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Food as medicine: A possible preventive measure against coronavirus disease (COVID-19)

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The recent and ongoing outbreak of coronavirus disease (COVID-19) is a huge global challenge. The outbreak, which first occurred in Wuhan City, Hubei Province, China and then rapidly spread to other provinces and to more than 200 countries abroad, has been declared a global pandemic by the World Health Organization. Those with compromised immune systems and/or existing respiratory, metabolic or cardiac problems are more susceptible to the infection and are at higher risk of serious illness or even death. The present review was designed to report important functional food plants with immunomodulatory and anti-viral properties. Data on medicinal food plants were retrieved and downloaded from English-language journals using online search engines. The functional food plants herein documented might not only enhance the immune system and cure respiratory tract infections but can also greatly impact the overall health of the general public. As many people in the world are now confined to their homes, inclusion of these easily accessible plants in the daily diet may help to strengthen the immune system and guard against infection by SARS-CoV-2. This might reduce the risk of COVID-19 and initiate a rapid recovery in cases of SARS-CoV-2 infection.

KEYWORDS
COVID-19, immunomodulators, medicinal plants, respiratory tract infections, SARS-CoV

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1 | INTRODUCTION

Coronaviruses (CoVs) are enveloped, positive-sense, single-stranded RNA viruses belonging to the family Coronaviridae. CoVs can affect the respiratory and digestive systems of animals and humans but were not considered as seriously infectious to humans until the outbreak of severe acute respiratory syndrome (SARS) in 2002 and 2003 in Guangdong, China (Guan, et al., 2003) and Middle East respiratory syndrome (MERS) in the Middle East in 2013 (Hemida, et al., 2013). SARS infected more than 8,000 people and caused the deaths of nearly 800 people, with a fatality rate of 9.6%. Similarly, MERS was confirmed in more than 2,500 people, causing the deaths of more than 850 people, with a mortality rate of 35%. These two outbreaks led to extensive research in understanding CoVs. The origins of SARS-CoV and MERS-CoV are thought to be from bats, and they were transmitted to humans through civets and camels, respectively (Cui, Li, & Shi, 2019; Hu et al., 2017). Due to the high occurrence, varied distribution, great genetic diversity and recurrent recombination of their genomes and their elevated human–animal interfaces, CoVs are very likely to emerge periodically in humans.

The ongoing pandemic occurred approximately 7 years after the outbreak of MERS-CoV. The International Committee on Taxonomy of Viruses named the virus as SARS-CoV-2, which causes coronavirus disease (COVID-19). On 30 December 2019, a first four pneumonia cases were reported by Wuhan Municipal Health Commission in Wuhan City, Hubei Province, China (Zhu et al., 2020). All of these cases were linked to the Huanan Seafood Wholesale Market, a live animal and seafood market in Jianghan District, Wuhan. The local government afterwards took prompt sanitation and disinfection measures to prevent the infection from spreading. The symptoms of the cases documented were: fever, breathing problems, coughing, SARS, and kidney failure in severe cases (WHO, 2020). The number of cases increased rapidly, and many more were identified in other cities of China and now in more than 200 countries (Figure 1). The latest report issued by World Health Organization (WHO) confirmed more than 3.8 million cases and more than 260,000 deaths worldwide. Li, et al. (2020) reported that a large proportion of infected patients were above the age of 60 years, and most of them were male, which suggests that these people are not immune competent. Moreover, it was also reported that most of the patients who died of SARS-CoV-2 were already suffering from several other medical problems (Hong Kong Centre for Health Protection, 2020). This clearly indicates that a

healthy immune system and general good health are crucial for alleviating the risk factors associated with COVID-19 and for increasing the chances of survival and recovery. Moreover, a healthy immune system helps the host to control and prevent several pathogenic infections (Chaplin, 2010).

In the current situation, measures to control infection risk are crucial for disease management. Several preventive measures have been advised for general public health including, hand and respiratory hygiene and safe food practices (in relation to raw animal products) in order to reduce the risk from and transmission of SARS-CoV-2 (WHO, 2020). In the current situation, there is a great need to propose effective preventive therapeutic measures that might alleviate the risk of COVID-19 infection until a vaccine or other antiviral agents are designed.

Plants have been used for centuries in almost all cultures worldwide as traditional medicines to cure many chronic infections, including viral diseases (Salehi et al., 2019a; Sharifi-Rad, et al., 2019; Salehi, et al., 2020). In recent decades, scientists have been attempting to scientifically validate the health-improving potential of functional and nutraceutical foods (Sharifi-Rad, et al., 2018; Salehi et al., 2019b; Salehi et al., 2019c). The aim of the present review is to document common and easily accessible functional food plants that can modulate the immune system and are biologically active against several medical problems arising from respiratory tract infections. We hypothesise that functional food plants may help individuals to overcome the infection by: (a) modulating the body's immune system, (b) generating antiviral activity against the infection, and (c) reducing other respiratory problems. This review will provide guidelines to the general public to include important medicinal food plants in their daily diet for strengthening and improving their immune system and overall health.

2 | METHODOLOGY

The data on medicinal food plants were retrieved and downloaded using different search engines, including Web of Science, PubMed, Google Scholar and Scopus. The present review includes only those articles that were published in English-language journals that meet required quality standards in relation to information. Moreover, only those medicinal plants that are commonly used as vegetables, fruits, spices and are active against respiratory tract infections were
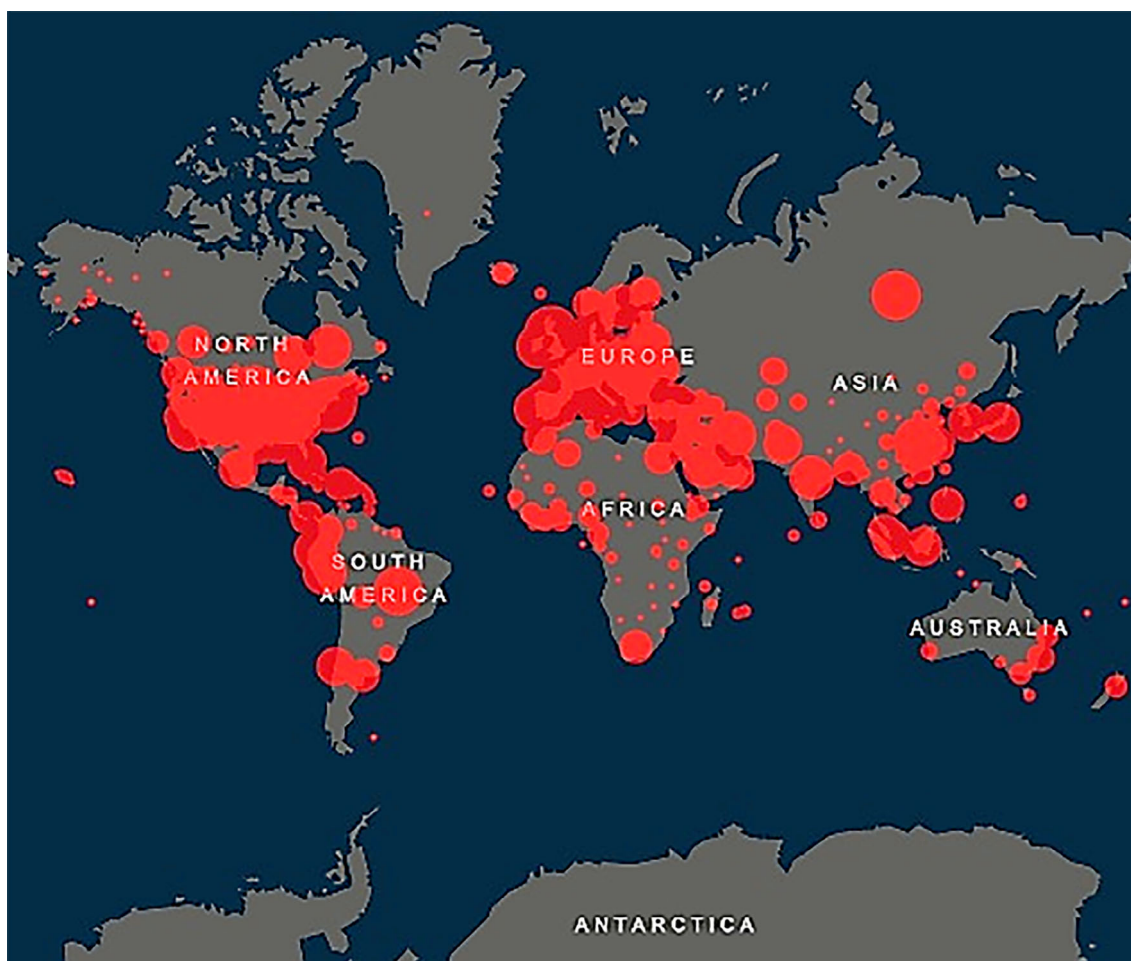
FIGURE 1 Global distribution of COVID-19. *Source:* Center for Systems Science and Engineering (CSSE, Johns Hopkins University, 28 April 2020) [Colour figure can be viewed at wileyonlinelibrary.com]

selected. Different keywords were used for the data search, including 'ethnomedicinal usage of food plants', 'immunomodulatory action of functional food plants' and 'antiviral and biological activities'. The data were organised and analysed in Microsoft Excel (2010) software and then summarised in to tables and figures. For the taxonomic treatment of the documented plant species, the online botanical databases 'The Plant List' (Royal Botanic Gardens, Kew, UK and Missouri Botanical Garden, USA) and 'Tropicos' (Missouri Botanical Garden, USA) were used.

3 | DISCUSSION

Plants have been cultivated and used by humans for a very long time, providing not only food but also medicines for the treatment of chronic infections. Large numbers of ethnomedicines are currently being evaluated for their therapeutic properties. The medicinal properties of plants are due to the chemicals present in the different plant parts, which act in the same manner as conventional medical drugs. Recently, there has been a growing interest in using medicinal plants

for modulating the human immune system, and researchers have suggested that different classes of compounds, including alkaloids, flavonoids, terpenoids and polysaccharides, possess immunomodulatory properties with fewer side effects than allopathic drugs. (Wadood, et al., 2013).

3.1 | Immunomodulatory functional food plants

The human immune response is the body's most important defence mechanism against disease, and the survival of humans is greatly dependent on this system of fighting against foreign pathogenic microorganisms, including viruses. The possible immunomodulatory function of plants is a recent concept in the field of phytomedicines. Immunomodulators not only enhance humoral and cell-mediated immunity but also activate non-specific immune responses such as activation of the natural killer (NK) cells, macrophages, granulocytes and complement systems, which enhance resistance to infections non-specifically. Activation of these important immune cells results in the production of various molecules such as interferons (IFNs),

cytokines and chemokines involved in the enhancement of immune responses. In most SARS autopsies, the numbers of several immune cells present in the spleen, including lymphocytes [cluster of differentiation (CD)4+, CD8+, CD20+], dendritic cells (DT) and NK cells, decreased (Zhan, et al., 2006). Other studies have shown that the size of macrophages increased by more than 100%, and macrophages and T-lymphocytes have been reported to be infected with high viral loads (Farcas, et al., 2005; Gu, et al., 2005).

In this review, we have documented 20 functional food plants with immunomodulatory and antiviral properties, including liquorice (*Glycyrrhiza glabra* L.), garlic (*Allium sativum* L.), tea (*Camellia sinensis* [L.] Kuntze), ginger (*Zingiber officinale* Roscoe), turmeric (*Curcuma longa* L.), pomegranate (*Punica granatum* L.), black pepper (*Piper nigrum* L.) and several others (Table 1). These plants have been reported to induce the immune system in several ways.

For example, liquorice has been used as a medicinal and flavouring herb since ancient times. Traditionally, the dried roots are first crushed and then boiled to prepare an extract. The extract can be dried to a dark paste or powder and taken orally to treat different types of chronic infections (Asl & Hosseinzadeh, 2008). The root contains a saponin named glycyrrhizin, which is responsible for immunomodulation, antiviral and other biological activities (Seki et al., 2008). Innate immunity and adaptive immunity both greatly depend on the activity and function of the white blood cell (WBC) count, and it is also evident that most of the immune cells are produced from haematopoietic stem cells of bone marrow. Raphael and Kuttan (2003) reported that mice treated with glycyrrhizic acid showed an increased in WBCs, bone marrow cellularity and α-esterase positive cells. In addition, they analysed the humoral immune response by measuring the production of antibodies and the number of antibody-producing cells in the spleen, which were found to have increased in the treated mice. Moreover, the *in vitro* results showed that glycyrrhizin promotes the growth response of splenic T-lymphocytes to anti-CD3 monoclonal antibodies or concanavalin A (Con A) through improvement of interleukin-2 (IL-2) and IL-2 receptor (IL-2R) expression (Zhang, et al., 1993). Glycyrrhizin affects some post-receptor stages of signal transduction because the increased production of IL-2 by glycyrrhizin was also found in spleen cells. Dai et al. (2018) reported an increase in lipopolysaccharide-induced IL-12 p70 and p40 protein production in glycyrrhizin-treated mice by peritoneal macrophages due to up-regulation of IL-12 p35 and p40 messenger RNAs, which was associated with enhanced NF-kB (a protein complex that controls DNA transcription) activation, cytokine production and cell survival. It was further found that glycyrrhizin can interfere with immune responses by acting on dendritic cells (DCs). The results of flow cytometry analysis showed that in the mice spleen glycyrrhizin can up-regulate the expressions of maturation markers (MHC-II, CD40 and CD86) on DCs, which led to enhanced production of IL-12 by these cells. In addition, glycyrrhizin enhanced the production of T-cells and cytokines (IFN-c and IL-10) and reduced the production of IL-12 (Bordbar, Karimi, & Amirghofran, 2012). Liquorice polysaccharides were also found to possess immunomodulatory properties as investigated in invivo conditions. Low molecular weight polysaccharides showed

increased thymus/spleen index, T-lymphocytes (CD4+ and CD8 + 0) populations, IL-2, IL-6, IL-7 levels and decreased tumor necrosis factor alpha (TNF-α) levels (Ayeka, Bian, Githaiga, & Zhao, 2017). Extensive research on liquorice shows that it has strong immunomodulation activity and could be most helpful in enhancing the body's immune system against pathogenic infections.

Garlic has been one of the most popular herbal remedies since ancient times. It is believed that freshly crushed garlic mixed with honey, or without, can strengthen the immune system, as well as having antiviral and other biological properties, which might be due to the presence of several bioactive sulphur-containing compounds including sulphoxide, proteins and polyphenols (Anywar et al., 2019; Sahoo & Banik, 2018). Several studies have suggested interesting beneficial effects of garlic on the immune cells and on immunity in general. For example, Kuttan (2000) reported the immunostimulatory effects of sulphur compounds (diallyl sulphide, diallyl disulphide and allyl methyl sulphide) in mice. Amongst the compounds studied, mice treated with diallyl disulphide showed higher numbers of WBCs (17,900 cells/mm^3) and antibody titers than mice treated with other compounds. These compounds also significantly improved the bone marrow cellularity, the number of α-esterase positive cells and the number of plaque-forming cells in the spleen. Other studies have reported that garlic protein fraction 4 (F4) improved the cytotoxicity of human peripheral blood lymphocytes (PBL) against NK sensitive (K562) and NK-resistant (M14) cell lines. F4 further improved IL-2-induced and Con A-induced proliferation and their receptor expressions of PBL (Ishikawa et al., 2006). Moreover, liquid garlic extract and protein fraction showed modulatory effects on macrophages and T-lymphocyte functions. These findings were further supported by the identification of three protein components of ~13 kD (QR-1, QR-2 and QR-3) from garlic extract exhibiting mitogenic activity on certain immune cells that include, lymphocytes, mast cells and basophils (Clement et al., 2010). Other studies have shown that garlic oil has dual effects on T-helper cells; for example, at low concentrations, the response of T-cells was elevated towards that of the Th1 type, whereas at high concentrations, the response triggered the Th2 type (Liu et al., 2009). However, another study reported that oral garlic administration supported the Th2 response by increasing IL-4 production in the spleen lymphocytes of rats (Zamani et al., 2009). In addition, using peripheral blood monocytes, aged garlic extract up-regulated IL-10 by inhibiting the production of pro-inflammatory cytokines such as TNF-α and IL-6, whereas it decreased IL-12 production, which could further down-regulate pro-inflammatory cytokines such as interferon gamma IFN-γ and IL-2 produced by T-cells (Gazzinelli, Oswald, James, & Sher, 1992; Hodge, Hodge, & Han, 2002). The immunostimulatory potential of garlic could be beneficial in clinical applications because it can boost both innate and specific cell immunity as well as can enhance host resistance.

Similarly, other documented plants also possess immunostimulatory properties, such as curcumin derived from *C. longa*, which can interact with several types of immune cells, including dendritic cells, B- and T-lymphocytes, macrophages and cytokines (Catanzaro et al., 2018; Momtazi-Borojeni et al., 2018) and enhance the defence

TABLE 1 Immunomodulatory and anti-viral functional food plants

Plant	Family	English Name	Part Used	Formulation	Compounds	References
Allium cepa L.	Amaryllidaceae	Onion	Bulb	Crushed & mixed with honey	Quercetin, thiosulfinates, and anthocyanins	Mirabeau and Samson, 2012; Gansukh et al., 2016
Allium sativum L.	Amaryllidaceae	Garlic	Bulb	Crushed & mixed with honey	Diallyl disulphide, alliin, polyphenols, proteins (QR-1, QR- 2, and QR-3)	Ishikawa et al., 2006; Clement et al., 2009; Liu et al., 2009; Mehrbod et al., 2009; Zamani et al., 2009; Sahoo and Banik 2018; Anywar et al., 2019;
Berberis vulgaris L.	Berberidaceae	Barberry	Fruit, stem and root	Boiled extract and poultice	Berbamine, berberine	Wu et al., 2011; Shin et al., 2015; Kalmarzi et al., 2019
Camellia sinensis (L.) Kuntze	Theaceae	Tea Plant	Leaf	Boiled and drunk	Catechins, quercetin, gallic acid, theaflavin-3,3´-digallate	Zvetkova et al., 2001; Chen et al., 2005; Chattopadhyay et al., 2011; Kumar et al., 2012; Lee et al., 2014; Karimi et al., 2016; Reygaert et al., 2018
Carica papaya L.	Caricaceae	Papaya	Fruit and leaves	Leaves are ground to prepare juice; fruit can be directly eaten	Caricaxanthin, violaxanthin, zeaxanthin, carpaine, dehydrocarpaine I and II and cardenolide	Kala, 2012; Pandey et al., 2016; Radhakrishnan et al., 2017;
Citrus aurantium L.	Rutaceae	Bitter orange	Fruit and Peel	Dried peel or fruit juice	Polysaccharides, polyphenolic compounds	Shen et al., 2017; Mannucci et al., 2018
Curcuma longa L.	Zingiberaceae	Turmeric	Rhizome	Pounded, tincture, powder	Curcumin	Srivastava et al., 2011; Catanzaro et al., 2018; Momtazi-Borojeni et al., 2018; Anywar et al., 2019
Ficus carica L.	Moraceae	Fig	Fruit, leaves	Decoction with honey	Terpenoids, anthocyanins, steroids	Idolo et al., 2010; Patil et al., 2010c; Aref et al., 2011a, b
Glycine max (L.) Merr.	Fabaceae	Soybean	Seeds	Cooked or roasted	Isoflavones, flavonoids, phytosterols, organic acid and saponins	Hayashi et al., 1997; Kinjo et al., 1999; Anitha et al., 2015
Glycyrrhiza glabra L.	Fabaceae	Liquorice	Root	Dried roots extracted. The extract is vacuum dried to a dark paste, or maybe dried to a powder	Glycyrrhizin	Jeong and Kim, 2002; Cinatl et al., 2003; Raphael and Kuttan, 2003; Asl & Hosseinzadeh 2008; Seki et al., 2008; Michaelis et al., 2010; Smirnov et al., 2012
Lycium barbarum L.	Solanaceae	Wolfberry	Fruit	Fresh fruit directly eaten	Polysaccharide-protein complexes, phenolic compounds	Tang et al., 2012; Cheng et al., 2015; Byambasuren et al., 2019
Mangifera indica L.	Anacardiaceae	Mango	Bark, leaves, roots, fruits, and flowers	Boiling or powdering of bark, leaves, root and flowers, while fruit can be directly eaten	Flavonoids, xanthones (Mangiferin), phenolic acids, triterpenes	Makare et al., 2001; Garrido et al., 2005; Rawi et al., 2019

TABLE 1 (Continued)

Plant	Family	English Name	Part Used	Formulation	Compounds	References
Morus alba L.	Moraceae	Mulberry	Fruit leaf, root	Fruit juice, leaves and root bark decoction or tea	Carotene, vitamin B1, folic acid, folinic acid, vitamin D, polyhydroxylated alkaloids, glycoprotein, Anthocyanins, benzofurans, stilbenes	Singh et al., 2013; Grienke et al., 2016. Wei et al., 2016; Kim and Chung, 2018
Nigella sativa L.	Ranunculaceae	Black Cumin	Seeds	Roasted anend eat	Quinones, alkaloids, saponins	Ahmad et al., 2013; Koshak et al., 2018
Piper longum L.	Piperaceae	Long pepper	Fruit and root	Decoction	Piperine	Koul & Kapil, 1993; Tripathi et al., 1999; Sunila and Kuttan, 2004; Kumar et al., 2010
Piper nigrum L.	Piperaceae	Black pepper	fruit	Dried and used as spice	Piperine	Majeed and Prakash, 2000; Chaudhry and Tariq, 2006
Prunus domestica L.	Rosaceae	Plum	Fruit	Eaten fresh	Anthocyanins, protocatechuic acid	Kayano et al., 2002; Walle et al., 2003; Rasne et al., 2018
Psidium guajava L.	Myrtaceae	Guava	Fruit, shoots, leaves	Fruit can be directly eaten. Decoction and poultice of leaves and shoots	Phenolic, flavonoid, carotenoid, terpenoid and triterpenes	Gutierrez et al., 2008; Sriwilaijaroen et al., 2012; Ravi and Divyashree, 2014
Punica granatum L.	Lythraceae	Pomegranate	Fruit, Seeds, Bark	Fruit juice, decoction of seeds, dried bark	Anthocyanins, fatty acids, alkaloids, vitamins	Bhowmik et al., 2013; Howell and Souza, 2013; Moradi et al., 2017
Zingiber officinale Roscoe	Zingiberaceae	Ginger	Root	Dried or roasted and eaten with honey	Essential oil, crude fiber, proteins, fatty oils, carbohydrates	Sahoo and Banik, 2018; Mahboubi, 2019

Note: 1) Immunomodulatory properties of these plants are for overall body immune system, not for any particular disease, infection or organ. 2) while antiviral properties are mostly against respiratory tract infectious viruses (references are provided for all plants, but only some of them are discussed in this article)

mechanism of the host. A black tea (*C. sinensis*) decoction in cultured human peripheral mononuclear cells showed increased lympho-proliferative action at 72 h (Chattopadhyay et al., 2012). In human mononuclear cell cultures, green tea (also from *C. sinensis*) extract showed increased production of neopterin (potential marker for activation of cell-mediated immunity) in unstimulated peripheral mononuclear cells, whereas a reduction in neopterin was observed in cells stimulated with Con A, phytohemagglutinin and gamma interferon, confirming the immunomodulatory properties of green tea (Zvetkova et al., 2001). These immunostimulatory properties of black tea and green tea are due to the presence of (–)-epigallocatechin gallate, quercetin and gallic acid in the leaves (Kumar et al., 2012). Furthermore, Patil, Bhangale, and Patil (2011) found that oral administration of ethanolic leaves extracts of the common fig (*Ficus carica* L.) ameliorated humoral and cell-mediated immune responses. Traditionally, this plant has also been used against several respiratory, gastrointestinal, inflammatory and cardiovascular problems (Duke, Bogenschutz-Godwin, Du Celliar, & Duke, 2002). Moreover, methanolic extracts of mango (*Mangifera indica* L.) bark (rich in mangiferin) enhanced delayed type hypersensitivity and humoral antibody titers, confirming its possible immunomodulatory properties (Makare et al., 2001). *In vivo* oral administration of hexane leaves extract of mango increased the WBC count and the size of the thymus and spleen, indicating immuno-modulation in WBCs and bone marrow haematopoietic cells (Shailajan, Menon, Kulkarni, & Tiwari, 2016). Other plants reported in this review, including pomegranate (*P. granatum*), black pepper (*P. nigrum*), long pepper (*Piper longum* L.), black caraway (also known as black cumin; *Nigella sativa* L.), barberry (*Berberis vulgaris* L.), papaya (also known as pawpaw; *Carica papaya* L.), white mulberry (*Morus alba* L.), Chinese boxthorn (also known as the Himalayan goji; *Lycium barbarum* L.), bitter (or Seville) orange (*Citrus aurantium* L.), European plum (*Prunus domestica* L.) and soybean (or soya bean; *Glycine max* [L.] Merr.) all possess immunomodulatory activity in one way or another, supporting our first hypothesis that these functional food plants boost the immune response of the host and could be used as a preventive measure against COVID-19. As mentioned earlier, in SARS autopsies, reductions in the concentrations of various immune cells were observed. Moreover, clinical evidence has shown the infection of T-lymphocytes and macrophages/monocytes in circulating blood, spleen, lungs and lymph nodes in SARS autopsies (Zhan et al., 2006; Farcas et al., 2005). These immune cells are involved in both the innate and adaptive immune systems, and any infection in these cells would result in a weakened immune system in SARS patients. These findings further strengthen our hypothesis and give an insight into the possible role of these reported phytocompounds in clinical applications against COVID-19.

3.2 | Antiviral functional food plants

According to WHO, respiratory tract infections are the leading cause of mortality amongst all infectious diseases. Viral diseases are life-threatening due to their rapid outbreak in developing as well as developed countries, whereas treating them is a huge challenge due to, easy adaptation, resistant viral pathogens, and the emergence of new viral strains and the ineffectiveness of antibiotics (Amber, Adnan, Tariq, & Mussarat, 2017). The first genome sequence of SARS-CoV-2 has been compared with those of SARS-CoV and MERS-CoV, and the results show that SARS-CoV-2 shares a closer genome sequence homology with SARS-CoV, mostly in ORF1a and S-proteins (which facilitate the attachment of the virus to the host receptor). Later, it was found that SARS-CoV-2 showed an 85% identity with SARS-like CoV (bat-SL-CoVZC45, MG772933.1). Following these observations, SARS-CoV-2 has been clustered with beta-coronavirus genera, including SARS and SARS-like coronaviruses (Xu, et al., 2020; Zhu, et al., 2020). The initial symptoms of SARS-CoV-2 infection include fever, coughing, sneezing and shortening of breath, whereas severe symptoms include lower respiratory tract infection or pneumonia (Li et al., 2020). In histopathological investigations, the lungs of SARS patients showed diffuse alveolar damage, collapse of alveoli, extensive oedema, fibrous tissue in the alveolar spaces, hyaline membrane formation, desquamation of alveolar epithelial cells, leading to acute lung damage or pneumonia (Gu & Korteweg, 2007).

All of these investigations clearly indicate that this virus causes respiratory distress, and, bearing this in mind, several common and easily accessible functional food plants have been documented in this review that possess immunomodulatory, antiviral (especially for respiratory tract infections) and other biological activities. For example, glycyrrhizin isolated from *G. glabra* was tested on SARS-CoV-infected patients admitted to the Clinical Centre of Frankfurt University, Germany (Cinatl et al., 2003). The results of this study showed that glycyrrhizin was the most effective inhibitor of SARS-CoV replication, with a selectivity index of 67 in Vero cells, compared with other tested compounds. Furthermore, this compound inhibited not only replication but also the adsorption and penetration of the virus. Although the exact mechanism by which glycyrrhizin inhibits SARS-CoV adsorption, penetration and replication is unclear, a literature review revealed that it affects cellular signalling pathways, including protein kinase C, transcription factors and casein kinase II. Also, glycyrrhizin enhances production and expression of nitrous oxide (NO) in macrophages, which remarkably inhibits virus replication (Jeong & Kim, 2002; Lin, et al., 1997). In addition, glycyrrhizin possesses potent activity against influenza A virus (H5N1), which is also an emerging virus and, like SARS-CoV, targeting the lungs. These viruses also have certain pathological similarities and differences. Previous studies have reported that a 100 μg/ml concentration of glycyrrhizin reduced the capacity of H5N1 to affect chemokine and interleukin (IL-6) production, as well as H5N1-induced apoptosis (Michaelis et al., 2010). H5N1 replication was found to be enhanced at the high-mobility-group box1 (HMGB1) DNA binding site, but glycyrrhizin inhibited the polymerase activity of H5N1 by affecting HMGB1 binding to DNA (Smirnov et al., 2012). Therefore, this compound could be considered as a potent antiviral agent and should be given serious attention. Moreover, the 3C-like protease of SARS-CoV is an important target for drug discovery and development because it is involved in proteolytic procession during maturation of the virus.

Chen et al. (2005) tested different compounds derived from *C. sinensis*, including tannic acid, 3-isotheaflavin-3-gallate (TF2B) and several catechins, on 3CL protease activity. It has been suggested that catechins do not show inhibitory potential; however, both tannic acid (IC$_{50}$ = 7 μM) and TF2B (IC$_{50}$ = 3 μM) were found to be potent inhibitors. These results suggest the potent role of the tea plant against SARS-CoV infection, but further investigation of its possible inhibitory action on the replication of CoV in cell culture might strengthen its claim to antiviral activity. Similar to SARS-CoV and influenza viruses, respiratory syncytial virus (RSV) also causes acute respiratory infections and is considered a major threat to people of different ages globally. Berberine, an alkaloid isolated from *B. vulgaris*, has been tested and found to significantly reduce RSV replication in epithelial cells by decreasing synthesis of mRNA and viral proteins. Such inhibition might be due to suppression of RSV-induced phosphorylation of p38 mitogen-activated protein kinase, which is very important for successful infection of RSV (Shin et al., 2015). Furthermore, curcumin derived from *C. longa* decreased the yield of influenza virus by more than 90% in cell culture at 30 μM concentration, which might have been because it affected the synthesis of viral proteins such as haemagglutinin, neuraminidase and matrix protein (Chen et al., 2010). Curcumin was also found to be effective against RSV, by inhibiting its replication and budding in the nasal epithelial cells of humans, and it also improved epithelial barrier activity (Obata, et al., 2013). Similarly, other reported immunomodulatory functional food plants in this review also exhibit elevated antiviral activity, particularly against viruses causing respiratory tract problems, and so should be considered as potential antiviral agents.

3.3 | Other biological properties

The medicinal food plants described in this review not only possess immunomodulatory and antiviral properties but also exhibit several other biological actions, including antibacterial, antifungal, anti-inflammatory, antioxidant, anti-nephroprotective and anticancer activity

(Figure 2). Curcumin derived from *C. longa* was tested against *Staphylococcus aureus* surface protein attaching transpeptidase (Sortase A) and showed inhibitory activity at an IC$_{50}$ of 13.8 mg/ml concentration. However, curcumin did not show an inhibitory effect on the growth of the bacteria, but both pathogenesis and acute infection were decreased due to inhibition of Sortase A (Park, et al., 2005). *S. aureus* is a multi-drug-resistant bacterium causing respiratory tract problems, including pneumonia and skin infections. *C. longa* is also very effective against several other groups of pathogenic bacteria and fungi, including *Escherichia* spp., *Pseudomonas* spp., *Aspergillus* spp. and *Candida* spp. (Praditya, et al., 2019). It has been shown that oral administration of *C. longa* can reduce inflammation by inhibiting the synthesis of inflammatory prostaglandin and neutrophil functions effectively (Cronin, 2003). An ethanolic extract of *F. carica* was found to be a potent antipyretic (reducing body temperature) in a dose-dependent manner (100, 200 and 300 mg/kg; Badgujar, Patel, Bandivdekar, & Mahajan, 2014). An ethanolic extract of *F. carica* was further reported to be active against carrageenan-induced rat paw oedema, and hence possess anti-inflammatory properties (Patil and Patil, 2011). *F.icarica* is also very potent against several pathogenic microbial strains, different cancer cell lines and other biological problems of humans (Badgujar et al., 2014). *In vitro* investigation revealed that an aqueous extract of *G. glabra* showed increased inhibition of bacteria causing respiratory tract infections, including *S. aureus* and *S. pyogenes* (Damle, 2014) cultures, which may have been due to the presence of glycyrrhizin. Furthermore, glycyrrhizic acid displays potent hepatoprotective activity by reducing free radical production and lipid peroxidation (Jeong, et al., 2002). Piperine extracted from *P. nigrum* also showed antimicrobial properties by inhibiting the growth of *S. aureus* due to its high activity against the NorA efflux pump, which contributes to microbial resistance to antibiotics (Sangwan et al., 2008). Black pepper extracts were also found to be very potent against other bacterial infections caused by *E. coli*, *Pseudomonas* spp., *Bacillus* spp., and so forth (Butt et al., 2013). All of the documented plants in this review have a large range of pharmacological properties, and so could be very useful for maintaining good health.
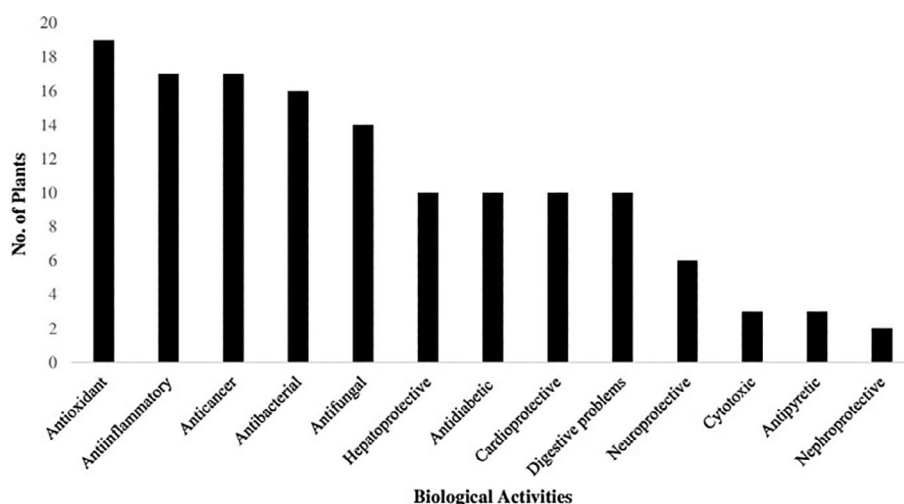
FIGURE 2 Biological activities of functional immunomodulatory and antiviral food plants

In SARS cases, a number of co-infections were reported being caused by *S. aureus*, *Streptococcus* spp., *Pseudomonas aeruginosa*, *Aspergillus* spp. and *Klebsiella* spp. (Chong, et al., 2004; Hwang, et al., 2005). Moreover, as mentioned earlier, most of the patients who died as a result of COVID-19 already had several other health-related problems. Therefore, the functional food plants documented in this review would not only enhance the immune system and cure respiratory tract infections but would also greatly impact the overall health of the general public. This could possibly reduce the risk of COVID-19 and initiate a rapid recovery in cases of SARS-CoV-2 infection. In the current situation of COVID-19, most of the people in China and other countries are restricted to their homes; therefore, these functional food plants, which are easily accessible, could serve them as a cheap way of maintaining a healthy immune system and general good health. It is highly recommended to include these medicinal food plants in the daily diet as a preventive measure for effective health management.

3.4 | Toxicology of functional food plants

In contrast of the positive effects, some functional food plants also possess toxic effects to the human body if taken in an excessive amount. For example; liquorice and glycyrrhizin lead to certain harmful impacts on human health if the consumption level is higher and the duration of consumption is prolonged. It is well known that licorice produces less side effects if taken orally, rather than by intraperitoneal or intravenous injection, but even oral administration for several weeks or longer can cause toxic effects (Hosseinzadeh, et al., 2005; Nassiri Asl & Parvardeh, 2015). Previous studies reported that the most important side effects of licorice and glycyrrhizin are hypertension and hypokalemic-induced secondary disorders, with the acceptable daily intake reported for glycyrrhizin as 0.2 mg/kg/day (Nazari, Rameshrad, & Hosseinzadeh, 2017; Snafi-Al, 2018). Moreover, a low dose of liquorice and glycyrrhizin can be toxic for people having cardiovascular, kidney and blood pressure problems. Clinical evidence also suggests that the daily intake of low doses this plant species can cause serious complications in pregnant women and breast-feeding children (Choi, et al., 2013; Cuzzolin, et al., 2010).

While the Food and Drug Administration considers garlic as safe for humans, the species can induce several complications (diarrhoea, dizziness, nausea, vomiting, headache and flatulence) if ingested in high doses especially on an empty stomach. Oral or intraperitoneal administration of garlic at 50 mg/kg concentration per day did not show any toxic effects on lung and liver tissues, whereas 250–1,000 mg/kg concentration per day resulted in severe deformities in the lung and liver tissues of the rats (Rana, Pal, Vaiphei, Sharma, & Ola, 2011). In another study, garlic extracts at the concentration of 300–600 mg for 3 weeks resulted in delayed growth in male and female rats (Mikaili, Maadirad, Moloudizargari, Aghajanshakeri, & Sarahroodi, 2013). The recommended doses of the garlic are 4 g (raw form) or 7.2 g (aged garlic extract) or one tablet of dried garlic powder

twice or thrice per day for adults (Tattelman, 2005). Curcumin derived from *C. longa*, does not cause any severe toxicity at a dose of up to 8 g per day, over a short period of time. However, human based studies showed that curcumin at doses ranging from 0.9 to 3.6 g per day for 1–4 months can cause nausea and diarrhoea (Somasundaram, et al., 2002). In addition, higher amount of green tea consumption can pose hepatotoxic and gastrointestinal problems if taken on an empty stomach (Bedrood et al., 2018). Similarly, other functional food plants reported in this review also possess variety of toxic effects on living system if taken in higher amount and for longer period of time. Hence, it is really important to have an updated knowledge on the risk-benefits of functional food plants.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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