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REVIEW

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Combination of natural antivirals and potent immune invigorators: A natural remedy to combat COVID-19

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The flare-up in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that emerged in December 2019 in Wuhan, China, and spread expeditiously worldwide has become a health challenge globally. The rapid transmission, absence of anti-SARS-CoV-2 drugs, and inexistence of vaccine are further exacerbating the situation. Several drugs, including chloroquine, remdesivir, and favipiravir, are presently undergoing clinical investigation to further scrutinize their effectiveness and validity in the management of COVID-19. Natural products (NPs) in general, and plants constituents specifically, are unique sources for various effective and novel drugs. Immunostimulants, including vitamins, iron, zinc, chrysin, caffeic acid, and gallic acid, act as potent weapons against COVID-19 by reinvigorating the defensive mechanisms of the immune system. Immunity boosters prevent COVID-19 by stimulating the proliferation of T-cells, B-cells, and neutrophils, neutralizing the free radicals, inhibiting the immunosuppressive agents, and promoting cytokine production. Presently, antiviral therapy includes several lead compounds, such as baicalin, glycyrrhizin, theaflavin, and herbacetin, all of which seem to act against SARS-CoV-2 via particular targets, such as blocking virus entry, attachment to host cell receptor, inhibiting viral replication, and assembly and release.

KEYWORDS
antivirals, COVID-19, immunostimulants, phytochemicals, SARS-CoV-2

1 | INTRODUCTION

Even with the invested enormous scientific efforts, the emergence of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains a paramount concern for human health (Wu, Zhao, et al., 2020). The continuing flare-up of the novel pandemic COVID-19 caused by SARS-CoV-2 has become the leading health issue worldwide (Li et al., 2020). Several research institutes are making efforts to develop vaccines to quell and manage the COVID-19, but there is no vaccine available so far. Now, the vaccine is under trial in different countries, and there is not any particular efficacious antiviral therapy for COVID-19 (Kwok et al., 2021; Nusbaum, 2020; Zhou et al., 2020).

Natural components may also afford protection against COVID-19. They are generally readily available and safer than synthetic agents (Islam et al., 2020). To date, 30 such compounds have been identified (Dong, Hu, et al., 2020).

The therapeutic effects of plants have been long recognized (Sarfraz et al., 2020; Thomford et al., 2018). Many diseases have been treated with medicinal plants due to their phytochemical diversity (Thomford et al., 2018), and natural products (NPs) are commonly used to promote health care and prevent diseases (Chen et al., 2018). Since the discovery of the first antibiotic, more than 23,000 NPs have been identified (Nawaz et al., 2020). According to WHO, 80% of the human population rely on medicinal plants for maintaining a healthy lifestyle (Sarfraz et al., 2020). NPs serve as an incomparable source of unparalleled and distinctive compounds that can prevent inflammation and fight against cancer (Chahyadi et al., 2014; Wei, Rasul, et al., 2019). In addition to these activities, NPs have the ability to boost the immune system, protecting against infectious diseases (Amor et al., 2007; Sarfraz et al., 2020).

The most important strategy to prevent and control SARS-CoV-2 is to boost the immune system. During the incubation stage, it is necessary to eradicate the virus and prevent its replication, by mounting an efficient immune response.

Nutraceuticals have the ability to boost and restore both innate and adaptive immune responses (Ibrahim & El-Sayed, 2016). The competence of the immune system depends upon the nutritional status, and the deficiency of micronutrients can lead to the impairment of the immune system (Alpert, 2017). It has been shown that the immune system functions optimally when micronutrients such as vitamins and minerals for their synergistic roles in supporting the immune system are at adequate levels (Gombart et al., 2020). Micronutrients strengthen the immune system as they enhance the skin epithelium barrier, boost antibody synthesis, stimulate cell-mediated immune response, regulate inflammation, and maintain antioxidant/oxidant balance in the body (Alpert, 2017; Farhan Aslam et al., 2017; Gombart et al., 2020).

In spite of the progression in the field of immunomodulation and vaccination, there is still a lack of preventive measures and antiviral medicaments for several infections (Lin et al., 2014). Thus, antiviral agents obtained from natural origin may play an essential role in preventing infection or killing the virus (Lateef Mousa, 2015; Wang et al., 2012). An ideal antiviral should inhibit the replication of the virus (Lalani & Poh, 2020) and targeting membranes by which virus enters into the host cell (Lalani & Poh, 2020; Vázquez-Calvo et al., 2017). It is obviously known that the western drugs have lofty importance than natural antivirals that possess both immune-boosting and antiviral properties having a significant role in the cure and elimination of disease (Moghbelli et al., 2020). NPs acquiring antiviral properties remain a leading source that could provide dominant and safest therapies for the future progress in the treatment of fatal diseases (El Sayed, 2000).

The aim of this review is to discuss NPs as antivirals and potent invigorators of the immune system because of their phenomenal biological and pharmacological activities. The outcomes of different NPs discussed herein should pave the way for further research on them regarding the prevention and treatment of COVID-19.

2 | THERAPEUTIC STRATEGIES AGAINST COVID-19

Vitamins, minerals, and trace elements are required for the optimal functioning of the immune system (Alpert, 2017). Nutraceuticals boost immunity and promote the proliferation of T-cells and B-cells. T-cells protect the body from pathogens, and B-cells produce antibody-producing plasma cells. Nutraceuticals stimulate macrophages and neutrophils, which are involved in the phagocytosis of microbes (Gombart et al., 2020). One of the major steps against any viral disease is to prevent the immunosuppressive activities within the body. One of the immunosuppressive agents is PGE_2, which is blocked by vitamin E (Lee & Han, 2018). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) at high concentrations can inactivate cellular molecules (Farhan Aslam et al., 2017). Along with nutraceuticals, phytochemicals are also used for their immunostimulant activity (Boothapandi & Ramanibai, 2019). Different phytochemicals also regulate the assembly and release of various cytokines, including IL-12p70, TNF, INF-γ, MCP-1, and IL-6, which are very requisite for the activation of different immune cells (Reyes et al., 2018). The cytokines not only boost immunity but also act as potent weapons against viruses, such as interferon (INF), and various phytochemicals utilize this strategy to combat COVID-19 (Laguno et al., 2008).

The first and the most important strategy against viral infections is to block the host receptor, inhibiting the fusion mechanism of viruses with host cell membranes (Du et al., 2009; Sieczkarski & Whittaker, 2002). The main strategy of antivirals is the inhibition of viral enzymes such as PLpro, 3CLpro, and RdRp, leading to the inhibition of viral replication (Wu, Liu, et al., 2020). Another strategy is the inhibition of viral gene expression, which includes translation and transcription of viral RNA (Chen, Liu, & et al., 2020). Strategies targeting host factors, such as the inhibition of virus–host interactions, and altering the pH of endosomes also play a central role in combating COVID-19 (Abramo et al., 2012).

3 | IMMUNOSTIMULATION BY NATURAL PRODUCTS

The immune system is a complex web of cells, tissues, and organs that provides resistance to infection and toxins. It has been recognized that vitamins, minerals, and other phytonutrients are key players in stimulating the immune system (Alpert, 2017; Ibrahim & El-Sayed, 2016). COVID-19 has a higher degree of occurrence in older men who are immunocompromised (Author & Society, n.d.).

NPs having immunostimulatory activity are exclusively used for a wide range of afflictions (Mohamed et al., 2017). Compounds derived from plants, such as glycosides, alkaloids, β-glucan, vitamins, sterols, essential oils, and flavonoids, and part of our diets such as fruit, vegetables, and grains are NPs (Chakraborty & Hancz, 2011). Figure 2 summarizes natural immunostimulators that may help to combat COVID-19.

immunostimulant nutraceuticals.

The fat-soluble vitamin, retinol, plays a remarkable role in invigorating the immune system including both innate and adaptive immune responses (Alpert, 2017). It has been found that vitamin A also has antiviral effects (Elenius et al., 2017). One of the most notable functions of vitamin A is that it assists in regulating IL-2 and TNF-α production, which then further promotes microbe killing and respiratory burst stimulation by macrophage activation (Gombart et al., 2020) (Table 1). Vitamin A also increases the concentration of antibodies (Alpert, 2017) and is associated with the increased level of IFN-γ, which ultimately provides protection against viral afflictions by increasing the number of natural killer (NK) cells (Elenius et al., 2017; Maggini et al., 2007). Its natural sources include *Spinacia oleracea* (spinach), *Brassica oleracea* (broccoli), *Prunus armeniaca* (apricot), *Daucus carota* (carrot), *Ipomoea batatas* (sweet potato), and *Pistacia vera* (pistachio) (Farhan Aslam et al., 2017).

Pyridoxine or vitamin B_6 is a water-soluble vitamin that plays a significant role in maintaining the optimal levels of homocysteine in blood (Farhan Aslam et al., 2017). Vitamin B_6 is utilized for the synthesis of serotonin and is also crucial for the absorption of vitamin B_{12}. In addition, it has a vital role in stimulating the immune system (Farhan Aslam et al., 2017), by regulating inflammation, lymphocyte multiplication, and differentiation (Gombart et al., 2020). Vitamin B_6 also increases the antibody titer (Farhan Aslam et al., 2017), modulates NK cell function, and Th1-mediated immune response (Wintergerst et al., 2007) (Table 1). It is present in *Thunnini* (tuna), *Salmo salar* (salmon), *Allium cepa* (onions), *Oryza sativa* (rice), *Cicer arietinum* (chickpea), beef liver, and cereals (Farhan Aslam et al., 2017).

Folic acid or vitamin B_9 plays an influential role in the human body in the form of tetrahydrofolate for the synthesis of proteins and nucleic acids (Alpert, 2017). Deficiency in folic acid disrupts metabolic reactions and consequentially affects both innate and adaptive

TABLE 1 Nutraceutical immunity revitalizers, their sources, and their polypharmacological mechanisms

Copper	*Theobroma cacao* *Sesamum indicum* *C. arietinum*	Enhances the level of IL-12p40. Promotes phagocytosis and killing by activating the immune cells.	(Richter et al., 2019)
Iron	*P. lunatus* *S. tuberosum* *P. sativum*	Causes the production of toxic radicals by macrophages. Stimulates the activation of lymphocytes, NK cells, and monocytes.	(Theurl et al., 2005; Weiss, 2002)
Magnesium	*Scomber scombrus* *A. esculentus* *Ocimum basilicum*	Protection against oxidative damage.Role in antibody synthesis.Adhesion of immune cells. Leukocyte activation.	(Gombart et al., 2020; Malavolta, 2018)
Selenium	*Mytilus edulis* *A. sativum* *Bertholletia excelsa*	Maintains antibody levels.Protection against oxidative stress via GPx.Promotes T-cell proliferation.Production of IFN-γ.	(Gombart et al., 2020; Ibrahim & El-Sayed, 2016)
Vitamin-A	*Gadus morhua* *D. carota* *B. oleracea*	Promotes the respiratory burst of macrophages. Improves the number and function of NK cells. Improves antibody concentration	(Alpert, 2017; Gombart et al., 2020)
Vitamin-C	*Foeniculum vulgare* *C. sinensis* *Citrus limon*	Chemotactic factor for neutrophils.Promotes antibody production.Potent antioxidant.T-cell escalation.	(Vitamin C and the immune system | SpringerLink, n.d.)
Vitamin-D	*Oncorhynchus gorbuscha* *Scomber scombrus*	Activates macrophages and dendritic cells.Regulates antimicrobial protein expression.Enhances respiratory burst of macrophages.	(Farhan Aslam et al., 2017; Gombart et al., 2020)
Vitamin-E	*P. dulcis* *H. annus* *A. hypogaea*	Promotes T-cell multiplication.Boosts antibody response.Inhibits PGE_2.	(Ibrahim & El-Sayed, 2016; Lee & Han, 2018)
Vitamin-B_6	*Thunnini* *Sus* *S. salar*	Intensifies NK cell activity.Promotes the formation of cytokines.Sustains TH1 response.Causes antibody production.	(Farhan Aslam et al., 2017; Gombart et al., 2020)
Vitamin-B_9	*L. sativa* *Beta vulgaris* *Persea americana*	Acts as antioxidant.Regulates neutrophil function. Causes T-cell growth.	(Ibrahim & El-Sayed, 2016; Rosenthal et al., 2019)
Vitamin-B_{12}	*Oncorhynchus mykiss* *Lentinula edodes* *Brachyura*	Facilitates methylation reaction.Expedites T-cell proliferation.Increases NK cell activity.Promotes antibody production	(Morris et al., 2007; Rosenthal et al., 2019)
Zinc	*P. granatum* *M. acuminata* *Citrullus lanatus*	Reduces ROS and RNS.Promotes the production of IL-1, IL-6, IL-12, and TNF-α.Increases NK cells. Hampers the apoptosis of B-cells.	(Gombart et al., 2020; Maares & Haase, 2016)

Note: IL-12: Interleukin-12, NK cells: natural killer cells, TNF: tumor necrosis factor, CTL: cytotoxic T-lymphocytes, ROS: reactive oxygen species, DTH: delayed-type hypersensitivity, INF: interferon, MCP: monocyte chemoattractant protein, TH: T-helper cell, PGE_2: prostaglandin.

immune responses (Rosenthal et al., 2019). It is a potent antioxidant (Zehra & Khan, 2020), and it intensifies NK cell activity, crucial for Treg cell survival, and is important for the synthesis of antibodies (Gombart et al., 2020). It expedites T-cell escalation, and its deficiency is associated with reduced CD8+ T-cell generation (Rosenthal et al., 2019). The activity of neutrophils is also impaired due to the lack of vitamin B_9 (Ibrahim & El-Sayed, 2016). The dietary sources of vitamin B_9 are *S. oleracea* (spinach), *Persea americana* (avocado), *S. salar* (salmon), *O. sativa* (rice), *Arachis hypogaea* (peanuts), *Lactuca sativa* (lettuce), *Phaseolus vulgaris* (kidney beans), eggs, and shellfish (Farhan Aslam et al., 2017).

Vitamin B_{12}, also named as cobalamin, plays a major role in protection against bacterial and viral afflictions by reinforcing the immune response (Farhan Aslam et al., 2017). It promotes proliferation and multiplication of white blood cells (Alpert, 2017). It has significant immunomodulatory effects on the activity of cytotoxic T-lymphocytes and NK cells, and promotes the growth of T-cells (Gombart et al., 2020). Deficiency of vitamin B_{12} is associated with neutropenia and leukopenia (Ibrahim & El-Sayed, 2016) and alters the CD4+/CD8+ ratio and represses the activity of NK cells (Wintergerst et al., 2007). Microbes in the intestine utilize vitamin B_{12} for several metabolic reactions; thus, the gut barrier is also supported by vitamin B_{12} (Gombart et al., 2020). Natural sources of vitamin B_{12} include milk, eggs, cheese, trout, and cereals (Farhan Aslam et al., 2017).

Vitamin C, also known as ascorbic acid having astonishing antiviral and anticancer activity, also plays an astounding role in strengthening the immune system (Alpert, 2017). It affects iron transport, plays a crucial role in cellular proliferation and maturation, and assists the formation of carnitine and neurotransmitters such as serotonin and norepinephrine (Farhan Aslam et al., 2017). It not only provides protection against reactive oxygen species but also promotes the reclamation of other antioxidants such as vitamin E (Wintergerst et al., 2007). It protects against viral infections by promoting the conversion of CD4+ T cells into helper T cells, which produce high levels of IFN-γ, and also stimulates migration of neutrophils to the infection site (Vitamin C and the Immune System | SpringerLink, n.d.). It alters PG production, provides protection against histamine- and leukocyte-mediated immunosuppressive activities, stimulates chemokine production, and neutralizes treacherous free radicals (Ibrahim & El-Sayed, 2016). Recently, in China, treatment of patients with coronavirus disease with large doses of vitamin C has been posited to decrease the mortality rate (Adams et al., 2020; Carr, 2020). *Lycopersicon esculentum* (tomato), *Citrus sinensis* (orange) (Figure 2), *B. oleracea* (cabbage), *S. oleracea* (spinach), *Pisum sativum* (green pea), and *Cucumis melo* (cantaloupe) include NPs having vitamin C (Farhan Aslam et al., 2017).

Ergocalciferol and cholecalciferol, also named vitamin D_2 and vitamin D_3, respectively, are found chiefly in teeth and bony structures, help to maintain them (Farhan Aslam et al., 2017), and may play an important role in boosting the immune system against COVID-19. Calcitriol boosts innate immunity by enhancing the maturation of monocytes and causing the expansion of oxidative burst activity (Gombart et al., 2020) (Table 1). Calcitriol functions to stimulate the synthesis of proteins that have defensive action against certain microbes (Farhan Aslam et al., 2017) and therefore has a protective effect against pulmonary infections (Ibrahim & El-Sayed, 2016). Calcitriol also influences antibody and cytokine generation (Ibrahim & El-Sayed, 2016). Vitamin D_3 is naturally produced by the human body in the presence of ultraviolet radiations, whereas vitamin D_2 is synthesized by plants (Farhan Aslam et al., 2017). Deficiency of vitamin D is associated with respiratory tract infections and to ARDS. As COVID-19 has a link to SARS, vitamin D may play a role in providing resistance to coronavirus (Adams et al., 2020). Natural sources of vitamin D include *Thunnini* (tuna), *C. sinensis* (orange), *S. salar* (salmon), milk, yogurt, egg, cheese, and cod liver oil (Farhan Aslam et al., 2017).

Vitamin E, a cumulative term for four tocotrienols and four tocopherols, is well known for its exceptional antioxidant activity and signal transduction modulation role (Lee & Han, 2018). Supplementation with antioxidants such as vitamin E has been shown to restore the action on both cell-mediated and innate immune responses (Ibrahim & El-Sayed, 2016). Vitamin E causes lymphocytes multiplication, enhances NK cell functions and IL-2 synthesis, stimulates phagocytosis and averse infections by activating the Th1 immune response (Wintergerst et al., 2007), decreases the formation of immunosuppressant agents like PGE_2 (Figure 1), prevents the oxidation of PUFAs, and facilitates the antibody response (Lee & Han, 2018). Vitamin E deficiency causes retinopathy and ataxia. Vitamin E is present in *Helianthus annus* (sunflower), *Carthamus tinctorius* (safflower), *A. hypogaea* (peanut), *S. oleracea* (spinach), *L. esculentum* (tomato), and *B. oleracea* (broccoli) (Farhan Aslam et al., 2017).

Iron is an indispensable mineral because it plays a central role in the electron transport chain, citric acid cycle, nucleic acid synthesis (DNA), and oxygen transport by hemoglobin (Weiss, 2002) and can mitigate SARS-CoV-2 infections. Older red blood cells are recycled by macrophages, leading to the recycling of iron (Alpert, 2017). Iron also plays a vital role in gene regulation, cellular proliferation, and maturation (Wintergerst et al., 2007). In addition to these functions, iron also has a dominant role in modulating the immune response, as it activates neutrophils for bacterial destruction by hydroxyl radical, facilitates cytokines actions, causes T-cell escalation, and acts as a crucial element of enzymes required for the proper functioning of the immune system (Gombart et al., 2020; Weiss, 2002). Iron also stimulates microbe-killing pathways of macrophages and promotes the multiplication of monocytes and NK cells (Theurl et al., 2005). Iron-rich foods include *Musa acuminata* (banana), *Solanum tuberosum* (potato) (Figure 2), bread, grains, pasta, pork, eggs, fruits, vegetables, biscuits, beef, kumara, and milk (Menzies, 2019; Sandstead, 2000).

Zinc is a vital trace element for catalyzing and restoring the humoral and cell-mediated immune responses (Maares & Haase, 2016). The plasma level of zinc is 12–16 μm (Maares & Haase, 2016). Zinc has a major role in the structural regulation of proteins and transcription factors (Ibrahim & El-Sayed, 2016), and it is essential for SOD activity, interferes with cytokine production growth, and activates the Th1-mediated immune response

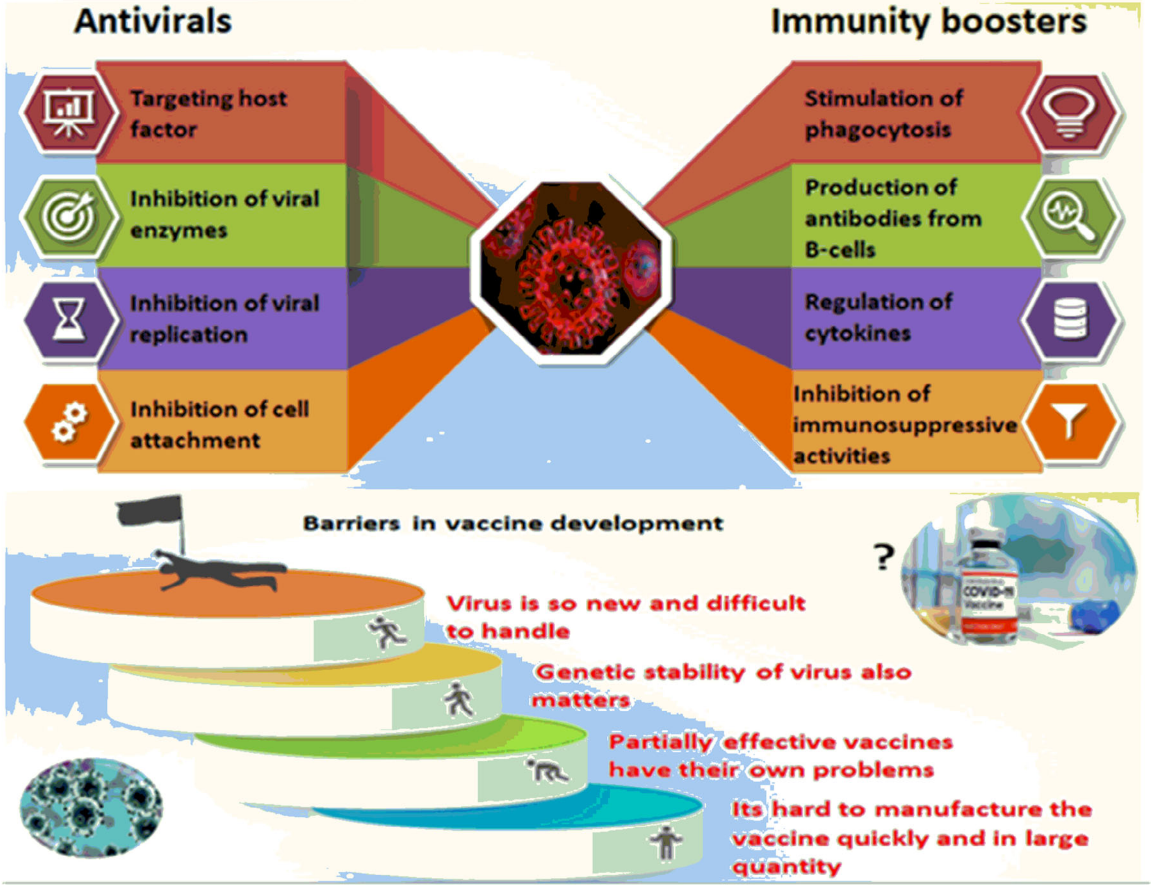

FIGURE 1 A diagrammatic presentation and brief strategic plan of therapeutic targets in combating COVID-19

(Wintergerst et al., 2007). It activates macrophages for phagocytosis, stimulates NK cells, causes the production of IL-6, IL-12, TNF-α, maintains the integrity of skin and mucosa, and has a defensive action against reactive oxygen species (Gombart et al., 2020). Zinc improves the antibody response (Figure 3), promotes CD8+ cells multiplication, causes NK cell production, and reduces NADPH oxidase actions, and ZIP10 inhibits the apoptosis of B cells (Alpert, 2017; Maares & Haase, 2016). Zinc inhibits viral replication and RNA polymerase activity of SARS-CoV (Stipp, 2020). Natural dietary sources of zinc include *Anacardium occidentale* (cashew), *Brachyura* (crab), *C. arietinum* (chickpea), *P. amygdalus* (almond), *P. sativum* (pea), cereals, oatmeal, pork chop, baked beans, yogurt, and kidney beans (Gu & Zhang, 2017).

Selenium plays a phenomenal role in the development of body and has significant importance for immunosurveillance (Avery & Hoffmann, 2018). The immune system depends upon an appropriate amount of selenium intake as it supports the proliferation of T-lymphocytes and enhances IFN-γ production (Avery & Hoffmann, 2018; Ibrahim & El-Sayed, 2016). It modulates the activities of NK cells and leukocytes, increases Th cells, maintains antibody levels, and counteracts ROS (Gombart et al., 2020). The main mechanism by which selenoproteins protect against oxidative harm is via glutathione peroxidase (GPx), a selenium-dependent enzyme (Table 1). The immune system requires selenium for efficient functioning of T-cells (Figure 3), macrophages, and neutrophils (Nkengfack et al., 2019). Food sources of selenium include cereals, grains, fish, meat, milk, *Morchella vulgaris* (fungi), and *Boletus edulis* (mushroom) (Falandysz, 2008; Olza et al., 2017).

Copper is required for several physiological processes including the proper functioning of the immune system (Alpert, 2017). It has potent antioxidant activity and is required for the conversion of superoxide free radical to O_2 and hydrogen peroxide (Maggini et al., 2007). Copper interacts with macrophages to encounter the infections, promotes NK cell functions, modulates the actions of neutrophils and monocytes, enhances IL-2 production, and increases the concentration of neutrophils (Alpert, 2017). It also promotes T-cell growth and differentiation (Gombart et al., 2020) (Figure 3), increases the number of circulating B cells, stimulates B-cell responses, and maintains the activity of SOD (Ibrahim & El-Sayed, 2016; Wintergerst et al., 2007). Copper-rich foods include *S. melongena* (eggplant), *A. hypogaea* (groundnut), *Bos taurus indicus* (beef), *Clarias gariepinus* (catfish), *Juglans regia* (walnut), and *Abelmoschus esculentus* (okra) (Shokunbi et al., 2019).

Magnesium is an alkaline-earth element and the second most abundant mineral after potassium having a remarkable role in several physiological processes such as glycolysis, oxidative phosphorylation, and synthesis of nucleic acids and proteins (Malavolta, 2018). It has a regulatory effect on the activation of leukocytes, acts as a cofactor for

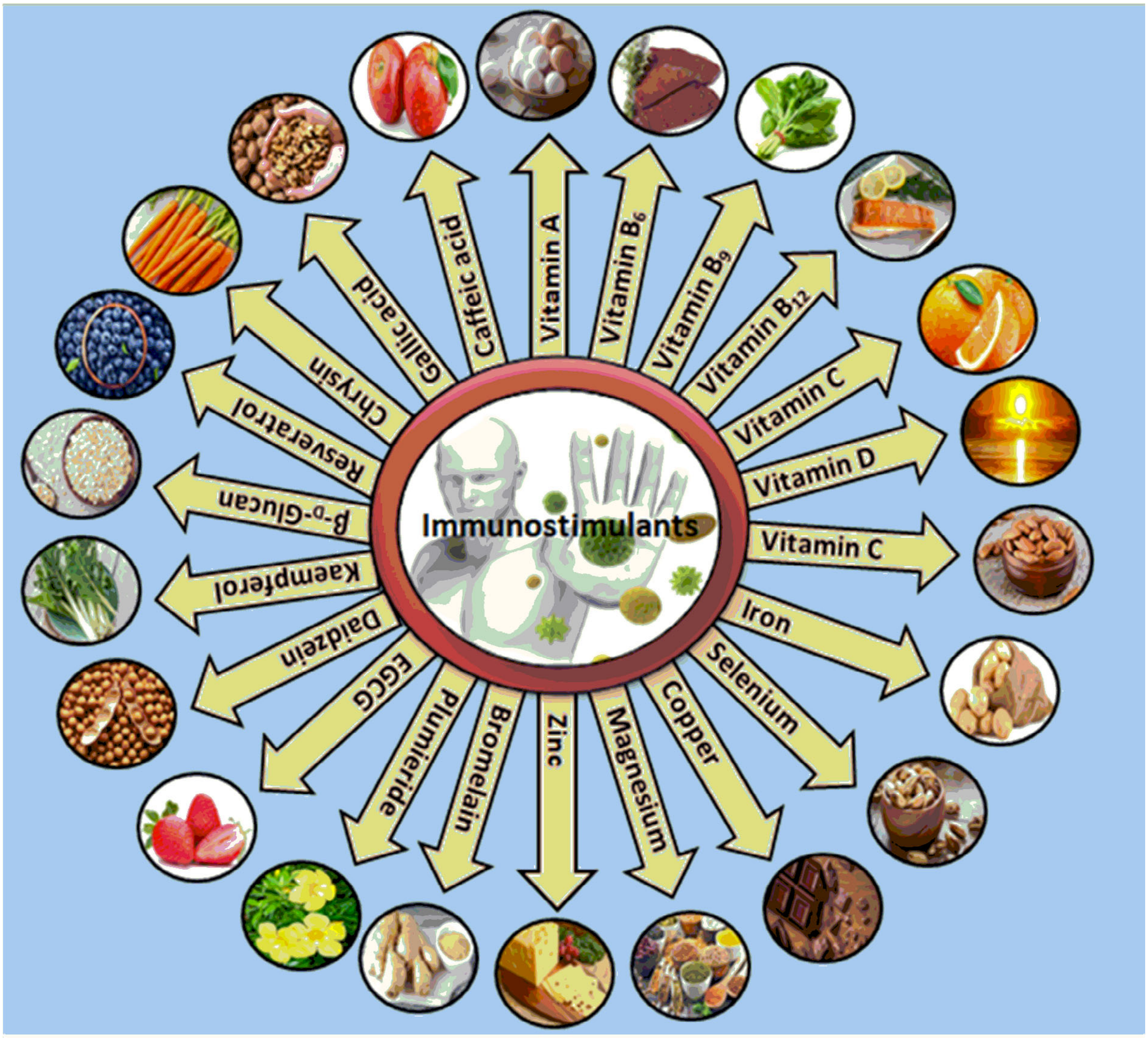

FIGURE 2 A diagrammatic illustration of natural immunostimulators along with their sources. Immunostimulators enriched diet can help to combat the severity of COVID-19

antibody synthesis, promotes antibody-dependent dissolution of cells, facilitates IgM binding to lymphocytes, provides structural stability to DNA, shields DNA against oxidative harm, and lessens superoxide production (Gombart et al., 2020). It activates macrophages towards lymphokines and facilitates the adherence of helper T cells and B cells (Malavolta, 2018). The deficiency of magnesium is associated with the enhanced production of free radicals, DNA damages, and lipid peroxidation (Malavolta, 2018). Natural sources of magnesium include fruits, vegetables, fish, whole grain bread, dried fruit, walnuts, and legumes (Kokubo et al., 2018).

3.1 | Immunostimulant phytochemicals

Diterpene andrographolide pharmacological actions include immune-stimulating, antiviral, anticancer, hepatoprotective, antioxidant, antibacterial, and neuroprotective activities (Ajaya Kumar et al., 2004; Banerjee et al., 2017; Gupta et al., 2017; Liao et al., 2019; Luo et al., 2020; Nagalekshmi et al., 2011; Xu et al., 2019). Andrographolide is isolated from medicinal herbaceous plant *Andrographis paniculata* (Ajaya Kumar et al., 2004). Mechanistically, andrographolide boosts humoral immunity by increasing peripheral blood lymphocyte levels (Table 2), improves T-lymphocyte activities, and antibody-dependent cell-mediated cytotoxicity. In addition, andrographolide stimulates the function of NK cells by promoting cytokine (IFN-γ, IFN-α, and TNF-α) release from peripheral blood mononuclear cells, as well as enhances the phagocytosis (Ajaya Kumar et al., 2004; Gupta et al., 2017).

β-Glucan commonly known as β-$_D$-glucan is a favorable immune-boosting agent, which is chemically a glucose polymer linked with each other through glycosidic linkage (Hussain et al., 2018; Meena et al., 2013). Most commonly, β-glucans are procured from *Avena sativa*, cereals, mushrooms, and barely (Hussain et al., 2018; Mohamed et al., 2017). β-Glucans are recognized for their extensive

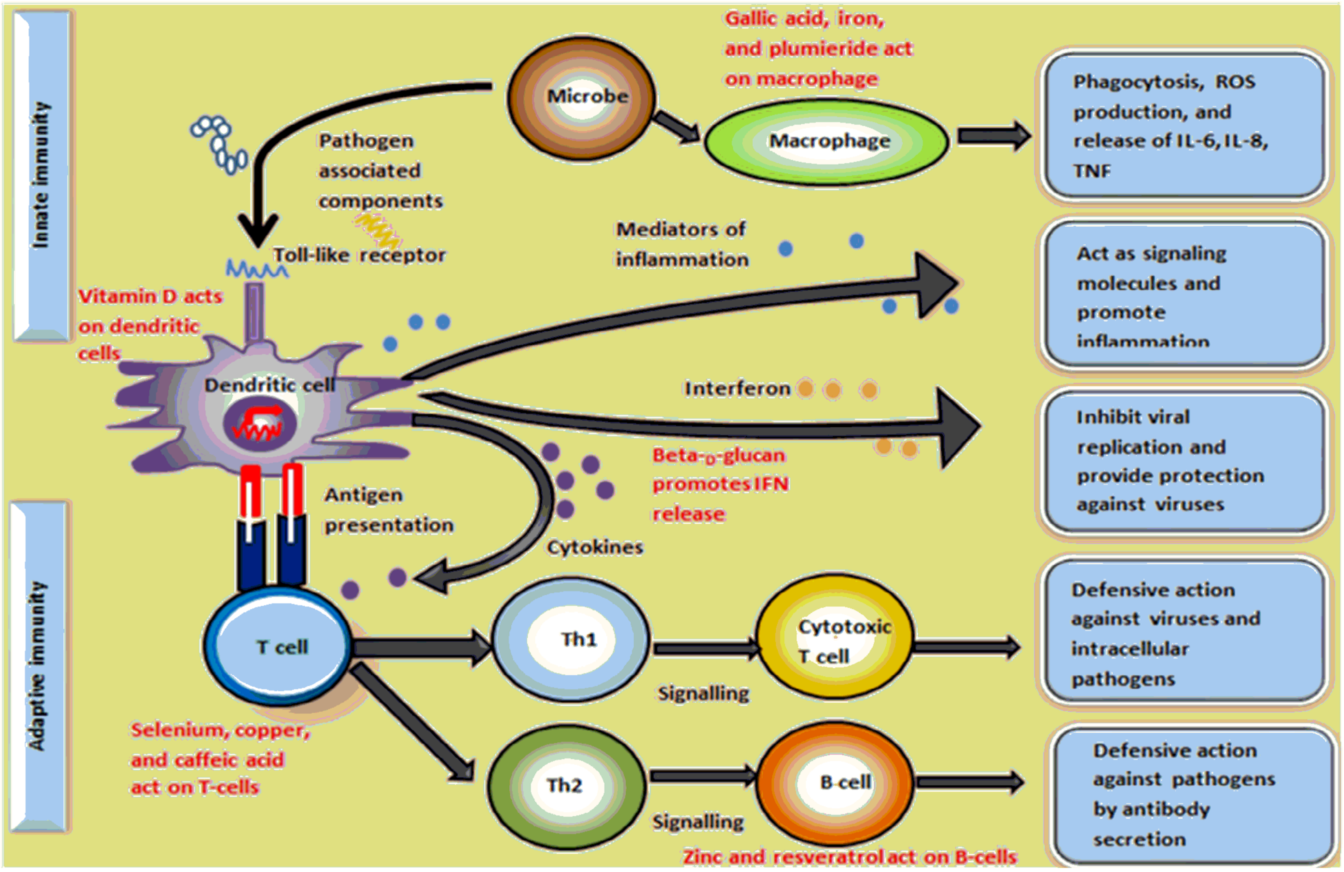

FIGURE 3 A general schematic representation of the mechanistic pathways of natural immunity strengtheners. Different agents target different cells of the immune system. The microbe activates macrophages, which in turn alert the dendritic cells leading to the activation of T-cells. Here, selenium, copper, and caffeic acid act on T-cells to potentiate their killing action by promoting the activation of cytotoxic and helper T-cells. B-cells are also activated, and different natural agents including zinc and resveratrol promote this activation and enhance the release of antibodies. Phytochemicals such as gallic acid, iron, and plumieride stimulate macrophages, which in turn play a role in stimulating innate immunity by enhancing phagocytosis along with the different agents like beta-$_D$-glucan, which promotes the release of INF

pharmacological activities including immune-boosting, anticancer, and antidiabetic activities (Choromanska et al., 2015; Liu et al., 2016; Mohamed et al., 2017). β-$_D$-Glucan is capable of activating functional cells of the immune system particularly macrophages, dendritic cells, monocytes, NK cells, and neutrophils by binding to specific glucan receptors (dectin-1, Toll-like receptor, complement receptor 3) located on these immune cells. β-$_D$-Glucan also assists the release of cytokines (IL-12, TNFα, INF-γ, IL-2, and IL-1α/β) and liberation of NO and H_2O_2 from activated macrophages. Phagocytic activity is additionally promoted by β-$_D$-glucan (Mohamed et al., 2017) (Figure 3).

The most significant phytochemical, caffeic acid, belonging to the class phenolic acid, confers varied pharmacological properties. Caffeic acid is present in numerous products, which are available naturally like in coffee and olive oil (Lima et al., 2016). Caffeic acid holds several biological activities including immune-boosting, antimicrobial, antithrombotic, antihypertensive, antifibrinolytic, and antioxidant effects (Bhullar et al., 2014; Kilani-Jaziri et al., 2017; Lima et al., 2016; Lu et al., 2015; Mia & Bank, 2016). The potent immune-boosting ability of caffeic acid is due to the hydroxyl group at places 3 and 4. Phagocytic action is accomplished by the liberation of an appropriate amount of lysosomal enzymes, and fortunately, caffeic acid promotes the assembly and liberation of enzymes from cellular lysosomes and successfully stimulates phagocytosis. Caffeic acid amplifies the humoral (by stimulating the assassinating action of NK cells and cytotoxic T-cells) as well as acquired immunity (by stimulating the production of B and T cells) (Figure 3) and thus proved to be an immunostimulant phytochemical (Kilani-Jaziri et al., 2017).

A phytoconstituents, chrysin, (5,7-di-OH-flavone) is a renowned flavonoid and also the most important component of *Oroxylum indicum* and *Passiflora caerulea* (Pushpavalli et al., 2010) (Table 2). Along with this, the presence of chrysin is present in honey and propolis (Mani & Natesan, 2018). Chrysin possesses multiple biological functions including immune-boosting, hepatoprotective, antioxidant, anticancer, antihypertensive, antidiabetic, and antidyslipidemic activities (Boothapandi & Ramanibai, 2019; Mani & Natesan, 2018; Pushpavalli et al., 2010; Ramírez-Espinosa et al., 2018; Veerappan & Malarvili, 2019). Chrysin possesses the potential for enhancing the innate immune response by promoting the proliferation and activation

TABLE 2 Phytochemicals as immunity revitalizers, their sources, and their polypharmacological mechanisms

Constituents	Biological source	Mechanism of action	References
Andrographolide	*A. paniculata*	Promotes human peripheral blood lymphocytes. Stimulates the production of IL-2.	(Ajaya Kumar et al., 2004)
β-Glucan	*Hordeum vulgare* *Avena sativa* *Ganoderma lucidum*	Activates macrophages, monocytes, neutrophils, NK cells, and dendritic cells. Stimulates the synthesis of cytokines (IL-1α/ββ, TNF-α, IL-2, IFN-γ, and IL-12) and promotes phagocytosis.	(Mohamed et al., 2017)
Bromelain	*Ananas comosus* *Asparagus officinalis* *Actinidia deliciosa*	Triggers NK cell activity. Intensifies TNF-α, IFN-γ, IL-1, IL-2, and IL-6 production.	(Amini et al., 2016)
Caffeic acid	*Theobroma cacao* *Mentha spicata* *Coffea arabica*	Increases the level of B- and T- lymphocytes, and promotes the activity of NK cells and CTL cells. Promotes phagocytosis.	(Kilani-Jaziri et al., 2017)
Chrysin	*Passiflora ligularis* *Oroxylum indicum*	Promotes phagocytosis without having any adverse effect on macrophages.	(Boothapandi & Ramanibai, 2019)
Cytochalasin D	*Xylaris sp.*	Enhances the level of IL-12p40. Promotes phagocytosis and killing by activating the immune cells.	(Richter et al., 2019)
Daidzein	*P. tuberosa* *Glycine max*	Stimulates the proliferation of monocytes and lymphocytes. Potentiates the phagocytosis. Reduces the DTH response.	(Maji et al., 2014)
Epigallocatechin gallate	*Actinidia deliciosa* *P. persica* *M. domestica*	Stimulates the level of cytotoxic CD8 T-lymphocytes. Promotes the release of IL-12 Promotes Th-1 response.	(Mohamed et al., 2017)
Gallic acid	*Cynomorium coccineum* *P. granatum* *V. vinifera*	Enhances the synthesis of IL-12p70. TNF, INF-γ, MCP-1, and IL-16. Promotes macrophage ability of phagocytosis.	(Reyes et al., 2018)
Kaempferol	*Aloe vera* *B. oleracea* *M. domestica*	It invigorates the granulocyte macrophage colony-stimulating factor.	(Bandyopadhyay et al., 2008)
Plumieride	*P. acutifolia*	Stimulates T- and B-lymphocytes functioning. Promotes the functioning of macrophages. Raises the level phagocytes. Enhances the level of TNF-γ, IL-2, and TNF-α in CD4 T-lymphocytes.	(Singh et al., 2017)
Puerarin	*P. lobata* *Tuberosa phaseoloides* *Pueraria mirifica*	Enhances the proliferation of monocytes and lymphocytes. Promotes phagocytosis. Reduces DTH response.	(Maji et al., 2014)
Resveratrol	*V. vinifera* *P. vera* *A. hypogaea*	Promotes CD4/CD8 ratio Stimulates T-cell growth and division. Enhances B-cell–mediated immune response. Restorative effect on NK cells.	(Mohamed et al., 2017)
(Z)-Propenyl-sec-butyl-disulphide	*A. sativum*	Promotes the calcium influx in neutrophils. Promotes ROS production. Stimulates synthesis of phagocytes.	(Özek et al., 2017)

Note: IL-12: Interleukin-12, NK cells: natural killer cells, TNF: tumor necrosis factor, CTL: cytotoxic T-lymphocytes, ROS: reactive oxygen species, DTH: delayed-type hypersensitivity, INF: interferon.

of macrophages and stimulates phagocytosis (Boothapandi & Ramanibai, 2019). It also plays a role in boosting the performance of NK cells and cytotoxic T-lymphocytes (Sassi et al., 2017).

The fungal metabolite, cytochalasin D, isolated from a fungal strain of *Xylaris* sp. (Table 1) possesses several biological actions, including immune stimulation, and anticancer activities (da Silva et al., 2019; Richter et al., 2019; Takanezawa et al., 2017). The immune-stimulating mechanism of cytochalasin D is unique as it acts in two ways. One way is by promoting the level of IL-12p40, which activates the immune response by activating dendritic cells and macrophages. Activated macrophages accelerate the phagocytosis, in turn, activating the innate immune response. In the case of adaptive immune response, IL-12 enhances the release of INF-γ by immune cells and promotes the multiplication of T-cells and NK cells, and via the second way, it directly activates the T-cells and boosts immunity (Richter et al., 2019).

A vital isoflavone, daidzein (7,4-di-OH-flavone) is isolated from various plant species including *Pueraria tuberosa* and *Glycine max* (Maji et al., 2014; Montalesi et al., 2020; Prahastuti et al., 2019) (Figure 2). Daidzein has a wide spectrum of pharmacological actions, including immune-boosting, anticancer, neuroprotective, and antioxidant functions (Maji et al., 2014; Montalesi et al., 2020; Prahastuti et al., 2019; Wei, Yang, et al., 2019). Daidzein modulate the cellular immune response of the body by stimulating the assembly of macrophages, dendritic cells, and lymphocytes. Because the levels of monocytes and lymphocytes increase, it promotes phagocytosis. As far as the humoral immune response is concerned, IgG and IgM play a key role in activating the complement system and neutralizing toxins. Daidzein increases the serum level of IgG and IgM and has a proven immune-boosting activity (Maji et al., 2014).

A phytochemical, epigallocatechin gallate, isolated from herbal green tea after extraction, is a polyphenol (Mohamed et al., 2017). Epigallocatechin gallate has antiplatelet, antioxidant, and anticancer functions (Chen, Hsieh, et al., 2020; Joo et al., 2018; Liu et al., 2019). The proliferation of cytotoxic CD8 cells is enhanced by epigallocatechin gallate, and, in turn, it stimulates the killing activity of T-lymphocytes and acts as a potent anticancer agent and also as an immunostimulant (Mohamed et al., 2017). Epigallocatechin gallate (EGCG) promotes the release of IL-12 (Mohamed et al., 2017), which, in turn, stimulates the production of IFN-γ from NK cells and boosts up immunity indirectly (Mohamed et al., 2017; Roquilly et al., 2017) (Table 2).

The polyphenolic compound, gallic acid, with diverse pharmacological activities is the eminent constituent of *Mangifera indica*, *Vitis vinifera*, *J. regia*, *Camellia sinensis*, and *Punica granatum* (Latief et al., 2016; Reyes et al., 2018) (Table 1). The multiple functions of gallic acid include immunostimulant, anticancer, antioxidant, antimicrobial, and hepatoprotective activities (Latief et al., 2016; Reckziegel et al., 2016; Reyes et al., 2018; Sarjit et al., 2015; Zhang, Ma, et al., 2019). Gallic acid activates both humoral and cell-mediated immunity by boosting the activity of IL-12p70, TNF, INF-γ, MCP-1, and IL-6. The discharge of IL-12 stimulates the liberation of INF-γ, which, in turn, promotes the phagocytosis by activating macrophages (Figure 3). MCP-1 enhances the migration of monocytes including neutrophils and dendritic cells (Reyes et al., 2018). IL-6 promotes the activation of helper T-lymphocytes to stimulate humoral immunity (Zhang, Wu, Li, et al., 2020).

Another flavonoid, kaempferol, is significantly isolated from *B. oleracea*, *Malus domestica*, and *C. sinensis* (Chen & Chen, 2013) (Table 2). It has gained a great importance due to its biological implications including immunostimulant, antidiabetic, anticancer, and antioxidant activities (Alkhalidy et al., 2018; Bandyopadhyay et al., 2008; Kashyap et al., 2017; Liao et al., 2016). Kaempferol displays immunostimulant activity by promoting the release of granulocyte-macrophage colony-stimulating factor (GM-CSF), which, in turn, has gained a great attention by promoting the activation and chemotaxis of dendritic cells, enhancing the accumulation of neutrophils, and most significantly activating macrophages (Bandyopadhyay et al., 2008; Castellani et al., 2019).

A potent phytochemical, plumieride belongs to a multiplex class, iridoid glycoside, and is obtained after extraction from *Plumeria acutifolia*, *Plumeria alba*, and *Allamanda cathartica* (Boeing et al., 2018; Gupta, 2016; Singh et al., 2017). It possesses significant pharmacological activities including immune-boosting, antidepressant, and antioxidant functions (Boeing et al., 2018; Bonomini et al., 2017; Singh et al., 2017). Plumieride boosts the humoral immunity as well as cell-mediated immunity, and promotes the assembly and liberation of various cytokines including IL-2, IFN-γ, and IFN-α (Figure 1). Mechanistically, it activates CD_4 cells, which, in turn, enhance phagocytosis by promoting the proliferation of macrophages and also activates T and B-lymphocytes (Singh et al., 2017) (Figure 3).

An isoflavone glycoside, puerarin, a constituent of *P. tuberosa* and *Pueraria lobata*, functions as immunostimulant, reno protective, antioxidant, antidiabetic, anticancer, and hepatoprotective (Maji et al., 2014; Fu-Liang et al., 2006; Wang et al., 2013; Wu et al., 2013; Xia et al., 2013). Puerarin plays a key role in boosting the immune response by promoting the level of monocytes and lymphocytes via enhancing their proliferation (Table 1). In addition, puerarin elevates the level of phagocytes and increases immunity by stimulating phagocytosis (Maji et al., 2014).

A phytochemical, resveratrol (3,4,5-trihydroxystilbene) has drawn a lot of research attention because of its exciting biological potential, and it is isolated from several plants including *V. vinifera* and *A. hypogea* (Berman et al., 2017). The key effects of resveratrol include immune-boosting, anticancer, antidiabetic, antimicrobial, hepatoprotective, and neuroprotective functions (Ahmed et al., 2017; Lai et al., 2016; Mattio et al., 2019; Mrkus et al., 2019; Wang et al., 2015; Zhang et al., 2017). Resveratrol potentiates the immune response by upregulating the phagocytic index K, enhances the action of NF-kβ (Lai et al., 2016), and elevates the CD_4/CD_8 ratio by accelerating the multiplication of T-cells. In addition, it has a restorative effect on NK cells and along with this boosts the level of antibodies by enhancing the B-cell–mediated immune response (Mohamed et al., 2017) (Figure 3).

An important volatile oil, (Z)-propenyl sec-butyl disulphide, isolated from *Ferula gummosa*, *Ferula iliensis*, and *Ferula* (Özek et al., 2017; Pavela et al., 2020; Zomorodian et al., 2018) (Table 2) is approved for varied pharmacological actions including immunostimulant, insecticidal, and antimicrobial functions (Özek et al., 2017; Pavela et al., 2020; Zomorodian et al., 2018). The immune system may be significantly enhanced by immune-boosting action of (Z)-propenyl-sec-butyl disulphide. This volatile oil enhances the killing action of neutrophils by promoting the Ca^{++} influx in neutrophils, which leads to the effective generation of ROS from neutrophils, and, together with this, potentiates the phagocytosis by raising the level of phagocytes (Özek et al., 2017).

A phytochemical, bromelain, known for its fibrinolytic, antithrombotic, and anticoagulant activities, is found in the enzymes of *Ananas comosus* (pineapple) (Setiasih et al., 2019). Bromelain is an enzyme complex containing peroxidase, acid phosphatase, glycosidase, cellulose, and others (Setiasih et al., 2019; Whitworth et al., 2006). Bromelain also enhances immune defense against infections as it promotes T-lymphocytes binding to antigens and also modulates the number of circulating CD4+ and CD8+ lymphocytes (Whitworth et al., 2006). The major immunomodulatory effects involve the activation of T-lymphocytes and stimulation of (TNF-α, INF-γ, IL-1, IL-2, IL-6, and GM-SCF) production (Amini et al., 2016).

4 | NATURAL PRODUCTS AS ANTIVIRALS

A virus is a chunk of bad scoop swaddled in a protein coat (Sohail et al., 2011). Viral infections are considered as one of the prime threats for human life (Arakawa et al., 2009). It has been recognized that NPs from different natural origins are the most important source of antivirals for the management of COVID-19 (Liu & Du, 2012; Yonesi & Rezazadeh, 2020) (Figure 4).

4.1 | Inhibition of S-protein and ACE2

SARS-CoV-2 entry into the host cell depends upon angiotensin-converting enzyme-2 (ACE2), which is also known as the SARS-CoV receptor (Inhibitor et al., 2020). The receptor-binding domain present in the SARS-CoV spike (S) protein has a major role in binding to ACE2 of the host cell (Ge et al., 2013). The SARS-CoV S-protein causes viral attachment and pathogenesis (Du et al., 2009). However, for the entry of SARS-CoV, the association between SARS-CoV-2 S-protein and ACE-2 is the most crucial step (Du et al., 2009) (Figure 1). Emodin, obtained from *Rheum* and *Polygonum*, baicalin obtained from *Scutellaria baicalensis*, and luteolin obtained from *Veronica thymoides* act by inhibiting the S1 domain of S-protein attachment to the host cell receptor ACE2 (Alves et al., 2004; Deng et al., 2012; Ho et al., 2007; Li-Weber, 2009; Lopez-Lazaro, 2008; Rane et al., 2020; Yeung et al., 2006) (Table 3). The S1 domain consists of two subdomains—N-terminal domain (NTD) and C-terminal domain (CTD) both of which act as receptor-binding domains (RBDs) (Belouzard et al., 2012). Thus, inhibiting the attachment of S-protein to ACE2 is essential for treating the SARS-CoV-2 infection (Zhang & Liu, 2020). Emodin also functions as hepato-protective and as an anticancer agent (Dong, Zeng, et al., 2020; Hsu & Chung, 2012). *S. baicalensis* have multiple biological effects, such as treating respiratory infections, diarrhea, insomnia, and hypertension (Ding et al., 2019; Zhao et al., 2019). Luteolin has other benefits, including antioxidant or pro-oxidant and anti-allergy activity (Kawai et al., 2007; Lin et al., 2008).

4.2 | Inhibition of entry of the virus into host cell

The entry of CoV-2 into the host cell depends upon the attachment of viral particles to cell-surface receptors and the endocytosis of virus receptor complexes (Figure 1). Enveloped virus entrance into cells

FIGURE 4 Nature as a source of splendid antivirals holding anti-SARS-CoV-2 interest with their viral life cycle restricting activity

TABLE 3 Natural compounds, their origins, and sites of action showing the antiviral natural compounds, their origin and mechanism of action

Constituents	Class of constituents	Biological source/origin	Mechanism of action	References
Apigenin	Flavone	*Matricaria chamomilla*	Blocks the proteolytic activity of SARS-CoV-2 3CLpro.	(Baumann, 2008; Jo et al., 2020)
Baicalin	Flavonoid	*S. baicalensis*	Prevents viral attachment to the host cell.	(Li-Weber, 2009)
β-Sitosterol	Phytosterol	*Isatis indigotica*	Blocks the SARS-3CLpro enzyme cleavage activity.	(Lin et al., 2005)
Dihydrotanshinone	Biterpenoids	*Salvia miltiorrhiza*	Inhibits virus entry into the cell.	(Kim et al., 2018; Zhang, Wu, Zhang, et al., 2020)
Emodin	Anthraquinone	*Rheum* and *polygonum*	Inhibits attachment of surface spike protein of SARS-CoV-2 with the host cell.	(Alves et al., 2004; Ho et al., 2007)
Epigallocatechin gallate	Flavan	*C. sinensis*	Anti-SARS 3CLpro enzyme activity.	(Jo et al., 2020; Westbrook et al., 2018)
Gallocatechin gallate	Flavan	*Litchi chinensis sonn*.	Anti-SARS 3CLpro enzyme activity.	(Jo et al., 2020)
Gnidicin	Diterpene esters	*Gnidia lamprantha*	Inhibit SARS-CoV-2 RdRp.	(Bhandurge et al., 2013)
Gniditrin	Diterpene esters	*Gnidia lamprantha*	Inhibit SARS-CoV-2 RdRp.	(Bhandurge et al., 2013)
Glycyrrhizin	Saponin	*G. radix*.	Active against viral adsorption and penetration.	(Cinatl et al., 2003; Ong, 2002)
Herbacetin	Flavonol	*M. paniculata*	Anti-proteolytic activity of SARS-CoV 3CLpro.	(Harborne, 1969; Jo et al., 2020)
Hesperidin	Flavonoid	*Citrus* spp.	Inhibits helicase of SARS-CoV-2.	(Man et al., 2019; Wu, Liu, et al., 2020)
Hesperetin	Flavonoid	*Isatis indigotica*	Blocks cell-based division of SARS-M pro (3CLpro).	(De Clercq, 2006)
Indigo	Glycoside	*Isatis indigotica*	Blocks the SARS-3CLpro enzyme cleavage activity.	(Lin et al., 2005)
Isobavachalcone	Flavonoid	*Psoralea corylifolia*	Inhibits the enzymatic functioning of MERS-CoV 3CLpro.	(Jo et al., 2019)
Kaempferol	Flavonol	*B. oleraceaS. oleracea*	Blocks the 3a channel of coronavirus.	(Zakaryan et al., 2017)
Luteolin	Flavone	*V. linariifolia*	Inhibits attachment of spike proteins of SARS-CoV-2 with the host cell in an avid manner.	(Yi et al., 2004)
Maco-flavanone E	Flavonoid	*M. tanarius*	Blocks viral assembly and release.	(Gupta et al., 2020)
Pectolinarin	Flavone	*Cirsium* spp.	Anti-SARS 3CLpro enzyme activity.	(Cho et al., 2016; Jo et al., 2020)
Puerarin	Iso-flavone	*Pueraria lobata*	Anti-SARS CoV 3CLpro proteolytic activity.	(Jo et al., 2020; Zhou et al., 2014)
Phaithanthrin	Alkaloid	*Isatis indigotica*	Inhibition of PLpro activity.	(Wu, Liu, et al., 2020)
Phyllaemblicin	Terpenoids	*P. emblica*	Inhibits helicase activity of SARS-CoV-2.	(Wu, Liu, et al., 2020; Zhang, Kaunda, et al., 2019)
Phyllaemblinol	Terpenoids	*P. emblica*	Anti-SARS-CoV-2 helicase activity.	(Wu, Liu, et al., 2020; Zhang, Kaunda, et al., 2019)
Platycodin D	Triterpenoidal saponin	*P. grandiflorum*	Inhibit PLpro activity of SARS-CoV-2.	(Khan et al., 2016; Wu, Liu, et al., 2020)
Quercetin	Flavonol	*C. sinensis*	Inhibition of SARS-CoV-2 3CLpro.	(Wu et al., 2015)
Rhoifolin	Flavone	*Citrus paradisi*, *Citrus aurantium*, *Citrus limon*	Inhibits the enzymatic action of SARS-CoV-2 3CLpro.	(Jo et al., 2020)
Rutin	Glycoside	*R. graveolens*	Inhibits the helicase of SARS-CoV-2.	(Ganeshpurkar & Saluja, 2017; Wu, Liu, et al., 2020)

TABLE 3 (Continued)

Constituents	Class of constituents	Biological source/origin	Mechanism of action	References
Saikosaponin	Terpenoids	*R. bupleuri*	Impedes early stage of HCOV-22E9 infection including the attachment and penetration of virus.	(Cheng et al., 2006; Li, Li, et al., 2018)
Sinigrin	Glucoside	*Isatis indigotica*	Blocks the SARS-3CLpro enzyme cleavage activity.	(Lin et al., 2005)
Sugetriol-3,9-diacetate	Sesqui-terpenoids	*Cyperus rotundus L.*	Anti-SARS-CoV-2 PLpro activity.	(Kim et al., 2013)
Tetrandrine	Alkaloid	*Stephania tetrandra S.*	Blockage of spike and nucleocapsid protein expression in HCOV-OC43.	(Kim et al., 2019)
Tetra-O-galloyl-β-D-glucose	Gallate Ester	*Galla chinensis*	Attaches with the surface spike protein of SARS-CoV-2 in an avid manner.	(Yi et al., 2004)
Theaflavin	Flavonoid	*C. sinensis*	Inhibition of SARS-CoV-2 RdRp.	(Leung et al., 2001)
Vibsanol A	Lignan	*V. odoratissimum*	Blocks viral assembly and release.	(Gupta et al., 2020)

Note: SARS-CoV: Severe acute respiratory syndrome coronavirus, 3CLpro: 3 chymotrypsin-like protease, M pro: main protease, RdRp: RNA-dependent RNA polymerase, MERS-CoV: Middle East respiratory syndrome coronavirus, PLpro: papain-like protease.

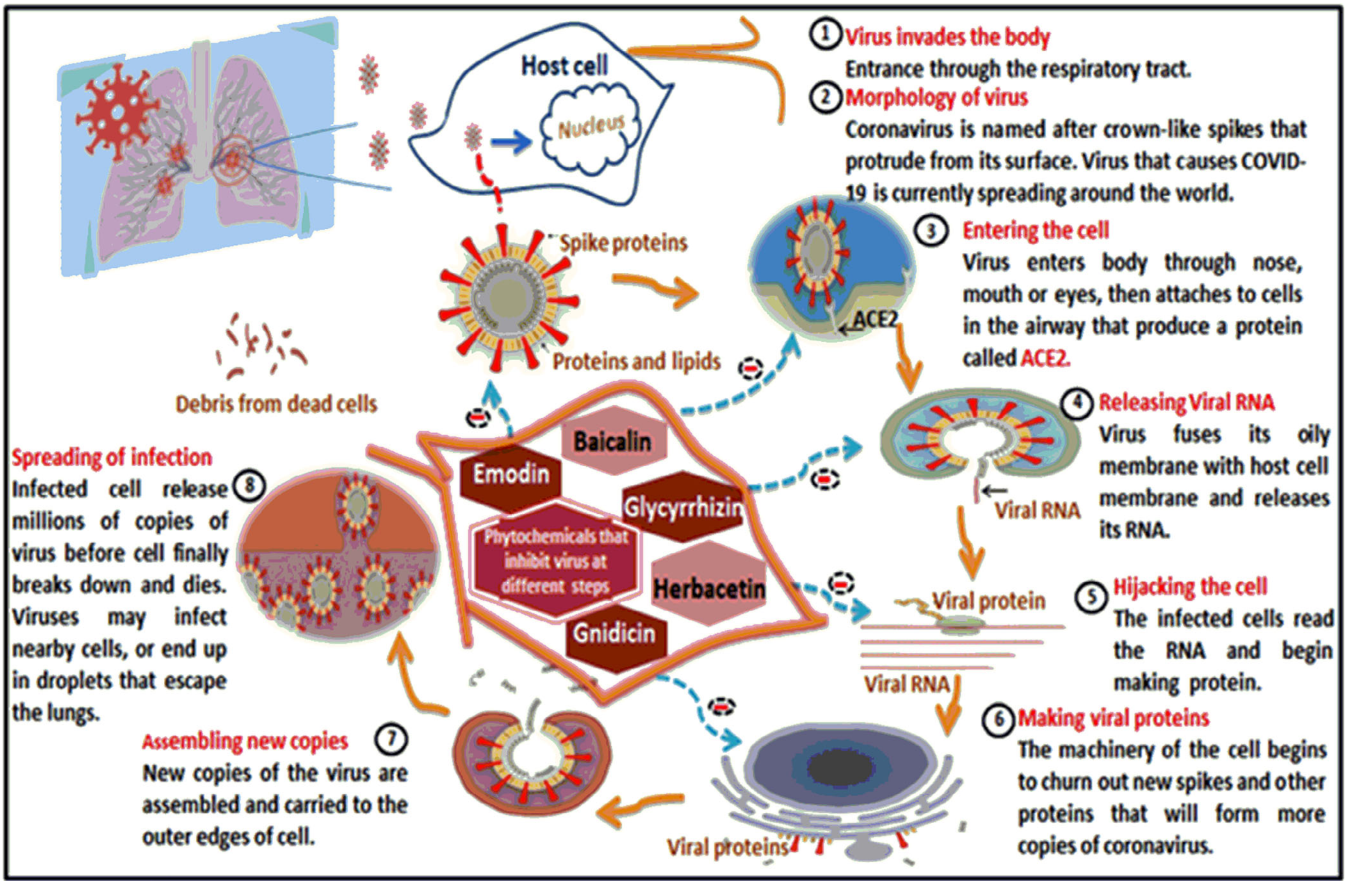

FIGURE 5 Diagrammatic representation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral life cycle and potential drug targets. Proposed targets of selected repurposed and investigational products are noted as shown in the figure. These host-based pathways are targetable to control viral infection

takes place by two main processes: Some of the viruses transfer their genomes into the cytosol where the envelope merges with the plasma membrane of the host cell, and some act on the endocytic mechanism of the cell (Figure 5). In the latter process, endosomal acidic pH-mediated endocytosed virus causes the activation shift in the endosome, resulting in the viral fusion with endosomal membrane and secrete genome of the virus in the cytosol of the host cell. Thus, the endocytic mechanism is pH-dependent, but direct fusion with the membrane is independent of pH (Pelkmans & Helenius, 2003; Sieczkarski & Whittaker, 2002). Glycyrrhizin obtained from *Glycyrrhizae radix*, saikosaponins extracted from *Radix bupleuri*, and dihydrotanshinone obtained from *Salvia miltiorrhiza* block the entry of SARS-CoV-2 into the host cell by inhibiting the endocytosis of the virus into the host cell (Cheng et al., 2006; Cinatl et al., 2003; Kim et al., 2018; Li, Song, et al., 2018; Ong, 2002; Zhang, Wu, Zhang, et al., 2020) (Table 3). Along with virustatic activity, glycyrrhizin acts as a hepatoprotective agent and cough suppressor (Kamei et al., 2003; van Rossum et al., 1998). Saikosaponin is used as a neuroregulatory agent given its anticonvulsant activity (Li, Li, et al., 2018; Yuan et al., 2017). Dihydrotanshinone is used to treat Alzheimer's disease and as a cardioprotective agent (Chen et al., 2019; Jiang et al., 2019).

4.3 | Inhibition of RNA synthesis and replication

Many antivirals target viral enzymes and disrupt viral replication (Louten, 2016) (Figure 1). As the most important functional proteins of CoV, nonstructural protein (NSp) has a key role in the transcription and translation of RNA, synthesis of proteins, replication of virus, and its proliferation in the host. In this process, 3CLpro, RdRp, PLpro, and helicase are the most interesting choices for the antivirals (Wu, Liu, et al., 2020).

4.3.1 | Inhibition of papain-like protease (PLpro)

Two viral proteases have a role in encoding the replicase polyproteins for SARS-CoV-2. One of the proteases, papain-like protease (PLpro), has a role in releasing the NSp1, NSp2, and NSp3 (necessary for the correction of viral replication) by the N-terminus cleavage of replicase poly-protein (Harcourt et al., 2004). PLpro also has a crucial role in antagonizing the innate immunity of the host cell by blocking the interferon regulatory factor 3 (IRF3) pathway and IFN production (Chen et al., 2014; Li, Wang, et al., 2016; Yuan et al., 2015). Platycodin D obtained from *Platycodon grandiflorum*, sugetriol-3,9-diacetate obtained from *Cyperus rotundus* L, and phaithanthrin D obtained from *Isatis indigotica* may play a role as anti-COVID-19 agents by inhibiting the cleavage of N-terminus of polyproteins (Khan et al., 2016; Kim et al., 2013; Wu, Liu, et al., 2020) (Table 3).

4.3.2 | Inhibition of 3-chymotrypsin-like protease (3CLpro)

3CLpro, another viral protease called NSp5, undergoes the cleavage process to synthesize mature enzymes (Yang et al., 2005). It is an interesting target (Figure 1) because it plays a key function in the translation of the viral genome by processing the polyproteins. Accordingly, it is called as the main protease (M pro) (Zhang, Lin, Sun, et al., 2020). CoV genome is comprised of six ORFs (open reading frames). Shifting between ORF1a and ORF1b causes the formation of polypeptides: pp1a and pp1ab that play a part in the formation of the replication transcription complex (RTC) (Chen, Liu, et al., 2020). The natural antivirals, apigenin obtained from *Matricaria chamomilla*, epigallocatechin gallate obtained from *C. sinensis*, herbacetin obtained from *Meconopsis paniculata*, pectolinarin obtained from *Cirsium* spp., puerarin obtained from *P. lobata*, rhoifolin obtained from *Citrus* spp., and quercetin obtained from *C. sinensis*, may protect against the virus by inhibiting the 3CLpro enzyme activity of SARS-CoV-2 (Article, 2012; Baumann, 2008; Cho et al., 2016; Finger et al., 1991; Harborne, 1969; Jo et al., 2020; Nguyen et al., 2012; Westbrook et al., 2018; Zhou et al., 2014) (Table 3). Apigenin has many potential benefits including antiplatelet and anticancer activity (Jang et al., 2008; Yan et al., 2017). EGCG is widely used for treating obesity and inflammation (Li, Gao, et al., 2018; Riegsecker et al., 2013). Herbacetin is a promising molecule for cancer prevention and bone loss (Kim et al., 2016; Li, Sapkota, et al., 2016). Pectolinarin reduces inflammation and also has analgesic property (Lim et al., 2008; Martínez-Vázquez et al., 1998). Puerarin is used to treat endometriosis and chronic liver diseases (Yu et al., 2015; Zhao et al., 2016). Rhoifolin functions as antidiabetic agent (Tzeng et al., 2011). Quercetin has a broad range of pharmacological activities along with antiviral activity including anticarcinogenic and antiinflammatory activity (Li, Yao, et al., 2016). Accordingly, all these natural antivirals are maybe therapeutically of value in preventing and treating COVID-19.

4.3.3 | Inhibition of RNA-dependent RNA polymerase (RdRp)

RNA-dependent RNA polymerase or RNA replicase of SARS-CoV-2 is the most dominant focus for the anti-SARS activity (Xu et al., 2003). Among the ORFs, the biggest ORF called replicase has a role in the encoding of enzymes, which then further cause translation and form structural proteins (Sawicki et al., 2007). NSp12 in coronavirus is an RNA-dependent RNA polymerase, which is a conserved protein. Thus, it is considered to be an essential enzyme transcription complex of coronavirus. The RdRp domain has a conserved Ser-Asp-Asp motif and location on the C-terminus (Subissi et al., 2014). NSp8 is capable of catalyzing the synthesis of template-dependent oligoribonucleotides, which is primarily used as a primer for RNA synthesis and catalyzes the NSp12 activity (Imbert et al., 2006). Theaflavin obtained from *C. sinensis* and the plant *Gnidia lamprantha* from the *Gnidia* species include phytochemicals, gnidicin, and gniditrin (Table 3), which have anti-SARS-CoV-2 activity, inhibiting the translation process of RNA-dependent RNA polymerase enzyme present in COVID-19 (Bhandurge et al., 2013; Leung et al., 2001; Wu, Liu, et al., 2020) (Figure 5). Thus, all these natural compounds may possess efficient antiviral activity against SARS-CoV-2.

4.3.4 | Inhibition of helicase

SARS-associated helicase is regarded as one of the most important targeted proteins for anti-SARS agent evolution (Tanner et al., 2003). Virus requires helicase for the conversion of double-stranded RNA to single-stranded RNA for the manipulation of polynucleotides (Briguglio et al., 2011). Helicase (NSp13) is a multifunctional protein that consists of the helicase domain (HEL) and the N-terminal metal-binding domain (MBD). NsP13 unwinds the double-stranded RNA in an NTP-dependent manner along the direction of 5′-3′ (Ivanov & Ziebuhr, 2004). Because helicase has a central role in the uncoiling of duplex RNA and RNA capping (Shum & Tanner, 2008) and is essential for replication and proliferation of the virus, it is believed to be a target for antiviral agents (Ivanov et al., 2004; Shum & Tanner, 2008) (Figure 1). Hesperidin obtained from *Citrus* spp., rutin obtained from *Ruta graveolens*, and the plant *Phyllanthus emblica* containing phyllaemblicin B and phyllaemblinol are known to show activity against SARS-CoV-2 by inhibiting the helicase NSp13 activity of SARS-COV-2 (Ganeshpurkar & Saluja, 2017; Man et al., 2019; Wu, Liu, et al., 2020; Zhang, Kaunda, et al., 2019) (Table 3).

4.4 | Virion assembly and release blockers

Virion particle assembly is the last and essential step for viral infection (Thomas & Gorelick, 2008). The generation of progenitors in coronavirus involves two major mechanisms: viral envelope assembly and helical nucleocapsid assembly (de Haan et al., 2000). Four structural proteins: S-protein, E-protein, M-protein, and N-protein play a key role in CoV assembly and viral infection (DeDiego et al., 2007). Among all the structural proteins, M-protein (membrane protein) is the protein, which is considered the main promoter for the assembly of COVID-19 and elucidates the envelope of the virus by the M-M protein interaction (Masters & Rottier, 2005; Neuman et al., 2011). N-protein acts by binding to the RNA genome of CoV, thus producing nucleocapsid (de Haan & Rottier, 2005). Binding to the RNA of the virus is the major interest of N-protein (Masters, 2006). Most SARS N-protein and RNA make a complex, called ribonucleoprotein complex, which is inserted into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) with S-protein, M-protein, and E-protein. Final virion assembly occurs in the intermediate compartment, and mature virions are released via smooth-walled vesicles by exocytosis (Nal et al., 2005) (Figure 5). The natural compound vibsanol A extracted from the flowers and leaves of *Viburnum odoratissimum* and macoflavanone E extracted from the leaves of *Macaranga tanarius* act by modifying the E-protein's normal ion channel activity, which factors in the pathogenesis of SARS-CoV-2 (Gupta et al., 2020; Kawakami et al., 2008; Shen et al., 2002) (Table 3). Natural antiviral compounds that inhibit the activity of N-protein have yet to be identified. (Table 4 summarizes the factors that serve as promising targets for SARS-CoV-2 particle assembly and release.

5 | CONCLUSION

This review establishes the role of phytonutrients as immunity boosters, and different phytochemicals are also used against COVID-19 because of their antiviral activity. It is crystal clear with this study that an acceptable amount of nutraceuticals and phytochemicals can improve the resistance against several infections. So, the deficiency of immunity intensifiers can be disastrous for the immune system. Unquestionably, the simplest way to reinvigorate the immune system is to intake nutrients that act as immunity-boosting tonics, and after nutrients, phytochemicals are the best, and both can be used as a powerful weapon against SARS-CoV-2. But if the immune system fails to cope with the virus, then antivirals serve as the marvelous therapy against the viral infections. The use of the antivirals is to solicit both direct antiviral impressions against viruses and specific immune cell activation. The present review posits that natural antivirals may act on different targets of SARS-CoV-2 to impede infection and afford efficient treatment. Compounds from natural origin may therefore play a significant role in the management of anti-SARS-CoV-2 therapy, but additional research is required to better understand their mechanisms in-depth.

CONFLICT OF INTEREST

The authors of this article have no conflict of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

TABLE 4 Factors involved in HCoV, virion assembly, and release

Host factor(s)	HCoV (other CoV)	Function	References
Tubulin	HCoV-229E, HCoV-NL63, (TGEV)	Binds to the cytosolic domain of S protein; facilitates the assembly and release of the virus.	(Rüdiger et al., 2016)
Β-Actin	(IBV)	Binds to M protein; promotes particle assembly and release.	(Wang et al., 2009)
Vimentin	(TGEV)	Binds to N protein; ease the process of viral assembly and release.	(Zhang et al., 2015)

Note: HCoV-229E, human coronavirus-229E; HCoV-NL63, human coronavirus-NL63; TGEV, transmissible gastroenteritis virus; IBV, infectious bronchitis virus.

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