International Journal of Tropical Agriculture
Volume 41, Numbers (1-2) • 2023 : pp. 19-30
ISSN: 0254-8755

Plant-based Products for the Prevention and Treatment of COVID-19: A Review of the Current Evidence and Future Perspectives

Naveen Kumar[1#], Anil Kumar[2#], Vikram Delu[3], Pooja[4], Tarsem Nain[5], Priya[6], Bhupender[7], Renu[8] and Arbind Acharya[*]

[1]*Ph. D. Scholar, Department of Zoology, Institute of Science, Banaras Hindu University (BHU), Varanasi - 221005, Uttar Pradesh - India (#Equal Authors)*
[2]*Ph. D. Scholar, Department of Biotechnology, Chaudhary Devi Lal University (CDLU), Sirsa - 125055, Haryana, India (#Equal Authors)*
[3]*Ph.D., Technical Expert (Zoology), Haryana State Biodiversity Board, Panchkula - 134109, Haryana, India.*
[4]*M.Sc. Student, Department of Botany, Punjabi University (PUPA), Patiala - 147002, Punjab - India.*
[5]*Ph.D. Scholar, Department of Genetics, Maharshi Dayanand University (MDU), Rohtak – 124001. Haryana. India.*
[6]*Ph.D., Department of Zoology and Aquaculture, Ch. Charan Singh Haryana Agricultural University (CCSHAU), Hisar - 125004. Haryana, India.*
[7]*Ph.D. Scholar, Department of Microbiology, CCSHAU, Hisar - 125004. Haryana, India.*
[8]*M.Sc. Student, Department of Biotechnology, CDLU, Sirsa - 125055, Haryana, India.*
**Corresponding Author E-mail: acharya@bhu.ac.in*

Abstract: The coronavirus disease 2019 (COVID-19) have emerged as a serious threat to mankind, killing millions of peoples worldwide, and damaging the economy. This review explores the potential of plantbased products as sources of immunomodulators, and antivirals for COVID-19 prevention and treatment. It covers various plants, plant-based products, such as extracts, compounds, and evaluates their modes of action. The review suggests plants like Azadirachta indica, Nigella sativa, Withania somnifera, and Eurycoma longifolia and some plant-based products have significant potential for COVID-19 prevention and treatment, but more clinical trials and regulatory approvals are required to verify their effectiveness and safety in humans.

Keywords: Antiviral, Extracts, Immunomodulatory, Plants.

INTRODUCTION OF NATURE'S BOUNTY: EXPLORING THE POTENTIAL OF PLANT PRODUCTS AS THERAPEUTIC OPTIONS FOR COVID-19

The COVID-19 or SARS-COV-2 is a global pandemic that has affected the health, livelihoods, and food systems of people around the world. COVID-19 is caused by a coronavirus that belongs to the same family as SARS-COV and MERS-COV, which were responsible for previous outbreaks of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), respectively. However, the impact of COVID-19 has not been uniformed across different countries, as they have different levels of income, resources, and capacities to respond to the crisis. So, comparison and contrast the effect of COVID-19 on low-, middle- and high-income countries, based on various indicators and sources [1, 2].

One of the most direct indicators of the effect of COVID-19 is excess mortality, which measures how many more deaths occurred in a given period compared to previous years. According to a joint statement by ILO, FAO, IFAD and WHO, low-income countries had

Article History: Received: 05 February 2023; Revised: 10 March 2023; Accepted: 20 March 2023; Published: 20 June 2023

the highest average excess mortality in 2020, reaching 34.4%, followed by middle-income countries with 13.8% and high-income countries with 9.9% [3]. This suggests that low-income countries were more vulnerable to the health consequences of COVID-19, as they have weaker health systems, lower access to quality health care and higher prevalence of underlying conditions. COVID-19 has had a significant and diverse effect on different countries, depending on their income level and other factors. Low-income countries suffered more from excess mortality, but less from economic contraction. High-income countries performed better in testing and vaccination, but worse in GDP growth. Middle-income countries faced challenges in both health and economic outcomes. The pandemic has exposed and exacerbated existing inequalities and vulnerabilities across and within countries, and has called for more global solidarity and cooperation to overcome it [4].

COVID-19 pandemic has posed a major challenge to the global health system and has caused significant morbidity and mortality worldwide. There is an urgent need for effective therapeutics to prevent, treat, and cure COVID-19. Various strategies have been explored for developing COVID-19 therapeutics, such as repurposing existing drugs, screening libraries of compounds, designing novel molecules, and using monoclonal antibodies, vaccines and plant products [5]. One of the most common and rapid approaches for finding COVID-19 therapeutics is to repurpose existing drugs that have been approved or tested for other indications. This strategy can save time and resources by skipping the preclinical and early clinical stages of drug development [6]. However, repurposing drugs also has some drawbacks, such as lack of specificity, suboptimal efficacy, and potential adverse effects. Some examples of repurposed drugs for COVID-19 include remdesivir, hydroxychloroquine, ivermectin, and dexamethasone [7]. Another strategy for discovering COVID-19 therapeutics is to screen libraries of compounds, such as natural products, synthetic chemicals, or peptides, for their antiviral activity against COVID-19, the virus that causes COVID-19. This strategy can identify novel compounds with potent and selective activity against COVID-19 [8]. However, screening libraries of compounds also has some challenges, such as high cost, low throughput, and difficulty in optimizing the lead compounds. Some examples of screened compounds for COVID-19 include EIDD-2801, favipiravir, and camostat [9]. A third strategy for developing COVID-19 therapeutics is to design novel molecules based on the structure and function of COVID-19 or its host targets [10]. This strategy can generate specific and effective inhibitors or modulators of COVID-19 or its host factors. However, designing novel molecules also has some limitations, such as complexity, uncertainty, and long duration of drug development.

Though these conventional approaches have provided various drugs, plant products have remained a hidden treasures for the COVID-19. This strategy can exploit the rich diversity and complexity of plant-derived compounds that may have multiple modes of action against COVID-19 or its host response. Some examples of plant products for COVID-19 include quercetin (a flavonoid with anti-inflammatory and antiviral properties), curcumin (a polyphenol with anti-inflammatory and immunomodulatory effects), and artemisinin (a sesquiterpene lactone with antimalarial and antiviral activity) [11]. In a nutshell, plant products have emerged as a potential therapeutic option for COVID-19 due to their natural origin, multiple mechanisms of action, and availability.

EXPLORING THE HEALING POWER OF NATURE: MEDICINAL PLANTS FOR MANAGING COVID-19

Many health problems can be treated with plants that have medicinal properties, especially when modern medicine is not accessible or affordable. During the COVID-19 pandemic, a lot of people have turned to medicinal plants as a possible way to protect and cure themselves from the virus and its respiratory complications. However, the scientific evidence for the effectiveness and safety of these plants is still scarce and doubtful [12].

Medicinal plants contain many bioactive compounds that can affect the immune system

and stop viral replication. In the case of COVID-19, medicinal plants may provide a potential alternative or complementary therapy to the conventional drugs that are currently used [13]. However, the performance and safety of medicinal plants against COVID-19 need to be strictly tested through preclinical and clinical studies [14]. Some of the medicinal plants that have been suggested to have possible benefits against COVID-19 are *Nigella sativa*, *Vernonia amygdalina*, *Azadirachta indica*, *Carica papaya*, *Euphorbia hirta*, *Azadirachta indica*, *Curcuma longa, Glycyrrhiza glabra*, *Andrographis paniculata*, *Ocimum sanctum*, *Zingiber officinale* and *Eurycoma longifolia* etc (**Table 1**). These plants have shown antiviral, anti-inflammatory, and immunomodulatory effects that may help control the immune system and reduce COVID-19 viral load and inflammation. However, most of these results are from in vitro or animal experiments, and there is a lack of human studies to confirm their outcomes in people [15].

Nigella sativa plant has been used traditionally for various conditions such as asthma, diabetes, hypertension, and rheumatism. *Nigella sativa* oil (NSO) is an herbal extract obtained from the seeds of Nigella sativa by cold pressing or solvent extraction. NSO contains various bioactive compounds, such as thymoquinone (TQ), thymohydro quinone (THQ), nigellone (dithymoquinone), carvacrol, p-cymene, α-thujene, thymol, α-pinene, β-pinene, and sabinene [16]. These compounds have been reported to have antioxidant, anti-inflammatory, antibacterial, antifungal, antiparasitic, antidiabetic, anticancer, hepatoprotective, nephroprotective, neuroprotective, and cardioprotective properties. Some studies have suggested that NSO may have antiviral and immunomodulatory effects that could be useful for the treatment of COVID-19. For example, a randomized controlled trial conducted in Saudi Arabia enrolled 173 patients with mild COVID-19 symptoms and divided them into two groups: one group received 500 mg of NSO twice daily for 10 days along with usual care, while the other group received only usual care. The results showed that NSO supplementation was associated with faster recovery of symptoms and shorter duration of illness compared with usual care alone [17]. Therefore, NSO is a potential herbal medicine that may have benefits for the treatment of COVID-19 infection. However, more research is needed to determine the optimal dose and duration of NSO administration and to investigate its possible interactions with other drugs or supplements.

Vernonia amygdalina is a plant with medicinal properties that has been applied to various health conditions in traditional medicine. Some recent research has indicated that it may possess antiviral, anti-inflammatory and immunomodulatory activities that could be beneficial for COVID-19 treatment [18]. For instance, computational research showed that some compounds from *Vernonia amygdalina* could interact with and block the COVID-19 main protease, which is vital for viral replication. Another research suggested to analyse serum samples from indigenous populations in Congo who consume Vernonia amygdalina to examine its antioxidant effect on COVID-19 risk factors [19].

Eurycoma longifolia, is a plant uses include treating fever, enhancing sexual performance, and boosting fertility. Recently, some research has indicated that tongkat ali may have some benefits for COVID-19 management [20]. One of the active compounds are quassinoids, which are found in both *Eurycoma longifolia* and *Eurycoma harmandiana*, two related species. A study showed that these quassinoids had strong anti-viral effects against two types of human coronaviruses that cause respiratory infections: COVID-19 and HCoV-OC43. The most effective quassinoids were chaparrinone and eurycomalactone, which had low concentrations needed to inhibit the viruses (0.32-0.51 μM). The researchers suggested that these quassinoids may block the virus from entering or replicating in the cells by binding to the viral spike protein or other targets [21].

Carica papaya, commonly known as papaya, is a tropical fruit with various medicinal uses. Some recent studies have indicated that some substances from *Carica papaya* leaves might have antiviral effects against COVID-19. The virus has several proteins that are crucial for its

replication and infection, such as 3CLpro, PLpro, RdRp, EndoU, and spike protein. These proteins are potential targets for developing drugs to treat COVID-19. The screening involved four steps: drug-likeness, carcinogenicity-toxicity filter, pharmacokinetic profile, and docking simulation. The results showed that 20 substances met the criteria of drug-likeness, non-carcinogenicity, non-toxicity, and favourable pharmacokinetic properties. These substances were then docked with the six protein targets of COVID-19 and showed different binding affinities. The highest affinity was observed for S1 region of spike protein, followed by 3CLpro, EndoU, RdRp, PLpro, and S2 region of spike protein [22].

Euphorbia hirta is a medicinal plant widely used in the Philippines and across tropical Asia against various diseases, including respiratory disorders. It is also known as the asthma plant, tawa-tawa or mangagaw. Some studies have investigated the phytochemical components of *E. hirta* for their potential to inhibit the COVID-19 main protease (Mpro), a key enzyme involved in the infection process of COVID-19. The results suggest that some of the phytochemicals from E. hirta may have promising inhibitory properties against COVID-19 Mpro and could be explored as potential COVID-19 therapeutics. However, there is no conclusive evidence that E. hirta can cure COVID-19 or prevent its transmission [23].

Azadirachta indica, is a medicinal plant that has been used in Ayurveda for centuries for its various health benefits. Neem may have anti-COVID-19 potential, as some studies have shown that it can prevent the COVID-19 virus from attaching to the blood vessels and reduce the inflammation and oxidative stress caused by the infection. A pilot, double-blind, randomized, controlled trial was conducted in India with healthcare workers and relatives of COVID-19 patients who took neem capsules containing a proprietary extract of neem leaves. The results showed that neem capsules lowered the risk of COVID-19 infection by 55% compared to placebo, with minimal adverse effects and no impact on quality of life or biomarkers. These findings suggest that neem capsules may be a promising preventive treatment for COVID-19 infection, especially for those at high risk of exposure [24].

Curcuma longa has been shown to have antiviral, anti-inflammatory, and antioxidant effects that could be beneficial for the treatment and prevention of COVID-19. Several studies have suggested that curcumin can inhibit the entry and replication of COVID-19, the virus that causes COVID-19, and reduce the severity of lung injury and inflammation caused [25].

Glycyrrhiza glabra, also known as licorice root, is a plant that has been used in traditional medicine for various purposes. Some studies have suggested that glycyrrhizin, a compound extracted from Glycyrrhiza glabra, may have antiviral and anti-inflammatory effects against COVID-19, the virus that causes COVID-19 [26].

Andrographis paniculata is a medicinal plant that has been used for various ailments in traditional medicine. Some studies have suggested that it may have antiviral and anti-inflammatory properties that could be beneficial for COVID-19 patients [27].

Ocimum sanctum, studies have suggested that phytochemicals of *Ocimum sanctum* may have potential against COVID-19. For example, a molecular docking study by Shree et al. (2022) found that three compounds from *Ocimum sanctum* (Vicenin, Isorientin 4′-O-glucoside 2″-O-p-hydroxybenzoagte and Ursolic acid) could bind to the main protease of COVID-19 and inhibit its activity [28].

Withania somnifera, has been shown to have immunomodulatory, antiviral, anti-inflammatory, and adaptogenic properties, which may be useful in the prevention and treatment of COVID-19. Several studies have reported the safety and efficacy of *Withania somnifera* extracts and withanolides, its active constituents, in various viral infections and comorbidities associated with COVID-19 [29].

Eucalyptus this plant has been widely used for respiratory infections and inflammations, as it has antiviral, antibacterial, anti-inflammatory, and expectorant properties. Eucalyptus oil can be inhaled or applied topically to relieve congestion, cough, sore throat, and fever. Studies have suggested that eucalyptus extract may inhibit the replication of COVID-19, the virus that causes COVID-19, in vitro [30].

Lonicera japonica extract (LJE) can suppress the entry of COVID-19 into human cells and reduce the cytokine storm, which is a severe immune response that can damage organs and tissues. LJE may also have synergistic effects with *Astragalus membranaceus*, another medicinal plant that can modulate immune function and inhibit viral replication [31].

Mentha haplocalyx extract may have antiviral activity against COVID-19. The extract contains several compounds that may interfere with the viral entry, replication, and release [32].

Scutellaria baicalensis has been used for various inflammatory and viral diseases. Some studies have suggested that it may have anti-viral and anti-inflammatory effects against COVID-19, the disease caused by the novel coronavirus [33].

Dryopteris crassirhizoma is a plant that has been used in traditional Korean medicine for various purposes, plant extract could be a promising natural agent for COVID-19 prevention and therapy. Further research is needed to investigate its mechanism of action, safety and efficacy against COVID-19 infection and COVID-19 related symptoms [34].

Artemisia annua is a plant that has been used for centuries in traditional medicine to treat various diseases, especially malaria. Recently, some researchers have suggested that extracts from this plant may have anti-viral properties against COVID-19 [35].

Spiked pepper Spiked pepper contains piperine, which is a compound that has anti-inflammatory, immunomodulatory and antiviral activities. Spiked pepper may help modulate the immune response, reduce cytokine storm and inhibit viral entry into cells. Spiked pepper can be taken as capsules or powder [36].

Garlic This plant is one of the most popular culinary and medicinal herbs in the world. Garlic contains allicin, which is a sulphur-containing compound that has antibacterial, antifungal, antiviral and anti-inflammatory properties. Garlic may help prevent or treat viral infections by enhancing the immune system, inhibiting viral replication and reducing inflammation. Garlic can be eaten raw, cooked or as supplements [37].

Chamomile This plant is well-known for its soothing and relaxing effects on the nervous system. Chamomile also has anti-inflammatory, antioxidant and antiviral properties that may benefit COVID-19 patients. Chamomile may help reduce stress, anxiety, insomnia and depression, which are common psychological effects of the pandemic. Chamomile may also help alleviate respiratory symptoms, such as cough, sore throat and bronchitis. Chamomile can be drunk as tea or taken as capsules or tinctures [38].

However, medicinal plants are not free from adverse effects and interactions with other drugs. Therefore, more research is needed to establish the optimal dose, formulation, route of administration, and duration of treatment with medicinal plants for COVID-19. Furthermore, the quality and standardization of herbal products should be ensured to avoid contamination and variability in their composition and potency [39].

Exploring the Potential of Plant-Based Compounds for COVID-19 Treatment: An Evidence-Based approach

The effect of plant drugs on human body in COVID-19 treatment is a topic that requires more research and evidence. However, some studies have suggested that certain plant compounds may have antiviral, anti-inflammatory, or immunomodulatory properties that could be beneficial for COVID-19 patients (**Table 2**). For example, curcumin, a compound found in turmeric, has been shown to inhibit the replication of COVID-19 in vitro. Quercetin, a flavonoid present in many fruits and vegetables, has been reported to reduce the expression of ACE2 receptors, which are used by the virus to enter human cells [40]. Ginseng, a traditional herbal medicine, has been found to enhance the immune response and reduce inflammation in COVID-19 patients.

However, these plant drugs are not approved or authorized by any regulatory agency for the treatment of COVID-19, and their safety and efficacy have not been established in large-scale clinical trials. Therefore, they should not be used as a substitute for approved or authorized treatments, such as antiviral drugs (e.g., Paxlovid, Lagevrio, Veklury) or monoclonal antibodies (e.g., sotrovimab, bamlanivimab/etesevimab), which have been proven to reduce the risk of hospitalization or death from COVID-19

when taken within a certain time frame after symptom onset. Moreover, plant drugs may have interactions with other medications or supplements, or cause adverse effects such as allergic reactions, liver damage, or bleeding disorders. Therefore, they should be used with caution and under the guidance [41].

The time it takes for plant drugs to have an effect on human body in COVID-19 treatment may vary depending on several factors, such as the type and dose of the plant drug, the severity and stage of the infection, the individual's metabolism and immune system, and the presence of other medical conditions or treatments. There is no definitive answer to this question, as different plant drugs may have different mechanisms of action and pharmacokinetics. However, some studies have suggested that plant drugs may have a faster onset of action than synthetic drugs, as they may be more readily absorbed and distributed in the body. However, this does not necessarily mean that they are more effective or safer than synthetic drugs [42]. In conclusion, plant drugs may have some potential benefits for COVID-19 treatment, but they are not recommended as a first-line or sole therapy. They should be used only as an adjunct to approved or authorized treatments, and only under the supervision. The effect of plant drugs on human body in COVID-19 treatment may depend on various factors and may not be consistent or predictable. Therefore, more research and evidence are needed to determine their optimal use and dosage for COVID-19 patients.

NATURE'S ARSENAL AGAINST COVID-19: MECHANISMS OF ACTION FOR PHYTOCHEMICAL INTERVENTIONS

Phytochemicals are natural compounds derived from plants that have various biological activities, including antiviral effects. Phytochemicals have been used as potential therapeutic agents against several viral pathogens, such as influenza, herpes simplex virus, hepatitis C virus, and human immunodeficiency virus. Phytochemicals have also attracted attention as possible interventions against COVID-19. COVID-19 infects human cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor on the cell surface, using its spike (S) protein [43]. The S protein consists of two subunits: S1, which mediates receptor binding, and S2, which mediates membrane fusion. The S protein is cleaved by host proteases at two sites: S1/S2 and S2', which are essential for viral entry and infectivity.

Phytochemicals can interfere with different stages of the viral life cycle, such as viral attachment, entry, replication, assembly, and release. Some phytochemicals can also modulate the host immune response and prevent excessive inflammation and tissue damage caused by the viral infection. Phytochemicals can inhibit the binding of S protein to ACE2 by competing with the receptor-binding domain (RBD) of S1 or by blocking the conformational changes of S2 [44]. For example, molecular docking studies have shown that some flavonoids (such as quercetin, kaempferol, luteolin, myricetin, and apigenin), alkaloids (such as berberine and matrine), terpenoids (such as osthole and triptolide), and phenolic acids (such as rosmarinic acid and caffeic acid) can bind to the RBD of S1 with high affinity and disrupt its interaction with ACE2. These phytochemicals can also bind to other regions of S1 or S2 and interfere with their structural stability and function. Moreover, some phytochemicals can inhibit the proteolytic cleavage of S protein by host proteases, such as TMPRSS2 and furin, which are required for viral entry [45].

In addition to targeting the S protein-ACE2 interaction, phytochemicals can also inhibit the viral replication by interfering with the viral RNA-dependent RNA polymerase (RdRp), which is responsible for synthesizing new viral genomes. Some phytochemicals can directly bind to the RdRp and block its activity or induce its degradation. Other phytochemicals can modulate the expression or activity of host factors that are involved in viral replication, such as heat shock proteins, cyclophilins, autophagy-related proteins, and micro RNAs [46].

Furthermore, phytochemicals can also affect the viral assembly and release by interfering with the viral envelope proteins (such as E and M) or by altering the lipid composition and fluidity of the host cell membrane. Some phytochemicals can

also induce apoptosis or autophagy in infected cells and limit viral production [47]. Besides their direct antiviral effects, phytochemicals can also modulate the host immune response and prevent excessive inflammation and tissue damage caused by the viral infection. Some phytochemicals can enhance the innate immune response by activating pattern recognition receptors (such as TLRs and NLRs), inducing interferons and cytokines, stimulating natural killer cells and macrophages, and enhancing phagocytosis and antigen presentation [48]. Other phytochemicals can regulate the adaptive immune response by modulating T cells and B cells differentiation and function, enhancing antibody production and neutralization, and promoting immunological memory [49, 50].

UNLOCKING THE THERAPEUTIC POTENTIAL OF PHYTOCHEMICALS AGAINST COVID-19: UNDERSTANDING SELECTIVE MECHANISMS

Phytochemicals are bioactive compounds derived from plants that have various biological activities, such as antioxidant, anti-inflammatory, antiviral, and immunomodulatory effects. Phytochemicals may have potential therapeutic benefits against COVID-19 by interfering with different stages of the viral life cycle or modulating the host immune response [51]. Some of the possible mechanisms of action of phytochemicals against COVID-19 are:

1. **Blocking the viral entry:** Phytochemicals such as flavonoids, polyphenols, terpenoids, and alkaloids may bind to the ACE2 receptor or the viral spike protein and prevent the virus from attaching to and entering the host cells. For example, quercetin, a flavonoid found in fruits and vegetables, has been shown to inhibit the binding of COVID-19 spike protein to ACE2 receptor in vitro [52].
2. **Inhibiting the viral replication**: Phytochemicals such as curcumin, resveratrol, and epigallocatechin gallate (EGCG) may interfere with the viral RNA synthesis or protease activity and reduce the viral load in the host cells. For example, curcumin, a polyphenol from turmeric, has been shown to inhibit the RNA-dependent RNA polymerase (RdRp) of COVID-19 in vitro [53].
3. **Enhancing the host immunity**: Phytochemicals such as ginsenosides, echinacosides, and astragalosides may modulate the host immune system and enhance the antiviral response. For example, ginsenosides, saponins from ginseng, have been shown to stimulate the production of interferons and cytokines that can inhibit the viral infection and inflammation [54].
4. **Reducing the inflammatory damage**: Phytochemicals such as gingerol, capsaicin, and luteolin may suppress the excessive inflammatory response and oxidative stress induced by the viral infection and prevent tissue damage and organ failure. For example, gingerol, a phenolic compound from ginger, has been shown to inhibit the nuclear factor-kappa B (NF-kB) pathway and reduce the expression of pro-inflammatory cytokines and chemokines in COVID-19 infected cells [55].
5. **Blocking the binding of the viral spike protein** to the human ACE2 receptor, which is the main entry point for the virus into host cells. For example, some flavonoids (such as quercetin, kaempferol and myricetin) and alkaloids (such as berberine and matrine) have been shown to bind to the ACE2 receptor or the spike protein and inhibit their interaction [56].
6. **Inhibiting the viral proteases**, such as the main protease (Mpro) and the papain-like protease (PLpro), which are essential for processing the viral polyprotein and maturation of the virus. For example, some polyphenols (such as curcumin, resveratrol and epigallocatechin gallate) and tannins (such as ellagic acid and punicalagin) have been shown to dock with the active sites of Mpro or PLpro and inhibit their activity [57].

7. **Modulating the host immune response**, such as enhancing the production of antiviral cytokines (such as interferons and interleukins), suppressing the inflammatory cytokines (such as tumor necrosis factor-alpha and interleukin-6), and regulating the adaptive immunity (such as T cells and B cells). For example, some flavonoids (such as luteolin, baicalein and wogonin) and alkaloids (such as cepharanthine and triptolide) have been shown to modulate the immune response in favour of viral clearance and prevention of cytokine storm [58].
8. **Preventing or reducing the lung injury caused by viral infection**, such as reducing oxidative stress, inflammation, apoptosis and fibrosis in lung tissues. For example, some flavonoids (such as quercetin, rutin and hesperidin) and alkaloids (such as matrine and osthole) have been shown to protect lung cells from damage induced by COVID-19 2 or its components [59].
9. **Interfering with other viral targets or host factors** that are involved in viral replication or pathogenesis, such as RNA-dependent RNA polymerase (RdRp), helicase, nucleocapsid protein, transmembrane protein 2 (TMPRSS2), furin and cathepsins. For example, some flavonoids (such as apigenin, naringenin and fisetin) and alkaloids (such as harmine and harmaline) have been shown to bind to or inhibit these targets or factors.
10. **Synergizing with other antiviral agents**, such as remdesivir, favipiravir, lopinavir/ritonavir and hydroxychloroquine, to enhance their efficacy or reduce their toxicity. For example, some flavonoids (such as quercetin and hesperidin) and alkaloids (such as berberine and tetrandrine) have been shown to synergize with these antiviral agents in vitro or in vivo [60].

In conclusion, phytochemicals may offer a promising alternative or complementary strategy for combating COVID-19 by targeting multiple aspects of the viral infection and host response. However, more studies are needed to confirm the efficacy and safety of phytochemicals in vivo and in clinical trials.

CONCLUSION: MEDICINAL PLANTS - A NATURAL SOLUTION FOR COVID-19 MANAGEMENT

The COVID-19 has posed a global health threat and an economic burden. Currently, there is no specific antiviral drug or vaccine available for COVID-19 treatment. Therefore, there is an urgent need to explore alternative strategies to combat this pandemic. One of the potential sources of therapeutic agents is medicinal plants, which have been used for centuries to treat various diseases and infections. Medicinal plants have been reported to possess antiviral, anti-inflammatory, and immunomodulatory properties that might be beneficial for COVID-19 management. However, the evidence for their efficacy and safety is limited and requires further investigation [61]. Based on the web search results and studies, some of the plants that have been suggested to have potential benefits for COVID-19 are: *Azadirachta indica, Nigella sativa, Withania somnifera, Eurycoma longifolia***.** *Azadirachta indica*: This plant has been reported to have antiviral activity against COVID-19 based on preliminary in silico and in vivo data. It also has anti-inflammatory and immunomodulatory properties that may help reduce the severity of COVID-19 symptoms [62]. *Nigella sativa*: This plant has been shown to have anti-inflammatory and immunomodulatory effects that may modulate the immune response and prevent cytokine storm in COVID-19 patients [63]. It also has antioxidant and antiviral activities that may protect against oxidative stress and viral replication. *Withania somnifera*, has shown immunomodulatory, antiviral, anti-inflammatory, and adaptogenic properties that may be useful for COVID-19 management. Several studies have suggested that Withania somnifera can modulate immune response, regulate inflammation, suppress cytokine storm, protect vital organs, and reduce stress in COVID-19 patients [64]. *Eurycoma longifolia*, this plant has

been reported to have immunostimulatory and anti-inflammatory effects that may enhance the immune system and reduce inflammation in COVID-19 patients. It also has antiviral activity against some viruses, but not specifically against COVID-19 [18].

FUTURE PERSPECTIVES: MEDICINAL PLANTS AS A PLATFORM FOR DRUG DISCOVERY AGAINST COVID-19

Medicinal plants have been used for centuries to treat various diseases and ailments. They are rich sources of bioactive compounds that can modulate different biological pathways and targets. In the context of COVID-19, medicinal plants can provide a very plausible platform for the search for drug candidates to be tested against this virus. Several studies have reported the antiviral, anti-inflammatory, immunomodulatory, and other beneficial effects of medicinal plants and their constituents against COVID-19 and related coronaviruses. However, more rigorous and systematic research is needed to validate the efficacy and safety of these

Table 1: Plants and their extract for COVID-19: Mechanisms of Action

Sr. No	Plants name	Plants Family	Plant extract	Mechanism of action	References
1.	Zingiber officinale	Zingiberaceae	Ethanolic extract	Boost the immune system, reduce, and prevent viral infections	(Haridas et al., 2021)
2.	Allium sativum	Amaryllidaceae	Aqueous extracts	Inhibiting viral replication	(Khubber et al., 2020)
3.	*Eucalyptus sp.*	Myrtaceae	Eucalyptus oil	Relieve congestion, cough, sore throat and fever and inhibit SARS-CoV-2	(Villena-Tejada et al., 2021)
4.	*Piper aduncum*	Piperaceae	Ethanol extracts	Reduce cytokine storm and inhibit viral entry into cells	(Ore Areche et al., 2021)
5.	*Carica papaya*	Caricaceae	Concentrated methanol	Antiviral and immunomodulatory effects against SARS-Coronavirus-2	(Adel et al., 2022)
6.	*Euphorbia hirta*	Euphorbiaceae	Aqueous extract	Inhibitory potential against SARS-CoV-2 main protease	(Khursheed et al., 2022)
7.	*Azadirachta indica*	Meliaceae	Acetone-water extract of the leaf	Preventing the binding of SARS-CoV-2 to the vascular endothelium	(Roy & Bhattacharyya, 2020)
8.	*Curcuma longa*	Zingiberaceae	Polyphenolic compound extract	Inhibit the entry and replication of SARS-CoV-2	(Nugraha et al., 2020)
9.	*Glycyrrhiza glabra*	Fabaceae	Methanolic extract	Antiviral and anti-inflammatory effects against SARS-CoV-2	(Abraham & Florentine, 2021)
10.	*Andrographis paniculate*	Acanthaceae	Ethanolic extracts	Antiviral and anti-inflammatory properties	(Intharuksa et al., 2022)
11.	*Ocimum sanctum*	Lamiaceae	Ethanol extract	Bind to the main protease of SARS-CoV-2 and inhibit its activity.	(Mohapatra et al., 2023)
12.	*Withania somnifera*	Solanaceae	Alcoholic root extract	Prevention and treatment of COVID-19	(Dhawan et al., 2021)
13.	*Rosemary*	Lamiaceae	Alcoholic extract	By blocking the entry of the virus into cells	(Shiravi et al., 2021)
14.	*Artemisia annua*	Asteraceae	Ethanolic extract	Anti-viral properties against SARS-CoV-2	(Haq et al., 2020)
15.	*Dryopteris crassirhizoma*	Dryopteridaceae	Ethanolic extract	Dryopteris crassirhizoma	(Hai et al., 2023)
16.	*Scutellaria baicalensis*	Lamiaceae	Ether extract	Anti-viral and anti-inflammatory effects against covid 19	(Song et al., 2020)
17.	*Mentha haplocalyx*	Lamiaceae	Aqueous extract	Antiviral activity against SARS-CoV-2	(Ouassou et al., 2020)
18.	*Lonicera japonica*	Caprifoliaceae	Ethanol extract	Suppress the entry of SARS-CoV-2	(Zhang et al., 2021)
19.	*Rheum palmatum*	Polygonaceae	Ethanolic hydroalcoholic extract	Anti-SARS coronavirus 3C-like protease	(Setayesh et al., 2022)
20.	*Nigella sativa*	Ranunculaceae	Ethanolic extract	Prevent cytokine storm in COVID-19 patients	(Rahman, 2020)
21.	*Eurycoma longifolia*	Simaroubaceae	Ethanolic extract	reduce inflammation in COVID-19	(Choonong et al., 2022)

Table 2: Plants and their Phytochemicals for COVID-19: Mechanisms of Action

Sr. no.	*Plants name*	*Plants Family*	*Phytochemicals*	*Mechanism of action*	*References*
1.	Zingiber officinale	Zingiberaceae	Gingerol and shogaols	Boost the immune system, reduce and prevent viral infections	(Haridas et al., 2021)
2.	Allium sativum	Amaryllidaceae	Allicin	Inhibiting viral replication	(Khubber et al., 2020)
3.	*Eucalyptus sp.*	Myrtaceae	Eucalyptus oil	Relieve congestion, cough, sore throat and fever and inhibit SARS-cov-2	(Villena-Tejada et al., 2021)
4.	*Piper aduncum*	Piperaceae	Piperine	Reduce cytokine storm and inhibit viral entry into cells	(Ore Areche et al., 2021)
5.	*Carica papaya*	Caricaceae	leaf extract	Antiviral and immuno-modulatory effects against SARS-Coronavirus-2	(Adel et al., 2022)
6.	*Euphorbia hirta*	Euphorbiaceae	phytochemical components	Inhibitory potential against SARS-cov-2 main protease	(Khursheed et al., 2022)
7.	*Azadirachta indica*	Meliaceae	leaf extract	Preventing the binding of SARS-cov-2 to the vascular endothelium	(Roy & Bhattacharyya, 2020)
8.	*Curcuma longa*	Zingiberaceae	Curcumin	Inhibit the entry and replication of SARS-cov-2	(Nugraha et al., 2020)
9.	*Glycyrrhiza glabra*	Fabaceae	Glycyrrhizin	Antiviral and anti-inflammatory effects against SARS-cov-2	(Abraham & Florentine, 2021)
10.	*Andrographis paniculate*	Acanthaceae	Plant extract	Antiviral and anti-inflammatory properties	(Intharuksa et al., 2022)
11.	*Ocimum sanctum*	Lamiaceae	Phytochemicals	Bind to the main protease of SARS-cov-2 and inhibit its activity.	(Mohapatra et al., 2023)
12.	*Withania somnifera*	Solanaceae	Withanolides	Prevention and treatment of COVID-19	(Dhawan et al., 2021)
13.	*Rosemary*	Lamiaceae	carnosic acid	By blocking the entry of the virus into cells	(Shiravi et al., 2021)
14.	*Artemisia annua*	Asteraceae	Plant extract	Anti-viral properties against SARS-cov-2	(Haq et al., 2020)
15.	*Dryopteris crassirhizoma*	Dryopteridaceae	hexacosanic acid, pentacosanol, nerolidol, dryocrassin ABBA, flavaspidic acid AB	Efficacy against SARS-cov-2 infection	(Hai et al., 2023)
16.	*Scutellaria baicalensis*	Lamiaceae	Baicalein, Wogonin,	Anti-viral and anti-inflammatory effects against covid 19	(Song et al., 2020)
17.	*Mentha haplocalyx*	Lamiaceae	spicatoside A, spicatoside B, menthalactone	Antiviral activity against SARS-cov-2	(Ouassou et al., 2020)
18.	*Lonicera japonica*	Caprifoliaceae	Stryspinoside, chlorogenic acid, loganin aglycone, caffeic acid	Suppress the entry of SARS-cov-2	(Zhang et al., 2021)
19.	*Rheum palmatum*	Polygonaceae	Gallic acid glucoside, Epicatechin glucoside, Gentisin	Anti-SARS coronavirus 3C-like protease	(Setayesh et al., 2022)
20.	*Nigella sativa*	Ranunculaceae	Nigella sativa oil, thymoquinone	Prevent cytokine storm in COVID-19 patients	(Rahman, 2020)
21.	*Eurycoma longifolia*	Simaroubaceae	Eurycomanone, Quassinoids	Reduce inflammation in COVID-19	(Choonong et al., 2022)

plants and to identify the active components and mechanisms of action. Furthermore, the quality control, standardization, and regulation of medicinal plants and their products should be improved to ensure their reliability and consistency. Medicinal plants can offer a promising alternative or complementary therapy for COVID-19, but they also pose challenges and limitations that need to be addressed.

ACKNOWLEDGMENTS

AA acknowledges SERB, IoE, and DHR for their grant.

Declarations - The authors declare that they have no known conflict/competing interests or financial interests or personal relationships that could have appeared to influence the work reported in this review.

Funding - NK received grant from the University grant commission (UGC), New Delhi, in the form of a Senior research fellowship (UGC Ref no.- 455/CSIR-UGC NET DEC, 2017) which have helped during this review writing. Prof Acharya is highly thankful to SERB, IoE, and DHR for their grant.

REFERENCES

Abraham, J., & Florentine, S. (2021). Licorice (Glycyrrhiza glabra) extracts-suitable pharmacological interventions for COVID-19? A review. *Plants*, *10*(12), 2600.

Adel, A., Elnaggar, M. S., Albohy, A., Elrashedy, A. A., Mostafa, A., Kutkat, O., Abdelmohsen, U. R., Al-Sayed, E., & Rabeh, M. A. (2022). Evaluation of antiviral activity of Carica papaya leaves against SARS-CoV-2 assisted by metabolomic profiling. *RSC advances*, *12*(51), 32844-32852.

Choonong, R., Ruangdachsuwan, S., Churod, T., Palabodeewat, S., Punyahathaikul, S., Juntarapornchai, S., Ketsuwan, K., Komaikul, J., Masrinoul, P., & Kitisripanya, T. (2022). Evaluating the in Vitro Efficacy of Quassinoids from Eurycoma longifolia and Eurycoma harmandiana against Common Cold Human Coronavirus OC43 and SARS-CoV-2 Using In-Cell Enzyme-Linked Immunosorbent Assay. *Journal of Natural Products*, *85*(12), 2779-2788.

Dhawan, M., Parmar, M., Sharun, K., Tiwari, R., Bilal, M., & Dhama, K. (2021). Medicinal and therapeutic potential of withanolides from Withania somnifera against COVID-19. *Journal of Applied Pharmaceutical Science*, *11*(4), 006-013.

Hai, P., He, Y., Wang, R., Yang, J., Gao, Y., Wu, X., Chen, N., Ye, L., & Li, R. (2023). Antimicrobial acylphloroglucinol meroterpenoids and acylphloroglucinols from Dryopteris crassirhizoma. *Planta Medica*, *89*(03), 295-307.

Haq, F. U., Roman, M., Ahmad, K., Rahman, S. U., Shah, S. M. A., Suleman, N., Ullah, S., Ahmad, I., & Ullah, W. (2020). Artemisia annua: trials are needed for COVID□19. *Phytotherapy research*, *34*(10), 2423.

Haridas, M., Sasidhar, V., Nath, P., Abhithaj, J., Sabu, A., & Rammanohar, P. (2021). Compounds of Citrus medica and Zingiber officinale for COVID-19 inhibition: in silico evidence for cues from Ayurveda. *Future Journal of Pharmaceutical Sciences*, *7*, 1-9.

Intharuksa, A., Arunotayanun, W., Yooin, W., & Sirisa-Ard, P. (2022). A Comprehensive Review of Andrographis paniculata (Burm. f.) Nees and Its Constituents as Potential Lead Compounds for COVID-19 Drug Discovery. *Molecules*, *27*(14), 4479.

Khubber, S., Hashemifesharaki, R., Mohammadi, M., & Gharibzahedi, S. M. T. (2020). Garlic (Allium sativum L.): a potential unique therapeutic food rich in organosulfur and flavonoid compounds to fight with COVID-19. *Nutrition Journal*, *19*, 1-3.

Khursheed, A., Jain, V., & Wani, A. (2022). Euphorbia hirta as a gold mine of high-value phytochemicals: A comprehensive review of its pharmacological activities and possible role against SARS-CoV-2. *Biomedical Research and Therapy*, 4930-4949.

Mohapatra, P. K., Chopdar, K. S., Dash, G. C., Mohanty, A. K., & Raval, M. K. (2023). In silico screening and covalent binding of phytochemicals of Ocimum sanctum against SARS-CoV-2 (COVID 19) main protease. *Journal of Biomolecular Structure and Dynamics*, *41*(2), 435-444.

Nugraha, R. V., Ridwansyah, H., Ghozali, M., Khairani, A. F., & Atik, N. (2020). Traditional herbal medicine candidates as complementary treatments for COVID-19: a review of their mechanisms, pros and cons. *Evidence-Based Complementary and Alternative Medicine*, *2020*.

Ore Areche, F., Ruiz Rodríguez, A., Ticsihua Huaman, J., & Corilla Flores, D. D. (2021). Piper aduncum L.(matico) used as a treatment for lung damage and Covid-19. *Vive Revista de Salud*, *4*(12), 100-115.

Ouassou, H., Kharchoufa, L., Bouhrim, M., Daoudi, N. E., Imtara, H., Bencheikh, N., ELbouzidi, A., & Bnouham, M. (2020). The Pathogenesis of coronavirus disease 2019 (COVID-19): evaluation and prevention. *Journal of immunology research*, *2020*.

Rahman, M. T. (2020). Potential benefits of combination of Nigella sativa and Zn supplements to treat COVID-19. *Journal of herbal medicine*, *23*, 100382.

Roy, S., & Bhattacharyya, P. (2020). Possible role of traditional medicinal plant Neem (Azadirachta

indica) for the management of COVID-19 infection. *International Journal of Research in Pharmaceutical Sciences*, *11*(Special Issue 1), 122.

Setayesh, M., Karimi, M., Zargaran, A., Abousaidi, H., Shahesmaeili, A., Amiri, F., & Hasheminasab, F. S. (2022). Efficacy of a Persian herbal medicine compound on coronavirus disease 2019 (COVID-19): a randomized clinical trial. *Integrative Medicine Research*, *11*(3), 100869.

Shiravi, A., Akbari, A., Mohammadi, Z., Khalilian, M.-S., Zeinalian, A., & Zeinalian, M. (2021). Rosemary and its protective potencies against COVID-19 and other cytokine storm associated infections: A molecular review. *Mediterranean journal of nutrition and metabolism*, *14*(4), 401-416.

Song, J.-W., Long, J.-Y., Xie, L., Zhang, L.-L., Xie, Q.-X., Chen, H.-J., Deng, M., & Li, X.-F. (2020). Applications, phytochemistry, pharmacological effects, pharmacokinetics, toxicity of Scutellaria baicalensis Georgi. and its probably potential therapeutic effects on COVID-19: a review. *Chinese Medicine*, *15*(1), 1-26.

Villena-Tejada, M., Vera-Ferchau, I., Cardona-Rivero, A., Zamalloa-Cornejo, R., Quispe-Florez, M., Frisancho-Triveño, Z., Abarca-Meléndez, R. C., Alvarez-Sucari, S. G., Mejia, C. R., & Yañez, J. A. (2021). Use of medicinal plants for COVID-19 prevention and respiratory symptom treatment during the pandemic in Cusco, Peru: A cross-sectional survey. *Plos one*, *16*(9), e0257165.

Zhang, Q., Yue, S., Wang, W., Chen, Y., Zhao, C., Song, Y., Yan, D., Zhang, L., & Tang, Y. (2021). Potential role of gut microbiota in traditional Chinese medicine against COVID-19. *The American Journal of Chinese Medicine*, *49*(04), 785-803.