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REVIEW

A Review on the Antiviral Activity of Functional Foods Against COVID-19 and Viral Respiratory Tract Infections

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Abstract: Due to the absence of successful therapy, vaccines for protection are continuously being developed. Since vaccines must be thoroughly tested, viral respiratory tract infections (VRTIs), mainly coronaviruses, have seriously affected human health worldwide in recent years. In this review, we presented the relevant data which originated from trusted publishers regarding the practical benefits of functional foods (FFs) and their dietary sources, in addition to natural plant products, in viral respiratory and COVID-19 prevention and immune-boosting activities. As a result, FFs were confirmed to be functionally active ingredients for preventing COVID-19 and VRTIs. Furthermore, the antiviral activity and immunological effects of FFs against VRTIs and COVID-19 and their potential main mechanisms of action are also being reviewed. Therefore, to prevent COVID-19 and VRTIs, it is critical to identify controlling the activities and immune-enhancing functional food constituents as early as possible. We further aimed to summarize functional food constituents as a dietary supplement that aids in immune system boosting and may effectively reduce VRTIs and COVID-19 and promote therapeutic efficacy.

Keywords: functional foods, COVID-19, immune-boosting, viral respiratory infection

Introduction

The worldwide pandemic coronavirus disease 2019 (COVID-19), which started in December 2019 in a food market in Wuhan, Republic of China, has been linked to a highly contagious novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-COV-2).[1–3] The global rate of morbidity and mortality associated with COVID-19 continues to be high despite considerable progress over the past two years. The worldwide morbidity rate due to COVID-19 is 472,816,657 confirmed cases, and its mortality rate reaches 6,099,380 confirmed deaths until 23 March 2022.[4] In addition, the application of FFs provides significant benefits in discovering new approaches for safer and more effective medicine of COVID-19 and boost immunity.[5] FFs have been applied for an extended time, supplying necessary for individual life and used as natural alternative medications to manage disease.[6,7] Different nations have recognized the significance of functional food, which is necessary for human survival and enhances functional processes and immune enhancements.[8,9] The application of FFs, including polyphenols, flavonoids, propolis, curcumin, prebiotic and probiotic, and also food supplements such as zinc (Zn), vitamin C, D, and E, has been increasing over the past few years for modulating immunity and to boost biological function.[10,11]

Vitamin D offers a wide range of health benefits, including possible involvement in preventing pulmonary inflammation. Pneumonia and acute respiratory distress syndrome are more expected when vitamin D deficiency is in the bloodstream.[12] Hariyanto et al[12] reviewed the relationship between vitamin D and COVID-19. The authors indicated that taking more vitamin D decreased the number of COVID-19 cases referred to the critical care unit, reduced the need for mechanical ventilation, and reduced the death rate. The microbiota influences the human body's function; SARS-

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COV-2 in the older may be linked to a reduced variety of the gut microbiota. Due to various changes in gut microbiota composition-related inflammation, the aged are more prone to illness, dysfunction, weakness, and even early death than the general population.[13]

The complexities that go into defining functional foods are still questionable or controversial. In the early 1980s, the word "functional food" was introduced in Japan. Since there is no universal definition of FFs, one of the most prevalent and fundamental definitions is "processed foods that have disease-prevention and/or health-promoting effects in addition to their nutritional value".[10,14,15] The term "functional food" originated in Japan; furthermore, in 1991, Japan was the first nation to establish the term "foods of specified health use" (FOSHU). Products that follow such guidelines (Table 1) will carry the FOSHU label, as stated by the Japanese Ministry of Health.[10,16] There is, however, no agreement on an accurate description between both the United States and Europe at this time. There is also clearly no globally accepted definition of FFs; furthermore, numerous organizations have created their meanings (Table 2). The new model is that FFs are now

Table 1 The "FOSHU" Standards for Functional Foods are Used in Japan[10,213]

1. Foods with applicable constituents are likely to have a specific health impact or foods that already have allergens removed.
2. Foods for which the impact of such a modification (addition or removal) has been clinically tested and permitted to make claims about the potential health benefits anticipated from their intake have been given.
3. Based on naturally occurring foods, products should be in the form of ordinary foods (ie, not powder, pills, or capsules).
4. Foods should have been part of a regular daily diet.
5. Foods serve a specific function in the human body, including;
   - improve immune system function,
   - prevent specific diseases,
   - aid in the treatment of specific diseases,
   - control physical and mental complaints,
   - delay the ageing process.

Table 2 Functional Foods Definitions by Different Nations and Organizations

Organization	Nations	Definitions	References
FOSHU	Japan	Processed foods containing ingredients that aid specific bodily functions in addition to being nutritious	10,16
FUFOSE	Europe	Functional food has specific beneficial effects on one or more target functions in the body beyond the basic nutritional effects resulting from improved health state and well-being or reduced risk of diseases. It is consumed as a part of a regular diet and is not used in the form of pill or capsule, or any other form of dietary supplement	214
BNS	Canada	Similar in appearance to conventional food, consumed as part of the usual diet, with demonstrated physiological benefits, and/or to reduce the risk of chronic disease beyond basic nutritional functions	215
IFIC	USA	"Foods or dietary components that may provide a health benefit beyond basic nutrition"	216
ILSI	USA	Foods that, by virtue of physiologically active food components, provide health benefits beyond basic nutrition	216
EC	Europe	Satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either an improved state of health and well-being and/or reduction of risk of disease	217
IOM	USA	Foods in which the concentrations of one or more ingredients have been manipulated or modified to enhance their contribution to a healthful diet	215
ADA	USA	Whole foods and fortified, enriched, or enhanced foods, have a potentially beneficial effect on health when consumed as part of a varied diet and regularly, at adequate levels	215
FFC	USA	Natural or processed foods that contain known or unknown biologically active compounds; which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic disease	218

Abbreviations: FOSHU, foods of specified health use; FUFOSE, Functional Food Science in Europe; BNS, Bureau of Nutritional Sciences; IFIC, International Food Information Council; ILSI, International Life Sciences Institute of North America; EC, European Commission; IOM, Institute of Medicine of the National Academy of Sciences; ADA, American Dietetic Association; FFC, Functional Food Center; USA, United States of America.

intended to improve health by focusing on specific biological functions that contribute to preventive medicine. Therefore, they positively impact human health and are essential for most diets.[10] Functional foods are classified into the plant, animal, microbial, and miscellaneous (algae, mushrooms, etc.) functional foods based on their source of origin (Figure 1).[17]

Several FFs with antiviral, antimicrobial, and anti-inflammatory activities have been classified across the preceding years.[9,18] The previous studies of naturally occurring compounds suppressing coronaviruses were based on the similarity of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19. Unfortunately, there are currently no recognized treatments for COVID-19, and protective vaccines are continuously being made and must be thoroughly tested. As a result, the condition highlights the importance of effective immune-boosting and antivirals to be developed for prophylaxis of COVID-19.[19] Moreover, the ingestion of a healthy meal will aid in the improvement of human immune systems, which is also a positive start in fighting COVID-19. It's fair to say that no studies have been done on the influence of food substitutes in combating COVID-19 in particular. However, previous research has found that consuming certain FFs can improve our health and help our bodies to combat some infective pathogens.[17] Several FFs (Table 3) from various dietary sources have already been confirmed for antiviral efficacy against multiple viruses. This review documented a list of the essential FFs that seem to have antiviral activity, besides their anti-inflammatory, antioxidant, and antibacterial characteristics, along with FFs used to enhance and boost immunity.

Functional Foods as Antiviral Substances

Because of their rapid outbreaks, viral infections are life-threatening, whereas managing viral infections is a big task due to quick adaptation, the resistance of viruses, and the development of new strains of the virus, and ineffective drugs.[20,21] Firstly, COVID-19 symptoms are not well-defined, but fever, cough, nausea/vomiting, diarrhoea, sneezing, and shortened breathing can be considered initial symptoms of CoVID-19 and respiratory viral infection, while severe symptoms include pneumonia.[22] Furthermore, in histopathological studies, individuals with COVID-19 had diffused alveolar lesions in their lungs, oedema; also, the lungs appear congested, with patches of hemorrhagic necrosis, while inflammation of alveoli with atrophy, proliferation, and desquamation of alveolar epithelial cells, with the appearance of exudate macrophages and monocytes, are prominent features microscopically.[22,23]

In this article, various common and readily available FFs were documented the antiviral characteristics, particularly those FFs effective against VRTIs. Cinatl et al[24] showed the antiviral activity of glycyrrhizin against SARS-coronavirus. Glycyrrhizin was the most effective treatment in preventing the multiplication of the SARS-associated virus based on the medication of two clinical isolates of coronavirus from SARS cases hospitalized to the Clinical Center of Frankfurt University in Germany. The results of Hoever et al[25] were very comparable. According to studies, liquorice has high

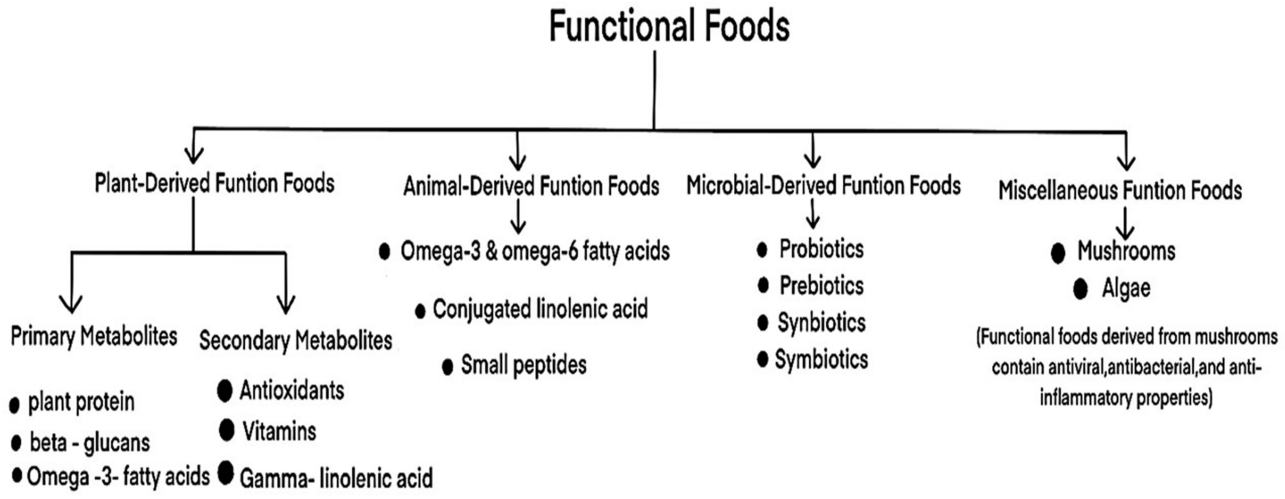

Figure 1 Classification of functional foods based on their sources of origin.

Table 3 Functional Foods and Their Antiviral Properties with the Primary Dietary Sources

Functional Foods	Main Dietary Sources	Functional Description	References
Vitamin A	Milk, eggs, liver, oily fish, fortified cereals, dark orange or green vegetables, orange fruits, and tomato juice.	Decreased pneumonia morbidity and helps relieve clinical symptoms and signs of pneumonia and shorten the length of hospital stay in children.	219,220
Vitamin C	Oranges and orange juice, red and green peppers, strawberries, blackcurrants, kiwi, broccoli, potatoes	Vitamin C reduced the duration of common colds, reduced the intensity of colds, and reduced the incidence and duration of pneumonia.	221,222
Vitamin D	Oily fish, liver, eggs, fortified foods (spreads and some breakfast cereals)	Vitamin D has been shown to reduce the incidence of respiratory infections. Conversely, vitamin D insufficiency has been linked to an increased risk of community-acquired pneumonia.	223,224
Vitamin E	Wheat germ, nuts and seeds, vegetable oils	Increases the activity of natural killer cells and has anti-inflammatory effects against colds and pneumonia.	225
Zinc, Copper, and Iron	Shellfish, meat, cheese, some grains and seeds, cereals, nuts, liver, and some vegetables	Chinese children with recurrent respiratory infections showed reduced zinc, copper, and iron levels in their hair.	226
Zinc	Shellfish, meat, cheese, and cereals	Oral zinc formulations may help to decrease the duration of common cold symptoms; they also reduce the prevalence of pneumonia	227,228
Quercetin	Capers, onions, apple, berries, and Cilantro (coriander)	Interaction with the HA2 viral subunit to inhibit the H5N1 virus inhibitory activity in the early stage of influenza infection inhibits binding station ACE.	229,230
Curcumin	Rhizome of turmeric (*Curcuma longa*)	Binding to three protein receptors: RBD-S (PDB ID:6LXT), PD-ACE2 (PDB ID:6VW1), and SARS-CoV-2 protease (PDB ID:6LU7)	231,232
Polyphenols	Pomegranate, apricots, peaches, mango, spinach, broccoli, orange, tomato, apple and berries	Reduce the inflammatory response in adipocytes, macrophages, and other immune cells to prevent and combat inflammation.	171,233

immunomodulation activity and is helpful, especially in improving the body's immune system's ability to combat microbial diseases. Krawitz et al[26] recorded the antiviral action of elderberry extract against common cold and influenza viruses; the author also showed elderberry's antibacterial activity against pathogens responsible for upper respiratory tract infections. Antiviral effects of Sambucol, a black elderberry extract, were demonstrated against several influenza virus strains in another study by Barak et al.[27] The flu symptoms were shortened to 3–4 days using Sambucol and their practical actions in vitro against ten influenza virus strains.

Ground garlic, whether with or without honey, is thought to improve immunity and has antiviral activities, which may be attributed to some bioactive sulfur-containing substances such as proteins, polyphenols, and sulfoxide.[21,28] Garlic's immunostimulatory properties may be helpful in clinical settings as it can increase innate and specific cell immunity while increasing host resistance. Garlic and its organosulfur compounds (*Allium sativum L.*) were shown to have antiviral effects against common cold, influenza, and acute respiratory viral infections in various clinical studies.[29,30]

Antiviral compounds in various fruits and plants can prevent infection by acting on viruses and host cells. For example, the pomegranate peel extract and its parts can avoid replicating the influenza A virus (IAV) in vitro.[31] Similarly, in another vitro investigation, Nikolaeva-Glomb et al[32] investigated the antiviral action of numerous berry extracts and realized that berry fruit extracts prevented the replication of IAV.

Immunomodulatory and Anti-Inflammatory Effects of Functional Foods

The body's most potent natural response towards infection is the individual immune response. Personal life depends significantly on defending against various external causative microorganisms, such as viruses. Man's innate and adaptive

immune systems could serve a defensive role on SARS-COV-2 since no medical interventions have been presented.[9,21] Different nations introduced the concepts of FFs to stimulate biological functions and immune reactions besides their vital role in life.[8,33] Numerous researches have revealed the immune-modulating and antiviral activities of FFs. Flavonoids, curcumin, and quercetin are examples of FFs that can modulate and support immunity, act as antioxidants, have anti-inflammatory and antiviral activities.[34,35] Vitamin A and C are easily accessible in the food, act as antioxidants and protect immune cells from destruction;[10] vitamin D supplements decrease the threat of VRTIs, flu, and COVID-19.[5,36] Sambucol dramatically boosted the formation of inflammatory cytokines (IL-1, TNF-alpha, IL-6, and IL-8). Sambucol can thus be helpful in the activation of the immunity and the inflammatory response in healthy people and individuals with different illnesses. In addition, when combined with chemotherapeutic or other drugs, Sambucol may have immunoprotective or immunostimulatory impacts in cancer or AIDS patients.[27]

Herbs may be used to cure various diseases, which is not a new concept. In ancient times, herbs and spices were used to treat infectious diseases, including pneumonia and flu.[37,38] Several medicinal mushrooms have been studied to learn more about their immune-boosting properties, and > 270 identified mushroom species have been identified as having immune-boosting effects.[39] The antiviral action of honey has been studied, and it has antiviral activity against the Rubella virus. It's also used topically to treat herpes simplex virus-induced chronic lesions. Because of its antiviral properties, this compound will effectively prevent influenza virus replication.[40,41] Fresh ginger (*Zingiber officinale*) has been found to have antiviral action and is effective against the respiratory syncytial virus (RSV).[42] Salem & Hossain[43] reported the antiviral impact of black seed oil from *Nigella sativa* against murine cytomegalovirus. Lemon balm (*Melissa officinalis* L.) extracts were found to prevent influenza virus duplication at different steps of the multiplication cycle, specifically during direct interaction with virus particles, also their antiviral action against human immunodeficiency virus type 1 (HIV-1).[44,45]

Antiviral Defence Mechanisms of Functional Foods

The term "nutritional immunity" was first coined to describe iron (Fe), but it was later expanded to include other essential trace elements, including selenium (Se) and Zn. According to in vitro studies, elevated intracellular Zn^{2+} concentrations can interfere with replicating various RNA viruses, including influenza virus and poliovirus. It also impacts a common step in the cell replication cycle.[46] The immune system comprises two main types of cells: innate (speedy to respond) and adaptive immune cells. The cells are sustained mainly by granulocytes and macrophages, specifically entrap pathogens, including viruses and bacteria.[47,48] There is a decrease in the synthesis of antibodies when Zn is depleted. The innate immune system is also affected by a decline in the activity of natural killer cells in this condition. Mononuclear cells produce fewer cytokines when Zn deficiency is present, and neutrophil chemotaxis and respiratory burst are both diminished as a result.[49] As mentioned above, upon the onset of disease, the immune system plays a critical function in defending our bodies from infectious particles such as viruses. Therefore, numerous abundant substances in various herbs, fruits, and vegetables may help improve the body's immunity, reduce the risk of contagious diseases, and aid in disease care. These substances are polyphenols, fatty acids, fibres, flavonoids, soy proteins, minerals, vitamins, and pre- and pro-biotics.

Intake of FFs of a wide range of plant, animal, and fungal resources, consumed through various diets and cultural aspects, would boost antiviral immunity. Traditional herbal medicines like teas, roots, mushrooms, and dried plants and leaves, along with olive oils, fish oil, nuts, fruits, and vegetables, are among these functional foods. Most of the products mentioned above contain natural vitamins (such as vitamins A, C, and D) and minerals (like Zn, Fe, and Se) and other phenols that are particularly immunoprotective due to their antioxidant and anti-inflammatory effects.[10,50] Innate immunological responses are improved, immune-modulatory effects are achieved by boosting T cell activities, and immunoglobulin synthesis is increased due to vitamin C intake.[51,52] According to Rayman,[53] Se deficiency is linked to reduced immunological activity. Se has long been known to have immune-stimulant effects, including increased T- and natural killer- cells. Se deficiency is frequent in immunocompromised people, which could explain their greater susceptibility to pathogens (eg bacterial and viral) infections.[54]

Glycyrrhizin has immunomodulatory and anti-inflammatory properties.[55] The antiviral activity of glycyrrhizin was investigated in an animal model study. Glycyrrhizin could protect mice following lethal doses of influenza virus A2 infection by stimulating interferon-gamma production via T cells, as T cells are interferon-gamma producer cells when

enabled with glycyrrhizin.[56] The mechanism of glycyrrhizin antiviral activity seems to be induced through antiviral functions of the host.[56]

Polyphenols act as immunomodulators, improving T cell function and increasing anti-influenza virus IgG and IgA antibody formation. They also suppress viral replication, inhibit viral hemagglutination, reduce viral replication, increase secretion of type I interferon and pro-inflammatory cytokines.[57,58] Polyphenols were shown to inhibit viral RNA and protein synthesis, viral hemagglutination, viral binding to and penetration into host cells.[59,60] Various researches have shown the management and protection of influenza, common cold, and acute upper respiratory tract infections with FFs, such as vitamin C, probiotics, garlic, and others. Vitamin C and garlic reduce the duration and severity of colds while also boosting the immune system.[61,62] Yoghurt ingestion has been shown to raise the synthesis of cytokines, principally interferon γ, and enhance monocyte cytokine production.[10,16]

Probiotics boost innate immunity by improving natural killer cell activity. Further, they enhance gut and respiratory, immune responses by increasing influenza-specific IgA and IgG antibodies and modifying the host's innate immunity. Probiotics have been shown to prevent viral attachment to target cells, boost the activity of natural killer cells, and enhance cytokine responsiveness.[63,64] In addition, probiotics boost immunity by indirectly stimulating cytokines and modulating the intestinal microbiota. Probiotics also interact with the gut microbiota to increase immunity, stimulate specific immunological pathways, and enhance immunity, and all have functional and therapeutic significance.[65,66] Lipopeptides like subtilisin (*Bacillus amyloliquefaciens*), curvacin A (*Lactobacillus curvatus*), sakacin P (*Lactobacillus sakei*), lactococci Gb (*Lactococcus lactis*) derived from different probiotic strain have demonstrated that have an affinity to bind with S-protein of SARS-CoV-2 and human angiotensin-converting enzyme II receptor (ACE2) for entry into the expressing cells.[67,68] Furthermore, the study of Verma's group[69] has shown that the human ACE2 is expressed and secreted in *Lactobacillus paracasei*.[69] Therefore, the binding of this secreted ACE2 to COVID-19 binding protein could represent a way of blocking SARS-COV-2 entry into cells.[70]

Functional Food Ingredients Were Effective in Virus Infections

All stages of the virus lifecycle depend on the host; therefore, immune cells, as the first line of defence, play a vital role in protecting our body against pathogens and viruses. Due to the inadequacy of vaccines, drugs, and increased mutation rates in the viral genomes, boosting the immune system could be a reasonable alternative to fight COVID-19.[71] The food sector has been affected since the inception of COVID-19, and the demand for functional, organic, and sustainable foods has increased.[72] Many functional food ingredients have been claimed to have potentially immunomodulatory and antiviral properties.[73] Here, we will highlight the possible advantages of flavonoids, propolis, elderberry, resveratrol, curcumin, pre-and probiotics, and supplementing nutrients including vitamin D, vitamin C, and Zn. Various investigations have demonstrated a link between these substances' ingestion and the protection, delay, or management of viral infections and immune disorders.[65,74,75] The studies also indicate that micronutrient supplements alone or with antiviral and anti-inflammatory medications may be modestly valuable in preventing COVID-19 and improving their clinical course. Therefore, this review also discusses the relationship between these compounds and their antiviral properties.

Flavonoids

Flavonoids are an important group of secondary plant metabolites present in the diet. They have numerous biologically beneficial activities in the human body, including anti-inflammatory, antioxidant, anti-mutagenic, and antiviral properties.[76] Flavonoids can be found in various plants such as grapes, apples, onions, and cherries. In addition, it has also been discovered that multiple flavonoids inhibit other viral targets, such as the *coronaviridae* family.[72,77,78] There are various mechanisms that flavonoids can prevent, treat, and interact with the immune system to help fight off viruses. For example, flavonoids can lower the viral load by interfering with host components essential for infection or regulating immunity. In addition, flavonoids act as inhibitors of viral adhesion or penetration into host cells, bind to viruses, and alter their structures. The virus can still enter the body, but the process of viral uncoating has slowed down considerably.[77] The basic molecular mechanisms of flavonoid antiviral actions are the suppression of viral neuraminidase, proteases, and DNA/RNA polymerases and the alteration of numerous viral proteins.[79]

A molecular docking study was conducted to recognize the anti-inflammatory and antiviral properties of 10 flavonoid substances. This work described that flavonoid naringin has the highest binding affinity with spike protein compared with COVID-19 common medications.[80,81] In addition, other flavonoids such as curcumin,[82] herbacetin, quercetin, kaempferol,[83–85] luteolin[86] have been proposed as potential interactions with the above-mention receptor in similar studies.

$3CL^{pro}$ and PL^{pro} of SARS-COV-2 are efficient targets in discovering anti-SARS drugs and play essential roles in translating and replicating COVID-19.[87] Furthermore, it was reported that flavonoids such as tangertin, rhoifolin, pectolinarint, herbactin, helichristetine, and narigenin could attach firmly to MERS-COV and SARS-COV-2 protease $3CL^{pro}$, as well as nutritional flavonoids, namely kaempferol, quercetin, and isoliquiritigenin, have a synergistic impact on $3CL^{pro}$ and PL^{pro} in vitro.[88,89] RNA-dependent RNA-polymerase (RdRp) is one of the significant druggable targets of SARS-COV-2.[90,91] Many investigations have been conducted to analyze the role of flavonoids concerning RdRp. For example, Singh et al[92] used a molecular docking method to target RdRp of SARS-COV-2. They revealed that epigallocatechin gallate, hesperidin, and quercetin could inhibit RdRp activity and, in this way, block replication and prevent viral transcription. Studies demonstrated that flavonoids (herbacetins, rhoifolins, and pectolinarins) have an antiviral effect against coronavirus. SARS-COV $3CL^{pro}$ enzymatic activity was effectively blocked by the flavonoids mentioned above.[93] In another similar recent study, the proteolytic activity of SARS-COV-2 $3CL^{pro}$ has been discovered to be blocked by flavonoids, including baicalin, herbacetin, and pectolinarin.[94]

Based on the reports, VRTIs can be treated more effectively when vitamin D and C are combined with quercetin.[95,96] Moreover, flavonoids could relieve the respiratory symptoms of COVID-19 in the case of individuals managed with hydroxychloroquine.[97] In addition, the use of combination curcumin and Zn have also been proposed to modulate the immune system to combat coronavirus infections.[98] However, as potent anti-inflammatory agents, flavonoids are valuable biomarkers for assessing human health. Therefore, administering flavonoids alone or in combination with other natural medicines should be addressed.

Propolis

Propolis (bee glue) is a bee-metabolized sticky material of various plant sources. It has a wide application with antioxidant, anticancer, anti-parasite, immunomodulatory, antimicrobial, and anti-inflammatory properties. In addition, propolis and its constituents possess antiviral activity toward different viruses and several biological activities. Most of these properties are attributed to the presence of several natural compounds,[99,100] and this variety is significantly dependent on plants, climatic regions, environmental conditions, and collection seasons. Moreover, flavonoids and esters of phenolic acid are commonly considered bioactive compounds with antimicrobial activity. They are also proposed as a potentially promising alternative in therapy against pathogens that cause severe respiratory syndromes.[100,101] Several investigations accepted the antiviral action of propolis, which was found to block the viral entrance toward the host cells and inhibit virus duplication.[100,102] In March 2020, responding to the current pandemic scenario of COVID-19, propolis is considered a functional food and a possible complementary treatment that could help reduce infection during this lethal outbreak.[103]

It was reported that caffeic acid (the bioactive ingredient of propolis) and caffeic acid phenethyl ester (CAPE) could bind strongly to angiotensin-converting enzyme II receptor (ACE2) as compared to nelfinavir.[104] Furthermore, the obtained results in the other study revealed that the propolis components had higher values of ACE inhibition among samples tested.[105] Moreover, the ability of various active ingredients from honeybee and propolis to prevent SARS-COV-2 main protease was investigated. It was observed that CAPE, galangin, and chrysin have a strong binding with COVID-19 main protease, and they might be used as an effective virus inhibitor.[106,107]

Based on results, propolis is identified to boost immunity; therefore, it could be accepted as an adjuvant treatment to reduce the inflammatory response and inhibit cytokines storm that cause damage to extrapulmonary tissues and organs during the pathogenic coronavirus infection. Furthermore, CAPE has also been proven to have anti-inflammatory and immunomodulatory properties as an essential active component of propolis. It has been reported that it prevents infection with the coronavirus. Thus, inhibiting or reducing lung fibrosis with this therapy may be successful. In addition, quercetin, hesperidin, kaempferol, chrycin, rutin, myricetin, and artepillin C (is a significant constituent of Brazilian

green propolis) can also be able to alleviate the violence of inflammatory agents caused by SARS-COV-2.[108–111] Although data specifically on SARS-COV-2 randomized controlled studies have not been conducted, the enumerated evidence from the literature strongly suggested that propolis and its constituents can be a promising source of pharmacological for prevention and symptomatic treatment in patients infected with COVID-19.

Pro-and Pre-Biotics

Various practical antiviral protection actions against VRTIs have been reported for probiotics, along with increased interferon-gamma and alpha production, increased secretory immunoglobulin A production, decreased expression of pro-inflammatory cytokines, enhanced anti-inflammatory cytokine production, increased regulatory T-cells, and enhanced natural killer cell activity.[112,113] It has been shown that viral infections in the respiratory tract, such as coronaviruses, by increasing permeability of the gastrointestinal tract, cause destructive impacts on the gut microbiota and increase pathogenic bacteria in the host.[114–116] Furthermore, Xu et al[117] suggested that the intestinal damage caused by COVID-19 is even more significant and more prolonged than the lungs. Additionally, SARS-COV-2 RNA has been identified in the stools of COVID-19 cases even after improving respiratory symptoms.[118] Therefore, the gut may act as a reservoir for the virus.[119] Thus, probiotics have a crucial role in the restoration of the composition of human gut microflora, protection of the gut barrier function, reducing duration and symptoms of VRTI, competition with pathogens for adhesion to gut epithelium and nutrition, and playing a regulatory role on the gut-lung axis.[92,120,121] In addition, probiotic bacteria can directly bind to the virus, prevent entry into the host's respiratory and gastrointestinal tract epithelial cells, and prevent the pathogen-host cell receptor interaction.[122]

Baud et al[123] compiled the commonest probiotics that could affect the COVID-19 pandemic scenario, including *Lactobacillus casei, Lactobacillus gasseri, Bifidobacterium breve, Pediococcus pentosaceus*, and *Leuconostoc mesenteroides*. Based on clinical studies and human trials, some of the species mentioned above significantly reduce the risk of upper respiratory infections, common cold, the symptoms of influenza viral infection, and preventing antibiotic-associated diarrhoea by 40% to 70%.[122] In addition, it was recently discovered that medication with probiotic bacteria using Bifidobacteria and Lactobacillus offers a strong possibility of restoration from COVID-19.[124]

Currently, it has been shown that probiotics modulate intestinal epithelial defence responses by producing various antiviral compounds.[125] In addition, a computational docking analysis has demonstrated that metabolites derived from *Lactobacillus Plantarum* are more responsible for adhering to the S-protein of SARS-COV-2 and preventing entrance by attaching to ACE2 receptors.[126] d'Ettorre et al[127] published a recent cohort study in which individuals hospitalized with COVID-19 treated with a probiotic were compared to those who did not receive a probiotic and found that the probiotic group had alleviation of COVID-19 related symptoms, an 8-fold reduction in respiratory complications, and no deaths were observed in this group (compared to those who did not receive the probiotic).

Prebiotics contribute to short-chain fatty acid production that can modulate the immune system by enhancing anti-inflammatory cytokine production and decreasing pro-inflammatory cytokine development.[128,129] It was also revealed that some compounds such as unsaturated fatty acids, polyphenols, fibre, inulin, glycan, and polysaccharides are included in prebiotics and have therapeutic effects in infections.[130–132] In addition, several recent reviews described the importance of pro-and prebiotics as an adjuvant therapeutic option to aid COVID-19 management.[113,126,133]

Some pro-and prebiotics indicates that they can be considered adjuvant vaccines and may modulate responses to vaccinations.[134,135] Therefore, they could be used to develop anti-coronavirus vaccines.[136] Thus, despite the lack of clinical data, these data indicate that pro-and prebiotics could benefit individuals with COVID-linked gastrointestinal manifestations and a potential immunomodulatory strategy for COVID-19.

Zinc (Zn)

Zn is a vital micronutrient and a critical factor for innate (non-specific) and adaptive (specific) antiviral immune responses. In addition, Zn is a crucial cofactor for numerous viral enzymes, proteases, and polymerase; therefore, Zn is a critical factor to inhibit viral replication and dissemination.[137,138] It seems that Zn exhibits antiviral effects by enhancing the cell's resistance to the entry of the virus, inhibition of viral replication, viral attachment, destabilizing the viral envelope, RNA synthesis, DNA polymerase, and reverse transcriptase.[139,140]

Several studies showed that Zn supplementation as a general stimulant of antiviral immunity affected the role of innate immunity such as natural killer cells, improved the secretion of pro-inflammatory cytokines and macrophages,[49,115] reduced the levels of reactive oxygen species[141] decreased apoptosis of lymphocytes;[142] thus it leads to reduce the susceptibility to systemic inflammation, lung injury and minimize secondary infections.[143,144] In addition, it has also been shown that Zn administration leads to positive impacts on clinical outcomes such as shortened infectivity, amelioration of clinical symptoms, duration of the common cold, and reduction of rates of acute respiratory infection up to 45%.[75,145,146] Therefore, Zn deficiency can decrease resistance to viral infection in susceptible persons (eg, old age) linked with the elevated mortality risk.[147,148]

It was recently reported that the specimens obtained from the non-surviving COVID-19 cases had notably low Zn levels.[149,150] According to similar studies, adding Zn to the combination of hydroxychloroquine or chloroquine and azithromycin for treating individuals with COVID-19 may help lower the mortality rate and hospitalization and improve clinical practice outcomes in high-risk patients.[151,152] Clinical studies on serum Zn content in COVID-19 patients observed a strong correlation between low serum Zn levels and the severity of COVID-19, as well as mortality.[153,154] On the other hand, Zn intake has been shown in earlier research to be beneficial in inhibiting entrance into the host cell.[155] A vivo model reported that a high level of Zn inhibited the expression of ACE2; thus, it can be assumed that Zn administration can block SARS-COV-2 cellular entry.[143] It could also act synergistically when co-administered with azithromycin and triclabendazole or emetine on the expression of ACE-2.[156,157]

A molecular docking study suggested that a high intracellular concentration of Zn could interact with the enzymatic activities of $3CL^{pro}$ and RdRp of SARS-COV-2; therefore, it can be recommended that Zn show action against viral replication of SARS-COV-2.[158] Zn supplementation has been recommended to improve antibody titers and viral vaccination responses during the social vaccination program to enhance the adaptive immune response against SARS-CoV-2 and a better humoral immune response after vaccination.[137,159] Zn intake alone or in conjunction with hydroxychloroquine is being studied in clinical studies to prevent and treat COVID-19. Men should consume 11 milligrams of zinc daily, while non-pregnant women should take 8 milligrams. In registered clinical trials, zinc sulfate 220 mg (50 mg of elemental zinc) twice daily is the maximal dose for patients with COVID-19. Zinc treatment for COVID-19 is currently not supported by enough evidence to provide a recommendation for or against its usage.[160] Deficiency of Zn availability may impair immunization outcomes. However, when combined with other antiviral and anti-inflammatory medicines, these properties make Zn an excellent potential candidate for use in the case of a viral infection.

Elderberry

Elderberry's antiviral activity is attributed to increasing inflammatory cytokine production.[161] It was discovered that elderberry juice has a considerable antiviral effect against influenza virus infection in humans when tested on the human IAV using concentrated elderberry juice.[162] Besides, some studies have shown that the elderberry's flavonoid components inhibit neuraminidase;[163] and bind to the envelope of influenza.[164] Furthermore, it was proved that elderberry syrup is effective against IAV infections. Zakay-Rones et al[165] conducted a study on patients suffering influenza-like symptoms. Following the onset of influenza-like symptoms in the trial participants, the author gave them 15 mL of elderberry or placebo syrup four times a day for five days (within 48 hours of the symptoms). The severity of their symptoms was measured using a visual analogue scale, and the duration was practically as short as that of the placebo syrup.

On the other hand, air travellers consumed elderberry capsules in a double-blind, placebo-controlled, randomized study (600 mg daily, ten days before the travel). The dosage was increased two days before departure and 4–5 days after arrival (900 mg daily). The results of this study, on the other hand, showed that elderberry could shorten the duration and severity of a cold by two days ($p=0.05$).[166] In addition, the study conducted by Krawitz et al[26] showed that elderberry liquid extract is active against pathogenic respiratory bacteria and influenza viruses.

In the aggregate, black elder contains many valuable compounds for general health and may be beneficial to control COVID-19. Recently, Schön et al[167] demonstrated that elderberry extract has antiviral activity and inhibits the release of pro-inflammatory cytokines TNF- and α, IFN-γ, and IL-2, indicating that elderberries act as immunomodulators. Additionally, the elderberry extract possesses substantial antiviral bioavailability, as demonstrated by its high virucidal

efficacy against the modified vaccinia virus Ankara, which is reduced by up to 95%. Thus, the proprietary elderberry extract's anti-inflammatory and antiviral properties recommend its usage as an immunomodulatory health product.

Resveratrol

Resveratrol is a natural polyphenol compound derived from grapes, red wine, mulberry, peanuts, and other plant sources. Resveratrol has antioxidant, anticancer, antiviral, and free radical scavenging activities.[168] In addition, resveratrol's antiviral activity may be connected to its immunomodulatory impacts on IFN-a, IL-2, and IL-12.[169] The coagulation disorders and thrombotic events are the consequences of COVID-19, which increases inflammatory cytokines. For these reasons, speculated that resveratrol, as a natural substance with anti-thrombotic characteristics, could effectively protect against COVID-19.[170] Resveratrol has been reported to significantly inhibit MERS-Coronavirus replication and reduce cell death (25%) after virus infection. This study also found that resveratrol treatment inhibited MERS-Coronavirus nucleocapsid as well as RNA expression.[171]

In vivo study showed that ACE2 levels were increased in resveratrol-fed mice.[172] Moreover, the addition of resveratrol to the diet can reduce the adverse effects of high fat on ACE2 gene expression.[173] In addition, resveratrol destroyed the pseudorabies virus by inhibiting intracellular viral reproduction.[174]

Researchers discovered that resveratrol had a beneficial impact on the Duck enteritis virus (DEV), a member of the *alphaherpesvirinae* family. In addition, they found that resveratrol may considerably reduce DEV replication. A recent study by Beijers et al[175] found a reduction of inflammation and oxidative stress in the lungs due to chronic obstructive pulmonary disease after treatment with resveratrol because of the drop in the activation of several inflammatory cytokines, including nuclear factor kappa B, tumour necrosis factor, and matrix metalloprotease-9 protein expression in lymphocytes. Due to the limitations of resveratrol's bioavailability, stability, and solubility, the combination of this compound with a β-glucan improves the stability of resveratrol.[176] The study conducted by Baldassarre et al[177] proved that a solution containing resveratrol plus carboxymethyl-β-glucan reduces some respiratory signs in infants with the common cold. The above studies demonstrate that resveratrol can be used as a novel therapy for COVID-19. However, further investigations are needed to prove it.

Vitamin D

Low vitamin D levels drop immune system function due to vitamin D's immunomodulatory activity.[178] When exposed to infections, macrophages, dendritic cells, and the active form of vitamin D begin to be synthesized.[179] Therefore, vitamin D is an integral part of innate immunity, and vitamin D deficiency can cause immune system disorders.[180] Furthermore, vitamin D affects interferon γ and tumour necrosis factor α and subsequently decreases the cytokine storm.[181] Moreover, vitamin D regulates T cells and IL-4, and it has an inhibitory effect on IFN-γ, IL-17.[182]

In patients with chronic hepatitis C virus, correcting vitamin D deficiency resulted in a considerable reduction in interferon gamma-induced protein 10 and enzyme dipeptidyl peptidase-4, both linked to inflammatory reactions in the condition.[183] Furthermore, a study of elderly COVID-19 patients who received a combination of 1000 IU of vitamin D, 500 µg of vitamin B12, and 150 mg of magnesium found that they were considerably less likely to necessitate oxygen therapy.[184] In addition, a retrospective observational study in Belgium demonstrated that vitamin D insufficiency enhanced the risk factor for COVID-19.[185]

Vitamin D decreases the danger of contagions by several mechanisms, including inducing defensins and cathelicidins, which reduce virus replication. Reducing pro-inflammatory concentration and increasing cytokine's anti-inflammatory concentration are considered other mechanisms.[186] Taking 10,000 IU/d of vitamin D for a few weeks was suggested by Grant et al[186] for people at risk of influenza and coronavirus infection. In addition, results obtained from a retrospective study in the mainland of the USA recommended that sunshine and vitamin D possibly reduce the risk of disease and mortality associated with COVID-19.[2] Due to the effects of vitamin D on various organs, we hypothesized that vitamin D has effects against VRTIs. However, the evidence obtained is not sufficient to prove this point and to prove it, a more detailed study is needed.

Vitamin C

Vitamin C possesses immunomodulatory and antiviral effects.[187] In addition, antioxidants were found to prevent lung inflammation and injury induced by viruses.[188] However, according to the findings of the other study, early use of high-dose vitamin C can improve respiratory problems caused by COVID-19.[189] Intravenous using vitamin C can reduce the risk of cytokine storms in the late stages of COVID-19.[190] In vitro study demonstrated that vitamin C inhibits the formation of IVA nucleoproteins and neuraminidase. This suppression effect was dose-dependent.[191]

Furthermore, it was found that 1–2 g/day of vitamin C inhibits VRTIs.[138] Thus, a high dose of vitamin C may be a therapeutic agent for improving oxidative stress and inflammation caused by coronavirus infection, preventing virus replication, improving the antiviral immune system and adrenal function.[192] A daily intake of 1 g vitamin C and 30 mg Zn can help to prevent viral symptoms in flu patients.[193] The other study indicated that dietary-rich vitamin C enhances macrophage function.[194] Furthermore, combining vitamin C, curcumin, and glycyrrhizic acid can protect against viral infection by boosting interferon synthesis, modulating the innate immune response, activating and balancing T-cells.[195]

Antioxidants in vitamin C improve the production of interleukin-2, natural killer cell activity, and T lymphocyte response.[196] Vitamin C and quercetin have synergistic antiviral action. They can be used to treat COVID-19 as adjunctive for promising agents such as Remdesivir or convalescent plasma.[96] Vitamin C appears to potentially affect oxidative stress and the generation of free radicals caused by burning and helps decrease overall fluid requirements and improve endothelial function.[197]

FFs have been shown to have antiviral properties in clinical trials. Since vitamin C is well-known for preventing respiratory infection, it has been used extensively in clinical trials. According to the findings of a clinical investigation, vitamin C can be used as a therapeutic medicine to reduce the severity of lung inflammation caused by viral infection.[198] Study participants (n=214) with SARS-COV-2 infection were given zinc gluconate (50 mg), vitamin C (8000 mg), or a combination of the two supplements, and the duration of symptoms did not differ substantially across groups compared with standard of care in a randomized clinical trial study.[199] In a pilot therapeutic trial in China, 56 patients with COVID-19 in the critical care unit were randomly assigned to receive 24 g of intravenous vitamin C per day or a placebo for 7 days. Unfortunately, the trial was halted early due to a decrease in COVID-19 cases in China. However, the paper identifies no variations in mortality and mechanical ventilation time.[200] Short three-arm pilot research evaluated two IV vitamin C doses (50 and 200 mg/kg per day) to placebo in 24 sepsis patients. During the 4-day investigation, individuals who received vitamin C (either 50 or 200 mg/kg per day) showed lower proinflammatory markers than those who received placebo.[201]

Curcumin

Curcumin possesses antiviral properties against numerous viruses, such as vesicular stomatitis virus, parainfluenza virus type 3, and RSV.[202] For COVID-19 management, there is a suggestion that curcumin may have a beneficial effect on viral encapsulation, cytokine storm protection, and cellular signalling pathways by blocking virus entry and viral protease encapsulation.[203] Furthermore, curcumin also alters the structure of viral surface proteins, making it difficult for the virus to enter the host cell.[204] Moreover, the ACE2 binding site for viral spike protein is better bound by curcumin.[205] While this may be the case, curcumin is anticipated to inhibit the spike protein's receptor-binding area.[206]

Moreover, the coronaviruses also use the dipeptidyl peptidase 4 to enter the host cell.[207] Therefore, it has been suggested that topical application of curcumin as an emulsion can effectively prevent entering the SARS-COV2 to the human body through ACE2 receptors distributed in the nasal cells, respiratory mucosa, and eyes.[208] Furthermore, curcumin prevents the replication of SARS-COV-2 by targeting the virus to penetrate the cell and attack the components that the virus needs to replicate.[209] Additionally, the spread of viral particles from infected cells is inhibited by curcumin.[210]

Curcumin suppresses the transcription factor of activated B cells (NF-κB) by inhibiting Ang II-stimulated angiotensin AT1 receptor signalling in COVID-19.[211] Furthermore, the study results show that curcumin can reduce the inflammatory response caused by IAV in the lung by inhibiting NF-κB.[117] Further, curcumin has been reported to inhibit the release of critical cytokines IL-6, IL-10, interferon γ and reverse the fatal cytokine storm.[212] Collectively, according to anti-fibrotic,

pulmonoprotective and inhibitory effects on NF-κB and several pro-inflammatory cytokines by curcumin on the lung tissue, making it helpful in treating patients with COVID-19.

Conclusions

Due to the lack of a viable medicine, VRTIs, particularly coronaviruses, have significantly influenced people worldwide. Vaccines for protection are continuously being developed and must be carefully and systematically tested. Considerable scientific evidence supports FFs as a strategy to get health benefits from a food-based diet. FFs have also been shown to have antiviral activity, becoming increasingly apparent. Boosting the immune system is another way to combat viral infection. Polyphenols, flavonoids, propolis, curcumin, prebiotics, probiotics, and food supplements like Zn, vitamin C, D, and E are examples of functional food ingredients that might be referred to as natural immune boosters. The data suggested several processes by which FFs combat viruses that cause respiratory illness. In addition, the use of dietary supplements to prevent and cure VRTI was also found to be effective. Therefore, research into the potential role of FFs and functional food ingredients in the prevention and treatment of VRTIs, particularly in cases with COVID-19, is highly suggested in the future.

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