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Role of different Medicinal Plants in the prevention and management of Covid-19 : A Comprehensive Review

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ABSTRACT

The global pandemic of SARS-CoV-2, or severe acute respiratory syndrome coronavirus, in 2020 claimed millions of lives globally. The clinical manifestation of this virus is called COVID-19, and it can cause everything from flu-like symptoms to severe clinical consequences and even death. The global health organization (WHO) created awareness campaigns to reduce infection rates and slow the virus's rapid spread because there was no proven medication that could treat this infection or lessen its problems with little to no negative effects on the health of the patients. Despite the fact that vaccinations have been created as preventative measures, people still prefer to use conventional herbal drugs because it offers exceptional health benefits and, with comparatively minor side effects, can either prevent a viral infection or restrict the development of serious symptoms through various mechanistic pathways. This thorough analysis offers empirical data clarifying the protective effect of various

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plants against SARS-CoV-2, opening the door for additional research to reevaluate plant-based extracts—rich in bioactive compounds—in more sophisticated clinical evaluations to determine their effect on COVID-19 patients.

KEY-WORDS

Covid-19, Corona virus, Zoonotic, Vaccine, Medicinal plants

INTRODUCTION

The coronavirus SARS-CoV-2 is the source of the 2019 coronavirus illness, or COVID-19. China's Wuhan city reported the first occurrence in December of 2019.[1] According to the majority of experts, the SARS-CoV-2 virus infiltrated human populations by natural zoonosis, which is consistent with other pandemics in human history and comparable to the SARS-CoV-1 and MERS-CoV outbreaks.[2][3] The probability of such zoonotic spillover was raised by social and environmental variables such as wildlife commerce, natural habitat degradation, and climate change.[4–7]The illness swiftly spread around the world, sparking the COVID-19 pandemic. Although COVID-19 symptoms might vary, they frequently include fever, exhaustion, coughing, dyspnea, loss of taste and smell, and fever [14].[8–10]One to fourteen days after being exposed to the virus, symptoms may start. Among those infected, at least one-third do not show any symptoms at all.[11,12]When symptoms become apparent enough to be categorized as patients, the majority experience mild to moderate symptoms (up to mild pneumonia), followed by severe symptoms (14%), severe symptoms (dyspnea, hypoxia, or more than 50% lung involvement on imaging), and critical symptoms (respiratory failure, shock, or multiorgan dysfunction).[13]Severe symptoms are more likely to strike older adults. Certain difficulties lead to demise. Organ damage has been reported, and some persons endure a variety of side symptoms (long COVID) months or years after infection.[14] Multi-year studies are underway to further investigate the long-term effects of the disease.[15] Covid-19 transmission occurs when infectious particles are breathed in or come into contact with the eyes, nose, or mouth. The risk is highest when people are in close proximity, but small airborne particles containing the virus can remain suspended in the air and travel over longer distances, particularly indoors.

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Transmission can also occur when people touch their eyes, nose or mouth after touching surfaces or objects that have been contaminated by the virus. People remain contagious for up to 20 days and can spread the virus even if they do not develop symptoms.[16] Testing methods for COVID-19 to detect the virus's nucleic acid include real-time reverse transcription polymerase chain reaction (RT-PCR),[17,18] transcription-mediated amplification,[19-21] and reverse transcription loop-mediated isothermal amplification (RT-LAMP) from a nasopharyngeal swab. Several COVID-19 vaccines have been approved and distributed in various countries, many of which have initiated mass vaccination campaigns. Other preventive measures include physical or social distancing, quarantining, ventilation of indoor spaces, use of face masks or coverings in public, covering coughs and sneezes, hand washing, and keeping unwashed hands away from the face. While drugs have been developed to inhibit the virus, the primary treatment is still symptomatic, managing the disease through supportive care, isolation, and experimental measures.

Various studies shown that COVID-19 can be prevented and its severity reduced by using herbal medicinal plants. [22, 23] China and India use modern therapy with traditional medicinal plants to boost patients' immunity.[24, 25] Reducing death and recurrence rates of the virus, as well as alleviating clinical symptoms, were all notable outcomes of traditional Chinese medicine.[26] According to earlier research, taking supplements containing echinacea may result in lower levels of the pro-inflammatory cytokines TNF, IL-6, and IL-8 and higher levels of the anti-inflammatory cytokine IL-10.[27] Curcumin, it's interesting to note, has been demonstrated in silico studies to block SARS-CoV-2 entrance into cells and viral multiplication, and a recent experimental study suggests that bromelain may likewise block viral entry into cells. [28] Furthermore, potential specific antiviral agents such as the decoy mini protein CTC-445.2d, protease inhibitors, mainly against the Main protein, nucleoside analogs, such as molnupiravir, and compounds blocking the replication transcription complex proteins, such as plitidepsin and zotatifin are under investigation against COVID-19.[29]

Additionally, herbal medicinal plants have been shown to mitigate the symptoms of viral disorders like SARS-CoV-2. There is evidence to suggest that using herbal medication can help manage and lower the risk of COVID-19. In conjunction with

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contemporary medicine, herbal medicine has been used as an alternative treatment for COVID-19 and has produced a number of suggestions for herbal therapy. [30] The effectiveness of many botanical medications as antiviral agents means that the use of herbal medicine for medical objectives shouldn't be undervalued. As traditional therapies are still not very effective, well-known herbal medications with antiviral properties are currently being employed as an extra therapy to inhibit SARS-CoV-2.[31]

SIGN & SYMPTOMS[32]

The Centers for Disease Control and Prevention (CDC) estimate that SARS-CoV-2 takes between four and five days to incubate on average. But it might vary from two to fourteen days.Trusted Source. Not every person infected with SARS-CoV-2 will have symptoms. It is feasible to have the virus yet not show any signs of illness. When they do appear, symptoms are usually minor and appear gradually.

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The most common symptoms are:

- a gradually worsening fever
- a gradually worsening cough
- fatigue
- shortness of breath
- loss of taste or smell

Some people with COVID-19 may sometimes experience additional symptoms, such as:

- runny or stuffy nose
- sore throat

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- headache
- muscle aches and pains
- diarrhea, vomiting, and other gastrointestinal symptoms
- chills
- discoloration of the fingers and toes

Symptoms that require an immediate visit to the emergency room (ER) include:

- difficulty in breathing
- persistent chest pain or pressure in the chest
- confusion
- difficulty waking up or staying awake
- cyanosis, which causes blue lips or a blue face

PATHOGENESIS

ACE2 serves as a crucial cell receptor for infection, which coronaviruses employ to infect the lower respiratory tract and other organs. When respiratory droplets from both symptomatic and asymptomatic infected individuals are inhaled, human infection results. Additionally, researchers found that MERS-CoV used dipeptidyl peptidase 4 (DPP4) as a critical receptor for host cell attachment and infection, whereas SARS-CoV-2, SARS, and HCoV-NL63 used ACE2 as a significant receptor.

Numerous researchers have discovered that cellular proteases, including as cathepsins, human airway trypsin-like protease (HAT), and transmembrane protease serine 2 (TMPRSS2), are also necessary for coronavirus entry. These proteases break the viral spike protein, resulting in further structural alterations that promote infection. According to studies, the S protein of SARS-CoV-2 binds to the host cell receptor (ACE2), causing the virus to fuse with the membrane of the host cell and release its RNA into the cytoplasm of the host cell. The lower respiratory tract, kidney, heart,

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liver, and intestinal tract are among the bodily organs having ACE2 receptors that are susceptible to infection by SARS-CoV-2. Moreover, other researchers stated that cytoplasmic viral replication and transcription involved a coordinated process of RNA synthesis, mediated by viral replicase, which is a huge protein complex encoded by the 20-kb replicase gene. The viral structural proteins (S, E, M, and N) and nonstructural proteins (viral nucleic acid RNA, and other enzymes) are processed in the endoplasmic reticulum and Golgi apparatus of the host cell. These proteins assemble at the host cell membrane to form mature viral progeny, which are released through the secretory vesicles via exocytosis and can infect surrounding cells. Some of these viral progeny may enter the bloodstream, causing primary viremia.

A new study showed that the spread and insertion of the virus into various body organs (heart, kidney, intestine, and liver) that have ACE2 receptors cause robust host immune responses, leading to the uncontrollable release of pro-inflammatory chemokines (like CCL2, CCL3, TXCL8, TXCL9, and CXCL10) and pro-inflammatory cytokines (like IFN-α, INF-η, IL-1β, IL-6, IL-12, IL18, IL-3, TNF-α, TGF-β, IL-2, IL-10, MCP1, IL-1RA, GCSF, IP-10, MCAP-1, and MIP-1α) into the bloodstream. The unchecked release of chemokines and cytokines damages pulmonary and alveolar tissue, which in turn results in acute respiratory distress syndrome (ARDS) and ultimately the patient's mortality, according to the researchers.[33]

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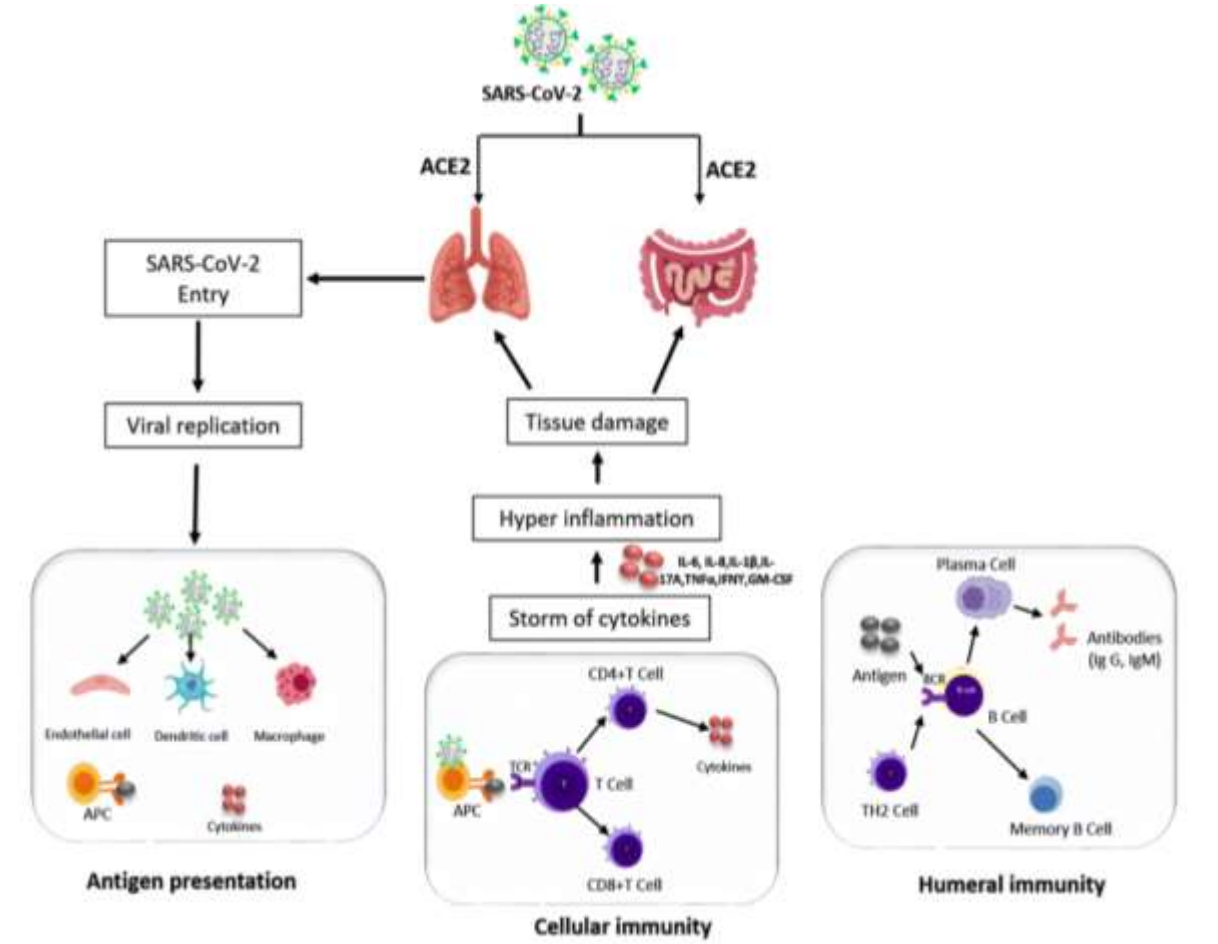

Fig 1: Pathogenesis of Covid-19

ROLE OF MEDICINAL PLANTS IN THE PREVENTION AND MANAGEMENT OF COVID-19

1. Curcuma longa

The SARS-CoV-2 viral protein can be neutralized by curcumin that has been extracted from turmeric.[34] Using an in silico method, the study showed that curcumin bound to both the viral attachment sites of the ACE 2 receptor and the RBD site of the viral S protein. Curcumin has the ability to inhibit pathways linked to fibrosis and pulmonary edema brought on by COVID-19 infection. [35] It functions through a number of molecular pathways and inhibits the toll-like receptor,

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chemokines, inflammatory cytokines, and bradykinin.[36] When it comes to SARS-CoV-2 (Mpro), dialethylcurcumin that was isolated from C. longa has been reported to be more effective than nelfinavir.[37] Many hospitalized patients in India had an increase in immunity and preventive defense against COVID-19 infections as a result of consuming curcumin together with zinc and vitamin C.[38] Therefore, curcumin could be considered as a preventive herb in the inhibition of transmission of COVID-19.

2. Allium sativum and Allium cepa

Allium sativum, or garlic, and Allium cepa, or onion, are frequently utilized as herbal remedies for a variety of illnesses. The goal of using onion, which has long been used in traditional medicine to treat a variety of illnesses and diseases, was to eradicate the H9N2 avian influenza virus. Because of its antiviral, antithrombotic, and anti-inflammatory properties, onions have been shown by researchers to be a promising option for managing COVID-19 patients. The main reasons it's utilized are for its antitumor, anticarcinogenic, antihypertensive, antithrombotic, antidiabetic, immunomodulatory, antibacterial, antioxidant, and prebiotic properties. Garlic's active metabolites may be divided into two groups, such as those that include sulfur and those that do not. allicin and alliin are the major sulfur-containing compounds, while the principal sulfur-free active compounds include flavonoids and saponins. Garlic’s ability to inhibit the SARS-CoV-2 was perceived in silico by forming hydrogen bonds between amino acids with the binding site of the main structural protease of SARS-CoV-2 and its bioactive parts that protease being responsible for viral production.Usually, COVID-19 patients have reduced the number of T helper cells, if we take garlic leads to a significant upregulation in the T helper cells, cytotoxic T cells, and NK cells, as well as downregulation of the levels of leptin, leptin receptor, TNF-α, IL-6, and proliferator-activated receptor gamma (PPAR-γ). So, it could be one possible option for the management of COVID-19 because of the ability to modulate cytokine secretion, immunoglobulin production, phagocytosis, and macrophage activation.[39-42]

3. Zingiber officinalis

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Due to its many historic medical uses, ginger is a plant with antibacterial, antioxidant, antiviral, analgesic, and antipyretic qualities. Ginger is a promising candidate for drug discovery against COVID-19, as evidenced by the phytocompound 6-gingerol obtained from the root vegetable. DFT (Density Functional Theory) study showed that ginger had the highest binding affinity with multiple targets of SARS-CoV-2, including viral proteases, RNA binding proteins, and viral proteases. Ginger's improved antioxidant properties are thought to fortify the body's defenses. 6. An essential substance found in ginger called shodhaol aids the patient in getting rid of respiratory problems. Aqueous extract of fresh ginger showed antiviral activity against human respiratory syncytial virus in human respiratory tract cell lines (Hep-2(human laryngeal carcinoma) and A549 (Adeno carcinomic human alveolar)), reducing the plaque count**.** Ginger stimulates IFN-β secretion which counteracts viral infection. Reduction in total nasal symptom scores (TNSS) in patients suffering from rhinitis allergy was also reported by taking oral alcoholic ginger extract**.**[43-46]

4. ***Azadirachta indica***

Neem (Azadirachta indica A. Juss) is a widely accessible tree, the products of which have been utilized for ages in tropical nations as traditional medicine. It is well recognized to possess bioactive compounds with antiviral and anti-inflammatory qualities.[48–47] Early research has demonstrated that neem extracts may strongly block the coxsackie B group of viruses, dengue fever, HIV, polio, and other viruses at an early stage of viral genome replication. The binding site of neem compounds on conserved regions of the influenza virus nucleoprotein has recently been convincingly identified by molecular docking experiments on the virus[49,50]. Additionally, the probable mechanism of neem compounds' antiviral action has been established. Additionally, several classical texts mention that neem has antimicrobial properties (Jantughna/Krimighna) and is useful for intermittent fevers (Vishama jwara). Neem leaves have also been reported to remove toxins, purify blood, and prevent damage through its medicinal properties.[51] Neem’s anti-inflammatory and antiviral effects make it a potential agent for use in COVID-19 prophylaxis.[52]

5. ***Mentha piperita***

The world's oldest herbal treatment for a variety of ailments is peppermint (M. piperita). Since 1000 BCE, dry peppermint has been cultivated, and ancient Egyptian, Greek, and traditional Chinese medicinal traditions have all noted its significance.

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Because menthol and menthone are abundant phytochemicals, peppermint has strong antibacterial and antifungal action against both Gram-positive and Gram-negative bacteria, yeast, and fungus.[53] However, to the best of our knowledge, a study done of Saudi Arabia stated that about 78% of non-hospitalized patients used peppermint, compared with only 22% of hospitalized patients without using peppermint supplement, due to COVID-pandemic so that use of peppermint during infection with COVID-19 was associated with lower odds of hospitalization.[54]

6. Piper nigrum

It is commonly recognized that piperine, which is present in black pepper, has antitumor, anti-asthmatic, antihypertensive, and anti-carcinogenic qualities. [55] Black pepper's distinct pungent fragrance is attributed to its alkaloid content.[56]Choudhary et al.[57] state that peperine that has been separated from black pepper may be useful in preventing the spread of viral particles because it prevents RNA packaging into the capsid protein. After conducting a computer analysis, scientists from the Department of Physics at IIT Dhanbad discovered that piperine, which is present in black pepper, can suppress the SARS-CoV-2 virus. According to research by Davella et al., the phenolic compounds methysticin and kadsurenin L from Piper nigrum were discovered to inhibit COVID-19 primary protease.[58]

7. *Glycyrrhiza glabra*

An alkaloid called glycyrrhizin is extracted from the root of Glycyrrhiza glabra and has some antiviral and anti-inflammatory qualities. Furthermore, this component is thought to be the cause of the therapeutic properties of this root, which has been widely utilized, especially by practitioners of traditional Chinese medicine (TCM), to cure respiratory infections, colds, and coughs.As with other viruses, glycyrrhizin may lessen the amount of SARS-CoV-2 that enters the host cell by blocking the action of the host cell receptor for the angiotensin-converting enzyme 2 (ACE2). Furthermore, this substance also lessens the inflammatory alarmin high-mobility group box 1 (HMGB1) activity.[59]

8. Nigella sativa

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Terpenes such dithymoquinone (DTQ), carvone, thymoquinone (TQ), limonine, trans-anethol, and p-cymene, as well as isoquinoline alkaloids like nigellicimine, nigellicimine-N-oxide, and α-hederin, are among the phytoconstituents found in black cumin.[60]It is well recognized for treating a variety of conditions, including as rheumatism, diabetes, conjunctivitis, fever, bronchitis, cough, and jaundice.[61] Research has demonstrated that TQ exhibits strong antagonistic activity against ACE 2 receptors and an inhibitory effect on SARS-CoV-2 protease.[62] At least eight in silico experiments have shown that molecules of N. sativa have moderate to high affinity with SARS-CoV-2 enzymes and proteins, according to Koshak and Koshak [63].

9. Ocimum sanctum

Tulsi is referred regarded as the "Elixir of Life" in Ayurveda because of its healing abilities for a variety of illnesses, including rheumatism, asthma, stomach and hepatic diseases, bronchitis, and microbiological infections.O. sanctum is well-known for its ability to relieve stress and enhance health during cancer treatment. It is also used as an adaptogen and nervine tonic. Tulasi contains several compounds such as flavonoids, phenolics, phenylpropanoids, essential oil, fixed oil, terpenoids, coumarins, and fatty acid derivatives. Tulsinol (A, B, C, D, E, F, G) and dihydrodieugenol-B, which are found in tulsi, inhibit the papain-like protease and the primary protease of COVID-19. They also have ACE 2 blocking qualities and immune-modulatory qualities. The ethanolic extract of aerial parts of Holy Basil contain flavonoids and polyphenolic acids especially luteolin-7-O-glucuronide and chlorogenic acid may bind covalently to the active residue Cys145 of main protease of SARS-CoV-2 and inhibit the viral enzyme irreversibly when screened *in silico*.[64]

10. ***Tinospora cordifolia***

With benefits that include antioxidant, immunomodulatory, anti-inflammatory, anti-allergic, anti-cancer, and anti-viral hyperglycemic properties, T. cordifolia is an Ayurvedic immune-modulator drug. There have been reports of 31 different chemical compounds identified in T. cordifolia, including glycosides, steroids, alkaloids, sesquiterpenoid and aliphatic chemicals, and diterpenoid lactones. Research on this

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medication by scientists may result in a new approach and understanding of COVID-19 management, prevention, and the creation of a new treatment element.

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11. Isatis indigotica

More than forty different kinds of alkaloids, including indole alkaloids, have been identified from the leaves and roots of Isatis tinctoria (also known as Isatis indigotica; Brassicaceae). Isatis tinctoria has also been linked to a number of biological and pharmacological activities, including cytotoxic, analgesic, neuroprotective, nitric oxide inhibitor, and anti-inflammatory properties. Moreover, in vitro and in silico investigations on Isatis tinctoria revealed anti-SARS-CoV properties. According to Lin and colleagues, the indole alkaloids from Isatis tinctoria root, namely Indigo, Indirubin, and Indican, shown anti-SARS-CoV activity via 3CLpro inhibition at 300 µM, 293 µM, and 112 µM, in that order. Additionally, in a docking research, Ghosh and colleagues demonstrated that the polyphenols of Isatis tinctoria root inhibited the RdRp and major proteases of SARS-CoV-2.[65]

12. Withania somnifera

On a variety of immune cells, such as T-leukemia cells, B- and T-lymphocytes, and natural killer cells, ashwagandha has demonstrated strong immunomodulatory effects. Withanolides, one of ashwagandha's active ingredients, can improve immune system performance by increasing the generation of immune cells and cytokines. Studies on humans and animals have both noted these effects. The innate immune response relies heavily on natural killer cells, which ashwagandha increases in both quantity and function. Additionally, it raises the B- and T-lymphocyte counts, which are in charge of the adaptive immune response. Furthermore, ashwagandha inhibits the growth of T-leukemia cells and affects the development of COVID-19. Withanone interacts with the interface of angiotensinconverting enzyme 2 and S-protein receptor binding domain. This interaction can prevent COVID-19 by weakening or blocking the interaction between S-protein and angiotensin-converting enzyme 2. Withanoside V and somniferine provide more binding energy than natural ligand N3. By reducing the binding with Mpro, they inhibit viral transcription and replication.Therefore,

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ashwagandha may one day become an alternative or complementary treatment for COVID-19.[66]

DISCUSSION & CONCLUSION

The body's immune systems are crucial in the battle against pathogens, including bacteria, fungi, viruses, and other microorganisms, as well as a host of other disorders. Many allopathic medications are available to strengthen our immune systems, but we are also aware of their high cost and numerous adverse effects. For this reason, we identify alternative sources such as medicinal plants and Ayurvedic products, which not only give the body a healthy environment but also strengthen the immune system without having any negative side effects. Numerous studies show that in the current COVID-19 epidemic, individuals with stronger immune systems recover from the virus more quickly. Although using Ayurvedic items won't be able to fully treat COVID-19, they may be able to minimize the danger of infection and lower the death rate. We have long been aware of the health benefits of Ayurvedic and medicinal plant products, which are used to treat illnesses including infections and other ailments. Given their low cost, low toxicity, and widespread distribution throughout the nation, these botanical plants have the potential to boost immunity against COVID-19 and other infectious diseases, as well as play a significant part in making India and the rest of the globe more fit and healthy.

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