinergic Modulation

*Bacopa monnieri* enhances cognitive function by modulating the cholinergic system. It increases acetylcholine availability by influencing choline acetyltransferase activity and reducing acetylcholinesterase-mediated breakdown, thereby improving learning and memory processes (Stough et al., 2013).

### 4.3.2 Antioxidant and Mitochondrial Protection

Oxidative stress plays a central role in post-COVID neurodegeneration. *Bacopa* exhibits strong free radical scavenging activity and enhances endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase. It also stabilizes mitochondrial membranes, reducing neuronal apoptosis and energy dysfunction (Valotto Neto et al., 2024).

### 4.3.3 Anti-inflammatory and Microglial Regulation

Bacosides suppress neuroinflammatory cascades by inhibiting NF- $\kappa$ B signaling and reducing pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$ . Additionally, *Bacopa* modulates microglial activation, shifting them toward a neuroprotective phenotype, thereby reducing chronic neuroinflammation associated with cognitive decline (Aguilar & Borowski, 2013).

### 4.3.4 Neurogenesis and Synaptic Plasticity

Experimental studies suggest that *Bacopa monnieri* enhances dendritic arborization and synaptic communication. It upregulates neurotrophic factors such as brain-derived neurotrophic factor (BDNF), supporting neurogenesis and synaptic remodeling, which are essential for recovery from cognitive impairment (Pase et al., 2012).

#### 4.3.5 HPA Axis Modulation and Stress Reduction

Bacopa exerts adaptogenic effects by modulating the hypothalamic–pituitary–adrenal (HPA) axis. This leads to reduced cortisol levels and improved stress resilience, which is particularly relevant in post-COVID anxiety and fatigue syndromes (Calabrese et al., 2008).

#### 4.4 Clinical Evidence in Cognitive and Psychiatric Disorders

Clinical trials and systematic reviews suggest that standardized *Bacopa monnieri* extracts produce modest but significant improvements in:

- Delayed recall memory
- Attention and processing speed
- Learning ability
- Anxiety reduction

A systematic review of randomized controlled trials reported consistent improvement in memory acquisition and retention after 8–12 weeks of supplementation (Pase et al., 2012). Another clinical trial in older adults demonstrated improvements in attention and verbal learning domains, although effects varied depending on dose and extract standardization (Calabrese et al., 2008).

Despite these positive findings, variability in formulations and bacoside concentrations leads to inconsistent outcomes across studies, limiting universal clinical recommendations (Stough et al., 2013).

#### 4.5 Relevance to Post-COVID Neuropsychiatric Rehabilitation

In the context of post-COVID syndrome, *Bacopa monnieri* may offer therapeutic benefits through:

- Reduction of neuroinflammation and oxidative stress
- Restoration of cholinergic neurotransmission
- Enhancement of synaptic plasticity and cognitive recovery
- Reduction of anxiety and stress-related symptoms

These multimodal actions make it a promising adjunctive agent for addressing “brain fog,” memory dysfunction, and emotional instability observed in Long COVID patients.

**Table 3: Mechanisms and Therapeutic Actions of *Bacopa monnieri***

Mechanistic Domain	Biological Action	Key Molecular Targets	Clinical Relevance in Post-COVID	References
Cholinergic enhancement	Increased acetylcholine availability	Choline acetyltransferase, acetylcholinesterase inhibition	Improves memory and attention	Stough et al., 2013

Antioxidant activity	ROS scavenging, mitochondrial protection	SOD, catalase, lipid peroxidation inhibition	Reduces neurodegeneration and fatigue	Valotto Neto et al., 2024
Anti-inflammatory effect	Suppression of cytokines	NF- $\kappa$ B, IL-6, TNF- $\alpha$	Reduces neuroinflammation and brain fog	Aguiar & Borowski, 2013
Neurogenesis support	Synaptic remodeling, dendritic growth	BDNF, CREB signaling	Enhances cognitive recovery	Pase et al., 2012
Stress modulation	HPA axis regulation	Cortisol reduction	Improves anxiety and PTSD-like symptoms	Calabrese et al., 2008

## 5. *Centella asiatica*: Neuropharmacology, Anxiolytic Mechanisms, and Clinical Evidence

### 5.1 Introduction and Ethnomedicinal Background

*Centella asiatica* (commonly known as Mandukaparni or Gotu Kola) is a perennial medicinal herb widely used in Ayurveda, Traditional Chinese Medicine, and Southeast Asian ethnomedicine for enhancing cognition, reducing anxiety, and promoting wound healing. It is traditionally classified as a medhya rasayana (brain tonic), similar to *Bacopa monnieri*, and is especially valued for its calming, neuroprotective, and regenerative effects on the nervous system (Byl et al., 2020). Modern research has confirmed that *Centella asiatica* exerts significant anxiolytic, antidepressant, and neurorestorative effects, making it highly relevant for post-COVID neuropsychiatric rehabilitation.

### 5.2 Phytochemistry and Bioactive Constituents

The pharmacological actions of *Centella asiatica* are primarily attributed to its triterpenoid saponins and flavonoids, including:

- Asiaticoside
- Madecassoside
- Asiatic acid
- Madecassic acid
- Kaempferol and quercetin derivatives

These compounds exhibit potent antioxidant, anti-inflammatory, neurogenic, and GABA-modulating activities (Gray et al., 2018).

### 5.3 Neuropharmacological Mechanisms of Action

#### 5.3.1 GABAergic Modulation and Anxiolytic Activity

One of the most important mechanisms of *Centella asiatica* is its ability to modulate the gamma-aminobutyric acid (GABA) system. GABA is the primary inhibitory neurotransmitter in the CNS, responsible for reducing neuronal excitability. Extracts of *Centella asiatica* enhance GABAergic

signaling, leading to anxiolytic and calming effects without significant sedation (Gray et al., 2018). This mechanism is particularly relevant for post-COVID anxiety, irritability, and sleep disturbances.

### **5.3.2 Neuroprotection and Antioxidant Activity**

*Centella asiatica* demonstrates strong antioxidant potential by scavenging reactive oxygen species (ROS) and enhancing endogenous antioxidant enzymes such as glutathione peroxidase and superoxide dismutase. This reduces oxidative neuronal damage, which is a key contributor to post-COVID cognitive dysfunction (Byl et al., 2020).

### **5.3.3 Anti-inflammatory and Microglial Regulation**

Asiaticoside and madecassoside inhibit pro-inflammatory mediators including IL-1 $\beta$ , IL-6, and TNF- $\alpha$ . Additionally, *Centella asiatica* suppresses NF- $\kappa$ B signaling pathways, thereby reducing neuroinflammation and microglial overactivation (Orhan, 2012).

### **5.3.4 Neurogenesis and Synaptic Plasticity**

Preclinical studies show that *Centella asiatica* promotes dendritic growth, synaptogenesis, and neuronal regeneration. It enhances brain-derived neurotrophic factor (BDNF) expression, which is essential for learning, memory formation, and recovery from neurodegeneration (Gray et al., 2018).

### **5.3.5 HPA Axis Regulation and Stress Adaptation**

*Centella asiatica* exhibits adaptogenic properties by regulating the hypothalamic–pituitary–adrenal (HPA) axis, thereby reducing cortisol levels and improving stress resilience. This is particularly important in post-COVID patients experiencing chronic fatigue, emotional instability, and stress-related disorders.

## **5.4 Clinical Evidence in Anxiety, Cognition, and Mood Disorders**

Clinical studies suggest that standardized extracts of *Centella asiatica* significantly improve:

- Anxiety symptoms
- Mood stability
- Working memory and attention
- Sleep quality

A randomized controlled trial demonstrated that acute and chronic administration of *Centella asiatica* reduced anxiety scores and improved self-rated mood in healthy volunteers (Bradwejn et al., 2000). Another study reported cognitive enhancement and improved alertness following supplementation, particularly in individuals with stress-related cognitive decline (Wattanathorn et al., 2008).

However, clinical evidence remains limited in large-scale populations, and variability in extract composition remains a challenge for standardization.

## 5.5 Relevance to Post-COVID Neuropsychiatric Rehabilitation

In post-COVID syndrome, *Centella asiatica* may be particularly beneficial due to its ability to:

- Reduce anxiety and emotional instability
- Improve sleep quality and stress resilience
- Enhance cognitive performance and attention
- Protect neurons from oxidative and inflammatory damage
- Support neuroplasticity and recovery of brain function

Its anxiolytic and adaptogenic profile complements the cognitive-enhancing properties of *Bacopa monnieri*, making them a rational combination in integrative neurorehabilitation strategies.

**Table 4: Mechanisms and Therapeutic Actions of *Centella asiatica***

Mechanistic Domain	Biological Action	Molecular Targets	Relevance in Post-COVID	References
GABAergic modulation	Increased inhibitory neurotransmission	GABA receptors	Reduces anxiety, irritability, insomnia	Gray et al., 2018
Antioxidant activity	ROS scavenging, enzyme upregulation	SOD, glutathione pathways	Reduces oxidative brain injury	Byl et al., 2020
Anti-inflammatory effect	Cytokine suppression	NF- $\kappa$ B, IL-6, TNF- $\alpha$	Reduces neuroinflammation and brain fog	Orhan, 2012
Neurogenesis support	Synaptic growth and repair	BDNF, neuronal differentiation pathways	Enhances cognitive recovery	Gray et al., 2018
HPA axis regulation	Cortisol reduction	Stress hormone modulation	Improves fatigue and emotional stress	Wattanathorn et al., 2008

## 6. Synergistic Potential and Integrative Rehabilitation Strategy

### 6.1 Complementary Mechanisms of *Bacopa monnieri* and *Centella asiatica*

The combination of *Bacopa monnieri* and *Centella asiatica* represents a rational polyherbal strategy in post-COVID neuropsychiatric rehabilitation due to their overlapping yet complementary pharmacodynamic profiles. While *Bacopa monnieri* primarily enhances cognition through cholinergic modulation, synaptic plasticity, and memory consolidation, *Centella asiatica* predominantly exerts anxiolytic and stress-modulating effects via GABAergic pathways and hypothalamic–pituitary–adrenal (HPA) axis regulation (Aguiar & Borowski, 2013; Gray et al., 2018). This dual-action approach targets both cognitive deficits (“brain fog”) and emotional disturbances (anxiety, depression), which are hallmark features of Long COVID.

## 6.2 Combined Effects on Cognition, Mood, and Neuroinflammation

The synergistic interaction between these two herbs may produce a broader neurotherapeutic spectrum than either agent alone. Their combined effects include:

- **Cognitive enhancement:** Improved memory retention, attention, and executive function via cholinergic and neurotrophic pathways
- **Mood stabilization:** Reduction in anxiety, irritability, and depressive symptoms through GABAergic and serotonergic modulation
- **Anti-neuroinflammatory action:** Downregulation of pro-inflammatory cytokines (IL-6, TNF- $\alpha$ ) and NF- $\kappa$ B signaling
- **Neuroprotection:** Reduction of oxidative stress and mitochondrial dysfunction
- **Stress resilience:** Improved adaptation to chronic psychological and physiological stressors

Together, these effects address the multi-dimensional nature of post-COVID neuropsychiatric dysfunction (Pase et al., 2012; Orhan, 2012).

## 6.3 Possible Formulations and Nutraceutical Combinations

Several pharmaceutical and nutraceutical strategies can be considered for optimizing the therapeutic potential of this combination:

### 6.3.1 Polyherbal Extracts

Standardized extracts combining bacosides from *Bacopa monnieri* and triterpenoids (asiaticoside, madecassoside) from *Centella asiatica* can be formulated in capsule or tablet form to ensure consistent bioavailability.

### 6.3.2 Functional Nutraceutical Blends

Combination with complementary nootropics and adaptogens such as:

- *Withania somnifera* (Ashwagandha) for stress reduction
- Omega-3 fatty acids for neuronal membrane stabilization
- Phosphatidylserine for cognitive support

### 6.3.3 Advanced Delivery Systems

- Nanoemulsion-based herbal formulations for improved CNS penetration
- Liposomal encapsulation for enhanced bioavailability
- Sustained-release formulations for long-term neuroprotection

These approaches aim to improve pharmacokinetic stability and therapeutic consistency.

## 6.4 Integration with Psychotherapy, Cognitive Rehabilitation, and Lifestyle Interventions

Phytotherapeutic interventions should not be considered in isolation but as part of a multimodal rehabilitation strategy:

### 6.4.1 Psychotherapy

- Cognitive Behavioral Therapy (CBT) for depression and anxiety
- Trauma-focused therapy for PTSD-like symptoms
- Stress management counseling

### 6.4.2 Cognitive Rehabilitation

- Memory training exercises
- Attention enhancement tasks
- Computer-assisted cognitive remediation programs

### 6.4.3 Lifestyle Modifications

- Regular aerobic physical activity to enhance neurogenesis
- Yoga and meditation for autonomic balance
- Sleep hygiene optimization to restore circadian rhythm
- Anti-inflammatory diet rich in antioxidants and polyphenols

This integrative model enhances neuroplasticity and supports long-term recovery in post-COVID patients.

## 6.5 Safety Profile, Dosage Considerations, and Herb–Drug Interactions

### 6.5.1 Safety Profile

Both *Bacopa monnieri* and *Centella asiatica* are generally considered safe when used within therapeutic dosage ranges. Reported adverse effects are mild and may include gastrointestinal discomfort, nausea, or drowsiness in sensitive individuals (Pase et al., 2012; Gray et al., 2018).

### 6.5.2 Dosage Considerations (General Clinical Ranges)

- *Bacopa monnieri*: 300–450 mg/day standardized extract (typically 45–55% bacosides)
- *Centella asiatica*: 300–600 mg/day standardized extract (asiaticoside-rich formulations)

Therapeutic effects are typically observed after 4–8 weeks of consistent use due to cumulative neuroadaptive mechanisms.

### 6.5.3 Herb–Drug Interactions

Potential interactions include:

- **Sedatives/benzodiazepines:** additive CNS depressant effects (especially with *Centella asiatica*)
- **Anticholinergic drugs:** possible reduction in efficacy due to cholinergic enhancement by *Bacopa*
- **Antidepressants (SSRIs/SNRIs):** theoretical serotonergic modulation requiring monitoring
- **Antihypertensive drugs:** possible additive hypotensive effects

Clinical supervision is recommended when used alongside conventional pharmacotherapy.

**Table 5: Synergistic and Integrative Actions of *Bacopa monnieri* and *Centella asiatica***

Domain	<i>Bacopa monnieri</i> Action	<i>Centella asiatica</i> Action	Combined Synergistic Outcome	References
Cognition	Cholinergic enhancement, memory consolidation	Neurogenesis, synaptic repair	Improved memory, attention, executive function	Aguiar & Borowski, 2013; Gray et al., 2018
Mood regulation	Stress reduction via HPA modulation	GABAergic anxiolysis	Reduced anxiety and depressive symptoms	Calabrese et al., 2008; Bradwejn et al., 2000
Neuroinflammation	NF- $\kappa$ B inhibition, cytokine reduction	Anti-inflammatory triterpenoids	Reduced brain fog and neuroinflammation	Orhan, 2012; Valotto Neto et al., 2024
Oxidative stress	Antioxidant enzyme upregulation	ROS scavenging activity	Enhanced neuroprotection	Pase et al., 2012; Byl et al., 2020
Stress resilience	Cortisol regulation	HPA axis stabilization	Improved adaptation to chronic stress	Gray et al., 2018; Calabrese et al., 2008

## 7. Future Perspectives, Clinical Applications, Biomarkers, and Research Directions

### 7.1 Overview: Need for Translational Neurorehabilitation in Post-COVID Syndrome

Post-COVID syndrome represents a complex, multisystem condition with persistent neuropsychiatric involvement that is not yet fully understood. Despite growing recognition of cognitive impairment, mood disorders, and fatigue as core components of Long COVID, there remains a lack of standardized therapeutic protocols targeting neurorestoration. This gap highlights the need for translational strategies that integrate neuropharmacology, immunology, psychiatry, and phytochemistry into a unified rehabilitation framework (Proal & VanElzakker, 2021).

In this context, medicinal plants such as *Bacopa monnieri* and *Centella asiatica* provide a promising foundation for adjunctive neurotherapeutic development.

## 7.2 Clinical Applications in Neuropsychiatric Rehabilitation

### 7.2.1 Cognitive Recovery Programs

Future clinical applications should focus on structured cognitive recovery protocols where standardized herbal interventions are used alongside cognitive training. *Bacopa monnieri* may be positioned as a core nootropic agent to improve memory consolidation and attention, while *Centella asiatica* supports stress reduction and emotional stabilization.

### 7.2.2 Post-COVID Mental Health Clinics

Dedicated Long COVID clinics may incorporate integrative medicine units where phytotherapy is used as an adjunct to:

- Psychiatric evaluation
- Neuropsychological testing
- Psychotherapy (CBT, mindfulness-based therapy)
- Pharmacological management when necessary

### 7.2.3 Preventive Neuroprotection

Early intervention in post-acute COVID patients may reduce progression to chronic neuropsychiatric syndromes. Herbal neuroprotectants could potentially serve as preventive adjuncts in high-risk populations with persistent inflammatory or cognitive symptoms.

## 7.3 Biomarkers for Monitoring Neurorehabilitation Outcomes

A critical future direction involves identifying objective biomarkers to evaluate therapeutic response in post-COVID neuropsychiatric conditions.

### 7.3.1 Inflammatory Biomarkers

- Interleukin-6 (IL-6)
- Tumor necrosis factor-alpha (TNF- $\alpha$ )
- C-reactive protein (CRP)

These markers reflect systemic and neuroinflammatory burden (Wilson et al., 2020).

### 7.3.2 Neurodegeneration and Plasticity Markers

- Brain-derived neurotrophic factor (BDNF)
- S100B protein (blood–brain barrier integrity marker)
- Neurofilament light chain (NfL)

These are useful for assessing neuronal injury and recovery dynamics.

### 7.3.3 Neurocognitive Assessment Tools

- Montreal Cognitive Assessment (MoCA)
- Digit Span and working memory tests
- Computerized neurocognitive batteries

These functional tools help quantify improvement in cognitive domains.

## 7.4 Research Directions and Evidence Gaps

### 7.4.1 Large-Scale Randomized Controlled Trials

There is a significant need for well-designed, multicenter randomized controlled trials evaluating:

- Standardized *Bacopa monnieri* and *Centella asiatica* extracts
- Optimal dosing regimens
- Long-term safety in post-COVID populations
- Comparative efficacy against conventional nootropics

### 7.4.2 Mechanistic Neuroimaging Studies

Advanced imaging techniques such as:

- Functional MRI (fMRI)
- Positron emission tomography (PET)
- Diffusion tensor imaging (DTI)

can help elucidate how these herbs influence brain connectivity, neuroinflammation, and synaptic plasticity.

### 7.4.3 Systems Biology and Multi-Omics Approaches

Future research should integrate:

- Transcriptomics (gene expression changes)
- Proteomics (inflammatory and neurotrophic proteins)
- Metabolomics (tryptophan–kynurenine pathway alterations)

to fully understand the multi-target effects of herbal neurotherapeutics.

## 7.5 Standardization, Quality Control, and Regulatory Challenges

One of the major barriers to clinical translation is variability in herbal product quality. Future development must ensure:

- Standardized bacoside content in *Bacopa monnieri*
- Standardized asiaticoside/madecassoside ratios in *Centella asiatica*
- Good Manufacturing Practice (GMP) compliance
- Toxicological safety validation
- Regulatory approval frameworks for herbal neurotherapeutics

Without standardization, clinical reproducibility remains limited.

## 7.6 Integrative Model for Future Neurorehabilitation

A future ideal model for post-COVID neuropsychiatric rehabilitation may include:

- **Biomedical layer:** antivirals, antidepressants, symptomatic management
- **Neurorehabilitation layer:** cognitive training, psychotherapy, neurofeedback
- **Phytotherapeutic layer:** *Bacopa monnieri* + *Centella asiatica*
- **Lifestyle layer:** yoga, exercise, sleep optimization, nutrition
- **Biomarker monitoring layer:** inflammatory + neuroplasticity markers

This multi-layered model reflects a precision integrative medicine approach.

## 7.7 Conclusion

Post-COVID neuropsychiatric syndrome represents a long-term global health challenge requiring innovative, multimodal therapeutic strategies. The combined use of *Bacopa monnieri* and *Centella asiatica* offers a scientifically plausible and mechanistically supported approach to cognitive and emotional rehabilitation.

However, future progress depends on rigorous clinical validation, biomarker-guided therapy, and standardized formulations. Integrating phytomedicine with modern neuroscience may ultimately provide a holistic and sustainable pathway for restoring mental health and cognitive function in post-COVID populations.

## References

- Aguiar, S., & Borowski, T. (2013). Neuropharmacological review of *Bacopa monnieri*. *Rejuvenation Research*, 16(4), 313–326. <https://doi.org/10.1089/rej.2013.1431>
- Becker, J. H., Lin, J. J., Doernberg, M., Stone, K., Navis, A., Festa, J. R., & Wisnivesky, J. P. (2021). Assessment of cognitive function in patients after COVID-19 infection. *JAMA Network Open*, 4(10), e2130645. <https://doi.org/10.1001/jamanetworkopen.2021.30645>
- Bradwejn, J., Zhou, Y., Koszycki, D., Shlik, J., Markovska, V., & Mason, P. (2000). A double-blind, placebo-controlled study on the effects of *Centella asiatica* in anxiety. *Journal of Clinical Psychopharmacology*, 20(6), 680–684.

- Byl, K. N., et al. (2020). Neuroprotective effects of medicinal plants in CNS disorders: Focus on *Centella asiatica*. *Neurochemistry International*, 138, 104756. <https://doi.org/10.1016/j.neuint.2020.104756>
- Calabrese, C., Gregory, W. L., Leo, M., Kraemer, D., Bone, K., & Oken, B. (2008). Effects of standardized *Bacopa monnieri* extract on cognitive performance, anxiety, and depression. *Journal of Alternative and Complementary Medicine*, 14(7), 707–713.
- Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature Reviews Neuroscience*, 9(1), 46–56. <https://doi.org/10.1038/nrn2297>
- Ellul, M. A., Benjamin, L., Singh, B., Lant, S., Michael, B. D., Easton, A., ... Solomon, T. (2020). Neurological associations of COVID-19. *The Lancet Neurology*, 19(9), 767–783. [https://doi.org/10.1016/S1474-4422\(20\)30221-0](https://doi.org/10.1016/S1474-4422(20)30221-0)
- Gray, N. E., et al. (2018). *Centella asiatica*: Phytochemistry and mechanisms of neuroprotection. *Journal of Ethnopharmacology*, 224, 1–12. <https://doi.org/10.1016/j.jep.2018.05.003>
- Heneka, M. T., Golenbock, D., Latz, E., Morgan, D., & Brown, R. (2020). Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. *Alzheimer's Research & Therapy*, 12, 69. <https://doi.org/10.1186/s13195-020-00640-3>
- Komaroff, A. L., & Lipkin, W. I. (2021). Insights from myalgic encephalomyelitis/chronic fatigue syndrome may help understand post-COVID syndrome. *Trends in Molecular Medicine*, 27(9), 895–906. <https://doi.org/10.1016/j.molmed.2021.05.003>
- Mahalakshmi, A. M., Ray, B., Tuladhar, S., Bhat, A. H., Panicker, M. M., & Arjunan, A. (2021). Does COVID-19 contribute to development of neurological disease? *Translational Neuroscience*, 12(1), 42–50. <https://doi.org/10.1515/tnsci-2020-0189>
- Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., ... Hu, B. (2020). Neurologic manifestations of hospitalized patients with COVID-19 in Wuhan, China. *JAMA Neurology*, 77(6), 683–690. <https://doi.org/10.1001/jamaneurol.2020.1127>
- Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nature Reviews Immunology*, 16(1), 22–34. <https://doi.org/10.1038/nri.2015.5>
- Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M. V., McGroder, C., Stevens, J. S., ... Wan, E. Y. (2021). Post-acute COVID-19 syndrome. *Nature Medicine*, 27(4), 601–615. <https://doi.org/10.1038/s41591-021-01283-z>
- Orhan, I. E. (2012). *Centella asiatica* (L.) Urban: From traditional medicine to modern pharmacology. *Journal of Ethnopharmacology*, 142(2), 419–425. <https://doi.org/10.1016/j.jep.2012.05.009>
- Pase, M. P., Kean, J., Sarris, J., Neale, C., Scholey, A. B., & Stough, C. (2012). The cognitive-enhancing effects of *Bacopa monnieri*: A systematic review of randomized controlled trials. *Journal of Ethnopharmacology*, 142(1), 1–10.
- Pellegrini, L., Albecka, A., Mallery, D. L., Kellner, M. J., & Diamond, I. (2020). SARS-CoV-2 infects the brain choroid plexus and disrupts the blood–CSF barrier. *Cell Stem Cell*, 27(6), 951–961.e5. <https://doi.org/10.1016/j.stem.2020.10.001>

- Proal, A. D., & VanElzakker, M. B. (2021). Long COVID or post-acute sequelae of COVID-19 (PASC): An overview of biological factors. *Frontiers in Microbiology*, *12*, 698169. <https://doi.org/10.3389/fmicb.2021.698169>
- Rogers, J. P., Chesney, E., Oliver, D., Pollak, T. A., McGuire, P., Fusar-Poli, P., & David, A. S. (2020). Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections. *The Lancet Psychiatry*, *7*(7), 611–627. [https://doi.org/10.1016/S2215-0366\(20\)30203-0](https://doi.org/10.1016/S2215-0366(20)30203-0)
- Taquet, M., Geddes, J. R., Husain, M., Luciano, S., & Harrison, P. J. (2021). Neurological and psychiatric outcomes after COVID-19 infection. *The Lancet Psychiatry*, *8*(5), 416–427. [https://doi.org/10.1016/S2215-0366\(21\)00084-5](https://doi.org/10.1016/S2215-0366(21)00084-5)
- Valotto Neto, L. J., et al. (2024). Investigating the neuroprotective and cognitive-enhancing effects of *Bacopa monnieri*. *Antioxidants*, *13*(4), 393. <https://doi.org/10.3390/antiox13040393>
- Wattanathorn, J., Chonpathompikunlert, P., Muchimapura, S., & Priprem, A. (2008). Cognitive-enhancing effects of *Centella asiatica* in healthy elderly volunteers. *Journal of Ethnopharmacology*, *116*(3), 325–332. <https://doi.org/10.1016/j.jep.2007.12.008>
- Wilson, J. G., et al. (2020). Cytokine profiles and inflammatory signatures in COVID-19. *Nature Reviews Immunology*, *20*, 585–588. <https://doi.org/10.1038/s41577-020-0346-8>
- World Health Organization. (2021). *A clinical case definition of post COVID-19 condition by a Delphi consensus*. <https://www.who.int>

## Chapter 10: Future Perspectives of Herbal Antivirals and Adaptogens: *Nigella sativa* and *Panax ginseng* in COVID-19 and Neuropsychiatric Disorders

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### Abstract

The COVID-19 pandemic has not only caused acute respiratory illness but has also led to long-term neurological and neuropsychiatric complications collectively termed post-COVID syndrome or Long COVID. Increasing clinical and experimental evidence highlights the central role of immune dysregulation, persistent neuroinflammation, oxidative stress, mitochondrial dysfunction, endothelial injury, and hypothalamic–pituitary–adrenal (HPA) axis imbalance in the development of anxiety, depression, cognitive impairment, sleep disturbances, and chronic fatigue following SARS-CoV-2 infection. These multifactorial alterations suggest that post-COVID syndrome is not merely a residual infectious condition but a complex systemic disorder involving interconnected neuroimmune and neuroendocrine pathways. In this context, herbal antivirals and adaptogens have gained renewed scientific attention as potential multi-target therapeutic agents capable of restoring physiological balance and modulating disease-associated pathways. Unlike single-target synthetic drugs, medicinal plants offer a broad spectrum of bioactive compounds that act synergistically on multiple molecular targets, making them particularly relevant for complex conditions such as COVID-19 and its long-term sequelae. *Nigella sativa* (black seed) and *Panax ginseng* (Asian ginseng) are two well-documented medicinal plants with extensive pharmacological profiles, including antiviral, anti-inflammatory, immunomodulatory, antioxidant, and neuroprotective activities. The principal bioactive compound of *N. sativa*, thymoquinone, has demonstrated significant regulatory effects on nuclear factor-kappa B (NF-κB) signaling, pro-inflammatory cytokine production (IL-6, TNF-α, IL-1β), and oxidative stress pathways. These actions contribute to reduced systemic inflammation, protection against neuronal injury, and improved immune homeostasis. Similarly, *Panax ginseng* contains a diverse group of pharmacologically active constituents known as ginsenosides, which exert neuroprotective and immunoregulatory effects through modulation of the hypothalamic–pituitary–adrenal axis, enhancement of cholinergic transmission, regulation of dopaminergic and serotonergic systems, and attenuation of microglial activation. These mechanisms collectively support cognitive function, emotional stability, and stress resilience. Furthermore, both *Nigella sativa* and *Panax ginseng* exhibit adaptogenic properties that help the body maintain homeostasis under physiological and psychological stress. This adaptogenic action may be particularly beneficial in post-COVID patients, where chronic stress, fatigue, and neurochemical imbalance are commonly observed. By improving stress response regulation, energy metabolism, and immune adaptability, these herbs may contribute to improved mental health outcomes and enhanced recovery trajectories. This chapter explores the mechanistic basis, experimental findings, and clinical evidence supporting the therapeutic relevance of *Nigella sativa* and *Panax ginseng* in COVID-19 management and associated neuropsychiatric disorders.

### Keywords

COVID-19; Long COVID; *Nigella sativa*; *Panax ginseng*; adaptogens; herbal antivirals; neuroinflammation; neuropsychiatric disorders; oxidative stress; immunomodulation; thymoquinone; ginsenosides; depression; anxiety; cognitive dysfunction

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## 1. Introduction: Rationale and Emerging Role of Herbal Antivirals and Adaptogens

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has created an unprecedented global health crisis, affecting millions of individuals worldwide and exerting long-lasting consequences that extend beyond acute respiratory illness. While the primary clinical focus initially centered on pulmonary complications and mortality, it has become increasingly evident that the infection also induces significant systemic and neurological disturbances. A substantial proportion of recovered patients continue to experience persistent symptoms such as fatigue, dyspnea, cognitive impairment, sleep disturbances, and mood disorders, collectively referred to as post-COVID syndrome or Long COVID. This condition has emerged as a major public health concern due to its chronic nature and impact on quality of life and productivity (Nalbandian et al., 2021; Mahalakshmi et al., 2021).

Among the most concerning sequelae of COVID-19 is the rise in neuropsychiatric disorders. Clinical and observational studies have reported increased incidence of depression, generalized anxiety disorder, post-traumatic stress disorder (PTSD), and cognitive dysfunction in post-COVID individuals. These manifestations are believed to arise from a complex interplay of neuroinflammation, immune dysregulation, endothelial dysfunction, hypoxia, and dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis. SARS-CoV-2 has also been implicated in disrupting blood–brain barrier integrity and inducing microglial activation, thereby contributing to long-term neurochemical imbalance and neurodegeneration (Taquet et al., 2021; Boldrini et al., 2021). Consequently, post-COVID neuropsychiatric complications are now recognized as a significant dimension of the pandemic’s long-term burden.

In response to these multifaceted challenges, there is a growing interest in complementary and integrative therapeutic strategies, particularly herbal antivirals and adaptogens. Herbal antivirals are natural compounds derived from medicinal plants that exhibit inhibitory activity against viral entry, replication, or host–virus interactions, often through multi-target mechanisms. Adaptogens, on the other hand, are biologically active plant-derived substances that enhance the body’s resilience to physical, emotional, and environmental stress while restoring homeostasis. Unlike single-target synthetic drugs, these phytotherapeutic agents act on complex biological networks, including immune regulation, oxidative stress pathways, and neuroendocrine signaling systems, making them particularly suitable for complex diseases such as COVID-19 and its neuropsychiatric consequences (Panossian & Wikman, 2010).

The scientific rationale for integrating herbal antivirals and adaptogens into modern pharmacotherapy is supported by their pleiotropic mechanisms of action. These include modulation of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- $\alpha$ ), enhancement of antioxidant defense systems such as nuclear factor erythroid 2–related factor 2 (Nrf2) signaling, and regulation of neurotransmitters involved in mood and cognition, including serotonin, dopamine, and gamma-aminobutyric acid (GABA). This multi-target pharmacological profile aligns well with the pathophysiology of both viral infections and neuropsychiatric disorders, which are inherently multifactorial in nature.

Within this context, *Nigella sativa* (black seed) and *Panax ginseng* (Asian ginseng) have emerged as particularly promising medicinal plants. *Nigella sativa*, a widely used herb in traditional Unani and

Ayurvedic systems, contains thymoquinone as its principal bioactive compound, which has demonstrated antiviral, anti-inflammatory, antioxidant, and neuroprotective activities in multiple experimental models. Similarly, *Panax ginseng*, a cornerstone of traditional East Asian medicine, is rich in ginsenosides that exhibit adaptogenic, immunomodulatory, and neurocognitive-enhancing properties. Both herbs have shown potential in regulating immune responses, reducing oxidative stress, and improving stress resilience, thereby addressing key pathological mechanisms involved in COVID-19 and post-COVID neuropsychiatric disorders (Ahmad et al., 2020; Attele et al., 1999).

The selection of these two botanicals is further justified by their strong ethnopharmacological background combined with emerging scientific validation. Ethnopharmacology provides a historical foundation for the therapeutic use of medicinal plants, while modern pharmacological and clinical research offers evidence-based validation of their efficacy and safety. The convergence of these two disciplines supports the development of integrative medicine approaches that bridge traditional knowledge with contemporary biomedical science. This integration is particularly important in the context of complex, systemic diseases such as COVID-19, where single-target pharmacological strategies may be insufficient.

In conclusion, the emerging role of herbal antivirals and adaptogens represents a promising frontier in the management of COVID-19 and its associated neuropsychiatric complications. *Nigella sativa* and *Panax ginseng* exemplify the therapeutic potential of phytomedicine in addressing both viral pathogenesis and mental health outcomes through multi-target, systems-based mechanisms. Continued interdisciplinary research combining ethnopharmacology, molecular biology, and clinical medicine is essential to fully realize their translational potential in modern healthcare systems.

## 2. COVID-19 Pathophysiology and Neuropsychiatric Sequelae

### 2.1 SARS-CoV-2 Infection Mechanisms: ACE2 Receptor, Cytokine Storm, and Oxidative Stress

SARS-CoV-2 enters host cells primarily through the angiotensin-converting enzyme 2 (ACE2) receptor, which is widely expressed in the respiratory epithelium, vascular endothelium, gastrointestinal tract, and central nervous system. The viral spike (S) protein binds to ACE2, followed by priming via transmembrane protease serine 2 (TMPRSS2), facilitating viral entry and replication. This interaction not only promotes viral dissemination but also downregulates ACE2 expression, disrupting the renin–angiotensin system (RAS), leading to vasoconstriction, inflammation, and oxidative stress (Hoffmann et al., 2020; Varga et al., 2020).

A hallmark of severe COVID-19 is the cytokine storm, characterized by excessive release of pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-1 $\beta$ , and tumor necrosis factor-alpha (TNF- $\alpha$ ). This hyperinflammatory state contributes to multi-organ damage, including neural tissue injury. Simultaneously, oxidative stress is significantly elevated due to mitochondrial dysfunction and excessive reactive oxygen species (ROS) production, further aggravating cellular damage and neurotoxicity (Del Valle et al., 2020).

## 2.2 Neuroinflammation and Blood–Brain Barrier (BBB) Disruption

SARS-CoV-2 affects the central nervous system (CNS) through multiple pathways, including hematogenous spread, neuronal retrograde transport, and immune-mediated injury. One of the critical mechanisms is blood–brain barrier (BBB) disruption, which allows peripheral immune cells and inflammatory mediators to infiltrate the CNS. Once inside the CNS, activated microglia and astrocytes initiate a neuroinflammatory cascade, releasing cytokines and chemokines that impair neuronal function and synaptic plasticity. This chronic inflammatory state has been linked to cognitive decline, mood disorders, and neurodegenerative changes (Pellegrini et al., 2020; Matschke et al., 2020).

## 2.3 Post-COVID Syndrome (Long COVID): Neurological and Psychiatric Manifestations

Post-COVID syndrome, also known as Long COVID, is characterized by persistent symptoms lasting weeks to months after acute infection. Neurological and psychiatric manifestations are among the most frequently reported symptoms.

**Table 1: Major Neuropsychiatric Manifestations of Long COVID**

System Domain	Clinical Manifestations	Underlying Mechanisms
Cognitive	Memory impairment, brain fog, reduced attention	Neuroinflammation, synaptic dysfunction
Psychiatric	Depression, anxiety, PTSD, irritability	HPA axis dysregulation, cytokine imbalance
Neurological	Headache, dizziness, neuropathic pain	Neurovascular injury, oxidative stress
Sleep-related	Insomnia, disrupted circadian rhythm	Melatonin dysregulation, stress response
Fatigue-related	Chronic fatigue syndrome-like symptoms	Mitochondrial dysfunction, immune exhaustion

These manifestations significantly reduce quality of life and functional capacity, often persisting even after viral clearance (Nalbandian et al., 2021; Taquet et al., 2021).

## 2.4 Role of Immune Dysregulation in Mood and Cognitive Disorders

Immune dysregulation plays a central role in the development of neuropsychiatric symptoms following COVID-19. Elevated inflammatory markers such as IL-6, CRP, and TNF- $\alpha$  are strongly associated with depressive symptoms and cognitive impairment. These cytokines influence neurotransmitter metabolism by reducing serotonin availability, altering dopamine signaling, and impairing neurogenesis in the hippocampus. Moreover, chronic immune activation leads to HPA axis hyperactivation, resulting in sustained cortisol release. Prolonged cortisol exposure negatively affects hippocampal neurons, contributing to memory deficits and emotional dysregulation (Dantzer et al., 2008; Miller & Raison, 2016).

## 2.5 Viral Infection and Chronic Neurodegeneration Link

Emerging evidence suggests that SARS-CoV-2 infection may increase the long-term risk of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. This association is driven by persistent neuroinflammation, protein misfolding, oxidative stress, and mitochondrial dysfunction.

Activated microglia release neurotoxic mediators that accelerate neuronal loss, while oxidative stress promotes beta-amyloid aggregation and tau phosphorylation. Additionally, viral-induced endothelial dysfunction may contribute to cerebral hypoperfusion, further exacerbating neurodegeneration (Heneka et al., 2020; Matschke et al., 2020).

**Table 2: Pathophysiological Pathways Linking COVID-19 to Neuropsychiatric Outcomes**

Pathway	Biological Effect	Clinical Outcome
ACE2 downregulation	RAS imbalance, vasoconstriction	Neurovascular injury
Cytokine storm	Excess IL-6, TNF- $\alpha$ release	Depression, anxiety
BBB disruption	Immune cell infiltration into CNS	Neuroinflammation
Oxidative stress	ROS-mediated neuronal damage	Cognitive decline
HPA axis dysregulation	Cortisol imbalance	PTSD, mood disorders
Mitochondrial dysfunction	Energy failure in neurons	Chronic fatigue syndrome

COVID-19 is not merely a respiratory illness but a complex multisystem disease with profound neurological and psychiatric consequences. The interplay between viral entry mechanisms, immune hyperactivation, oxidative stress, and neuroinflammation creates a biological environment conducive to both acute CNS injury and long-term neuropsychiatric sequelae. Understanding these mechanisms is essential for developing targeted therapeutic strategies, including emerging interest in immunomodulatory and neuroprotective phytotherapeutics.

## 3. Pharmacological Profile of *Nigella sativa* (Black Seed)

### 3.1 Botanical Background and Bioactive Constituents

*Nigella sativa* (Ranunculaceae), commonly known as black seed or "kalonji," has been widely used in traditional Unani, Ayurvedic, and Middle Eastern medicine for centuries. Its therapeutic potential is primarily attributed to a rich phytochemical profile, including thymoquinone (TQ), thymohydroquinone, dithymoquinone, nigellidine, and  $\alpha$ -hederin. Among these, thymoquinone is considered the principal bioactive molecule responsible for most pharmacological activities (Randhawa & Alghamdi, 2011).

### 3.2 Antiviral and Immunomodulatory Properties

*N. sativa* exhibits broad-spectrum antiviral activity through multiple mechanisms, including inhibition of viral entry, suppression of viral replication enzymes, and modulation of host immune responses. Experimental studies suggest that thymoquinone may interfere with viral proteases and reduce viral load

by enhancing innate immune responses. Additionally, it modulates both humoral and cell-mediated immunity by regulating T-helper cell balance (Th1/Th2 shift) and enhancing natural killer (NK) cell activity. This immunomodulatory effect is particularly relevant in COVID-19, where immune overactivation and cytokine dysregulation play a central role (Ahmad et al., 2020).

### 3.3 Anti-inflammatory and Antioxidant Mechanisms

A major therapeutic benefit of *Nigella sativa* is its strong anti-inflammatory action mediated through suppression of nuclear factor kappa B (NF- $\kappa$ B) signaling. This results in decreased production of pro-inflammatory cytokines such as IL-6, IL-1 $\beta$ , and TNF- $\alpha$ . Simultaneously, it enhances antioxidant defense systems by upregulating enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. This dual action reduces oxidative stress, a key contributor to both COVID-19 severity and neuropsychiatric complications (Gholamnezhad et al., 2019).

### 3.4 Neuroprotective and Psychopharmacological Effects

*Nigella sativa* demonstrates significant neuroprotective properties through modulation of neurotransmitters and attenuation of neuroinflammation. Thymoquinone has been shown to enhance serotonin and dopamine levels, contributing to antidepressant and anxiolytic effects.

It also inhibits microglial activation and reduces neuronal apoptosis, thereby protecting against cognitive decline and neurodegeneration. These properties make it a potential candidate for managing post-COVID depression, anxiety, and cognitive dysfunction (Ismail et al., 2013).

**Table 3. Pharmacological Actions of *Nigella sativa* Relevant to COVID-19 and Neuropsychiatric Disorders**

Pharmacological Action	Molecular Target	Therapeutic Outcome
Antiviral activity	Viral proteases, replication pathways	Reduced viral load
Anti-inflammatory	NF- $\kappa$ B, IL-6, TNF- $\alpha$	Cytokine suppression
Antioxidant	SOD, catalase, glutathione	Reduced oxidative stress
Immunomodulatory	T-cell balance, NK cells	Immune homeostasis
Neuroprotective	Microglial inhibition	Cognitive protection
Antidepressant-like	Serotonin, dopamine pathways	Mood stabilization

### 3.5 Evidence from Preclinical and Clinical Studies

Preclinical studies consistently demonstrate that thymoquinone reduces lung inflammation, improves survival in sepsis models, and protects neural tissue from oxidative damage. In clinical settings, *Nigella sativa* supplementation has shown benefits in improving respiratory symptoms, glycemic control, and inflammatory markers in COVID-19 patients. A randomized controlled trial reported faster symptom resolution and reduced hospitalization duration in patients receiving black seed supplementation, suggesting its adjunct therapeutic potential (Koshak et al., 2021).

### 3.6 Safety Profile and Limitations

*Nigella sativa* is generally considered safe when used within therapeutic doses. However, high doses may cause gastrointestinal discomfort or hypotension in sensitive individuals. Potential interactions with anticoagulants and antihypertensive drugs should be carefully monitored. Despite promising evidence, limitations include variability in extract standardization, small sample sizes in clinical trials, and lack of large-scale multicenter randomized studies.

*Nigella sativa* represents a multifaceted medicinal plant with strong antiviral, immunomodulatory, antioxidant, and neuroprotective properties. Its principal compound, thymoquinone, targets key molecular pathways involved in both COVID-19 pathogenesis and neuropsychiatric disorders, making it a promising candidate for integrative therapeutic strategies. However, further rigorous clinical validation is essential to establish standardized dosing and long-term safety.

## 4. Pharmacological Profile of *Panax ginseng* (Asian Ginseng)

### 4.1 Botanical Background and Major Bioactive Constituents

*Panax ginseng* C.A. Meyer (Araliaceae), commonly known as Asian ginseng, is one of the most extensively studied medicinal plants in traditional East Asian medicine. It has been used for centuries as a “Qi tonic” to enhance vitality, physical endurance, cognitive performance, and resistance to stress-related disorders. The pharmacological activity of *Panax ginseng* is primarily attributed to a diverse group of triterpene saponins known as ginsenosides, along with polysaccharides, peptides, and polyacetylenes. Major ginsenosides include Rb1, Rg1, Rg3, Re, and Rd, each exhibiting distinct neuroprotective, immunomodulatory, and adaptogenic properties (Attele et al., 1999; Christensen, 2009).

### 4.2 Adaptogenic Activity and HPA Axis Regulation

One of the defining features of *Panax ginseng* is its adaptogenic effect, meaning its ability to enhance the body’s nonspecific resistance to physical, chemical, and biological stressors. This action is primarily mediated through modulation of the hypothalamic–pituitary–adrenal (HPA) axis.

Ginsenosides regulate cortisol secretion, stabilize stress hormone levels, and improve resilience to chronic stress. This is particularly relevant in post-COVID patients, where HPA axis dysregulation contributes to fatigue, anxiety, and depressive symptoms (Panossian & Wikman, 2010).

### 4.3 Immunomodulatory and Antiviral Mechanisms

*Panax ginseng* enhances both innate and adaptive immune responses. It increases macrophage activity, enhances natural killer (NK) cell cytotoxicity, and promotes T-cell proliferation. These effects improve host defense against viral infections.

In viral contexts, ginsenosides have demonstrated inhibitory effects on viral attachment and replication, while also reducing excessive inflammatory responses. This dual immunomodulatory action is critical in preventing both viral progression and cytokine-mediated tissue damage (Sen & Chavan, 2011).

#### 4.4 Neuroprotective and Cognitive Enhancing Effects

Ginsenosides exert strong neuroprotective effects through multiple mechanisms, including inhibition of neuronal apoptosis, enhancement of neurogenesis, and protection against oxidative stress-induced neuronal injury.

They modulate neurotransmitter systems, particularly acetylcholine, dopamine, and serotonin pathways, leading to improvements in memory, attention, and executive function. These effects make *Panax ginseng* particularly relevant for post-COVID cognitive dysfunction and “brain fog” (Kennedy & Scholey, 2003).

Additionally, ginsenosides suppress microglial activation and reduce neuroinflammation, thereby protecting against long-term neurodegenerative changes.

#### 4.5 Antioxidant and Anti-inflammatory Pathways

*Panax ginseng* enhances endogenous antioxidant defenses by upregulating enzymes such as superoxide dismutase (SOD), glutathione peroxidase, and catalase. It also reduces lipid peroxidation and mitochondrial dysfunction.

Anti-inflammatory effects are mediated through suppression of NF- $\kappa$ B signaling and downregulation of pro-inflammatory cytokines including IL-6, IL-1 $\beta$ , and TNF- $\alpha$ . These pathways are highly relevant in COVID-19-related systemic inflammation and neuropsychiatric sequelae (Lee et al., 2015).

**Table 4: Pharmacological Actions of *Panax ginseng* Relevant to COVID-19 and Neuropsychiatric Disorders**

Pharmacological Action	Key Molecular Targets	Therapeutic Outcome
Adaptogenic effect	HPA axis, cortisol regulation	Stress resilience, fatigue reduction
Immunomodulation	NK cells, T-cells, macrophages	Enhanced antiviral defense
Antiviral activity	Viral entry/replication pathways	Reduced viral proliferation
Neuroprotection	Neuronal apoptosis, microglia	Cognitive preservation
Antioxidant effect	SOD, catalase, glutathione	Reduced oxidative stress
Antidepressant-like	Dopamine, serotonin pathways	Mood improvement

#### 4.6 Clinical Evidence and Therapeutic Applications

Clinical studies have shown that *Panax ginseng* supplementation improves physical performance, reduces fatigue, and enhances cognitive function in both healthy individuals and patients with chronic illnesses.

In the context of viral infections, ginseng has been associated with reduced incidence and duration of respiratory infections. Some clinical trials suggest improved immune response to influenza vaccination, indicating its role as an immune enhancer.

In neuropsychiatric conditions, ginseng has demonstrated benefits in improving working memory, attention, and mood regulation, particularly in stress-related disorders and mild cognitive impairment (Reay et al., 2005; Kennedy et al., 2011).

#### 4.7 Safety Profile and Limitations

*Panax ginseng* is generally well tolerated when used at recommended doses. However, excessive intake may lead to side effects such as insomnia, hypertension, nervousness, or gastrointestinal disturbances.

Drug interactions may occur with anticoagulants, antidiabetic agents, and antidepressants, requiring careful monitoring. Additionally, variability in ginsenoside content among commercial preparations remains a major challenge for standardization and reproducibility of clinical outcomes.

*Panax ginseng* is a powerful adaptogenic and neuroprotective medicinal plant with broad immunomodulatory, antiviral, antioxidant, and cognitive-enhancing properties. Its active constituents, particularly ginsenosides, target multiple biological pathways relevant to both COVID-19 pathophysiology and neuropsychiatric disorders. These characteristics position *Panax ginseng* as a promising candidate for integrative management of post-COVID syndrome and stress-related neurological dysfunctions.

### 5. Mechanistic Synergy in COVID-19 and Neuropsychiatric Disorders

#### 5.1 Concept of Phytopharmacological Synergy

The combined use of *Nigella sativa* and *Panax ginseng* represents a multi-target phytotherapeutic strategy based on the principle of pharmacological synergy. Unlike single-molecule drugs, these botanicals act on interconnected biological networks involved in viral infection, immune dysregulation, oxidative stress, and neuropsychiatric dysfunction.

Synergy occurs when the combined therapeutic effect exceeds the sum of individual effects due to complementary modulation of molecular pathways. In the context of COVID-19 and post-COVID neuropsychiatric disorders, this approach is particularly relevant because of the disease's multifactorial pathophysiology (Panossian & Wikman, 2010).

#### 5.2 Combined Antiviral Mechanisms

Both *Nigella sativa* (thymoquinone) and *Panax ginseng* (ginsenosides) exhibit antiviral activity through distinct but complementary mechanisms:

- Inhibition of viral entry via modulation of host cell receptors and membrane fusion processes
- Suppression of viral replication enzymes and protease activity

- Enhancement of innate immune antiviral defenses (NK cell activation, interferon signaling)

While *N. sativa* primarily interferes with inflammatory viral cascades, *P. ginseng* strengthens host resistance, creating a dual-layer antiviral defense system (Ahmad et al., 2020; Sen & Chavan, 2011).

### 5.3 Immunomodulation and Cytokine Storm Regulation

A central feature of severe COVID-19 is the cytokine storm characterized by excessive IL-6, TNF- $\alpha$ , and IL-1 $\beta$  production. Both herbs modulate immune responses but through complementary pathways:

- *Nigella sativa* suppresses NF- $\kappa$ B signaling and reduces pro-inflammatory cytokine synthesis
- *Panax ginseng* regulates macrophage and T-cell activity while preventing immune exhaustion

Together, they help restore immune homeostasis, reducing the risk of hyperinflammation while maintaining antiviral defense capacity (Del Valle et al., 2020).

**Table 5: Complementary Immunomodulatory Actions of *Nigella sativa* and *Panax ginseng***

Immune Pathway	<i>Nigella sativa</i> Effect	<i>Panax ginseng</i> Effect	Combined Outcome
NF- $\kappa$ B signaling	Strong inhibition	Moderate inhibition	Reduced cytokine storm
IL-6 / TNF- $\alpha$	Downregulation	Regulation via immune balance	Controlled inflammation
T-cell response	Th1/Th2 modulation	T-cell activation support	Immune equilibrium
NK cell activity	Enhancement	Strong activation	Improved antiviral defense
Oxidative stress	High antioxidant activity	Moderate antioxidant support	Synergistic ROS reduction

### 5.4 Neuroinflammation and Brain Protection Synergy

Post-COVID neuropsychiatric disorders are strongly linked to persistent neuroinflammation and microglial activation. Both herbs act synergistically in the CNS:

- *Nigella sativa* reduces microglial activation and neuronal apoptosis via thymoquinone
- *Panax ginseng* enhances neurogenesis and synaptic plasticity via ginsenosides

This combination provides dual neuroprotection, targeting both inflammatory and degenerative pathways, thereby reducing risk of cognitive decline and mood disorders (Heneka et al., 2020).

### 5.5 Neurotransmitter and HPA Axis Regulation

Neuropsychiatric symptoms such as depression, anxiety, and PTSD in Long COVID are associated with neurotransmitter imbalance and HPA axis dysregulation.

- *Nigella sativa* increases serotonin and GABAergic activity, producing anxiolytic and antidepressant-like effects
- *Panax ginseng* modulates dopamine, acetylcholine, and cortisol levels, improving motivation, cognition, and stress response

Their combined action leads to multi-neurotransmitter stabilization, improving emotional regulation and cognitive performance.

### 5.6 Mitochondrial Function and Oxidative Stress Protection

Mitochondrial dysfunction is a key driver of post-viral fatigue and neurocognitive impairment.

- *Nigella sativa* enhances antioxidant enzyme activity (SOD, catalase, glutathione)
- *Panax ginseng* improves mitochondrial energy metabolism and ATP production

Together, they restore cellular bioenergetics and reduce oxidative damage, addressing chronic fatigue and “brain fog” symptoms seen in Long COVID.

### 5.7 Gut–Brain–Immune Axis Modulation

Emerging evidence suggests that COVID-19-related neuropsychiatric symptoms are influenced by gut microbiota dysbiosis.

- *Nigella sativa* exhibits antimicrobial and gut-protective effects
- *Panax ginseng* supports beneficial microbiota and intestinal barrier integrity

This leads to improved gut–brain–immune axis stability, indirectly enhancing mental health and immune regulation.

**Table 6: Integrated Mechanistic Synergy in COVID-19 and Neuropsychiatric Disorders**

Pathological Domain	<i>Nigella sativa</i> Action	<i>Panax ginseng</i> Action	Therapeutic Synergy
Viral replication	Protease inhibition	Immune activation	Reduced viral load
Cytokine storm	NF-κB suppression	Immune modulation	Controlled inflammation
Neuroinflammation	Microglial inhibition	Neurogenesis support	Brain protection
Neurotransmission	Serotonin/GABA increase	Dopamine/acetylcholine balance	Mood stabilization
Mitochondria	Antioxidant defense	ATP enhancement	Fatigue reduction
Gut–brain axis	Gut protection	Microbiota support	Systemic homeostasis

### 5.8 Clinical and Translational Implications

The synergistic combination of *Nigella sativa* and *Panax ginseng* provides a rational basis for integrative therapeutic strategies targeting both COVID-19 and post-COVID neuropsychiatric complications. Their

multi-target actions align with systems biology approaches, making them suitable for adjunct therapy rather than monotherapy.

However, translation into clinical practice requires:

- Standardized extract formulations
- Dose optimization studies
- Large-scale randomized controlled trials
- Pharmacokinetic and interaction profiling

The mechanistic synergy between *Nigella sativa* and *Panax ginseng* offers a comprehensive therapeutic approach addressing viral pathology, immune dysregulation, oxidative stress, and neuropsychiatric dysfunction. Their complementary pharmacological actions support the concept of multi-target phytotherapy in managing complex post-COVID conditions.

## 6. Clinical Evidence, Safety, and Therapeutic Limitations

### 6.1 Overview of Clinical Evidence in COVID-19 and Related Disorders

The clinical evaluation of *Nigella sativa* and *Panax ginseng* in viral infections and neuropsychiatric conditions has expanded in recent years, although robust large-scale randomized controlled trials (RCTs) specifically targeting COVID-19 and Long COVID remain limited. Most available evidence is derived from small clinical studies, observational cohorts, and extrapolation from respiratory and immune-related disorders.

In COVID-19 settings, *Nigella sativa* has demonstrated potential benefits in reducing symptom severity, improving oxygen saturation, and shortening recovery time when used as an adjunct therapy. Similarly, *Panax ginseng* has been associated with improved immune response, reduced fatigue, and enhanced recovery in respiratory infections and post-viral fatigue states (Koshak et al., 2021; McElhaney et al., 2011).

### 6.2 Clinical Evidence of *Nigella sativa*

Several clinical investigations have explored the therapeutic role of *Nigella sativa* in infectious and inflammatory conditions:

- Adjunct supplementation with black seed oil has been associated with faster symptom resolution in COVID-19 patients
- Improvement in inflammatory markers such as CRP and IL-6 has been observed
- Enhanced respiratory function and reduced hospitalization duration have been reported in mild to moderate cases

These findings suggest that *Nigella sativa* may act as a supportive therapy in viral infections through immunomodulatory and anti-inflammatory pathways (Koshak et al., 2021).

### 6.3 Clinical Evidence of *Panax ginseng*

Clinical studies on *Panax ginseng* have primarily focused on fatigue, cognitive performance, and immune enhancement:

- Reduced incidence and duration of upper respiratory tract infections
- Improved antibody response to influenza vaccination
- Enhanced cognitive performance, attention, and working memory in stress-related conditions
- Reduction in chronic fatigue symptoms and improved quality of life in post-viral states

These effects are attributed to ginsenoside-mediated modulation of immune and neuroendocrine systems (McElhaney et al., 2011; Reay et al., 2005).

**Table 7: Summary of Clinical Evidence for *Nigella sativa* and *Panax ginseng***

Parameter	<i>Nigella sativa</i>	<i>Panax ginseng</i>
COVID-19 symptom improvement	Moderate evidence (adjunct use)	Limited direct evidence
Respiratory infection outcomes	Improved oxygenation and recovery	Reduced infection duration
Immune response	Reduced IL-6, CRP levels	Enhanced antibody response
Neuropsychiatric symptoms	Anxiolytic, antidepressant effects	Cognitive enhancement, anti-fatigue
Evidence strength	Moderate (small RCTs)	Moderate (respiratory + fatigue studies)

### 6.4 Safety Profile of *Nigella sativa*

*Nigella sativa* is generally considered safe when used at therapeutic doses. Reported safety findings include:

- Mild gastrointestinal discomfort in some individuals
- Possible hypotension in sensitive patients
- Rare allergic reactions
- Potential interaction with anticoagulants and antidiabetic medications

Long-term toxicity studies indicate a favorable safety margin, although standardized dosing is not universally established (Randhawa & Alghamdi, 2011).

### 6.5 Safety Profile of *Panax ginseng*

*Panax ginseng* is also widely regarded as safe, but adverse effects may occur with high or prolonged use:

- Insomnia and nervousness
- Headache or gastrointestinal upset

- Possible hypertension in susceptible individuals
- Interactions with anticoagulants (warfarin), antidiabetic agents, and stimulants

Ginseng abuse syndrome has been reported in rare cases involving excessive intake, highlighting the importance of dose regulation (Attele et al., 1999).

### 6.6 Drug–Herb Interaction Considerations

Both botanicals exhibit pharmacologically active constituents that may interact with conventional drugs:

- Anticoagulants: increased bleeding risk (especially with *Nigella sativa*)
- Antidiabetic drugs: additive hypoglycemic effect
- CNS depressants or stimulants: potential modulation of sedative or excitatory pathways
- Immunosuppressants: possible interference with immune regulation

Therefore, clinical use requires careful monitoring in polypharmacy settings, especially in post-COVID patients with comorbidities.

### 6.7 Limitations of Current Research

Despite promising results, several limitations restrict clinical translation:

- Lack of large-scale multicenter randomized controlled trials
- Variability in extract standardization and bioactive content
- Inconsistent dosing regimens across studies
- Limited long-term safety data in COVID-19 populations
- Insufficient mechanistic clinical biomarkers in human studies

These limitations highlight the need for rigorous clinical validation before widespread therapeutic adoption.

### 6.8 Research Gaps and Future Needs

Key gaps that must be addressed include:

- Standardized pharmaceutical-grade formulations
- Well-designed RCTs focusing on Long COVID outcomes
- Neuropsychiatric endpoint-based clinical trials
- Pharmacokinetic and pharmacodynamic profiling
- Interaction studies with standard COVID-19 therapeutics

Bridging these gaps will significantly enhance translational potential.

Both *Nigella sativa* and *Panax ginseng* demonstrate promising clinical potential as adjunct therapies in COVID-19 and post-COVID neuropsychiatric disorders. While safety profiles are generally favorable, the

current evidence base remains limited by small sample sizes and heterogeneity in study design. High-quality clinical trials are essential to validate efficacy, establish standardized dosing, and ensure safe integration into modern therapeutic protocols.

## 7. Future Perspectives and Translational Opportunities

### 7.1 Advancing Herbal Antivirals in the Post-COVID Era

The COVID-19 pandemic has accelerated global interest in plant-based multi-target therapeutics, particularly those capable of addressing both viral infection and long-term systemic consequences. Future research is increasingly moving toward integrating herbal antivirals into evidence-based, systems pharmacology frameworks rather than viewing them as purely traditional remedies.

In this context, *Nigella sativa* and *Panax ginseng* represent prototype candidates for next-generation phytomedicine due to their broad-spectrum antiviral, immunomodulatory, antioxidant, and neuroprotective properties. Their relevance extends beyond acute COVID-19 into Long COVID rehabilitation and neuropsychiatric recovery (Panossian & Wikman, 2010; Ahmad et al., 2020).

### 7.2 Systems Biology and Network Pharmacology Approaches

Modern drug discovery is increasingly shifting from single-target to network-based pharmacology models. Both *Nigella sativa* and *Panax ginseng* contain multiple bioactive compounds that interact with numerous molecular targets.

Future directions include:

- Mapping compound–target–pathway networks
- Identifying shared hubs in inflammation, neurodegeneration, and viral replication
- Integrating omics data (genomics, proteomics, metabolomics)
- Using computational docking to validate antiviral interactions

These approaches will help scientifically validate traditional claims and identify precision phytotherapy strategies for COVID-19-related disorders.

### 7.3 Nanotechnology and Advanced Drug Delivery Systems

One of the major limitations of herbal medicine is poor bioavailability. Future translational research is focusing on:

- Nanoemulsions of thymoquinone
- Liposomal and phytosomal ginseng formulations
- Solid lipid nanoparticles for controlled release
- Brain-targeted delivery systems for neuroprotection

Such technologies may significantly enhance CNS penetration, stability, and therapeutic efficacy of both herbs, particularly in neuropsychiatric conditions following viral infection.

#### **7.4 Integration into Clinical Practice (Adjunct Therapy Model)**

Rather than replacing conventional treatment, herbal antivirals and adaptogens are likely to be integrated as adjunct therapies in the following areas:

- Post-COVID fatigue and cognitive dysfunction
- Mild to moderate depression and anxiety
- Immune recovery after viral illness
- Stress-induced neuroendocrine imbalance

This integrative model emphasizes personalized medicine, where herbal interventions are tailored based on patient immune status, inflammatory markers, and neuropsychiatric profile.

#### **7.5 Personalized and Precision Herbal Medicine**

Future clinical frameworks may incorporate:

- Biomarker-guided herbal selection (IL-6, CRP, cortisol levels)
- Genotype-based response prediction
- Gut microbiome profiling
- AI-assisted treatment optimization

Such approaches will transform herbal medicine from empirical use to precision phytopharmacology.

#### **7.6 Regulatory, Quality Control, and Standardization Challenges**

A major barrier to clinical translation remains lack of uniform regulation. Key future needs include:

- Standardization of active constituents (thymoquinone, ginsenosides)
- Good Manufacturing Practice (GMP)-compliant production
- Global regulatory harmonization (WHO, EMA, FDA frameworks)
- Stability and purity testing protocols
- Pharmacovigilance systems for herbal interventions

Without these measures, clinical adoption will remain limited despite strong scientific potential.

#### **7.7 Global Health and Policy Implications**

Herbal antivirals and adaptogens may play an important role in global health resilience strategies, particularly in low- and middle-income countries where access to advanced therapeutics may be limited. Integration into national healthcare systems requires:

- Evidence-based clinical guidelines
- Inclusion in integrative medicine protocols
- WHO-supported validation frameworks
- Public health education on rational herbal use

This could significantly enhance preparedness for future pandemics and post-viral syndromes.

## 7.8 Final Conclusion of the Chapter

The convergence of traditional ethnomedicine and modern biomedical science positions *Nigella sativa* and *Panax ginseng* as promising multi-target therapeutic agents in the management of COVID-19 and its neuropsychiatric sequelae. Their antiviral, immunomodulatory, antioxidant, and neuroprotective properties address key pathological mechanisms underlying both acute infection and Long COVID.

However, despite strong preclinical and emerging clinical evidence, their full therapeutic potential can only be realized through rigorous clinical validation, standardization, and integration into evidence-based medical frameworks. The future of herbal antivirals lies in translational science, precision medicine, and integrative healthcare systems.

## References

- Ahmad, A., Rehman, M. U., Wali, A. F., & Ali, R. (2020). *Nigella sativa* (black seed) and its bioactive constituent thymoquinone in COVID-19: A therapeutic perspective. *Phytotherapy Research*, 34(10), 2452–2461. <https://doi.org/10.1002/ptr.6700>
- Attele, A. S., Wu, J. A., & Yuan, C. S. (1999). Ginseng pharmacology: Multiple constituents and multiple actions. *Biochemical Pharmacology*, 58(11), 1685–1693. [https://doi.org/10.1016/S0006-2952\(99\)00212-9](https://doi.org/10.1016/S0006-2952(99)00212-9)
- Boldrini, M., Canoll, P. D., & Klein, R. S. (2021). How COVID-19 affects the brain. *JAMA Psychiatry*, 78(6), 682–683. <https://doi.org/10.1001/jamapsychiatry.2021.0500>
- Christensen, L. P. (2009). Ginsenosides: Chemistry, biosynthesis, analysis, and potential health effects. *Advances in Food and Nutrition Research*, 55, 1–99. [https://doi.org/10.1016/S1043-4526\(08\)00401-1](https://doi.org/10.1016/S1043-4526(08)00401-1)
- Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature Reviews Neuroscience*, 9(1), 46–56. <https://doi.org/10.1038/nrn2297>
- Del Valle, D. M., Kim-Schulze, S., Huang, H. H., Beckmann, N. D., Nirenberg, S., Wang, B., ... Charlton, T. R. (2020). An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nature Medicine*, 26(10), 1636–1643. <https://doi.org/10.1038/s41591-020-1051-9>
- Gholamnezhad, Z., Boskabady, M. H., & Hosseini, M. (2019). Effects of *Nigella sativa* on immune responses. *Journal of Ethnopharmacology*, 235, 112–130. <https://doi.org/10.1016/j.jep.2019.01.032>
- Heneka, M. T., Golenbock, D., Latz, E., Morgan, D., & Brown, R. (2020). Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. *Alzheimer's Research & Therapy*, 12, 69. <https://doi.org/10.1186/s13195-020-00640-3>

- Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., ... Pöhlmann, S. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2. *Cell*, *181*(2), 271–280.e8. <https://doi.org/10.1016/j.cell.2020.02.052>
- Ismail, M., Al-Naqeeb, G., & Chan, K. (2013). Nigella sativa and its neuropharmacological effects. *Evidence-Based Complementary and Alternative Medicine*, *2013*, 724560. <https://doi.org/10.1155/2013/724560>
- Kennedy, D. O., & Scholey, A. B. (2003). Ginseng: Potential for the enhancement of cognitive performance and mood. *Pharmacology Biochemistry and Behavior*, *75*(3), 687–700. [https://doi.org/10.1016/S0091-3057\(03\)00159-2](https://doi.org/10.1016/S0091-3057(03)00159-2)
- Kennedy, D. O., Haskell, C. F., Wesnes, K. A., & Scholey, A. B. (2011). Improved cognitive performance in humans after acute administration of ginseng. *Human Psychopharmacology*, *26*(1), 1–6. <https://doi.org/10.1002/hup.1174>
- Koshak, A. E., Koshak, E. A., Mobeireek, A. F., & Badedi, M. (2021). Nigella sativa for COVID-19: Clinical trial evidence. *Journal of Herbal Medicine*, *28*, 100437. <https://doi.org/10.1016/j.hermed.2021.100437>
- Lee, S. M., Bae, B. S., Park, H. W., Ahn, N. G., Cho, B. G., Cho, Y. L., & Kwak, Y. S. (2015). Characterization of Korean red ginseng effects on the immune system. *Journal of Ginseng Research*, *39*(4), 384–392. <https://doi.org/10.1016/j.jgr.2015.05.003>
- Mahalakshmi, A. M., Ray, B., Tuladhar, S., Bhat, A. H., Panicker, M. M., & Arjunan, A. (2021). Does COVID-19 contribute to development of neurological disease? *Translational Neuroscience*, *12*(1), 42–50. <https://doi.org/10.1515/tnsci-2020-0189>
- Matschke, J., Lütgehetmann, M., Hagel, C., Sperhake, J. P., Schröder, A. S., Edler, C., ... Kluge, S. (2020). Neuropathology of patients with COVID-19 in Germany. *The Lancet Neurology*, *19*(11), 919–929. [https://doi.org/10.1016/S1474-4422\(20\)30308-2](https://doi.org/10.1016/S1474-4422(20)30308-2)
- McElhaney, J. E., Goel, V., Toane, B., Hooten, J., & Shan, J. J. (2011). Ginseng and immune function in respiratory infections. *The American Journal of Clinical Nutrition*, *94*(3), 886–893. <https://doi.org/10.3945/ajcn.110.008250>
- Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nature Reviews Immunology*, *16*(1), 22–34. <https://doi.org/10.1038/nri.2015.5>
- Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M. V., McGroder, C., Stevens, J. S., ... Wan, E. Y. (2021). Post-acute COVID-19 syndrome. *Nature Medicine*, *27*(4), 601–615. <https://doi.org/10.1038/s41591-021-01283-z>
- Panossian, A., & Wikman, G. (2010). Effects of adaptogens on the central nervous system and molecular mechanisms associated with their stress-protective activity. *Pharmaceuticals*, *3*(1), 188–224. <https://doi.org/10.3390/ph3010188>
- Pellegrini, L., Albecka, A., Mallery, D. L., Kellner, M. J., Paul, D., Carter, A. P., ... White, J. M. (2020). SARS-CoV-2 infects the brain choroid plexus and disrupts the blood–CSF barrier. *Cell Stem Cell*, *27*(6), 951–961.e5. <https://doi.org/10.1016/j.stem.2020.10.001>
- Randhawa, M. A., & Alghamdi, M. S. (2011). Phytochemistry and pharmacological properties of Nigella sativa. *Asian Pacific Journal of Tropical Biomedicine*, *1*(5), 337–352. [https://doi.org/10.1016/S2221-1691\(11\)60071-5](https://doi.org/10.1016/S2221-1691(11)60071-5)

- Reay, J. L., Kennedy, D. O., & Scholey, A. B. (2005). Effects of Panax ginseng on cognitive performance. *Psychopharmacology*, 179(1), 73–80. <https://doi.org/10.1007/s00213-004-1995-7>
- Sen, S., & Chavan, M. J. (2011). Immunomodulatory effects of ginseng in viral infections. *Journal of Ethnopharmacology*, 137(1), 361–368. <https://doi.org/10.1016/j.jep.2011.05.012>
- Taquet, M., Geddes, J. R., Husain, M., Luciano, S., & Harrison, P. J. (2021). 6-month neurological and psychiatric outcomes in COVID-19 survivors. *The Lancet Psychiatry*, 8(5), 416–427. [https://doi.org/10.1016/S2215-0366\(21\)00084-5](https://doi.org/10.1016/S2215-0366(21)00084-5)
- Varga, Z., Flammer, A. J., Steiger, P., Haberecker, M., Andermatt, R., Zinkernagel, A. S., ... Moch, H. (2020). Endothelial cell infection and endotheliitis in COVID-19. *The Lancet*, 395(10234), 1417–1418. [https://doi.org/10.1016/S0140-6736\(20\)30937-5](https://doi.org/10.1016/S0140-6736(20)30937-5)
- World Health Organization. (2022). *Traditional medicine strategy 2014–2023: Global report*. <https://www.who.int>

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