BIOCELL
2023 47(4): 677-695

Tech Science Press

Indian medicinal plants are effective in the treatment and management of COVID-19

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Key words: Antiviral, Corona virus, Diagnosis, Immunity, Herbs

Abstract: Indian medicinal plants are referred to as the "nectar of life" owing to their phytochemicals and bioactive complexes that are beneficial in treating diseases. Coronavirus disease 2019 (COVID-19) is a global health issue without any proper medication. The indigenous plants of India can be exploited to control the precise signs of SARS-CoV-2. The Ministry of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy) has advised routine usage of medicinal plants for COVID-19. Medicinal plants like *Zingiber officinalis, Azadirachta indica, Ocimum sanctum, Nigella sativa, Withania somnifera, Curcuma longa, Piper nigrum, Allium sativum, Tinospora cordifolia*, etc. have immunity-boosting, antiviral, antibacterial, antioxidant and anti-inflammatory actions that can suppress and treat symptoms of COVID-19. *In vitro, in vivo* as well as *in silico* validation, these phytochemicals can help us to manage and treat COVID-19 disease. This integration of traditional knowledge in the prophylaxis of corona infection and current skills validating it for the development of precise and powerful therapeutic approaches will more efficiently resolve different clinical aspects of COVID-19. The review focuses on both traditional and emergent methods to prevent and treat COVID-19 with various Indian medicinal plants along with their phytochemicals.

Introduction

The ancient system of Indian Medicines is one of the world's oldest medicinal practices. Sushruta Samhita, Atharvaveda, Charak Samhita, and Rigveda are some of the ancient Indian writings that mention using medicinal plants to treat illnesses. Worldwide, different medicinal herbs and plants from India are used for their curative qualities. In India, there are roughly 16,000–17,000 flowering species, of which 6,000 have medicinal qualities. Approximately 80% of the world's population's medical needs are satisfied by herbal medicine. The acceptance of herbal drugs was aided by factors such as antimicrobial resistance, a lack of an efficient drug regimen, the unavailability of conventional drugs, etc. (Parasuraman *et al.*, 2014). For centuries, Indians have used medicinal plants to treat wounds and inflammation. In the colonial era, Indian medicinal plants were also used to treat epidemic diseases like smallpox, cholera, and malaria, as well as illnesses like pneumonia, tuberculosis, diarrhea, malaria, and asthma. These conventional plants are still employed in the treatment of various conditions, including diabetes, piles, parasitic infections, skin disorders, neurological, gastrointestinal, and skeletal problems, viral infections, etc. (Prasathkumar *et al.*, 2021).

There was a spike in research after the coronavirus disease 2019 (COVID-19) pandemic broke out in an effort to develop cures or medications for it. The current COVID-19 global pandemic triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might be controlled with the aid of Indian medicinal plants and

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Received: 15 August 2022; Accepted: 23 November 2022

Doi: 10.32604/biocell.2023.026081

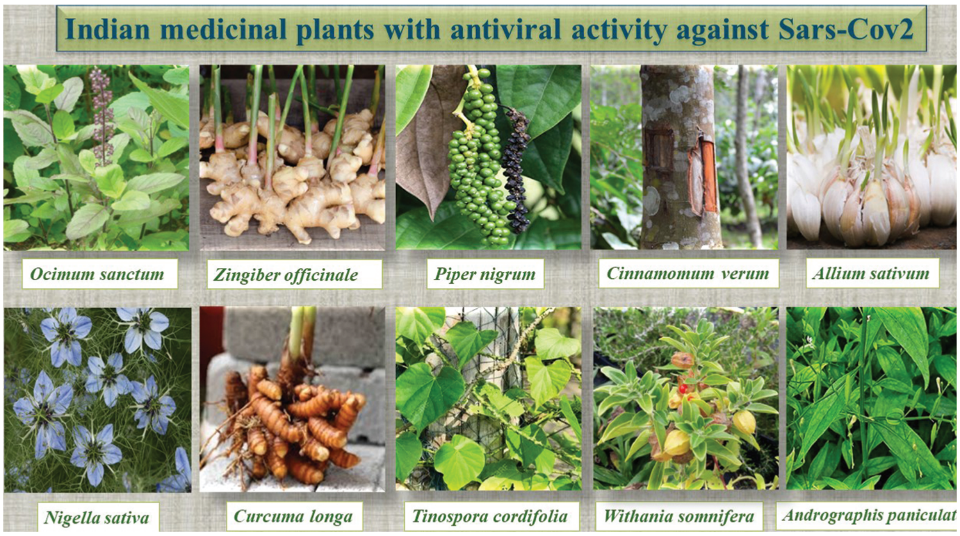

FIGURE 1. Some Indian Medicinal plants are effective against severe acute respiratory syndrome coronavirus 2.

their phytochemicals. Numerous Indian medicinal plants with powerful pharmacological properties can be repurposed for COVID-19 therapy and prevention (Fig. 1, Suppl. Tables S1–S4). To understand the efficacy of these medicinal plants and their phytochemicals, studies are being done to establish their anti-inflammatory, immunomodulatory, and antiviral actions against Sars-CoV-2 symptoms. Concomitantly, many researchers tried molecular docking of phytochemicals to find *in silico* evidence for the use of traditional plants in the treatment and management of COVID-19 (Fuzimoto, 2021).

A comprehensive understanding of plants and their phytochemicals effective in can SARS-CoV-2 lead to obtaining promising drug leads for COVID-19. The objective of this review is to understand the efficacy of Indian medicinal plants and their phytoconstituents in suppressing the symptoms of COVID-19. This review will help students and scientists to develop and discovers novel drugs effective in COVID-19 from conventional Indian medicinal plants.

Coronavirus disease 2019 (COVID-19)

Coronaviruses are composed of long RNA polymers bound by nucleocapsids. Coronavirus spreads via several routes, including aerosolized transmission, fecal-oral transmission, droplets, and surface transmission. COVID-19 affects multiple organs like the lungs, heart, etc. The symptoms of COVID-19 range from slight to severe respiratory distress with fever, cough, headache, sore throat, myalgia, headache, fatigue, and breath shortness. Infections can develop into respiratory failure, pneumonia, and also even death. Acute lung and renal injury and shock are common. This evolution is caused by inflammatory cytokines like granulocyte colony-stimulating factor, interferon γ-induced protein-10, macrophage Inflammatory Proteins1A, Monocyte chemoattractant protein-1, interleukin (IL)2, IL7, IL10, and tumor necrosis factor (TNF)-α (Chen *et al.*, 2020). The angiotensin converting enzyme-2 (ACE-2) receptor in the nasal and oral mucosa allows the coronavirus 'S' protein to bind to host cells. The virus binds to ACE-2 receptor protein-positive organs. Other cytokines include IL-1B, IL-6, interferon (IFN)-α, IFN-γ, IL-18, IL-33, TNF-α, etc. Cell-mediated immunity becomes vigorous during this stage, and numerous proinflammatory cytokines are released (Abdulamir and Hafidh, 2020; Xu *et al.*, 2020).

COVID-19 is diagnosed by identifying SARS-CoV-2 through PCR testing from nasopharyngeal swabs (Kumar, 2020a). As the virus and illness caused are not well-studied, no actual treatment is yet established for COVID-19. Only symptomatic treatment is possible in the absence of a specific treatment (Kesh and Palai, 2022). The use of anti-inflammatory medications (preferably non-steroids) for inflammatory conditions, anti-histamine medications for allergic conditions, paracetamol for high fevers, and antibiotics for secondary bacterial infections are required for symptomatic treatment. Improvements can be made by taking steps to lessen the specific symptoms of SARS-CoV-2, which include immunomodulation, homeostasis, and protecting the function of the heart, kidneys, and gastrointestinal system during inflammatory responses (Chen *et al.*, 2022).

The Ministry of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy) suggests various COVID-19 treatment modalities based on symptoms and stage. It suggests using basil, cinnamon, black pepper, raisins, and jaggery or lemon juice decoction to boost immunity. Turmeric in milk is also recommended. Some simple ayurvedic procedures recommended include nasal application of sesame oil/coconut oil and swill in the mouth as oil-pulling therapy. Steam inhalation of fresh mint leaves or caraway seeds is recommended during a dry cough or sore throat. Cough/throat irritation can also be relieved by combining clove with natural sugar or honey (Radhika and Malik, 2021). For asymptomatic COVID, Ayush 64, Kabasura Kudineer, and Ayush Kwath are prescribed; for symptomatic COVID-19, Ayush 64, Kabasura Kudineer, and Ayush Kwath are prescribed. Sudharsan Ghanvati can help with severe fever and body aches. Vyosadi Vati can help with coughs, common colds, and sore throats (Singh *et al.*, 2021).

AYUSH-64

It is a poly-herbal formulation established by CCRAS, Ministry of AYUSH, Government of India. The preparation contains four ingredients with antiviral, antipyretic, antioxidant, anti-inflammatory, and immunomodulatory properties. It halts the life-threatening inflammatory retorts in COVID-19, leading to substantial morbidity. AYUSH-64 is included in the National COVID supervision procedure, Government of India, built on Ayurveda and Yoga for asymptomatic and mild cases of COVID-19 (Panda *et al.*, 2022).

Kabasura Kudineer

Ayush recommends the second formalization. Some of the ingredients include Guduchi, ginger, Ajwain, clove, Dusparsha, Malabar nut, Kusta, *Piper longum*, Bharangi, Kalamegha, Raja pata, Kokilaksha, Musta, and Neer. Kabasura Kudineer pointedly condenses SARS-CoV-2 viral load in asymptomatic COVID-19 cases with a significant decrease in the neutrophil/lymphocyte ratio and length of hospital stay, and time required to alleviate COVID-19 symptoms. Furthermore, numerous molecular docking studies revealed that the bioactive phytochemicals of Kabasura Kudineer, like andrographolide, apigenin, vasicine, cordiofoliside B, and pyrethrin, had a high affinity for the Spike(S) glycoprotein of SARSCoV-2, preventing host receptor binding. Similarly, another molecular docking study revealed that the bioactive phytochemicals of Kabasura Kudineer, like chrysoeriol and luteolin, have good binding affinity and binding interactions with the spike glycoprotein of SARS-CoV-2 to prevent the binding of host receptors. Acetoside, rutin, luteolin 7-rutinoside, chebulagic acid, violanthin, acanthoside, andrographidine C, syrigaresinol, and myricetin were found to have high binding affinity for the three Chymotrysin-like protease (3CLpro) enzyme, which plays an important role in SARSCoV-2 replication (Natarajan *et al.*, 2021).

In comparison to synthetic drugs like ivermectin, lopinavir, ritonavir, oseltamivir, hydroxychloroquine, and azithromycin, these phytocompounds demonstrate a higher binding affinity for 3CLpro. Another molecular docking study of Kabasura Kudineer bioactive phytoconstituents demonstrated that phytocompounds such as clerodane 6,7 dione, β-amyrin, furanolactone, berberine, piperlongumine, sesamine, lupeol, piperine, and β-sitosterol have a more binding affinity for the main protease enzyme of SARS-CoV-2 and the phytocompounds like clerodanedione, β-sitosterol, beta amyrin, *Piper longumine*, sesamine, piperine, furanolactone, lupeol, and berberine show more binding affinity towards RNA dependent RNA polymerase (RdRP) (Maideen, 2021).

Ayush Kwath

This ayurvedic formulation was mentioned in a Ministry of AYUSH advisory to combat COVID-19 and is being used as a therapeutic option for patients with COVID-19. AYUSH Kwath may be the drug of choice in the treatment of COVID-19, implying its role in prophylactic, curative, and therapeutic care. It is made up of Tulsi, Dalchini, Sunthi, and Krishna Marich. Sacred Orchid. TNF, cytokines storm, i.e., upregulation of proinflammatory cytokines in the blood like interleukin IL-1, IL-6, and TNF, was inhibited by *Cinnamomum zeylanicum* bark extract in severe COVID-19. The presence of linoleic acid in fixed oil has the ability to block both the cyclooxygenase and lipoxygenase pathways of arachidonate metabolism, contributing to its anti-inflammatory action. Because of its immune stimulatory properties, *C. zeylanicum* essential oil and powder have angiotensin-converting enzyme inhibitory and antiviral activity (Abdulamir and Hafidh, 2020). Shogaol and Gingerol compounds in *Zingiber officinale* inhibit the synthesis of prostaglandins and leukotrienes. These also inhibit the production of proinflammatory cytokines such as TNF-α, IL-8, and IL-1. Shogaol also reduced the expression of the *COX-2* gene. Piperine inhibited not only IgM antibody secretion but also CD86 cluster of differentiation expression. The anti-inflammatory activity of piperine is mediated by the inhibition of the inducible nitric oxide synthase (i-NOS) and cyclooxygenase-2 (COX-2). In moderate clinical cases of COVID-19, Ayush Kwath is used as a preventive, curative, and restorative intervention with the goal of resolving symptoms, arresting pathogenesis, and shortening the recovery phase. Nonetheless, more preclinical and clinical trials are needed to assess the protection of this polyherbal formulation (Gautam *et al.*, 2020).

Sudharsan Ghanvati

Sudarshan Ghanvati is a highly recommended formula for the prevention of mild to moderate fevers caused by coughing, colds, allergies, indigestion, and diarrhea. It stimulates the liver, aids in blood detoxification, and improves digestion. It is used for the treatment of fever caused by dyspepsia, anorexia, fatigue, and nausea It increases immunity to fight allergens and infections. It contains Chitrak, Ashwagandha, Turmeric, Clove, Black Pepper, Nut Grass, and Ginger, and it aids in the development of immunity. It relieves body aches and combats fatigue, stress, and anxiety. It helps treat respiratory infections and alleviates tuberculosis symptoms. It reduces inflammation or swelling caused by an injury, improves digestion, and reduces stomach acidity. Sudarshan Ghanvati contains antibiotic, anti-inflammatory, and expectorant properties; therefore, this herbal proprietary preparation is useful in treating the common cold, persistent cough, and flu, and can thus help with COVID-19 symptoms. The bio-active mechanisms of the perfumed herbs help to boost immunity and prevent bacterial infestation (Ritesh and Roushan, 2021).

Vati vyosadi

It is a traditional and proprietary ayurvedic medication designed specifically to treat and manage respiratory and digestive disorders. In Ayurveda, Talispatra, Chitrak, Jeera, Chavya, Tintidika, Tejpata, Dalchini, Elaichi, and jaggery are used to treat the common cold virus and are very helpful for releasing nasal discharge, congestion, irritation, and inflammation. This preparation is also beneficial for sneezing, cough, sore throat, breathing troubles, and allergic rhinitis. It is also extremely beneficial in the treatment of bronchitis, asthma, sinusitis, and other respiratory ailments. With potent antimicrobial, antibacterial, and antiseptic properties, this incredible herbal concoction plays a critical role in preventing various infections. It also decreases the risk of dengue, fever, tuberculosis, and bacterial and fungal infections (Sahoo *et al.*, 2022).

Thus, these Indian medicinal plants have a holistic approach to combat the COVID-19 pandemic. Global research on Indian medicinal herbs for COVID-19 has found the efficacy of its active phytoconstituents (Suppl. Table S1). Medicinal plants like *Glycyrrhiza glabra, Andrographis paniculata, Withania somnifera, Tinospora cordifolia*, herbs used in cooking like *Z. officinale, Allium sativum, Moringa oleifera, Piper nigrum, Cinnamomum verum, Curcuma longa*, and essential oil-bearing plants like *Ocimum sanctum, Azadirachta indica, Syzygium arromaticum, Eucalyptus globulus* (Palai and Kesh, 2021) possesses phytochemicals having antioxidant, antiviral, and immunomodulatory properties (Fig. 1, Suppl. Tables S1–S4).

Some Indian Medicinal Plants with Antiviral Activity against Severe Acute Respiratory Syndrome Coronavirus 2

Ocimum sanctum Linn (Tulsi/basil/Holy basil)

O. sanctum (Tulsi) is known as the 'Elixir of Life' in Ayurveda. It's a nerve tonic and stress reliever. It is beneficial in conditions like asthma, rheumatism, digestive and liver disorders, bronchitis, and microbial contamination. Natural essential oils such as camphene, cineole, and eugenol found in *O. sanctum* relieve colds and chest congestion. Eugenol has pain-relieving properties and can help with body aches, colds, coughs, and other symptoms. It contains oleanolic acid, estragole, carvacrol, ursolic acid, and terpenes (Padalia and Verma, 2011; Sundaram *et al.*, 2012). *O. sanctum* contains camphene, cineole, and eugenol, which aid in the relief of colds and chest congestion. Ocimumosides A and B reduce stress and help the neurotransmitters serotonin and dopamine balance in the brain. *O. sanctum* has anti-inflammatory properties that reduce inflammation and blood pressure. It contains phytochemicals with powerful antioxidant properties that aid in the therapy and prophylaxis of liver malignancy, cardiovascular disease, skin malignancy, oral cancer, and lung cancer. It contains high vitamin C and zinc and works as a natural immune booster. Terpenoids and polyphenols in *O. sanctum* methanolic extract have antiviral properties against DENV1 and H9N2 (Ghoke *et al.*, 2018). Tulsi contains Tulsinols (A-G) and dihydrodieugenol-B, which inhibit COVID-19 main protease and papain-like protease exhibiting immune-modulatory properties (Varshney *et al.*, 2020).

Zingiber officinale Roscoe (Saunth/dried ginger)

For thousands of years, *Z. officinale* (ginger) has been used in numerous ailments like migraines, arthritis, colds, nausea, and hypertension. The primary polyphenols in fresh ginger are gingerols such as 6-gingerol, 8-gingerol, and 10-gingerol. Among the phenolic compounds found in *Z. officinale* are quercetin, zingerone, gingerenome-A, and 6-dehydrogingerdione (Chakotiya *et al.*, 2017). Gingerols can be converted to shogaols through heat treatment or long-term storage (Stoner, 2013). A key ginger compound, 6-Shogaol, aids the patient in resolving respiratory issues (Logeswari *et al.*, 2020). 6-gingerol is a gifted candidate drug for COVID-19, as it has the strongest binding affinity with manifold SARS-CoV-2 targets like RNA binding proteins and viral proteases (Rathinavel *et al.*, 2020). *Z. officinale* inhibited the development of a multidrug-resistant bacterial strain of *Pseudomonas aeruginosa* by altering membrane integrity and decreasing biofilm formation (Chakotiya *et al.*, 2017). Owing to its phenolic compounds, *Z. officinale* has exceptional antimicrobial effects and effectively controls viral, Gram positive and negative bacterial, and fungal disease. *Z. officinale* has high antioxidant activity due to its oil, which protects against DNA damage. *Z. officinale* inhibits PG synthesis and interferes with cytokine signaling, thereby reducing inflammation (Al-Awwadi, 2017). Ginger stimulates IFN-secretion, which aids in the fight against viral infection (Yamprasert *et al.*, 2020). *In silico* research has revealed the inhibitory potential of ginger phytocompounds in two important coronavirus targets, 6LU7 and 7JTL. Gingeronone A exhibits substantial inhibitory potential against some coronavirus targets. Thus, phytocompounds derived from ginger could be extremely beneficial against COVID-19 (Pandey *et al.*, 2020).

Piper nigrum L (Krishna Marich/black pepper)

It is also popular as the "King of Spices" because it contains numerous bioactive constituents like flavonoids, terpenes, phenolics, and sterols with therapeutic properties like analgesic, antiplatelet, antihypertensive, anticancer, antioxidant, and so on. The essential oil profile of seeds of black pepper contains a high amount of caryophyllene, sabinene, α-pinene, limonene, β-bisabolene, etc. Pepper leaves possess a high amount of nerolidol, α-pinene, and nerolidol. Piperine, being the main bioactive component, augments the beneficial effects of several nutrients, vaccines, and drugs through the increase in bioavailability by inhibiting numerous digestive enzymes. It inhibits the exudation of hepatitis B virus surface antigen (HBsAg) and hepatitis B virus e antigen with remarkable HBV activity (HBeAg) (Jiang *et al.*, 2013). Piperine may be effective against viral particle proliferation because it inhibits RNA packaging within the capsid protein (Choudhary *et al.*, 2020). *Piper nigrum* phenolic compounds can inhibit the main protease of COVID-19 (Davella *et al.*, 2021). *In silico* studies have revealed the inhibitory potential of selected phytocompound ligands on the coronavirus targets 6LU7 and 7JTL. The significant inhibitory potential against selected coronavirus targets can be very useful in combating COVID-19 (Pandey *et al.*, 2020). Piperine can be a gifted entrant for inhibiting RNA packaging in the nucleocapsid, and thus, viral replication. Also, black pepper can combat SARS-CoV-2 directly through immunomodulatory and antiviral effects (Choudhary *et al.*, 2020).

Cinnamomum verum J. S. Presl (Dalchini/cinnamon)

C. verum is a well-known medicinal herb with antioxidant, anti-inflammatory, antimicrobial, wound healing, and immunostimulant properties that have been shown to be beneficial in cancer, diabetes, Parkinson's disease, AIDS, and anxiety. Volatile oils found in the plant include eugenol, cinnamaldehyde, cinnamyl acetate, copane, cinnamic acid, cinnamate, cinnamaldehyde, and camphor (Pathak and Sharma, 2021). Cinnamomum bark is active against HIV-1 and HIV-2-like rapidly spreading viruses, as evidenced by virus-induced pathogenicity in MT-4 cells (Premanathan *et al.*, 2000). *C. verum* inhibits the replication of the Newcastle disease virus in chickens primarily by moderating total protein, globulin, lysozyme activity, and total antioxidant action, as well as meaningfully increasing phagocytic actions (Islam *et al.*, 2021). When combined with other essential oils, *C. zeylanicum* essential oil demonstrated effective antiviral activity against HSV1 and H1N1 viruses (Ahmad *et al.*, 2021). The extract of *C. verum* bark acts as an immunomodulator, significantly increasing neutrophil adhesion antibody titer, phagocytic index, and serum immunoglobulins (Balekar *et al.*, 2014). Pphytoconstituents like procyanidine exhibits anti-inflammatory properties in carrageenan-induced edema (Qadir *et al.*, 2018). It can alleviate the symptoms of COVID-19, being an immunomodulatory, anti-inflammatory agent effective against viruses.

Allium sativum (garlic)

A. sativum (garlic) is the most widely cultivated Allium species. Hundreds of phytochemicals are found in the bulb of *A. sativum*, including sulfur-containing complexes such as allicin, alliin, ajoenes, and vinyl dithiins (Al-Sanfi, 2013). Garlic's chemical constituents are primarily sulfur-based like ajoene, alliin, S-allyl cysteine, vinyldithiin, diallylpolysulfides, etc. (Sánchez-Sánchez *et al.*, 2020; Arreola *et al.*, 2015). Garlic's antibacterial activity is linked to allicin activity, which exhibits wide spectrum action against Gram-positive and Gram-negative bacteria like *Shigella* species and *Escherichia coli* (Ross *et al.*, 2001). Garlic extracts inhibit the replication of parainfluenza virus type 3, influenza B, human rhinovirus type 2, herpes simplex type 1, human cytomegalovirus vaccinia virus, and vesicular stomatitis virus (Jang *et al.*, 2018). Because garlic contains immune-boosting chemicals, it can be used to prevent COVID-19 infection by strengthening the immune system and suppressing the production and release of proinflammatory adipose-derived hormone leptin and cytokines. The *A. sativum* can reduce proinflammatory cytokine expression and reverse immunological abnormalities. Thus, *A. sativum* has been recommended as a useful preventative medication for SARS-CoV-2 virus infection (Percival, 2016; Bathia *et al.*, 2020).

Nigella sativa L.

N. sativa (Black cumin) is the "curative black seed". Terpenes like thymol, carvacrol, dithymoquinone, thymohydroquinone, α-pinene, d-citronellol, p-cymene, and d-limonene are among phytoconstituents found in black cumin. Its volatile oil contains t-anethole, carvacrol, 4-terpineol, longifolene, P-cymene, etc. *N. sativa* contains vitamins, fats, carbohydrates, minerals, and proteins with essential amino acids. Thymoquinone is antinociceptive and anti-inflammatory. These protective properties are accredited to its repeatable radical scavenging effect and collaboration with many molecular targets involved in inflammation, like cytokines and proinflammatory enzymes (Amin and Hosseinzadeh, 2016). Thymoquinone prevents viral infection and causes cell death at high concentrations indicating cytotoxic effects. *N. sativa* extracts combined with *Z. officinale* enhanced liver function and reduced viral load in the hepatitis C virus. Thymoquinone inhibits SARS-CoV-2 protease and has clear antagonistic activity against ACE 2 receptors. *In silico* studies demonstrated moderate to high affinity of *N. sativa* compounds for SARS-CoV-2 proteins and enzymes (Badary *et al.*, 2021) *N. sativa* may successfully inhibit SARS-CoV-2 spike recognition and fixation by tightly binding to cell-surface HSPA5 (host cell receptors recognized by the viral spike protein). Thymoquinone has an anti-inflammatory effect and acts against the Coronavirus by preventing viral entry (Abdelrahim *et al.*, 2022).

Curcuma longa

Tumeric *(C. longa)* is a yellow spice made from cooked, dried, and ground rhizomes or roots. Curcumin is the active ingredient in turmeric, accounting for 2 to 8% of the spice (Arun and Nalini, 2002). Curcumin has antioxidant and anti-inflammatory effects and influences cellular enzymes and angiogenesis (Chainani-Wu, 2003; Hua and Cheng, 2007). *C. longa* contains phenolic compounds and terpenoids like diarylheptanoids, sesquiterpenes, diterpenes, monoterpenes, triterpenoids, alkaloids, and sterols (Lv and She, 2010). Curcuminoids, diarylheptanoids, diphenylheptanoids, and curcumin or di-feruloyl methane are active ingredients (Jayaprakasha *et al.*, 2006). *C. longa* is shown to be effective against respiratory viruses like the respiratory syncytial virus, and influenza A causing acute respiratory infections (Dai *et al.*, 2018). Curcumin prevents influenza A virus (IAV) hemagglutinins, a homotrimer membrane glycoprotein, from binding to the host cell receptor. It can also inhibit pulmonary edema and fibrosis-related paths of COVID-19 pathogenesis (Zahedipour *et al.*, 2020). It inhibits inflammatory cytokines, toll-like receptors, bradykinin, and chemokines via several molecular mechanisms (Babaei *et al.*, 2020). SARS-CoV-2 viral protein access can be prevented by curcumin isolated from turmeric. In an *in-silico* analysis, curcumin was found to bind to the receptor-binding domain (RBD) site of the viral S protein as well as the viral attachment sites of the ACE 2 receptor (Das *et al.*, 2021). Curcumin can act as a defensive herb in the controlling of COVID-19 spread.

Tinospora cordifolia (willd.) Hook. f.

T. cordifolia (Guduchi) is a remedial herb used for treating various diseases, including gonorrhea. The root has a strong emetic effect and is used to treat intestinal blockage. A wide range of chemicals are isolated from aerial parts, roots, entire plant of *T. cordifolia*. It has immunomodulatory properties due to the presence of berberine, tinosporin, palmatine, tembetarine, choline, isocolumbin, etc., like compounds (Sharma *et al.*, 2019). *T. cordifolia* improves the immune protective response to the Infectious Bursal Disease vaccine in chicks (Sachan *et al.*, 2019). In a humanized zebrafish model of SARS-CoV-2, spike-protein-induced disease confirmed behavioral fever indicated by increased body temperature, which was inverted after treatment with *T. cordifolia* and Thomson aqueous extracts as Giloy Ghanvati (GG) tablets test formulation. It upturned the proinflammatory cell infiltration in the swim bladder and also saved the kidney from tubular injury and necrosis. The cytological, behavioral, and morphological changes of SARS-CoV-2 spike-protein induction were restored after using Giloy Ghanvati (Balkrishna *et al.*, 2021). Natural components isolated from *T. cordifolia*, such as isocolumbin, magnoflorine, berberine, and tinocordiside, were tested using *in silico* methods against 4 SARS-CoV-2 targets like receptor binding domain (6M0J), RNA-dependent RNA polymerase (6M71), surface glycoprotein (6VSB), and main protease (6M71) (6Y84). Giloy is a potentially useful herb in the therapy of COVID-19 infection because all four compounds demonstrated strong binding efficacy against a total of four targets (Sagar and Kumar, 2020).

Withania somnifera L.

The common name of *W. somnifera L.* (Ashwagandha) comes from the phrase "the smell and strength of a horse," denoting its aphrodisiacal actions. *W. somnifera* roots are used as a sedative for swellings and tumors. Withanine, withanolides, psuedowithanine, somnine, somniferinine, and withaferin A are among the alkaloids found in the root. Withaferin A can treat the common cold, infertility, and other gynecological ailments. They improve immune homeostasis by increasing macrophage NOS activity. They have anti-inflammatory and antioxidant properties and can decrease IL-1, IL-6, and TNF. Withanolides have antiviral properties against influenza and herpes simplex viruses (Kalra *et al.*, 2021). Withanolides are also effective immune boosters. It can be helpful in SARS-CoV-2 infection by modulating host Th-1/Th-2 immunity (Mehrotra, 2020). *In-silico* studies have revealed that it has a strong affinity for the ACE2-RBD interface, potentially preventing SARS-COV-2 from infecting cells (Parihar, 2022). According to the results of *in silico* docking and molecular dynamics, Withanoside X and Quercetin glucoside from *W. somnifera* have favorable exchanges at the binding sites of selected proteins, 6W01 and 6M0J, and can be used as SARS-COV-2 protein inhibitors (Chikhale *et al.*, 2021). Ashwagandha can be used to treat SARS-CoV-2 because it prevents cytokine storms and viral infections.

Andrographis paniculata

Traditionally, the herb *A. paniculate* (Kalmegh) is termed as "King of bitter" as every component of the plant is extremely bitter. It has antiviral and antibacterial properties that reduce fever as well as muscle and bodily discomfort. It has both hepatoprotective and hepatostimulative properties (Kishore *et al.*, 2003). The leaf, entire plant, and stem of *A. aniculate* yielded over 22 diterpenoids and 10 flavonoids after ethanolic or methanolic extraction (Li *et al.*, 2007). Several isolated compounds from *A. paniculate*, like isoandrograpaholide inhibited tumors and proinflammatory intermediaries (NO, IL-1, and IL-6) as well as allergic intermediaries (Chandrasekaran *et al.*, 2011). Andrographolide protects against deoxyribonucleic acid viruses (herpes simplex virus 1 and Epstein-Barr virus) and ribonucleic acid viruses (HIV, IAV, hepatitis C, dengue virus, and Japanese encephalitis virus) (Gupta *et al.*, 2017). Andrographolide and its analogs can potentially be used in the treatment of various virus infections, including SARS-CoV-2. Andrographolide is made up of the cytotoxic gamma-butyrolactone moiety, an alpha-alkylidyne moiety, and three hydroxyls at C-3, C-19, and C-14 can be an effective chemotherapeutic agent having pharmacological properties (Verma *et al.*, 2011). An *in-silico* analysis revealed that andrographolide contains likely SARS-CoV-2's main protease inhibitors (Enmozhi *et al.*, 2020).

Various Mechanisms of Phytochemicals against Coronaviruses (Especially Severe Acute Respiratory Syndrome Coronavirus 2)

Through *in vitro* and *in vivo* testing of phytochemicals against coronaviruses (especially SARS-CoV-2), as well as computer docking model studies that predict the anti-SARS-CoV-2 effects of these compounds against the coronavirus specifically, SARS-CoV-2, the use of natural compounds for the treatment of related complications of COVID-19, is being investigated. According to those studies, natural polyphenol compounds with prominent anti-coronavirus properties include quercetin, ocimumosides, kaempferol, myricetin, cinnamaldehyde, apigenin, allicin, piperine, and nimbin. Considering the aforementioned, it can be concluded that phytochemicals are potential sources for the development of potent anti-coronavirus medications, particularly anti-SARS-CoV-2 medications (Majnooni *et al.*, 2020).

Inhibiting the SARS-COV-2 infection is accomplished through numerous mechanisms, including the antiviral effect regulating the stage of viral entry, gene replication, and formation of mature functional proteins. It may be an effective triple target receptor inhibitor to halt the launch of SARs-COV-2, ACE-2, host cell TMPRSS2 receptors, and virus Spike protein. The use of *W. somnifera*, *Piper retrofractum*, *Plumbago zeylanica* decreases oxidative factors like ROS and free radicals extending the antioxidant effect. The therapeutic plants inhibited neutrophil and cell infiltration in BALF, downregulated the extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) pathway and increased antioxidant activities to reduce lipopolysaccharide (LPS)-induced lung injury complications. The plant *O. sanctum* extends anti-inflammatory effect by improving hemoglobin concentration and inhibiting the NF-Kb classical pathway. Also, *P. nigrum, A. sativum, N. sativa, T. cordifolia* reduces the symptoms of pulmonary infections through p38 MAPK pathways. The immunomodulatory effect of *Z. officinale, C. longa, Azadirachta indica*, etc. boosts antiviral immune responses, have direct anti-SARS-CoV-2 effects, and inhibits macrophage and inflammasome-mediated inflammatory actions (Mukherjee *et al.*, 2022).

In-silico trials of active phytoconstituents of Indian medicinal plants like *T. cordifolia, W. somnifera*, *O.*

sanctum, etc. predicted significant inhibition of SARS-CoV-2 main protease (Mpro or 3Clpro). Through molecular docking and molecular dynamic simulation, phytochemicals like somniferine, vicenin, withanoside V, ursolic acid, tinocordiside, and isorientin 4′-o-glucoside 2″-O-p-hydroxybenzoagte inhibited SARS-CoV-2 Mpro action. The better-docked compounds are safe compounds with no toxicity based on their drug-likeness and the absorption, distribution, metabolism, excretion, and toxicity (ADMET) profile (Shree *et al.*, 2022).

Anti-coronavirus effect of phytochemicals

Natural phytochemical components are of particular interest among the many inhibitory substances introduced against coronaviruses via the. Plant secondary and primary metabolites are being investigated as possible coronavirus inhibitory medicaments. The IC50 value (the concentration at which 50% of enzyme activity is lost), molecular docking score, and binding energy are all parameters used to determine a metabolite's ability to inhibit a specific virus. Polyphenols, alkaloids, terpenoids, organosulfur compounds, saponins, essential oil, saikosaponins, lectins, nicotianamine, etc., are examples of secondary plant metabolites (Farshi *et al.*, 2022). Usual compounds derived from tulsi and neem possess more binding efficacy against SARS-CoV-2 targets tangled in viral attachment and replication for the treatment of SARS-CoV-2 infections (Shrestha *et al.*, 2022). The high binding efficacy is observed against SARS-CoV-2 surface spike glycoprotein, RNA polymerase, and the major protease. Furthermore, natural chemicals are capable of suppressing human coronavirus OC43 replication and viral S and N protein expression, binding to 3CLpro and PLpro, blocking PLP 2 activity of HCoV NL63, inhibiting ATPase activity of nsP13, and binding to the ATPase domain of nsP13 (Suppl. Table S4).

Anti-inflammatory effect of phytochemicals against acute lung injury

Many animal models demonstrated a defensive effect against acute lung injury. *O. Sanctum* alcoholic extracts, for example, demonstrated anti-asthmatic potential via an inflammatory mechanism by inhibiting leukotriene C4, leukotriene A4, and COX-2 in HL-60 cell lines and reducing inflammation in a mouse model for asthma (Soni *et al.*, 2015). The aqueous extract of leaves inhibited histamine fusion in both rat peritoneal and mast cells (Negi and Dave, 2010). GA could suppress caveolin-1/NF-B expression by activating ACE2. GA activated the ACE2 and caveolin-1 pathways, alleviating LPS-induced ALI and providing a novel prospect of GA-ameliorated ALI by inducing ACE2. Thus, ACE2 and caveolin-1/NF-B signaling may be associated with the mechanism of the protective effect of GA in LPS-induced ALI (Chen *et al.*, 2021).

Also, the anti-inflammatory effect of *Nymphaea alba* flower in Swiss albino mice (RS *et al.*, 2013), *Datura metel* linn amelioration of asthma symptoms in BALB/c mice (Rifa'i *et al.*, 2014), garlic protection in allergen-induced airway inflammation in mouse (Hsieh *et al.*, 2019), and aid of *Ocimum basilicum* in tracheal reaction, lung inflammatory cells and antioxidant (Eftekhar *et al.*, 2019).

Pharmacokinetics

These selected flavonoids have a better absorption rate. Their volume of distribution at steady-state, skin permeability, central nervous system permeability, and blood-brain barrier permeability were also examined because they have an important role in drug distribution. Among the various cytochromes P450 (CYPs) enzymes, cytochrome P450 3A4 (CYP3A4) was discovered to be inhibited by flavonoids, implying that these flavonoids may be metabolized in the liver (Shrestha *et al.*, 2022).

Safety

ProTox-II, which calculates median lethal dose (LD50) values and toxicity classes, was also used to predict the toxicity of the selected flavonoids. The LD50 values and toxicity classes of 37 flavonoids predicted by ProTox-II are mentioned in Suppl. Table S4. In terms of acute oral toxicity, flavonoids in the toxicity class have LD50 values ranging from 2000 to 5000 and LD50 values greater than 5000. The flavonoids are also toxic class III (50 LD50 300) and toxicity class 300 LD50 2000. Malvidin and cyanidin have LD50s of 5000, tomentin E of 10,000, 4′-O-methyldiplacol and mimulone of 2000, and neobavaisoavone of 2500. Lipinski's criteria were mostly met by the flavonoids, indicating that they can be used as drugs (Shrestha *et al.*, 2022).

The relationship between docking score and IC50 value was investigated, and for the majority of molecules, the docking score was negative, indicating that they have better druggability (Sherin and Manojkumar, 2022). Active plant phytoconstituents *T. cordifolia, W. somnifera*, and *O. sanctum* have been projected to interact with SARS-CoV-2 Mpro or 3CLpro protease. These phytochemicals were found to be safe in ADMET studies using molecular docking (Shree *et al.*, 2022). This implies that compounds derived from plants may be useful in developing strategies for managing COVID-19 because they have fewer side effects and significant functional capability (Ullah *et al.*, 2022).

Conclusions

The traditional medicinal plants of India are a highly advantageous alternative herbal remedy for COVID-19. According to general AYUSH recommendations, medicinal plants with anti-inflammatory, antioxidant, immunomodulatory, and antiviral properties are useful for both the prevention and supportive treatment of COVID-19. The current review lists several important Indian medicinal plants that have been tested experimentally against COVID-19 and details the claimed plants' active phytochemicals in addition to the antiviral research that has been conducted on them globally. The antiviral properties of these herbal remedies can be clarified with the aid of bioinformatics databases and tools. The effectiveness of the phytoconstituents in Indian medicinal plants is also demonstrated by the safety factors and inhibitory concentrations. Combining them all, the literature review contends that COVID-19 disease can be beaten by combining traditional and modern sciences.

Funding Statement: The authors received no specific funding for this study.

Author Contributions: The authors confirm contribution to the paper as follows: study conception and design: S.C., M.I., H.D.M.C. and S.P.; data collection: E.F.F.M.; analysis and interpretation of results: I.C.P.N.; C.L.G.R. and E.M.d.A.; draft manuscript preparation: R.S.d.A. and H.D.M.C. All authors reviewed the results and approved the final version of the manuscript.

Availability of Data and Materials: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval: Not applicable.

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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Supplementary Materials

TABLE S1

Details of Indian medicinal plants in Ayush 64

Sl. No.	Scientific name Common name	Geographical location	Parts used	Phytoconstituents	Images	Mechanism of action in COVID-19	*In silico* studies	Reference
1	*Alstonia scholaris* R. Br. Saptaparna Doddapala Family: Apocynaceae	Sub-Himalayan tracts from Jammu eastwards and western peninsula	Stem, Latex leaf, barks, stems, roots	Picrinine, nareline, akuammicine, scholarine, strictamine		These plants prevent COVID-19 from developing into severe inflammatory responses, which progress to significant morbidity.	The results of a molecular docking study showed that Mpro-Akuammicine N-Oxide, which has the highest Mpro binding energy, and 34 other phytoconstituents with comparable antiviral activity against SARS-CoV-2, were present.	Panda *et al.* (2022)
2	*Picrorhiza kurroa* Royle ex. Benth Katuki Family: Plantaginaceae	Himalayan regions of India, China, Pakistan, Bhutan, and Nepa	Root	Iridoids, cucurbitacin, acetophenones				Raina *et al.* (2021)
3	*Swertia chirata* Pexbex. Karst Chirayata Family: Gentianaceae	Temperate Himalayas	Whole Plant	Ophelicacid, oleic acid, chiratin, palmitic acid, stearic acid				Kumar and Van Staden (2016)

(Continued)

Table S1 (continued)

Sl. No.	Scientific name Common name	Geographical location	Parts used	Phytoconstituents	Images	Mechanism of action in COVID-19	*In silico* studies	Reference
4	*Caesalpinia crista* L. Kuberaksha/ Latakaaranj Family: Caesalpiniaceae	Subtropical and tropical regions of Southeast Asia	Leaves, Fruits, Roots.	Bonbucin, Sitosterol, Phytosterol, Heptocosanc				Kumar *et al.* (2017)

TABLE S2

Details of Indian medicinal plant with activity against severe acute respiratory syndrome coronavirus 2

Sl. No.	Name of the plant Common name Family	Geographical location	Part used	Phytoconstituents	Mechanism of action in COVID-19	Effects	Other health benefits	Reference
1.	*Ocimum sanctum* Linn (Tulsi/basil), Family: Lamiaceae	Indian subcontinent, Southeast Asia's tropics	Leaves, whole plant, oil	Ocimumosides A & B, carvacrol, apigenin, rosmarinic acid, eugenol, β–sitosterol	Improves hemoglobin concentration and activity, increases SRBC, decreases CoX-2 and LoX-5 enzyme activity, and inhibits the NF-Kb classical pathway.	Antiviral, immunomodulatory, antioxidant, antistress, anticancerous hypoglycaemic, hypolipidemic properties	Respiratory & cardiovascular disorders, fever, wound, diabetes, kidney stone, skin problems, asthma	Baliga *et al.* (2013), Ravi Kumar *et al.* (2020)
2.	*Zingiber officinale* Roscoe (Saunth/dried ginger) Family: Zingiberace	Maritime Southern Asia Australia, Asia	Rhizome	Gingerols and parasols gingerols, shogaols, paradols	Boosts antiviral immune responses, have direct anti-SARS-CoV-2 effects, and inhibits macrophage and inflammasome-facilitated inflammatory effects.	Antiobesity, antidiabetic, neuroprotective, cardiovascular protective, antimicrobial, respiratory protective, antioxidant, and anticancer activities	Headaches, respiratory disorders, colds, nausea, emesis, cardiovascular diseases, obesity	Mao *et al.* (2019), Jafarzadeh *et al.* (2021)
3.	*Piper nigrum* L (Krishna Marich/ black pepper) Family Piperaceae	Malabar Coast of India, South India	Dried seeds	α-pinene, α & β-phellandrene, sabinene, 3-carene, D-limonene, caryophyllene	Augment immunomodulatory effect, enzymatic activity, WBC count, antioxidant, bioavailability enhancer, lipid peroxidation, and inhibit adipogenesis	Antioxidant inflammatory, and antimicrobial, cardio-protective, reno-protective, and antibacterial, antifungal properties	Cold, cough, worms, intermittent fever, dysentery, dyspnea, throat diseases, stomachache, piles	Ashokkumar et al. (2021), Joshi *et al.* (2018)
4.	*Cinnamomum verum* J. S. Presl (Dalchini/ cinnamon) Family Lauraceae	Native to Sri Lanka. South India	Dried inner bark of the tree	Eugenol, cinnamaldehyde, cinnamyl acetate, copane, camphor.	Suppresses the phosphorylation of extracellular signal-regulated kinases, Jun N-terminal kinases in LPS-activated RAW 264.7 macrophages. and p38 mitogen-activated protein kinases (p38 MAPK).	Antimicrobial, wound healing, antioxidative anti-inflammatory, and immunomodulatory actions	Diabetic, HIV, anxiety, Parkinson's disease	Pathak and Sharma (2021), Yakhchali *et al.* (2021)
5.	*Allium sativum* L. (Garlic) Family: Alliaceae	India, Italy, central Asia, France	Bulbs	Allicin, alliin, diallyl disulfide, diallyl trisulfide, diallyl sulfide, ajoene	Significant upsurges in CD4 + and CD8 + T cells, stimulation of NK cells, reductions in leptin receptor, leptin, IL-6, peroxisome proliferator-activated receptor-gamma concentrations.	Anti-inflammatory, anti-obesity, neuroprotective, immunomodulatory, anticancer, hepatoprotective, antitumoral, and renal protective properties	Intestinal worms, diabetes, facial paralysis, liver disorders, fevers, tuberculosis, tumors, bronchitis, dysentery rheumatism, colic	Shang *et al.* (2019), Donma and Donma (2020)
6.	*Nigella sativa* L. (Black Cumin, Small Fennel) Family: Ranunculaceae	Southwest Asia, India	Seeds	Thymoquinone, dithymoquinone, nigellone, thymol hymohydroquinone,	Increasing serum IFN-γ and CD4+ helper T cell numbers affects antibody titer, serum immunoglobulins, eosinophil count, Th1/ Th2 balance, and cytokine profiles.	Immunomodulator, analgesic, hepato-protective, renal protective, gastro-protective, antioxidant antimicrobial, appetite stimulant properties	Antihypertensive, liver tonics, spasm, diarrhea, diuretics, digestive, skin disorders	Ahmad *et al.* (2013), Khazdair *et al.* (2021)
7.	*Curcuma longa* L. (turmeric) Family: Zingiberaceae	South or Southeast Asia, India, China	Rhizomes (underground stems)	Curcumin, demethoxycurcumin, and bisdemethoxycurcumin	Effective triple target receptor inhibitor to halt the launch of SARS-CoV-2, angiotensin converting enzyme-2 (ACE-2), host cell TMPRSS2 receptors, and virus Spike protein.	Antioxidant, antifertility, antidepressant, anti-neuroprotective, antimicrobial, hepatoprotective, cardioprotective, and immunomodulatory, properties	Urticaria, dermatitis, hepatitis infection, jaundice, menstrual troubles, hematuria, inflammatory joints, sore throat, cancer, wounds, allergy, dermatophytosis, flatulence, hemorrhage	Kumar *et al.* (2021), Fuloria *et al.* (2022)

(Continued)

Table S2 (continued)

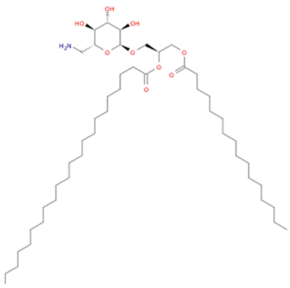
Sl. No.	Name of the plant Common name Family	Geographical location	Part used	Phytoconstituents	Mechanism of action in COVID-19	Effects	Other health benefits	Reference
8.	*Tinospora cordifolia* (Guduchi) Family: Menispermaceae	India	Root, stems, and leaves of the whole plant	Tinocordiside, tinocordifolioside, berberine, tembertarine, tinosporin, magniflorine, palmatine,	Reduces the symptoms induced through viral infections like pulmonary inflammation through p38 MAPK pathways.	Antipyretic, anti-allergic, immunomodulatory, hypoglycemic, antineoplastic, anti-inflammatory, and antioxidant properties	Fever, jaundice, cancer, pain, asthma, gout, poisonous insect, snake bite, eye disorders, dysentery, bone fracture, chronic diarrhea, viral hepatitis, skin disease,	Khan *et al.* (2016), Nema *et al.* (2021)
9.	*Withania somnifera* L. (Ashwagandha) Family: Solanaceae	India, Africa, Middle East.	Leaves, bark, root, flower, stem, seed	Withanolides, cuscohygrine	Restrict inflammatory response in COVID-19 hyperinflammation by controlling cytokine expression, altering inflammatory receptor proteins, and blocking the NF-B pathway.	Aphrodisiac, liver tonic, anti-inflammatory agent, astringent, anti-diabetic, gastroprotective actions	Stress, strain, fatigue, pain, diabetes, bronchitis, asthma, ulcers, skin diseases, emaciation, insomnia, senile dementia	Verma and Kumar (2011), Saggam *et al.* (2021)
10.	*Andrographis paniculata* Linn (Kalmegh) Family: Acanthaceae	India, Sri Lanka, Southeast Asia, Bangladesh, Pakistan	Aerial parts, roots	Andrographolide, ferulic acid, caffeic acid, cinnamic acid	Significantly reduced the amount of SARS-CoV-2 infectious virions produced.	Antimicrobial, anti-inflammatory, hepato-& reno-protective, antioxidant, cytotoxicity, insecticidal, immunostimulant, antiprotozoan, antiangiogenic actions	Jaundice, cancer, ulcer, leprosy, colic, influenza, bronchitis, skin diseases, dyspepsia, malaria, diabetes, high blood pressure, flatulence, dysentery	Okhuarobo *et al.* (2014), Sa-Ngiamsuntorn *et al.* (2021)
11.	*Piper retrofractum* Vahl. Chavya/Javanese long pepper Family: Piperaceae	India, Indonesia, Malaysia, Thailand, Vietnam, China	Fruit, root	Piperine, sitosterol, piplatine	Possibly attach to ACE2 and competitively prevent viral entry and binding.	Immunomodulatory, antioxidant, antibacterial, antiulcer	Malaria, cholera, dysentery, indigestion, abdominal colic, poisoning, anorexia diarrhea, and stomach complaints.	Abdelli *et al.* (2021)
12.	*Azadirachta indica* (*A. indica*) A. Juss Neem/nimtree or Indian lilac Family: Meliaceae	South Asia, Malaysia, Indonesia.	Nimbin, Epinimbin	Leaves, flowers, seeds, fruits, roots, bark	Significantly reduces newly emerged human—Coronavirus SARS-CoV-2 infection and replication *in vitro*, primarily by inhibiting viral infection and replication in the cells.	Immunomodulatory, antibacterial, antiulcer, antioxidant, antifungal, antimutagenic, anticarcinogenic, antiviral, anti-inflammatory, antimalarial, antihyperglycemic	Malaria, loss of appetite, stomach, and leprosy, skin ulcers, intestinal ulcers, eye disorders, skin disorders, intestinal worms	Subapriya and Nagini (2005), Sarkar *et al.* (2022)
13.	*Plumbago zeylanica* L. Chitrak Family: Plumbaginaceae	South-East Asia,	Plumbagin	Fresh root and as well as a dry drug (root), whole plant	Decreases ROS, plumbagin inhibits viral entry into host cells and causes viral RNA degradation, acting as an antiviral therapeutic.	Antidiabetic, anti-obesity, antioxidant, antifertility, antimalarial, wound healing, anti-sickling, memory-inducing activities	Stubborn chronic rheumatoid arthritis, skin diseases	Nadhan *et al.* (2021)
14.	*Elettaria cardamomum* Green cardamom /chhoti elaichi Family: Zingiberaceae	Seeds	Southern Asia and India:	α-terpinyl acetate	Significantly lower innate inflammatory cytokine (IL-6 and TNF-) gene expression levels.	Anti-inflammatory, anticancer, carminative, antioxidant, detoxifier, antioxidant, anti-inflammatory, antimicrobial activities	Cancer, multiple sclerosis, diabetes, rheumatoid arthritis, psoriasis	Cárdenas Garza et al. (2021)
15.	*Cinnamomum tamala* (Buch. Ham.) T.Nees & Eberm. Tejpat, tejapatta, Malabar leaf Family: Lauraceae	Tejpata	Dried leaves	Eugenol, myrcene, methyl eugenol, limonene, α-pinene, p-cymene, camphene	Restricted the SARS-CoV2 infection in hamsters' lungs' viral entry and replication.	Antimutagenic, antifungal, antithrombotic, anticarcinogenic, antibacterial, vasodilatory	Bad odor from mouth, dental caries, black spots on the face, throat infection	Mir *et al.* (2004), Rizvi *et al.* (2021)

TABLE S3

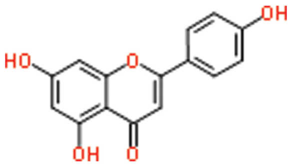
Structure of phytochemicals from Indian medicinal plants

Phytochemicals present in Indian medicinal plants

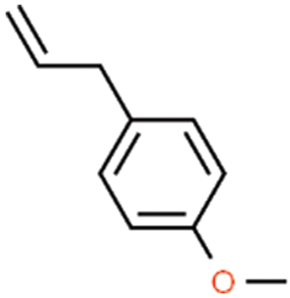
A. *Ocimum sanctum* Linn



Eugenol

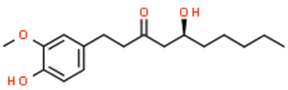


Apigenin

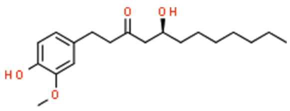


estragole

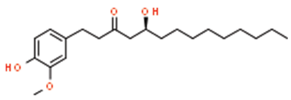
B. *Zingiber officinale* Roscoe



6-gingerol

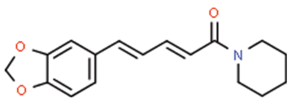


8-gingerol



10-gingerol

C. *Piper nigrum* L

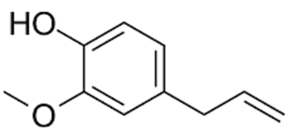


Piperine

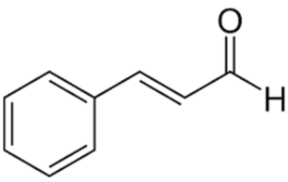
D-limonene

sabinene

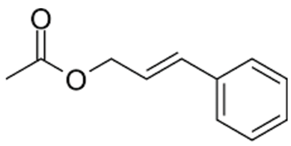
D. *Cinnamomum verum* J. S. Presl



Eugenol

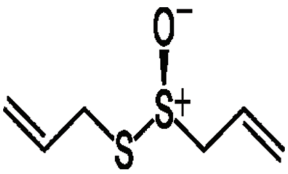


Cinnamaldehyde

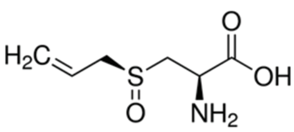


cinnamyl acetate

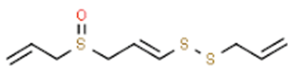
E. *Allium sativum L.*



Allicin



Alliin



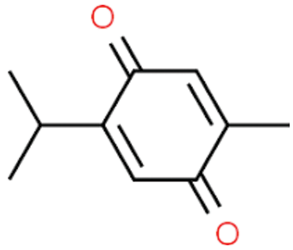
ajoenes

(Continued)

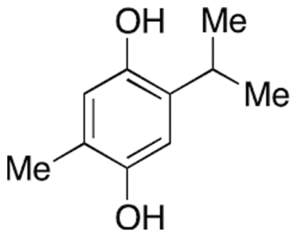
Table S3 (continued)

Phytochemicals present in Indian medicinal plants

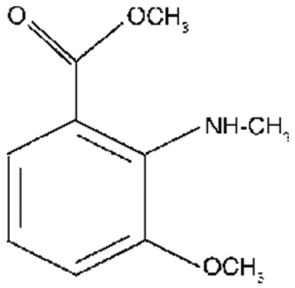
F. *Nigella sativa L.*



Thymoquinone

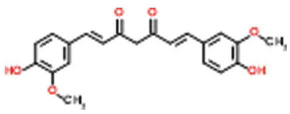


thymohydroquinone

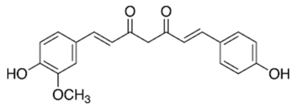


nigellone

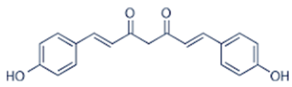
G. *Curcuma longa L.*



Curcumin

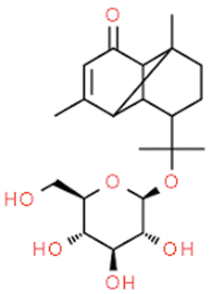


demethoxycurcumin

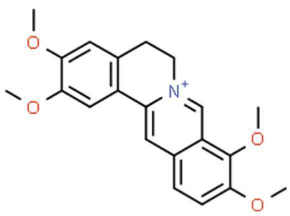


bisdemethoxycurcumin

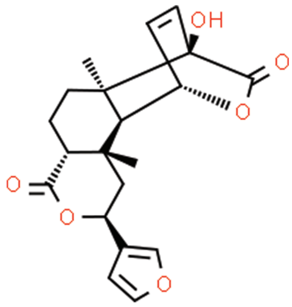
***H. Tinospora cordifolia* (willd.) Hook. f.**



Tinocordiside

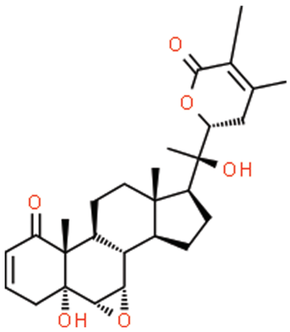


Palmatine

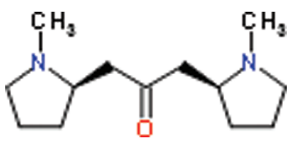


tinosporin

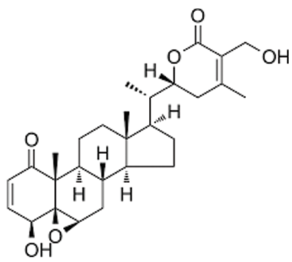
I. *Withania somnifera* L.



Withaniol

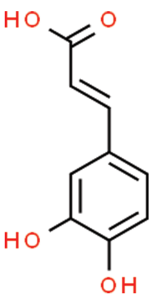


Cuscohygrine

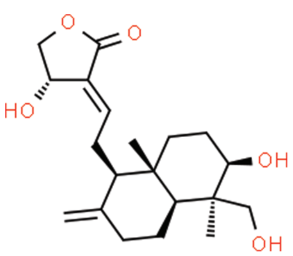


withaferine A

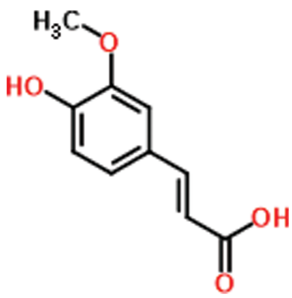
J. *Andrographis paniculata* Linn



caffeic acid



isoandrograpaholide



ferulic acid

TABLE S4

IC50 against various targets of SARS-CoV-2

Sl. No.	Compound	IC50 value (μM)	Targets of SARS-CoV-2	Reference
1	Methyl eugenol	1.74 ± 0.06	Surface spike glycoprotein (6VSB)	Kumar (2020a)
2	Oleanolic acid	2.04 ± 0.16		Kumar (2020a)
3	Ursolic acid	1.59 ± 0.06		Kumar (2020a)
4	Epoxyazadiradione	4.71 ± 0.26		Kumar (2020a)
5	Gedunin	4.53 ± 0.21		Kumar (2020a)
6	Methyl eugenol	2.42 ± 0.07	RNA-dependent RNA polymerase (6M71)	Kumar (2020a)
7	Oleanolic acid	2.99 ± 0.15		Kumar (2020a)
8	Ursolic acid	2.94 ± 0.13		Kumar (2020a)
9	Epoxyazadiradione	6.72 ± 0.39		Kumar (2020a)
10	Gedunin	5.35 ± 0.13		Kumar (2020a)
11	Methyl eugenol	0.79 ± 0.06	Main Protease (6Y84)	Kumar (2020a)
12	Oleanolic acid	0.67 ± 0.03		Kumar (2020a)
13	Ursolic acid	0.53 ± 0.03		Kumar (2020a)
14	Epoxyazadiradione	2.94 ± 0.28		Kumar (2020a)
15	Gedunin	0.35 ± 0.02		Kumar (2020a)
16	Tetrandrine	0.33 ± 0.03	Suppressing human coronavirus (HCoV)-OC43 replication and viral S and N protein expression	Kim *et al.* (2019)
17	Fangchinoline	1.01 ± 0.07		Kim *et al.* (2019)
18	Ceparanthine	1.01 ± 0.07		Kim *et al.* (2019)
19	Kaempferol	116.3 ± 7.1	Binding to 3CLpro	Park *et al.* (2017)
20	Quercetin	52.7 ± 4.1		Park *et al.* (2017)
21	Isoliquiritigenin	61.9 ± 11.0		Park *et al.* (2017)
22	Kaempferol	16.3 ± 2.1	Binding to PLpro	Park *et al.* (2017)
23	Quercetin	8.6 ± 3.2		Park *et al.* (2017)
24	Isoliquiritigenin	24.6 ± 1.0		Park *et al.* (2017)
25	Indigodole B	2.09 ± 0.89	Blocking the PLP 2 activity of HCoV NL63	Tsai *et al.* (2020)
26	Tryptantrin	0.06 ± 0.04		Tsai *et al.* (2020)
27	Scutellarein	0.86 ± 0.48	Inhibiting ATPase activity of nsP13	Yu *et al.* (2012)
28	Myricetin	2.71 ± 0.19		Yu *et al.* (2012)
29	Baicalein	0.47 ± 0.09	Binding to ATPase domain of nsP13	Keum *et al.* (2013)
30	Scutellarein	2.71 ± 0.19		Keum *et al.* (2013)