Review

Dietary supplements, vitamins and minerals as potential interventions against viruses: Perspectives for COVID-19

Muhammad Torequl Islam[1], Cristina Quispe[2], Miquel Martorell[3,4], Anca Oana Docea[5], Bahare Salehi[6], Daniela Calina[7], Željko Reiner[8], and Javad Sharifi-Rad[9,10]

[1] Department of Pharmacy, Life Science Faculty, Bangabandhu Sheikh Mujibur Rahman Science and Technology University, Bangladesh
[2] Facultad de Ciencias de la Salud, Universidad Arturo Prat, Chile
[3] Department of Nutrition and Dietetics, Faculty of Pharmacy, and Centre for Healthy Living, University of Concepción, Concepción, Chile
[4] Universidad de Concepción, Unidad de Desarrollo Tecnológico (UDT), Concepción, Chile
[5] Department of Toxicology, University of Medicine and Pharmacy of Craiova, Romania
[6] Medical Ethics and Law Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[7] Department of Clinical Pharmacy, University of Medicine and Pharmacy of Craiova, Romania
[8] Department of Internal Medicine, University Hospital Centre Zagreb, School of Medicine, University of Zagreb, Croatia
[9] Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[10] Facultad de Medicina, Universidad del Azuay, Cuenca, Ecuador

Abstract: The novel coronavirus (SARS-CoV-2) causing COVID-19 disease pandemic has infected millions of people and caused more than thousands of deaths in many countries across the world. The number of infected cases is increasing day by day. Unfortunately, we do not have a vaccine and specific treatment for it. Along with the protective measures, respiratory and/or circulatory supports and some antiviral and retroviral drugs have been used against SARS-CoV-2, but there are no more extensive studies proving their efficacy. In this study, the latest publications in the field have been reviewed, focusing on the modulatory effects on the immunity of some natural antiviral dietary supplements, vitamins and minerals. Findings suggest that several dietary supplements, including black seeds, garlic, ginger, cranberry, orange, omega-3 and -6 polyunsaturated fatty acids, vitamins (e.g., A, B vitamins, C, D, E), and minerals (e.g., Cu, Fe, Mg, Mn, Na, Se, Zn) have anti-viral effects. Many of them act against various species of respiratory viruses, including severe acute respiratory syndrome-related coronaviruses. Therefore, dietary supplements, including vitamins and minerals, probiotics as well as individual nutritional behaviour can be used as adjuvant therapy together with antiviral medicines in the management of COVID-19 disease.

Keywords: respiratory viruses, coronavirus, pandemic COVID-19, immune system, dietary supplements, micronutrients, vitamins, minerals

Introduction

Coronaviruses (CoV) are a large family of viruses that cause diseases, from the common cold to more severe diseases, such as the Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV). COVID-19 is an infectious disease caused by the most recently discovered coronavirus. The new virus was not known before the outbreak in Wuhan, China, in December 2019. [1–3]. As is the case with other viruses, bacteria or parasites that invade the body, the immune system is activated and performs a series of processes when it encounters the SARS-CoV-2 virus. [4]. First, antigen-presenting cells (APCs) incorporate the virus, digest it, and fragment the proteins to obtain only the specific portions of SARS-CoV-2, which act as antigens [5]. The APCs subsequently present these antigens to cytotoxic T lymphocytes. There are two types of immune responses to this antigenic presentation: humoral and cellular. Details of these processes are extrapolated mainly from the knowledge of the SARS virus [6].

Several protective measures such as isolation, quarantine, social distancing, avoidance of large gatherings,

staying away from the people with lung infections, handwashing in a regular manner, and wearing personal protective equipment (PPE) have been suggested by the experts around the world [7–9]. Respiratory and/or circulatory supports along with some other antiviral and retroviral drugs have also been used, but there are no large trials to prove their efficacy [10, 11]. However, along with the protection and treatment strategies, immunostimulatory dietary supplements and nutritional behaviour may help to manage SARS-CoV-2 infection in humans [12].

Nutrition and pathogenic stress interact with the physiological malfunctions in animals [13] and can cause hepatic [14], cardiovascular [15], neurological [16] and many other diseases. A diet that is rich in polysaccharides (e.g., cereals, onion, garlic, ginger, and algae), proteins and fats (e.g., fish, meat, and soy) is necessary for the health. Natural antioxidants such as quercetin and alliin decrease the incidence of inflammatory bowel disease [17, 18]. A diet containing a high amount of unsaturated fatty acids: omega-3, omega-6 fatty acids (e.g., arachidonic acids, docosahexaenoic, eicosapentaenoic, linolenic, linoleic etc.) [19], and low glycemic index carbohydrates help to maintain healthy metabolic profiles [20, 21]. Generally, foods containing high carbohydrate and fat, and low fibre have beneficial effects on the regulation of the immune system [22].

Food supplements may potentially be beneficial to manage the infection with SARS-CoV-2 [12]. In a study food additives such as phosphoric acid, citric acid, or fumaric acid were found to reduce porcine delta coronavirus (CoV) in infected pigs [23], while ascorbate (vitamin C, Vit-C) increased resistance to CoV infection in chicken embryo tracheal organ cultures [24]. Generally, vitamins act as modulators of immunological functions. CoV infection causes stress in infected host cells. Therefore, it inhibits protein synthesis [25]. SARS-CoV-2 infection increases the levels of plasma pro-inflammatory cytokines [26]. Many vitamins (e.g., Vit-A, C, E) have antioxidant and anti-inflammatory effects. On the other hand, dietary contents, such as omega-3 [27] and omega-6 [28] also have anti-inflammatory effects.

Wheeler, Sariol [29] demonstrated that healthy microglia are required for the protection against lethal CoV encephalitis in mice. Specific natural dietary components, such as flavonoids, phytoestrogens, polyunsaturated fatty acids as well as vitamins have protective effects on glial cells [30]. Moreover, some anti-inflammatory drugs and dietary modifications, for example, methionine restriction and the adoption of low-calorie or ketogenic diet, may prevent gliomas in animals [31].

This review aims to sketch a scenario on the dietary contents, including minerals and vitamins that may act as adjuvant therapy against SARS-CoV-2 infection.

Potential nutritional interventions against human pathogenic viruses, including SARS-CoV-2

Currently, various treatment options for coronaviruses and particularly SARS-CoV-2 are being explored. Most of them are pharmacological. The main goal is to cure clinical signs such as severe pneumonia, which is responsible for most deaths [32]. However, researchers are beginning to investigate also other ways to manage COVID-19 disease. Many of them are based on the administration of dietary supplements and micronutrients in high doses (Figure 1).

Antiviral natural dietary supplements other than vitamins and minerals: possibilities for COVID-19 treatment

Nutritional supplements with antiviral effect inhibit the development and spread of viruses. The most effective extracts with antiviral effect act on the immune system, which strengthens it to suppress the virus effectively. Because antivirals activate the immune system, they are also useful in mutating viruses which are resistant to conventional treatments.

Nigella sativa L. or its oil is used as a regular dietary supplement [33]. One study report that *N. sativa* can have anti-CoVs effects [34]. In this study, the authors have also reported an anti-CoV effect of *Citrus sinensis* (L.) Osbeck. On the other hand, *N. sativa* and/or *Zingiber officinale* Roscoe ethanolic extracts were shown to inhibit hepatitis C virus improving the altered liver function in the patients with hepatitis C virus [35]. Ginkgolic acid has been reported to be effective in acute infections caused by many viruses, including CoVs, ebola virus, zika virus, influenza A virus, measles, herpes simplex virus (HSV)-1 and -2, and varicella-zoster virus [36].

The garlic (*Allium sativum* L.) is useful against common cold [37]. In a study, garlic extract inhibited the infectious bronchitis virus (one of the CoVs) in the chick embryo [38]. In an *in silico* study, 17 organosulfur compounds from essential garlic oil were found to inhibit angiotensin-converting enzyme 2 (ACE2) and the main protease (PDB6LU7) protein of SARS-CoV-2 [39]. Among the other garlic compounds, carvone has been found to show an immunostimulatory effect via modulating the $CD3^+$ T cell infiltration and expression of mRNA coding for interleukin 1 beta (IL-1β), tumour necrosis factor-alpha (TNF-α), and IL-6 cytokines. It can also increase interferon-gamma (IFN-γ) in BALB/c mice [40]. The human ACE2 receptor (ACE2R) serves as the main entry point into cells for nCoV-19 [41].

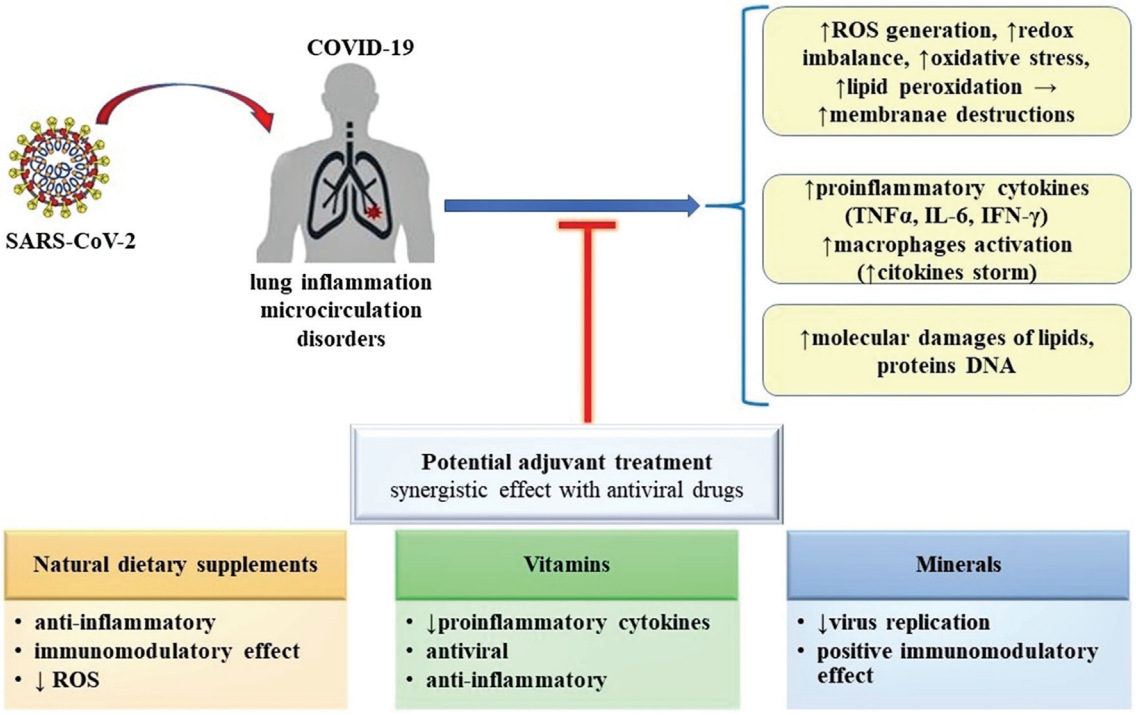

Figure 1. Summarized scheme with potential adjuvant antiviral natural dietary supplements, vitamins and minerals and their possible mechanisms of action. CoV coronavirus; IFN-γ interferon-gamma; IL interleukin; ROS reactive oxygen species; SARS severe acute respiratory syndrome; TNFα tumour necrosis factor-alpha.

Alpha-lipoic acid, a vitamin-like chemical and an antioxidant down-regulated ADAM17 and preserved ACE2 compensatory activity in Neuro2A cells [42]. Dietary animal proteins, such as dried animal plasma and milk proteins, were found to increase immune response in experimental animals [43]. They are also used as an alternative to antibiotics for farm animals [44].

Cranberries contain phytonutrients, such as anthocyanins with anti-oxidant and anti-inflammatory role [45]. Cranberries have anti-viral effects on influenza viruses [46]. Soy flavonoids (e.g., isoflavones) are also known to show anti-viral effects against many viruses [47]. In a study, both cranberry polyphenol and enriched soy proteins were found to inhibit influenza viruses (e.g., H7N1, H5N3, H3N2) replication as well as their infectivity more effectively than the standard anti-viral drug [48]. Coumarins (benzo-α-pyrone) are considered as potential anti-viral substances and can have high affinity and specificity to different molecular targets [49].

Scientific evidence suggests that some substances, such as miswak (*Salvadora persica* L.), which is used for teeth hygiene, has many important therapeutic potentials, including anti-bacterial, anti-fungal and anti-viral [50]. In a study, benzyl isothiocyanate isolated from the root of *S. persica* had an anti-viral effect on the herpes simplex virus-1 [51].

Curcuma longa L. extract with its main polyphenol, curcumin, is the subject of a wide range of clinical studies showing its antimicrobial and antiviral effects [52]. Curcumin inhibits the replication of viruses, suppressing the action of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) necessary for virus multiplication [53]. Besides, it has protective effects on infected cells, preventing their death due to virus infection. The intense anti-inflammatory action of curcumin influences directly specific inflammatory cytokines that are detected in acute respiratory and lung diseases [54]. Curcumin also reduces serum concentrations of high-sensitivity C-reactive Protein (hs-CRP). This C-reactive protein is associated with the body's inflammatory response to infection, injury, or chronic disease [55].

A diet containing linoleic acid, a polyunsaturated omega-6 fatty acid, downregulates NLRP3 in human blood neutrophils [56, 57]. On the other hand, an omega-3 polyunsaturated fatty acid-derived lipid mediator, protectin D1 effectively reduces the influenza virus replication through RNA export mechanism and given together with peramivir it protected the infected mice from influenza-induced mortality [58].

Melatonin is a hormone that regulates the cycles of wakefulness and sleep. It has been shown that this substance can prevent influenza. Melatonin causes a decrease in cytokines

production. Cytokines are proteins that can stimulate inflammatory processes [59]. Globally, there have been only a few deaths in patients with COVID-19 under the age of nine years. It is essential to know that in SARS-CoV-2 infection, the mortality rate increases linearly with age, the highest being observed in patients over 80 years of age. Therefore, experts are trying to find an answer to the question of why COVID-19 does not affect or does not have a severe clinical picture in young children. Melatonin is well known for its chronobiotic effects, regulating the body's biological clock. Numerous studies have shown that melatonin has effects beyond regulating the sleep-wake cycle. In a patient, regardless of age, has an adequate level of melatonin, the infectivity of SARS-CoV-2 can be significantly reduced, and the risk of developing complications will be substantially reduced as well [60]. Melatonin may be one of the reasons why young children rarely have less severe symptoms. Indeed, children may have mild or no symptoms, even if they have been infected with SARS-CoV-2 [61]. The highest concentration of melatonin occurs between 2.00 and 3.00 in the morning, regardless of age. According to a study published in 2016, the maximum melatonin levels measured in healthy adults aged between 65 and 70 years appears to be around 49.3 pg/mL. Adults over 75 years of age have a maximum melatonin level of 27.8 pg/mL [62]. Young children have an extremely high level of melatonin compared to adults. Maximum levels in children show a decrease as children grew older than 6 years. Children aged 1 to 5 years have maximum melatonin concentration 325 pg/mL, while those between 5 and 11 years have melatonin 133 pg/mL. The fact that young children have such high levels of melatonin may be one of the explanations for mild symptoms after COVID-19 infection [63].

Specialists from all over the world are beginning to decipher the mysteries surrounding the coronavirus, trying to understand how it works in our body. Thus, they came to probiotics. A new theory has been launched by some researchers, who have thoroughly analyzed the behaviour of microbial populations that colonize our body so that they can explain the differences between the categories of people at risk of disease and those who manage to stay healthy. Thus, it came to the surprising conclusion that probiotics could be useful in therapy against COVID-19. Experts show that the new coronavirus could infect certain bacteria in the body and thus actually hide the virus. Specifically, the virus is said to infect Prevotella bacteria, which cause further inflammation that can be fatal. It is well known that infections involving Prevotella cause respiratory infections, including acute ones. It is precisely from this aspect that SARS-COV-2, the virus, could at some point in those people who have a well-represented microflora determine this coinfection, we could say, a bacterium with a virus, and so to explain why at some point those people take a severe form. Children, with a less represented flora, make light shapes, this could be a hypothesis, of course, it is difficult to sustain, and it is difficult to know if this is the case, we need studies that be represented by a large number of people. It seems that probiotics can prevent Prevotella from forming biofilms, which is one of how bacteria defend themselves against our immune system and antibiotics. The results of the studies are promising, but so far there is no certainty. However, it should also be mentioned that the research team of the University of Colorado intends to use a genetically modified version of the bacterium lactobacillus acidophilus, which is usually found in yoghurt [64].

Vitamins

Vitamins are the organic essential macromolecules that are needed in small quantities for the growth, development and proper functioning of the body [65, 66]. Generally, 13 vitamins are necessary – Vit-A, B (e.g., thiamine, riboflavin, niacin, pantothenic acid, biotin, Vit B_6, Vit-B^{12} and folate), C, D, E and K [67]. Scientific evidence suggests that vitamins act against different species of viruses, including the SARS and MERS CoVs. The antiviral effects of vitamins are presented below.

Vitamin A

Vitamin A is a fat-soluble vitamin (fat-soluble), with an essential role in the human body, which refers to several substances, including retinol, retinal, retinoic acid, retinoids and cartenoids. The most important benefits and functions of vitamin A are: antioxidant, role in night vision, correct color distinction, role in the formation of antibodies and supports the immune system, skin's integrity [68]. Vit-A is also called "*anti-infective*" vitamin as it can be efficient against many infectious agents [69]. Vit-A supplementation reduced the morbidity and mortality in different infectious diseases, including pneumonia, human immunodeficiency virus (HIV) and malaria [70, 71]. A low Vit-A diet may reduce the effectiveness of bovine CoV vaccines and increase the risk of infectious disease [72]. A similar result was seen in Vit-A deficient diet on a chicken model [73]. Vit-A, as well as retinoids, were found to inhibit measles virus replication by upregulating the elements of the innate immune response in uninfected by stander cells, thereby inhibiting viral replication [74].

Vitamin B

B vitamins (e.g., B_1, B_2, B_3, B_6, B_7, B_9, and B_{12}) play essential roles in the immune system [75–80]. Vit-B2 with ultraviolet (UV) light significantly reduced the titer of MERS-CoV in human plasma products [81]. On the other hand, Vit-B3

had an anti-inflammatory effect and effectively inhibited neutrophil infiltration in the lungs [82].

Vitamin C

Vitamin C (ascorbic acid, AA) as an immunostimulatory substance has direct effects on the immune system by [83]:

i) increased IFN production, which prevents cells from becoming infected with viruses;
ii) stimulates antibody activity;
iii) increases the function of phagocytosis, the natural process by which the body eliminates harmful pathogens;
iv) increases the production of immune cells T, B, NK;
v) inactivates virus RNA and DNA;
vi) decreases the action of pro-inflammatory cytokines.

Vitamin C and respiratory viruses: Vit-C is useful in the management of common cold in experimental animals [84]. A Vit-C deficiency results with immune system dysfunction and an increased risk of susceptibility to microbial infections [85, 86]. Vit-C supplementation appears to be able to both prevent and treat respiratory and systemic diseases [87, 88]. Prophylactic prevention of infection requires dietary Vit-C intakes that provide adequate plasma levels (i.e., 100–200 mg/d), which ensure optimal intracellular levels [89].

Vit-C can be used to treat infections caused by the influenza virus [90]. It inhibits influenza virus proliferation [91]. Vit-C inhibits different phases of the cell cycle of various viruses and inhibits the integration of RNA viral genetic material into the host genome [92, 93]. Therefore, this vitamin may be effective against influenza, corona, or picorna viruses.

Vit-C stimulates liver X receptor alpha (LXR-α) gene expression, which downregulates c-myc gene, resulting in cell cycle arrest at G0G1 phase, thus restricting the entrance of cells in S phase and reducing the number of cells at a G2 M phase of viral genome integration [94, 95]. Vit-C also inhibits viral replication of other RNA viruses such as the HIV and avian tumour virus [96].

Vit-C combined with iron was shown to have a sustained anti-viral effect against the influenza virus [97]. It may be due to the pro-oxidant fact of this vitamin [98]. Dehydroascorbate has shown this effect better than the ascorbate form [99]. However, to show a pro-oxidant impact in bronchial epithelium, the availability of iron and oxidants such as H_2O_2 should not be a limiting factor for locally available Vit-C because iron and H_2O_2 are present in the vicinity of the bronchial epithelium [100].

Influenza virus infection produces matrix metalloprotease (e.g., MMP-9) in epithelial cells, which is thought to be a mechanism supporting the spread of the virus [101]. Vit-C reduced the gene expression of MMP-9 in peripheral blood-derived mononuclear cells [94] and MMP-9 synthesis induced by H_2O_2 in an *in vitro* chorioamnionitis membrane model [102]. MMPs have an essential role in cancer metastasis, and Vit-C inhibited the migration of cancer cells [103]. Therefore, Vit-C may act against influenza virus infection by inhibiting the mediator of inflammation, MMP-9, and reducing the extent of damage to the respiratory epithelium. Vot-C 3 g/d was reported to prevent the common cold and flu symptoms in human (18–30 years of age) [104]. At a dose of 300 mg/d, Vit-C was found to help influenza patients and reduced for 25% hospitalization length when compared with the control group [105].

Vit-C has a beneficial effect not only on the common cold but also on asthma and pneumonia [88]. In a study, *C. sinensis* extract (rich in Vit-C) was found to inhibit the replication of CoV in infected cultured cells [34]. Moreover, in 21 trials with 1766 patients having high blood pressure, infections, bronchoconstriction, atrial fibrillation, and acute kidney injury, Vit-C (in oral dose 1–3 g/d) reduced the length of hospitalization in intensive care unit on average by 7.8–18.2%. Vit-C reinforces the maintenance of the alveolar epithelial barrier and transcriptionally upregulates the protein channels (CFTR, aquaporin-5, ENaC, and Na^+/K^+ ATPase) regulating the alveolar fluid clearance.

Clinical studies on the potential effect of Vit-C on SARS-CoV-2 infection showed that Vit-C could be used as an adjuvant substance in COVID-19 pharmacotherapy. A clinical survey of 140 participants is ongoing investigating the effect of Vit-C against SARS-CoV-2. Vit-C was administered intravenously at doses of 12,000 to 24,000 mg/d. High doses of Vit-C can stimulate the body's natural defence system and reduce the incidence and duration of viral diseases. Besides, the increased intake of Vit-C causes the activation of lymphocytes. But this is just a study that has only been approved. Nevertheless, no definite anti-SARS-CoV-2 effects of Vit-C in COVID-19 patients have yet been reported [106].

Other studies indicated that the use of hydrocortisone, thiamine and Vit-C might be useful in the treatment of sepsis [107]. Sepsis and organ failure are the two leading causes of death due to SARS-CoV-2 infection. Another function of this combination of drugs is to repair the dysfunction of the endothelial barrier of the lungs [108].

Vitamin D

Vitamin D is a fat-soluble vitamin and is found in the body in two main forms: Vitamin D2 (ergocalciferol) and Vitamin D3 (cholecalciferol). Vit-D is not a vitamin in the strict sense as it can be synthesized in the human body following exposure of the skin to ultraviolet radiation [109]. Pro-Vit-D (7-dehydrocholesterol) is converted to pre-Vit-D which is further modified by a series of reactions to the active form – 1,25-dihydroxy vitamin D. A certain amount of Vit-D

may be provided via some dietary sources like fortified cereals and milk [110]. Vit-D helps to develop the proper functioning of the immune system [111]. Calcitriol (the active form of Vit-D) modulated the expression of ACE2 in lipopolysaccharide-induced lung injury in Wistar rats [112]. In another study, this vitamin also attenuated angiotensin II-induced nitrogen oxides (NOx) activation and reactive oxygen species (ROS) production [113]. However, a high glucose diet can activate ACE2R in human [114].

Vitamin D and immunity: Vit-D affects specific mechanism in the immune system, namely the ability of dendritic cells to activate T cells. Lymphocytes (T cells) that kill bacteria and viruses are less active in patients who have low levels of Vit-D. These cells do not move unless their receptors identify Vit-D in the circulation. In the absence of this vitamin, lymphocytes remain at rest. The presence of Vit-D activates them to move to the site of viral infection [115].

Vitamin D and respiratory viruses: maintaining a concentration of more than 50 ng/mL of Vit-D in the blood reduces the risk of infection with a flu-like virus by 27% [116]. Moreover, the intake of Vit-D deactivates the production of renin, an enzyme necessary for the production of angiotensin II. Angiotensin II has a vasoconstrictor effect, causing increased blood pressure and inflammation. CoV infection is closely related to the increased production of this enzyme [117]. Viral and bacterial pneumonia kills more children than any other illnesses (19% of total deaths of children less than five years of age) and under-nutrition, which includes Vit-D insufficiency/deficiency, has been implicated in 53% of all these deaths [118, 119].

Vit-D deficiency has been linked to an increased risk of viral upper- and lower- respiratory tract infections (especially during winter time), wheezing, and asthma-related hospitalizations in infants and children [116, 120]. Normal to high serum 25(OH)D appears to have some beneficial influence on the incidence and severity of these infections [121]. This vitamin has immunomodulatory actions [122]. On the other hand, it seems that its metabolites do not consistently influence replication or clearance of rhinovirus, respiratory syncytial virus or influenza A virus in human respiratory epithelial cells. This is even though they modulate expression and secretion of type 1 IFN, chemokines including IL-8 or chemokine (C-X-C motif) ligand 8 (CXCL8) and INF-γ-induced protein 10 (IP-10) or CXCL10 and proinflammatory cytokines, such as TNF and IL-6 [123]. Vit-D is associated with less allergic disorders due to its anti-inflammatory activity [124].

The effective supplementation of Vit-D needs to start before the onset of respiratory tract infection [116, 125]. The explanation of the mechanisms that involve Vit-D deficiency in viral diseases development is inconclusive [120]. Still, it seems that they include anti-viral immune induction, modulation of immunoregulatory defence, induction of autophagy and apoptosis, and genetic or epigenetic regulation [126]. Vit-D reduces the risk of viral infections [127]. The protective role of Vit-D in SARS-CoV-2 infection has been shown by increased fatality rates in patients with chronic disease comorbidity and older age, in which lower concentrations of 25(OH)D have been reported [128]. This is a cause of concern because of globally Vit-D deficiency prevalence, particularly in the elderly [129], and may have contributed to the first outbreak of COVID-19 during winter 2019 [130]. For people at COVID-19 risk, the goal should be to increase the concentrations of 25(OH)D above 40–60 ng/mL by Vit-D_3 supplementation 10,000 IU/d for a few weeks, followed by 5000 IU/d [131]. Generally, Vit-D is known to mitigate the scope of acquired immunity and regenerate endothelial lining [132]. This may be beneficial in minimizing the alveolar damage caused in acute respiratory distress syndrome (ARDS) [133]. A rapid change in ambient temperature is associated with increased risk of SARS-CoVs [134]. Influenza transmission is often enhanced in the presence of cold and/or dry air [135]. In northern Europe, low temperature and low UV indexes were correlated with peaks of influenza virus infections during 2010–2018 [136]. Vit-D receptor gene polymorphisms are associated with diabetic nephropathy risk in diabetes mellitus patients [137]. Therefore, these patients might be at higher risk if they get COVID-19.

Vit-D_3 acts on T immune cells that are activated to defend from viruses and bacteria. T cells have Vit-D_3 receptors, which means that their effectiveness is achieved only in the presence of this vitamin. As a result, Vit-D_3 deficiency is associated with an impaired immune system prone to infections. Vit-D_3 also activates a peptide with antimicrobial effect and allows the elimination of bacteria before the onset of disease [138]. Antiviral effect of Vit-D_3 is supported by the Vit-D_3 on the inflammatory response triggered by a viral infection. The virus causes the release of proinflammatory cytokines, aggravating the disease. Vit-D_3 decreases the secretion of these cytokines, diminishing the effects of infection [139] (Figure 2).

In a recent clinical study, which proved the effectiveness of high single or monthly doses of Vit-D_3, monthly supplementation of high-dose Vit-D_3 did not prevent acute respiratory infections in older adults with low levels of Vit-D. In this randomized, double-blind, placebo-controlled study on 5,110 adults' participants were given 200,000 IU of Vit-D_3, followed by 100,000 IU per month (in 2,558 patients) or placebo (in 2,552 patients). The mean follow-up was 1.6 years [140]. The results of this study suggested that monthly high-dose Vit-D_3 supplementation did not prevent acute respiratory infections in older adults with a low prevalence of profound vitamin D deficiency at baseline. [140].

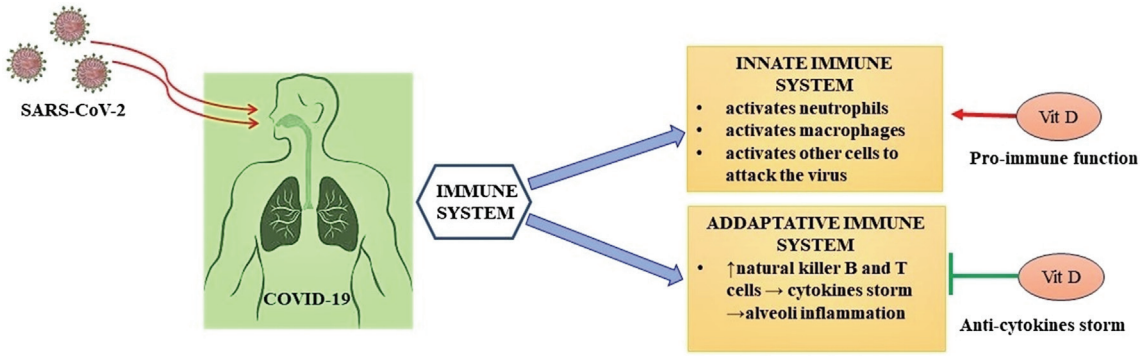

Figure 2. Summarized scheme of possible mechanisms of action of vitamin D in COVID-19.

Vitamin E

Vit-E plays many essential functions in the immune system, including cell-mediated microorganism destruction and antibody production [141, 142]. Vit-E deficiency stimulated the myocardial injury in mice infected by the RNA virus and coxsackievirus B3 [143, 144]. Moreover, a decrease in Vit-D and Vit-E significantly increased the risk of bovine CoV infection in calves [145].

Minerals and trace elements

Zinc

Zinc is a dietary trace element which is important for the immune system [146]. Deficiency of this element results in dysfunction of the immune system, thereby, increasing susceptibility towards the infectious agents [147]. Maximum tolerance limit for zinc ingestion is 40 mg/day, an amount that represents the daily maximum zinc intake which does not cause harmful effects for persons older than 18 years [148]. Acute zinc overdose is manifested by nausea, vomiting, loss of appetite, fever, headache, and chronic excessive intake causes a decrease in the concentration of copper, hypochromic anaemia and a reduction in the effectiveness of the immune system [148].

The role of zinc in immunity: Zinc is involved in over 300 enzymes, having a catalytic, regulatory and structural function. Zinc has a role in both – non-specific immune response, as well as the specific one. Regarding the nonspecific immune response, at the level of the epithelial barrier, zinc plays an important role. Its low level causes the rupture of intercellular junctional complexes and disorganizes the cytoskeleton. [149]. Other negative effects of low zinc levels on innate immune response: decreasing of natural activity killer (NK) and natural killer T (NKT) cells; alteration in phagocytosis and antigen presentation in macrophages; decreased maturation and expression of the major complex of histocompatibility class II by dendritic cells; change of cytokine production in mast cells are also [150]. The specific immune response can be severely endangered by zinc deficiency. The presence of zinc is necessary for the activity of thymulin, a polypeptide responsible for differentiating immature cells with the formation of L (lymphocytes) TH1 (helper) [7].

Zinc deficiency causes an alteration of the formation of immunocompetent LT at thymus and lymphatic tissue atrophy [8] associated with a decreased percentage of LT $CD8^+$ $CD73^+$ which are considered precursors of cytotoxic $CD8^+$ LTs [151]. Zinc deficiency causes an imbalance of the ratio between LTH1, and LTH2, which is not influenced by zinc. Zinc deficiency also causes a decrease in the concentration of IFN-γ, tumour necrosis factor TNF-α and IL-2 (synthesized by the LTH1), compared to the constant maintenance of the level of IL 4, 5, 6 and 10 (synthesized by LTH2). Zinc also has antioxidant effects achieved by inhibiting nicotinamide adenine dinucleotide phosphate (NADPH) oxidase responsible for producing the free radical of oxygen, the superoxide ion O2. Zinc, together with copper, are required for the functioning of superoxide dismutase (SOD1) isoenzymes, located in the cytosol, mitochondria, intermembrane space and SOD3, located extracellularly. Superoxide dismutases are a family of metalloenzymes, with antioxidant effects which are achieved by reducing the superoxide anion to H_2O_2 [152].

From all the above-mentioned data, it is clear that zinc is essential for cell protection from the harmful effects of oxygen radicals. In infections, zinc is introduced into the hepatocyte by Zrt-Irt-like protein transporters 14 (ZIP 14) and stored in the liver in the form of metallothionein (MT). MT is considered to be an acute phase reactant. Its synthesis is induced by zinc, glucagon, glucocorticoids, reactive oxygen species, endotoxins, IL-1, IL-6, and TNF-α [153]. MT has an antioxidant role since it removes nitric oxide, ion superoxide and hydroxyl radical. At the cellular level, zinc has an antiapoptotic role, protecting the cell from oxidative stress with the reversible formation of a thiolate complex, protecting the proteins against reactive oxygen species and blocking the activation of caspase 3, within the caspase cascade, responsible for cell death [154]. Zinc deficiency causes an increase in the production of glucocorticoids,

hormones which have a proapoptotic role for precursors of lymphocytes. Zinc deficiency causes lymphopenia of T and B lymphocytes. Zinc is required for DNA synthesis, RNA transcription, cell division and activation of cells. Zinc deficiency causes also a decrease of number and function of T, B lymphocytes, macrophages, $CD4^+$ /$CD8^+$ ratio and decreased NK cell activity [155].

Zinc and respiratory viruses: the antiviral activity of zinc was first recorded 40 years ago, in 1980, when 5 mg of zinc gluconate was administered to a three-year-old child with a history of chronic respiratory tract infections This was done with the idea to increase the resistance of the immune system. Following oral administration of zinc gluconate tablets, the symptoms of respiratory tract infections were significantly reduced [156]. Zinc supplement was also found to reduce measles-related morbidity and mortality in children [157].

Many studies showed that zinc-based supplements might be useful in reducing common cold and its symptoms. A survey of a small group of volunteers diagnosed with a common cold or flu, 50 of whom were treated with zinc acetate at a dose of 13 mg every two or three hours, showed that the duration of the disease was significantly shorter (4–5 days) in patients who were given zinc acetate compared to other patients who were not given zinc acetate (about 8 days). Although the maximum daily dose of zinc acetate given to these patients was 80 mg (well above the recommended daily dose), no adverse effects were reported in this short period [158].

The mechanism of action of zinc in respiratory tract infections is unknown. Some researchers claim that the administration of zinc-based supplements prevents the virus from entering the cells by forming a bond with a protein that facilitates this. Others argue that zinc causes a decrease in inflammatory cytokines [159].

Zinc and SARS-CoV-2: in a recent study, an increased concentration of intracellular zinc was reported to decrease the replication of several RNA viruses [160]. Moreover, a combination of zinc and pyrithione inhibited the replication of SARS-CoV-2 even at low concentrations [160]. Zinc at a dose of 150 or 2,500 mg/kg increased systemic transmissible gastroenteritis virus (a single-stranded RNA virus) specific serum antibody response, thereby suppressing infection with this virus in piglets [161].

Some researchers claim that zinc-based (zinc gluconate, zinc acetate or zinc citrate) dietary supplements might reduce the duration of the clinical syndrome caused by COVID-19, mainly if administered with some drugs, but no real data are confirming this [162, 163].

Zinc acts on three levels (Figure 3):

i) Zinc administration most probably inhibits virus replication (including SARS-CoV-2) and aggravation of symptoms associated with a viral infection;
ii) Zinc increases mucociliary clearance by stimulating the elimination of viral particles and bacteria by improving ciliary morphology and increasing the rhythm of the ciliary movement frequency;
iii) Zinc supplementation stimulates and activates the natural antiviral response of the immune system, especially in zinc deficiency.

Another recent study showed that hydroxychloroquine in combination with zinc and Vit-A and Vit-D might have a beneficial effect as an alternative therapy in COVID-19 [164]. Zinc promotes the penetration of hydroxychloroquine into infected cells helping to destroy the virus, and Vit-C and Vit-D stimulate the function of the immune system. Regarding the dose of zinc-containing preparations and the duration of administration of these preparations, current evidence indicates that a maximum dose of 150 mg/day of zinc administered for a short period, does not cause zinc poisoning (clinicaltrials.gov, NCT04335084).

Copper

Copper has strong virucidal properties [165]. Copper at a high concentration of chelating copper caused moderate effects on influenza A/WSN/33 (H1N1) viral growth in cultured human lung (A549) cells [166]. Copper-mediated mechanisms are considered as a therapeutic target for chronic lung inflammation [167] and defence against different microorganisms, including bacteria [168, 169], fungi [170] and DNA or RNA viruses such as influenza A [171], norovirus [172], bronchitis virus, poliovirus, and HIV-1 [173]. Lymphocytic choriomeningitis virus-infected mice treated with Mn(III) tetrakis(4-benzoic acid)porphyrin chloride resulted in a significantly increased virus-specific IgM and IgG antibody-secreting cells in animals [174]. Solid-state Cu_2O was seen to disrupt host cell recognition by denaturing protein structures on influenza A virus (A/PR8/H1N1) surface, resulting in inactivation of viruses [175].

Iron

Iron plays a key role in the immune system, and nutritional iron deficiency can impair host immunity, while iron overload can cause oxidative stress to propagate harmful viral mutations. [176]. Lack of this essential element increases the risk of recurrent acute respiratory tract infections in experimental animals [177]. Iron is required for the synthesis of viral proteins in the host [178]. An overloaded of iron was seen to increase oxidative stress and impair nutritional immunity against pancreatic necrosis virus in *Salmo salar* [179]. Chromium (III) (200–1000 μM) and iron (III) (200–1000 μM) have a synergistic antiviral effect against Herpes simplex virus type 1 and Bovine viral diarrhoea virus HSV-1 in Hep-2 cells [180].

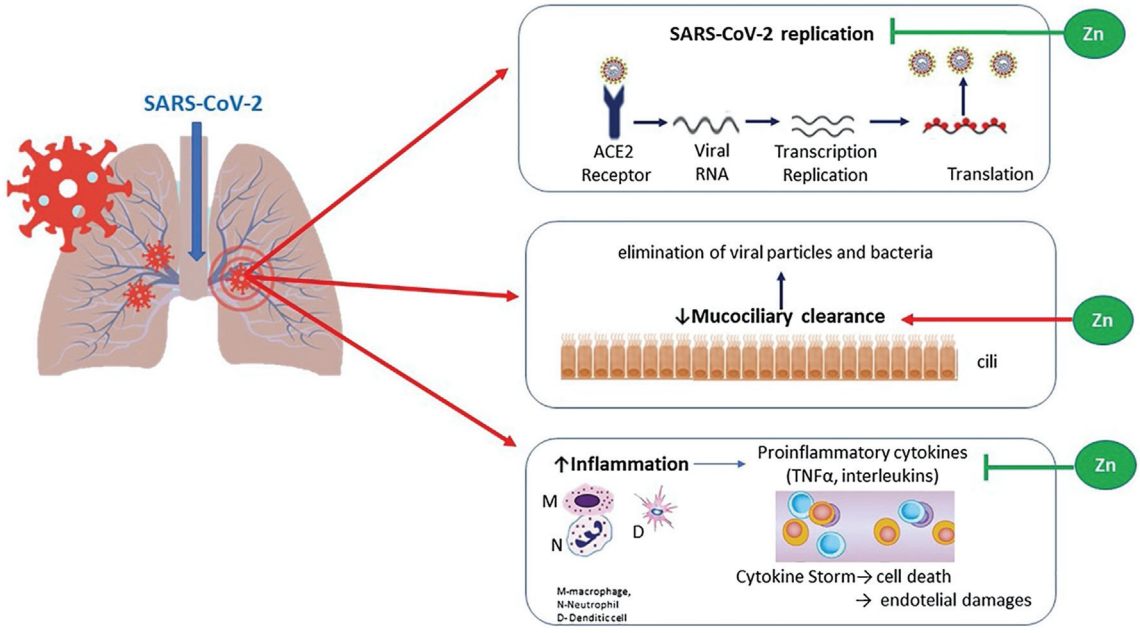

Figure 3. Potential antiviral mechanism of zinc in COVID-19. ACE2 angiotensin-converting enzyme 2; CoV coronavirus; D dendritic cell; M macrophage; N neutrophil; SARS severe acute respiratory syndrome; TNFα tumour necrosis factor-alpha.

Selenium

Selenium has an important role in antioxidant defence, redox signalling and redox homeostasis, which is crucial since reactive oxygen species (ROS) are frequently produced during viral infections. [181]. Selenium deficiency reduces the immune response and may also increase the virulence of RNA viruses [182, 183] as well as help to change the coxsackievirus genome, resulting in a more virulent genetic configuration of the virus [184]. Selenium has a positive synergistic effect with ginseng stem-leaf saponins on a live bivalent Newcastle disease virus (NDV) and infectious bronchitis virus (IBV) CoV vaccine in chickens promoting a stronger antibody response [185].

Sodium chloride

Sodium chloride (NaCl) or 'table salt' is used as a coating material on the fibre surface of the filtration unit of the surgical mask effectively deactivating several influenza virus species. This suggests a new strategy in protective measures to avoid primary/secondary infection and transmission of many viruses [186]. On the other hand, the natural adsorbents, including clay, charcoal, and clay minerals showed 99.99% adsorption of CoV in an *in vitro* model [187].

Calcium chloride

Calcium chloride can be used to detect virus particles by detecting the interaction of the surface of enveloped viruses with DNA [188]. The protein kinase R (PKR), is an interferon-induced kinase, which plays a key defensive role in the innate immunity pathway against viral infection. Adenovirus encodes VAI (a highly-structured RNA inhibitor) and binds with PKR.

Magnesium, Potassium, Calcium

Magnesium can modulate the interaction capability of VAI with PKR, where two PKR monomers bind in the absence, while a single monomer binds in the presence of this metal ion (Mg^{2+}) [189]. Low plasma Mg^{2+} level was associated with the high Epstein-Barr virus load in peripheral blood in endemic Burkitt lymphoma in humans [190]. Moreover, Mg^{2+}-dependent viruses such as retroviruses can be detected by using Mg^{2+}-based reverse transcriptase assay [191]. On the other hand, low pH (<6.0) and high potassium ion (K^{+}) influx is required for efficient uncoating of influenza A virus and infection of the host cell [192].

Generally, potassium triggers a conformational change in the fusion spike of an enveloped Ribonucleic acid (RNA) virus. Blocking K^{+} channel was found to be associated with an inhibitory effect of Hazara virus infection in BHK and A549 cells [193].

Calcium in a low pH surrounding caused fusion to an E1 membrane protein of rubella virus in the early endosome compartment [194].

Table 1 summarizes the most relevant studies regarding potential beneficial effects of dietary supplements, vitamins and minerals in SARS-CoV-2 infection.

Table 1. The most relevant studies regarding potential beneficial effects of dietary supplements, vitamins and minerals in SARS-CoV-2 infection

Name	Antiviral Mechanisms of action	Common use and potential effects	Potential uses in COVID-19	Ref
		Dietary Supplements		
Garlic (*Allium sativum* L.)	Antiviral	Preventing common cold	*In silico*:↓ACE2, ↓main protease PDB6LU7 protein of SARS-CoV-2	[39]
			In vivo: ↑$CD3^+$ T, ↑mRNA, ↑IL-1β, ↑TNF-α, ↑IL-6, ↑IFN-γ	[40]
Cranberries	Inhibit influenza viruses H7N1, H5N3, H3N2 ↓Replication, ↓infectivity	Antiviral	Potential antiviral	[46]
Curcumin *(Curcuma longa* L.)	↓Replication, ↓NF-κB	Antimicrobial	Potential antiviral	[54]
	↓inflammatory cytokines	Antiviral		
	↓ C-reactive protein	Antiinflammatory		
		Antioxidant		
Polyunsaturated omega-6 fatty acid	↓NLRP3 in human blood neutrophils	Cardioprotecive	Potential antiviral	[56]
	↓influenza virus ↓replication			
	↓RNA			
Melatonin	↓ Citokines	Regulates the cycles of wakefulness and sleep	↓ Infectivity of SARS-CoV-2	[60]
			↓Risk of developing complications	
Probiotics	Prevent Prevotella from forming biofilms	Beneficial effects for human health: gastrointestinal disorders, immunomodulation	potential adjuvant	[64]
		Vitamins		
Vitamin A	↓ Morbidity and mortality in different infectious diseases, including pneumonia, human immunodeficiency virus and malaria, viral replication ↑Formation of antibodies	Antioxidant immunostimulatory	Potential adjuvant	[70] [71]
vitamin B	↓Titer of MERS-CoV in human plasma products	Brain function cell metabolism	Potential adjuvant	[81]
Vitamin C	Immunostimulatory	↑Iron absorption	Adjuvant substance in COVID-19 pharmacotherapy	[84]
	↓Incidence and ↓duration of viral diseases	Antioxidant		
		↑Recovery in convalescence		
Vitamin D	↓NOx	Maintains normal levels of calcium, phosphorus in the blood	In vivo: ↓ACE2 in lipopolysaccharide-induced lung injury in Wistar rats	[112]
	↓ROS	↑Calcium absorption	Protective role of Vitamin D in SARS-CoV-2 infection	[128]
	↑T cells decreases the secretion of these cytokines, diminishing the effects of infection	Immunostimulatory	Regenerate endothelial lining	[132]
		Minerals and Trace Elements		
Zinc	Resistance of the immune system	Important role in: cell-mediated immunity	↓Replication of RNA	[160]
	↓Common cold symptoms	Bone formation	↑Mucociliary clearance by stimulating the elimination of viral particles	[164]
	Prevents the virus from entering the cells	Tissue growth	Potential alternative therapy	
Selenium	Role in antioxidant defence, redox signalling and redox homeostasis ↓ROS		Potential alternative therapy	[181]

Abbreviations: ACE2 angiotensin-converting enzyme 2; CoV coronavirus; IFN-γ interferon-gamma; IL interleukin; MERS Middle East respiratory syndrome; NF-κB nuclear factor kappa-light-chain-enhancer of activated B; NOx nitrogen oxides; ROS reactive oxygen species; SARS severe acute respiratory syndrome; TNF-α tumour necrosis factor-alpha.

Future perspectives and clinical importance for COVID-19 pharmacotherapeutic management

Development of a vaccine is a priority in dealing with COVID-19 and mass immunization of the population with this vaccine is a very important goal [195]. Ensuring the quality, safety and efficacy of COVID-19 vaccines is fundamental and requires time and testing on healthy volunteers [196, 197]. However, besides protective and preventive measures, effective curative treatment strategies will always be needed.

Nutritional interventions play an essential role in the treatment and management of various diseases [198–203]. Dietary factors can modulate the environmental influences as well as genetic predisposition which are responsible for many diseases [204]. Moreover, the essential components of diet have direct (protective or harmful) effects on the biological processes involved in many organs, including lung, disease development, and outcomes [66, 205]. The impact of early-life and cumulative dietary choices during the lifetime has been recognized as essential factors for respiratory diseases, thus offering a greater window of opportunity for diseases prevention [206].

It has been shown that antihypertensive drugs – ACE inhibitors and angiotensin receptor blockers (ARB) upregulate ACE2R and increase ACE2. Since ACE2 is a protein that facilitates coronavirus entry into cells, there was serious concern that these drugs could increase the risk of developing a severe and fatal form of COVID-19. On the other hand, this might be one of the potential targets to inhibit SARS-CoV-2 invasion in lung cells [207]. Generally, ACE2 converts angiotensin II to angiotensin 1–7, results in vasodilation and has protective effects on the cardiovascular system [208]. ACE2 deficiency causes loss of normal endothelial functions in the cerebral arteries and may amplify endothelial dysfunction in older animals [209]. Therefore, ACE2–angiotensin 1–7 pathway might be a therapeutic target in patients with cardiovascular disease, especially those who have an overactive renin-angiotensin system [208, 210]. Kuster, Pfister [208] recommended ACE1 and angiotensin II type 1 receptor blockers for the patients having heart failure, hypertension, or myocardial infarction with COVID-19.

However, it has been shown that the loss of nuclear factor-erythroid 2 p45-related factor 2 (Nrf2) upregulated ACE2R expression in renal proximal tubular cells in Akita mice [211]. CoV infection causes ER stress, and increases unfolded protein response (UPR) in the infected cells, which may be associated with pro-inflammatory responses [212]. Nrf2 expression levels vary depending on the pathophysiological context. Therefore, the appropriate manipulation of its expression might help to manage the ACE2R expression in CoV infection [213]. Until today, P4 and P5 peptides and N-(2-aminoethyls)-1-aziridineethanamine (NAAE) have been marketed claiming that they interact with ACE2 and block SARS-CoV-2 S-mediated cell fusion [214, 215]. However, these drugs have a narrow spectrum of activity. Therefore, they may change some essential biological functions for worse, including regulation of blood pressure. Emodin, an anthraquinone derived from genus *Rheum,* and *Polygonum* blocks the S protein of SARS-CoV-2 spike protein and ACE2 interaction in a dose-dependent manner [216]. It also inhibited the infectivity of Vero E6 cells by the viral S protein. Kesic, Simmons [217] found an inverse relationship between the levels of Nrf2 expression and influenza A viral entry/replication in human nasal epithelial cells. Moreover, melatonin (an anti-inflammatory and anti-oxidative molecule) acts against acute lung injury (ALI)/ARDS caused by viral and other pathogens, which might be beneficial in SARS-CoV-2 infection management [59]. Nrf2 activated by melatonin through the MT1/MT2 receptor pathway stimulates endoplasmic reticulum-associated degradation, thereby inhibiting NF-κB and endoplasmic reticulum mediated stress [218].

RNA viruses in cytoplasmic tweak divergent NF-κB expression, reprogram the landscape of the host cellular chromatin adequately, leading to orchestrate the legitimate expression of genes involving various functions, including immunoregulatory and metabolic activities [219]. ACE2 upregulation is associated with chronic liver injury [220, 221], inflammation and insulin resistance [222], myocardial dysfunction [223], acute decompensated heart failure [224], diabetes [225], while deletion or loss of its activity causes atherosclerotic renal injury, kidney diseases [226], heart failure [227], pulmonary arterial hypertension [228] and stroke [229]. Therefore, targeting Nrf2 alone or Nrf2-ACE2 might be helpful for these types of patients with COVID-19. Natural products activate Nrf2, thereby improving diabetes in experimental animals [230].

More research should be performed on copper, iron, selenium and zinc. Sodium chloride can be incorporated in the PPE, especially on the mask. It can also be used to wash PPE. Adequate research is also necessary on the medicinal plants *N. sativa*, *C. sinensis*, Cranberry, garlic, ginger, and *S. persica* since they have shown potential anti-viral effects against many viruses, including CoVs. Studies are also required on substances like ginkgolic acids, linoleic acid, protectin D1, dietary animal proteins (e.g., milk proteins), 2-deoxy-D-glucose and soy flavonoids. Finally, Vit-A, B and E should be taken into consideration because of their anti-CoV effects. Moreover, combination therapy strategies can be developed using these anti-viral substances.

Conclusion

A diet containing substances, such as carbohydrates, proteins, fats or their derivatives; minerals and vitamins may be helpful to fight COVID-19 and other viral infections.

These substances can stimulate and strengthen the immune system, which may help to suppress viral infections. Moreover, in this way antibodies produced in sufficient quantities may act against viruses. Therefore, by taking these substances in the daily diet or by modifying food habits, the risk SARS-CoV-2 infection might be reduced as well as the incidence of morbidity and mortality in COVID-19.

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ORCID
Javad Sharifi-Rad
https://orcid.org/0000-0002-7301-8151

Javad Sharifi-Rad
Shahid Beheshti University of Medical Sciences
Tehran, Iran
javad.sharifirad@gmail.com

