Review Article

The role of selected bioactive compounds and micronutrients with immune-enhancing activity on the prevention and mitigation of SARS-CoV-2

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ABSTRACT

While the world is fighting against SARS-CoV-2, this virus continues to mutate around the world, infecting with new variants and causing the death of people. According to the World Health Organization (WHO) data, there were over 255 million confirmed cases and more than 5 million deaths globally as of November. To date, approximately 7.4 billion doses of vaccine have been administered. However, no therapeutic drugs have been found yet. By considering a significant part of the global population remains unvaccinated and the potential of the constantly mutating virus to become partially resistant to vaccines, it is understood that a healthy immune system is one of the important weapons in the fight against COVID-19. It is essential to consume food products containing sufficient amounts of bioactive compounds and micronutrients to strengthen overall immune functions and prevent this life-threatening infection. In the context of COVID-19, boosting the immune system has been considered a viable approach to both prevent and alleviate the infection. Bioactive compounds and micronutrients can present antiviral capacity either by interfering with target viruses directly by entering the defense mechanism or indirectly by activating adaptive immune system-related cells. This review presents the effects of bioactive compounds (phenolic compounds, polyphenols), vitamins (A, B, C, D, E, K), minerals (zinc, selenium, iron, copper, magnesium), ω-3 fatty acids and probiotics on the body's defense mechanisms against SARS-CoV-2. It also provides information on the evidence surrounding the specific effects of these compounds to potentially reduce the morbidity and mortality rates of COVID-19 patients, and how they may act in key immunological pathways.

Keywords: SARS-CoV-2, COVID-19, Bioactive compounds, Micronutrients, Immune system

1. INTRODUCTION

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread across many countries since the emergence of the coronavirus infection in December, 2019. SARS-CoV-2 has caused numerous deaths, with millions of confirmed cases all over the world [1]. It is a serious public health threat [2]. Globally, as of November 2021, there have been 255.324.963 confirmed cases of COVID-19, including 5.127.696 deaths, reported to WHO [3]. As of November 2021, a total of 7.370.902.499 vaccine doses have been administered [3]. Since the outbreak of the pandemic, few clinical studies have been conducted on the efficacy of existing anti-inflammatory and anti-viral drugs as an alternative treatment for the disease [4]. Despite the attempts, there is still no drugs have been developed to cure the disease, except a few vaccines that have been applied so far. On the other hand, in the fight against the COVID-19 pandemic around the world, the scientific community has accelerated its efforts to explore the bioactive compounds that can support the immune system, protect against lower respiratory tract viruses, and limit the transmission of SARS-CoV-2 [5]. It is possible to fight against several harmful infections with a strong immune system. A strong immune system is achieved by a diet containing necessary and sufficient amounts of bioactive compounds. This is helpful to keep our bodies healthy both physically and mentally [6]. People become aware of consuming natural food product includes several bioactive compounds to stay away from this disease or to be recovered easily from COVID-19. A significant role of a healthy and balanced diet to strengthen the immune system cannot be ignored [6]. This can improve our body defense and keep it in perfect condition which allows the immune system to better fight against coronavirus. Several studies have explored that nutritional deficiency causes an increase in both morbidity and mortality rates [6–8]. Bioactive compounds present in various plants, vegetables, fruits, whole grains, nuts and oils [9] are capable of modulating the functions of receptors, enzymes such as inhibition and induction, in addition to antioxidant properties [10]. Epidemiological studies show that the higher consumption of food products with bioactive compounds such as phytochemicals, vitamins, phenolic compounds, carotenoids and flavonoids have positive impacts on human health [11]. Rather than bioactive compounds, probiotic bacteria such as *Saccharomyces, Lactobacillus* and *Bifidobacterium* [12] also support defense mechanisms via modulating the function of macrophages, dendritic cells, B-lymphocytes and T-lymphocytes. Probiotics can act either by signaling pathways in the host's cells or by gene expression regulation mechanisms [13]. This review provides that bioactive compounds, vitamins, minerals, ω-3 fatty acids and probiotics have a crucial role to support the human immune system and reduce the risk of infection. In addition, the effects of these compounds on defense mechanisms against SARS-CoV-2 and how they can act in basic immunological pathways are evaluated. The main bioactive food compounds for strong immune system were examined. Therefore, this review also attempts to see the potential of these bioactive food compounds in the context of infection with the novel coronavirus SARS-CoV-2.

2. COVID-19

Coronaviruses are a large family of enveloped and positive strained RNA viruses containing the largest and complicated RNA genomes up to 31 kb in length [1]. These can cause several infectious diseases such as respiratory, intestinal, liver and neurological disorders in different hosts including humans, pigs, cows, cats, dogs, horses, mice and birds [2]. The severe acute respiratory syndrome coronavirus (SARS-CoV-2), which causes COVID-19, is a new strain of coronavirus and threatens human health in all over the world [2]. The most common symptoms related to COVID-19 can be listed as dry cough, fever, shortness of breath, headache, and myalgia or fatigue [14]. On the other hand, hemoptysis, shortness of breath and diarrhea are rare among patients during hospitalization [15]. After initial SARS-

CoV-2 infection, the patients are continuing to get gradually worse. Symptoms are usually developed after an incubation period of 5–6 days and showed up to 14 days in some cases [16]. After incubation, the virus firstly affects the respiratory system directly, causing severe hypoxia and a lack of oxygen in tissues and organs [17]. In the second stage of infection, granulocyte colony-stimulating factor (G-CSF), inflammatory cytokines and biomarkers like interleukin (IL-2, IL-6, IL-7), tumor necrosis factor-α (TNF-α), macrophage inflammatory protein 1-α, D -dimer, C-reactive protein (CRP) and ferritin are significantly elevated in critically ill patients [18]. In the third stage, patients infected with COVID-19 are prone to develop shock, respiratory failure, cardiopulmonary collapse [19], acute kidney injury (AKI) [20], liver damage, gastrointestinal system tissue damage, blood clots, and nervous system damage [1]. A high number of reactive species can be produced, often resulting in an imbalance of cellular redox homeostasis following viral replication. As a result, a lack of balance between free radicals and antioxidants in the cell (oxidative stress) causes viral infection and increases the production of reactive oxygen species (ROS) [21]. Besides the immune system, the lungs are the main organ most affected by the coronavirus disease [1]. Furthermore, AKI is also reported to be associated with coronavirus disease [22]. The specific receptor for the binding of SARS-CoV-2 was found to be angiotensin converting enzyme 2 (ACE-2), which predominates in pulmonary epithelial cells [15].

3. HUMAN IMMUNE SYSTEM

Although the human body has a complex and highly developed system, it can be vulnerable to invaders that adversely affect the body, such as diseases and infections. While some diseases caused by the disfunction of organs or fluids in the human body, some other diseases are caused by bacteria, viruses and bacteria. These microorganisms can cause various diseases such as tuberculosis, dysentery, and fatal viral diseases such as AIDS and COVID-19, which are incurable. Our immune system protect our body from such diseases. This immune system destroys microbes, or foreign particles, from the bloodstream or the target area through immune cells such as lymphocytes (B-cells and T-cells), macrophages, and monocytes [23]. T-cells, CD4+T and CD8+T cells, known as T helper cells, play an important antiviral role, especially balancing the fight against pathogens and the risk of developing autoimmunity or excessive inflammation. CD4+T cells activate T-dependent B cells, promoting the production of virus-specific antibodies [24]. However, CD8+T cells are cytotoxic and can kill infected cells [25]. In addition, T helper cells produce proinflammatory cytokines through the NF-κB signaling pathway [26]. White blood cells that can circulate throughout the body through blood vessels play a key role in the immune system. The body exchanges cells and fluids between blood and lymphatic vessels to track invading microbes through the lymphatic system [27]. Lymph containing special compartments where they can encounter antigens are carried out by lymphatic vessels. Through the lymphatic vessels, immune cells and foreign particles enter special compartments in the lymph nodes. In this way, they are transported to the tissues in the body. These continue the cycle, patrolling for foreign antigens and back into the lymphatic system [27].

There are two types of immunity: innate immunity (fast response) and adaptive immunity (slow response). While the innate immunity provides the first barrier against invaders, adaptive immunity is the second barrier to infection and acquired later in life, for example after a vaccine [28]. The immune system consists mainly of white blood cells, antibodies, bone marrow, complement system, lymphatic system, spleen, and thymus. Lymphocytes consist of T lymphocytes (helper T cells and cytotoxic T cells), B lymphocytes and natural killer cells. Immune cell development takes place in the bone marrow [29]. The innate immune response is non-specific rapid warnings against pathogens. For example, tear and mucus secretions act as traps and barriers against pathogens entering the body while cilia (very fine hairs) in the nasal passages and respiratory tract move mucous-containing pathogens from the body [30]. Since innate immune responses are associated with hard-wired communication that are gene-encoded in the host's germline, these responses allow for easy detection of microbial structures present in most organisms. In addition, the innate immune system is the first line of defense against pathogenic agents [31]. The adaptive immune system produces fewer cells with high specificity against pathogens. The adaptive immune response system enhances antigen-antibody binding for different pathogens through mechanisms encoded by genes with high specificity. The adaptive response is triggered after activation of the innate immune response [31]. With their wide spectrum of specificity, adaptive immune receptors can easily detect antigens and effectively inhibit pathogens [32]. Skin and inflammatory responses begin when the body is affected. As with COVID-19, when the body first encounters the virus, the immune system does not work properly and illness may occur [33]. When the cells of the immune system are trained, they complete their task by circulating between the central and peripheral lymphoid organs and passing through the relevant regions through the blood. In the case of a SARS-CoV-2 attack, the innate immune system quickly realizes the infection and is prompted a few hours after infection. Innate immunity strives to inhibit virus replication within cells and provides a rich medium containing type I interferon to prepare the adaptive immune response. After this preparatory effect, it takes 6 to 10 days for the adaptive immune response to produce enough cells to counter a viral infection [34]. Figure 1 shows the effectiveness of bioactive food compounds and micronutrients against SARS-CoV-2 in the infection pathway.

Let's look at the Fig. 1 in details: After SARS-CoV-2 infects macrophages, macrophages present SARS-CoV-2 antigens to T cells on the extracellular side. This process produces T cell subset Th17-related cytokines, leading to T cell differentiation and activation. Then there is a massive release of cytokine to amplify the immune response. The production of these mediators because of viral persistence has a negative effect on NK and CD8+T cell activation. However, CD8+T cells produce quiet efficient mediators to clear SARS-CoV-2 (Fig. 1). On the intracellular side, SARS-CoV-2 binds to DPP4R located on the host cell membrane via the S protein and then causes genomic RNA to be appeared in the cytoplasm. An immune response against double-stranded RNA virus (dsRNA) can be partially generated during SARS-Cov-2 replication. TLR-3 sensitized by dsRNA and cascades of signaling pathways (IRFs and NF-κB activation, respectively) are activated for the production of Type I-IFNs and proinflammatory cytokines. To protect uninfected cells, it is necessary to increase the release of antiviral proteins. In this respect, the production of Type I-IFNs becomes more important. Sometimes, supporting proteins of SARS-CoV-2 can interfere with TLR-3 signaling and bind the dsRNA of SARS-CoV-2 for the purpose of prevention TLR-3 activation during replication and evade the immune response. TLR-4 can recognize the S protein and lead to activation of proinflammatory cytokines by the MyD88-dependent signaling pathway. Virus-cell interactions lead to potent production of immune mediators. In response to SARS-CoV-2 infection, the releasability of large amounts of chemokines and cytokines (IL-1, IL-6, IL-8, IL-21, TNF-β, and MCP-1) is promoted in infected cells (Fig.1). These chemokines and cytokines gathers lymphocytes and leukocytes to the site of infection [24].

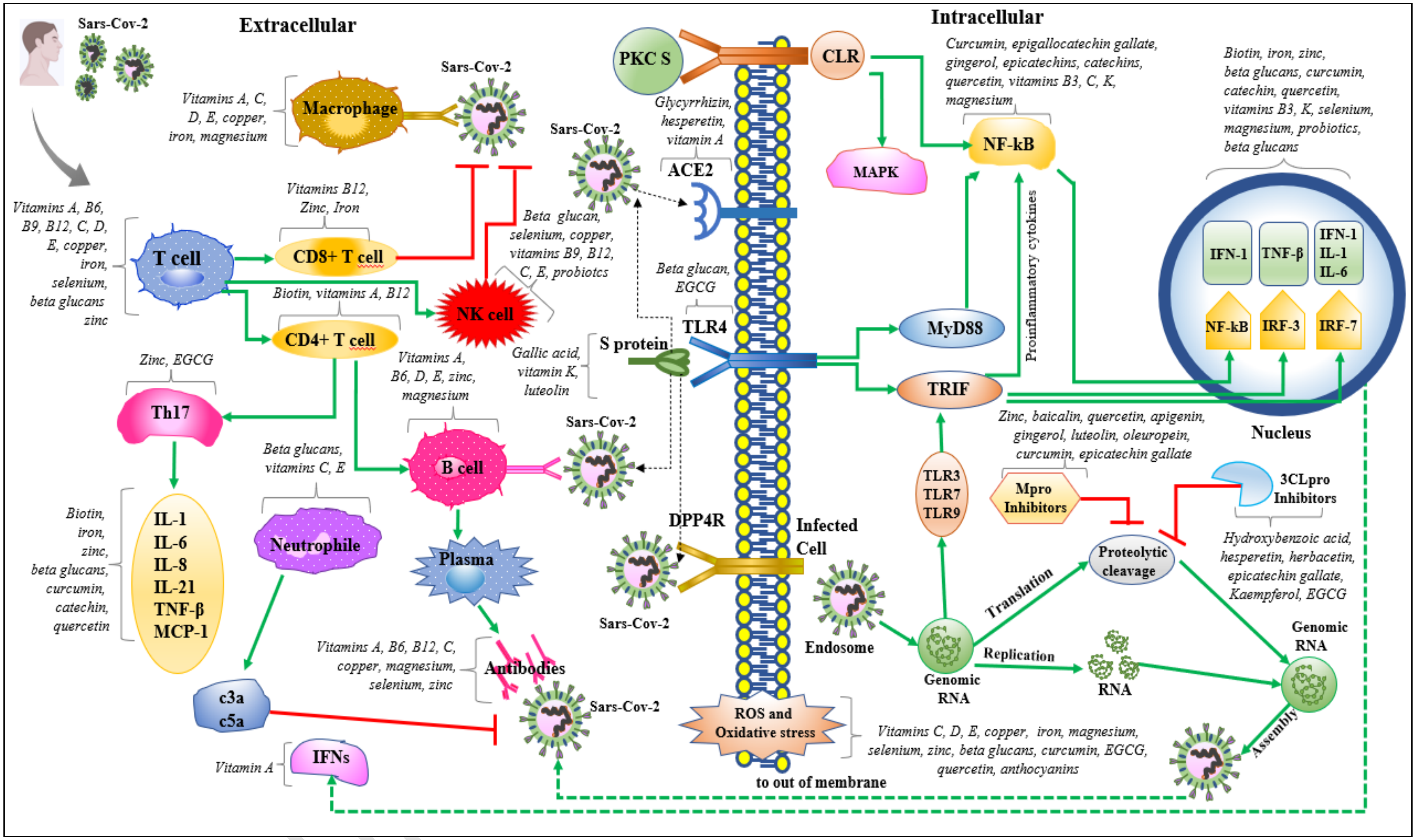

Fig. 1 Immune responses against SARS-CoV-2 and contributions of some micronutrients and bioactive compounds to various cell and cytokines involved in the defense mechanism during infection (red lines refer to inhibitory effects; green lines refer to activating effects). Adapted from Li *et al.*[24] and Arruda de Souza Monnerat *et al.*[246]

4. BIOACTIVE COMPOUNDS AND MICRONUTRIENTS AGAINST SARS-CoV-2

4.1 Omega (ω)-3 fatty acid/polyunsaturated fatty acid (PUFA)

ω-3 fatty acids are long-chain fatty acids with several positive effects on human health [35]. ω-3 fatty acids metabolites play an important role in the synthesis of different inflammatory mediators such as prostaglandins (PG), leukotrienes (LT), thromboxanes (TX), preservatives and resolvins [36]. ω-3 fatty acids affect T-cells, macrophages and neutrophils positively in enhancing the immune system of the human body [37]. T-cells are lymphocytes originating from the thymus that recognize antigens presented by the T-cell receptor (TCR). The first contact of a TCR with antigen-presenting cells (APCs) such as macrophages or dendritic cells (DCs) activates T-cells. Along with T cells, B cells are the main adaptive branch lymphocytes of the immune response. Macrophages play an important role as part of the innate immune system. ω-3 fatty acids lead to important changes on the macrophage gene regulation [38]. ω-3 fatty acids stimulate the ability of phagocytosis by secreting cytokines and chemokines. It also activates macrophages through polarization which leads to improvement of their function [39]. Treatment of docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA) macrophages results in significant changes in gene expression of T-helper type (THP) 1-derived lipopolysaccharide (LPS) [40]. High dietary intake of EPA inhibits proinflammatory cytokines and suppresses the THP-1 response [41]. ω-3 fatty acids (DHA and EPA) lead to significant changes in the microRNA (miRNA) profile as well as create the cell culture environment for macrophages. Neutrophils, the first cells where inflammation occurs, has a crucial role in removing pathogens [42]. Neutrophils can contact with the adaptive immune system through the incorporation of native T cells into THP-1 cells and have B cell antinegens in the spleen. ω-3 fatty acids are absorbed into phospholipids and metabolized by neutrophils into eucotrienes, maresins, prostaglandins, preservatives, resolvins and thromboxanes. The neutrophil role of ω-3 fatty acids and their metabolites are adjusted through phagocytic capacity, cytokines, neutrophil migration, and reactive oxygen species (ROS) production. Integration and control of immune cells into the cell membrane is achieved by in vitro stimulation or dietary supplementation via ω-3 fatty acids [37]. Marine ω-3 PUFAs promote resolvin production from EPA and DHA [43]. Resolvins are molecules produced during the resolution phase of an inflammatory response and have a significant role in inflammation prevention and pre-solubility. ω-3 fatty acids such as EPA and DHA have been found to regulate the resolution phase by biosynthesis of the E- and D-resolvin series. DHA metabolites such as preservatives and maresins have been found to have anti-inflammatory effects [44]. Szabó et al [45] recommends EPA and DHA supplementation in the potential management of cytokine storm in COVID-19 due to their anti-inflammatory effects. EPA and DHA can be seen as a powerful and effective weapon to fight against SARS-CoV-2 infection. Due to the properties mentioned previously, ω-3 fatty acids can be useful to fight against COVID-19 by improving the immune system.

4.2 Vitamins

4.2.1 Vitamin-A

Vitamin A, which has anti-inflammatory properties, contributes to the better immune system by showing regulatory roles in cellular and humoral immune responses and processes. In addition, it has important functions such as maintaining vision, supporting growth and development, and protecting the integrity of the epithelium and mucus in the body [38]. It has been reported that vitamin A supplementation can reduce the risks of mortality and morbidity from certain diseases such as diarrhea, measles, human immunodeficiency virus (HIV) infection and malaria in preschool children [46]. Likewise, Zlotkin [47] reported that vitamin A can reduce the mortality rate in children infected with the virus. Vitamin A develops the many major cells' functions by supporting the immune system in fighting pathogens such as neutrophils, natural killer cells, T cells, B cells, and monocytes or macrophages. In addition, it promotes antibody production, cytokine expression, lymphopoiesis, apoptosis, and mucin and keratin production [48]. Vitamin A plays an important role in the innate immunity of the intestines and the maintenance of the intestinal barrier [49]. Retinol, retinal and retinoic acids are the active forms of vitamin A. Among the carotenoids present in pro-vitamin A, β-carotene is absorbed by conversion of it to retinol in the human intestine. Retinioc acid, a different form of vitamin A, has a bioactive structure and can increase the production of anti-inflammatory cytokines and especially IgA antibodies which have a protective role against viral infections such as measles [50]. Manicassamy & Pulendran [51] studied with the retinoic acid to modulate the immune response in dendritic cells and regulate the differentiation of T cells and B Cells. The study elicited an enhanced B cell-mediated IgA response of retinoic acid to antigens. Vitamin A plays an important role in the development and differentiation of T lymphocytes. It suppresses the production of IL-12, TNF-α and IFN-y by Th1 lymphocytes and supports the antibody-mediated Th2 response. Therefore, Vitamin A deficiency can lead to increased proinflammatory response and antibody response damage [52]. In addition, Sarohan [53] determined that the reduction of retinoic acid causes limitation on the synthesis pathway of type 1 interferon which leads to the collapse of the immune system during inflammatory diseases such as COVID-19. In another study, it was stated that β-cryptoxanthin, a precursor of Vitamin A, increased the serum IL-4, IgG, IgM and IgA levels when tested in rabbits [54]. In shortly, Vitamin A may reduce the susceptibility to SARS-CoV-2 and support immune function. For example, isotretinoin, a form of vitamin A, is capable of interacting with the down-regulation of angiotensin converting enzyme 2 (ACE2), which SARS-CoV-2 needs to enter the body [48]. It can be evaluated with the intake of vitamin A in the prevention of lung infections and in the treatment of the new coronavirus.

4.2.2 Vitamin-B

Vitamin B9 (Folic acid), a water-soluble compound, is the precursor of coenzyme tetrahydrofolate and is involved in the synthesis of nucleic bases, purines and pyrimidines that make up nucleic acids of genetic material [55]. An animal model study demonstrated that folic acid deficiency causes thymus and spleen atrophy, and decreased circulating T-lymphocyte counts [55]. Similarly, Sheybani *et al.* [56] reported that folic acid can inhibit furin activity, which facilitates the cleavage between ACE-2 and spike proteins of SARS-CoV-2. Folic acid is involved in intestinal immune regulation, increasing NK cell cytotoxic activity [57], which can improve the body's ability to fight against SARS-CoV-2. Vitamin B9 (Folate) deficiency, which performs DNA and protein synthesis in the body to a large extent, leads to a decrease in cell-mediated immunity. B9 deficiency reduces the blastogenic response of T lymphocytes to certain mitogens in humans and animals, and the thymus is modified [58]. Some of the food products rich in vitamin B9 are whole grains, green leafy vegetables, liver, seafood and nuts. It was reported that by Sharma [59] B9 supplementation in 23-month-old mice increased T-cell distribution and mitotic activity, and was found equal to 12-month-old mice when CD4+ cells and T cells were measured. This result showed that folate supplementation could strengthen the immune system. Ibrahim and El-Sayed [60] reported that vitamin B6 (pyridoxine) deficiency destroys lymphocyte maturation, growth and proliferation, and antibody production. Moreover, this deficiency inhibits the production of Th1 cytokines which supports Th2 responses [61]. It was found that even though low vitamin B6 in serious patients affected interleukin-2 (IL-2) production and responses to T and B cell mitogens in older people, short-term supplementation with 50 mg/day improved immune function Cheng et al. [62]. In addition to vitamin B6, vitamin B12 and folic acids were reported as supporters of natural killer cells, which may be important in antiviral defense, and CD8+ cytotoxic T-lymphocyte effects Maggini *et al.* [28]. For this reason, it was recommended that food products such as fruits, vegetables, eggs, and fish that are rich in vitamin B6 should be consumed by daily. On the other hand, vitamin B12 (cobalamin) which is a water-soluble vitamin needed to be taken in every day [63]. It has been reported that cobalamin slows the progression of the disease by affecting the ability of pathogens infection [64]. Immunoglobulin synthesis of B cells and T cell proliferative responses to concanavalin A are enhanced by vitamin B12. Vitamin B12 deficiency in animals weakens the protective immune responses against viruses and bacteria [65]. It was reported that low amount of vitamin B12 caused a decrease in bactericidal activity in adult megaloblastic anemia patients as well as neutropenia, leukopenia and related white blood abnormalities in children [66]. Vitamin B12 deficiency can damage the antibody production as well as cause hyperhomocysteinemia, which induces blood clot formations in the lungs and beyond [67]. It has been reported that optimal levels of vitamins (B12 and D) might be a factor in reducing the intensity of SARS-CoV-2 infection in COVID-19 patients [68]. In vitamin B12 deficiency, the resulting 5-methyl tetrahydrofolate retention can result in a secondary folate deficiency with disruptions in thymidine and purine synthesis and subsequent DNA and RNA synthesis, resulting in changes in immunoglobulin secretion [69]. In a study, a significant decrease was determined in the number of lymphocytes and CD8+ cells and the ratio of CD4+ cells in patients with vitamin B12 deficiency [70]. It has been reported that vitamin B12 supplementation reverses these effects and therefore may be a modulatory agent for cellular immunity [70]. Since vitamin B12 is very effective on pathogens, it can be recommended in the fight against COVID-19. Vitamin B8 (Biotin) acts as a coenzyme for five carboxylases and binds to different lysine residues in histones, affecting chromatin structure and mediating gene regulation [71]. Biotin deficiency leads to adverse effects on cellular and humoral immune functions. In a study conducted on rodents, it was revealed that biotin deficiency reduces antibody synthesis, spleen cell count and B-lymphocyte percentage, and impairs thymocyte maturation [72]. On the other hand, niacin (nicotinic acid), a form of Vitamin B3, regulates TNF-α, IL-6, IL-1β and NF-κB activation in alveolar macrophages [73].

4.2.3 Vitamin-C

It has been reported that vitamin C may be beneficial for patients affected by different herpes viruses or influenza virus. Since vitamin C has the capacity to increase the production of interferon and decrease the production of different cytokines, it has been reported to have positive effects in terms of immunomodulation in patients affected by different viral infections [74]. Vitamin C plays an important role in the immune system thanks to its functions such as the development immune cells and the production of antibodies. Vitamin C promotes collagen synthesis and protects cell membranes from the damage caused by free radicals which supports the integrity of epithelial barriers [75]. It also facilitates keratinocyte differentiation and lipid synthesis, as well as increases fibroblast proliferation and migration [76]. It was recommended by the doctors in the treatment of pneumonia, vitamin C is vital in maintaining epithelial integrity and is used in collagen biosynthesis [76]. Vitamin C supports the cellular functions of the adaptive and innate immune systems and also protects them against oxidative stress [77]. Vitamin C is able to involved in the proliferation, functionality and movement of neutrophils, monocytes, and phagocytes [78]. It maintains and/or improves NK cell activities and chemotaxis, increases phagocytosis and ROS generation, and improves microcidal effect [75,78]. It is also helpful in apoptosis and clearance of neutrophils from infection sites by macrophages [76]. It prevents the formation of extracellular traps and reduces associated tissue damage [79]. In addition, it increases serum levels of complement proteins and plays a role in the production of IFNγ [76]. It maintains redox homeostasis within cells and protects ROS and RNS during oxidative burst [75]. Moreover, it reactivates other important antioxidants such as glutathione and vitamin E [80]. It modulates cytokine production and reduces histamine levels. Vitamin C plays a role in the production, differentiation and proliferation of T cells, especially cytotoxic T cells. It also promotes proliferation of lymphocytes which results in increased antibody formation [76]. Vitamin C stimulates the production and function of leukocytes, mainly the movement of neutrophils and monocytes, and is easily mobilized during infection [81]. Vitamin C accumulates in leukocytes in high concentrations and is used during infection. By increasing oxidation levels, it triggers the signal cascade and provides activation of nuclear factor κB (NF-κB). NF-κB plays a role in inflammatory responses, pathogenesis of some diseases and viral infection [82]. In vitamin C deficiency, the bactericidal effect of neurophiles and macrophages decreases and accordingly, the risk of getting microbial infection increases [83]. Vitamin C immune stimulation mechanisms include modulation of Prostaglandin (PG) synthesis, protection of 5'-lipoxygenase, enhancement of cytokine production, modulation of intracellular cyclic nucleotide level, antagonism of immunosuppressive interactions of histamine and leukocytes, and neutralization of phagocyte-derived autoreactive and immunosuppressive oxidants [76]. Some reactive oxygen species that act as oxidizing agents are produced by activated phagocytes during infection. Vitamin C counteracts these effects thanks to its antioxidant properties [84]. A diet low in vitamin C in healthy young adult humans has been reported to reduce mononuclear cell by 50% and T-lymphocyte-mediated immune responses to antigens [85]. In addition, vitamin C supplementation has been reported to be effective against upper respiratory tract infections caused by the common cold [55]. Consumption of fruits and vegetables rich in vitamin C can be effective in fighting the new corona virus by strengthening the immune system. By the ability of vitamin C to defend the body against oxidative stress and to improve the immune system, including inflammatory aspects, it can be possible to suggest the benefits of consuming vitamin C in the management of COVID-19.

4.2.4 Vitamin-D

Vitamin D, a fat-soluble vitamin, plays an important role in calcium metabolism and bone homeostasis in the human body as well as in innate (mainly monocytes and macrophages) and adaptive immune (dendritic cells and T-cells) responses [82]. A negative correlation was determined between vitamin D levels and the number of COVID-19 cases according to the data collected from 20 European countries [86]. Vitamin D enhances phagocytosis, superoxide production and bactericidal effect by innate immune cells. It also promotes differentiation of monocytes and antigen processing by dendritic cells [87]. COVID-19 causes endothelial cell damage which is related to excessive production of cytokines. This cytokine storm leads to acute respiratory distress syndrome that results in death [88]. Vitamin D deficiency affects both cytokine and immunoglobulin production, leading to various respiratory tract infections [89]. The presence of adequate amounts of vitamin D suppresses general inflammation, lowers CRP levels, suppresses cytokines and prevents COVID-19 complications associated with cytokine storm [90]. Vitamin D enhances innate cellular immunity by stimulating the expression of antimicrobial peptides such as cathelicidin and defensins. Defensins increase the expression of antioxidative genes and maintain both tight and gap junctions. Influenza-like viruses increase the risk of infection and pulmonary oedema and significantly damage the integrity of epithelial tight junctions [82]. Vitamin D maintains the integrity of these connections. Vitamin D also increases superoxide production, phagocytosis and bacterial degradation, and promotes the differentiation of monocytes into macrophages. Furthermore, vitamin D can modulate the adaptive immune response by suppressing T helper type-1 (Th1) cell function and reducing the production of pro-inflammatory cytokines IL-2 and interferon-gamma (INF-γ). In addition, vitamin D promotes anti-inflammatory cytokines through TH2 cells and also stimulates suppressive regulatory T cells [91]. SARS-CoV-2 uses Angiotensin Converting Enzyme-2 (ACE2) receptors as a tool to enter alveolar cells, intestinal cells, mucous membranes, and endothelial cells in the lungs. Adequate concentrations of active vitamin D strengthen the immune system, increasing the concentration of ACE2 to fight against COVID-19. In brief, adequate vitamin D reduces the entry of COVID-19 viruses into the cells and increases their degradation [92]. This vitamin protects against adipose tissue inflammation [45] and induces antimicrobial peptide synthesis in epithelial cells and macrophages [87]. It was reported that there is a negative linear correlation between vitamin D in the blood and respiratory tract infections, and a 10 nmol/l increase in serum 25(OH)-vitamin D provides a 7% reduction in the risk of respiratory tract infections [93]. Higher serum 25(OH)D concentrations let people infected with COVID-19 to develop antibodies to the virus quickly, making it easier to overcome the clinical syndrome associated with this disease [94]. Vitamin D deficiency has been reported to increase individual susceptibility to different viral diseases such as influenza, HIV, and hepatitis C [95]. Since the SARS-CoV-2 is the respiratory tract infection virus, vitamin D may also play a vital role in the prevention of COVID-19.

4.2.5 Vitamin-E

Vitamin E is a powerful antioxidant that can protect the human body from infections, bacteria and viruses, and it has an important role in maintaining the general health and boosting immune system of older people [82]. Vitamin E, which cannot be synthesized in the body, must be taken through food. Foods rich in vitamin E are nuts, seeds and vegetable oils. A daily intake of approximately 15 mg of vitamin E is recommended [96]. Vitamin E is an important fat-soluble antioxidant that can protect polyunsaturated fatty acids from oxidation in the biological membranes of cells, regulate the production of reactive oxygen species and reactive nitrogen species, and modulate signal transduction [82,97]. Vitamin E increases resistance to respiratory tract infections by increasing the number of T cells, mitogenic lymphocyte responses, IL-2 cytokine secretion, NK cell activity and reducing the risk of infection [98]. Clinical trial results have shown that vitamin E reduces the risk of upper respiratory tract infections [99], improves T cell-mediated immune function [100], improves natural killer cell activity, neutrophil chemotaxis and phagocytosis, and mitogen-induced lymphocyte proliferation [101]. Vitamin E supplementation has been reported to increase immune functions, which can modulate host defense against infectious pathogens [99]. It has been stated that immunosuppressive factors such as prostaglandin PGE2 and hydrogen peroxide are reduced and lymphocyte proliferation is suppressed by vitamin E [102]. It has also been demonstrated that vitamin E can alter cytokine formation from T cells or macrophages [103]. It was reported that around 40 mg of vitamin E has the best immunological benefit [83]. In the light of all this information, it is thought that adequate intake of vitamin E will help protect the immune system against Covid-19.

4.2.6 Vitamin-K

Vitamin K is an important vitamin since its role in the production of many factors such as factors II (prothrombin), VII, IX, and X (vitamin K-dependent coagulation factors) in the coagulation stage [104]. The most important symptom of COVID-19 caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) is respiratory failure because of pneumonia. Thrombosis is another common symptom of COVID-19 [105]. Vitamin K supports the activation of protein S which plays a significant role in the activation of anticoagulant factors and prevention of local thrombosis in the liver [105]. dp-ucMGP levels are shown an increase in several diseases associated with elastic fiber calcification and degradation such as diabetes [106], hypertension [107] CVD [108], chronic kidney disease [106] and obesity [109]. Vitamin K supplementation reduces dp-ucMGP levels [110]. Vitamin K deficiency damages MGP activation, possibly causing further elastic fiber damage and elevation of circulating dp-ucMGP [111]. Vitamin K, which available mostly in green leafy vegetables, exists in two forms, phylloquinone (K1) and menaquinone (K2). It has an important role in bone health [112]. Myneni and Mezey [113] observed that vitamin K2 suppresses T Cell proliferation and therefore reduces the likelihood of hip, vertebral and non-vertebral fractures. Hodges et al. [114] reported that vitamin K shows anti-inflammatory activity by inhibiting NF-κB signaling. Vitamin K2 also modulates immune and inflammatory responses by suppressing TNF-α, IL-1α and IL-1β gene regulation in a dose-dependent manner [115].

4.3 Minerals

4.3.1 Zinc

Zinc, an essential micronutrient in cell growth and survival, serves as an intracellular signaling molecule for the immune system and body defense cells. In addition, it reduces level of cytokines [116]. Zinc has an important role in the regulation of intracellular signaling pathways in both adaptive and innate immune cells [117]. SARS-CoV-2 may cause parageusia by destroying sensory cells in the oral mucosa. Chelation of zinc by immune mechanisms causes alteration of zinc homeostasis in oral taste cells. This mechanism may be the reason for the taste disorders in zinc deficiency [118]. Therefore, zinc supplementation may also play an important role in the prophylaxis and treatment of COVID-19 [119]. Since zinc inhibits the RNA polymerase enzyme, it prevents SARS-CoV-2 replication and reduces the progression of the disease. SARS-CoV-2 uses RNA polymerase for the replication of human cells [120]. In addition, zinc, which is a good anti-inflammatory agent, suppresses pro-inflammatory Th17 and Th9 cells [121]. It was shown that zinc affects several components of the immune system, from the skin barrier to gene regulation by lymphocytes [122]. It has been reported that zinc deficiency causes changes in immune cell numbers and activities, which causes the development of provocative infections and increased susceptibility to diseases [97]. In addition, the deficiency of this mineral has an impact on many important processes such as cytokine production, phagocytosis and intracellular killing [123]. The body needs at least 300 enzymes and coenzymes to carry out vital cellular functions such as energy metabolism, DNA synthesis, and RNA transcription. Zinc is required for the activation and inactivation of these enzymes and coenzymes [117]. In the light of the literature, it can be said that zinc may have an antiviral effect in reducing the intensity of COVID-19 and other respiratory tract infections, with its suppression of viral replication and increasing immune responses [124]. Foods high in zinc include seafoods such as oysters and lobsters, and various meat products such as lamb, beef, and chicken [125]. Other sources have also include zinc mineral are mushrooms, celery, sunflower seeds, almonds, soy foods, black rice, black sesame, lentils, and many other legumes and nuts [126].

4.3.2 Selenium

Selenium is a mineral that is effective in increasing immunity and scavenging free radicals, protecting from oxidative stress, cellular differentiation and maintaining antibody levels [127]. Selenium available in whole grains and dairy products has an important role in glutathione peroxidases which prevents the oxidative damage [28]. Selenium is a trace element that stands out with its antioxidant and anti-inflammatory properties and has a wide range of pleiotropic effects. Two components of the immune system (adaptive and innate immune systems) are affected by selenium [128]. It has been reported that oxidative stress in cells as a result of viral infections is associated with the production of reactive oxygen species [129]. The antioxidant activity and free radical scavenging properties of selenium are related to selenocysteine, which contains selenoprotein enzymes such as glutathione peroxidase, glutathione reductase, selenoprotein P, thioredoxin reductase [130]. Selenoproteins have some properties such as antioxidant activity, redox regulation and interferon production [57]. Goldson et al [131] observed a significant increase in selenoprotein S expression induced by 50 µg/day selenium supplementation. This result showed that selenoprotein S has a big role in immune function. In a similar study, it was reported that daily supplementation of 200 µg selenium showed virucidal effects during infections [57]. It has also been reported that selenium supplementation is effective against HIV, hepatitis and influenza A viruses [132]. Selenium deficiency increases the risk of mortality, weakens immune function and causes cognitive decline [133]. High selenium concentration or selenium supplementation exerts antiviral effects [134]. Selenium supplementation lead to an increase in the plasma selenium levels, lymphocyte phospholipid and cytosolic glutathione peroxidase activities as well as cellular immune response i.e. IFN-g and other cytokines, with an increase in T-helper cells and an early peak in T-cell proliferation [134]. Selenium, which has been determined to stimulate the activation of T cells and NK cell activity, is important to maintain a good immune response [135]. It has been reported that a daily supplement of 50 mg of selenium has a beneficial effect in increasing immunity [6]. It was stated that selenium supplements may be a good option to strengthen immunity after flu vaccination by Ivory *et al.* [136]. Reducing the severity of pneumonia and inflammation may be achieved by strengthening the immune response, and hence reducing the incidence rate and mortality of COVID-19 [137].

4.3.3 Iron

Iron plays an important role in systemic oxygen transfer and acts as an electron donor/acceptor in many biological functions. It is one of the most important minerals for all age groups [138] and supports the immune system [139]. Iron leads to disruption of respiratory burst, killing bacteria, proliferation of T cells and development of cytokines. In addition, the iron found in hemoglobin is responsible for providing oxygen in the tissues in the human body [140]. Its deficiency weakens immunity, which increases the risk of contracting acute respiratory tract infections, which is an important symptom of COVID-19 disease [141]. Iron deficiency causes thymus atrophy and affects the activity of naïve T lymphocytes. Indicators of iron deficiency may include damaged respiratory burst, natural killer cell activity, or decreased T lymphocyte proliferation [142]. Iron deficiency causes damaged cell-mediated immunity [143]. Maintaining the sufficient amount of iron level is important for better immunity. Just like its deficiency, its excess amounts are also harmful for the immune system. For these reasons, iron is an important mineral in reducing the risk factors associated with COVID-19 [142]. Iron regulates the growth and activity of several microorganisms, including viruses. Therefore, it was emphasized that iron levels should be carefully controlled in humans to limit the access of iron to pathogens [144]. Iron intake is recommended as 19 mg/day for men and 29 mg/day for women [153]. Iron modulates the production of myeloperoxidase, which expresses antimicrobial activity for neutrophils [28]. Limiting the iron supply in COVID-19 patients to inhibit viral replication and reduce the risk and severity of infection was suggested in the study of Liu et al. [145]. Meat, poultry, fish, shellfish, legumes, nuts, seeds, cruciferous vegetables and dried fruits are good sources of iron. Consuming foods rich in iron along with vitamin C is important for iron absorption [146]. Iron is needed for the development of hemoglobin, which provides oxygen transport in the circulatory system [147]. Iron acts as a cofactor for the enzyme in oxidation/reduction reactions, which are vital for the energy metabolism of cells [147]. Iron is essential for immune cell production and development, particularly lymphocytes, which are associated with infection-specific reactions [148]. Iron sequestration is a significant intrinsic host defense system since many pathogens rely on this fundamental component [149]. Iron absorption is influenced by the levels of iron stores and consumed dietary components [150]. While the vitamin C and animal proteins increases organic iron absorption, calcium, phytates, polyphenol, and vegetable proteins decreases the absorption [147].

4.3.4 Copper

Copper is an essential micronutrient involved in the functions of critical immune cells such as T helper cells, B cells, neutrophils, natural killer (NK) cells, and macrophages, and in the production of cell-mediated immunity and pathogen-specific antibodies [151]. It was shown that copper can effectively inhibit the spread of respiratory viruses, including SARS and MERS [152]. In this study, it was emphasized that copper alloys inactivate the corona virus within a few minutes when it comes into contact with the corona virus, and therefore, copper containers can be used to prevent the spread of COVID-19 on surfaces. Copper damages the replication and propagation abilities of SARS-CoV-2, influenza and other respiratory viruses [153]. Cortes and Zuñiga [154] proposed that copper oxide or nano-compounds could be used as nanoparticles in the manufacture of filters, face masks and clothing. Copper plays a very important role in immunity by contributing to the development and differentiation of immune cells [155]. In vitro studies have shown that Thujaplicin-copper chelates inhibit the replication of human influenza viruses [156], while intracellular copper regulates the life cycle of influenza virus [157]. These findings might be a proof to show that copper has antiviral properties. In the absences of sufficient copper in the body, IL-2, T cell proliferation levels and superoxide anion production decrease, and accordingly, the ability to kill ingested microorganisms is reduced [158]. It has been reported that copper participates in the production of interleukin (IL-2) that supports the development of T cells, adaptive immune responses and inflammatory responses [57]. Vincent *et al.* [159] showed that copper ion is effective against HI-virus through synthesis of virus-specific antigens. Some foods rich in copper are oysters, nuts, seeds, shiitake mushrooms, lobster, liver, green leafy vegetables and dark chocolate [59].

4.3.5 Magnesium

Evidence from clinical studies has shown beneficial effects of magnesium supplementation on lung diseases such as asthma and pneumonia [160]. It has been reported that magnesium sulfate inhibits inflammatory molecules including chemokine (macrophage inflammatory protein-2), cytokine (IL-6), prostaglandin E2 and cyclooxygenase-2, possibly by inhibiting L-type calcium channels in lung tissue [161]. Magnesium sulfate inhibits bronchial smooth muscle contraction and promotes bronchodilation [162]. It also reduces inflammatory response & oxidative stress, and improves lung inflammation, possibly by inhibiting the IL-6 pathway, NF-κB pathway and L-type calcium channels [161]. Therefore, it has been stated that Magnesium sulfate could be a drug in the treatment of COVID-19, especially for patients in serious condition, with promising beneficial medical effects [163]. Magnesium has an important place in immune system control by affecting properties such as immunoglobulin synthesis, immune cell adherence, antibody dependent cytolysis, immunoglobulin M (IgM) lymphocyte binding, macrophage response to lymphokines and T helper-B cell adherence [164]. In addition, Magnesium helps strengthen the natural killer cells of our immune system and lymphocytes. It acts as an essential cofactor in the cell, binding to DNA, RNA, the cellular energy carrier adenosine triphosphate (ATP), or enzymes [165]. Magnesium is also helpful to increase hemoglobin levels in our blood which is responsible for delivering oxygen from our lungs to the entire body [166]. Magnesium acts as a cofactor for enzymes of nucleic acid metabolism and stabilizes the structure of nucleic acids, as well as takes part in DNA replication and repairment [167]; It promotes antigen binding to macrophages, plays a role in leukocyte activation and regulation of apoptosis [168]. Additionally, magnesium may help to protect DNA from oxidative damage [167] and its high concentrations reduce superoxide anion production [169]. It also acts as a cofactor in antibody synthesis and is involved in antibody-dependent cytolysis and IgM lymphocyte binding. Moreover, it plays a key role in antigen binding to macrophage RNA and is involved in antibody-dependent cytolysis [168]. Magnesium, which plays an important role in both innate and adaptive immune responses [170], is found mostly in dark chocolate, black beans, avocados and whole grains [171]. In magnesium deficiency, immune cell activity decreases while IL-6-containing inflammation, which is at the center of the COVID-19 associated cytokine storm pathology, increases [57].

4.4 Probiotics

Probiotics are live microorganisms that provide a number of health benefits to the host, particularly to the gastrointestinal tract [142] They also stimulate immune response by increasing the antibody production [172]. Probiotic bacteria modulate the immune response and counteract the inflammatory process [173] by increasing macrophage phagocytosis and natural killer cell activity [174]. On the other hand, they prevent the pathogen attachment on the host epithelium [175], colonize the intestinal epithelium by inducing antimicrobial peptides in the host cell, and improve the intestinal function [176]. It was reported that by Dumas et al. [177] probiotics show significant microbial inhibitory properties through alveolar macrophages, neutrophils, natural killer cells, and high levels of proinflammatory cytokines such as TNF-α and IL-6 in the lung. Probiotics can strengthen intestinal immunity [178] and contribute to immune function even in areas far from the intestine [179]. A recent study has shown that probiotic supplementation improves vaccine responses in individuals [180]. Several meta-analyses and reviews have confirmed that probiotics enhance the antibody response to influenza vaccination [181–183]. It has been emphasized that the severity of infection or infection time is shortened with the supplementation of *Lactobacillus* and *Bifidobacterium* probiotics. Especially, *Lactobacillus* is very effective in the treatment of respiratory tract infections with viral origins [180]. In another study, it was determined that there was a relationship between *bifidobacterium* and increased immune function and gut microbiota in the elderly people [184]. It has been reported that probiotics are effective in the prevention and treatment of infections [185], and play a supportive role in increasing immune responses [181]. Due to its probiotic content, it has been reported that yogurt has a strong antiviral effect against RNA virus such as enterovirus 71. This reduces the effect of respiratory tract infections caused by influenza virus [186]. However, it was shown in the research from National Center for Biotechnology Information (NCBI) one of the most appropriate ways to reduce the incidence of respiratory tract infections in children is the consumption of probiotics. A research has revealed that various probiotics, especially lactobacilli and bifidobacteria, significantly reduce the incidence and severity of respiratory tract infections [187]. In a recent study, it was revealed that Bifidobacteria and Lactobacillus probiotic bacteria provide a significant improvement against COVID-19 [188]. Probiotic microorganisms such as Lactobacillus acidophilus, *Lactobacillus casei*, *Enterococcus faecium* and *Bifidobacterium* are available in fermented foods such as yogurt, kefir or kimchi [29].

4.5 Prebiotics

Prebiotics are food materials such as fiber and oligosaccharides that are metabolized by probiotics in the colon through fermentation [189]. It has been reported that galactooligosaccharide supplementation to healthy elderly people causes an increase in bifidobacterial, phagocytosis, NK cell activity, anti-inflammatory cytokine interleukin-10 (IL-10), and a decrease in the production of proinflammatory cytokines [190]. In another study, it was reported that dietary supplementation containing lactobacilli and fructooligosaccharides to healthy elderly people vaccinated with influenza and pneumococci increased the natural killer cell activity and IL-2 production [191]. The effectiveness of prebiotics depends on the metabolism of the microbiota. The fermented prebiotics produce short-chain fatty acids such as acetate, propionate or butyrate, which are potential fuels for epithelial tissues [192]. Probiotics can inhibit the growth of pathogens by producing antibacterial substances such as bacteriocins and acids such as acetic, lactic and probiotic. Therefore, it is important to consume diets rich in probiotics for a healthy gut that can fight against COVID-19 [55]. In a study, it was observed that butyrate improves the intestinal barrier by regulating the attachment of tight-linked proteins in enterocyte models [193]. In another study, it was shown that a fiber-rich diet was effective on lung microbiota as well as gut microbiota [194]. This suggests that a proper diet enhanced with probiotics and prebiotics can have an impact on lung immunity and help people to fight against COVID-19.

4.6 Phenolic compounds

Phenolic compounds are secondary metabolites found in natural plant products such as fruits, vegetables, seeds and flowers, and they show excellent antioxidant properties [195]. These are the main class of compounds that show significant activity against various viruses such as etrovirus, HI-virus, influenza virus, hepadnavirus, hespesvirus, herpes simplex virus, dengue virus, polio virus [196]. A recent study focus on the therapeutic potential of polyphenols against SARS-CoV-2 [197]. Phenolic compounds are the most promising active compounds among the various natural therapeutic agents used against SARS-CoV-2 due to their antiviral and antimicrobial properties [198]. It has been reported that phenolic compounds such as quercetin, rosmarinic acid and hesperetin may be effective in the treatment of COVID-19 as they show good binding affinity with SARS-CoV-2 viral protein targets and can support the immune system [199]. Hesperetin, a predominant flavonoid in citrus and well known in traditional Chinese medicine, dose-dependently suppresses the degradation activity of the 3C-like protease (3CLpro) of SARS-CoV-2 [200]. Entrance of the virus into the cell occurs by binding of the S protein of the viral membrane with the host cell transmembrane receptor ACE2 [201]. To prevent the virus from this pathway, either the S protein of the viral membrane or the ACE2 receptor is blocked (Fig. 2) [202]. In this way, bioactive compounds such as hesperetin [203] show the potential to prevent infection with SARS-CoV-2 by blocking ACE2.

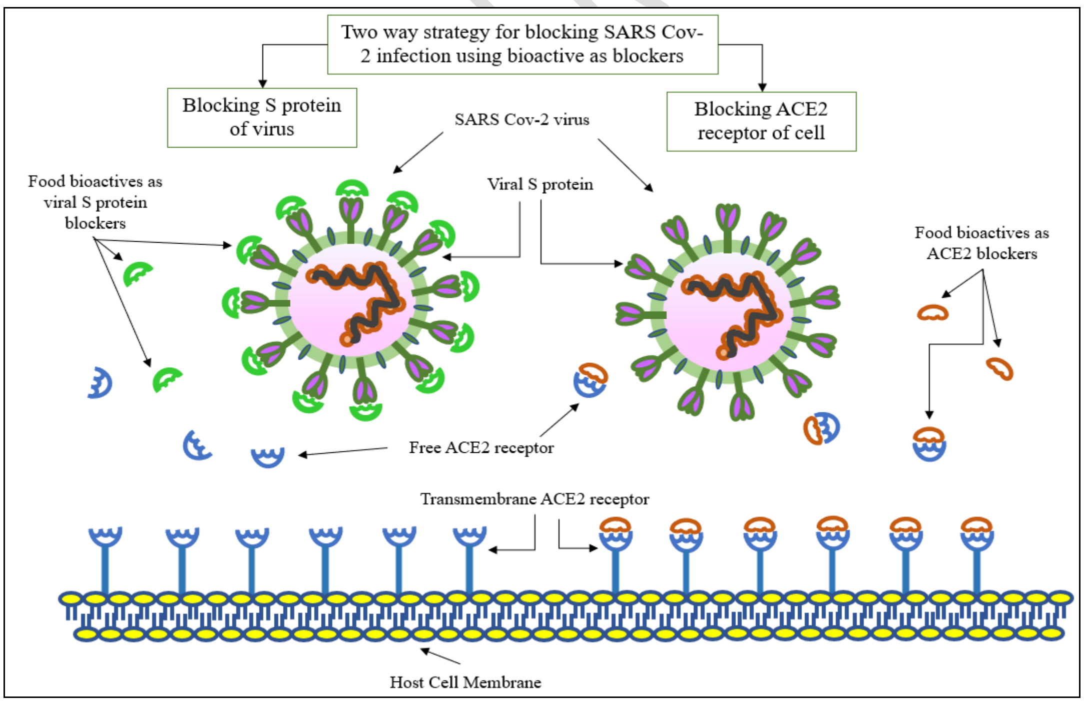

Fig. 2 Two-way strategy showing the use of food bioactives as inhibitors of viral S protein and host ACE2 receptor. Adapted from Bhushan *et al.* [202]

Baicalin, another traditional Chinese herbal medicine, is a flavone isolated from Scutellaria baicalensis and has been shown by neutralization tests to have antiviral activity against 10 SARS-CoV-2 isolates [204]. By inhibiting viral proteases, phenolic compounds can prevent virus replication and infection. Polyphenols such as betulinic acid, indigo, luteolin, quinomethyl triterpenoids, quercetin and gallates can provide a starting point for the development of new anti-COVID-19 formulations [205]. Xu et al. [206] found that sinigrin and hesperetin phenolic compounds in *Isatis indigotica* root water extract showed anti-SARS-CoV-2-3CL proproperties. These researchers proved that the SARS-CoV-2 major protease has shown approximately 96% similarity with SARS-CoV-2-Mpro. Inhibitors of protease Mpro and 3CLpro prevent the replication of SARS-CoV-2 (Fig. 2)[207]. In the study, inhibition of Mpro was attributed to fluoronates, flavonoids and pseudo-opeptides. The most promising inhibitors of SARS-CoV-2 were phloroglucin (1,3,5-trihydroxybenzene) oligomers derived from the brown algae *Sergassum spinuligerum*, while the most active inhibitors compounds were from the fluorotannin group (8,8′-Bieckol, 6,6′-Bieckol, Dieckol), isolated from the brown alga *Ecklonia cava* [208]. The results obtained from these studies revealed that anthocyanins and/or tannins with specific structure can be used as effective anti-COVID-19 natural components. In a patient treated with hydroxychloroquine and antibiotics, the Quercetin and N-acetylcysteine nebulized formula was noted to significantly reduce respiratory symptoms of SARS-CoV-2 [209]. Theaflavins, the polyphenols of black tea, have been found to have antiviral effects on vaccinia virus, influenza virus, polio virus-1, herpes simplex virus, coxsackie virus and human rotavirus [210]. Quercetin was reported to exert antiviral effects by inhibiting the 3CLpro of SARS-CoV-2 [211] and blocking the entrance of SARS-CoV-2 into host cells [212]. Quercetin derivatives such as 7-O-arylmethylquercetin and quercetin-3-β-galactoside were reported to be able to fight as anti-SARS-CoV-2 agent [211]. Tetra-O-ga-loilo-β-d-glucose and luteolin have been confirmed to be active defenders against SARS-CoV-2 [200]. Glycyrrhizin, an active ingredient in licorice, has been reported to effectively inhibit the in vitro replication of SARS-associated CoV [213]. Haiying *et al.* [214] also reported that this compound is clinically effective in the treatment of SARS. Glycyrrhizin has been predicted to have the ability to bind ACE2 with potential anti-COVID-19 effects [203]. It has been reported that the lycorin component in the extract of Lycoris radiata can show a good activity against SARS-CoV-2 [200]. It has been reported that gallic acid can be effective by binding to the surface spike protein of SARS-CoV-2 [212]. It was reported by Kesel [215] that hydrobenzoic acid may be effective against SARS-CoV-2 as it inhibits the replication and entry of 3CLpro. It has been emphasized that Kaempferol and its derivatives, which inhibit the 3a ion channel of CoVs, may be an effective compound against SARS-CoV-2 [216]. Similarly, Park et al. [217] found that kaempferol was effective against MERS-coV by inhibiting PLpro and against SARS-CoV-2 by inhibiting SARS-3CLpro activity. In another study, it was shown that quercetin can be effective against MERS virus by inhibiting the degradation activity of MERS-3CLpro enzyme [218]. Myricetin may act against SARS-Cov-2 by affecting ATPase activity, inhibiting nsP13 and acting as a SARS-CoV-2 helicase inhibitor [219]. It has been reported that herbacetin is effective against MERS and SARS-Cov viruses as it inhibits the degradation activity of MERS-3CLpro enzyme [218] and blocks the enzymatic activity of SARS-CoV-2 3CLpro [220]. Kaempferol, quercetin, luteolin-7-glucoside, dethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, epicatechingallate, zingerol, gingerol and allicin block the enzymatic activity of SARS-CoV-2-Mpro and act as CoV-2-Mpro inhibitors [221]. Apigenin inhibits PLpro and SARS-CoV-2pro activity, thereby acting against SARS-CoV-2 virus [222]. Luteolin binds to the surface spike protein of SARS-CoV-2 [212]. Epigallocatechin gallate (EGCG), gallocatechin gallate, epicatechingallate [223], gallocatechin-3-gallate [224], which are the green tea flavanols, fight against SARS-CoV-2 by inhibiting the activation of SARS-3CLpro. It has been reported that 19 hydrolysable tannins were described as anti-COVID-19 therapeutic compounds against SARS-CoV-2 [225].

4.7 Beta glucans

β-glucan is a non-starch polysaccharide with proven health benefits and industrial applications [226]. It can be extracted from a variety of sources such as grains, bacteria, molds and fungi [227]. β-glucan obtained from yeast is effective in asthma, allergy and crohn's diseases [226]. It is known that β-glucan, a soluble dietary polysaccharide, has a cholesterolemic activity and is good for heart health. β-glucan can inhibit virus particles or present indirect activity by enhancing host immunity [228]. The same researchers observed the immunomodulatory effect of β-glucan on herbes simplex virus type 1. It was figured out that β-glucan stimulates the production of cytokines and the activation of natural killer cells, T lymphocytes and dendritic cells, leading to increased host immunity. Similarly, it was reported by Daou and Zhang [229] β-glucan modulates cytokine production, is beneficial in respiratory problems, prevents infection and viral diseases by stimulating the immune system, and activates natural killer cells, T-cells and B-cells. Chaichian et al. [230] reported that β-glucan is effective against HIV infections. Mechanisms by which β-glucan can modulate the immune system by binding to pattern recognition receptors on cells of dectin-1 and Toll-Like receptors were proposed by Vogt et al. [231]. It has been reported that β-glucan is associated with immunomodulatory effects such as nitric oxide production, which is a potent viral replication inhibitor, and the release of reactive oxygen species and cytokines [232]. Brown and Gordon [233] attributed the activation of β-glucan in leukocytes for the production of cytokines and chemokines such as interleukins and tumor necrosis factors. These findings indicated that β-glucan could act as an immunostimulatory agent by activating macrophages and natural killer cells [127]. Murphy et al [234] reported that 1.5–10 mg/mL β-glucan reduced inflammatory responses associated with in vitro acute respiratory distress syndrome (ARDS), including cytokine production, oxidative stress, necrosis, and apoptosis. The authors stated that β-glucan can be used in the treatment of SARS-CoV-2 with its role in preventing cytokine storm. *Shiitake* mushroom-derived from β-Glucans were also reported to reduce populations of multi-antibiotic resistant isolate Klebsiella pneumoniae in an in vivo lung infection model [235]. Findings from this study showed that β-glucan improved lung physiological parameters, decreased white cell count protein inflammation in lung, decreased bacterial levels in bronchoalveolar lavage and arterial blood parameter, and significantly supported oxygen pressure (pO_2) as well as promoted lung cellular repairment. In another study, it was reported that β-glucan lead to reduction in inflammatory cytokine release (tumor necrosis factor-α, interleukin-1β and interleukin-β) and prevention of acute lung injury [236]. Kim et al. [237] observed that β-glucan supplementation reduced the white blood cells, neutrophils, serum tumor necrosis factor (TNF-α), cortisol, and haptoglobin, and down-regulated immune genes such as IL1B, IL6, and TNF-α.

Table 1. Summary of possible effects of some micronutrients and bioactive compounds against SARS-CoV-2

Micronutrients and bioactive compounds	Sources (Food, plant, algae)	Mode of Action against SARS-CoV-2 and boosting immunity	References
Omega (ω)-3 fatty acid	Salmon, herring, tuna, other fish	• Anti-inflammatory effects	[36–38, 44,45,238]
		• Modulate the immune response and function	[40,239,240]
Vitamin A	Orange, carrots, sweet potatoes, broccoli, pumpkin, squash, kale, spinach, milk, cheese, oily fish, liver, eggs, fortified cereals, apricots, papaya, peaches, mango, tomato juice, cantaloupe melon	• Promotion of innate immunity	[49]
		• It suppresses the production of IL-12, TNF-α and IFN-y by Th1 lymphocytes and supports the antibody-mediated Th2 response	[52]
		• Restricting ACE2 activity	[48,241]
		• Increasing serum IL-4, IgG, IgM and IgA levels	[54]
		• Supporting immunity by facilitating type 1 interferon (IFN) synthesis	[53]
Vitamin B3 (niacin)	Beef, liver, poultry, eggs, dairy products, fish, nuts, seeds, legumes, avocados, whole grains, bread	• Down-regulating TNF-α, IL-6, IL-1β and NF-kB activation in alveolar macrophages	[73]
Vitamin B6 (pyridoxine)	Chicken, turkey, pork, some fish, peanuts, soya beans, wheatgerm, oats, bananas	• Promote lymphocyte development and antibody production	[60]
		• Supports the production of Th1 cytokines	[61]
Vitamin B8 (biotin)	Offal, meat, egg yolks and dairy products, leguminous vegetables, dried beans, peas, nuts, bananas, redcurrants, strawberries, apples, cabbage, mushrooms, tomatoes, spinach, avocado, carrots, soya, yeast and cereals	• Support cellular and humoral immune functions	[72]
Vitamin B9 (folic acid)	Turnip greens, spinach, romaine lettuce, asparagus, brussels sprouts, broccoli, beans, peanuts, sunflower seeds, fresh fruits, whole grains, liver, seafood, eggs	• Supporting cell-mediated immunity, Enhance the blastogenic response of T lymphocytes to certain mitogens	[58]
		• Regulating intestinal immunity by increasing NK cell cytotoxic activity	[57]
		• Strengthen the immune system	[59]
Vitamin B12 (cobalamin)	Meat, fish, milk, cheese, eggs, some fortified breakfast cereals	• Support killer cells and CD8+ cytotoxic T-lymphocyte	[28]
		• Promoting B cells' immunoglobulin synthesis, enhancing T cell proliferative responses. Strengthening protective immune responses against viruses and bacteria	[65]

Table 1. (continued)

Micronutrients and bioactive compounds	Sources (Food, plant, algae)	Mode of Action against SARS-CoV-2 • and boosting immunity	References
Vitamin C	Broccoli, brussels sprouts, cauliflower, green and red peppers, spinach, cabbage, turnip greens, and other leafy greens, sweet and white potatoes, tomatoes and tomato juice, winter squash	• Increase the production of interferon and decrease the production of different cytokines	[74]
		• Supports the integrity of the cell epithelial barrier by promoting collagen synthesis, treatment of pneumonia	[75,76]
		• Supporting adaptive and innate immune systems	[77]
		• Involved in the proliferation, function and movement of neutrophils, monocytes and phagocytes, Improving NK cell activities and chemotaxis	[78]
		• Providing activation of nuclear factor κB (NF-κB)	[82]
		• Modulates the synthesis of inflammatory cytokines, • function in respiratory infection prevention and management	[242]
Vitamin D	Fatty fish, like tuna, mackerel, and salmon, foods fortified with vitamin d, like some dairy products, orange juice, soy milk, and cereals, beef liver, cheese, egg yolks	• Regulate the immune system	[243]
		• Supporting innate (mainly monocytes and macrophages) and adaptive immune (dendritic cells and T cells) responses	[82]
		• Enhance phagocytosis, superoxide production and bactericidal effect by innate immune cells	[91]
		• It also supports differentiation of monocytes and antigen processing by dendritic cells.	[87]
		• Suppresses inflammation, lowers CRP levels, suppresses cytokines and prevents COVID-19 complications due to cytokine storm	[90]
		• Reducing the risk of respiratory infections	[93]
Vitamin-E	Nuts, seeds, vegetable oils, wheat germ	• Strong antioxidative effect and strengthening immunity	[82]
		• Regulating the production of reactive oxygen and reactive nitrogen species and modulating signal transduction	[82,97]
		• Increasing T cell count, mitogenic lymphocyte responses, IL-2 cytokine secretion, NK cell activity and increasing resistance to respiratory tract infections	[98]
		• Improving natural killer cell activity, neutrophil chemotaxis and phagocytosis, and mitogen-induced lymphocyte proliferation	[101]

Table 1. (continued)

Micronutrients and bioactive compounds	Sources (Food, plant, algae)	Mode of Action against SARS-CoV-2 and boosting immunity	References
Vitamin-K	Green leafy vegetables, such as kale, spinach, turnip greens, collards, swiss chard, mustard greens, parsley, romaine, and green leaf lettuce. vegetables such as brussels sprouts, broccoli, cauliflower, and cabbage. fish, liver, meat, eggs, and cereals	• Contributes to blood coagulation	[104]
		• Activating protein S involved in the prevention of local thrombosis in the liver	[105]
		• Reducing dp-ucMGP levels	[110]
		• Phylloquinone (K1) and menaquinone (K2) play an important role in bone health	[112]
		• Suppressing T Cell proliferation	[113]
		• Showing anti-inflammatory activity by inhibiting NF-kB signaling	[114]
		• Modulating immune and inflammatory responses by suppressing TNF-α, IL-1α and IL-1β gene regulation	[115]
Zinc	Oysters and lobsters, and various meat products such as lamb, beef, chicken, as well as mushrooms, celery, sunflower seeds, almonds, soy foods, black rice, black sesame, lentils, and many other legumes and nuts	• Reducing levels of cytokines, intracellular signaling molecule (for immune system and body defense cells)	[116]
		• Regulation of intracellular signaling pathways in adaptive and innate immune cells	[117]
		• Preventing taste disorders in SARS-CoV-2 by chelation	[118]
		• Playing an important role in the prophylaxis and treatment of COVID-19	[119]
		• By inhibiting the RNA polymerase enzyme, inhibiting SARS-CoV-2 replication and reducing disease progression	[120]
		• Ensuring the activation and inactivation of enzymes and coenzymes in the body's energy metabolism, DNA synthesis and RNA transcription	[117]
		• Reducing the number of autoimmune T helper cells, Influencing the proliferative response of T and B cell lymphocytes, regulating T cell activation	[244]
Selenium	Beef, turkey, chicken, fish, shellfish, and eggs, many whole grains and dairy products, including milk and yogurt, are good sources of selenium, brocolli, spinach, green peas, beans, and potatoes	• Boost immunity, scavenge free radicals, protect from oxidative stress, maintain cellular differentiation and antibody levels	[127]
		• Selenium-containing selenoproteins→ antioxidant activity, redox regulation, leukocytes and natural killer cell production and interferon production, supporting immune function and virucidal effect	[57,131]
		• Increasing T-helper cells, IFN-g and other cytokines	[134]

Table 1. (continued)

Micronutrients and bioactive compounds	Sources (Food, plant, algae)	Mode of Action against SARS-CoV-2 and boosting immunity	References
Iron	Meat, poultry, fish, shellfish, legumes, nuts, seeds, cruciferous vegetables and dried fruits	• Supporting the immune system	[139]
		• Prevent respiratory burst, kill bacteria, replicate T cells, enhance cytokines, supply oxygen to tissues	[140]
		• Strengthening immunity, reducing the risk of contracting acute respiratory infections	[141]
		• Production and development of immune cells, especially lymphocytes	[148]
		• Modulating myeloperoxidase production for neutrophils	[28]
Copper	Oysters, nuts, seeds, shiitake mushrooms, lobster, liver, green leafy vegetables and dark chocolate	• Supporting the functions of T helper cells, B cells, neutrophils, natural killer (NK) cells, and macrophages, producing cell-mediated immunity and pathogen-specific antibodies	[151]
		• Preventing the spread of respiratory viruses, including SARS and MERS	[152]
		• Destroy the replication and spread ability of SARS-CoV-2, influenza and other respiratory viruses	[153]
		• Contribute to the development and differentiation of immune cells	[155]
		• Promoting interleukin (IL-2), T cell proliferation levels and superoxide anion production, developing adaptive immune responses and inflammatory responses	[57,158]
Magnesium	Black beans, avocado, and whole grains, pumpkin seed, almonds, spinach, cashews, peanuts, quinoa, milk, yogurt, chocolate	• Beneficial effect in lung diseases such as asthma and pneumonia	[160].
		• Inhibiting inflammatory molecules including chemokine (macrophage inflammatory protein-2), cytokine (IL-6), prostaglandin E2 and cyclooxygenase-2	[161]
		• Reducing inflammatory response and oxidative stress and improving lung inflammation, possibly by inhibiting the IL-6 pathway, NF-κB pathway and L-type calcium channels	[161]
		• Enabling antigen binding to macrophage RNA	[164]
		• Immune system control by affecting functions such as immunoglobulin synthesis, immune cell adherence, antibody dependent cytolysis, immunoglobulin M (IgM) lymphocyte binding, macrophage response to lymphokines and T helper-B cell adherence	[168]

Table 1. (continued)

Micronutrients and bioactive compounds	Sources (Food, plant, algae)	Mode of Action against SARS-CoV-2 and boosting immunity	References
Probiotics	Fermented foods such as yogurt, kefir or kimchi, sauerkraut, miso soup, soft cheeses, kefir, sourdough bread, acidophilus milk, sour pickles	• Enhancing macrophage phagocytosis and natural killer cell activity, modulating immune response and countering the inflammatory process	[173,174]
		• Inhibit the attachment of pathogens to the host epithelium, colonize the intestinal epithelium by inducing antimicrobial peptides in the host cell, modulate IL-10 increase, IL-6 and TNF-α decrease, improve intestinal function	[175–177]
		• Boosting gut immunity	[178]
		• Improving vaccine responses	[180]
		• Lactobacilli and bifidobacteria, significantly reduce the incidence and severity of respiratory tract infections and provide a significant improvement against COVID-19	[187,188]
		• Increasing natural killer cell activity and IL-2 production	[191]
Rosmarinic acid	*Lamiaceae* herbs such as lemon balm, rosemary, oregano, sage, thyme, and peppermint	• Good binding affinity with SARS-CoV-2 viral protein targets and supporting the immune system	[199]
Gallic acid	Blueberry, blackberry, strawberry, plums, grapes, mango, cashew nut, hazelnut, walnut, tea, wine	• Binding to the surface spike protein of SARS-CoV-2	[212]
Hydroxybenzoic acid	Berries	• Blocking replication and entry of 3CLpro	[215]
Beta glucans	Grains, bacteria, molds, fungi, barley fiber, oats, whole grains, reishi, maitake and shiitake mushrooms, seaweed, algae	• Effective in asthma, allergies and crohn's diseases and supports immunity	[226]
		• Have cholesterolemic activity, inhibiting virus particles by enhancing host immunity, immunomodulatory effect on herbes simplex virus type 1. Enhance host immunity by stimulating cytokine production and activation of natural killer cells, T lymphocytes and dendritic cells	[228]
		• Effect against HIV infections	[230]
		• Ability to modulate the immune system by binding to pattern recognition receptors on cells of dectin-1 and Toll-Like receptors	[231]
		• Immunomodulatory effects such as nitric oxide production, release of reactive oxygen species and cytokines	[232]

Table 1. (continued)

Micronutrients and bioactive compounds	Sources (Food, plant, algae)	Mode of Action against SARS-CoV-2 and boosting immunity	References
		• Production of chemokines such as cytokines, interleukins, and tumor necrosis factors in leukocytes	[233]
		• Reducing inflammatory responses associated with acute respiratory distress syndrome (ARDS) in vitro, including cytokine production, oxidative stress, necrosis, and apoptosis	[234]
		• Improving lung physiological parameters, reducing white cell count protein inflammation in lung, reducing bacteria levels and arterial blood parameter in bronchoalveolar lavage and promoting oxygen pressure (pO2), as well as promoting lung cellular repair	[235]
		• Reducing inflammatory cytokine release (tumor necrosis factor-α, interleukin-1β and interleukin-β) and preventing acute lung injury	[236]
		• Reducing white blood cells, neutrophils, serum tumor necrosis factor (TNF-α), cortisol and haptoglobin, and down-regulated immune genes such as IL1B, IL6 and TNF-α	[237]
• **Phenolic compounds**			
Hesperetin	Peppermint, *Citrus aurantium* L., *Citrus sinensis*, lemon, lime, grapefruit, leaves of *agathosma serratifolia*	• Suppressing the degradation activity of the 3C-like protease (3CLpro) of SARS-CoV-2 • Preventing infection with SARS-CoV-2 by blocking ACE2 • Good binding affinity with SARS-CoV-2 viral protein targets and supporting the immune system	[200] [203] [199]
Baicalin	*Scutellaria baicalensis*, *Scutellaria rivularis, Scutellaria lateriflora, Oroxylum indicum* (Indian trumpetflower) and Thyme	• Antiviral activity against SARS-CoV-2 isolate • SARS-CoV-2-Mpro inhibition	[204] [206]
Anthocyanins and tannins	Anthocyanins→ berries, currants, grapes, and some tropical fruits, blue-colored leafy vegetables, grains, roots, and tubers Tannins→ coffee, tea, wine, grapes, cranberries, strawberries, blueberries, apples, apricots, barley, peaches, dry fruits, mint, basil, rosemary etc.	• Inhibiting SARS-CoV-2	[208]
Herbacetin	Flaxseed hulls, rhizome of *Rhodiola rosea*	• Inhibiting the degradation activity of the MERS-3CLpro enzyme, Blocking the enzymatic activity of SARS-CoV-2 3CLpro	[218,220]

Table 1. (continued)

Micronutrients and bioactive compounds	Sources (Food, plant, algae)	Mode of Action against SARS-CoV-2 and boosting immunity	References
Quercetin	Citrus fruits, apples, onions, parsley, sage, tea, olive oil, grapes, dark cherries, and dark berries such as blueberries, blackberries, and bilberries	• Reducing respiratory symptoms of SARS-CoV-2 • Good binding affinity with SARS-CoV-2 viral protein targets and supporting the immune system • Blocking the enzymatic activity of SARS-CoV-2-Mpro and acting as CoV-2-Mpro inhibitors	[209] [199] [221]
Myricetin	Vegetables, fruits, nuts, berries, herbs, plants together with beverages, such as tea, wine, fruit and medicinal plants	• Inhibiting nsP13 by affecting ATPase activity	[219]
Apigenin	Parsley, chamomile, celery, vine-spinach, artichokes, oregano, onions, oranges, tea, wheat sprouts	• Inhibiting PLpro and SARS-CoV-2pro activity • Blocking the enzymatic activity of SARS-CoV-2-Mpro and acting as CoV-2-Mpro inhibitors	[222] [221]
Gingerol	Fresh ginger	• Blocking the enzymatic activity of SARS-CoV-2-Mpro and acting as CoV-2-Mpro inhibitors	[245]
Luteolin	Celery, parsley, broccoli, onion leaves, carrots, peppers, cabbages, apple skins, and chrysanthemum flowers	• Binding to the surface spike protein of SARS-CoV-2 • Blocking the enzymatic activity of SARS-CoV-2-Mpro and acting as CoV-2-Mpro inhibitors	[212] [245]
Theaflavins	Black and oolong teas	• Antiviral effect on vaccinia virus, influenza virus, polio virus-1, herpes simplex virus, coxsackie virus and human rotavirus	[210]
Glycyrrhizin	Licorice root of *Glycyrrhiza glabra* L.	• Inhibiting in vitro replication of SARS-associated CoV, ability to bind ACE2	[203,213]
Oleuropein	Green olive skin, flesh, seeds, and leaves, and argan oil	• Blocking the enzymatic activity of SARS-CoV-2-Mpro and acting as CoV-2-Mpro inhibitors	[245]
Curcumin	Turmeric (*Curcuma longa*)	• Blocking the enzymatic activity of SARS-CoV-2-Mpro and acting as CoV-2-Mpro inhibitors	[245]
Epicatechin gallate	Tea, apples, blackberries, broad beans, cherries, black grapes, pears, raspberries	• Inhibiting SARS-3CLpro activation • Blocking the enzymatic activity of SARS-CoV-2-Mpro and acting as CoV-2-Mpro inhibitors	[223,224] [221]
Kaempferol	Apples, grapes, tomatoes, green tea, potatoes, onions, broccoli, Brussels sprouts, squash, cucumbers, lettuce, green beans, peaches, blackberries, raspberries, and spinach	• Action against MERS-coV by inhibiting PLpro and SARS-CoV-2 by inhibiting SARS-3CLpro activity • Inhibiting the 3a ion channel of CoVs	[217] [216]

5. CONCLUSION

This review provides evidence that bioactive compounds and micronutrients have key roles in supporting the human immune system and reducing the risk of infection. Immunization is one of the most important strategies to fight against SARS-CoV-2. The innate immune response inhibits virus replication, promotes virus clearance, induces tissue repair, and triggers a prolonged adaptive immune response against viruses. Consuming food products rich in bioactive compounds, minerals, vitamins and omega fatty acids improves immune system against diseases caused by bacteria and viruses. Many of these compounds have been proposed as potential inhibitors of SARS-CoV-2 transmission. There are several researches suggesting that these compounds bind to cell surface receptors of immune cells and lead to several signaling pathways that regulate the immune system. During viral infections, some compounds inhibit the adsorption and absorption of viruses on the cell surface. The immunomodulatory effect of bioactive compounds and micronutrients can enhance immunity by modulating the function of macrophages against infections as anti-inflammatory agents. Therefore, these compounds can be used as a complementary force in the treatment of COVID-19 by various mechanisms such as individual immune support, inhibition of RNA replication of SARS-CoV-2, and prevention of virus entrance into the cell. Iron is one of the important minerals that supports the immune system against SARS-Cov-2. However, iron regulates the growth and activity of various microorganisms, including viruses. Therefore, it should be noted that iron levels must be carefully controlled in humans to limit the access of iron to pathogens.To increase the effectiveness of existing vaccines and to fight against SARS-CoV-2, we need to listen immunotherapeutic recommendations. Apart from viral pathogenicity in this pandemic, an important issue to be considered is to keep cytokine production and inflammatory response under control in the case of CoV pneumonia. From a perspective where prevention is better than cure, based on all the information found in this review, we think that an adequate and balanced diet in terms of bioactive compounds and micronutrients is important to maintain immune system balance and consequent immune response against SARS-CoV-2. Appropriate use of these compounds can help reduce morbidity and mortality associated with SARS-CoV-2. In addition, more well-designed animal studies are still needed to investigate the mechanism of action and safety profile of bioactive compounds isolated from plants and algae.

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