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Medicinal Plants for Managing Post-COVID-19 Complications

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ABSTRACT

Post-COVID-19 syndrome symptoms include circulatory abnormalities, respiratory problems, mental health concerns, and chronic fatigue. The burden that these illnesses placed on the global healthcare system led to a rise in complementary and alternative medicine, particularly medicinal plant therapies. Medicinal plants have long been used in traditional medicine for their antiviral, immunomodulatory, antioxidant, and anti-inflammatory properties. These properties are currently being studied. By lowering oxidative damage, immune response modulation, and chronic inflammation, these compounds with bioactive properties could assist in lessening the long-term consequences of COVID-19. Additional clinical trials were needed to verify the safety and efficacy of these medicines, even though initial study results suggested that medicinal plants might aid COVID-19 patients in recovering and living longer. The article provides comprehensive medical strategies that consider the needs of patients post COVID-19. It is recommended to use evidence-based medicinal herbs in addition to traditional therapy.

1. Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the newly identified coronavirus illness (COVID-19), which currently places pressure on healthcare systems globally [1]. The cause of COVID-19 is infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was initially isolated and discovered in patients exposed in December 2019 at a seafood market in Wuhan City, Hubei Province, China [2]. There have been three significant coronavirus outbreaks documented to far, the most recent of which was caused by the 2019 novel coronavirus (2019-nCoV, or more recently SARS-CoV-2), which is the causative agent of Coronavirus Disease-2019 (COVID-19) [3]. A worldwide pandemic had been declared by the World Health Organization on March 11, 2020, caused by the novel coronavirus (COVID-19) pandemic[4]. According to research on SARS-CoV and the Middle East respiratory syndrome, SARS-CoV-2 is thought to transmit mostly through human-to-human contact and is thought to cross species to cause primary human infections [2].COVID-19, also known as "Post-COVID-19 manifestations," has had a lasting effect on people's everyday lives and general health. These effects include a range of symptoms that extend beyond the acute stage of the illness. The NICE guideline on post-COVID-19 conditions states that post-COVID-19 conditions

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occur during or after a SARS-CoV-2 infection and persist for more than four weeks.Post-COVID-19 symptoms indicate that multiple organs are involved [5].

These illnesses had a high death rate and left survivors with chronic respiratory problems, exhaustion, and a reduced quality of life overall. Patients also had a heavy burden of mental health conditions that made it hard for them to find work after they were released from the hospital. Survivors reported physical injury and chronic breathing issues [6].Some investigations found that femoral head necrosis and respiratory fibrosis remained the main side effects of treatment. Delays in diagnosis and the use of steroids caused secondary infections such as *Aspergillus*, CMV, and mucormycosis to affect a significant portion of healthcare professionals. Investigations into past outbreaks and their consequences might be beneficial for the rehabilitation of COVID-19 sufferers and associated medical management [7].

According to estimates from the World Health Organization (WHO), more than 65% of people worldwide only take medicinal remedies made from plants [8]. Medicinal plant-derived phytochemical compounds with antiviral properties were suggested as potential therapeutic agents for the treatment of COVID-19 [9]. The review study by Khan et al. emphasized the role of phytomedicine in the fight against COVID-19 and described the molecular properties of significant phytochemical substances that have demonstrated anti-coronavirus capabilities. Glycyrrhizin derived from Glycyrrhiza glabra roots had shown encouraging promise in combating the SARS-CoV coronavirus, which was formerly ubiquitous. To combat SARS-CoV, Other significant plants have been used, including Artemisia annua, Isatis indigotica, Lindera aggregate, Pelargonium sidoides, and Glycyrrhiza spp. Myricetin, scutellarin, apigenin, luteolin, betulonic acid, emodin, reserpine, aescin, and myricetin are the active compounds that had demonstrated encouraging outcomes against the coronaviruses. Through mechanisms like blocking virus release, inhibiting viral entrance, and inhibiting replication enzymes, phytochemicals have shown effectiveness against coronaviruses [10].

In this review, we evaluated the potential benefits of employing medicinal herbs to help manage COVID-19-related conditions. In order to combat viruses and COVID-19-related problems, we also examined how phytocomponents, which are present in herbal treatments, can alter immunological and inflammatory responses as well as the antiviral activities of plants.

2. Post-COVID-19 Complications

2.1. Respiratory complications

The most common cause of mortality from SARS-CoV-2 infection is the emergence of viral pneumonia-induced acute respiratory distress syndrome [11]. COVID-19 has been linked to a wide range of long-term respiratory problems, from pulmonary fibrosis, vascular issues, and decreased respiratory physiology to radiologically detectable alterations and persistent symptoms. Respiratory sequelae associated with post-acute SARS-CoV-2 infection remain poorly known and unexplored even after two years [12]. The COVID-19 virus has been responsible for numerous long-term pulmonary problems. Sleeplessness, ventilator dependability, oxygen dependence, abnormalities in the pulmonary function test, and fibrotic lung disease are just some of these. The most frequent pulmonary symptom after COVID-19 is breathing difficulties, which might last for two months from the beginning of symptoms in 22.9% to 53% of patients [13].

The mechanisms that the SARS-CoV-2 can induce lung damage are several. Acute infections can cause a number of alterations that can lead to fibrosis and long-term issues. Viral entrance directly into cells, particularly type II alveolar epithelial cells that maintain the epithelial barrier, causes cell death, which raises proinflammatory cytokines. Diffuse alveolar damage and the cytokines that follow stimulate neutrophils, macrophages, and lymphocytes, which in turn attract fibroblasts and cause fibrosis [14]. There have also been observations of injury to the pulmonary vasculature in addition to direct harm to the lung tissue. Early dissection investigations revealed that micro thrombi were present in the pulmonary vasculature's tiny capillaries [15]. Because the virus ruptures the lungs' tiny air spaces, respiration, fibrotic alterations, absorption capacity,

ground-glass opacity, intervening edema, fibrosis symptoms, and exercise ability are all restricted [7].

The NHS recently published guidelines that identify probable respiratory conditions like fibrotic lung disease, bronchiectasis, chronic cough, and pulmonary vascular disease, as well as the expected post-COVID-19 aftercare requirements for patients. Acute COVID-19 symptoms, acute respiratory distress syndrome (ARDS) data, and extrapolations from the 2003 SARS pandemic provide the majority of the evidence for these possible aftereffects [16].

2.2. Cardiovascular complications

After COVID-19, cardiac complications were common complaint after hospital being released [17]. Particular patients with heart conditions even showed symptoms of mild to severe heart damage following a COVID infection, as a result of an overreactive immune system response that caused abnormal cardiac muscle and irregular heartbeats [18]. According to a study from the University of Frankfurt in Germany, 60% of patients with COVID-19 had cardiac inflammation, and over 78% of patients had cardiac problems [19]. Wuhan studied 187 COVID-19 patients nearly 70% survived. Among these individuals, 35% had high blood pressure, arterial disease, and cardiomyopathy, and 27.8% had elevated Cardiac troponin values, indicating cardiac damage. Additionally, there was an increase in heart muscle growth, which led to blood coagulation and the dissolution of cytotoxic lipids, which in turn caused a myocardial infarct with weakening in the pulse [20].

Survivors frequently experience myocardial fibrosis, a rapid heartbeat cardiovascular and pulmonary rhythm problems myocarditis, abnormal cardiovascular imaging results, nonischemic late gadolinium supplements treatment improvements, ischemic coronary syndrome, a serious myocardial infarction or stroke, prolonged hypotension, increased heart consumption, and heart attack. In female Takotsubo people, serious heart conditions were recorded. Like other organ systems, elderly individuals with illnesses had been more likely to suffer it. Persistent medical, 'echocardiographic', and 'electrocardiographic' surveillance could have monitored acutely unwell individuals with chronic heart symptoms or abnormalities [7]. There had been several theories put out on the pathophysiology of SARS-CoV-2-induced heart damage.RT-PCR positive for SARS-CoV-2, myocardial enlargement and necrosis, interstitial inflammatory infiltration, and other abnormalities on histological investigation of the heart have been noted in compiled data from early descriptive autopsy studies [21].

2.3. Neurological complications

One of the main signs of SARS-CoV-2 infection in children is neurological problems [22]. COVID-19 survivors were observed experiencing depressed symptoms, sleep disturbances, generalised myalgia, and persistent malaise[23]. Another characteristic of SARS-CoV-2 infection that sets it apart from other viral illnesses is loss of taste and smell. Between 11% and 13.1% of patients had persistent loss of taste and smell at the 2-month mark [24]. `

Additional COVID-19 post-acute symptoms include headaches that resemble migraines and headaches that start later and are linked to elevated cytokine levels[25]. Some specific viral processes may be relevant, even if the precise mechanisms underlying many of these symptoms are unclear and most likely caused by the same mechanisms underlying other long-haul COVID-19 symptoms. After shock, a traumatic experience, postpartum hormonal changes, or an acute febrile sickness or viral infection, telogen effluvium refers to the phenomena of transitory hair loss in the form of non-scarring alopecia, usually lasting less than six months [26].

2.4. Endocrine complications

COVID-19 endocrinological problems were uncommon but could affect the results of patients. Previous endocrinologic diseases were susceptible to COVID-19. The thyroid gland, the pancreatic, the adrenal glands, the neuroendocrine framework, gonadal glands, and glands that produce parathyroid hormone were among the major endocrinologic system that SARS-CoV-2 targeted [27].

Two serious side effects of COVID-19's involvement of the pancreas include acute and necrotizing pancreatitis, which, if left untreated, can be fatal [28]. SAT, ST, PT, HT, and GD are

among the various forms of thyroid inflammation that COVID-19, a virus, can provoke [29]. In men with severe infections, serum luteinizing hormone (LH) is markedly elevated, and the ratio of testosterone (T) to LH (T:LH) falls precipitously [30]. Additionally, autoimmune thyroid conditions like Hashimoto's thyroiditis or Graves' disease might be made worse by COVID-19 [31].

2.5. Fatigue Complications

Fatigue is acknowledged as one of the most often reported chronic problems among those who have had a prior SARS-CoV-2 infection [32]. Over the course of several years or months, after the first attack, tiredness caused by the coronavirus may continue to manifest [33].In addition to symptoms and illnesses, older persons had frequently experienced fatigue, which had unsatisfied treatment needs. One typical COVID-19 complaint both during and after sickness was fatigue. There was no disease or pathogenetic mechanism could explain weariness in its entirety. Probable reasons included: pain, mitochondrial dysfunction, irregular sleep patterns, sympathetic nervous system issues, and malnourishment [34]. According to a meta-analysis, about one-third of people reported having ongoing fatigue over 12 weeks or more after receiving a confirmed diagnosis of COVID-19[35].Relevant studies also show that post-COVID-19 weariness is linked to an accumulation of cerebrospinal fluid in the lymphatic system, in addition to the presence of the SARS-CoV-2 spike protein in the central nervous system. An excess of CSF in the lymphatic system results in idiopathic intracranial hypertension, which causes post-COVID-19 weariness [36].

2.6. Renal Complications

Patients with SARS-CoV-2 infections are most likely to have renal involvement, and because chronic inflammation and injury can last for months, kidney function gradually deteriorates until kidney failure occurs [37]. In acute COVID-19, acute kidney injury is prevalent, and inpatient renal replacement therapy is necessary for 5% of all hospitalized patients [38]. Acute kidney injury has a complex etiology, with direct viral damage, systemic oxygen deprivation inflammatory cytokine effects, and aberrant coagulation all playing a role. Although glomerulopathy and microvascular thrombosis are also observed, acute tubular necrosis is the most frequent histological the outcome [24].

In the presence of serious tube necrosis, glomerulopathy and small blood vessels were common histological discoveries. Survivors may have had chronic kidney failure, and hospital deaths from early kidney damage had been greater. Another ongoing study found that 30% of acute dialysis patients continued to require therapy after being discharged, while 35% of patients with acute kidney damage had insufficient renal function. Recurrent renal illness occurred in 14% of those who recovered before departure, while 36% of those with residual kidney disease at discharge recovered upon further investigation (average 21 days). At six months of age, 35% of COVID-19 recipients showed renal impairment, and 13% experienced abrupt renal failure following normal kidney function, according to a different study [13].

2.7. Gastrointestinal Complications

In COVID-19 survivors, mild-to-moderate gastrointestinal issues have been documented. On the eleventh day following negative RT-PCR results, the presence of viral debris, such as ribonucleic acid, has been reported in feces [39]. Gastrointestinal symptoms are common in acute COVID-19 patients and may manifest later in the healing process. With a frequency of 6%, diarrhea was among the top 10 most common symptoms in a systematic examination of post-acute COVID-19 manifestations. Other persistent symptoms include nausea, vomiting, appetite loss, and abdominal pain [40]. An adverse outcome is linked to chronic metabolic conditions like obesity and elevated cholesterol levels. Leptin levels rising and adiponectin levels falling in COVID-19 worsen the inflammatory state and prognosis [41].

In individuals with COVID-19, electrolyte imbalance can worsen their clinical symptoms and even cause cardiac arrhythmia. It manifests as hypokalemia, hyponatremia, hyperkalemia, and hypernatremia. Fluid resuscitation and electrolyte control in COVID-19 patients are necessary to

avoid this [42]. Additionally, changes in the microbiota of the intestinal tract are linked to COVID-19, however it's unclear how these changes affect long-term symptoms [43]. The biological processes of damage include systemic inflammation, oxygen deprivation coagulation disorders, unfavorable medication effects, and direct viral cytotoxicity, especially in the biliary tree [44]. Acute liver damage survivors may experience persistent abnormalities in liver function that progressively improve over the course of weeks to months [45]. In COVID-19, it was discovered that the butyrate-producing anaerobe Faecalibacterium prausnitzii, which is linked to excellent health, was inversely correlated with the severity of the illness [23].

2.8. Dermatological complications

After recovering from COVID-19, about 20% of individuals experience dermatological complications [46]. The virus's dermatic manifestations occurred either after (64%) or concurrently with (15%) other post-COVID-19 symptoms in a global sample of 716 COVID-19 patients. An estimated 7.9 days passed between the beginning of upper respiratory symptoms and dermatological results in adults [47]. Post-COVID-19 syndrome is the name given to this illness, which is typified by hyper inflammation and abnormalities in CD8+ T-cell humoral response [46]. According to the post-acute COVID-19 Chinese investigation, only 3% of patients had a skin rash at the 6-month follow-up [48].

There are several different viral mechanisms that might be relevant, even if the precise mechanisms underlying many of these symptoms are unknown and probably related to the same mechanisms underlying other long-haul COVID-19 symptoms. After shock, a traumatic experience, postpartum hormonal changes, or an acute febrile sickness or viral infection, telogen effluvium refers to the phenomena of transitory hair loss in the form of non-scarring alopecia, usually lasting less than six months [26].

3. Medicinal Plants and Their Potential in Managing Post-COVID-19 Complications

3.1. General overview of medicinal plant therapies

All throughout history, humans have relied on nature to meet their basic needs, including transportation, fertiliser, food, clothing, scents, medicines, shelter, and food [49]. Nearly 80% of people in developing countries are thought to rely on complementary and alternative medicine for their basic medical needs, according to estimates from the World Health Organization. The use of medicinal plants as treatments has been growing significantly even now because of their many benefits, including their low cost and widespread acceptability from the public due to their long history of use [50]. A medical plant is any type of plant whose parts flowers, leaves, roots, stems, fruits, or seeds are used either directly or in a preparation as medicine to treat a disease or other ailment. An important tool for maintaining the biological and cultural diversity of many ethnic groups is knowledge of the health benefits of medicinal plants [51].

Many marine creatures, as well as bacteria, fungi, and plants, create secondary metabolites [52]. The secondary metabolites of medicinal plants have pharmacological qualities that make them useful [53]. Compounds from plants have controlled the growth of certain microorganisms [49]. The diverse range of secondary metabolites or compounds discovered in medicinal plants, including flavonoids, alkaloids, terpenoids, and tannins, contribute to plants therapeutic effectiveness, particularly their antimicrobial properties [54].

Approximately over 4,000 diverse phytochemicals could have the capability to prevent a variety of diseases, including cancer and degenerative or metabolic disorders [55].The rate of moderate, severe, and overall mortality as well as the overall duration of the disease appear to have decreased with the use of traditional Chinese medicine. In conjunction with contemporary biomedicine, herbal remedies may have antiviral, immunoregulatory, anti-inflammatory, and hypoxemia and chronic obstructive pulmonary disease-relieving properties. Many viral infections can be effectively treated using medicinal plants and their bioactive components, which have minimum adverse reactions and excellent efficiency [56].

In all, 694 species of medicinal plants belonging to 152 families including Adenoviridae, Alloherpesviridae, Arteriviridae, Birnaviridae, Coronaviridae, Flaviviridae, Herpesviridae, Nimaviridae, Orthomyxoviridae, Papillomaviridae, Parvoviridae, Picornaviridae, Poxviridae, Reoviridae, Retroviridae, and Togaviridae were chosen from the scientific study to be tested against 17 virus families. The plant families with the highest citation rates include Fabaceae (11.38%), Euphorbiaceae (3.02%), Rubiaceae (3.45%), Asteraceae (5.61%), and Lamiaceae (5.90%). Zingiber officinale, Azadirachta indica, and Allium sativum are the three most widely known species that can heal a variety of viral illnesses. [57].

3.2. Potential mechanisms of action of medicinal plants

3.2.1. Anti-inflammatory properties

These plants essential oils, which have anti-inflammatory properties, have been used extensively to treat ailments like joint inflammation, inflammatory skin disorders, and cardiovascular problems [58]. The dysregulation of inflammatory responses in SARS-CoV-2 infections is demonstrated by the activation of the T-helper 17 and node-like receptor pyrin 3 inflammasome, which increase proinflammatory cytokines and promote neutrophil recruitment. [59]. Herbal remedies and plant-derived cures were promising for controlling inflammation and inflammatory conditions. Many herbal anti-inflammatory and antiphlogistic remedies did not have the adverse effects of steroidal medicine for inflammation or anti-inflammatory drugs such as including gastro-erosive side effects. Medicinal herbal extracts having anti-inflammatory properties were typically multicomponent, meaning they probably affect the intricate balance of whole immunological systems by working on several targets [60]. *Curcumin* can reduce lung inflammation by downregulating the expression of many proinflammatory cytokines and chemokines, most likely via deactivating nuclear factor kappa B [61].

Numerous beneficial characteristics of *N. sativa* include immune response modulation, antiviral effects, increased eosinophil counts and serum levels of immunoglobulin E , and decreased levels of several pro-inflammatory cytokines, including interleukin-4 [IL-4], interleukin-1b [IL-1b], IL-6, transforming growth factor beta [TGF-b], and interleukin-17 [IL-17] [62]. Pulmonary infections cause a strong cytokine storm due to the substantial activation of the NLRP3 inflammasome. Certain bioactive substances that are derived from ginger, such as shogaols and gingerols, have the ability to block the and node-like receptor pyrin 3 inflammasome, which results in a sharp drop in cytokine levels. This stops the cytokine storm and many of the symptoms that follow [63].

Quercetin and other *Ginkgo Biloba* Extract components reduce excessive inflammation and hypercytokinemia conditions by inhibiting the activation of Th17 and the NLRP3 inflammatory enzyme. By reducing inflammatory reactions, this helps to lessen the severity of COVID-19 symptoms [64].

3.2.2. Immune Modulation

The immune system serves as a barrier to keep infections and other disorders out of the body. Increased immunity or suppression may lead to a variety of diseases. Depending on the need for therapy, immunomodulators have the ability to either stimulate or inhibit immunity. Since the beginning of time, the body's defences have been altered using natural elements. Prominent examples of traditional medical systems that offered a range of proof demonstrating their wide-ranging pharmacological effects were Ayurveda, Unani, and Traditional Chinese medicine [65]. The effects of *Azadirachta indica* flower aqueous extract on humoral and cell-mediated immune responses to ovalbumin, as well as the phagocytic activity assessed using the carbon clearance test and the cyclophosphamide-induced myelosuppression model, were examined. By inducing humoral and cell-mediated immunity as well as a non-specific immune response through macrophage phagocytic activity, the outcome demonstrated strong immunomodulatory activity [66].

A thorough search of online databases yielded 115 published research studies from 2020 to 2024, which allowed for the selection of 50 plants that are commonly used for immune support. Examples of plants include *Allium sativum* (garlic), *Withania somnifera* (ashwagandha), *Curcuma*

longa (turmeric), *Tinospora cordifolia* (guduchi), *Ocimum sanctum* (holy basil), *Phyllanthus emblica* (amla), *Aloe vera* (aloe vera), *Amomum subulatum* (black cardamom), *Cucurbita pepo* (pumpkin), *Punica granatum* (pomegranate), *Psidium guajava* (guava), *Moringa oleifera* (moringa), *Nigella sativa* (black cumin), *Citrus limon* (lemon), *Cymbopogon citratus* (lemongrass), *Carica papaya* (papaya), and *Camellia sinensis* (green tea). Terpenoids, alkaloids, and flavonoids are bioactive compounds found in these plants that are believed to have antiviral, anti-inflammatory, and immune-stimulating properties [67].The plant *S. nigrum's* polysaccharides are well known for their immune-modulating properties [68]. Additionally, *flavonoids* with notable immunomodulatory properties, such as *myricetin*, *rutin*, *quercetin*, and *kaempferol*, are found in a variety of plants [69].

3.2.3. Antioxidant effects

The pathophysiology of SARS-CoV-2 infection is associated with the overproduction of ROS and the depletion of antioxidant mechanisms, which may result in multiple organ failure [70]. Over the course of the past several years, a developing curiosity in the antioxidant properties of medicinal plants was emerged [71]. Aromatic herbs was the interest of many researches due to the fact that they included antioxidant and antibacterial components, in addition to other health benefits such as the prevention of cardiovascular disease, coronary artery disease, inflammatory diseases, and malignancy. Products derived from the family Lamiaceae (including rosemary extract, sage, oregano as the herb marjoram, rosemary, thyme, basil, mints, and balm), family Apiaceae (which involves cumin, fennel seeds and the herb caraway), and Zingiberaceae of plants that rich in antioxidants. The antioxidant properties of medicinal plants were dependent on growth factors, processing, the amount of antioxidants on hand, and the nutritional content of the plant. Also crucial for herbal product quality checks were gathered and antioxidant capacity procedures [72].

Studies have shown that *Ginger* leaves and rhizomes have strong antioxidant properties because of the presence of phenolic and terpenoid components. These investigations demonstrated its antioxidant and radical scavenging properties using the DPPH and ABTS tests, respectively [73]. By indirectly reducing the cytokine storm or lowering oxidative stress, which is beneficial for viral survival in the host, *T. officinale's* antioxidant activity offers a potential herbal therapy to help lessen COVID-19 symptoms [74]. *Patchouli alcohol* showed a strong affinity for SARS-CoV-2 enzymes, such as PLpro, 3CLpro, and NSP15, according to molecular docking and molecular dynamics simulation experiments, preventing the virus from invading host cells [75].

3.2.4. Antiviral effects

A number of medications with strong antiviral qualities have long been produced using medicinal herbs, which is interesting [76]. Potential antiviral properties are shown by a variety of plant constituents, including essential oils and phytocompounds such *phenolic acids*, *flavonoids*, *terpenes*, *lignans*, *coumarins*, and *alkaloids.* Therefore, medicinal plants hold promise as a means of treating viral infections [77].A therapeutic plant's antiviral activity was mediated by a variety of mechanisms, such as the reduction of propagation of viruses, the inhibition of viral particles putting together within cells, the limitation of viral infection, the limitation of DNA and RNA polymerase enzyme, viral neuraminidase, protease, the enzyme reverse transcriptase, and virus-associated protein expression respectively, among a lot of people [78].

Numerous separate investigations have demonstrated the strong inhibitory effects of substances extracted from various medicinal plants, including *curcumin*, *caffeic acid*, *chalcones*, *cinnamic acid*, and *betulinic acid*, on the SARS-CoV 3CLpro protease [79]. According to studies, a selenium shortage in the diet causes changes in the viral genome under oxidative stress, which intensifies viral pathogenesis. Consequently, consuming selenium could be a wise decision for managing new infectious coronaviruses [80].

Molecular docking studies of 100 major phytocompounds from ten selected medicinal plants (*Rheum emodi*, *Thymus serpyllum*, *Cymbopogon citratus*, *Moringa oleifera*, *Thalictrum foliolosum*, *Berberis aristata*, *Piper nigrum*, *Allium sativum*, *Myristica fragrans*, and *Zanthoxylum armatum*) were recently reported by Rolta et al. (2020). According to the molecular docking investigation, 5 phytocompounds—*emodin*, *anthrarufin*, *alizarine*, *aloe-emodin*, and *dantron* of

Rheum emodi—exhibited acceptable pharmacokinetic characteristics and binding affinity with the NTD of the RNA binding domain of the *SARS-CoV-2* nucleocapsid phosphoprotein [81].

Other significant plants that have been used to combat *SARS-CoV* include *Artemisia annua*, *Isatis indigotica*, *Lindera aggregate*, *Pelargonium sidoides*, and *Glycyrrhiza* spp. Promising responses against the coronaviruses have been observed with active ingredients such as *emodin*, *reserpine*, *aescin*, *myricetin*, *scutellarin*, *apigenin*, *luteolin*, and *betulonic acid*. Through mechanisms like blocking virus release, inhibiting viral entrance, and inhibiting replication enzymes, phytochemicals have shown effectiveness against coronaviruses. Phytomedicines should be thoroughly assessed before use, nevertheless, as their mechanisms are less well understood than those of synthetic pharmaceuticals [82]. It has been reported that the flowering buds of *Syzygium aromaticum* (L.) Merr. & L.M. Perry (Myrtaceae) contain *eugenol*, *acetyl eugenol*, *β-caryophyllene*, *vanillin*, *eugenin*, *kaempferol*, *rhamnetin*, and *eugenitin*. They also have antiviral potential against the hepatitis C virus, *SARS-CoV-2*, herpes simplex virus I, and herpes simplex virus II [83].

4. Medicinal Plants Effectiveness in Controlling COVID-19 Complications

4.1. Respiratory Complications

Patients with COVID-19 who are hospitalized experience pulmonary embolism, pneumonia, lung fibrosis, and persistent coughing [84]. Acute lung infections have been found to be effectively treated by a number of phytomolecules derived from plants that modulate the NF-κB, MAPK, and Nrf2 signaling pathways due to their anti-inflammatory and antioxidant properties [85].The findings demonstrated that *Solanum nigrum* fruit extract and phytochemicals have a major role in treating acute lung injury and pulmonary conditions, suggesting that they may be used to treat COVID-19-related pulmonary problems [39]. The review conducted by MF Jubayer et al. in 2024 looked at the potential of several medicinal plants, including *Echinacea*, *Glycyrrhiza* (Licorice), and *Nigella sativa* (Black Cumin), as well as their phytoconstituents, in the treatment of respiratory diseases, with a focus on COVID-19[86].

The control of inflammatory cytokine levels is one of the primary therapy objectives for respiratory illnesses. It has been shown that extracts from *Astragalus membranaceus* and *Lonicera japonica* increase specific microRNAs, decrease SARS-CoV-2 pathogenesis, and block proinflammatory cytokines like IL-6 or TNF-α, all of which are significant pathogenic contributors in cytokine storms [87]. *Sterculia lychnophora* has also long been used to treat inflammatory respiratory conditions, including pharyngitis, by blocking the production of prostaglandins, histamine, serotonin, and bradykinin—all of which act as key mediators of acute inflammatory conditions [88]. Reducing the amount of reactive oxygen species, which damages the lungs, is another major therapy objective. Antioxidants found in *Mentha piperita* and *Houttuynia cordata* extracts have been shown to scavenge free radicals and reduce lung cell damage [89].

Additionally found in *Folium mori* are rutin, choline, and folic acid, all of which have anti-inflammatory qualities that could be beneficial in the medical management of inflammatory disorders of the respiratory system [90]. In order to produce surfactant, a naturally occurring surfactant made of glycerophospholipids, inside the alveoli, *hederine*, which is derived from *hederacoside C*, indirectly stimulates adrenergic receptors found in smooth muscle from the trachea to terminal vesicles. This complex consists of dipalmitolecithin and a carrier protein called apoprotein. The ciliary-mucosal clearance is improved, smooth muscle relaxation occurs, airway secretion viscosity decreases, and elastic resistance to lung respiratory work decreases [91].

In animal models of chemically induced pulmonary fibrosis, ginger consumption has been associated with protective effects against pneumonia and pulmonary fibrosis, as well as a reduction in oxidative stress and the inflammatory response in the latter condition [92]. Garlic's bioactive compounds have been associated with acute lung injury, pulmonary fibrosis, sepsis, respiratory tract infections, and intra-alveolar edema [92].

4.2. Cardiovascular complications

Numerous patients have experienced cardiovascular disease exacerbated by the COVID-19 virus during the new COVID-19 outbreak. May damage the cardiovascular system via an unclarified pathogenic mechanism [93].The common post-recovery complications of COVID-19 include arrhythmia, myocardial infarction, cardiac failure, chest discomfort, and excruciating chest pain. *S. nigrum* has historically been suggested to have a possible use in the treatment of a variety of heart conditions [94].

The most essential component of oligomeric proanthocyanidins is *epicatechin*. The cardiac muscle is attracted to the anthocyanins found in *Crataegus* fruits. According to in vitro research, the probable mechanism of action of *hawthorn* raw materials includes thromboxane biosynthesis promotion, c-AMP phosphodiesterase activity suppression, and a decrease in cell membrane permeability to ATP-ase, Na+, and K+[10]. *Rasayana* is commonly utilized in Ayurveda as an anti-inflammatory agent, anti-stress, and antioxidant medication which additionally supports patients' hearts [95].

Citrus species include *hesperidin*, *naringenin*, and *naringin*. They prevented the production of pro-inflammatory cytokines in macrophages, reduced cytokines by blocking the expression of *HMGB1*, and blocked the coronavirus's ability to attach to the ACE2 receptor [95]. In patients with COVID-19, *curcumin* from *Curcuma longa* has anti-inflammatory properties and inhibited the release of pro-inflammatory cytokines, IL-1, IL-6, and TNF-α [96].

Similar to glucocorticoids and mineralocorticoids, *glycyrrhizic acid* and *glycyrrhetinic acid*, which are derived from *Glycyrrhiza glabra*, have been shown to possess anti-inflammatory qualities, making them viable options for the management of inflammatory conditions. Cardioprotective properties are also possessed by *Glycyrrhiza glabra* flavonoids and triterpenoids [97]. Extracts from *Piper nigrum* have also been found to exhibit anti-inflammatory and cardioprotective qualities by inhibiting the synthesis of COX-1 and COX-2 and reducing TNF-a-induced NF-kB activation [98].

4.3. Neurological Complications

Herbs have been traditionally employed for managing neurological conditions [99]. There have also been observations involving neurological issues in those infected with SARS-CoV-2. SARS-CoV-2 infection has been shown to decrease the number of ACE2 receptors in the brain stem, which causes many baroreceptors to stop working and neurons to die. Moreover, migraine-like and late-onset headaches were linked to increased cytokine levels post COVID. Following COVID-19 recovery, issues like epilepsy, schizophrenia, PTSD, and auditory and visual hallucinations have been observed as well [100]. One well-researched therapeutic food for Parkinsonism management is *fructus barbarum.* Since its inception, *Fructus barbarum* has been recognized for its antioxidant properties, which have been shown to support neuroprotection and neuroplasticity two critical aspects of treating neurological disorders like Parkinsonism [101]. Furthermore, *S. nigrum* assists with neurological disorders [99]. Studies conducted in vivo revealed that lavender oil enhanced memory retention in mice given scopolamine [102]. Depression was treated with TCM botanicals such as *Lilium* bulbs, *Rehmannia* spp., *Anemarrhena* spp., and *Glycyrrhiza* (ganmai dazao decoctions) [103].

Moreover, it was found that geniposides have antidepressant qualities, which could help post-COVID patients with their depression symptoms [104]. To treat post-COVID vertigo, *Gastrodia elata* may be a useful medicinal meal[105]. *Gastrodia elata* may be used as a therapeutic food for managing neurological conditions that have developed after COVID [104].

4.4. Liver Complications

The risk of death was raised for COVID-19 individuals with pre-existing liver disease who also had concomitant conditions such diabetes (48%) and hypertension (68%) [106]. As a result, all of these experiments demonstrated that *S. nigrum* could display hepatoprotective effect and be helpful in preventing hepatic problems following COVID-19 [39]. *Lawsonia inermis* L. (leaves), *Eclipta*

officinalis, *Eclipta alba* (L.) Hassk. (leaves), *Clitoria ternatea* L. (leaves), *Cassia angustifolia*, *Tinospora cordifolia* (leaf, stem, and root), and *Momordica charantia* L. (fruit), *Abrus precatorius* L. (seeds), *Argemone mexicana* L. (leaves), and *Morus* Vahl (leaves) normalized high bilirubin, ALT, ALP, and AST levels in vivo [11]. Extracts from *Cassia fistula* have been demonstrated to lower ALP, SGOT, and SGPT levels in the event that the liver has been implicated after COVID, decreasing oxidative stress and hepatic toxicity markers [107]. Likewise, it has been demonstrated that *foeniculum vulgare* and its active ingredient trans-anethole increase the thiol content and catalase activity of high-density lipoprotein cholesterol and enhance hepatic toxicity markers, hence reducing liver fibrosis and damage [108].

4.5. Renal Complications

According to CDC data, 74.8% of individuals hospitalized for COVID-19 with underlying health conditions in the United States had chronic kidney disease; nevertheless, these patients made up just 3% of all cases [109]. The primary SARS-CoV-2 binding site is the ACE2 protein, which is significantly more abundant in the kidney than in the lungs. Patients with acute and chronic kidney disease improved from *Lespedeza* (*Lespedeza capitata* Michx.) tincture [110]. It may be possible to treat decreased renal function by combining *Rheum officinale* Baill with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and the Chinese-patented medication Rheum [111].

Reducing renal inflammation is one of the main therapy objectives. One medicinal plant that can do this is *Olea europaea*. The glycosylated secoiridoid oleeuropein, which is present in the fruit and leaves of the *Olea europaea* plant, is a type of phenolic bitter molecule that can inhibit the activation of NF-kB and inflammatory cytokines like IL-6, TNF-α, and IL-1. Consequently, this intensifies anti-inflammatory effects [112]. It has been demonstrated that *rhizoma dioscorea* lowers IL-1b, IL-6, and TNF-a levels to lessen renal inflammation [113].

A naturally occurring flavonoid, *quercetin* can be found in a variety of fruits, vegetables, leaves, and cereals, such as bog blueberries and red onions. Its anti-inflammatory and antioxidant qualities are widely recognized. Extracellular signal-related kinases are strong inducers of inflammatory gene expression and protein release, and *quercetin* inhibits TNF-α from directly activating them [114].

4.6. Fatigue Complications

Relevant study also suggests that post-COVID-19 weariness is linked to an accumulation of cerebrospinal fluid in the lymphatic system, in addition to the presence of the SARS-CoV-2 spike protein in the central nervous system. A high concentration of CSF in the lymphatic system results in abnormal intracranial hypertension, which in turn causes post-COVID-19 fatigue [36]. Clinical research indicates that several medicinal herbs may be able to successfully reduce fatigue following COVID-19. It has been discovered that these plants contain modes of action linked to exhaustion, including antioxidant activity, anti-inflammatory qualities, and the restoration of compromised mitochondrial function, all of which may be pertinent to post-COVID-19 fatigue [115].

4.7. Dermatological complications

The most typical sign of a patient recovering from COVID-19 is hair loss [116]. Examples of symptoms that have been documented include blisters, ulcers, and lesions [117]. There have also been reports of rash formation in kids recuperating from SARS-CoV-2 infections. This may primarily be explained by interactions between the basal epidermal cell ACE2 receptor and the SARS-CoV-2 spike protein [118].

Additionally, evidence from both traditional and scientific sources point to the plant's potential involvement in alopecia and other skin conditions. *S. nigrum* may therefore be helpful in treating dermatological issues following COVID-19 [39]. It was also shown that using *Prunus mume* in

conjunction with probiotics significantly reduced the development of skin lesions while lowering serum IgE levels and the peripheral eosinophil ratio [118].

5. Conclusion

The development of the most recent coronavirus, SARS-CoV-2, sparked the COVID-19 pandemic. Infection with COVID-19 led to problems, even in those with minimal symptoms. This pandemic appeared to have the most harmful effects on neurological conditions, including anxiety, depression, and mixed anxiety-depressive syndromes; renal function; and the functioning of the respiratory, circulatory, and cardiovascular systems. The respiratory, circulatory, and cardiac systems may all suffer from these disorders. According to the medical professionals, phytotherapy may be beneficial for each of these ailments. Clinical investigations confirmed this potential. Several distinct targets and signaling pathways implicated in the pathophysiology of COVID-19 were impacted by medicinal plants and their contents. Herbal treatments worked in a variety of ways. The processes at play include antiviral properties, anti-inflammatory advantages, immune system regulation, antioxidant capabilities, and respiratory support. By exhibiting antiviral properties, herbal items may directly restrict the ability of SARS-CoV-2, the virus that causes COVID-19, to proliferate. The suppression of viral reproduction and the prevention of viral entry were key strategies. Certain plant chemicals, like flavonoids and other polyphenols, had the ability to prevent the virus from infecting host cells by preventing the spike protein from interacting with the human cells' ACE2 receptor. Additionally, several plant substances were able to inhibit the function of viral metabolic enzymes that are critical for replication, particularly RNA polymerase, which is dependent on protein and RNA proteases. A thorough assessment of the plant's safety and quality was necessary when utilizing it medicinally to treat COVID-19 in order to ensure its efficacy and avoid any unfavourable side effects.

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6. References

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دور النباتات الطبية في إدارة مضاعفات ما بعد COVID-19

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معلومات البحث

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الكلمات المفتاحية

COVID-19 ، المضاعفات ، آليات عمل النباتات الطبية ، الأعشاب الطبية

الملخص

تشمل أعراض متلازمة ما بعد COVID-19 تشوهات الدورة الدموية ومشاكل الجهاز التنفسي والمشاكل العقلية والتعب المزمن. أصبح الطب التكميلي والبديل ، وخاصة العلاجات العشبية ، أكثر شيوعا نتيجة للضغط الذي تضعه هذه الأمراض على أنظمة الرعاية الصحية في العالم. يتم حاليا البحث في الصفات المضادة للفيروسات والمعدلة للمناعة ومضادات الأكسدة والمضادة للالتهابات للنباتات الطبية - والتي تم استخدامها على مر العصور في الطب التقليدي. قد تقلل هذه المواد النشطة بيولوجيا من الآثار طويلة المدى ل COVID-19 عن طريق تقليل الالتهاب المزمن وتنظيم الاستجابة المناعية وتخفيف الضرر التأكسدي. على الرغم من أن الأبحاث الأولية تشير إلى أن النباتات الطبية قد تساعد مرضى COVID-19 على التعافي والبقاء على قيد الحياة لفترة أطول ، إلا أن هناك حاجة إلى مزيد من التجارب السريرية لتأكيد سلامة وفعالية هذه العلاجات. يسلط هذا العمل الضوء على نهج طبي شامل يأخذ احتياجات المرضى في الاعتبار بعد COVID-19. بالإضافة إلى العلاج التقليدي ، يجب استخدام النباتات الطبية المدعومة بالأدلة.

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