

# Antiviral Potential of Selected Medicinal Herbs against SARS-CoV-2: A Systematic Review

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**Abstract:** The phytochemicals and bioactive substances found in Indian medicinal plants are said to be naturally occurring and have health advantages. Native Indian botanicals are used to manage specific SARS-CoV-2 symptoms. The Ministry of Homeopathy, Siddha, Unani, Naturopathy, and Ayurveda recommends using medicinal plants daily to fight COVID-19. Medicinal plants that boost immunity and have antiviral, antibacterial, antioxidant, and anti-inflammatory qualities can be used to cure and suppress COVID-19 symptoms. Regarding 'COVID-19' therapy, these phytochemicals have proven effective *in vitro*, *in vivo*, and by *in silico* validation. Different clinical aspects of COVID-19 will be addressed more effectively by integrating traditional knowledge of infection prevention with contemporary methods that validate it for accurate and effective therapeutic approaches. This review examines the use of phytochemicals from various Indian medicinal plants for traditional and cutting-edge COVID-19 prevention and treatment.

**Keywords:** herbal remedies; antiviral drugs; immunity; COVID-19; Indian medicinal plants.

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## 1. Introduction

The Long RNA polymers encapsulated in nucleocapsids make up Coronaviruses. Droplets, aerosolized transmission, fecal-oral transmission, and surface transmission are among the ways Coronavirus can spread. COVID-19 affects the heart, lungs, and other organs. Its symptoms include fever, coughing, headaches, sore throat, myalgia, exhaustion, and shortness of breath [1]. They might vary in severity from minor breathing difficulties to serious ones. Pneumonia, respiratory failure, and even death can result from infections. Shocks, as well as acute lung and renal damage, are frequent. Inflammatory cytokines such as GCSF, IP10, MIP1A, MCP1, IL2, IL7, IL10, and TNF- $\alpha$  are the cause of this evolution. The nasal and oral mucosa express ACE-2 receptors, which enable the Coronavirus's S protein to bind to host cells. The protein (ACE-2) receptor-expressing organs connect to the virus. PCR testing on nasopharyngeal swabs can identify SARS-CoV-2 and diagnose COVID-19. Since neither the

virus nor the illness it produces has been identified, there is currently no known treatment for COVID-19. Symptomatic therapy alone is practical in the absence of a specific treatment. Anti-inflammatory (preferably non-steroidal) medications are used to treat inflammatory diseases; antihistamine medications are used to treat allergy conditions; Antibiotics are used to treat secondary bacterial infections, while paracetamol is used to treat high fevers. Reducing the SARS-CoV-2 virus's unique symptoms, which protect the kidney, heart, and gastrointestinal tract against inflammatory responses, immunomodulation, and homeostasis, may lead to improvements [2].

Based on symptoms and stage, the Ayush Ministry recommends several COVID-19 treatment options. It proposes boosting immunity using a decoction of lemon juice, basil, cinnamon, black pepper, jaggery, and raisins. Milk infused with turmeric is also advised. Ayurvedic practitioners suggest simple practices, such as applying sesame or coconut oil to the nose and using it as an oil-pulling therapy by swishing it around the mouth. When you have a sore throat or dry cough, it helps to breathe in the steam of fresh mint leaves or caraway seeds. Cloves can also be used to relieve coughs and sore throats when combined with honey or natural sugar [3].

Perhaps the oldest healthcare system in the world is traditional Indian medicine. Several ancient Indian texts, including the Rigveda, Sushruta Samhita, Charak Samhita, and Atharvaveda, discuss the therapeutic application of medicinal herbs to alleviate ailments. India's therapeutic medicinal herbs are utilized globally for their therapeutic properties. Approximately 16,000-17,000 flowering species occur in India, of which 6,000 have therapeutic properties. Herbal medicine provides for the medicinal needs of almost 80% of the world's population. Antimicrobial resistance, ineffective treatment regimens, and the unavailability of conventional treatments, among other factors, contribute to the acceptability of herbal medications. Indians have long employed herbal remedies for inflammation and wounds. During the colonial era, India's medicinal techniques were widely recognized [4-6].

Following the COVID-19 pandemic, we observed a surge in scientific efforts to develop treatments and medications. Indian medicinal plants, sparked by SARS-CoV-2, contain phytochemicals that may help manage the current global pandemic, COVID-19 (coronavirus disease). More research is being conducted to investigate the efficacy of these herbs in their anti-inflammatory, antiviral, and immunomodulatory activities, as well as the phytochemicals they contain for the treatment of SARS-CoV-2 symptoms. Many researchers simultaneously docked phytochemical molecules to obtain *in silico* support for using traditional plants during COVID-19. A thorough understanding of plants and the phytochemicals they contain, which strongly target SARS-CoV-2, could yield potential COVID-19 care leads. This review aims to assess the effectiveness of Indian medicinal herbs and their phytoconstituents in alleviating COVID-19 symptoms. It will help researchers and students develop and identify new medications effective against COVID-19 using traditional Indian medicinal plants [7].

## 2. Sources and Methodology

The sources of scientific content collected between 2010 and 23 were PubMed, Google Scholar, Scopus, MDPI, Core Collection, Google Academic, Clarivate Analytical, Web of Science, and Scientific Electronic Library Online [SciELO]. Our search keywords were Coronavirus, herbal remedies, antiviral activity, and pharmacological effects (in vitro and in vivo). These publications were evaluated based on scientific evidence confirming their COVID-19 activity. Following evaluation and investigation, the number of antiviral and

COVID-19 articles was identified in two phases: (i) declaring traditional antiviral and SARS-CoV-2 actions of plants and their constituents, and (ii) expressing the SARS-CoV-2 and antiviral effects of extracts or pure substances from plants, wherein (*in vivo* and *in vitro*) SARS-CoV-2 activities of these products were investigated.

### 3. Traditional Medicinal Plants and Their Antiviral Activity

#### 3.1. *Ocimum sanctum* Linn (*Holy basil*).

*Ocimum sanctum* is called in Ayurveda as the ‘Elixir of Life’, or Tulsi. It is an anxiety reducer and nerve tonic. It helps with a variety of diseases, including rheumatism, bronchitis, liver and intestinal problems, and asthma. *O. sanctum* contains natural essential oils that treat colds and chest congestion, including cineole, camphene, and eugenol. Eugenol relieves discomfort and is beneficial for colds, coughs, muscular pain, and other disorders. It has terpenes, carvacrol, oleanolic acid, ursolic acid, and estragole [8,9]. The ingredients in *O. sanctum*, such as cineole, eugenol, and camphene, help reduce chest congestion and cold symptoms. Ocimumosides A and B have a calming effect on the brain by balancing the neurotransmitters serotonin and dopamine. Tulsi possesses anti-inflammatory properties that help lower blood pressure and reduce inflammation. Strong antioxidant phytochemicals present in Tulsi are helpful in the management and prophylaxis of lung cancer, skin cancer, heart disease, liver cancer, and mouth cancer. Its high zinc and vitamin C concentration make it a natural immune system enhancer. Terpenoids and polyphenols in Tulsi methanolic extract exhibit antiviral activity against H9N2 and DENV-1. Dihydrodieugenol–B and tulsinols (A–G) have been identified in tulsi. This has immune-modulatory effects by inhibiting the COVID-19 major protease and papain-like protease [10].

#### 3.2. *Zingiber officinale* (*ginger*).

People have used ginger, or *Zingiber officinale*, for thousands of years to treat ailments such as colds, headaches, arthritis, nausea, and high blood pressure. Gingerols, or the main polyphenols found in fresh ginger, are 6-gingerol, 8-gingerol, and 10-gingerol. Ginger has been shown to contain the phenolic compounds Zingerone, 6-dehydrogingerdione, quercetin, and gingerenone-A [11]. Gingerols can become shogaols when they are heated or stored for a longer period [12]. A significant ginger component, shodhaol, helps patients overcome respiratory problems. 6-gingerol has the highest binding affinity for many SARS-CoV-2 targets, including viral proteases and RNA-binding proteins, making it a promising option for COVID-19 drug discovery [13]. By altering membrane integrity and reducing biofilm formation, ginger prevented the growth of multidrug-resistant strains of *P. aeruginosa* and *Z. officinale*, which have remarkable antibacterial properties and successfully combat viral, Gram (+), and Gram (-) bacterial and fungal infections due to their phenolic components. Because of its oil, ginger has strong antioxidant activity that guards against DNA damage. *Z. officinale* reduces inflammation by blocking PG production and interfering with cytokine signaling [14]. IFN secretion is stimulated by ginger, helping to combat viral infection [15]. Ginger phytochemicals have been shown to have inhibitory potential against two significant Coronavirus targets, 6LU7 and 7JTL, through *in silico* research. Gingerone A demonstrated significant inhibitory activity against several coronavirus targets. Consequently, ginger-derived phytochemicals may be highly effective in combating COVID-19 [16].

### 3.3. *Cinnamomum verum* (dalchini).

This herb's antimicrobial properties are recognized for wound-healing, immunostimulant, anti-inflammatory, antioxidant, antidiabetic, Parkinson's disease, cancer, AIDS, and anxiety effects. The plant yields several volatile oils, including copaene, eugenol, camphor, cinnamate, and cinnamaldehyde [17]. The capability of cinnamon bark to inhibit “HIV-1 and HIV-2” like fast-growing viruses is shown by the pathogenicity that the viruses cause in MT-4 cells. *C. verum* primarily inhibits the lysozyme activity, total protein, globulin, and total antioxidant activity of the Newcastle disease virus in hens. Additionally, it greatly intensifies its phagocytic activities. Dalchini essential oil exhibits potent antiviral properties against HSV-1 and H1N1 viruses when mixed with other essential oils. The phagocytic index, neutrophil adhesion antibody titer, and serum immunoglobulins were all significantly increased by *C. verum* bark extracts, which acted as an immunomodulator. Procyanidin and other phytoconstituents have anti-inflammatory properties in carrageenan-induced edema. It can reduce COVID-19 symptoms since it is an immunomodulator and an anti-inflammatory drug with high antiviral properties [1,3].

### 3.4. *Allium sativum* (garlic).

The *Allium* species that is most commonly grown is garlic, or *Allium sativum*. The bulbs of garlic contain hundreds of phytochemicals, including compounds that contain sulfur, like vinyl dithiins, ajoenes, and allicin. Ajoene, alliin, S-allyl cysteine, vinyl dithiin, diallyl polysulfides, and other sulfur-based compounds make up the majority of garlic's chemical composition [18]. The antimicrobial activities of garlic are associated with allicin activity, which has broad-spectrum effects on both Gram (+) and Gram (-) bacteria, including *E. coli* and *Shigella* species [19]. According to Jang *et al.* [20], garlic extracts prevent the reproduction of vesicular stomatitis virus, type 1 herpes simplex, human cytomegalovirus, vaccinia virus, and human rhinovirus (type 2 and type 3 parainfluenza viruses). Garlic can help impede COVID-19 infection by fortifying the immune system and inhibiting the release and synthesis of pro-inflammatory cytokines and the adipose-derived hormone leptin. This is because garlic contains immune-boosting compounds [20]. *A. sativum* can counteract immunological abnormalities and lower the expression of pro-inflammatory cytokines. Therefore, it has been suggested that *A. sativum* is a helpful prophylactic drug for SARS-CoV-2 viral infection [21, 22].

### 3.5. *Curcuma longa* (haldi).

The rhizomes or roots of the turmeric plant (*Curcuma longa*) are ground, dried, and cooked to produce the yellow spice. Curcumin, the spice's active ingredient, accounts for 2-8% of the mixture [23]. According to Huang and Cheng [24], curcumin affects cellular enzymes and angiogenesis in addition to having antioxidant and anti-inflammatory properties [24]. Phenolic chemicals and terpenoids such as monoterpenes, diterpenes, triterpenoids, sesquiterpenes, alkaloids, and sterols are found in *C. longa*. The active constituents are curcumin or di-feruloyl methane, diarylheptanoids, diphenylheptanoids, and curcuminoids [25]. Studies have indicated that *C. longa* is strong against respiratory viruses that cause acute respiratory infections, such as influenza A and respiratory syncytial virus [26]. Curcumin inhibits the homotrimer membrane glycoprotein IAV hemagglutinins from attaching to the host cell receptor. Additionally, it can block pathways associated with COVID-19 pathogenesis,

including fibrosis and pulmonary edema. Through several molecular pathways, it suppresses chemokines, bradykinin, toll-like receptors, and inflammatory cytokines [27]. Turmeric's curcumin extract can prevent the SARS-CoV-2 virus from entering cells. Curcumin was found to bind both the ACE2 receptor attachment sites and the RBD site of the viral S protein using an *in silico* approach [28]. One protective herb that can be utilized to limit the spread of COVID-19 is curcumin.

### 3.6. *Tinospora cordifolia* (Hook).

It is a medicinal herb that is used to treat several illnesses, including gonorrhea. Its root has a strong convulsive action and is employed to treat gastrointestinal obstructions. Many different compounds have been isolated from *T. cordifolia*'s roots, aerial parts, and complete plant. Because of the presence of substances similar to berberine, tinosporin, palmatine, tembetarine, choline, isocolumbin, etc., it exhibits immunomodulatory characteristics. *T. cordifolia* enhances the immune system's defense against infectious bursal disease vaccination in chicks. As a test formulation for Giloy Ghanvati (GG) tablets, behavioral fever was confirmed in a humanized zebrafish model of SARS-CoV-2 spike protein-induced illness. This elevated body temperature was reversed after *T. cordifolia* aqueous extracts were administered. It reversed the inflow of pro-inflammatory cells into the swim bladder and avoided renal necrosis and tubular injury. Giloy Ghanvati reduced SARS-CoV-2 spike-protein induction's cytological, behavioral, and morphological effects [29]. The main protease (6M71), RNA-dependent RNA polymerase (6M71), surface glycoprotein (6VSB), and receptor binding domain (6M0J) are the four SARS-CoV-2 targets tested against Natural substances extracted from *T. cordifolia* using *in silico* methods, including tinocordiside (6Y84), magnoflorine, berberine, and isocolumbin. It is possible that giloy can be used as an herb to treat COVID-19 infection due to the potent binding activity of its four compounds against each of the four targets [30].

### 3.7. *Withania somnifera* L. (Ashwagandha).

*Withania somnifera* L, popularly referred to as Ashwagandha gets its popular name from the expression "the strength and smell of a horse," which refers to its sexual properties. The root of Ashwagandha is used as a sedative for tumors and swellings. Among the alkaloids present in the root are somnine, somniferinine, withaferin, psuedowithanine, withanine, and withanolides-A. The common cold, infertility, and other gynecological disorders can all be treated with withaferin A. By increasing macrophage nitric oxide synthase activity, it enhances immunological homeostasis. They can lower tumor necrosis factors, interleukin-1, and interleukin-6, and they have anti-inflammatory and antioxidant qualities. Herpes simplex and influenza viruses are both susceptible to the antiviral effects of withanolides [31]. Withanolides are powerful immunosuppressants as well. Modifying host Th-1/Th-2 immunity may be beneficial in the case of SARS-CoV-2 infection [32]. Based on its strong affinity for the ACE2-RBD interface, *in silico* studies suggest that it could prevent SARS-CoV-2 from infecting cells [33]. As SARS-COV-2 protein inhibitors, Withanoside-X and Quercetin glucoside from *Withanoside somnifera* exhibit favorable interactions at the binding sites of certain proteins, 6W01 and 6M0J, based on the outcomes of *in silico* docking and molecular dynamics [34]. It inhibits viral infections and cytokine storms; Ashwagandha has advantages for curing SARS-CoV-2.

3.8. *Andrographis paniculata* (kalmegh).

The "King of Bitters" is the herb *Andrographis paniculata* (Kalmegh), which helps relieve fevers and muscular aches due to its antibacterial and antiviral properties, and is claimed to have hepatoprotective and hepatostimulative properties [35]. When *A. paniculata* leaves are extracted using ethanol or methanol, they produce more than 22 diterpenoids and ten (10) flavonoids [36]. Chandrasekaran *et al.* [37] report that andrographolide, among other identified compounds from *A. paniculate*, inhibits immunological mediators, malignancies, and pro-inflammatory mediators (NO, IL-1, and IL-6). As well as ribonucleic acid viruses, andrographolide protects against deoxyribonucleic acid viruses such as Epstein-Barr virus and herpes simplex virus 1, as well as HIV, influenza virus A, hepatitis C, dengue virus, and Japanese encephalitis virus [37, 38]. You can treat other viral illnesses, such as SARS-CoV-2, with andrographolide and its analogs. With its combination of  $\alpha$  (alpha)-alkylidyne moiety, three hydroxyls at C-3, C-19, and C-14, and cytotoxic  $\gamma$  (gamma)-butyrolactone, andrographolide is a molecule with promising chemotherapeutic potential. One of the primary SARS-CoV-2 protease inhibitors, based on an *in silico* investigation, is likely andrographolide [39]. Many Indian medicinal plants with important pharmacological properties are being developed for COVID-19 prevention and therapy (Table 1).

**Table 1.** Indian medicinal herbs that help in combating SARS-CoV-2.

Plant name	Family	Part used	Phyto-constituents	Pharmacological applications	Reference
<i>Basella Alba</i>	Basellaceae	Leaves and stem	Basellasaponins, cyanide, ascorbic acid, arginine, isoleucine, leucine, lysine, threonine, folic acid, and carotenoids are included in tryptophan.	Wound healing, antioxidant, antidiabetic, hepatoprotective, CNS depressive, antiviral, antibacterial, anti-inflammatory, and anti-ulcer properties.	[40]
<i>Solanum torvum Sw.</i>	Solanaceae	Leaves, fruits, and flowers	Alkaline compounds, neochlorogenin (22 R, 23 S, 25 R), and 6-O- $\beta$ -D-quinovopyranoside (1) 23-trihydroxy-5 $\alpha$ -spirostane and 3- $\beta$ -6 $\alpha$ 6-(1 $\leftarrow$ 3)-O- $\beta$ -D-xylopyranosyl-2-quinovopyranoside ( $\beta$ -D).	Analgesics, diuretics, anti-tumor, antiviral, anti-inflammatory, antioxidant, sedative, and anti-platelet.	[41]
<i>Syzygium aromaticum</i>	Myrtaceae	Buds	Campesterol, ceategolic acid, kaempferol, stigmaterol, carvacrol, ellagic acid, quercetin, eugenin, bicornin, eugenitin, oleanolic acid, vanillin, eugenol, gallic acid, biflorin, myricetin, $\beta$ -caryophyllene, and rhamnetin.	Proliferative, antinociceptive, anti-protozoal, anti-inflammatory, antidepressant, analgesic, anti-thrombotic, anti-ulcer, anti-cancer, antimicrobial, antiviral, antipyretic, antifungal, anti-diabetic, and anti-proliferative.	[42, 21]
<i>Ocimum sanctum Linn</i>	Lamiaceae	Leaves, whole plant, oil	Eugenol, $\beta$ -sitosterol, carvacrol, apigenin, rosmarinic acid, and occimumosides A and B.	Antiviral, immunomodulatory agents, antioxidant, antistress, hypolipidemic, anticancer, and hypoglycemic effects.	[43, 44]
<i>Zingiber officinale Roscoe</i>	Zingiberaceae	Rhizome	Parasols and gingerols Shogaols, paradols, and gingerols.	Anti-inflammatory, anti-diabetic, neuroprotective, cardiovascular, antibacterial, respiratory, oxidative, and anti-oxidant effects.	[45, 46]
<i>Piper nigrum L</i>	Piperaceae	Dried seeds	Sabinene, 3-carene, D-limonene, caryophyllene, $\alpha$ -pinene, and $\alpha$ and $\beta$ -phellandrene.	Anti-inflammatory, antibacterial, antifungal, cardioprotective, and renoprotective capabilities.	[47]

Plant name	Family	Part used	Phyto-constituents	Pharmacological applications	Reference
<i>Cinnamomum verum</i> J. S. Presl	Lauraceae	Dried inner bark of the tree	Cinnamaldehyde, eugenol, copane, camphor, and cinnamonyl acetate.	Antibacterial, wound-healing, anti-inflammatory, antioxidant, and immunomodulatory abilities.	[17, 48]
<i>Allium sativum</i> L.	Alliaceae	Bulbs	Diallyl trisulfide, diallyl sulfide, diallyl disulfide, diallyl ajoene, and allicin.	Antitumoral, hepatoprotective, immunomodulatory, neuroprotective, anti-inflammatory, anti-obesity, and renal protective effects.	[49, 50]
<i>Nigella stiva</i> L.	Ranunculaceae	Seeds	Nigellone, thymol, hymohydroquinone, dithymoquinone, and thymol.	Appetite stimulant, immunomodulator, analgesic, hepatoprotective, renal protective, gastroprotective, antioxidant, and antimicrobial.	[51]
<i>Curcuma longa</i> L.	Zingiberaceae	Rhizomes (underground stems)	Demethoxycurcumin, Bisdemethoxycurcumin, and Curcumin.	Immunomodulatory, hepatoprotective, cardioprotective, anti-fertility, depressive, anti-neuroprotective, and antibacterial effects.	[52, 53]
<i>Tinospora cordifolia</i>	Menispermaceae	Roots, stems, and leaves of the whole plant.	Magniflorine, palmatine, berberine, temberartine, tinosporin, tinocordiside, and tinocordifolioside.	Antioxidant, immunomodulatory, antipyretic, anti-allergic, hypoglycemic, and antineoplastic abilities.	[54, 55]
<i>Withania somnifera</i> L.	Solanaceae	Leaves, bark, root, flower, stem, seed	Cuscohygrine and withanolides.	Astringent, anti-diabetic, anti-inflammatory, liver tonic, gastroprotective, and sedative.	[56]
<i>Andrographis paniculata</i> Linn	Acanthaceae	Aerial parts, roots	Caffeic acid, ferulic acid, andrographolide, as well as cinnamic acid.	Cytotoxicity, insecticidal, immunostimulant, antiprotozoal, antiangiogenic, hepatic and renoprotective, anti-inflammatory, antioxidant, and cytotoxic effects.	[57, 58]
<i>Azadirachta indica</i>	Meliaceae	Nimbin, Epinimbin	Nimbins, gallic acid, flavonoids, limonoids, phenols, and catechins.	Antiviral, anti-inflammatory, anti-malarial, antioxidant, antifungal, immunomodulatory, antibacterial, anti-ulcer, antimutagenic, anticarcinogenic, and antihyperglycemic.	[59, 60]
<i>Plumbago zeylanica</i> L.	Plumbaginaceae	plumbagin	Plumbagin, isoshinanolone, plumbagic acid, beta-sitosterol, 4-hydroxybenzaldehyde, trans-cinnamic acid, vanillic acid, 2, 5-dimethyl-7-hydroxychromone, and 3-carboxaldehyde indole.	Anti-inflammatory, anti-obesity, anti-malarial, anti-fertility, anti-sickling, anti-wrinkle, and memory-enhancing abilities.	[61]
<i>Elettaria cardamomum</i>	Zingiberaceae	Southern Asia and India:	$\alpha$ -terpinyl acetate, limonene, 1,8-cineole, linalyl acetate, linalool, terpineol, sabinene, and linalyl acetate.	Antioxidant, carminative, anti-inflammatory, anti-cancer, detoxifying, antibacterial, and antioxidant effects.	[62]
<i>Cinnamomum tamala</i>	Lauraceae	dried leaves	Limonene, $\alpha$ -pinene, p-cymene, camphene, myrcene, methyl eugenol, and eugenol.	Antibacterial, vasodilatory, antifungal, anti-thrombotic, antimutagenic, and anticarcinogenic.	[63, 64]

#### 4. Phytochemicals Inhibit Coronaviruses (SARS-CoV-2)

*In vitro* and *in vivo* investigations of phytochemicals against Coronaviruses, especially SARS-CoV-2, and computer docking model experiments are being conducted as part of an inquiry into the use of natural products to treat COVID-19-related problems, to predict how these compounds will affect the Coronavirus. This study found that apigenin, piperine, nimbin, kaempferol, myricetin, cinnamaldehyde, ocimumosides, quercetin, and allicin are natural polyphenols with potent anti-coronavirus activity. These phytochemicals may be used to create powerful anti-coronavirus drugs. This is especially true for drugs that specifically target SARS-CoV-2. Such conclusions can be drawn from the previously mentioned data. There are multiple mechanisms by which SARS-CoV-2 infection is inhibited, including antiviral effects that control viral entry, gene replication, and the production of fully functional proteins [65].

To inhibit the release of SARS-COV-2, ACE-2 (angiotensin-converting enzyme-2) TMPRSS2 receptors on host cells, and viral spike protein, a triple-target receptor inhibitor might be useful. Lowering oxidative variables, including free radicals and reactive oxygen species (ROS), *Plumbago zeylanica*, *Withania somnifera*, and *Piper retrofractum*, are used to enhance antioxidant action. The medical herbs inhibited neutrophil invasion and cell infiltration in BALF, downregulated the ERK/MAPK pathway, and enhanced antioxidant activity, thereby reducing the effects of LPS-induced lung injury [3].

*O. sanctum* enhances its anti-inflammatory properties by increasing hemoglobin concentration and blocking the NF-Kb classical pathway. Furthermore, by inhibiting the p38 MAPK pathway, *Tinospora cordifolia*, *Nigella sativa*, *Allium sativum*, and *Piper nigrum* lessen the symptoms of pulmonary infections. Immunomodulatory plants, such as *Curcuma longa*, *Azadirachta indica*, *Zingiber officinale*, and others, enhance antiviral immune responses, directly combat SARS-CoV-2, and prevent inflammation driven by macrophages and inflammasomes. Several herbs, such as *Tinospora cordifolia*, *Withania somnifera*, *Ocimum sanctum*, etc., effectively inhibited the major protease (Mpro or 3CLpro) of SARS-CoV-2, according to *in silico* analyses of the active phytoconstituents of Indian medicinal plants. Phytochemicals such as isorientin 4'-o-glucoside 2"-O-p-hydroxybenzoate, somniferine, vicenin, withanoside-V, ursolic acid, and tinocordiside were able to reduce the activity of SARS-CoV-2 Mpro employing molecular docking and molecular dynamics simulation. Given their drug-likeness and ADMET profile, the best-docked compounds are regarded as safe and free of toxicity [1, 66].

#### 5. Phytochemical's Anti-Coronavirus Effect

Among the various inhibitory chemicals developed to combat Coronaviruses, natural phytochemicals are a particular area of concern. Plant secondary and primary metabolites are being investigated as potential medications to inhibit the Coronavirus. The assessment of a metabolite's capacity to inhibit a particular virus involves using various parameters, including the molecular docking score, binding energy, and the IC<sub>50</sub> value, which represents the concentration at which 50% of enzyme activity is lost. Polyphenols, alkaloids, terpenoids, important oils, saponins, lectins, nicotinamide, and other substances are examples of secondary plant metabolites [67]. The significant binding activity of tulsi and neem-based medications against SARS-CoV-2 targets involved in viral attachment and replication makes them useful for treating SARS-CoV-2 infections.

High binding efficacy against SARS-CoV-2 surface spike glycoprotein and RNA polymerase was demonstrated by methyl eugenol (2.420.07 mM), oleanolic acid (2.990.15 mM), and ursolic acid (2.940.13). Greater success was achieved in binding the protease of SARS-CoV-2 by epoxyazadiradione (4.710.26 mM), Gedunin (4.530.21 mM), methyl eugenol (1.740.06 mM), oleanolic acid (2.040.16), and ursolic acid 1.590.06 mM. Natural compounds derived from medicinal plants such as tulsi and neem showed better binding efficacy than the prescription drugs Remdesivir and Lopinavir/Ritonavir. These therapeutic plants include the following phytochemicals with anti-SARS-CoV-2 activity: neobavaisoavone (18.3 M), mimulone (14.4 M), tomentin E (5.0 M), 4'-O-Methyldiplacol (9.2 M), cyanidin (65.1 to 14.6 M), and malvidin (0.04573 M) [68].

## 6. Phytochemicals' Anti-Inflammatory Effect on Acute Lung Damage

A preventive role in abrupt lung injury was demonstrated in multiple animal models. According to Soni *et al.* [69], *O. sanctum* alcoholic extract demonstrated potential as an anti-asthmatic agent by inhibiting LTC<sub>4</sub>, LTA<sub>4</sub>, and COX-2 in HL-60 cell lines and reducing inflammation in an influenza animal model [69]. Negi *et al.* [70] report that the aqueous extract of leaves inhibits histamine fusion in mast cells and peritoneal cells. By activating ACE2, GA may decrease the expression of caveolin-1 and NF- $\kappa$ B. GA provides a rare opportunity for GA-ameliorated ALI through ACE2 activation by activating the caveolin-1 and ACE2 pathways, which mitigates LPS-induced ALI [70]. According to Chen *et al.* [71], GA may therefore have a protective impact on LPS-induced ALI through a mechanism involving caveolin-1/NF-B signaling and ACE2 [71]. *Datura metal* line has been shown to lessen asthma symptoms in BALB/c mice, while garlic protects against allergen-induced airway inflammation in mice [72-74]. *O. basilicum* assists in the tracheal reaction, lung inflammatory cells, and antioxidants (Eftekhar *et al.*, [74] according to RS *et al.* [75] Swiss albino mice exhibit a reduction in inflammation when exposed to *Nymphaea alba* flowers [75].

## 7. Drug Kinetics

The absorption rate of these specific flavonoids is significant. Since these components are essential to drug distribution. Investigations were also conducted on the nervous system, the blood-brain barrier, skin permeability, and their steady-state volume distribution. Flavonoids have been demonstrated to inhibit cytochrome P450 3A4 (CYP3A4) among the many cytochrome P450 (CYP) enzymes, indicating that the liver may be the site of these flavonoids' metabolism [68].

## 8. Protection

ProTox-II was also used to forecast the toxicity of the chosen flavonoids. Calculations are made for the toxicity classes and median lethal dose (LD<sub>50</sub>). The LD<sub>50</sub> values of flavonoids in the toxicity class range from 2000 to 5000, with values above 5000 for acute oral toxicity. Furthermore, the flavonoids belong to hazardous class III (LD<sub>50</sub> 50) and class III (LD<sub>50</sub> 300). The LD<sub>50</sub> values for Neobavaisoavone are 5000, 10,000, and 2500 for malvidin, cyanidin, tomentin E, 4'-O-Methyldiplacol, and mimulone, in that order. Flavonoids mostly met Lipinski's criteria, suggesting they may be used in medicine. A study examining the

relationship between docking scores and IC50 values found that most compounds had negative docking scores, indicating they are more amenable to drug development [76].

Plant phytoconstituents *Tinospora cordifolia*, *Withania somnifera*, and *Ocimum sanctum* are expected to interact with 3CLpro protease or SARS-CoV-2 Mpro. ADMET testing employing molecular docking indicates that these phytochemicals are safe. Given their greater functionality and lower side effects, it is suggested that plant-derived chemicals could help develop COVID-19 management strategies [77].

## 9. Conclusions

An excellent alternative treatment for COVID-19 is provided via traditional Indian medicinal herbs. Medical plants having antioxidant, anti-inflammatory, immunomodulatory, and antiviral properties are beneficial for medicinal applications and COVID-19 prevention, according to AYUSH standards. Several important Indian medicinal herbs that have been the subject of clinical trials against COVID-19 are listed in the current investigation, along with details on the active phytochemicals of these plants and the global antiviral research conducted on them. The potential antiviral effects of these herbal remedies can be clarified with the aid of bioinformatics databases and techniques. The safety factors and inhibitory concentrations of Indian medicinal plants also attest to the phytoconstituents' potency. This review suggests COVID-19 disease is plausible when these factors are considered.

## Author Contributions

conceptualization, S.C.; writing—original draft preparation, S.C.; validation, K.S. and L.G.; data curation, D.J. and R.J.; writing—review and editing, D.J.; supervision, S.C. All authors have read and agreed to the published version of the manuscript.

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## Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable.

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## Conflicts of Interest

The authors declare no conflict of interest.

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