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Plant metabolites as potential therapeutics against COVID-19 and other viral diseases

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The COVID-19 pandemic caused by the novel coronavirus (SARS-CoV-2) posed a serious threat to human health worldwide. The death toll was immense in many countries, irrespective of their advanced healthcare system. Post-COVID complications are equally challenging. It was realized that a single method to manage the COVID-19 pandemic and related outbreaks is not adequate; rather, an integrated approach which includes spreading awareness and educating masses about the disease, development of antiviral drugs and other safer drugs for symptomatic treatment of the disease, and mass vaccination is needed to manage such pandemic. Plants used in traditional medicine systems contain diverse secondary metabolites. These have been screened against SARS-CoV-2 and have shown effective antiviral activities. Many of the plant products are also useful for symptomatic treatment. The immune-boosting properties of many phytochemicals have been well documented. In this review, the potential of traditional medicinal plants for effective management of the COVID-19 pandemic is presented.

Keywords: Antiviral phytochemicals, COVID-19, Immunity-boosters, Immuno-modulators, Plant metabolites, Plant-based nanoparticles, SARS-COV-2

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Introduction

Coronaviruses (CoVs) are positive-sense single-stranded enveloped RNA viruses and belong to the family Coronaviridae. Presently, seven types of Coronaviruses are known to infect humans. Four of these, viz. 229E (α Coronavirus), NL63 (α Coronavirus), OC43 (β Coronavirus), and HKU1 (β Coronavirus) generally infect people worldwide but do not cause severe infection[1]. The three coronaviruses, including MERS-CoV, SARS-CoV, and nCoV (also known as SARS-CoV-2), cause severe infection that leads to clinical complications and even death of the infected patients[1]. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), responsible for causing severe respiratory system-related disorders[2], is the etiological agent of Corona Virus Diseases-19 (COVID-19). The infected patient develops symptoms like fever, myalgia, cough, loss of smell or taste, or both, shortness of breath and pneumonia, and severe acute respiratory distress on disease progression[3]. SARS-CoV-2 caused significant morbidity and mortality globally. This disease is a major public health concern because it imposed a significant burden on our healthcare system in the last few years, and still, in some parts of the world, it is threatening us. Although many vaccines are currently available, there are reports of post-vaccination COVID-19 infections. Despite numerous attempts and some success in drug development as well as drug repurposing[4], no reliable, safe and specific antiviral drug is available against this virus, and the treatment is mostly supportive.

The first case of COVID-19 was reported in Wuhan City (China) in December 2019[5], and on investigation, SARS-CoV-2 was found to be

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responsible for it. The infection was highly contagious and spread rapidly outside the city, and within months' several countries fell prey to the disease. The World Health Organization declared COVID-19 as a pandemic on accessing the circumstances on 11th March 2020. The devastating effects of COVID-19 could be seen in different countries worldwide. India, the second-largest country in the world in terms of population, was severely affected by the SARS-CoV-2 infection. Although the number of cases in Brazil was lower than in India, the mortality rate was very high. The COVID-19 pandemic existed in many parts of the world, and new coronavirus variants threaten the world population for its re-emergence.

SARS-CoV-2 enters and invades humans through the respiratory tract[6]. However, other potential routes of transmission of SARS-CoV-2 are respiratory/droplet, indirect, fecal-oral, vertical, sexual, and ocular[7]. Therefore, patients who are infected with this virus experience respiratory problems; disorders of the heart, kidneys, and digestive tract may also be observed in the patients. Virions of coronaviruses are covered by spike proteins (S) that contain a variable receptor-binding domain (RBD). These proteins bind to angiotensin-converting enzyme-2 (ACE-2) receptors found on cells of target organs of humans to facilitate viral entry[8,9]. In addition to plasma membrane attachment, S-protein facilitates viral envelope and cell membrane fusion. Subsequently, the virus releases its RNA into the cytoplasm of the host cell, which is translated into proteins[10]. The genomic RNA is translated into two polyproteins (pp1a and pp1ab), which undergo a proteolytic cleavage generating 15–16 nonstructural proteins. The double-membrane vesicles are then formed from the rearrangement of the cellular membrane induced by the nonstructural proteins. On the other hand, the genomic RNA is transcribed into the sub-genomic RNA, which in turn gets translated into structural and accessory proteins such as M, S, and E proteins. These proteins remained insulated in the endoplasmic reticulum and assembled into virus particles in the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) and then released via the secretory pathway[11]. Meanwhile, the previously replicated genome directly joins with the N protein and moves into the ERGIC. In this compartment, nucleocapsids meet with several other structural proteins and form small wallet vesicles, which are exported out of the cell through exocytosis[12,13].

The incubation period of COVID-19 in humans is about 4–6 days (range 2–16 days). The most common symptoms include fever, dry cough, fatigue, and sore throat, while other symptoms include sputum production, headache, diarrhoea, dyspnea, and lymphopenia[14]. Based on specific clinical features, COVID-19 cannot be distinguished from other viral respiratory infections. The clinical attributes of COVID-19 vary from asymptomatic forms to clinical conditions characterized by respiratory failure, aseptic shock multi-organ dysfunction, or failure in severe cases[15,16]. Cardiovascular pathology like hypertension, different types of arrhythmias, and the formation of blood clots have also been reported in COVID-19 patients[17]. COVID-19 can also affect vital organs such as the lungs, liver, and kidneys adversely.

In the absence of specific antiviral drugs against SARS-CoV-2, people all over the world are dependent on their immune systems. Patients, therefore, are being treated to control the symptoms, not the actual disease. The high mutation rate in the coronavirus genome, which leads to the emergence of new strains, is still a major challenge around the world. In addition, post-COVID vaccination complications are emerging as a new challenge for clinicians(National Center for Immunization and Respiratory Diseases, NCIRD, Division of Viral Diseases 2021).

As learned from the worldwide experience, a single approach to control the COVID-19 pandemic or similar outbreaks would not be adequate; rather, an integrated approach is required for the effective management of such global threats. One of the important components of this approach is spreading awareness among the masses about COVID-appropriate behaviour, community containment and quarantine of the infected person, and educating people about the disease, its symptoms and management, and post-COVID care (Centre for Disease Control and Prevention). Nutritional interventions are one of the vital components of the integrated approach to COVID-19 pandemic management, as they address the general health condition and strengthening of the immune system[18–20]. The second wave of COVID-19 caused a lot of suffering and fatality worldwide. This necessitated the urgent development of a reliable and specific drug for the prevention of the progression of the disease, other than the vaccination approach, which requires years for successful development. For the reduction of morbidity and fatality rates in such pandemics, specific and reliable antiviral drugs are required. Unfortunately, there are not many effective antiviral drugs against SARS-CoV-2. Researchers are underway in the development of new potential antiviral drugs that may target the virus at different levels like RNA–dependent RNA polymerase (RdRp), viral protease, virus spike protein, etc[21]. Also, exploring safer drugs for the management of the disease symptoms is important. Mass vaccination is a promising strategy to manage the COVID-19 pandemic and a wide variety of vaccines have been developed, and a few more are under progression. These vaccines are grouped according to the technology used for their development. The most advanced SARS-CoV-2 vaccine candidates include mRNA vaccine (e.g. mRNA- 1273, Moderna), Inactivated pathogen vaccine (e.g. Covaxin), Replication-defective viral vector vaccine (e.g. Sputnik V), inactivated vaccine (e. g. Covishield), Protein subunit vaccine, and Virus-like particles[22]. The vaccine may serve as one of the prophylactic measures in preventing COVID-19 infection, but we cannot be fully dependent on these vaccines for the complete eradication of COVID-19 infections. The reported efficacy of vaccines, side effects and chances of reoccurrence of disease among vaccinated persons are some of the questions that need to be answered[23,24].

Natural plant products provide an alternative and safer option. In China, India, and many other countries worldwide, people rely on natural herbs for various ailments. It has been reported that millions of people around the world benefitted from natural products in the fight against COVID-19[25,26]. The herbal formulations of medicinal plants have shown promising results as antiviral agents against COVID-19 in clinical trials[27]. In this review, we have compiled the literature about traditional medicinal plants, which may be helpful for the development of an effective and reliable herbal formulation against COVID-19 and related diseases. The effective phytoconstituents that showed antiviral and immune-booster activities and may directly or in a synergistic act on the virus to manage the dreadful diseases are presented.

Plant-based traditional medicines for the management of COVID-19

Plant materials used in the traditional medical system may give symptomatic relief, kill or inactivate the disease pathogens, or improve immunity to help the body fight against the pathogens. Scientific communities across the world have tested diverse plants and their products against COVID-19. Since then, several plant products have been found to possess antiviral activity against SARS-CoV-2 and are on trial for further expansion and commercialization. Many traditional Chinese herbal medicines have been found promising in reducing the symptoms and shortening the course of viral infection[28]. A study performed in China showed that the COVID patients who received combined treatment of traditional Chinese medicine and modern medicine had lower fatality rates and better clinical outcomes[29]. China Food and Drug Administration recommended the use of Lian-Hua-Qing-Wen capsule (LHQWC), and Jin-Hua-Qing-Gan Granule (JHQGG) for the treatment of COVID-19[30]. LHQWC is composed of *Forsythia suspensa* (Thunb.) Vahl, *Lonicera japonica* Thunb., honey-fried *Ephedra sinica* Stapf, fried *Prunus sibirica* L., Gypsum Fibrosum, *Isatis tinctoria* L., *Dryopteris crassirhizoma* Nakai, *Houttuynia cordata* Thunb., *Pogostemon cablin* (Blanco) Benth., *Rheum palmatum* L., *Rhodiola crenulata* (Hook.f. and Thomson) H. Ohba, *Mentha canadensis* L. and *Glycyrrhiza glabra* L. and JHQGG is made from *Forsythia suspensa* (Thunb.) Vahl, *Lonicera japonica* Thunb., *Ephedra sinica* Stapf, *Prunus sibirica* L., l-Menthol, *Glycyrrhiza glabra* L., *Scutellaria baicalensis* Georgi, *Fritillaria thunbergii* Miq., *Anemarrhena asphodeloides* Bunge, *Arctium Appa* L. and *Artemisia annua* L.

Mukhtar *et al.*[31] tested 142 plant extracts against the influenza virus and reported the medicinal value of secondary metabolites present in many plants. These metabolites bind with virus proteins and enzymes, and thus inhibits viral penetration into the host cells and its replication process[32]. Quinine an antimalarial drug, is extracted from the bark of *Cinchona officinalis* L. trees. It possesses broad-spectrum antiviral activities, has regulatory effects on the immune system, and relieves symptomatic ailments in most patients. This made the Chinese State Council recommend the use of chloroquine phosphate, a structural analogue of quinine, for the treatment of COVID-19 patients[33,34]. Another compound, diammonium glycyrrhizinate, extracted from the roots of *Glycyrrhiza glabra* L. has anti-inflammatory activity and is being used in treating colds, coughs, and sore throats. Its combination with vitamin C has been proven effective for the treatment of severe cases of COVID-19[35]. Lianhua qingwen keli, Jinhua qinggan keli, and Xuebijing were officially approved by the China National Medical Products Administration for COVID-19 for the treatment of COVID-19 patients[36]. These drugs treat symptoms such as cough, weakness, and digestive system disorders in COVID-19 patients. Similarly, *Ageratum houstonianum* Mill. provides symptomatic relief from COVID-19 symptoms and has therapeutic potential; it is widely used to remove heat and toxic substances in the Chinese traditional medicine system[37]. Ecuadorian people also used *A. houstonianum* as an anti-inflammatory to relieve swelling and throat pain[37]. *Withania somnifera* (L.) Dunal is known to alleviate symptoms like tiredness, breathing problems, and cough in patients with chronic obstructive pulmonary disease. It has also been shown to be effective in the conditions of pulmonary fibrosis seen in many COVID-19 patients[38]. *Tinospora cordifolia* (Willd.) Hook.f. & Thomson extracts were used in diabetes, dyspepsia, jaundice, rheumatoid arthritis, pyrexia, inflammations, gout, cardiac debility, excess mucus, urinary disorders, and asthma. Also, the combination of *T. cordifolia*, *W. somnifera*, and *G. glabra* has been proven effective against tuberculosis. Similarly, phytochemicals such as berberine, choline, columbin, chasmanthin, jatrorrhizine, palmarine, palmatine, tinocordifolioside, tinosporon, tinosporic acid, tinosporin, tinosporol, tinosporaside, tembeterine, tinosporic acid, tinosporal, tinosporon present in this plant make it a suitable herbal medicine against several diseases[39]. *In silico* research revealed that some of these plant metabolites have a binding affinity towards SARS-CoV-2 MPro[40]. *Ocimum sanctum* L., a widely used plant in the Indian traditional medicine system, possesses antimicrobial, anti-inflammatory, anti-allergic, and anti-pyretic-analgesic activities which make it suitable against SARS CoV-2 virus. Ethanol extract of its leaves was reported effective for dyspnea in guinea pigs. Dose-dependent anti-asthmatic activity has also been found in bronchospasm[41]. *Andrographis paniculata* (Burm.f.) Nees is a medicinal plant of the family Acanthaceae, widely used in countries like Bangladesh, China, Hong Kong, India, Pakistan, Philippines, Malaysia, Indonesia, and Thailand. It contains phytochemicals like diterpenoids, diterpene glycosides, flavonoids, lactones, and flavonoid glycosides and is known to possess anti-inflammatory properties. Its dried extract tablet had a significant reduction in symptoms in patients suffering from the common cold[42] and sinusitis[43]. Andrographolide and neoandrographolide present in this plant are effective against inflammation[44]. Inflammation is controlled through inhibition of intercellular adhesion molecule-1 expression, nitric oxide synthase (iNOS) suppression, cyclooxygenase-2 (COX-2) expression in microglial cells and neutrophils, ERK1/2 phosphorylation reduction in murine T cells and IFN-γ[45,46].

Plants with antiviral properties

Viral infection can be checked by following two approaches, i.e., the use of antiviral compounds and immune boosters. The process of viral proliferation involves different steps like anchoring to the host cell membrane, invasion into the host cell, uncoating of the capsid, replicating its genome, translating its protein, and then assembling the genome with the protein. Targeting one or more steps can stop viral proliferation. In contrast to the modern approach, which is single target specific, plant products act at various levels and significantly reduce the viral load. In addition to inhibiting viral proliferation, plants also stimulate the immune system and enhance immunity.

Many plant biomolecules inhibit the viral genome replication in the host cell[47]. In the initial stage of infection, the virus attaches to the cell membrane of the host cell and subsequently penetrates and transfers its genetic material into the cytoplasm. Many plants-derived triterpenoids, flavonoids, polysaccharides, and their derivatives used in traditional Chinese medicines have been reported to inhibit the attachment of viruses. Also, the glycyrrhizin (GL) and its metabolite 18 beta-glycyrrhetinic acid are very effective in inhibiting of viruses' adsorption[5]. These compounds possess antioxidant, anti-inflammatory, and antiviral activities[48,49]. Polysaccharides similar to cell receptors prevent the binding and infiltration of viruses into the host cell[50,51]. Two polysaccharides obtained from *Stevia rebaudiana* (Bertoni) Bertoni leaves have been reported to have antiviral activity against HSV-1. Both molecules exert antiviral effects at the initial stage of HSV-1 infection by inhibiting viral adsorption. Similarly, polysaccharides extracted from *S. rebaudiana* may be used as an alternative treatment for HSV-1 infection. Ceole *et al.*[52], reported that in the cases where the extract did not eliminate latent HSV-1, it still prevented transmission of the virus (Table 1).

Table 1 — Plants possessing antiviral activity and their active components

S. No.	Name of the Plant	Common Name	Family	Country of origin	Activities	Active components	Molecular Formula	Reference
1	*Alnus japonica* (Thunb.) Steud.	East Asian alder	Betulaceae	Japan, Korea, Taiwan, Eastern China, Russia	Anti-influenza, Anti-inflammatory	Diarylheptanoids Catechol	$C_{21}H_{20}O_6$ $C_6H_6O_2$	86
2	*Allium sativum* L.	Garlic	Amaryllidaceae	Central Asia, Northeastern Iran	Antiviral	Saponins	$C_{58}H_{94}O_{27}$	89
3	*Capsicum annuum* L.	Capsicum	Solanaceae	South America	Antiviral against HSV-1, HSV-2, Poliovirus-1	Apigenin	$C_{15}H_{10}O_5$	69
4	*Cinchona officinalis* L.	Cinchona	Rubiaceae	Western South America, India	Antiviral against SARS-CoV, Rabies virus, HIV, Poliovirus, Zika virus, Antimalarial	Quinine Cinchonidine	$C_{20}H_{24}O_2N_2$ $C_{19}H_{22}N_2O$	15
5	*Citrus limon* (L.) Osbeck	Lemon	Rutaceae	India, Pakistan	Antiviral against Influenza virus, HCV, HAV, SARS-CoV	Hesperidin	$C_{28}H_{34}O_{15}$	70
6	*Citrus sinensis* (L.)	Sweet Orange	Rutaceae	Asia, Vietnam	Antiviral against HIV, Rabies	Linalool	$C_{10}H_{18}O$	69,87
7	*Curcuma longa* L.	Turmeric	Zingiberaceae	Indian Subcontinent, Southeast Asia	Antiviral against SARS CoV	Curcumin	$C_{21}H_{20}O_6$	81
8	*Eucalyptus globules* Labill.	Eucalyptus	Myrtaceae	India, Australia, Tasmania	Antiviral against SARS-CoV-2	Eucalyptol	$C_{10}H_{18}O$	61
9	*Lycoris radiata* (L'Heritier) Herbert.	Red spider lily	Amaryllidaceae	China, Korea, Nepal, United States	Antiviral against SARS-CoV, HIV, Flavivirus, Poliovirus	Lycorine	$C_{16}H_{17}NO_4$	60
10	*Myrica rubra* (Lour.) Siebold & Zucc.	Red bayberry	Myricaceae	China, Japan, Korea	Antiviral	Myricetin	$C_{15}H_{10}O_8$	94
11	*Pelargonium sidoides* DC.	African geranium	Geraniaceae	South Africa	Antiviral against Human Coronavirus	Proanthocyanidins	$C_{31}\cdot H_{28}O_{12}$	85
12	*Phaseolus vulgaris* L.	French bean	Fabaceae	India, America, Myanmar, China	Antiviral against SARS-CoV, RSV, HIV	Kaempferol	$C_{15}H_{10}O_6$	69,88
13	*Reynoutria multiflora* (Thunb.) Moldenke	Chinese Knotweed	Polygonaceae	Central and Southern China	Antiviral against SARS CoV	Emodin	$C_{15}H_{10}O_5$	80
14	*Scutellaria baicalensis* Georgi	Chinese skullcap	Lamiaceae	China, Korea, Mongolia, Russia	Antiviral against SARS-CoV	Scutellarein	$C_{21}H_{18}O_{12}$	79
15	*Strobilanthe scusia* (Nees) Kuntze	Assam indigo	Acanthaceae	Northeast India	Antiviral against Human Coronavirus NL63	Tryptanthrin	$C_{15}H_8N_2O_2$	78
16	*Syzygium aromaticum* (L.) Merr. & L.M.Perry	Clove	Myrtaceae	Indonesia, India	Antiviral against SARS CoV	Oleanolic acid	$C_{30}H_{48}O_3$	95
17	*Vincetoxicum indicum* (Burm.f.) Mabb.	Antmool	Apocynaceae	Southern India	Antiviral, Mucolytic, Expectorant	Tylophorine	$C_{24}H_{27}NO_4$	66
18	*Vigna radiata* (L.) R.Wilczek	Mung bean	Fabaceae	East Asia, Indian subcontinent	Antiviral And prophylactic activity against HSV-1 & Respiratory syncytial virus	Vitexin Isovitexin	$C_{21}H_{20}O_{10}$ $C_{21}H_{20}O_{10}$	72
19	*Withania somnifera* (L.) Dunal	Ashwagandha	Solanaceae	India	Antiviral against H1N1, HSV-1, HSV-2	Withanone	$C_{28}H_{38}O_6$	71,72

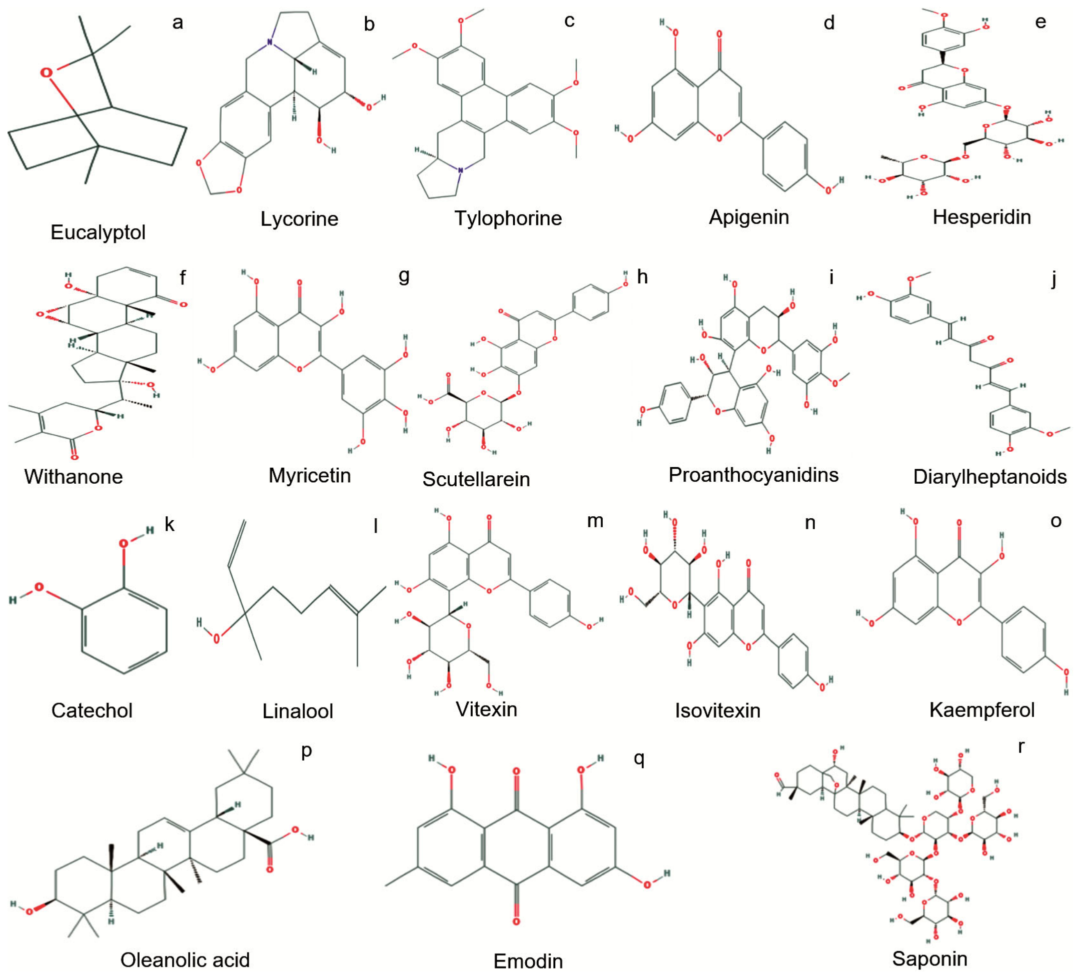

Fig. 1 — Phytoconstituents of plants showing antiviral activities.

Plant compounds that help in providing antiviral properties are mainly secondary metabolites such as alkaloids, terpenoids, flavonoids, phenolic acids, tannins, lignins, coumarins, stilbenes, among others. Essential oils present in many plants are capable of disrupting the phospholipid bilayer of coronaviruses and interfering with the structure of viral envelope proteins[53]. Eucalyptol (Fig. 1a) isolated from *Eucalyptus globules* Labill. is one such lipophilic essential oil that is effective against SARS-CoV-2[54]. 3C-like protease (SARS-CoV 3CLPro) is a viral encoded enzyme that regulates its replication; it can be a target for the development of drugs against SARS-CoV-2. Phytochemicals such as β-sitosterol, hesperetin, aloe-emodin, indigo, and sinigrin were found to have cleavage activity of SARS 3 CLPro enzyme[53,55]. Phenolic compounds present in the root extract of *Isatis tinctoria* L. have shown antiviral properties against human coronaviruses[56]. The activity of SARS-CoV 3CLPro was also inhibited by polyphenols[57], flavonoids and compounds like gallocatechin gallate, epigallocatechin gallate, pectolinarin and rhoifolin, quercetin and herbcetin, etc., present in *Litchi chinensis* Sonn. seeds[58] (Table 1).

Bhuiyan *et al.*[59] found about 219 plants from 83 families with antiviral activity. They proposed that plant metabolites can serve as potential anti-SARS-CoV-2 and drug development processes to combat COVID-19 and future pandemics caused by viruses. Lycorine, (Fig. 1b) an alkaloid present in *Lycoris radiata* (L'Hér.) Herb. has been reported to possess antiviral activity against many viruses, including SARS-CoV. Functionally, it suppresses protein synthesis in the virus and blocks the replication of the virus[60]. A study conducted by Li *et al.*[61] showed that lycorine was effective in inhibiting the cytopathic effects caused by SARS-

CoV infection. Chloroquine, a synthetic derivative of quinine possesses DNA intercalating properties and can be used in the development of a drug against SARS CoV[53]. Also, it showed antiviral activity against rabies virus, poliovirus, HIV, and Zikavirus. Moreover, its antiviral potential has been reported as beneficial in the treatment of SARS CoV infection[62], and lately against SARS CoV-2[63]. Chloroquine functionally inhibits the entry of viruses into the cells by inhibiting their binding to the cell surface receptors and inhibits replication of the virus *in vitro*[64]; also, it has been reported to interfere with the post-translational modifications of many viral proteins[65]. *Vincetoxicum indicum* (Burm.f.) Mabb., also known as *Tylophora indica*, is a vine plant belonging to the family Apocynaceae. It possesses mucolytic and expectorant properties and is useful in the treatment of respiratory diseases. Tylophorine (Fig. 1c), extracted from *T. indica* is a phenanthroindolizidine alkaloid, which possesses antiviral activity. Therefore, Tylophorine-based compounds have the potential to inhibit coronavirus infection[66]. *Capsicum annuum* L., a common spice contains various flavonoids, phenolics, and glucosides[67,68]. Apigenin (Fig. 1d) a natural flavone present in *C. annum*, possesses antiviral activity against a variety of viruses, including herpes simplex virus-1 (HSV-1), HSV-2, and poliovirus-1; it inhibits the replication process by binding with the proteases of the virus[69]. Peel of *Citrus limon* (L.) Osbeck (Rutaceae) contains a flavonoid hesperidin (Fig. 1e), which shows antiviral activity against the common cold virus, hepatitis C virus, and hepatitis A virus. Utomo & Meiyanto[70] suggested that this flavonoid binds to the cell receptors of SARS-CoV, and hence can be used for the treatment of coronavirus infection. *Withania somnifera* (L.) Dunal, commonly known as Ashwagandha, contains various secondary metabolites collectively known as withanolides[71], which possess antiviral activity against the H1N1, HSV-1, and HSV-2 virus. Withanone (Fig. 1f) inhibits the entry of novel coronavirus into the host cell by disrupting the interactions of the viral protein receptor-binding domain (RBD) with the host ACE2 receptor[39,72] (Table 1). A computational study has also predicted that withanone can interact with the main protease (MPro) of SARS-CoV-2, which is responsible for cleaving host transmembrane protease serine 2 (TMPRSS2) required for viral entry into the host cell[73]; it also downregulates TMPRSS2 transcription[74]. Likewise, the docking studies also showed that withaferin A, another major phytochemical of *W. somnifera* leaves, can bind to GRP78[75]. Balkrishna *et al.*[76] studied the inhibitory action of *W. somnifera* on host–pathogen-specific interaction between host ACE2 and viral RBD of S-protein of SARS-CoV-2 in a humanized zebrafish model of the disease.

Myrica rubra (Lour.) Siebold & Zucc., an evergreen tree, is a rich source of phytochemicals like flavonoids, phenolics, and organic acids. Myricetin (Fig. 1g), a flavonoid obtained from its fruits, has been reported to inhibit the activity of SARS CoV helicases by affecting the ATPase activity[77]. Similarly, tryptanthrin isolated from *Strobilanthes cusia* (Nees) Kuntze leaves was found effective against HCoV-NL63 infection and had the potential to treat respiratory virus infections[78]. It inhibits the viral replication process by blocking RNA genome synthesis and protease activity[78]. These compounds affect the production of virus progeny and reduce cytopathic effects. Another plant, *Scutellaria baicalensis* Georgi (Lamiaceae), used in Chinese herbal medicine for the treatment of respiratory infection, contains a flavonoid scutellarein (Fig. 1h). It shows antiviral activity against SARS-CoV by inhibiting the ATPase activity[79]. *Reynoutria multiflora* (Thunb.) Moldenke, commonly known as Chinese knotweed, contains an anthraquinone compound, emodin; this compound inhibits the activity of SARS CoV by blocking the interaction of S protein of the coronavirus with ACE2 receptors present in the host cells[80]. *Curcuma longa* L. is traditionally used as medicine for the treatment of various infections, inflammations, and blood disorders. Curcumin isolated from *C. longa* exhibits antiviral activity against SARS-CoV[81–83]. In a docking study, using Auto dock 4.2, onto the 6CRV and 6M0J, Patel *et al.*[7] reported that curcumin and its derivatives displayed binding energies, ΔG, ranging from −10.98 to −5.12 kcal/mol (6CRV) and −10.01 to −5.33 kcal/mol (6M0J). Also, drug-likeness and efficient pharmacokinetic parameters suggested the potential of curcumin and its derivatives as spike protein inhibitors of SARS-CoV-2 that can hamper viral entry. Similarly, a docking study of alkaloids from African medicinal plants on spike glycoprotein of SARS-CoV and MERS-CoV, and with ACE2-SARS-CoV-2 receptor-binding domain complex (ACE2-RBD) revealed that cryptospirolepine, 10 hydroxyusambarensine, and cryptoquindoline displayed strong binding affinities, stability of the alkaloid-protein complexes and amino acid interactions with important binding hotspots of the proteins. Therefore, these alkaloids have the potential to alter the capacity of SARS-CoV-2 membrane-mediated host cell entry by altering the ACE2-TMPRSS2 pathway[84].

Pelargonium sidoides DC. (Fig. 1i), has been used as antiviral herbal medicine to cure respiratory ailments since ancient times. EPs 7630, a herbal drug preparation from *P. sidoides*, interferes with the replication process of viruses, including human coronavirus[85]. Phytoconstituents of *Alnus japonica* (Thunb.) Steud. show anti-influenza, anti-inflammatory and anti-cancer properties; diarylheptanoids (Fig. 1j), catechol (Fig. 1k) extracted from *A. japonica* showed inhibitory activities against PL(pro) of SARS-CoV[86]. *Citrus sinensis* has been used as herbal medicine since ancient times. It contains a high number of flavonoids, linalool[87] (Fig. 1l), which have been reported to have anti-viral properties against HIV and Rabies virus[69]. Hafidh *et al.*[72] documented that Mung Bean sprouts extract has vitexin (Fig. 1m) and isovitexin (Fig. 1n) possess anti-viral and prophylactic activity against the Herpes Simplex Virus-1 and Respiratory Syncytial Virus. Kaempferol (Fig. 1o) a flavonoid present in *Phaseolus vulgaris* L. inhibits the 3CL protease of SARS CoV[88] and shows antiviral activity against RSV, HIV[69]. A variety of spices used in Indian kitchens possesses antiviral activities. Essential oils present in garlic *Allium sativum* L. show anti-viral activity by inhibiting proteases and interacting with the host receptor ACE 2[89]. Another Indian spice *Syzygium aromaticum* (L.) Merr. & L. M. Perry contains oleanolic acid (Fig. 1p) and shows antiviral activity by inhibiting SARS CoV protease[16]. Similarly, *Coptis chinensis* Franch. and *Phellodendron amurense* Rupr. contain Berberine, a natural isoquinoline alkaloid[90]. Berberine has anti-inflammatory and antiviral pharmacological activities[66,90]. It is a novel antiviral drug and therapeutic candidate that targets different phases of the viral life cycle and inhibits the replication of human cyto megalo virus (HCMV), herpes simplex virus (HSV), human papilloma virus (HPV), human immunodeficiency virus (HIV)[91].

Emodin (Fig. 1q) is an anthraquinone compound extracted from *Rheum officinale* Baill. (Dahuang), and has been demonstrated to possess anti-inflammatory, antioxidant, immunosuppressive, anti-tumour and antiviral activities[92]. Emodin is an ion channel inhibitor of SNE-encoded accessory 3a protein[93]. Also, studies have shown that emodin not only destroys the viral envelope during viral release but also leads to a decrease in RNA[80]. *Panax notoginseng* (Bur kill) F.H. Chen root, *Anemarrhena asphodeloides* Bunge rhizome, *Bupleurum chinense* DC. root (Chaihu) possess Saponins (Fig. 1r) which have a wide range of pharmacological effects and are the effective components of many traditional Chinese medicine. Saponins obtained from roots of *Panax ginseng* C.A. Mey. and *Glycyrrhiza uralensis* Fisch. ex-DC. have been used in Chinese traditional medicine against viruses[96,97].

Essential oils are an important potential therapeutic agent for the treatment of various viral infections, including SARS-CoV-2[54]. The essential oil of ginger (*Zingiber officinale* Roscoe) showed an inhibitory effect on HSV-2[98]. Similarly, the essential oil derived from the aerial portion of *Mentha canadensis* L. showed inhibitory effects on herpes simplex virus; its active principle is piperitenone oxide[99]. Extracts of *Dryopteris crassirhizoma* Nakai and *Morus alba* L. contain various flavonoids, which were reported most effective in the late stage of virus replication, while the extracts of *M. alba* were effective in the early stage of virus replication; its higher doses even have prophylactic activity[100]. The flowers of *Tussilago farfara* L. are used to treat cough, sputum, bronchitis and asthma[101]. *T. farfara* also has antioxidant, anti-inflammatory, neuroprotective activities, and antiviral activity[102] (Table 1).

Plant-based immune boosters

A strong immune system plays an important role in combating viral infections, including SARS-COV-2. People with a weak immune system are reported to be more vulnerable to COVID-19 virus infection. Once the virus enters the host body, both innate and adaptive immune responses get activated to provide defence against them. The innate immune cells recognize the virus through the interaction of pathogen recognition receptors like Toll-like receptors 3, 7, and 8, which leads to the secretion of interferon molecules[103]. Processing and presentation of viral antigens by the MHC class-II molecule to T_H-cells initiates cell-mediated immune response[103]. The humoral response of the adaptive immune system produces antibodies against SARS-CoV-2; antibodies against the S protein can be detected after 4-8 days of illness onset[104].

The host's immune response initiates upon viral entry and cell infection; this triggers the inflammatory response by antigen-presenting cells (APC). The APC performs two functions: (1) presenting the foreign antigen to $CD4^+$-T-helper (Th1) cells and (2) releasing interleukin-12 to further stimulate the Th1 cell. The Th1 cells stimulate $CD8^+$ T-killer (TK) cells to target any cell containing the foreign antigen. Also, activated Th1 cells stimulate B-cells to produce antigen-specific antibodies[105]. In the case of n-COV, the infections are caused by the herpes simplex virus, and when used with valacyclovir they decrease the chances of drug resistance and affect the interaction between the virus and host receptor proteins[106]. Many of the herbs, such as *Glycyrrhiza glabra* L. and *Tinospora cordifolia* (Willd.) Hook.f. & Thomson, *Uncaria tomentosa* (Willd. ex Schult.) DC.[107–109], and natural compounds including epigallocatechin gallate, Liquirtin (Fig. 2a) epicatechin gallate, gallocatechin-3-gallate, glycyrrhizin (Fig. 2b), bicyclogermacrene, tryptanthrin (Fig. 2c), β-sitosterol, indirubin, indican, indigo, hesperetin, chrysophanic acid, rhein, berberine, and β-caryophyllene have inhibitory

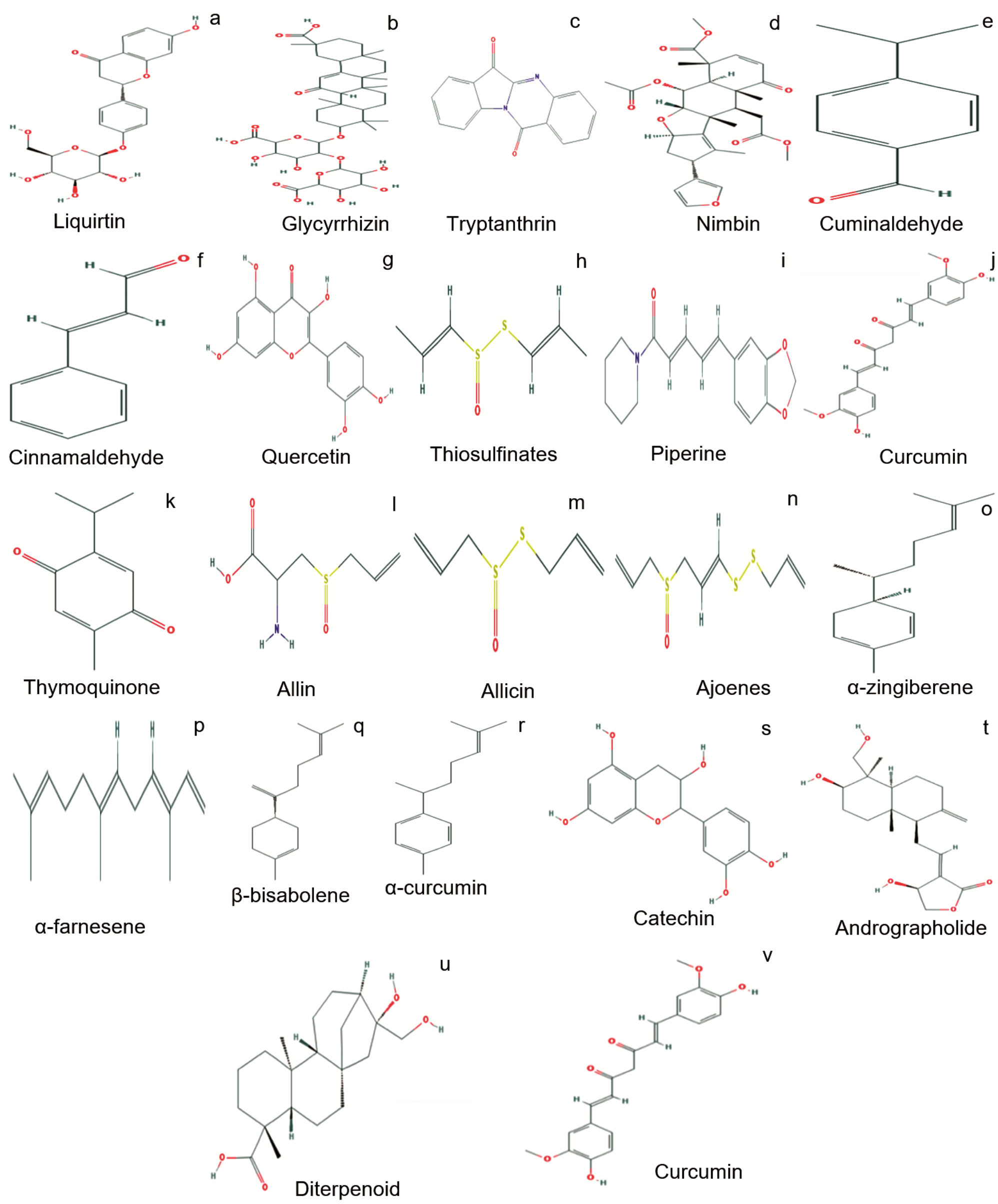

Fig. 2 — Phytoconstituents of plants showing immune-booster activities.

activity against MPro[110,111]. Antibodies are produced and secreted against spike protein (S protein); these antibodies resist the virus interaction with its host receptor ACE2 or destroy the infected cells by antibody-dependent cell toxicity (ADCC) mechanism[112]. Juno *et al.*[113] reported that B-cell generated an antibody CD19$^+$IgD- against spike and receptor-binding domain (RBD) proteins.

Many medicinal plants have been reported to enhance immunity against a variety of pathogens. These plants are widely used in traditional medicine systems as immune boosters to reduce the chances of infection[114,115]. There are reports where herbal medicines or plant products induce the production of interferon (IFN) and interleukin-12 (IL-2); these two cytokines are crucial against viral infection. If IFN binds to its receptor on the host cell membrane, it activates the genes that encode antiviral protein production. In addition to this, many plant products can induce Th1 cellular immunity to exert non-specific antiviral effects. In India, the Ministry of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy) recommended the use of KADHA an herbal tea that helps to strengthen the immunity against COVID-19. The kadha is a concoction of *Ocimum tenuiflorum* L., *Cinnamomum verum* J.Presl, *Piper nigrum* L., *Zingiber officinale* Roscoe, and *Vitis vinifera* L.[115]. Sang Ju Yin and Yu Ping Feng San are the two traditional Chinese herbal medicines found to improve the host defence system[116] (Table 2).

Plants have a variety of phytoconstituents that have immunomodulatory effects. *Moringa oleifera* Lam., commonly called drumstick, is used in Indian curries and is a rich source of vitamin C and vitamin A. It strengthens immunity and has anti-inflammatory properties[117]. *Phyllanthus emblica* L., Indian gooseberry, has high contents of vitamin C that contribute to enhancing host immunity. Its fruits contain polyphenols, tannins, minerals, vitamins, amino acids, and flavonoids. Gallic acid and ellagic acid are the main polyphenols, and rutin and quercetin are the main flavonoids[118]. Nimbin (Fig. 2d) in *Azadirachta indica* A. Juss. (Margosa) has been reported to possess immunomodulatory activities[119] and be involved in lymphocytic and cell-mediated immune system responses[120]. Cuminaldehyde (Fig. 2e) and cinnamaldehyde (Fig. 2f) from *Cinnamomum verum* J. Presl (Cinnamon), in general, acts as an immune stimulator and protects against viral infections. It has immunomodulatory and antioxidant properties. Cinnamon is also a rich source of manganese, calcium, and iron that act as a powerful agent in immune system strengthening[121]. *Allium cepa* L., (onion) is a powerful agent for boosting immunity. It is a rich source of vitamin C, sulfur, zinc, selenium, and, most importantly, quercetin (Fig. 2g), which play an important role in immune system strengthening. Thiosulfinates (Fig. 2h) possesses antiviral properties[122]. *Piper nigrum* L. (Black pepper) is a widely used spice worldwide; its main phytoconstituentis piperine (Fig. 2i) possesses antiviral, anti-bacterial, anti-inflammatory, antipyretic, anti-oxidative, antitumor, and immune booster properties[123]. *O. sanctum* L., the holy basil, has antiviral, anti-inflammatory, immune system booster, antibacterial, antiseptic, and anti-carcinogenic properties[124]. In a study, it was found that ethanol extracts of *O. sanctum* leaves showed a robust immunomodulatory activity on the host immune system[125]; it modulates humoral response by acting on antibody production and release of mediators of hypersensitivity reactions[126]. *Curcuma longa* L., commonly called turmeric, is a pungent Asian spice, and it is used all over the world[117]. It has anti-inflammatory, antimicrobial, and antiviral activity[31]. It also acts as an immunomodulatory agent. Turmeric powder in hot milk (golden milk) helps in enhancing immunity[115]. Curcumin (Fig. 2j) is a diarylheptanoid, belonging to the group of curcuminoids, which are natural phenols responsible for turmeric's yellow colour. It is the most important compound of turmeric and inhibits the replication of some viruses like Dengue virus, hepatitis B, and Zika virus[127]. *Echinacea angustifolia* DC. is used in various herbal preparations to improve immune functioning[128]. It contains phytochemicals like betain, sesquiterpenes, caryophylene, polyacetylene, rosmarinic acid, glycosides, echinacoside, chicoricacid, alkyl amides, arabinogalactan-proteins[129,130]. In a study, it has been found that alkyl amides have immunomodulatory activity[131,132]. Arabinogalactan-protein and other phytochemicals present in this plant were reported as stimulators of both the classical and alternative pathways of the complement system. *E. angustifolia* also activates natural killer cells, which are antiviral in nature[133]. *Withania somnifera* (L.) Dunal, Indian Ginseng has immunomodulatory and anti-inflammatory

Table 2 — Plants possessing immune-booster activity and their active components

S. No.	Name of the Plant	Common Name	Family	Country of origin	Activities of plant extracts	Active components	Molecular formula	Reference
1	*Allium cepa* L.	Onion	Amaryllidaceae	India, Egypt, USA, China	Antidiabetic, Antimicrobial, Antioxidant Antiproliferative	Phenolic acids Thiosulfinates, flavonoids Essential oils	 $C_6H_{10}OS_2$	121
2	*Allium sativum* L.	Garlic	Amaryllidaceae	Central Asia, Northeastern Iran	Immunomodulatory, AntimutgenicAntitumour, Antimicrobial, Antifungal, Anti-aging, Anti-cancer	Alliin Allicin Ajoenes sulfides Vinyldithins	$C_6H_{11}NO_3S$ $C_6H_{10}OS_2$ $C_9H_{14}OS_3$	152
3	*Andrographis paniculata* (Burm.f.) Nees	Green chiretta	Acanthaceae	India, Sri Lanka	Immune stimulant, Anti-inflammatory, Antiviral	Andrographolide	$C_{20}H_{30}O_5$	143,169
4	*Astragalus mongholicus* Bunge	Astragalus	Leguminosae	Asia, Europe, North America	Immune regulatory, Anti-inflammatory, Anti-oxidation, Anti-diabetes	Astragalus polysaccharide		200
5	*Azadirachta indica* A. Juss.	Neem	Meliaceae	Indian subcontinent	Antifungal, Antibacterial	Polyphenol flavonoid, quercetin Nimbin	 $C_{15}H_{10}O_7$ $C_{30}H_{36}O_9$	201
6	*Camellia sinensis* (L.) Kuntze	Green Tea	Theaceae	China, India	Antioxidant, Anti-inflammatory	Catechin	$C_{15}H_{14}O_6$	159,160
7	*Cinnamomum verum* J.Presl	Cinnamon	Lauraceae	Sri Lanka, Southern India	Antioxidant, Antimicrobial, Anti-inflammatory, Anticancer, Antidiabetic, wound healing,	Phenolics Essential oil Cuminaldehyde Cinnamaldehyde	 $C_{10}H_{12}O$ C_9H_8O	121
8	*Curcuma longa* L.	Turmeric	Zingiberaceae	Indian subcontinent, Southeast Asia	Antimicrobial, Anti-inflammatory, Antiviral	Curcumin	$C_{21}H_{20}O_6$	127
9	*Echinacea angustifolia* DC.	Purple coneflower	Asteraceae	Eastern and Central North America	Antidepression, Antianxiety, Antimutagenicity, Antiviral, Antioxidant,	Beta sesquiterpenes Glycosides polyacetylene		129
10	*Glycyrrhiza glabra* L.	Licorice	Fabaceae	Western Asia, Southern Europe	Immuno stimulator, Antispasmodic, Anti-inflammatory, Antioxidant, Antibacterial	Liquirtin, Glycyrrhizin Isoflavonoids	$C_{21}H_{22}O_9$ $C_{42}H_{62}O_{16}$	128
11	*Moringa oleifera* Lam.	Drumstick	Moringaceae	India, Asia Minor, Africa, Arabia	Antiviral, Anti-inflammatory, Anti-pyretic, Anti-fungal, Anti-spasmodic	Alkaloids Thiocarbamates Pterygospermin carbamate		117

(*contd.*)

Table 2 — Plants possessing immune-booster activity and their active components (*contd.*)

S. No.	Name of the Plant	Common Name	Family	Country of origin	Activities of plant extracts	Active components	Molecular formula	Reference
12	*Nigella sativa* L.	Black cumin	Ranunculaceae	Southern Europe, North Africa, India, Pakistan, Saudi Arabia	Antihypertensive, Antidiarrheal, Antibacterial, Anti-inflammatory, Analgesic	Thymoquinone Melanin	$C_{10}H_{12}O_2$	140,141,202
13	*Ocimum sanctum* L.	Tulsi	Lamiaceae	India, Southeast Asia	Antiviral, Antibacterial, Anti carcinogenic, Anti-inflammatory	Eugenol Urosolic avid Carvacol Saponins	$C_{10}H_{12}O_2$ $C_{30}H_{48}O_3$ $C_{10}H_{14}O$ $C_{58}H_{94}O_{27}$	124,203
14	*Piper nigrum* L.	Black Pepper	Piperaceae	Brazil, Indonesia, and India	Antioxidant, Antitumor, Immunomodulatory, Antispasmodic, Anti-inflammatory	Piperine Piper amine	$C_{17}H_{19}NO_3$ $C_{16}H_{19}NO_3$	123
15	*Phyllanthus emblica* L.	Amla or Indian gooseberry	Phyllanthaceae	India, Sri Lanka, Southeast Asia	Anti-inflammatory, Antioxidant, Antiaging, Antidiabetic	Polyphenol Flavone Glycosides Quercetin Tannins	 $C_{15}H_{10}O_7$	118
16	*Sambucus nigra* L.	Purple berry/ Elderberry	Adoxaceae	Europe, North America	Immunostimulatory, Antioxidant, Anti-inflammatory	Polyphenols anthocyanins		163
17	*Tinospora cordifolia* (Willd.) Hook. f. & Thomson	Giloy	Menispermaceae	India	Immunomodulatory, Antidiabetic, Antispasmodic, Anti-inflammatory	Alkaloids Diterpenoid Lactones Glycosides Steroids	 $C_{20}H_{32}O_4$	204
18	*Withania somnifera* (L.) Dunal	Ashwagandha	Solanaceae	India	Immunomodulatory, Anti-inflammatory, Antioxidant	Alkaloids Withanolides Saponins	 $C_{58}H_{94}O_{27}$	134
19	*Zingiber officinale* Roscoe	Zinger	Zingiberaceae	India, Sri Lanka, China	Immunoboosting, Anti-inflammatory, Antioxidant, Antimicrobial	α-zingiberene α-farnesene β-bisabolene α-curcumin	$C_{15}H_{24}$ $C_{15}H_{24}$ $C_{15}H_{24}$ $C_{15}H_{22}$	158,205

properties[134,135]. It helps in enhancing the responses of T Helper cells[136]. Ashwagandha also helps in the production of reactive nitrogen species in macrophage cells, which act as a potent antimicrobial agent and kill extracellular pathogens[137]. In a study, it was found that after consuming Ashwagandha, the level of $CD4^+$ T helper cells increased while the levels of $CD8^+$ T Helper cells and B cells decreased; also, a robust increase in the population of $CD56^+$ cells (Natural Killers) were observed[138]. Berberine, a natural compound, supports the host's immune response and helps in virus clearance. *Allium sativum* L. (Garlic), thymoquinone (Fig. 2k) in *Nigella sativa* L. (Black Cumin), and licorice (extract of the root of *Glycyrrhiza glabra*) are widely used in Chinese herbal treatment for enhancing immunity against COVID-19[139]. *N. sativa* is used in the form of decoction, possesses anti-inflammatory, immunomodulatory and antioxidant properties[140,141]; it is involved in improving T helper cell and Natural killer cell responses[139,142]. Roots of *Astragalus mongholicus* Bunge is another commonly used traditional Chinese herbal medicine[139]. It strengthens the immune system and acts as a powerful agent in regulating immune system functioning[143]. It also helps in enhancing the proliferation of human peripheral blood mononuclear cells (PBMC), activation of cytotoxic T-lymphocyte for tumour cell killing, increased phagocytosis of tumour cells, and the activation of cytokines such as TNF-alpha and IL-6[144]. Astragalus, a polysaccharide found in *A. mongholicus*, helps in inducing both humoral and cellular immune responses and in promoting lymphocyte proliferation[145]. *Glycyrrhiza glabra* L. has anti-inflammatory properties[146] and plays an important role in proper immune system functioning. It is involved in the production of IL-10 and a monocyte/macrophage-derived cytokine IL-12. It also helps in the development of T-helper type 1 (TH1) and cell-mediated immune responses[147]. Scientific evidence supports that *G. glabra* has immune-stimulating properties[128]. *A. sativum* has immunomodulatory antimicrobial, anti-inflammatory, and antimutagenic properties. It is involved in the proliferation of lymphocytes, macrophage phagocytosis, the release of IL-2, TNF-alpha, and IFN-γ and activation of natural killer cells[148,149]. Garlic helps in increasing the production of nitric oxide (NO). Alliin (Fig. 2l) Allicin (Fig. 2m), Ajoenes (Fig. 2n) present in the garlic[150] activates NK cells and macrophages[151]. It also contains micronutrients such as vitamins B1, B2, B3, B6, folate, magnesium, phosphorus, sodium, zinc, iron, manganese, and calcium[152]. It acts as a scavenger of free radicals and has the potential to regulate the activity of various antioxidant enzymes such as glutathione peroxides, glutathione S-transferase (GST), catalase, acid-soluble sulfhydryl (-SH) cytochrome B5 and cytochrome P450, and superoxide dismutase[153–156]. *Zingiber officinale* Roscoe, ginger has anti-inflammatory and immune-boosting properties[157]. The phytochemicals found in ginger include *α*-zingiberene (Fig. 2o), *α*-farnesene (Fig. 2p), *β*-bisabolene (Fig. 2q), *α-curcumin* (Fig. 2r), [6]-gingerol and [6]-shogaol, paradol, zingerones, and derivatives[158]. *Camellia sinensis* (L.) Kuntze**,** green tea, contains metabolites with antioxidant and anti-inflammatory properties[159]. Catechin (Fig. 2s) is an active compound of green tea[160], which includes epigallocatechin gallate (EGCG), involved in the production of cytokines[161]. Watson *et al.*[162] reported that EGCG plays an important role in recovery from enteric immune disorders and T cell-driven immune-pathologies. Fruits of purple berry, *Sambucus nigra* L. have antioxidant, anti-inflammatory, and immune-stimulating properties[163,164]. Several clinical studies reported its importance in fighting against respiratory infections[117,143,165,166]. Sambucol, a standardized formulation of black elderberry extract, is involved in the activation of the host immune system by increasing inflammatory cytokine production. The immune protective and immunostimulatory properties of Sambucol make it useful in the treatment of cancer or AIDS disease[167]. *Tinospora cordifolia* (Willd.) Hook.f. & Thomson, commonly called Giloy in India, has anti-inflammatory and immunomodulation properties and helps in the activation of macrophages[168]. Its fresh juice and decoction help in enhancing immunity against n-Cov infection[115]. *Andrographis paniculatais* Wall (Kalmegh) has immune stimulant activity[143]. Andrographolide (Fig. 2t), a diterpenoid (Fig. 2u), is an active compound extracted from its leaves and stem; it possesses anti-inflammatory and antiviral properties against a variety of viruses[169] (Table 2).

Micronutrients present in our daily food play a vital role in immune boosting[107]. An adequate number of various micronutrients in the diet are thus important in the COVID-19 pandemic situation[170,171]. It has also been found in clinical studies that micronutrients have antiviral effects against coronavirus[172]. Antioxidant properties have been reported in vitamins like vitamin C vitamin E and β- carotene. These are responsible for enhancing the immune response against the influenza virus by increasing the lymphocyte population[173].

Vitamin A helps in the proper functioning of the immune system and reduces the risk of infections. It is involved in the maturation of immune cells such as dendritic cells and $CD4^+$ T lymphocytes. Retinoic acid, the active metabolite of vitamin A promotes T lymphocyte movements in gut-associated lymphoid tissue (GALT) and is involved in the proliferation of $CD8^+$ T lymphocytes[174]. Further, vitamin A helps in the activation of natural killer cells that have antiviral roles. Isotretinoin, a derivative of vitamin A inhibits angiotensin-converting enzyme 2 (ACE2) which guides the entry of SARS-COV-2 into the host cells[108]. In a study, it was found that morbidity and mortality due to pneumonia in COVID patients were decreased by vitamin A intake[175].

Vitamin C is another micronutrient involved in boosting immunity in people of all ages. It possesses antioxidant properties and protects the immune cells from pro-oxidants and lung epithelial cells from antioxidants[176]. Vitamin C helps in the repair of all the body tissues[177]. The movement of leucocytes to the infection site is also increased by vitamin C[177]. It enhances the activity of natural killer cells[178] and suppresses the risk of infection in the lower respiratory tract[179].

Vitamin D is obtained in two different forms: vitamin D_3 (cholecalciferol), synthesized in the skin by exposure to UVB radiation, and vitamin D_2 (ergocalciferol), present in various plant materials, yeast, and fungi. Both forms get hydroxylated to 1,25-dihydroxy vitamin D, which enhances the expression of antimicrobial peptides, like human cathelicidin, LL-37, and defensins[180]. It also improves cellular immunity, suppresses the inflammation process, and activates T regulatory cells[139]. After COVID-19 infection, the innate immune system develops both anti-inflammatory and pro-inflammatory cytokines. Vitamin D decreases the development of pro-inflammatory Th1 cytokines[181] and increases the production of anti-inflammatory cytokines by macrophages[139]. Reduction in the level of Vitamin D increases the chances of influenza[182], chronic obstructive pulmonary disease[183], and allergic asthma[184].

Vitamin B-Complex has an important role in regulating the intestinal immune system. Folic acid enhances the population of circulating T lymphocytes. Vitamin B_{12} enhances the activity of neutrophils. Vitamin B_6 increases the population of T lymphocytes in the blood. Folic acid, Vitamin B_6, and B_{12} are also involved in the enhancement of the activity of natural killer cells[185,186].

Vitamin E acts as both an antioxidant and a scavenger of free radicals. Its insufficiency can hamper the various processes of the immune system such as phagocytosis, chemotaxis, and interleukin-2 production[187]. It also helps in enhancing the activities of T-helper lymphocytes[188]. Studies have shown that respiratory tract infections can be reduced by Vitamin E supplements[189].

Various minerals present in the diet improve the functioning of the immune system. Magnesium helps in strengthening immune cells such as natural killer cells and lymphocytes[190]. Zinc has been shown to have antiviral effects against nCov[191]. It enhances the response of both IgM and IgG antibodies. Zinc is also involved in decreasing the effect of pneumonia[192,193]. Selenium present in nuts plays an important role in both innate and adaptive immunity; it increases the activity of immune cells like T lymphocytes, B lymphocytes, and natural killer cells[194,195]. Studies have shown that copper enhances the response of immune cells like monocytes, natural killer cells, and neutrophils[196,197]. It also helps in the proliferation of lymphocytes[198]. Mao *et al.*[199] reported that copper supplementation can reduce the risk of respiratory tract infection.

Nanotechnology-based approach to managing covid-19

Nano-formulations of phytochemicals and plant-based materials have wide potential in the prevention, diagnosis, and treatment of viral diseases[206]. For nanoparticle synthesis, plant extracts are widely used as an alternative to reducing agents to reduce metal ions to the corresponding metal nanoparticles. Secondary metabolites act as reducing and stabilizing agents for nanoparticle synthesis. Plant-based nanoparticles are less expensive, eco-friendly, and less hazardous to the environment, and hence, can be used to combat viral infections, including SARS-COV-2[203,207]. Plant-based nanomaterials have the potential to deliver drugs to the pulmonary system and inhibit the interaction between angiotensin-converting enzyme 2 (ACE2) receptors and viral S protein. Moreover, nano-formulations can help design materials for immune modulation, either stimulating or suppressing the immune response, and can be applied for vaccine development for SARS-CoV-2 or to counteract the cytokine storm[208–211].

Some natural compounds possess antiviral potential and can be coupled with nanoparticles for synergistic therapeutic effects. In one study, the antiviral potency of hypericin (HY), an anthrone derivative obtained from *Hypericum perforatum* L. when loaded with graphene oxide (GO) exerted antiviral effects against a wide range of viruses. The low cytotoxicity and high loading capacity of GO helped to improve the antiviral efficacy of hypericin. The GO/HY complex inhibited viral replication, which was attributed to either suppression of viral attachment to the host cell or due to the inactivation of the virus itself[212]. The green synthesized silver nanoparticles *Lampranthus coccineus* (Haw.) N.E.Br. and *Malephora lutea* F. showed remarkable antiviral activity against HSV-1, HAV-10, and CoxB4 virus. The metabolomics profiling of the methanolic extract of *L. coccineus* and *M. lutea* revealed 12 compounds of biological significance, and the docking study predicted the patterns of interactions of these compounds with herpes simplex thymidine kinase, hepatitis A 3c proteinase, and Coxsackie virus B4 3c protease[213]. Silver nanoparticles (AgNPs) of *Andrographis paniculata* Wall, *Phyllanthus amarus* Schumach. & Thonn. And *Tinospora cordifolia* (Willd.) Hook.f. & Thomson showed antiviral properties against the chikungunya virus. Based on cytotoxicity assays, the degree of inhibition of cytopathic effects and an antiviral assay of AgNPs, *A. paniculata* was found to be most effective, followed by *T. cordifolia* and *P. niruri*[214].

Curcumin (Fig. 2v), a major component of *Curcuma longa* L., holds broad-spectrum antiviral properties and exerts its antiviral actions by various mechanisms. However, the poor solubility of curcumin in water-based solvents limits its application in the clinical system. Yang *et al.*[215] improved the solubility and biocompatibility of curcumin by loading it into GO nanoparticles (GSCC). After functionalization with sulfonate groups, the curcumin-loaded graphene oxide mimics a cell surface and inhibits viral anchoring by a competitive inhibition mechanism. Moreover, the GSCC exhibited antiviral activity, both pre-and post-viral infection of the host cell[215]. In a study, the carbon quantum dots created from curcumin possess greater antiviral properties and water solubility, when compared with natural curcumin. These carbon dots were very effective in preventing viral binding to the cell surface[216]. In a similar study, Ting *et al.*[217] reported that curcumin-based cationic carbon dots act as a multi-site viral inhibitor. This study involved the porcine epidemic diarrhoea virus, a member of the coronavirus family. The curcumin carbon dots altered the structure of the viral surface protein and hence inhibited the viral entry into the host cell. In addition to this, the carbon dots also blocked the formation of negative-strand RNA of virus and viral budding as well. Moreover, the carbon dots stimulate the production of pro-inflammatory cytokines and interferon-stimulating genes (ISGs) to prevent viral replication. A similar study also reported that curcumin-modified silver nanoparticles were very effective against viral infections[218].

Conclusion and future prospects

COVID-19 is caused by SARS-CoV-2 and primarily affects the respiratory system. Various vaccines have been developed, but natural plant products and traditional medicines also show promise in inhibiting viral proliferation and enhancing immune response. In conclusion, various plants and their phytochemical constituents have been found to possess antiviral and immunomodulatory properties. Compounds such as myricetin, tryptanthrin, scutellarein, emodin, curcumin, and berberine from different plants have been reported to exhibit antiviral activities against various viruses, including SARS-CoV-2. In addition, essential oils from plants like ginger and mentha, as well as extracts from Mung Bean sprouts, also show antiviral effects. Furthermore, plant-based immune boosters such as Ashwagandha, Echinacea, Astragalus, and Glycyrrhiza have been found to enhance the host's immune response against viral infections, including SARS-CoV-2. The consumption of micronutrients, particularly vitamins A, C, and E, has also been found to play a significant role in boosting the immune system and has been associated with antiviral effects against coronaviruses. Overall, the use of medicinal plants, plant-derived compounds, and essential oils as well as the consumption of micronutrients from natural sources can potentially provide effective strategies for combating viral infections and enhancing the immune response against COVID-19. In addition, traditional Chinese medicines and other plant-derived compounds have shown promising results in inhibiting viral proliferation and enhancing immune response. This integrated approach, which includes awareness, community containment, and quarantine measures, along with the use of natural herbs and plant products, is crucial for the effective management of the global COVID-19 pandemic and future viral outbreaks. Further research and development of specific antiviral drugs and therapeutic herbal formulations are needed to combat the threat posed by SARS-CoV-2 and other emerging pathogens.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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