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REVIEW ARTICLE

Exploring the Efficacy of Traditional Herbs in Combating COVID-19: A Comprehensive Review

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Abstract: ***Background***: The entire world witnessed the COVID-19 pandemic outbreak. It has become deadly everywhere across the globe. COVID-19 mortality varies across age groups and has been linked to an individual's innate immunity. In contrast, it was more lethal in immunocompromised people. The spread of viruses is slowed by both passive immunity and vaccine-aided acquired immunity. However, vaccine-induced immunity is transient, and there is no assurance that vaccine-mediated antibodies will be effective against all future virus mutants. As a result, natural immunity boosters have become essential supplements that must be used nowadays to stay immunized against such infections. In Ayurvedic medicine, traditional Indian spices have been used for a long time to boost the immune system and fight off different diseases.

Objective: This review aims to disseminate information about traditional natural medicine in repurposing as an immunity booster and for antiviral effects in COVID-19.

Methods: Using published articles from recent years, the *in silico* docking study, survey-based study, and *in vitro* and preclinical research work on selected traditional herbs for their anti-inflammatory, immunomodulating, and antiviral properties are summarized. *Withania somnifera*, *Piper nigrum*, *Emblica officinalis*, *Andrographis paniculate*, *Glycyrrhiza glabra*, *Ocimum sanctum*, *Piper longum*, and *Curcuma longa* are some of the most commonly used natural spices studied extensively and hence selected in this review.

Results: This context summarizes selected plants showing immunomodulatory and antiviral effects in experimental animals, simulation, and clinical studies.

Conclusion: By virtue of antiviral potential, the chosen herbs could be used for repurposing in COVID-19 management after thorough clinical investigations.

Keywords: COVID-19, immunity boosters, immunomodulators, herbal plants, natural therapeutics, traditional medicine.

1. INTRODUCTION

The COVID-19 outbreaks have had a global economic impact. It spread so quickly that it affected every part of the world. Because of its high mortality rate and rapid spreadability, the World Health Organization (WHO) announced it as a pandemic [1]. COVID-19's situation seems to be under control. Their prevalence and mortality rate have decreased. The immunity against COVID-19 was produced passively, termed herd immunity alternatively. The spread of COVID-19 has slowed down because of the majority of people developing herd immunity [2, 3]. However, the immunity developed through passive means is short-lived and decays over time. Most people need to actively produce antibodies, which can be accomplished through COVID-19 vaccine immunization [4-6].

Mutation is the process by which genetic information is transformed. The coronavirus is no exception to the mutation process. Because of the mutation process, the coronaviruses are transformed into different variants over time [7, 8]. The mutant termed Delta variant was responsible for the second wave of COVID-19 outbreak worldwide, which accounted highest mortality rate. The other variant, Omicron, was gen-

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erated and spread rapidly to all corners of the world in a relatively brief time compared to any other Corona variant [9-11]. The Omicron variant was less lethal than the Delta variant. However, it became deadly to the immunocompromised patient. There is a possibility that new Coronavirus variants will emerge over time [9-11].

The Omicron subvariant XBB and BQ, the latest concern variant, emerged in 2022 and was reported from epicenter China, showing a decrease in neutralizing antibodies during infection compared to infections caused by other variants. Considering this, WHO has not decreed the COVID-19 pandemic to an endemic and has advised people to take the necessary precautions to prevent its spread. Recent research has also revealed that people immunized with the COVID-19 vaccine are susceptible, suggesting that antibodies produced by the COVID-19 vaccine are not permanent and degrade over time [12]. Vaccines have now immunized most of the population. However, it is ascertained that the antibodies produced will be effective against all future coronavirus variants. The virus became lethal to all age groups except pediatrics. It has been discovered that it is fatal to immunocompromised patients, and people with good immunity have a higher chance of survival after infection, demonstrating the importance of natural immunity in combating the virus. A healthy lifestyle and using natural herbs can help boost immunity. Natural herbs (traditional medicine) are a valuable source of treatment for a wide range of illnesses [13, 14]. These herbs have become important in developing countries, where traditional herbs account for 75% of the general population's health care. To treat minor ailments, natural herbs in the form of Chywanprash or extracts and decoctions (kadha) can be administered to activate innate immunity. These plants have neuroprotective and antioxidant properties. Immunomodulatory and antiviral properties must be considered to treat various ailments [15, 16].

COVID-19 induces an inflammatory immune response, multiorgan failure, and acute respiratory disorders due to dysregulation of immunity functions and cytokine storms [17]. Natural traditional herbs have been found effective against infections caused by SARS-CoV-2. The different findings suggested that traditional herbal medicine may have a role in suppressing symptoms of COVID-19 [18, 19]. The combination of traditional herbs with current modern therapy has also been investigated and found effective in combating COVID-19 symptoms [20, 21]. Natural herbs have been used against viral diseases since ancient times. The role of traditional herbal medicine in suppressing SARS-CoV-2 has also been well documented [22, 23]. Several researchers' findings have unveiled the effect of herb medicaments in reducing the severity and prevention of COVID-19 [21, 24]. India and China have practised herbal medicines in COVID-19 management in addition to modern medicine for boosting immunity [25]. The mortality and recurrence rates declined after implementing Chinese medicine in the COVID-19 treatment protocol. Therefore, in addition to the existing treatment strategies, there is a need for long-term symptom management and immunity-boosting strategies to prevent infection [26, 27]. Despite the potential of herbal medicine in COVID-19 management, they pose limitations, such as dose proportionality and nonspecific drug targets [25]. Recently, research works published on herbs for COVID-19 were primarily focused on computer-assisted modeling (molecular docking/ molecular simulations). Therefore, current research emphasizes *in vitro* and *in vivo* investigation in addition to molecular simulation and molecular dynamic studies. Herbal medicinal plants with immunomodulatory and antiviral properties have shown potential in COVID-19 management [28, 29]. Natural spices like *Withania somnifera*, *Piper nigrum*, *Emblica officinalis*, *Andrographis paniculate*, *Glycyrrhiza glabra*, *Ocimum sanctum*, *Piper longum*, and *Curcuma longa* have been extensively researched for COVID-19 and other viral infectious diseases and thus chosen for this review.

2. *WITHANIA SOMNIFERA* (ASHWAGANDHA)

Withania somnifera is a plant belonging to the Solanaceae family, with the common name ashwagandha. It is also known as "Indian Ginseng" or "Indian Winter Cherry." a well-known and important herb in Ayurveda. Because of its numerous health benefits and ability to extend life, ashwagandha has become an important ingredient in Rasayana since ancient times. It promotes peak mental and physical health, as well as increases happiness. In most parts of India, *Withania somnifera* is a little shrub that reaches a height of two feet. The active constituents of withanolides contain alkaloids, steroidal lactones, and steroidal saponin. This herb has immune-modulatory, anti-aging, antimicrobial, ability to suppress inflammation, anti-diabetic, analgesic, antitumor, and anti-stress properties [30, 31].

Priya Shree *et al*. presented in their study the immunomodulatory role of phytoactive compounds of *Withania somnifera* and its derived substances for COVID-19. It was proposed in their literature to inhibit major protease with a phytoactive compound derived from the *Withania somnifera* plant. They discovered natural phytochemicals through molecular docking/simulation studies and checked the effectiveness against COVID-19. Studies found two compounds from ashwagandha being identified as an inhibitor for SARS-CoV-2 Main protease (M-pro) [32]. A study by Chikhale *et al*., performed through molecular docking and dynamic tests, identified two distinct target SARS-CoV-2 viz NSP15 endoribonuclease and the receptor binding domain of SARS-CoV-2 perfusion spike protein. They observed some of the *Withania somnifera*s phytoconstituents in a molecular docking study that phytoconstituents withanoside X and quercetin glucoside from *Withanoside somnifera* interact favorably at the target binding sites of two specific proteins, 6W01 and 6M0J. Withanoside X was identified as the most promising inhibitor from docking studies exposed to 100 ns molecular dynamics. This compound has the highest binding free energy and possesses affinity to fit the active receptor site more comfortably [33].

Chudasama and Singh conducted a clinical trial in which 37 underweight patients who experienced seasonal illnesses were given ashwagandha treatment for one month. The outcome showed significantly improved physical stamina, heart and lung capacity, short-term memory, and body weight. Similarly, the significant increase in serum IgA, IgG, and IgM levels indicates that *Withania somnifera* significantly improved the subjects' immunity. As a result, it may be recommended for patients with insufficient immunity to prevent seasonal infections [34]. Two research groups have proposed that Withaferin A, a steroidal lactone with anti-inflammatory and anti-tumorogenic properties, may attach to the SARS-CoV-2 on active site viral spike (S-) protein. They also discovered that Withaferin A does not affect the expression of Angiotensin-converting enzyme 2 (ACE2) in the lungs of female tumor mice. According to the research, the symptoms of COVID-19 have been reduced by ACE2 downregulation. Withaferin A can potentially cure or suppress the spread of COVID-19 because viral S-protein interference with host receptor binding does not affect ACE2 expression in the lungs [35].

3. *PIPER NIGRUM* (BLACK PEPPER)

Piper nigrum L, also known as kali mirch, black gold, and peppermint, is a Piperaceae family member and occurs in subtropical and tropical regions. The dried fruit of *Piper nigrum* is known as peppercorns, and it contains vitamins K and A as well as magnesium, potassium, phosphorus, calcium, carotene, and manganese. *Piper nigrum* also yields oleoresin, pepper oil, and ground pepper. *Piper nigrum*'s main active ingredient is piperine, which contains alkaloids, volatile oils, and oleoresins. The main alkaloids found in Maricha are piperine, piperidine, piperetine, and chavicine. Other constituents include steroids, terpenes, flavones, alkamides, and lignans [36]. *Piper nigrum* is effective against colds, coughs, and bronchitis [37].

The Ministry of AYUSH recommended 'Ayush Joshanda' or 'Ayush Kwath' or 'Ayush Kudineer,' which is made up of four herbs (medicinal): Tulsi (*Ocimum sanctum Linn*.), Dalchini (*Cinnamomum zeylanicum Breyn*.), Sunthi (*Zingiber officinale Rosc*.) and Marich (*Piper nigrum* Linn.). *Piper nigrum* aids in increasing bioavailability and thus improves the efficacy of drugs and nutrients. It also provides antioxidant, immune-modulatory, antiplatelets, antiasthmatic, anti-hypertensive, antipyretic, anti-inflammatory, antispasmodic, anti-carcinogenic, analgesic, anti-diarrheal, anti-depressants, anxiolytic, anti-ulcer, hepatoprotective, anti-thyroid, antibacterial, anti- apoptotic, antimutagenic, antifungal, anti-amoebic and anti-metastatic action. Piperine stimulates macrophage activation as well as B and T cell proliferation. It also regulates and balances the production of cytokines by Treg, Th1, Th2, and Th17 cells and inhibits the expression of IL-1b, IL-4, IL-6, RORgt, GATA3, TNF-, and IL-17A. Piperine also increases IL-10 and INF-g secretions in the Brocho-alveolar lavage fluid [38].

Rehman *et al*. investigated the potential of *Piper nigrum* in the treatment of airway disorders *via* bronchodilation. The crude black pepper extract was analyzed using an HPLC fingerprint, which revealed the presence of piperine, catechin, eugenol, and piperidine. In rats, crude extract and piperine alleviate carbachol-induced bronchospasm. An isolated guinea pig trachea, crude extract, and piperine were found to inhibit K^+ and carbachol-induced contractions, as well as suppress Ca^{2+} concentration-response curves. It was discovered that *Piper nigrum* has a bronchodilatory effect by inhibiting both Ca^{2+} influx and the phosphodiesterase enzyme [39]. Dhargawe *et al*. investigated anti-inflammatory, antipyretic, and analgesic activity in another experiment using Albino rats and Swiss mice in their study. The antipyretic activity was assessed using a pyrexia model induced by Baker's yeast. According to the results, piperine effectively lowers the rectal temperature after four hours. The percentage of inhibition of inflammation was 56% in the carrageenan-induced edema model and 40% in the formalin-induced arthritis model. Piperine was found to have a significant anti-pyretic and anti-inflammatory effect [40]. Roshdy *et al*. investigated the antiviral effect of *Piper nigrum*, developing EGYVIR, an immunomodulatory extract of herbal ingredients that was effective against COVID-19. The *in vitro* experiments on Huh-7 cell lines against SARS-CoV-2 demonstrated the significance of IL-6/NF-k/TNF during infection. EGYVIR inhibited the NF-k pathway while also limiting TNF- and IL-6 release. As a result, it may have antiviral activity [41]. Davella *et al*. used an integrated docking (molecular) and dynamics simulation study to investigate eight phenolic compounds against COVID-19. The studies revealed that the black pepper constituents Methysticin and Kadsurenin L are ligands that can inhibit and interact with the major COVID-19 protease network. These phytoconstituents can be used to create safe drugs [42]. Singh *et al*. investigated black pepper's *in vitro* antioxidant effect of pet ether extract in their study. The *Piper nigrum* extract was evaluated using DPPH (1,1-Diphenyl-2-picryl-hydrazyl) radical, nitric oxide, hydroxyl, and superoxide anion radical scavenging assays. The findings later demonstrated black pepper's antioxidant capacity [43]. Khanna *et al*. presented a plant-based therapeutic approach including a sunthi, lavanga (*Syzygium aromaticum*) decoction, and black pepper. It was recommended for COVID-19 patients and healthy individuals because the decoction supports cell-mediated and humoral responses while reducing nasal congestion [44].

4. *EMBLICA OFFICINALIS* (AMLA)

Emblica Officinalis is alternatively termed amla, a medicinal plant native to the Indian subcontinent belonging to the Euphorbiaceae family and used in Ayurveda and other traditional systems of medicine to have antiviral and immune-modulatory and tonic properties to replenish the body's lost vigour and energy [45]. *Emblica officinalis* species, which is known to be native to India and thrives in tropical and subtropical climates, is a pale yellowish, fleshy, rounded fruit. The flavor of Indian Emblica is sour, bitter, and astringent. It is enriched with vitamin C and ellagitannins and is well known to boost immunity against viral infections, making it popular in Ayurveda and other traditional medical systems [46-50]. Pedunculagin (14%), emblicanin A (37%), emblicanin B (33%), and punigluconin (12%) are some important constituents [51]. Punicafolin, phyllanemblinin A, phyllanemblin, ellagic acid, and gallic acid are flavonoids among the other phytoconstituents [49, 52]. The dry fruit contains approximately 70%-75% carbohydrates, 4-6% minerals (sodium, calcium, magnesium, potassium, zinc, iron, and so on), and the following ingredients: Residual moisture is 6-9%, fats are 1.5-2.0%, and protein is 2.5-3.5% [53].

Murugesan *et al*. presented a study on the phytoactive components of *Emblica officinalis* using molecular dynamics and docking, which revealed bioactive molecules have binding affinities with COVID-19's M-pro, which confirms antiviral potential [54]. Among several significant chemical components of amla fruit, including gallic acid, putrajivain A, reported by Zhang and colleagues, the Mucic acid 2-o-gallate, mucic acid 1, 4-lactone 6-methyl ester 2-o-gallate, mucic acid 6-methyl ester 2-o-gallate, mucic acid 1-methyl ester 2-o-gallate, mucic acid 1,4-lactone 2-o-gallate, mucic acid 1-methyl ester 2-o-gallate, and mucic acid 1,5-di-o-gallate are recognized to have multicategory medicinal property [48]. The study by Mohamed *et al*. research assessed the antioxidant and antiviral properties of *Emblica officinalis*, by characterization of bioactive chemical constituents. Their discovery revealed that *Emblica officinalis* contains tannins, phenolics, glycosides, flavonoids, phenols, and terpenoids with anti-Hepatitis C virus activity [55].

Varnasseri *et al*. reported antiviral potential in a randomized, double-blind, controlled trial using *Emblica officinalis* tea on 61 COVID-19 patients. The intervention group has shown improved parameters, like cough, fever, shortness of breath, oxygen saturation, and C-reactive protein test. They concluded that *Emblica officinalis* tea might hasten the recovery of COVID-19 patients [56]. An *in-silico* study of *Emblica officinalis* phytocompounds with antiviral potential was conducted by Srivastav *et al*. Their findings revealed that *Emblica officinalis* phytochemicals could target SARS-CoV-2 viral proteins, such as the ACE-2 receptor and M-pro, as the best choice for the development of nutraceuticals using molecular docking and molecular dynamics modeling of protein and phytochemicals [57]. Using molecular dynamics simulation and molecular docking, Pandey K. *et al*. investigated phytocompounds from *Emblica officinalis* that could target the SARS-CoV-2 RNA-dependent RNA polymerase than reference substance remdesivir. These findings suggest that phytocompounds from *Emblica officinalis* could be a powerful antiviral treatment for SARS-CoV-2 [58].

Chikhale and colleagues investigated the phytochemicals of *Emblica officinalis*, which is a high source of vitamin C and has antiviral potency against three proteins: the receptor binding domain of perfusion spike protein, endoribonuclease, and M-pro, out of the 66 substances tested, myricetin, chlorogenic acid, and quercitrin were the most effective, with the strongest binding to specific protein targets of SARS-CoV-2 [59].

Gupta *et al*. investigated the potential of *Emblica officinalis* alkaloid fraction to act as an adjuvant to immunological reactions to diphtheria-pertussis-tetanus (DPT) antigen and hepatitis in whole human blood using flow cytometry. Their results showed that, compared to the DPT control group, the alkaloid fraction significantly increased DPT-mediated blood counts at lower dosages [60]. Kaleem and colleagues investigated the effect of tannin extracts of *Emblica officinalis* on humoral immune responses and their effectiveness in protecting chickens against Eimeria infection. After receiving a 14-day dose of tannins extract, broiler chickens showed immunostimulatory qualities, increasing their defenses against coccidiosis [61].

Kaur *et al*. tested the leishmanicidal effect of Emblica officinalis phytochemicals to determine an immunomodulatory property. When animals were given medication significantly reduced the number of infectious parasites count [62]. Nath *et al*. investigated the antioxidant and immunomodulatory properties of Emblica officinalis using four endophytic fungi that were isolated from various areas of the Emblica officinalis plant. In this study, the endophytic fungi Phomopsis and Xylaria species had the highest antioxidant activity, indicating their immunomodulatory abilities [63]. Liu *et al*. studied the antiviral potential and immunomodulatory properties of some phenolic compounds from Emblica officinalis fruit, such as geraniin and iso-corilagin. The study's findings can be summarized as having high antioxidant activity and immunomodulatory properties [64].

Alamgir *et al*. investigated the immunomodulatory abilities of *Emblica officinalis* fruit extract in a rat model of arthritis. The outcome significantly emphasizes *Emblica officinalis* aqueous extracts immunomodulation [65]. Suja and colleagues used male Swiss Albino mice to test the immunomodulatory effects of an aqueous extract of dried *Emblica officinalis* fruit pulp powder, which significantly increased haemagglutination antibody titer, sheep red blood cell-induced hypersensitivity reaction, total leukocyte count, percentage lymphocyte distribution, serum globulin, and macrophage phagocyte in the groups that received it, confirming its immunomodulatory property. [66].

Ram *et al*. investigated amla's immunomodulatory and antioxidant properties using chromium as an immunosuppressive agent. *Emblica Officinalis* treatment significantly reduced the generation of free radicals caused by chromium and increased the number of antioxidants [67].

Mitra *et al*. discovered that the polyherbal formulation of *Emblica officinalis* improves the delayed-type hypersensitivity response in mice and the *in vitro* response of splenocytes to mitogenic challenges. *Ex vivo* lymphocyte proliferation was also stimulated by the *in vivo* therapy [68]. Halim *et al*. investigated the antioxidant capacity, total phenol, and total flavonoid contents of *Emblica officinalis.* The ethanolic extract of *Emblica officinalis* has been reported to have antioxidant and immunomodulatory effects [69].

5. *ANDROGRAPHIS PANICULATE* (KALMEGH)

Andrographis Paniculate is a significant medicinal plant that comes under the Acanthaceae family. Kiryata, Create, Kirta, Kalpnath, King of Bitters, Bhuineem, and Maha-tita are some other names for it. It has hepatoprotective, antipyretic, antimicrobial, cardiovascular, anti-inflammatory, anticancer, antiviral, anti-diarrheal, and hypoglycemic activities [70]. It contains flavonoids, xanthones, and trace elements such as zinc, copper, manganese, cobalt, noridiodes, potassium, and calcium [71]. *Andrographis Paniculate* was also added to the Ministry of Ayush's list of herbal plants for curing SARS-CoV-2.

Sa-ngiamsuntorn *et al*. investigated the activity of *Andrographis Paniculate* extract, which helps to inhibit the virulent protein of SARS-CoV-2. They investigated the main constituent andrographolide in human lung epithelial cells and organ cell representatives' cytotoxicity. Calu-3 was used in the study to investigate the antiviral potency of the extract. The plaque assay demonstrated that after treatment with *An-*

drographis paniculate an andrographolide, Calu-3 cells stopped producing infectious viruses. Thus, the results demonstrated *Andrographis paniculate* efficacy as an antiviral agent [72]. Banerjee *et al*. used LC-MS/MS investigation to examine *Andrographis paniculate* immunoprotective effect action against respiratory tract viral infections. It was discovered that the *Andrographis paniculate* biomolecules have antiviral activity against COVID-19. According to the findings, this herbal plant is effective and safe as an anti-inflammatory agent and can reduce pro-inflammatory and cytokine production in viral infections [73].

In another study, Rajagopal *et al*. used an *in silico* method to study the constituents of *Andrographis paniculate* against the virulent protein of SARS-CoV-2. For molecular docking studies, a glide module was used. The major constituents of *Andrographis paniculate*, dihydroxy dimethoxy flavone and andrographolide, showed a good binding affinity with the M-pro COVID-19. These findings could lead to the better and more efficient development of harmless drugs [74]. Maity *et al*. extracted arabinoxylan, a water-soluble molecule from *Andrographis paniculate*, to investigate its antioxidant potential. According to *in vitro* studies, it has hydroxide radical scavenging, superoxide radical scavenging, and ferrous ion chelation activity, demonstrating its antioxidant potential [75].

6. *GLYCYRRHIZA GLABRA*(LICORICE)

Another plant studied for COVID-19 efficacy is licorice. *Glycyrrhiza glabra* is the botanical name for licorice, a plant in the Leguminosae family [76]. It is abundant in Europe and Africa's Mediterranean region. Licorice is well known in Asia (India, China), Greece, and Europe for its use in arthritis and ulcers. It has been utilized to treat various ailments in the Chinese medical system, Arabic medicine, and Indian Ayurveda. Glycyrrhizin, isoliquiritin, glycyrrhizin acid, isoflavones, and other chemical constituents are present in *G. glabra*. The potential uses of *G. glabra* for treating inflammation, eye and liver disease, throat infections, arthritis, and peptic ulcers are described in the Indian Ayurvedic Pharmacopoeia. It was used to treat ulcers (gastric and peptic) in Greeks, while it was used to treat psoriasis in Europeans and Asians. It is an additional important component of traditional Persian medicine for respiratory problems. In Japan, licorice is used to cure chronic hepatitis. In addition to its antioxidant effects, the licorice plant contains anticancer, antispasmodic, hepatoprotective, neuroprotective, and estrogenic characteristics. Additionally, it helps to prevent hepatitis B and C from causing hepatic damage. It has long been known for its memory booster, blood cholesterol level maintenance, and antidepressant properties [77].

Researchers have investigated the antiviral properties of licorice. Ashfaq *et al*. investigated licorice extract's antiviral potential against the hepatitis C virus. A study using plant extract on viral strains reduced 50% of virus populations. Furthermore, the combined antiviral potential was assessed using interferon-alpha 2a. The synergistic effect of the combinational products with interferon was observed.

Furthermore, these findings were confirmed by transiently introducing the HCV 3a core plasmid into the liver cells [78]. Glycyrrhizin's antiviral efficacy against SARS-coronavirus replication was demonstrated in *in vitro* tests to investigate their antiviral efficacy against SARS-CoV. Hoever and colleagues synthesized 15 glycyrrhizin derivatives. Glycyrrhizin derivatives with 2-acetamido-beta-d-glucopyranosylamine have ten times the activity of the original compound [79].

Srivastava *et al*. conducted an *in-silico* computational study on active ingredients from *Glycyrrhiza glabra*, such as glycyrrhizin acid, liquiritigenin, and glabridin, which protect against the M-pro. The computational analysis discovered that the compound has a binding affinity with amino acid residues at active sites and strongly inhibits the enzyme. *In silico* studies predicted that *Glycyrrhiza glabra* would have good solubility and permeation, correlated with solubility behavior, absorption ability, permeation, and non-carcinogenic properties. Furthermore, they concluded that glycyrrhizic acid has a high potential to inhibit M-pro [80]. Christian Bailly and Gerard Vergoten investigated the natural product glycyrrhizin, and its glycyrrhizic derivative acid can cure COVID-19 infection and other respiratory diseases. Glycyrrhizic acid activates the disorganization of cholesterol-dependent lipid rafts, which helps virulent protein of SARS-CoV-2 invasion into the host cells. The protein HMGB1 (high mobility group box 1) can be trapped by glycyrrhizic acid. They also ran a molecular docking study to see how glycyrrhizic acid binds to cholesterol and the HMG box. Furthermore, they confirm glycyrrhizic acid's safety and suggest that it could efficiently experiment further to treat SARS-CoV-2 individually or in amalgamation with other constituents [81].

Another research by Lukas van de Sand *et al*. examined the anti-virulent activities of glycyrrhizin against SARS-CoV-2. They conducted an *in vitro* analysis to determine the anti-virulent efficiency against COVID-19 viral duplication. Glycyrrhizin specifically inhibits the M-pro COVID-19, resulting in the inhibition of the viral replication process. According to the available literature, pure glycyrrhizin or glycyrrhizin-containing crude drugs like licorice root tea, black licorice, and others could benefit SARS-CoV-2 patients [82]. One of the possible methods through which glycyrrhizin inhibits COVID-19 infection is i) by boosting the generation of nitrous oxide in macrophages. ii) changing the viral lipid bilayer membrane directly, iii) interfering with transcription factors and cellular signaling cascades, and iv) interacting with the ACE2 receptor [83].

Zhaoyanand and Co identified uncontrolled inflammatory processes in COVID-19-infected individuals as a major mortality risk. It is crucial to utilize safe and efficient treatment approaches to lessen viral damage and extreme inflammation because, presently, there is no permanent solution to treat such situations. This study used glycyrrhizic acid as a starting point to create highly biocompatible glycyrrhizic acid nanoparticles. Studies conducted *in vitro* showed that GANPs stop the murine coronavirus MHV-A59 from proliferating and lessen the quantity of pro-inflammatory cytokines produced by MHV-A59 or the SARS-CoV-2 virulent protein. In a COVID-19-induced surrogate mice model employing MHV-A59, GANPs particularly target areas of the body that experience severe inflammation, such as the lungs. This appears to encourage GANP accumulation and improve therapeutic effectiveness. Additionally, GANPs contain antiviral and anti-inflammatory capabilities that lessen organ damage and significantly increase the chance of survival for infected mice. Such a novel medicinal compound can be simply transformed into an effective COVID-19 drug [84].

7. *OCIMUM SANCTUM* (TULSI)

Ocimum sanctum is another plant belonging to the Lamiaceae family taken into consideration. Many phytochemical and botanical studies have been conducted on it, and considered sacred in the Indian subcontinent with proven traditional therapeutic herbal value. It is also known as tulsi, well-known as a "Herb for All Purposes." due to its multitherapy potency. The pharmacological properties of *Ocimum sanctum (O. sanctum)* phytochemicals can be used to create immunomodulatory formulations for antivirals in treating and managing life-threatening problems such as COVID-19 [37, 85]. According to the document, the use of the native plant as a source of medicine first appeared in Atharvaveda. *O. sanctum* plants are widely cultivated in the Eastern Himalayas and the Western Ghats [86]. Kulkarni *et al*. discovered that the tulsi plant's roots, leaves, and seeds contain compounds with therapeutic properties and a variety of actions in human physiology in their study. It treats a wide range of illnesses due to the chemical components it contains, accompanied by anticancer, immunomodulatory, and anti-ageing properties [87].

Among the phytoconstituents extracted from *the O. sanctum* plant as reported in highly indexed literature were cardinene, eugenol, cubenol, borneol, linolenic acid, linoleic acid, oleic acid, vallinin acid, gallic acid, orientin, circineol, vitamin A, vitamin C, phosphorus, palmitic acid, vallinin, steric acid, vicenin, vitexin, and iron [88].

In their analysis, Singh *et al*. reported the immunomodulatory properties of fixed oil from seeds of *O. sanctum* Linn on both stressed and unstressed animals. The findings concluded that when given at a dose of 3 ml/kg, anti-sheep red blood cell antibody titer increases significantly, the proportion of histamine produced by peritoneal mast cells in sensitized rats decreases (humoral immune responses), footpad thickness increases, and the percentage of leucocyte migration inhibition increases (cell-mediated immune responses). Thus, *O. sanctum* appears to have an effect that begins with humoral and cell-mediated immunomodulatory effects [89]. Another study by Jeba *et al*. reported that when rats were given orally about 100-200 mg per kg a day of *O. sanctum* aqueous extract produced more RBC, WBC, hemoglobin, and antibodies, suggesting that the isolated compounds from *O. sanctum* could be used as antiviral agent [90].

To access the immunomodulatory properties, Mondal *et al*. tested 24 healthy volunteers in two groups, one receiving a treatment of ethanolic extract 300 mg capsules and the other receiving a placebo. It was discovered in this study that the 22 study participants had higher levels of Th1 and Th2 cytokines, and after four weeks of the study protocol, their immunology factors, such as T-cytotoxic cells, T-helper, B-cells, and NK-cells, were significantly higher in levels of interferon, interleukin-4, and T-helper cell percentages than the placebo group. These findings support *O. sanctum* leaf extract's immune-suppressive properties [91]. In another study three phytochemicals identified in *O. sanctum,* including vicenin, ursolic acid and Isorientin 4′-O-glucoside 2″-O-p-hydroxybenzoate by Shree P. *et al*. as possible regulators of the SARS-CoV-2 M-pro, which demonstrated high binding affinity to in blocking viral protein translation to counterattack SARS-COV-2 infection built-in ligand N3 [32].

In a study by Kar *et al*., *in silico* molecular interventional findings, following careful molecular docking of phytochemicals at viral protein-binding sites, the phytochemical constituents of plants *O. sanctum,* were suggested to have SARS-CoV2 protein inhibitory potential. Anisotine and amarogentin were found to have significant molecular dynamics simulation evaluation activity against the SARS-CoV-2 protease. These findings indicate the need for more studies to hasten the advancement of effective SARS-CoV-2 inhibitor medications [92]. The phytochemicals from *O. sanctum* that were extracted using ethanol by Mohapatra *et al*. were demonstrated to be blockers of the major SARS-CoV-2 protease due to covalent binding association with the enzymatic residue Cys145. The flavonoids and polyphenol Luteolin-7-O-glucuronide in *O. sanctum* potentially link to Cys145 covalently, the primary protease's catalytic residue, permanently inhibiting the viral enzyme [93]. Muthumanickam *et al*. discovered nine compounds with qualities for ligand binding to the targeted N-catalytic protein's sites, viz baicalin, kaempferol-3-O-glucuronide, kaempferide, linarin, eudesmol, cadinene, geranyl acetate, alpha-thujene, germacrene A, and. These ligands are capable of targeting SAR-COV-2 proteins and thus confirm the anti-COVID-19 antiviral activity of the *O. sanctum* bioactive [94].

Umashankar *et al*. conducted an experimental study and discovered that *O. sanctum*s pure components, including ursolic acid, apigenin, and linalool, could combat RNA and DNA viruses by decreasing viral genome replication by using crude terpenoid and polyphenol-rich extract of *O. sanctum* [95]. According to a study presented by a seasoned dietician and applied nutritionist, supportive therapy plays a significant role as an immunomodulator [96]. Chiang *et al*. investigated *O. Sanctum* purified components and extracts for potential antiviral effects on hepatitis B, adenoviruses, herpes, and RNA viruses. Their purified components, ursolic acid, apigenin, and linalool, have a wide range of antiviral activity [97]. According to Jindal *et al*., two of *O. sanctum's* ingredients, vicenin and orientin, were very effective against the host receptor proteins ACE2 (angiotensin-converting enzyme) and TMPRSS2 (transmembrane serine protease 2). *In silico* study using molecular docking and protein-protein interaction resulted that phytocompounds target ACE2 and TMPRSS2 predict the SARS-antiviral CoV2 property [98].

Pant *et al*. used molecular dynamic simulation and molecular docking investigations to show that *O. sanctum* contains a variety of bioactive chemicals with therapeutic effects across a wide range of conditions, including immunity-boosting abilities. They suggested vicenin, ursolinic acid, and isoorientin 40-O-glucoside 200-P-hydroxybenzoate as pharmacological constituents of *O. sanctum* that can effectively suppress the M-proof SARS-CoV-2 [99]. According to research by Mediratta *et al*., administering *O. sanctum* seed oil to stressed and unstressed animals significantly increased anti-sheep red blood cells (SRBC) antibody titer, reduced the proportion of histamine produced from peritoneal mast cells in sensitized rats, decreased footpad penetration depth, and decreased the proportion of leucocyte migration inhibition [100].

Mukherjee *et al*. discovered that an aqueous extract of *O. sanctum* leaf reduced total bacterial count, raised neutrophil and lymphocyte concentration, and improved phagocytic activity and phagocytic score in bovine subclinical mastitis. Thus, *O. Sanctum* (leaf) crude aqueous extract contains antibacterial and immunomodulatory phytochemicals [101]. According to Mediratta *et al*., the alteration of albino rats' humoral immune responses by a steam-distilled concentrate from *O. sanctum* leaf extract may have been brought about by producing antibodies [102]. Ghoke *et al*. examined the antiviral effectiveness of three distinct leaf extracts from *O. sanctum* against the H9N2 virus using an *in vivo* model: crude extract, terpenoids, and polyphenols. Although all *O. sanctum* extracts were found to have major antimicrobial activity, crude and terpenoid extracts exhibited a proficient reduction in viral DNA at the minimal experimented doses. Consequently, terpenoids and unrefined extracts of *O. sanctum* leaves have demonstrated encouraging antiviral efficacy against the H9N2 virus [103]. Biologically active component eugenol of *O. sanctum* has immunomodulatory cardioprotective, antispasmodic, adaptogenic, antioxidant, hepatoprotective, antiallergic, antipyretic, antiviral, antiulcer, anti-inflammatory, anticancer, anti-diabetic, anti-fertility, antifungal, antimicrobial, CNS depressant, and anti-arthritis activities [104].

Vaghasiya *et al*. reported in their study that distilled extracted fresh leaves of *O. sanctum* caused antibody generation, tissue reactions, and the release of hypersensitive mediators in specific organs of rats [105]. Venkatachalam *et al*. conducted *in-vitro* and *in-vivo* tests in Wistar strain rats using extracts and a standard medication given orally for 14 days to assess measures such as Humoral Antibody Titre, Total Leucocyte Count, Delayed-Type Hypersensitivity, and Differential Leucocyte Count. The result was that *O. Sanctum* responded immunomodulatory, making it a superior herb for immunomodulatory function [106]. Patil demonstrated the antiviral efficiency of aqueous, chloroform, ethanol, and methanol extracts of powdered medicines against viruses, such as Orthmyxovirus and Paramyxovirus, in her *in vitro* cytotoxicity study, as well as a safety profile. The chloroform extract of the plant significantly inhibited orthomyxoviruses. This study suggests that *O. sanctum* may have antiviral properties [107]. A study on the effectiveness of a hot aqueous extract of *O. sanctum* leaves against the chicken embryo fibroblast monolayer culture-borne New Castle Disease Virus in poultry was presented by Jayati *et al*. The appearance of noncytopathic effects indicates that *O. sanctum* leaf extract is antiviral [108].

Ling *et al*. presented a study that used HepG2 cells to examine the impact of a methanolic *O. sanctum* extract on dengue viruses. The results were encouraging in this study as investigations have shown that HepG2 cells treated with *O. sanctum* extract at the Maximum Non-Toxic Dose and half of the MNTD showed inhibitory effects on the Dengue virus [109]. Bhatia *et al*. studied the immune impacts of *O. sanctum* leaf hot aqueous extract on chickens. The humoral and cell-mediated immune response against Salmonella typhimurium '0' antigen were measured using indirect ELISA and DNCB (l-chloro, 2, 4-dinitro chloro benzene) tests, respectively. On the seventh day after immunization, antibodies produced in chickens against the Salmonella typhimurium '0' antigen displayed a minor upturn in antibody titer; however, on the fourteenth day, a prominent variation was noticed in antibody titer amongst the *O. sanctum* fed along with control groups. As a result, they terminated the immunomodulatory activity [110].

8. *PIPER LONGUM* (INDIAN LONG PEPPER)

Piper longum, alternatively termed Piper Latifolium Hunter, Chavica Roxburghii Miq and Piper saramentosum Wall, belongs to the Piperaceae family. It is extremely useful for its pharmacological activities and has become a key component in most Ayurvedic formulations. *Piper longum* is a well-known and widely used spices [111]. According to Kirtikar *et al*., this plant originated in South Asia, as well as in some hotter parts of India and worldwide, including Malaysia, Singapore, Bhutan, and Myanmar [112]. Pipermonaline, piperundecalidine, piperine, piperlongumine, sylvatin, sesamin, and diaeudesmin piperlonguminine are the important chemical compounds that occur in the *Piper longum* [113, 114]. Three primary lignans found in the fruits are pulviatilol, sesamin, and fargesin. The two main organic acids found here are palmitic acid and tetrahydrobiopterin acid [115-117-123]. *Piper Longum* has been utilized as analgesic, carminative, anti-diarrheic, immunostimulant/modulatory and treatment for spleen disorder, leprosy, diabetes, rheumatoid arthritis, asthma, dementia, epilepsy, and other conditions in South Asia and the Indian subcontinent [118].

Choudhary *et al*. used molecular docking to assess the ability of 26 bioactive components found in spices *Piper longum* and *Piper nigrum* to prevent SARS-CoV-2. Moreover, the findings showed that piperine from *Piper longum* and *Piper nigrum* had a higher affinity for the nucleocapsid's RNA-binding site than adenosine monophosphate. This showed that the virus might inhibit its proliferation, possibly assisting in the battle against SARS-CoV-2 by having therapeutic potential [119]. The antiviral properties of phytocompounds from the plant *Piper longum* that have demonstrated inhibitory action against COVID-19 protease were studied by Pandey *et al*. using the Lipinski rule of five, molecular docking, and pharmacokinetic analysis to screen specific phytocompounds for antiviral activity. They identified two important coronavirus targets, 6LU7 and 7JTL, which can be utilized to block SARS-CoV-2 [120].

Nag *et al*. used computer docking simulation to test the usefulness of piperine alkaloid from *Piper nigrum* L. for the prospective antiviral medication. As targets for piperine's *in silico* docking, they selected eight Dengue and Ebola virus proteins that are essential structurally. Inhibiting the Methyltransferase of Dengue and the Interferon Inhibitory Domain of the Ebola viruses has been demonstrated to be possible with piperine using molecular dynamics modelling and binding free energy calculations [121]. The capacity of bioactive molecules from *P. guajava* L. and *Piper nigrum* L. to bind with virulent proteins, including the highly contagious spike component ACE2 and its primer TMPRSS2, was the focus of De Jesus *et al*. using molecular docking, it was found that guineensine, isoquercetin, terpinyl acetate, morin-3-O-lyxoside, brachyamide A, and terpinyl acetate have considerable adherence to all these different proteins [122].

Mahfouz *et al*. investigated AgNO3 and aqueous seed extracts from *Nigella sativa* and *Piper nigrum* to produce silver nanoparticles (AgNPs). AgNPs' antiviral, antibacterial, and anticancer activities were investigated. The reduced mortality and viral load suggest that the *N. sativa* and *P. nigrum* AgNPs have antiviral efficacy against herpes simplex virus-1 [123]. *Piper longum* has anti-hepatitis B activity against many viruses. When the anti-hepatitis properties of *Piper longum* were investigated, they revealed inhibitory qualities that were both inhibitory to their secretions and active against the HBeAg and Hepatitis B virus surface antigen (HBsAg) [124,125].

Saetang *et al*. investigated the piperine content of *Piper nigrum* extract, which contains a diversity of antioxidants that may reduce the harmfulness of doxorubicin. The study used five groups of tumor-bearing Sprague Dawley rats, and each group's internal organ weight, tumor burden, blood parameters, and immunological data were examined. Piperine extract and doxorubicin were given to the rats. They hypothesized that piperine use could reduce doxorubicin toxicity [126]. Priya investigated the antiviral properties of *Piper nigrum* and *Piper longum* seed methanolic and chloroform extracts, confirming piperidine by HPTLC analysis. Both extracts were evaluated because of their prowess in battling the human parainfluenza virus and the vesicular stomatitis virus. The results show that in the HeLa cell line, the human para influenza virus and vesicular stomatitis Indiana virus were more resistant to the antiviral effects of chloroform extract than methanolic extract [127]. In their study, Mair *et al*. isolated several piperamides from a *Piper longum* combined methanol/dichloromethane extract. They tested their ability to inhibit the replication of three distinct viruses connected to upper respiratory tract contaminants suppressed by Coxsackie virus type B3 in a cytopathic impact inhibition study. These findings shed light on *Piper longum's* antiviral potential [128].

According to Doshi *et al*., hosts have few biomolecules and their own promoters, as antiviral medications are gradually absorbed because they affect host cellular processes slowly. Thus, Ribosomal Inactivating Proteins can protect against viral infection [129]. An alcoholic fruit extract of *Piper longum* that contains piperine was shown to have immunomodulatory effects on Balb/c mice. The study found that injecting a *Piper longum* and piperine extract into Balb/c mice gradually improved the number of white blood cells and plaque-forming cells, producing antibodies. *Piper longum*, according to this, stimulates the humoral immune system [130]. The haemagglutination titer test, the macrophage movement rate, and the phagocytic indicator in mice to validate the immunostimulatory effect of *Piper longum* fruits were employed by Khushbu *et al*. at low dosages of *piper longum* were observed to improve nonspecific and specific immunity [131].

Virmani *et al*. reported current study's declared goal was to compare the *in vitro* efficiency of *Piper nigrum* aqueous and alcoholic extracts against the contagious bursal disease virus in primary chicken embryo fibroblast cell culture. The antiviral potency of the extracts was evaluated using the Reed and Muench formula. According to the findings, an aqueous extract of *Piper nigrum* seeds and leaves had antiviral activity [132]. In a dose-dependent and additive way, Majdalawieh looked into the potential molecular mechanism of aqueous black pepper formulations on increased cell proliferation. According to research using an enzyme-linked immunosorbent assay, black pepper significantly increases splenocyte production of T-helper cytokines. As a result, their findings reveal the immunomodulating potential of black pepper [133].

Sunila *et al*. evaluated the effects of piperine, an ingredient in an alcoholic extract of the *Piper longum* fruit, on Ehrlich ascites carcinoma (EAC) and Dalton's lymphoma ascites (DLA) cells at doses of 500 g/ml and 250 g/ml, respectively, for immunomodulatory effects. At 250 g/ml, piperine alcoholic extract was discovered to be toxic to DLA and EAC cells. This suggests that *Piper longum* may have immunomodulatory properties [134]. Tripathi *et al*. measured hemagglutination titer, macrophage movement index, and phagocytic index in mice to determine the precise and general immunostimulatory effects of *Piper longum* fruits. In tests using mice diseased with Giardia lamblia, the ayurvedic treatment *Piper longum* was discovered to raise macrophage migratory value and phagocytic score, implying an immunostimulatory impact [135].

9. *CURCUMA LONGA* (TURMERIC)

Curcuma longa (common name: turmeric, family Zingiberaceae) is an herbaceous, shrubby plant utilized in conventional Chinese, Indian, and Ayurvedic medicine. *Curcuma longa* has antiviral, analgesic, antibacterial, immunomodulatory, antiproliferative, and anti-inflammatory properties. *Curcuma longa* is a well-known spice around the world, including in India. The three primary curcuminoids responsible for turmeric's therapeutic effects are curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Among these three phytochemicals, curcumin is the most effective curcuminoid in turmeric (diferuloylmethane) [136].

The perspective of *in vitro* inhibition of SARS-CoV-2 Chymotripsin-like Protease (3CLPro) functionality by several plant extracts is examined by Carla Guijarro-Real *et al*. Severe acute respiratory replication may be prevented or suppressed with the help of inhibitors or extracts of the 3CLPro. They utilized a targeted method to identify around seventeen plant components in modern and traditional foods that demonstrated potential as SARS-CoV-2 3CLPro activity inhibitors [137].

Pandey *et al*. completed a molecular docking simulation study for spike glycoprotein affinity. The glycoprotein was thought to be present on the COVID-19 surface, preventing host cell recognition. As a result, the virulent cell enters the targeted cell with ease. The spike glycoprotein invades the cell after interacting with the human ACE2 receptor. When a glycoprotein binds to the ACE2 interface, the ACE2 binding site changes from its metastable state to its stable state, allowing a virus to invade the next host cell. They tested the affinity of various flavonoid/nonflavonoid compounds, including curcumin, to inhibit the virulent SARS-CoV-2's spike protein with molecular docking simulations. They also compared hydroxychloroquine, a repurposed FDA-approved drug. Molecular dynamics simulation and potential field studies suggested that a weak complex of hACE2-S could form [101]. Babaei and colleagues have described curcumin's ability as a phytochemical to inhibit the virulent protein of novel. Curcumin may be useful in COVID-19 to reduce the effects of cytokinin storm due to its medicinal properties and antioxidant potential. Through molecular mechanisms, it blocks NF-B, receptors, inflamed chemicals (cytokines and chemokines), and bradykinin [138].

Pawar and her colleagues conducted a clinical study on symptomatic COVID-19 patients using piperine and curcumin. A thirty-bed COVID-19 health center was chosen to conduct a double-blind clinical trial of these bioactive compounds. Curcumin-piperine (525:2.5 mg) was given to patients and designated as the treatment group, which was compared to a control patient who received a probiotic. The treatment group recovered from symptoms faster, had normal oxygen saturation levels, and performed better clinical outcomes than the control. Furthermore, the treatment group's hospitalization time was reduced. They concluded that curcumin combination treatment has a significant chance of providing symptomatic relief for COVID-19 patients, which may lower morbidity and death rates [139].

10. LIMITATION OF TRADITIONAL HERBS IN TRANSLATION RESEARCH

The effectiveness of herbs as immunomodulators with antiviral properties is uncertain and can take varying amounts of time to take effect [140]. Extracting phytoconstituents from plants presents challenges because a single plant can contain numerous phytochemicals, making ethnopharmacological research with any type of extract challenging and non-specific [141]. Promising drug targets, such as the chymotrypsin-like protease (3CLpro), an essential enzyme for SARS-CoV-2 replication, are poorly identified for human coronaviruses [142]. Developing bioactive components in phytopharmaceuticals for these pharmacological attributes of crude drugs poses challenges with quality control, identification, and standardization protocols, and commercial availability is yet to be realized. Ensuring safe and toxic parameters during the quality control process is time-consuming and subject to stringent regulatory standards [143]. Consistency and efficacy of herbal products are ensured by complying with standards based on their bioactive markers, but this can be difficult due to variations in batch-to-batch formulations of individual medicinal plants and inadequate toxicity studies specific to the formulation [144, 145]. Medical practitioners often recommend synthetic antiviral drugs for patient ailments, neglecting the potential of medicinal plants and herbs to boost immunity [146].

CONCLUSION

The international health community has been diligently striving to discover efficacious therapies and preventative strategies for COVID-19. Vaccines have demonstrated considerable efficacy in managing the transmission of the virus and mitigating its impact. Furthermore, ongoing research and development efforts are being dedicated to antiviral drugs and various therapeutic strategies.

Traditional plants have been used to boost immunity since ancient times. Selected traditional herb extracts contain active constituents with immunomodulatory, antiviral, and antipyretic properties. Because of these properties, medicinal herbs were used in mild COVID-19 during the first wave. The *in silico* simulation studies have confirmed the affinity of 5 plants towards the main protease of SARS-CoV2, namely *Withania somnifera, Emblica officinalis, Andrographis paniculate, Glycyrrhiza glabra and Ocimum sanctum* hence these plants could exhibit antiviral effect against SARS-CoV2. *Curcuma longa* (curcumin) and *Emblica officinalis* have been explored in clinical investigation. The Spo2 level improved, and patient hospitalization time decreased by treatment group compared with placebo by using *Curcuma longa* (curcumin) and *Emblica officinalis*, *Piper nigrum* (Piperine), *Glycyrrhiza glabra* (glycyrrhizine), *O. sanctum*, and curcumin. The main constituents of *O. sanctum*, *Piper nigrum*, and *Curcuma longa* have been found effective against cytokines, and hence, they have been used to suppress complications of cytokine storm in COVID-19 patients.

It is imperative to adopt a scientific approach when dealing with traditional herbal medicine, ensuring that any possible remedies undergo thorough clinical testing. Randomized controlled trials play a vital role in the establishment of the safety, efficacy, and appropriate dosages of herbal therapies. The amalgamation of conventional information and contemporary scientific methodologies has the potential to yield significant breakthroughs and facilitate the advancement of supplementary therapeutic approaches for the management of COVID-19. In addition, it is imperative for regulatory entities to assume responsibility for assessing and guaranteeing the safety and quality of herbal commodities accessible inside the marketplace.

Amidst the backdrop of a worldwide pandemic, such as COVID-19, the establishment of collaborative efforts among conventional healers, researchers, and medical professionals has the potential to cultivate a more holistic comprehension of the potential contributions of herbal therapy in the realm of illness treatment. By integrating the strengths of conventional and contemporary methodologies, we can boost our collective capacity to mitigate infection and optimize public health results. Ongoing research and a receptive attitude towards conventional herbal therapy have the potential to enhance a comprehensive healthcare approach and bolster our ability to address forthcoming health crises.

LIST OF ABBREVIATIONS

WHO	=	World Health Organization
COVID-19	=	Coronavirus Disease

SARS-CoV-2	=	Severe Acute Respiratory Syndrome
MD	=	Molecular Dynamics
M^{pro}	=	Main Protease
IgA	=	Immunoglobulin A
IgG	=	Immunoglobulin A
IgM	=	Immunoglobulin A
ACE2	=	Angiotensin-converting Enzyme 2
Treg	=	Regulatory T Cells
Th1	=	T Helper Type 1
Th2	=	T Helper Type 2
Th17 cells	=	T Helper 17 Cells
IL-1b	=	Interleukin 1 Beta
IL-4	=	Interleukin 4
IL-6	=	Interleukin 6
BALF	=	Brocho-alveolar Lavage Fluid
RORgt	=	Retinoid-related Orphan Receptor Gamma t
GATA3	=	GATA Binding Protein 3
TNF	=	α-Tumour Necrosis Factor-alpha
IL-17A	=	Interleukin-17 A
IL-10	=	Interleukin 10
INF-g	=	Interferon Gamma
HPLC	=	High-performance Liquid Chromatography
LC-MS/MS	=	Liquid Chromatography-mass Spectroscopy/ Mass Spectroscopy
HPTLC	=	High-performance Thin Layer Chromatography
TMPRSS2	=	Transmembrane Serine Protease 2
ICMR	=	Indian Council of Medical Research
AYUSH	=	Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy
GC-MS	=	Gas Chromatography-mass Spectroscopy
AgNO3	=	Silver Nitrate
RBC	=	Red blood Cells
WBC	=	White Blood Cells
AgNPs	=	Silver Nanoparticles
DPPH	=	(1,1-diphenyl-2-picryl-hydrazyl)
GLR	=	Glycyrrhizic Acid
HMGB1	=	High Mobility Group Box 1
SRBC	=	Anti-sheep Red Blood Cells
NF-k	=	Nuclear Factor Kappa

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CONFLICT OF INTEREST

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