



Review article

Traditional foods with their constituent's antiviral and immune system modulating properties

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ABSTRACT

Background: Viruses are responsible for several diseases, including severe acute respiratory syndrome, a condition caused by today's pandemic coronavirus disease (COVID-19). A negotiated immune system is a common risk factor for all viral infections, including COVID-19. To date, no specific therapies or vaccines have been approved for coronavirus. In these circumstances, antiviral and immune boosting foods may ensure protection against viral infections, especially SARS-CoV-2 by reducing risk and ensuring fast healing of SARS-CoV-2 illness.

Scope and approach: In this review, we have conducted an online search using several search engines (Google Scholar, PubMed, Web of Science and Science Direct) to find out some traditional foods (plant, animal and fungi species), which have antiviral and immune-boosting properties against numerous viral infections, particularly coronaviruses (CoVs) and others RNA-virus infections. Our review indicated some foods to be considered as potential immune enhancers, which may help individuals to overcome viral infections like COVID-19 by modulating immune systems and reducing respiratory problems. Furthermore, this review will provide information regarding biological properties of conventional foods and their ingredients to uphold general health.

Key Findings and Conclusions: We observed some foods with antiviral and immune-boosting properties, which possess bioactive compounds that showed significant antiviral properties against different viruses, particularly RNA viruses such as CoVs. Interestingly, some antiviral and immune-boosting mechanisms were very much similar to the antiviral drug of COVID-19 homologous SARS (Severe Acute Respiratory Syndrome Coronavirus) and MERS (Middle East Respiratory Syndrome Coronavirus). The transient nature and the devastating spreading capability of COVID-19 lead to ineffectiveness of many curative therapies. Therefore, body shielding and immune-modulating foods, which have previous scientific recognition, have been discussed in this review to discern the efficacy of these foods against viral infections, especially SARS-CoV-2.

1. Introduction

Many different viruses can infect respiratory tract, a disease known as viral respiratory infection, which is now considering one of the life threatening diseases leading to a significant morbidity and mortality all over the World (WHO, 2020a, b). The most common viruses have the capacity to spread from person to person, therefore, people living in developing or developed countries are scared about the devastating infectious diseases due to their fast transmission. Researchers all over the world are facing a real challenge to prevent or treat them owing to some reasons such as simple alteration, high spread capacity, resistant viral pathogens, appearance of new viral strains, and the incompetence of antibiotics (Amber et al., 2017). Currently, coronavirus disease

(COVID-19) is an infectious disease caused by newly discovered coronavirus (CoVs) and making serious health problems worldwide. The virus belongs to the family, Coronaviridae in the order Nidovirales, having four subgroups, including α , β , γ , and δ coronavirus (Banerjee et al., 2019). It is evident that CoVs are a group of highly contagious, positive-sense viruses with single-strand RNA genome that causes deadly diseases by affecting respiratory, enteric, hepatic, and neurologic systems (Chan et al., 2013). Primarily, they caused enzootic infections to their hosts, such as bat/civet and dromedary; however, they caused a major outbreak to humans in the last century (Lau et al., 2005). Two coronaviruses, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) emerged in 2002 and 2012 which led to 10% and 35% mortality rate,

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respectively. It was reported that CoVs can cross their species barriers, which made a serious threat to humans (Schoeman and Fielding, 2019). To date, no effective therapeutic regimens or vaccines have been approved for the treatment of COVID-19. The first Wuhan Viral Pneumonia cases were reported in China in late December 2019. Later WHO has declared the virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has named the resultant disease as coronavirus 2019 (COVID-19) (WHO, 2020a, b). The report shows that human to human transmission is confirmed among close contacts (within 6 ft distance) due to its massive spreading capability (Li et al., 2020a, b). Like SARS-CoV and MARS-CoV, the SARS-CoV-2 also belongs to the β -coronavirus family. The high throughput sequencing of virus genome has revealed that COVID-19 possesses positive single strand RNA genome structure that is highly homologous to SARS-CoV and MARS-CoV genome (Chen et al., 2020). A recently published report claims that COVID-19 has shown more than 82% similarity to those of the SARS-CoV (Chan et al., 2020). The common symptoms of COVID-19 include respiratory syndromes, fever, cough, fatigue, shortness of breath, and dyspnea, which are very identical to that of SARS-CoV and MERS-CoV infected cases. In severe cases, the diseases cause pneumonia, severe acute respiratory syndrome, kidney failure, and even death. People of all ages with weak immune systems or certain diseases (diabetes, CVD, kidney disease, asthma, lung disease, and so on) are at high risk and experiencing death to COVID-19 pandemic (Liu et al., 2020). This virus has raised a global concern due to its high transmission capability with high mobility and mortality rate. It has been accounted that a vast number of infected patients were over the age of sixty years with major figures in male suggests that they are immune incompetent. Besides, the people who expired of SARS-CoV-2 were previously distressing from some other health troubles (Liu et al., 2020), which evidently points out that a hale and hearty immune system and general good health are vital for reducing the risk factors connected with COVID-19 and for rising the probability of survival and healing. Furthermore, good physical immune systems assist the host to manage and avert some pathogenic illnesses (Chaplin, 2010).

In the current pandemic, some effective measures should be figured out to control infection that can manage the progression of such kind of infectious disease. As a means to reduce the threat of contamination and transmission of SARS-CoV-2, a variety of protective actions have been directed to promote public health, including regular hand washing, covering coughs, lockdown, social distancing measures and safe food practices (WHO, 2020a, b). By considering this emergency situation, an effective and efficient COVID-19 preventive therapeutics are urgently needed that might decrease the threat of COVID-19 illness until vaccines or other antiviral agents are approved. Although, over the past century several vaccines have been evolved for preventing and controlling numerous viruses' even common influenza where it took a significant amount of time and cost, but the present aspect of coronaviruses necessitates alternative complementary remedies for Covid-19 (Mahmoud, 2016).

From ancient times, various parts of plants and their active constituents have widely been considered as a rich reservoir and used as a conventional curative agent for many chronic infections, including viral diseases (Salehi et al., 2020; Sharifi-Rad et al., 2019). In the modern era, researchers across the world are endlessly trying to establish various types of foods and traditional medicines that are required for improving health, which indicate the potentiality of foods as supplementary therapies (Sharifi-Rad et al., 2018; Salehi et al., 2020). In this review, we mainly focused on available traditional foods (plant, animal and fungi species) that have antiviral as well as immune-stimulating properties and are biologically active against several health complications caused by viral respiratory tract infections. Our findings suggested that foods having antiviral and immune-boosting properties perhaps assist persons to overcome the viral infections by: (i) boosting up the immune system, (ii) accelerating antiviral effectiveness against the infection, and (iii) decreasing other complications associated with respiratory systems. Furthermore, the present review will offer a direction regarding the roles

of traditional foods and their constituents to maintain people's general health by taking these foods in their regular diet.

2. Methods

A website-based searching strategy, particularly Google Scholar, PubMed, Medline, Web of Science, and Science Direct were used to access and collect articles published in different scientific journals. Several keywords were considered for the data search, including ethnomedicinal usage of traditional foods, antiviral foods, immune-modulatory action of foods, coronavirus, SARS, MERS, COVID-19, SARS-CoV-2, and so on. Moreover, the information on conventional foods such as spices, fruits, vegetables, and fermented foods that are effective against respiratory problems and possess immune modulating properties were also incorporated. The resource materials were collected from March, 2020 to May, 2020. Our exclusion criteria were to omit those resources, which had a very lower confidence level compared to literature on the same topic. In addition, we reviewed the guidelines related to COVID-19 published on the WHO database. Notably, at the present time literature relating to this continuous issue is growing rapidly therefore previously searched results may differ quickly.

3. Traditional foods (plant, animal and fungi species) having antiviral and immune-modulating effects

3.1. *Nigella sativa*

Nigella sativa (*N. sativa*) L. (Ranunculaceae) is an indigenous nutrient-rich herbaceous plant found around the world. The plant has various recognition in different languages e.g., black cumin, black seed, black-caraway (English), Habbah Al-Sauda, seed of blessing (Arabic), chernushka (Russian), çörekotu (Turkish), and Cyah-daneh in Persian (Amin and Hosseinzadeh, 2016). *N. sativa* has attracted the attention of many healers in ancient civilizations and researchers in recent times. Since ancient times, it is used in different forms to treat illness, including asthma, hypertension, diabetes, inflammation, cough, bronchitis, headache, eczema, fever, dizziness, and influenza (Amin and Hosseinzadeh, 2016). However, numerous scientific studies are being conducted to validate the traditional uses of small seed of this species. Documentary evidence shows that seeds of *N. sativa* possess differential efficacy, including antiviral effects (Table 1). Past studies have revealed that Thymoquinone (TQ) is the most prominent constituent of its seeds and since 1960, approximately 406 research reports have been published on the 'Pub Med' database regarding TQ (Khader and Eckl, 2014). Components of *N. sativa*, particularly TQ, enhances immune-modulatory effects by boosting humoral immune system and induced the expression of cytokines, which lead to early viral clearance (Amin and Hosseinzadeh, 2016; Forouzanfar et al., 2014; Umar et al., 2016; Yimer et al., 2019). A growing number of evidence suggested that TQ demonstrated a significant antiviral efficacy against avian influenza virus (Umar et al., 2016), murine cytomegalovirus (Salem and Hossain, 2000), and hepatitis C virus (Barakat et al., 2013), where serum interferon-gamma levels were elevated and the total number of CD4+ helper T cells as well as macrophages were also increased. Recently, it was reported that the TQ analogues, (chloroquine and hydroxychloroquine) might be effective therapeutic drugs for treating world pandemic COVID-19 (Gautret et al., 2020).

3.2. *Garlic*

Allium sativum (*A. sativum*) L. (Garlic) has a long history to be used as prophylactic as well as therapeutic and dietary plant in different cultures. In addition to other beneficial effects, antiviral activity of garlic is widely documented. Therefore, garlic has widespread usages as antiviral supplements in different parts of the world. Garlic is the main source of organosulfur compounds, especially allicin, diallyltrisulfide, and ajoene,

Table 1. Foods having anti-viral efficacy against different virus strains.

Name of foods	Major components	Mechanisms of antiviral action	Virus strains	References
<i>Nigella sativa</i>	Thymoquinone	Increased helper-T, and cytotoxic T cells. Decreased viral proteins (integrase, protease) and RNA-polymerase-II to prevent viral replication.	Avian influenza virus (H9N2), Murine Cytomegalovirus (MCMV), Hepatitis C virus (HCV)	Amin et al. (2016); Umar et al., (2016); Salem and Hossain, 2000; Barakat et al. (2013)
<i>Garlic</i>	Allicin, diallyltrisulfide and ajoene, quercetin.	Hinder viral attachment to host cell, alter transcription and translation of viral genome in host cell and also affect viral assembly.	Influenza A (H1N1), Human cytomegalovirus HCMV, Rhinovirus, HIV, and Herpes simplex virus	Mehrbod et al. (2009) Meng et al. (1993) Tsai et al. (1985) Bayan et al. (2014)
Cinnamon	Cinnamaldehyd, cinnamic acid, cinnamyl alcohol, coumarin and eugenol	Inhibited HIV protease, integrase, reverse transcriptase, sp1-related genes (cell cycle arrest), Inhibited viral replication by preventing the expression of viral polymerase and viral envelope protein neuraminidase.	HIV-1 and HIV-2, Influenza A, Parainfluenza (Sendai) virus, and HSV-1 virus, Dengue and chikungunya.	Premanathan et al. (2000) Hayashi et al. (2007); Mishra et al. (2020); Yusufzai et al. (2018).
Licorice root	Glycyrrhizin (GL), 18 β -glycyrrhetic acid (GA), liquiritigenin (LTG), licochalcone A (LCA), licochalcone E (LCE) and glabridin (GLD)	Affect release step during infecting cell and Inhibit HCV full length viral particles and HCV core gene expression. Reduce adhesion force and stress between CCEC and PMN, Reduce HMGB1 binding to DNA, and inhibit influenza virus polymerase activity. Reduce the levels of viral proteins VP2, VP6 and NSP2 during virus entry. Prevent viral attachment, internalization and stimulate IFN secretion.	SARS-CoV, Hepatitis C virus (HCV), Human immunodeficiency virus (HIV), Coxsackievirus B3 (CVB3), Influenza virus, Duck hepatitis virus (DHV), Enterovirus 71 (EV71), Coxsackievirus A16 (CVA16), Herpes simplex virus type 1 (HSV1), Rotavirus, Human respiratory syncytial virus	Cinatl et al. (2003) Matsumoto et al. (2013) Wang et al. (2009) Zhang et al. (2012) Smirnov et al. (2012) Soufy et al. (2012) Wang et al. (2013) Lacoinet et al., (2014) Hardy et al. (2012) Yeh et al. (2013)
Black pepper	Piperine	Inhibited viral entry by preventing glycoprotein synthesis.	Coxsackie virus type B3 (CVB3), Vesicular stomatitis, Indiana virus (an enteric virus), and Human para influenza virus (a respiratory infection causing virus)	Priya et al. (2017)
<i>Moringaoleifera</i>	Alkaloids, saponins, glycosides, niazimin, phenolic compounds and terpenoids	Inhibition of HIV-1 integrase and virion production. Inhibited viral protein synthesis or nuclear transport of viral nucleoprotein (NP). Down regulated pgRNA expression to prevent viral replication.	Foot and Mouth disease virus (FMDV), Equine herpes virus, Rhinovirus (+sense ss RNA virus), and Influenza virus H9, Epstein Barr virus (EBV), HSV-1 (Herpes simplex virus type 1), Hepatitis B virus (HBV), Newcastle Disease Virus (NDV), Infectious bursal disease (IBD) virus, HIV/AIDS	Younus et al. (2015) Ashraf et al. (2017) Murakami et al. (1998) Lipipun et al. (2003) Waiyaput et al. (2012) Chollom et al. (2012) Ahmad et al. (2014) Burger et al. (2002) Biswas et al. (2020)
Mushroom	Polysaccharides, terpenoids, proteins, Lentinan,	Inhibited HIV-1 protease, Inhibition of binding of HIV-1 gp120 to immobilized CD4 receptor and of reverse transcriptase activity of viruses.	Influenza A virus (H3N2), Pox and HIV virus, Cytomegalovirus	Teplyakova et al. (2012) Stamets (2005) Tochikura et al. (1987)
Yogurt	Probiotics	Hinders the adsorption, cell internalization of the virus. Promotes the production of metabolites and substances to show direct antiviral effect, and crosstalk(immunomodulation) with the cells in establishing the antiviral protection.	RNA viruses (CA16, CB3, CB4),Influenza virus	Choi et al. (2009)
Honey	Sucrose, fructose, proline, gluconic acid methylglyoxal	Employ RNA-interference, Increased pathogen-associated molecular pattern (PAMP) triggered signal transduction cascades, and reactive oxygen species generation.	Sucrose, fructose, proline, gluconic acid methylglyoxal	Shahzad et al. (2012) Zareie (2011) Watanabe et al. (2014)
Spirulina	Phycocyanin, phycocyanobilin, calcium spirulan (Ca-SP) Cyanovirin-N (CV-N), sulpholipid	Inhibit the replication of enveloped viruses, Interfere at the initial stage of viral cycle to the host cells, Interfere the reverse transcription of HIV-RNA.	HIV-I, Mumps, and Measles virus, Herpes simplex virus type-I, Human cytomegalovirus, Influenza virus, and Enterovirus 71	Hayashi et al. (1996) Rechter et al. (2006) Shih et al. (2003)

which impart antiviral property and boost immunity (Schandalik et al., 1992). Such organosulfur compounds can prevent host cell attachment of virus, change transcription and translation of viral genome in host cells and also affect viral assembly. Another organosulfur compound, e.g. quercetin, can inhibit viral multiplication by passing through the cell membrane (Sharma 2019). Mehrbod et al. (2009) reported that garlic has potent activity against influenza virus. Previous studies revealed that garlic extracts showed antiviral activity against cytomegalovirus (Meng et al., 1993), rhinovirus, HIV, herpes simplex virus, viral pneumonia, and rotavirus (Tsai et al., 1985; Bayan et al., 2014). Therefore, having bioactive compounds and their antiviral mechanism to prevent viruses, especially SARS-CoV-2 homologous RNA viruses, garlic might be considered as an effective candidate for preventing severity of viral infection (Anywar et al., 2020; Sahoo and Banik, 2018).

3.3. Cinnamon

Cinnamon is a very common culinary item, which has been used as a spice as well as home remedy in several cultures for centuries. *Cinnamomum zeylanicum* and *C. cassia* are two herbs of this genus. Bark is the only part that is used as spice or medical purposes. Cinnamon bark contains cinnamaldehyde, cinnamic acid, cinnamyl alcohol, coumarin, and eugenol as the major components (Usta et al., 2003). In addition to its proven health beneficiary effects, cinnamon may also protect the body against viral infections. Premanathan et al. (2000) reported that cinnamon bark was highly effective against HIV-1 and HIV-2, where they halt viral DNA replication machinery through the inhibition of HIV protease, integrase, and reverse transcriptase. They also inhibited vpr, sp1-related genes expression (cell cycle arrest), Tat, Rev, and glycosylation. Cinnamaldehyde derived from bark of cinnamon exhibited both *in-vitro* and *in-vivo* inhibitory effects against highly pathogenic influenza, Sendai virus, and HSV-1 virus by inhibiting viral protein synthesis at the post-transcriptional level (Hayashi et al., 2007). Coumarin compounds (eleutheroside B1, and thiazolyl-coumarin hybrids) showed anti-influenza activity by inhibiting the expression of chemokine genes, POLR2A gene and gene for nucleoprotein, which control viral replication by preventing the expression of viral polymerase and viral envelope protein neuraminidase (Mishra et al., 2020). Cinnamon also showed significant antiviral activities against the Dengue and chikungunya viral infections, where 4-thiazolidinone-coumarin derivatives potentially inhibited viral protease activity and a phytoalexin (hydroxylated derivative of coumarin) led to suppression of dengue virus replication by preventing the translocation high mobility group box 1 (HMGB1) protein in nucleus (Yusufzai et al., 2018). Besides, a newly synthesized coumarin derivative, 7-[6-(2-methylimidazole) hexyloxy] coumarin, exhibited antiviral activity by inhibiting the entry of virus into the host cell by damaging glycoprotein. In addition, it also down-regulated the virus-induced autophagy by regulating Akt-mTOR pathway, thereby exhibited anti-viral activity (Mishra et al., 2020). Therefore, the active constituents of cinnamon might be potential weapons for introducing as therapeutic antiviral molecules, especially anti-SARSCoV-2, where they shared the common mechanism against RNA viruses like coronavirus.

3.4. Licorice root

Licorice root (*Glycyrrhiza glabra*), also known as Josthimodhu in Bengali, Mulethi in Hindi and “gancao” (meaning-sweet grass) in China, has been used as a traditional Chinese remedy since ancient times. Licorice was native to Southern Asia and then it spread to the Middle East and Southern Europe before spreading throughout the continent. Licorice root is considered as a life-enhancing agent and many studies have shown that this root possesses many pharmacological activities such as antiviral, antimicrobial, anti-inflammatory, and antitumor. Many people just chew it and make tea with it to get various remedies. Sometimes, the combination of licorice root and ginger is widely used to treat respiratory and digestive disorder as folkloric medicine. Licorice root contains more than

20 triterpenes and nearly 300 flavonoids. Among them, glycyrrhizin (GL) and 18 β -glycyrrhetic acid (GA) are showing antiviral properties (Table 1) (Matsumoto et al., 2013; Wang et al., 2015). Previous studies highlighted that GL exhibited potent antiviral effects against SARS-Cov-2 related viruses *in vitro* studies, that is why it had been suggested to treat SARS as an alternative option at that time (Cinatl et al., 2003). Adianti et al. (2014) reported that licorice root containing GL can play a vital role in treating patients suffering from chronic hepatitis C by inhibiting HCV full length viral particles and their core gene expression. Moreover, previous studies have revealed that viral infection caused by HIV can be prevented by GL treatment (Wang et al., 2015). Zhang's and Smirnov's study explained that GL can be considered as a promising antiviral agent for the treatment of coxsackievirus B3 (CVB3) and influenza virus, respectively, where GL significantly reduces the expression of nuclear factor- κ B, interleukin-1 β , and interleukin-6 cytokines for CVB3-induced myocarditis and inhibits polymerase activity of influenza virus (Wang et al., 2009; Zhang et al., 2012; Smirnov et al., 2012). Soufy et al. (2012) proposed that GL exhibited strong immune-stimulant properties by activating T lymphocyte proliferation against duck hepatitis virus (DHV). GL was also active against enterovirus 71 (EV71), coxsackievirus A16 (CVA16) and herpes simplex virus type 1 (HSV1) infection (Wang et al., 2013; Laconi et al., 2014). Several studies showed that the GL was also active to inhibit rotavirus replication and human respiratory syncytial virus (HRSV) activity by the mode of internalization, stimulating interferon (IFN) secretion, and preventing viral attachment (Hardy et al., 2012; Yeh et al., 2013). Taken together, the antiviral potentiality of the licorice root that shared a similar antiviral mechanism of much possible COVID-19 therapeutics might be an important candidate against coronavirus.

3.5. Black pepper

Black pepper (*Piper nigrum* L.) is considered as “king of spices” in every cuisine throughout the world. From ancient times, as a medicinal agent it is playing a potential role in nutraceutical and pharmaceutical applications. Moreover, *P. nigrum* contains enormous bioactive compounds, which have been shown to be health beneficiary and these compounds have disease preventing properties such as antiviral, anti-inflammatory, antipyretic, immune, and bioavailability enhancing qualities. Alkaloids, flavonoids, terpenes, steroids, phenolic, unique amino acid, and polyose are the major phytochemicals in peppers. Studies revealed that piperine, an alkaloid, has medicinal properties and effective against pungency (Vasavirama and Upendar, 2014). Black pepper is the wealthy source of healing agent for treating many diseases, including infectious diseases. As a strong antimicrobial agent, black pepper showed potential antiviral activity against coxsackie virus type B3 (CVB3), vesicular stomatitis indiana virus (an enteric virus), and human parainfluenza virus (a respiratory infection causing virus) (Priya and Kumari, 2017). However, black pepper has been recognized as an immune-modulator reservoir for treating many infectious diseases where piperine possessed promising potential as an immune-modulator (Tables 1 and 2). It has the capability to boost and support the number and efficiency of white cells and helps the body to raise a powerful defense against invading microbes. Bezerra et al. (2008) reported that piperine showed improved immune-competence that was hampered by 5-FU treatment. In other findings, piperine led to inhibition of proliferative responses caused by lipopolysaccharide (LPS) and immunoglobulin α -IgM antibody in B cell functioning and humoral immune response to T-un/dependent antigens (Bernardo et al., 2015). Lee et al. (2018) documented that piperine up-regulated IL-10 and NF- κ B by combining effect with gamma-aminobutyric acid (GABA), which activated p38, JNK, and MAPK pathway to increase the release of EPO and EPO-R expression.

Table 2. Foods having immune-modulating properties.

Name of foods	Major components	Immune functions	References
<i>Nigella sativa</i>	Thymoquinone	Boosting humoral immune system, and Cytokine gene expression.	Amin et al. (2016) Forouzanfar et al. (2014) Umar et al.,(2016); Yimer et al. (2019)
Licorice root	Glycyrrhizin (GL), 18 β -glycyrrhetic acid (GA)	Reduced expression of nuclear factor- κ B, Interleukin-1 β and interleukin-6 cytokines. Activating T lymphocyte proliferation. Stimulated interferon (IFN) secretion.	Wang et al. (2009) Zhang et al. (2012) Smirnov et al. (2012) Soufy et al. (2012)
Black pepper	Piperine	Up-regulate IL-10 and NF- κ B, Inhibition of proliferative response induced by lipopolysaccharide (LPS) and immunoglobulin α -IgM antibody, Increased white cells	Bernardo et al. (2015) Lee et al. (2018)
Mushroom	Polysaccharides, Tetracyclic triterpenes.	Fla-a- β , FA-2-b-Md, KS-2, LEM, SCG, and GLP(AI), Protein LZ 8	Mizuno et al. (2003) Chihara (1993) Ohno et al. (2000) Lee et al. (2003)
Yogurt	Probiotics	Increased cytokine production, Antibody production, Phagocytic activity and T cell function, Natural killer cell activity	Meydani and Woel-Lyu(2000)
Spirulina	Phycocyanin and polysaccharides, calcium spirulan (Ca-SP)	Increased mobilization of macrophages, Accumulation of NK cells, Antibodies generation, Cytokine production, and Mobilization of B and T cells, Interleukin-1 (IL-1), Stimulates hematopoiesis, Increased the IgA production and Natural Killer (NK) cell damage, Decreasing the secretion of IL-4 and IL-10, Increasing IL-17, TNF- α and IFN- γ , Increasing complete blood count (CBC), and Indoleamine 2,3-dioxygenase (IDO) enzyme activity	Khan et al. (2005) Hayashi et al. (1994) Hirahashiet al., (2002) Shokriet al., (2014) Pertovaaraet al., (2006)

3.6. *Moringa oleifera*

Moringa oleifera, *M. oleifera*, L. (Moringaceae) is an herbal plant having enormous medicinal and nutritional uses. The plant was native to the sub-Himalayan tracts of India, Pakistan, Bangladesh, and Afghanistan. It is now widely distributed all over the world. Drumstick tree, horseradish tree and suhanjna are some common names for *M. oleifera*. All parts (bark, leaf, root, seeds, gum, pod, fruit and flowers) are immensely nutrimental but leaves are the greatest nourishing part with high content of vitamins, minerals, antioxidants, nitrile glycosides, proteins, and phenolics (Younus et al., 2015; Ashraf et al., 2017). *M. oleifera* contains a rare combination of important bioactive components like zeatin, quercetin, beta-sitosterol, caffeoylquinic acid, kaempferol etc. Various parts of this plant have been reported to act as antiviral, antibacterial, cardiac and circulatory stimulants, anti-diabetic, hypolipidemic, antiulcer, antipyretic, antispasmodic, anti-inflammatory, antihypertensive, diuretic, antioxidant, and antifungal activities (Nworu et al., 2013) Therefore, it has a great appeal as folk or Ayurvedic traditional medicine in different cultures of the world. Due to its divergent nutritional, pharmacological and industrial applications, the plant is recognized as a “miracle tree” or a “wonder tree”, which bears a significant socio-economic importance. In the Philippines, the plant is known as ‘mother’s best friend’ because of its use to increase women’s milk production and sometimes it is also prescribed for anemia (Estrella et al., 2000). Besides its diverge range of medicinal use, the massive antiviral activity is due to the presence of alkaloids, saponins, glycosides, niazimin, terpenoids, and phenolic compounds (Table 1) (Nworu et al., 2013). Previous reports showed that thiocarbamate and niaziminin isolated from *M. oleifera* were highly efficient to inhibit the activation of tumor promoting virus, Epstein Barr virus (EBV) (Murakami et al., 1998). Lipipun et al. (2003) suggested that the leaf of *M. oleifera* may be considered as a prophylactic or therapeutic medicine for HSV-1 infection and may be effective against the virus of acyclovir-resistant variant (Lipipun et al., 2003). Accumulating evidence revealed that the fruit extract of *M. oleifera* showed significant anti-hepatitis B virus (HBV) activity,

whereas the seed of this plant showed potential antiviral activity against Newcastle Disease Virus (NDV) and Infectious Bursal Disease (IBD) virus (Waiyaput et al., 2012; Chollom et al., 2012; Ahmad et al., 2014). Younus et al. (2015) reported that *M. oleifera* exhibited potent antiviral activity against Foot and Mouth disease virus (FMDV), equine herpes virus, rhinovirus (positive sense ssRNA virus), and influenza virus H9 (Ashraf et al., 2017). Interestingly, some studies suggested that *M. oleifera* leaf can be used to support people living with HIV/AIDS (PLWHA) due to its nutritive and immune-boosting properties. In African traditional medicine, the plant is popularly used against AIDS and related secondary infections associated with HIV (Biswas et al., 2020). The proceedings of the 14th International AIDS Conference held in Barcelona, Spain in 2002 included a recommendation that the powder of *M. oleifera* can be considered as an alternative treatment for HIV-positive patients in Africa to boost their immune systems, where patients are not taking antiretroviral drugs or any treatment at all (Burger et al., 2002). Experimental evidence of *M. oleifera* showed antiviral efficacy against various viruses, including RNA virus/enveloped virus, thus, it can also be a prominent source for searching therapeutic agents against coronavirus.

3.7. Yogurt

Yogurt is produced from coagulated milk after fermentation of lactic acid in milks by *Lactobacillus bulgaricus* and *Streptococcus thermophilus*. It is known to all that yogurt is a highly efficient immune-modulatory food product. Many studies reported that immune-stimulatory and potential therapeutic effects of yogurt are due to their capability to change the gastrointestinal micro ecology (Bourlioux and Pochart, 1988), where increased the number of beneficiary bacteria suppresses the growth of pathogenic bacteria which contributes to reduce infection. Some studies conducted in human have showed that yogurt consumption increases cytokine production, antibody production, phagocytic activity and T cell function, and natural killer (NK) cell activity, which ultimately boost up immune system to prevent any diseases (Meydani & Woel-Kyu, 2000). Choi et al. (2009) reported that yogurt containing probiotics have strong

anti-viral efficacy against RNA virus like enterovirus 71, which also reduce the impact of influenza virus-induced respiratory infections. Furthermore, research articles published in the National Center for Biotechnology Information (NCBI), consumption of probiotics is a more feasible way to reduce the incidence of respiratory tract infections in children. The findings of systematic reviews and randomized controlled trials revealed that various probiotics, especially lactobacilli and bifidobacteria significantly reduced the incidence and severity of upper and lower respiratory tract infections (Calder, 2020). Although the effectiveness of probiotics in reducing COVID-19 infected patients has not yet been scientifically established, however, the prophylactic benefits for improving the immune system are supportive for their long term use. A recent study showed that the improved gut microbiota profile has a significant role in preventing COVID-19 in older and high-risk persons having negotiated immune systems (Dhar and Mohanty, 2020).

3.8. Honey

Honey has been used as a medicine and food source since ancient times. It has a long history to be used as medicine in the treatment of viral flu. Since 2000BC, honey has been used as medicine in Asia. In the Muslims holy book, "The Quran", where mentioned the uses of honey in preventing a lot of diseases. Sugar is the main component of honey in which fructose and glucose are predominant. In addition to organic acid e.g. gluconic acid, honey also contains proline as amino acid, which leads to various activities of honey (Cruz et al., 2019). Honey is a natural immune-stimulator for the human body. Research findings revealed that honey can be considered as an excellent treatment strategy to prevent zoster rash caused by varicella-zoster virus (Shahzad and Cohrs, 2012). Previous studies showed that methyl glyoxal, a component of honey, is very much competent to show antiviral effects against respiratory syncytial virus and influenza virus (Zareie, 2011; Watanabe et al., 2014). Honey also contains some minerals, particularly potassium, magnesium, sodium, zinc, calcium phosphorus, cobalt, iron, and copper, but many studies suggested that potassium is the most abundant mineral in different types of honey (Chua et al., 2010). Recent study have shown that potassium ion supplements for COVID-19 patients have a better chance of recovery, where honey might be considered as a profound source of potassium as well as immune-modulating agent (Nutrients and minerals are vital for immune system functioning) (Dong et al., 2020).

3.9. Mushroom

Mushroom, the general term of higher basidiomycetes, is being used as traditional medicine in different countries. To date, approximately 700 species of medicinal mushrooms with pharmacological properties have been documented. However, a very limited number of them are cultivated and used for medical purposes in different parts of the world. Various polysaccharides, lipids, steroids, organic acids, and tetracyclic triterpenes are some major components of various mushrooms (TePLYakova et al., 2012). Mushroom's antiviral effects are attributed by its compounds directly by inhibiting viral enzymes, viral nucleic acid synthesis, adsorption and uptake of viruses into mammalian cells or indirectly by immune-stimulating activity. Takehara et al. (1979) reported that lentinan from *Lentinus edodes* (shiitake), agaric and polypore mushrooms effectively fought the flu-causing influenza viruses. *Daedaleopsis confragosa* and *Ischnoderma bezouinum* species showed potent virus neutralizing effects against influenza A virus (TePLYakova et al., 2012). Some other mushrooms like *Piptoporus* sp. and *Ganoderma* sp. showed antiviral activity against pox and HIV virus by preventing virus adsorption by cells, blocking viral enzymes for nucleic acid synthesis and increasing cellular immunity (Stamets, 2005). Protein bound polysaccharides from *Tinea versicolor* were much active as antiviral agents against HIV and cytomegalovirus. Moreover, velutin from *Flammulina velutipes* caused inhibition of HIV-1 reverse transcriptase as an antiviral effect (Tochikura et al., 1987). Besides their antiviral effects, many

mushrooms have immune-modulatory effects that help researchers to produce immune-modulating drugs from mushrooms. For example, Agaricus and Himematsutake mushrooms act as a source of F10-a- β , FA-2-b-Md immune-modulator, whereas Lentinan, KS-2, LEM immune stimulator is reported from Shiitake and Golden Oak mushrooms (Mizuno et al., 2003; Chihara, 1993). Cauliflower mushroom and Reishi, Ling Zhi mushrooms are the immune-modulator of SCG, and GLP(AI), Ganopoly, Ganoderans, Protein LZ 8, respectively (Ohno et al., 2000; Lee et al., 2003).

4. Immune boosting dietary supplements

4.1. Spirulina

Spirulina, a dried biomass of cyanobacterial blue-green algae, is being used as a common 'nutritionally packed' dietary supplement available in different parts of the world. It has a long history to be used as a food source because of its diverse biological activities and nutritional significance. Spirulina possesses natural nutrients having bio-modulatory and immune-modulatory functions. *Spirulina platensis* and *S. maxima* are two species of spirulina for nutritional supplements, which can grow in fresh and marine waters throughout the world (Khan et al., 2005). Spirulina is mostly composed of protein. Besides, it contains vitamins (B₁₂ and provitaminA (β -carotenes) and minerals such as iron, phenolic acids, tocopherols and γ -linolenic acid, polysaccharides, glycolipids, and sulpholipids etc (Dillon et al., 1995). Many researchers reported that spirulina possessed promising biological activities such as antiviral, anti-inflammatory, anti-arthritis, anti-diabetics, cardio-active, reproductive performance enhancer, anti-tumor, anti-microbial, hypocholesterolemic, radio protective, and metallic protective effects and obviously most prominent immune modulating properties (Khan et al., 2005). Spirulina displays promising antiviral efficacy via the production of phycocyanobilin, phycocyanin, allophycocyanin and other significant compounds (Dillon et al., 1995). Previous reports showed that calcium spirulan (Ca-SP) isolated from *S. platensis* has shown antiviral effect against different enveloped viruses such as HIV-I, mumps virus, measles virus, *Herpes simplex* virus type-I, human cytomegalovirus, and influenza virus (Hayashi et al., 1996; Rechter et al., 2006). Allophycocyanin is an another compound of spirulina neutralizes cytoplasmic effects induced by the enterovirus 71 in human rhabdomyosarcoma cells by delaying RNA synthesis and increasing the apoptotic process in the infected cells (Shih et al., 2003). Some studies noted that Cyanovirin-N (CV-N), sulpholipid and Ca-Sp compounds derived from spirulina exhibited potent antiviral activity against HIV-I and other enveloped viral particles, whereas, Cyanovirin-N and Ca-Sp selectively inhibited the initial stage of viral life cycle in the host cells and sulpholipid interfered reverse transcription of HIV-RNA (Hayashi et al., 1996; Luescher-Mattli, 2003). Therefore, it is expected that spirulina might be a useful therapeutics for AIDS, and may lead to a longer normal life as well as to reduce prevalence of HIV/AIDS (Luescher-Mattli, 2003). Besides a long range of biological properties, some species of spirulina exhibited very strong immune-modulating and bio-modulating properties. Spirulina has direct effect on both innate and specific immunity that has been elicited through increased mobilization of macrophages, accumulation of NK cells, antibodies production, cytokine secretion, and mobilization of B and T cells to the site of infection (Khan et al., 2005). Experimental evidence showed that dietary intake of spirulina enhanced primary immune response by increasing the number of splenic antibody-producing cells against Sheep Red Blood Cells (SRBC), macrophages and interleukin-1 (IL-1) in mice (Hayashi et al., 1994). It was documented that spirulina up-regulated key cells and organs of the immune system in spite of the presence of toxins and infectious agents. Phycocyanin and polysaccharides of spirulina stimulate hematopoiesis, especially erythropoiesis, and white blood cells production and also enhance intestinal immune system (Khan et al., 2005). Ishii et al. (1999) reported that spirulina had a key role in mucosal immunity where it increased the IgA

Table 3. Vitamins with their sources and their roles in immune systems.

Vitamins	Sources	Functions in immune system	References
Vitamin-A	Carrots, sweet potato, oily fish, papaya, cheese, egg yolks, tofu, seeds, nuts, liver, legumes and whole grains.	Supports T-cells to find pathogens	British Nutrition Foundation (2020) Clare-collins,(2020)
Vitamin-B ₆	Egg yolk, cereals, legumes, fruit, nuts, and fish, chicken and meat, leafy vegetables, such as banana, avocado and green pepper.	Helps to produce new immune cells and neuronal communication. Metabolize antibodies.	Keil et al. (2016) Clare-collins, (2020)
Vitamin-B ₉	Nuts, green leafy vegetables, seeds and legumes.	Helps in immune development	Keil et al. (2016) Clare-collins, (2020)
Vitamin-B ₁₂	Eggs, meat and dairy and also in fortified soy milk	Helps to produce new immune cells	Keil et al. (2016) Clare-collins, (2020)
Vitamin-C	Citrus fruits, strawberries, blackcurrants, papaya, kiwi, green vegetables, capsicum and tomatoes.	Helps immune cells to attack pathogens, Helps to clear old immune cells from the site of infection, and Helps to maintain the skin fresh and alive to avoid infection.	Hemila (2003) Hemila (1997) British Nutrition Foundation (2020) Clare-collins, (2020)
Vitamin-D	Oily fish, eggs, fortified breakfast cereals, fortified spreads and fortified dairy products.	It increases the effectiveness of monocytes and macrophages to fight against pathogens.	Nonnecke et al. (2014) British Nutrition Foundation (2020) Clare-collins, (2020)

production in human saliva. A Japanese team concluded that spirulina increased the production of IFN- γ and NK cell damage after taking this microalga extract (Hirahashi et al., 2002). A recent study has revealed that spirulina exhibited remarkable immune-modulatory effect by decreasing the secretion of IL-4 and IL-10 and increasing the level of IL-17, TNF- α and IFN- γ in *Candida albicans* infected tumor bearing mice (Shokri et al., 2014). Based on available previous data, it was noted that spirulina supplementation can improve the anemia and immune function of senior citizens by increasing complete blood count (CBC) and indoleamine 2,3-dioxygenase (IDO) enzyme activity as a sign of immune function (Pertovaara et al., 2006). Therefore, antiviral and immune boosting evidence of spirulina might be an effective supplement to build strong shield against COVID-19 as like another preventive options, where prevention is still the best strategy to fight against COVID-19.

4.2. Vitamins

Body immune system is a complex network of cells and chemical compounds that help the body to show defense against infections. Foods contain a wide range of immune supportive nutrients, so that our body is able to fight against invading pathogens, including virus, bacteria, and toxins (Table 3). Firstly, the food sources like carrots, sweet potato, oily fish, papaya, cheese, egg yolks, tofu, seeds, nuts, legumes, and whole grains contain vitamin-A, which is considered as body's first line of defense to identify pathogens by supporting T-cells. Vitamin-A maintains the structure of cells in skin, gut, and respiratory tract (British Nutrition Foundation, 2020; Clare-collins, 2020). Evidence showed that supplements containing vitamin-A offer protection against life threatening infections like HIV, malaria, and lung diseases (Villamor et al., 2002). Once the body recognizes a pathogen, vitamin B in particular, B₆, B₉ and B₁₂ play the body's first response by influencing the production and activity of NK cells that lead to apoptosis. Meat, fish, shellfish, milk, sesame seeds, soya beans, cheese, eggs, yeast extract, and some fruit and vegetables such as green pepper, banana, and avocado are common sources of vitamin-B-complex (Clare-collins, 2020). Keil et al. (2016) reported that vitamin B₂ and UV light significantly reduced the titer of MERS-CoV in human plasma. Furthermore, vitamin-C is considered as the most popular supplement to shield against infection due to its valuable role in the immune system (Clare-collins, 2020). Previous report suggested that vitamin-C plays an important role in immune functions to protect from infection caused by CoVs (Hemila, 2003). Atherton et al. (1978) reported that vitamin-C increased the resistance against avian coronavirus in chick embryo tracheal organ cultures. Previously conducted three human controlled trials explored that vitamin-C supplements can significantly lower the incidence of pneumonia, which suggested that vitamin-C might prevent the susceptibility of lower respiratory tract infections in certain

conditions (Hemila, 1997). It was reported that COVID-19 caused lower respiratory tract infection, so vitamin C might be a fruitful choice to support corona affected patients. Citrus fruits, strawberries, green vegetables, papaya, blackcurrants, tomatoes, and peppers are some common sources of this vitamin (British Nutrition Foundation, 2020). Another vitamin, vitamin-D, is also essential to our health and proper functioning of immune systems. It increases the effectiveness of monocytes and macrophages to fight against pathogens. Research findings concluded that people having low levels of vitamin-D might have the great chance to be affected by upper respiratory tract infections, including influenza and allergic asthma (Priehl et al., 2013). In addition, a previous report found that calves with low levels of vitamin-D caused the infection of bovine coronavirus (Nonnecke et al., 2014). Therefore, vitamin-D could be an important immune-boosting nutrient to prevent corona symptoms.

5. Summary and outlook

In this review, we have summarized the effectiveness of some traditional foods (plant, animal, and fungi species), which can consume together with different diets and cultural practices as spices, roots, mushrooms, and fermented food products having significant antiviral and immune-modulating effects against viral infections, including SARS-CoVs (Tables 1 and 2). The majority of such foods contain various phytochemical compounds like phenolic, flavonoids, alkaloids, polysaccharides, amino acids etc. and naturally occurring vitamins and minerals (e.g., vitamins C, D, B₆, B₁₂, A, E, and minerals of zinc, copper, iron, and selenium), which are immune protective and antiviral agents in different pathways (López-Varela et al., 2002). Indeed, immune systems in the body are vital for confirming protection mechanisms against different ailments and the success of such systems against pathogenic microorganisms, including viruses, make sure the survival of humans. The aforementioned antiviral and immune modulating foods boost the body's specific immunity such as humoral and cell-mediated immunity and trigger various kinds of non-specific immune responses such as macrophages, NK cells, granulocytes, and complement systems, which increase resistance to infections. The activated immune cells increase the output of a variety of immune molecules such as cytokines, IFNs, and chemokines, which are involved in the improvement of immune responses (Yang et al., 2020). Foods that contain glycyrrhizin and other sulphur-containing bioactive compounds such as sulphoxide, proteins and polyphenols promote the function of macrophages, T-lymphocytes, and several cytokines and reduce the formation of IL-12 and TNF- α (Yang et al., 2020; Wang et al., 2015). In case of SARS-CoV-2 immunological studies, a number of immune molecules such as lymphocytes, dendrite and NK cells are exhausted that are very common in chronic viral infections. These findings suggest that the body loses their power to fight

against invading pathogens (Weiskopf et al. 2020; Zhan et al., 2006). Encouraging news is that early adaptive robust multi-factorial immune responses may ensure better clinical outcomes against SARS-CoV-2 affected patients (Thevarajan et al., 2020). On the other hand, a patient's age, gender, food habit, neuroendocrine-immune regulation and physical status are considered as the key regulating factors of an individual's immune system (Li, Genga, Penga, Menga and Lu, 2020). The mentioned factors play a key role in determining whether an individual is infected with a virus, the duration and severity of the diseases. Therefore, in the early stage as well as during the time of pandemic, the types of food which have significant evaluation against viral infection and immune development might be valuable complementary remedies against viral infections, including COVID-19. The statistics showed that older people are more vulnerable to COVID-19, where the highest death rate (13.4%) was recorded for people having 80 or over age compared to only 1.25% and 0.3% for 50s and 40s people, respectively (Begley, 2020). Weak immune systems and pre-existing disease conditions have been attributed to these figures. The literature suggests that food containing potential antiviral as well as immune-modulating effects possess many phytochemical compounds, which have a long history to appear as healing agents against infectious diseases. Glycyrrhizin is the active component of licorice roots that inhibits the replication of SARS associated viruses (Cinatl et al., 2003). Furthermore, like other phytochemicals of food, the compounds of flavonoid groups have antioxidant as well as antiviral properties. They showed anti-corona virus effects by preventing virus entry, inhibiting 3C-like protease (3CLpro) of coronavirus and they are also able to block the enzymatic activity of MERS and SARS-CoV/3CLpro (Jo et al., 2020; Jo et al., 2019). Moreover, some foods containing bioactive compounds also exhibited very strong antiviral and immune-modulating effects against SARS-CoV-2 homologous enveloped RNA viruses via preventing virus entry, transcription, and translation, replication, blocking viral enzymes, stimulating interferon secretion, and increasing cellular immunity (Hayashi et al., 1996; Luescher-Mattli, 2003). Therefore, our review demonstrated that selected traditional foods not only boost the body's immune systems and improve the respiratory problems but also progress the overall general health of the people. This could possibly reduce the risk of COVID-19 and initiate a rapid recovery in SARS-CoV-2 infection as like other viral infections. The current pandemic situation of SARS-CoV-2 makes us painfully realize that our ongoing strategies (social distancing, healthy measures, lockdown, quarantine and isolation etc.) to treat this fatal disease are not effective at all. Therefore, taking these traditional foods, which are easily available and consumable in daily diet chart, might play a great role to maintain a healthy immune system and to ensure proper general health. Finally, our reviews recommend people to include these traditional foods in the daily diet chart as a defensive measure in association with other health solutions to ensure protection against viral infections including today's global concern COVID-19 infection and also for keeping up efficient health management.

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