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Role of Medicinal Plants in the Treatment of COVID-19: A Review

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Abstract **Review Article**

As of right now, there is no evidence to support the idea that COVID-19 specific treatments exist; what is known is that the immune system is a major factor in the development and course of the illness. Chemicals of high efficacy and low toxicity have been found in plants and some of these chemicals are used as building blocks to create highly potent synthetic drugs. While the primary application of herbal treatments is in prevention, certain nations have published guidelines recommending the use of traditional remedies for varying stages of COVID-19 infection. Although Europe has a long and rich history of employing medicinal plants for therapeutic purposes, there aren't as many scientific trials for this kind of approach as there are in Asia. The ability to prevent and treat COVID-19 would be significantly impacted in this way by a bridge connecting tradition and science.

Keywords: COVID-19.

INTRODUCTION

Global pandemic alert: In March, the World Health Organisation (WHO) announced the coronavirus infection 2019 (COVID-19) to be spreading throughout the world [1, 2]. Given that the coronavirus pandemic has become the worst global health emergency since the influenza pandemic, some have suggested that it is the greatest problem facing humanity [3]. Over 6.000.000 people died as a result of it worldwide [4]. The pathogen is the enveloped beta-coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with non-segmented positive-sense RNA (Fig 1).

With a genetic makeup of roughly 30 kb, SARS-CoV-2 and SARS-CoV are 70% similar [5]. Using the same angiotensin-converting enzyme 2 receptor as SARS-CoV, SARS-CoV-2 produces an illness in the human respiratory system. SARS-CoV-2 can cause severe instances that lead to pro-inflammatory cytokine production and an inflammatory immune response with several downstream effects. Among these are multi-organ failure, cytokine storm, and acute respiratory syndrome [6]. For COVID-19 infections, there isn't a single, comprehensive treatment that works well. Although a number of vaccines have been developed to impede the spread of the COVID-19 pandemic, access to them remains difficult, particularly in underdeveloped nations [7].

As a result, the development of trustworthy and efficient antiviral treatments for SARS-CoV-2 is the primary focus of research. Herbal medicines could be a great method to start supporting anti-COVID-19 treatments that work. Since ancient times, people have used herbs as medicines to reduce the symptoms of many diseases. This is especially true for people from Asian countries like China, Japan, and India, as well as some tribes in Africa. This may be mostly explained by the fact that these cultures have abundant access to inexpensive therapeutic herbs [8]. However, herbs and their bioactive components may be used to create novel medicines with potential anti-COVID-19 potency [9]. Phytochemical metabolites that have demonstrated activity against pathogenic bacteria include tannins, terpenoids, alkaloids, coumarins, flavonoids, and polyphenols.

Their capacity to halt viral enzymatic and protein activities may be the reason for this, since it prevents viral entry and replication in the harmed host cells [8]. Consequently, a number of studies have suggested that herbal bioactive components are effective in lowering and controlling the risk of SARS-CoV-2 transmission [8]. Research highlights the possibility that using herbal medication to treat COVID-19 could be beneficial. However, little is known about the bioactivities of the anti-COVID-19 compounds developed from medicinal herbal extracts [10]. As an

alternative treatment for COVID-19, the National Health Commission of China has approved the use of herbal remedies in conjunction with Western medicine and has approved some recommendations for herbal therapy [10].

Since the usual treatment for SARS-CoV-2 infections is not very effective, herbal medicines with antiviral properties are currently used as a supplemental measure [11]. Traditional Chinese medicinal herbs are the mainstay of treatment for viral infections, particularly SARS-CoV-induced ones, in many different geographical zones. For example, Toona sinensis leaf extracts inhibit SARS-CoV replication [12]. Furthermore, it has been suggested that licorice is a possible treatment for SARS-CoV. Furthermore, natural compounds with the capacity to prevent SARS-CoV infection include curcumin, sesquiterpenoids, triterpenoids, and diterpenoids [11]. Additionally, nutritional and herbal medicine may work well as a COVID-19 adjuvant. There are bioactive components in some foods and herbs that have antibacterial, immunomodulatory, antioxidant, and anti-inflammatory properties.

By boosting the quantity and activity of cytokine suppressors, natural killer cells, lymphocytes, and macrophages, this may aid in pre-and/or post-exposure prophylaxis. As a result, the therapeutic plant ingredients may lessen the signs of respiratory illnesses and inflammation markers, enhancing healing [11]. The purpose of this review is to provide an overview of the most significant medicinal herbs and their bioactive components, as well as dietary supplements and functional foods that may have antiviral properties against COVID-19.

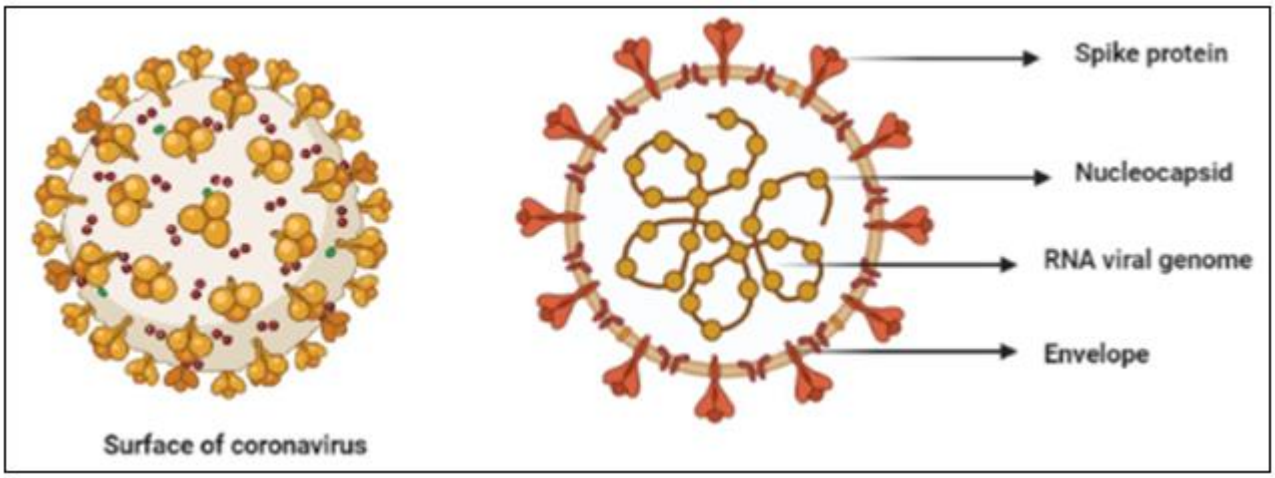

Fig 1: **Structure of SARS-COV-2 virus**

Transmission

SARS-COV-2 is spread via bodily fluids and droplets from infected people's coughs and sneezes. The illness can also be caught by touching contaminated surfaces or coming into contact with airborne droplets. The virus's RNA may be found in respiratory tract specimens up to eight days in moderate cases and longer in severe cases, starting 24–48 hours before clinical symptoms appeared. Blood, saliva, urine, tears, and breast milk can all contain SARS-COV-2 RNA [17]. It is yet to be established whether the detectable RNA in the compounds of human origin is contagious. Asymptomatic people have occasionally had laboratory testing reveal they are infected with the virus.

These people may go on to show symptoms later in the infection or they may show no symptoms at all [18]. Despite the fact that there is a far larger chance of contracting the illness from asymptomatic or even pre-symptomatic individuals, the disease can still spread from asymptomatic carriers [17]. As long as symptoms remain after undergoing clinical recovery, persons with symptoms can spread to others.

Testing for COVID-19

Diagnostic test samples from the lower (sputum or bronchoalveolar lavage) or higher (nasopharyngeal/oropharyngeal swabs, nasal aspirates, nasal wash, or saliva) respiratory tracts have all been utilised to detect SARS-CoV-2. For COVID19 diagnostic testing and screening, many detection assay types may be employed based on the anticipated result. These include assays utilising RT-PCR nucleic acid testing to identify the presence of SARS-CoV-2 RNA, as well as antigen and antibody tests to identify viral antigen and the presence of antibodies produced in response to the virus using chemiluminescence, lateral flow, and enzyme-linked immunosorbent assays, among other techniques.

In order to identify variations, whole genome sequencing can also be used to ascertain the virus's sequence in a sample. It was discovered that patient nasopharyngeal swab test sensitivity was approximately 98% as opposed to 91% for saliva testing [17, 19].

Current prevention of COVID-19

In terms of lowering the incidence of mild, severe, and overall mortality as well as reducing the overall length of the disease, traditional Chinese medicine appears to have shown promising outcomes. Herbal remedies may have immunoregulatory, anti-inflammatory, antiviral, and relief from hypoxemia and chronic obstructive pulmonary disease when used in conjunction with contemporary biomedicine [13]. In India, conventional treatment and immunisations are utilised in tandem with contemporary therapy to address COVID-19. The respiratory system can be categorised as "wet, heat, congestion" based on the signs and symptoms of COVID-19 infection.

Lung function is the first body organ to be impacted, according to Chinese traditional medicine. The term "wet" describes a substance that is sticky and has a high turbidity level, which can exacerbate an illness and impair bodily functions. "Hot" describes the elements that can cause the virus, such as heat, dryness, and growing turbidity. "Congestion" is one of the contributing factors that can impact blood flow and result in discomfort [15].

China will safeguard breathing capacity. Because of the viral situation, Yupingfeng San is used to select a type of preventive value. Astragalus can (increase lung function), Fangfeng (to relieve the pathogen), and Atractylodes (boost the spleen function and digestion and absorption of our body function) are the three types of plants used in this traditional Chinese herbal remedy. Research indicates that Yupingfeng San has the potential to effectively modulate the immune system [14]. Given this context, using home remedies, such as the utilisation of approved medicinal herbs, can offer an alternate strategy for battling COVID-19 in Ethiopia. To suppress viruses, some therapeutic items like garlic, ginger, turmeric, chile, lemon, and hot water with salt can be utilised.

Treatment of mild infection of COVID-19

COVID-19 Patients with mild infection often have a fever, headache, sweat, thirst, dry cough, sore throat, red tongue tip, and floating pulse. Based on the management it is different from a severe case of the disease. According to theories of Traditional Chinese Medicine, they used the method of two types of prescriptions, “clearing lung heat and dampness” to treat the lung. In China classified into two Sangju yin and Yinqiaosan, which are commonly used in clinical management. The main purpose is to clear lung heat, expel, relieve cough, regulate the patient’s lungs and restore normal respiratory function. Clinically, in China patients who had a high fever used Yinqiaosan, and patients who had a severe cough used Sangju yin [15]. A study done on different herbal supplements showed that ginger, lemon/orange, vitamin C, honey, black seed, costus have a significant impact on COVID-19 management [16].

Treatment of severe infection of COVID-19

In the early course of COVID-19 management, if the infection cannot be easily controlled, respiratory failure, multiple organ failure, and death will be worsened, then serious infection should be considered. These infectious patients have the following main manifestations: highgrade fever, dry cough, breathing difficulty, sweating, chest stiffness, fatigue, nausea, bloating, red or dark red tongue, yellow coating, and oily. Some of the preventive and supportive management of COVID-19 through tempering the immune system G. glabra, Thymus vulgaris, Allium sativum, Althea officinalis, and ginseng may become effective [14].

Herbs for the Treatment of Coronavirus-Dependent Diseases

For the purpose of treating disorders dependent on coronaviruses, plants and plant products may provide valuable sources of druglike compounds. The 2002 SARS outbreak demonstrated the successful fusion of western medicine and traditional Chinese herbal medicine in the treatment of infections resulting in clinically improved symptoms, such as relief or improvement in elevated body temperature, cough and breathing difficulties, and overall quality of life [20, 21]. By inhibiting the reproduction of the porcine epidemic diarrhoea virus (PEDV), [22] showed the toxicity of three medicinal plants: Dryopteris crassirhizoma Nakai, Dryopteridaceae; Saposhnikoviadivaricata (Turcz.) Schischk., Apiaceae; and Camellia japonica L., Theaceae. Pigs with significant infections and high mortality rates are victims of the coronavirus known as PEDV.

The RNA levels of the key genes and proteins needed for PEDV replication, GP6 nucleocapsid, GP2 spike, and GP5 membrane protein, were found to be reduced by four structurally representative oleanane-triterpenes characterised from C. japonica in a manner comparable to or even better than the positive control, azauridin. A new coumarin from the plant was shown to have more anti-PEDV activity than azauridine, the positive control, and coumarins isolated from S. divaricata showed dose-dependent anti-PEDV activity. The scientists demonstrated how functionalization plays a part in the antiviral effects of phytochemicals and how crucial the structure-function relationship is. Additionally, the phytochemicals known as phloroglucinol were found to be responsible for D. crassirhizoma's inhibitory action against PEDV.

Baicalin, which comes from the popular plant Scutellariabaicalensis Georgi, Lamiaceae, has been shown in Chinese herbal medicine to exhibit detectable in vitro antiviral activities in clinical isolates of SARS coronavirus using the foetal rhesus monkey kidney (fRhK-4) cell line, alongside well-known antiviral medications like lopinavir, ribavirin, and rimantadine [23]. When an alternate treatment is accessible and reasonably priced, it is advised to use intravenous

baicalin. Aside from SARS viruses, baicalin may also inhibit HIV1 at the level of cellular entry by conjugating with specific chemokines and obstructing their ability to activate vital cellular receptors; additionally, baicalin may inhibit HIV-1 reverse transcriptase by inhibiting the enzyme, potentially through obstructing the binding of viral RNA to the transcriptase in the vicinity of the enzyme's active site [23].

A study by [24] that assessed the anti-SARS-CoV properties of different phytocompounds, such as terpenoids, lignoids, and curcumin, using a cell-based test that measured the SARS-CoV-induced cytopathogenic effect on Vero E6 cells, revealed several of the substances had promising effects. Certain lignoids and diterpenoids of the abietane class, according to the authors, have potent anti-SARS-CoV properties. Sambucus formosana Nakai, a Chinese medicinal herb belonging to the Viburnaceae family, has been used for ethnomedical purposes in China. Its ethanol extract and its constituent phenolics have been studied for their antiviral properties against human coronavirus NL63 [25]. The extract demonstrated a noteworthy decrease in virus yield, plaque formation, and virus attachment, along with a comparatively mild cytotoxic but concentration-dependent anti-HCoV-NL63 action.

It was proposed that the plant's phenolic acids, caffeic acid, chlorogenic acid, and gallic acid, were partially or entirely responsible for the antiviral activity because they showed the ability to decrease the in vitro generation of offspring HCoV-NL63 particles.

By affecting HCoVNL63's binding to the ACE 2 receptor and co-receptors, caffeic acid may have a significant antiviral effect, according to the authors. Li and associates used 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4- sulfophenyl) in a study. Four Chinese medicinal herb extracts with possible antiviral activity were found using the -2H-tetrazolium inner salt (MTS) assay for virus-induced cytopathic effect (CPE). Lycoris radiata (L'Her.) Herb., Amaryllidaceae, the most potent extract, was further thoroughly characterised, resulting in the identification of lycorine, the active SARS-CoV agent, with an EC50 value of 15.7 ± 1.2 nM, a CC50 value of 14,980.0 ± 912.0 nM (in cytotoxicity assay), and a selective index (SI) > 900.

ANTIVIRAL PROPERTIES OF SPICES AND HERBS

Immunity boosters include Tinosporacordifolia (Giloy), Ocimumbasilicum (Tulsi), Allium sativum (garlic), and many other therapeutic plants and herbs [26]. A variety of spices, including black pepper, turmeric, clove, cinnamon, and ginger, are recognised for their antiviral and immunity-boosting qualities [27-29]. The antiviral properties of popular spices and herbs, such as curcumin, cinnamon, ginger, clove, black pepper, garlic, neem, giloy, and basil, that were employed during COVID-19 have been emphasised in this article, as shown in Figure 2. Numerous substances found in neem leaves, including zinc, quercetin, vitamin A, vitamin B1, vitamin B2, vitamin B6, vitamin C, vitamin E, and more, may strengthen immunity [30].

Curcuma longa L. (turmeric)

Native to India and Southeast Asia, turmeric (Curcuma longa L.) is a member of the ginger family (Zingiberaceae). This plant's rhizomes are rich in secondary metabolites, with polyphenol, steroids, sesquiterpenes, and curcuminoids being the main bioactive ingredients [31]. Curcumin, a naturally occurring polyphenol, has been extracted from turmeric (Curcuma longa) and has been utilised for millennia in Asian traditional medicine to treat a wide range of illnesses. Numerous research investigations have demonstrated that curcumin has certain pharmacological characteristics, including anti-inflammatory, anti-angiogenic, and anti-neoplastic effects, without causing any harm. It was classified as "Generally Recognised as Safe" by the Food and Drug Administration (FDA).

Clinical investigations have demonstrated that consuming up to 12 g/day of curcumin was safe for humans and did not cause any negative effects [32, 28]. Discovered that there was no harm from curcumin when the dose was increased from 2,500 to 8,000 mg daily for three months. Viral replication is inhibited by the dynamic antiviral curcumin. As specified in Table 1, curcumin has been shown to exhibit antiviral activity against a variety of viruses, including those that cause hepatitis, SARS coronavirus, influenza, human immunodeficiency virus (HIV), herpes simplex, dengue, chikungunya, and more. The manner that curcumin regulates different molecular targets that support different cellular functions, like transcription regulation and the activation of cellular signalling pathways, is further indication of its antiviral properties [33].

Curcumin's potential as an antiviral medication is enhanced by its ability to target many cellular pathways, hence impeding viral development and replication. Curcumin is said to bind to and inhibit target receptors that are involved in viral infection, such as spike glycoprotein RBD, PD-ACE2, and SARS-CoV-2 protease [34].

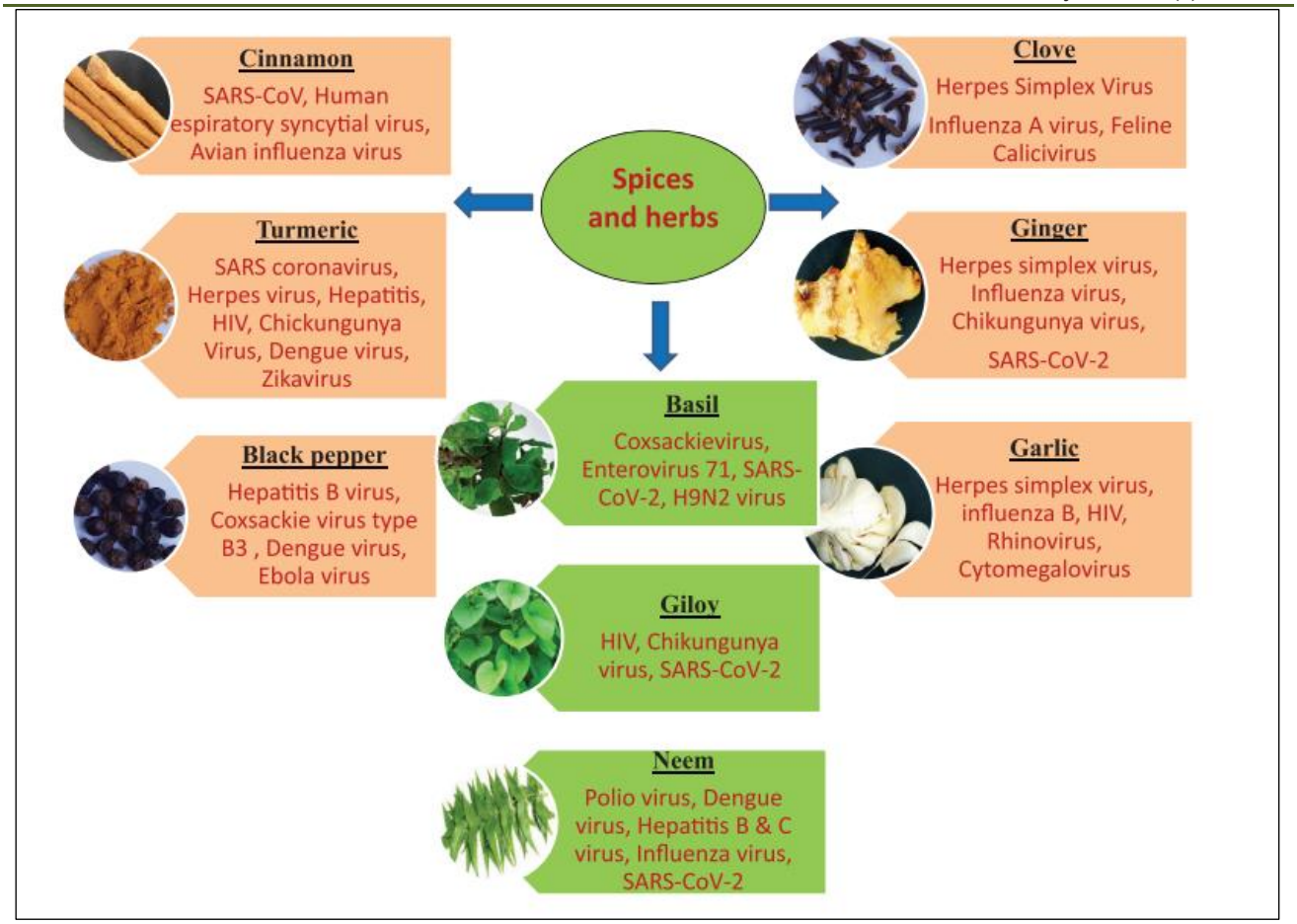

Fig 2: **Willey online library.com**

S. No	Virus	Mechanism of action	Reference
1	SARS Coronavirus	Replication and protease activity inhibitor	35
2	Herpes virus	Gene expression inhibitor	36
3	Hepatitis B virus	Replication inhibitor cccDNA inhibitor	37,38
4	Hepatitis c virus	Entry inhibitor	39
5	Human immunodeficiency virus	Protease Inhibitor Integrase inhibitor Tat protein inhibitor	40
6	Human Papiloma virus	Gene expression inhibition	41,42
7	Respiratory syncytical virus	Entry inhibitor replication and budding inhibition	43,44
8	Chicken gunya virus	Entry inhibitor	45,46
9	Dengue virus	Entry inhibitor, Particle production inhibitor	47,48
10	Zikavirus	Entry inhibitor	46
11	Influenza A virus	Inhibitor of virus uptake, replication and particle production	49,50

***Zingiber officinale* (ginger)**

Naturally occurring in many different countries, ginger is one of the major therapeutic herbs. Galangal, cardamom, and turmeric are some of the well-known plants in the Zingiberaceae family, which also includes ginger, Zingiber officinale. Cultivated in multiple countries, including India, the plant is native to Southeast Asia. Ayurvedic texts such as Charaka, Sushruta, Vagbhatta, and Chakra-dutta [51] describe ginger (*Zingiber officinale*), which is also known as Sunthi.

In the traditional Unani medical system, zanjabeel (*Zingiber officinale*) is a well-known herbal remedy [52]. Alkaloids, steroids, and phenolic groups are just a few of the bioactive substances found in abundance in ginger that have therapeutic properties. With counterparts including shogoals, paradol, and zingerone, zingiberol is the main aromatic agent of the rhizome. Ginger includes a number of sub-components in addition to the primary bioactive compounds, including 4-, 6-, and 8-gingerols, 10-gingerols, 6-shogaols, and 14-shogaols [53].

Their antiemetic, antipyretic, analgesic, antiarthritic, and anti-inflammatory properties have been documented. Numerous studies have demonstrated the effectiveness of ginger and its bioactive components in combating several viruses, including Chikungunya, Herpes simplex, Influenza, SARS-CoV-2, and Human respiratory syncytial virus [54-57]. Studies on the hepatitis C virus at concentrations ranging from 5 to 200 µg/mL have examined the antiviral efficacy of lyophilized juice derived from Zingiber officinale. A dose of 100 µg/mL was found to be efficient in inhibiting virus reproduction, as evidenced by the amplification of viral RNA segments [58].

Using a molecular docking research, [59] investigated the potential anti-SARSCoV-2 properties of a few bioactive compounds found in ginger, including gingerenone A, gingerol, geraniol, shogaol, zingiberene, zingiberenol, and zingerone. The bioactive chemicals contained in ginger were discovered to either inhibit MPro or prevent the spike (S) protein from attaching to the ACE2 receptor. The host cell's angiotensin-converting enzyme 2 (ACE2) receptor attaches to the S protein, which is in charge of allowing SARS-CoV-2 entry during the infection and creating the right conditions for viral replication [60]. During viral replication, Main Protease (MPro) is in charge of digesting the poly-proteins pp1a and pp1ab [61].

***Cinnamomum cassia* (cinnamon)**

The Lauraceae family of trees includes the aromatic species *Cinnamomum cassia*. For a very long time, cinnamon has been widely employed in traditional Chinese, Indian, Persian, and Unani medicine. For thousands of years, people from many nations have used cinnamon as a popular spice. The bark of the plant's young branches is used to make cinnamon, which is a common condiment used worldwide. It is highly valuable economically and can be utilised as a material for medicinal items. Many ailments, including flatulence, amenorrhoea, diarrhoea, toothache, fever, leukorrhea, common cold, and headache, are treated with it. Additionally, consistent usage of cinnamon has been proven to prevent throat infections [62].

21 chemical components, including eugenol (3.19%) and cinnamonaldehyde (60.41%), are said to have antibacterial properties when found in cinnamon bark. The antibacterial, antiviral, antifungal, antioxidant, antihypertensive, antidiabetic, anticancer, gastroprotective, and immunomodulatory properties of cinnamon have been demonstrated in a number of scientific investigations (Shen *et al*., 2012). A greater dose of cinnamon (100 mg/kg) significantly raised serum immunoglobulin levels, antibody titer, and phagocytic index, but a lower dose (10 mg/kg) of cinnamon simply enhanced serum immunoglobulin levels. Therefore, a greater dose boosts humoral immunity as well as cell-mediated immunity, while a lower dose solely had an impact on humoral immunity [63]. Herpes simplex virus-1 and the effects of a hydroalcoholic cinnamon extract.

Because the hydroalcoholic extract of cinnamon prevented the virus from attaching to cells, it was successful in lowering the HSV-1 viral titer [64].

***Syzygium aromaticum* (clove)**

Because of its antibacterial properties against oral germs, clove (*Syzygium aromaticum*), a member of the Myrtaceae family, is used as an antiseptic in medicine all over the world to prevent infectious infections. Because clove has antibacterial properties that extend its shelf life, it is frequently employed in the food business. As a food supplement, the FDA has verified the safety of clove buds, clove oil, oleoresins, and eugenol [65]. The WHO has determined that 2.5 mg/kg body weight of clove is the recommended daily intake for people [66]. Hydroxicinamic acids, hidroxibenzoic acids, hydroxiphenylpropanoids, and flavonoids are the primary phenolic chemicals found in cloves. Eugenol is clove's primary bioactive ingredient [67]. When it comes to bacteria, fungus, and acid-fact bacteria, eugenol demonstrates wide antibacterial activity.

Moreover, cloves are well known for their carminative and antiemetic qualities, which reduce nausea and vomiting. The chemical eugeniin, which was extracted from the herbal extracts of S. aromaticum and Geum japonicum, was found to have anti-Herpes Simplex Virus properties at a concentration of 5µg/mL. Eugenol has a lowering effect on infection and inhibits viral replication, whereas Eugeniin acts as a specific inhibitor of HSV-1 DNA polymerase to prevent the synthesis of viral DNA [68].

***Allium sativum* L. (garlic)**

Although the garlic plant, *Allium sativum* L., belongs to the Liliaceae family and is native to Asia, it is also grown in China, North Africa (Egypt), Europe, and Mexico. For thousands of years, it has been utilised as a therapeutic substance. The blossoms of this plant, which is a bulb that grows to a height of 25 to 70 cm, are used to taste and spice meals. Garlic has a high nutritional content, enhances food flavour, and relieves indigestion.

Numerous low-toxicity pharmacological actions of garlic include anthelmintics, anti-inflammatory, antioxidant, antifungal, and more [69]. Widespread antifungal and antiviral properties have been reported for allicin (diallyl-dithiosulfinate), which is generated from the alliin by the garlic enzyme alliinase. Ajoene, allicin, allyl methyl thiosulfanate, and methyl allyl thiosulfanate were the chemicals with virucidal activity in garlic, in decreasing order [70]. Studies on the antiviral action of garlic extract against the influenza virus A/H1N1 in cell culture have revealed that it prevents the virus from penetrating and multiplying in the culture [71]. On the infectious bronchitis virus (IBV-

a coronavirus) in the chicken embryo, the garlic extract exhibited inhibitory effect [72].

Neem plant, *Azadirachta indica*

Azadirachta indica, the scientific name for the neem tree, is an evergreen herb that grows quickly and is a member of the Meliaceae family. Since ancient times, several regions of Asia and Africa have utilised neem, a traditional medicinal plant of Indian origin, to cure a variety of acute and chronic illnesses. In traditional medicine, neem tree elements such as seeds, roots, leaves, blossoms, and bark have all been utilised as common domestic cures for a variety of human maladies. They possess spermicidal, insecticidal, antimicrobial, larvicidal, antimalarial, antibacterial, and antiviral properties [73]. The bark of this herb has been shown to contain many terpenoids, such as nimbin, nimbidin, nimbolide, limonoids, β-sistosterol, 6-desacetylnimbinene, nimbione, margocin, quercetin, and more [74].

Because of its ability to scavenge free radicals, a chemical known as "hyperoside" from neem leaf extract has demonstrated promise as a universal medication against influenza strains. The most effective findings with conserved residues of the influenza virus nucleoprotein were obtained using the hyperoside molecule derived from neem leaf extract in combination with the chemical medicines LGH, Naproxen, BMS-885838, and BMS-883559 [75].

The United Nations has designated neem as the "tree of the 21st century" (United Nations Environment Programme, 2012). Neem is an amazing plant. Many scientists have begun studying neem in an effort to find medications that combat SARS-COV-2 because of its well-established antiviral qualities and efficacy. The natural bioactive substances that are derived from tulsi and neem, specifically ursolic acid, oleanolic acid, and methyl eugenol, function as SARS-CoV-2 inhibitors. These bioactive substances bind to the spike glycoprotein, RNA polymerase, and/or its protease to effectively inhibit SARS-CoV-2 by preventing viral attachment and replication [76].

The major protease protein of COVID-19, which is essential for viral replication, was highly bound by over 20 chemicals that were extracted from neem leaf extract [78]. It has been shown that Nimbamritam, also known as Nimba and Amrita (A. indica and T. cordifolia), ligands may be screened in silico to assess anti-SARS-CoV-2 activity. The residues of spike protease or Mpro protease of SARSCoV-2 were discovered to interact with the ligand and be inhibited [77].

***Tinospora cordifolia* (giloy)**

Tinospora cordifolia, often known as giloy, is a Menispermaceae family member that is mostly found in Asian nations such as China, India, Sri Lanka, and Myanmar. Known by its popular name, Guduchi, this native Indian medicinal plant is utilised in Ayurvedic medicine formulations to treat a variety of ailments. T. cordifolia has been heavily used for commercial purposes due to its medical usefulness. It is utilised as an effective medicine for therapies against a variety of ailments, including jaundice, urinary disorders, skin diseases, diabetes, anaemia, inflammation, allergic conditions, and more [76, 79]. All of the pharmacological activity listed above are present in T. cordifolia's many components, including the leaves, stem, root, flower, seed, and so forth.

Additionally, this plant is utilised in Ayurvedic "Rasayanas" to strengthen the body's defences against illnesses and strengthen the immune system.

According to reports, the MTT test revealed that the crude extract of T. cordifolia's dry stem exhibited antiviral activity against the herpes simplex virus [80]. Based on molecular dynamics method, the five phytoconstituents of T. cordifolia (giloy) are berberine, b-sitosterol, coline, tetrahydropalmatine, and octacosanol. Berberine is reported to be able to suppress the action of 3CLpro protein, which in turn controls viral replication [81]. A molecular docking research [82] revealed that tinocordiside, one of the phytochemicals found in giloy, inhibited the primary protease of SARS-CoV-2.

High binding efficacy was demonstrated by the compounds berberine, isocolumbin, magnoflorine, and timocordiside that were isolated from Giloy against the four major SARS-CoV-2 target surface glycoproteins (6VSB), receptor-binding domain (6M0J), RNA dependent RNA polymerase (6M71), and main protease (6Y84) involved in virus attachment and replication [83].

***Allium cepa* (onion) and Olea europaea (olive)**

An onion is a member of the Liliaceae family and is rich in minerals, vitamins, terpenoids, phytoestrogens, anthocyanins, carotenoids, copaenes, and favonoids. Onion-derived phytochemicals have antibacterial, anti-parasitic, antiviral, anti-oxidant, and anti-inflammatory qualities. They also denature the virus's protein and genetic component. By preventing virus attachment, changing the transcription and translation processes of the viral genome, and influencing the virus's assembly, organo-sulfur compounds such as isorhamnetin, kaempferol, quercetin, and myricetin reduced viral infection. Onion exhibits effective inhibitory action against the primary protease of SARS-CoV-2 [58, 59]. Olive is a native of the Mediterranean region and has been shown to have antiviral, anti-inflammatory, anti-oxidant, and anti-cancer effects. Squalene and oleic acid are the two primary active ingredients in olives.

Strong antiviral properties are reported for olive leaf extracts. Olive secondary metabolites that affect

virus attachment and replication include oleeuropein, hydroxytyrosol, oleanolic, maslinic, and ursolic acid. Terpenoids alter the membrane's fluidity and eliminate the lipid layer and SARS-CoV-2's binding properties. It is thought that eating olives will boost immunity against a range of infections [84, 85].

Conclusion, Recommendations and future prespective

COVID-19 is a pathogenic and pandemic viral infection caused by the highly contagious coronavirus. Although the deployment and administration of vaccines have significantly improved the long-term effects of COVID-19, they are not entirely effective with the persistence of some severe symptoms. Additionally, time is crucial for the new development and vaccination across the global population. This creates a gap and scope for investigating other safe and effective remedies against SARS-CoV-2. Computer-aided drug discovery for rapid development processes with relatively low costs and preventing failures at the final stage are ongoing research carried out by various organizations. Supporting this, molecular docking studies have been performed recently for predicting the ability of bio-active compounds derived from plants to inhibit the spike and Mpro proteins of SARS-CoV-2 [86]. Natural products and bio-actives have traditionally been used to treat various infectious diseases. This has marked an initiating point for repurposing traditional knowledge to search and develop new metabolites against COVID-19 infection. The previous research studies were carried out in vitro with few experiments on animal models. Further, recent clinical trials have to be randomized as some traditional Chinese and Indian medicines have been shown to reduce the symptoms associated with COVID-19 [87, 88]. Interestingly, this knowledge made us develop low-calorie fermented ginger beer and fruit beverages using natural inherent yeast as a nutraceutical supplement that may potentially act as an immunity booster during the COVID-19 pandemic. This study comprehends knowledge concerning the potential of fermented ginger beer and fruit drinks as the possible approach for boosting immunity against COVID-19. Therefore, it is worthy to identify in future studies the exact constituents in the products and their mechanism of action against SARS-CoV-2 and to study the impacts of these products on the tissues infected with the virus. Moreover, a combined therapy using these probiotic products with a validated medication for preventing and treating COVID-19 infection should be considered. Additionally, new molecular methods such as high throughput screening must be employed to isolate the bio-active compounds from microbial sources. Thus, future studies should emphasize the investigation of more natural-based bi-actives and studying their mechanisms of action on the virus to know the effective treatment for COVID-19. The data discussed in the present study highlight the absolute need for effective preventive and treatment methods to fight emerging viral infections, mainly using natural products derived from microbes, invertebrates, and plants for more efficient, targeted, and safer remedies.

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