*Edited Book*

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


*Editors*

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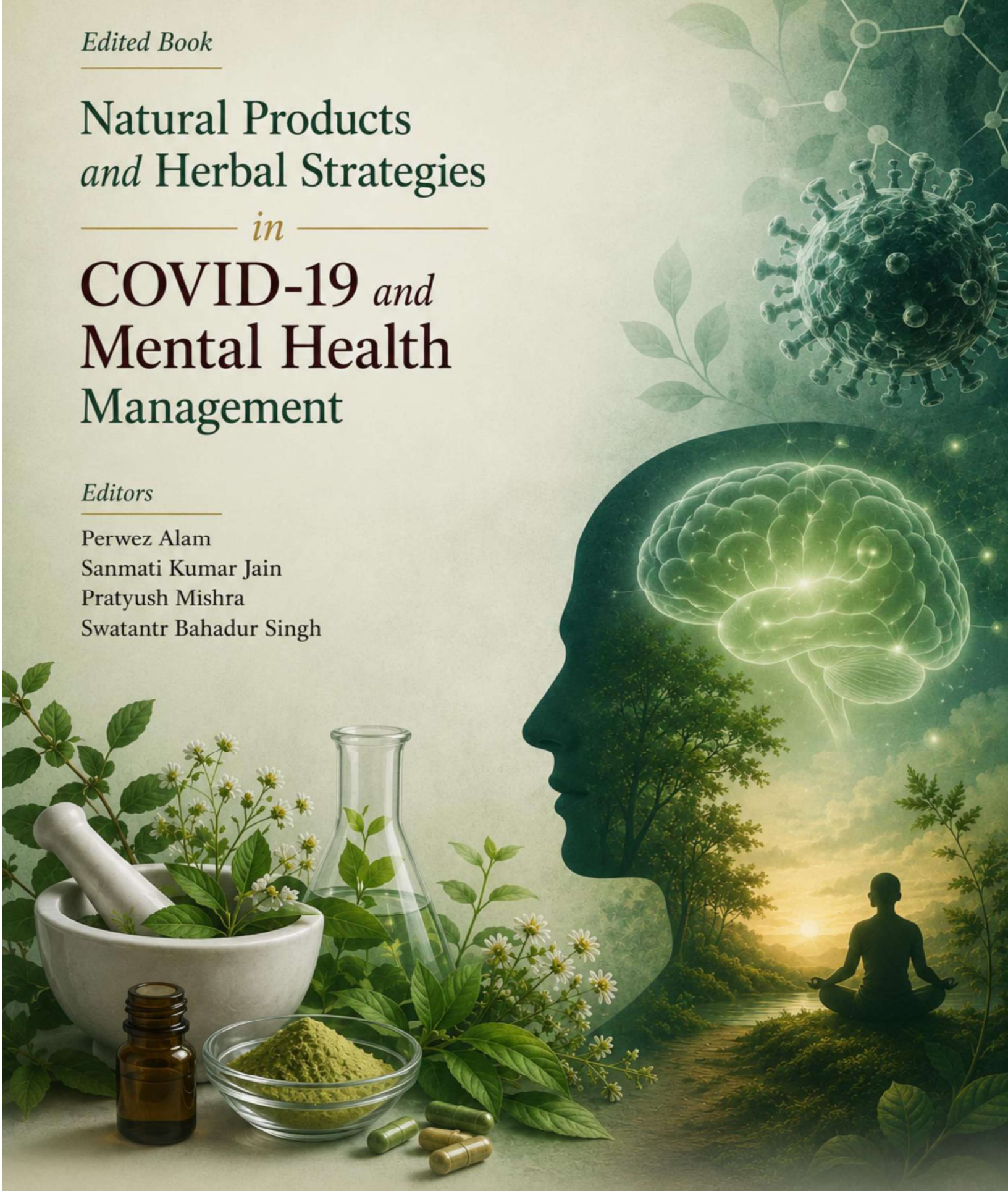


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## Book Title

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

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# 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-α), and interleukin-1 beta (IL-1β) 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 β-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-α 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 cardiotonic 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** | ***Momordica charantia*** | ***Terminalia arjuna*** | **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** |
|---|---|---|---|
| *Momordica charantia* | 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 |
| *Terminalia arjuna* | 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-α, IL-1β, 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-κB 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-α, 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 β-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-κB activation and downregulates pro-inflammatory mediators including IL-6 and TNF-α, 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-α
- IL-1β
- CRP

Simultaneously, antioxidant compounds reduce reactive oxygen species production and oxidative tissue injury.

#### NF-κB and Inflammatory Signaling Pathways

NF-κB signaling pathways play critical roles in cytokine storm syndrome and chronic inflammation. Experimental evidence indicates that both medicinal plants inhibit NF-κB 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 *Momordica charantia*** | **Role of *Terminalia arjuna*** |
|---|---|---|---|
| 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** | ***Momordica charantia*** | ***Terminalia arjuna*** | **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-α, and IL-1β. 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-κB and cytokine cascades that contribute to depressive behavior and neuronal dysfunction. *Momordica charantia* suppresses inflammatory mediators including IL-6 and TNF-α 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 *Momordica charantia*** | **Role of *Terminalia arjuna*** |
|---|---|---|---|
| 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** | ***Momordica charantia*** | ***Terminalia arjuna*** | **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-α
- Modulation of NF-κB 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 β-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 | *Momordica charantia* | *Terminalia arjuna* | 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 *Momordica charantia* | Evidence for *Terminalia arjuna* | 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