REVIEW PAPER

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Nutraceuticals in prevention and management of COVID-19

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Abstract

The immune system defends the host from many pathogenic microorganisms such as viruses, bacteria, parasites and fungi, including a large number of specific cell types, interrelated molecules, and biological responses. Due to infections, heightened immune system activity is accompanied by expanded metabolic activities, requiring appropriate energy supply, precursors for biosynthesis and regulatory molecules. Numerous vitamins and minerals play a crucial role in supporting body's immunity and fighting against viral infections. Other bioactive compounds like omega-3 fatty acids, probiotics and antioxidants (alpha-lipoic acid, quercetin) are also important in the immune response. COVID-19 may develop mild symptoms to severe damage of the respiratory epithelium followed by a cytokine storm. Many studies show that vitamin C, vitamin D, zinc and selenium are critical in defending against SARS-CoV-2 infection. Intestinal dysbiosis is a feature of many infectious diseases, including COVID-19, so dietary approaches to establishing a healthy microbiota are essential for improving immune function. This paper reviews the data on the roles and potential effectiveness of selected nutraceuticals in the prevention and treatment of COVID-19.

Key words: *COVID-19; SARS-CoV-2; immunity; micronutrients; biologically active compounds.*

INTRODUCTION

A novel generation of SARS-CoV-2 coronavirus was recognized in December 2019 and has affected almost all countries worldwide. Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus type 2 has resulted from none to a life-threatening illness, especially in vulnerable groups [1]. COVID-19 may be defeated more efficiently by amplifying immune-inflammatory regulation mechanisms [1]. Adequate nutrition is part of a healthy lifestyle and significantly strengthens the immune response. Numerous studies indicate an increased risk of viral infections or greater severity in people with inadequate macro- and micronutrient intake. Additionally, several micronutrients can notably impact disease severity through modulation of viral pathogenesis and supporting the optimal function of the immune system [2]. These nutrients can be obtained from a varied and well-balanced diet and are accessible as dietary supplements either alone or as multi-nutrient combinations. Given suggestive evidence that antioxidants (e.g., vitamin C and selenium (Se)) and anti-inflammatory representatives (e.g., vitamin D and zinc (Zn)) could help anti-COVID-19 treatment, this review will provide knowledge on available scientific data for selected micronutrients to date. Moreover, other potentially immune-relevant nutraceuticals such as omega-3 fatty acids (ω-3 FAs), alfa-lipoic acid (ALA), and non-nutritive dietary compounds like probiotics and quercetin (QUE) will also be discussed. **Figure 1** depicts nutraceuticals that are important for immune system function.

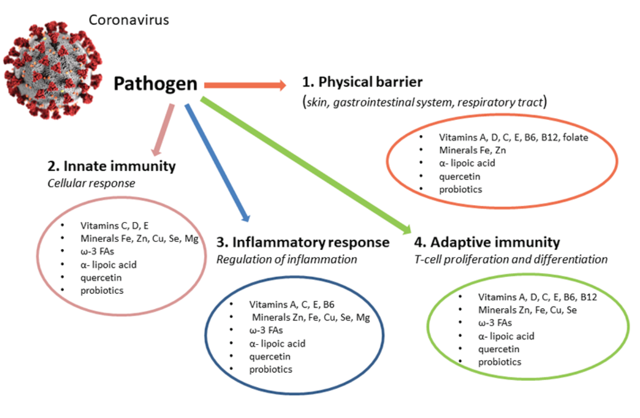

Figure 1. Overview of how nutraceuticals affect the immune system.

Vitamin C

Vitamin C is a hydrosoluble substance with essential antioxidative properties in intracellular and extracellular matrixes. It acts as a cofactor of many biological regulatory pathways in the immune response. Besides maintaining physical barriers (skin and mucosal membranes), vitamin C accumulates in immune cells such as leukocytes and neutrophils and affects microbial phagocytosis and programmed apoptosis [3]. Effects of vitamin C on inflammatory regulation include attenuation of pro-inflammatory cytokine production. The clinical syndrome of vitamin C deficiency is correlated with susceptibility to infections, especially respiratory infections and pneumonia [4]. In prolonged disease, oxidative stress and inflammation increase, therefore vitamin C requirements rise. Doses of ≥ 200 mg/day are recommended for health conditions, while requirements for vitamin C increase to 1-2 g/day in sick individuals. Because SARS-CoV-2 infection can cause sepsis and acute respiratory distress syndrome, treatment with high doses of vitamin C in COVID-19 patients has been studied. In a clinical trial performed in the United States, high oral doses of vitamin C and Zn (8 g of vitamin C and 50 mg of Zn-gluconate) were applied in hospitalized patients for ten days to follow the reduction in symptom severity. Treatment with vitamin C, Zn-gluconate, or a combination thereof did not remarkably affect the time required to reduce the heaviness of symptoms compared to standard care [5]. In a pilot study conducted in China, critical COVID-19 patients received a dose of 24 g/day of vitamin C intravenously for seven days. The study did not find differences in duration of mechanical ventilation, organ damage, or mortality between the treated and placebo groups. The study reported statistically significant improvements in oxygenation after seven days of treatment, compared to placebo [6]. A randomized controlled trial conducted in Pakistan showed improvement in symptoms and shortening of the hospital stay after intravenous administration of vitamin C at a dose of 50 mg/kg/day [7]. According to a comprehensive Cochrane review, specific reductions in the duration and severity of upper respiratory tract infections could be surveilled in ordinary supplementation trials, with inconsistent effects in therapeutic trials. Additionally, current evidence is not sufficient to confirm the beneficial effect of vitamin C in preventing and treating pneumonia in COVID-19, and further extensive research is needed.

Vitamin D

Vitamin D is the common name for a group of seven fat-soluble secosteroids. It can be synthesized in the skin from an endogenously formed cholesterol derivative (7-dehydrocholesterol). In addition to its primary role in maintaining calcium homeostasis, vitamin D exhibits immunomodulatory activity and regulates cell growth and differentiation. It acts via binding vitamin D receptor (VDR) and affects the expression of regulatory genes, mediates chromatin remodeling, epigenetic modifications, receptor recycling, and gene expression. VDR is widely expressed in bones, intestines, kidneys, parathyroid glands, melanocytes, cardiomyocytes, pancreas, blood vessels, neurons, and immune cells [8]. The major vitamin D (80-90%) comes from skin sunlight exposure, while the main dietary sources are fish oil, fish (tuna and salmon), egg yolks, offal and mushrooms. The European Food Safety Authority (EFSA) determines vitamin D deficiency when the plasma level of 25(OH)D is less than 25 nmol/L. Suboptimal vitamin D levels appear when it ranges between 25 and 50 nmol/L, while its concentrations between 50 and 75 nmol/L are considered normal [9]. Vitamin D deficiency is expected in the elderly, obese people and patients with chronic diseases (e.g., diabetes, cardiovascular and gastrointestinal disorders). Population groups with complications and high mortality due to COVID-19 coincide with groups with an affected vitamin D status. Therefore, it is assumed that the suboptimal status of vitamin D may be related to complications and increased mortality rate due to SARS-CoV-2 infection. Vitamin D improves innate immunity supporting the response of macrophages to the pathogen invasion in the epithelial membranes, which reduces the frequency and severity of acute respiratory infections. A sufficient 25(OH)D level is crucial for macrophage activation and its conversion to calcitriol. Such an active form of vitamin D initiates the transcription of genes for the synthesis of antimicrobial peptides that act against microorganisms. Also, vitamin D regulates the cellular immune response and reduces cytokine storm, an event with high fatal potential in SARS-CoV-2-induced pneumonia. Therefore, vitamin D addition is considered needed in subpopulations with a risk of its deficiency and adverse outcomes of SARS-CoV-2 infection to achieve optimal vitamin D status as quickly as possible [10, 11]. One Indian research group reported that daily high oral dose of vitamin D (as many as 60000 IU) for 10 days had reduced the inflammatory biomarkers without any side effects in the treatment of COVID-19 [12]. Current knowledge is very scarce or even contradictory regarding the impact of vitamin D on the SARS-CoV-2 infection. However, there are trustworthy data on the positive effects of calcitriol in diminishing viral respiratory infections in persons with low status of vitamin D. Thus, vitamin D supplementation can certainly positively contribute to the treatment and outcome of COVID-19 disease.

According to the general recommendations, 10 µg (400 IU) of vitamin D3 should be taken daily between October and March, when the photochemical synthesis in the skin is reduced. Doses of 25 and 50 μg/day (1000 and 2000 IU/day) are indicated for persons with detected deficiency, and it could be achieved by dietary supplements. The safe upper level (SUL) of intake for vitamin D was revised to 100 μg (4000 IU) by EFSA in 2012 [13].

Zinc

Zinc is an essential trace element in the human body with a wide array of physiological functions. Meat, eggs, fish, legumes, some seafood (such as crab and lobster), cheese, some grains and seeds are rich dietary Zn sources. Dietary reference values for Zn have been set between 7.5-16.3 mg/day for adults, while the SUL has been defined by EFSA as well as the National Institutes of Health as a daily intake of 25 mg and 40 mg, respectively [14, 15]. Zinc plays a key role in cell division and protein production, supporting functions related to energy metabolism and growth; contributes to the normal function of the immune system and response to infectious diseases, preventing pathogen entry and preserving physical barriers such as the respiratory tract epithelium [16]. It also regulates developing leukocytes and lymphocytes from proliferation to maturation, as well as modulation of inflammatory responses [17]. As a component of many viral enzymes, proteases, and polymerases, Zn can stimulate various signaling events related to both innate and humoral antiviral responses [17]. Zinc has been shown to impair viral protein translation and prevent fusion with the host cell membrane [18]. It may also reduce the risk of bacterial co-infection by improving barrier function and mucociliary clearance [19]. Mild to moderate Zn deficiency is found, especially in the elderly, vegans/vegetarians and immunosuppressed subjects. It is important to distinguish between long-term Zn deficiency and Zn deficiency resulting from viral infection and prolonged immune response [20]. According to these facts, Zn may have different applications in COVID-19: 1) a preventive role in correcting Zn deficiency and improving immune function resulting in a decreased susceptibility to infections; 2) a therapeutic role in maintaining immune health during viral infection. In addition, COVID-19-induced anosmia/ageusia may reflect Zn deficiency locally or systemically, alteration in chemoreceptors responsible for gustatory or olfactory sensations or their combination. Zinc acts as one of the growth factors in smell and taste function, activating stem cells in both olfactory epithelial cells and taste buds [21]. Khani *et al*. also suggest that salivary enzyme carbonic anhydrases are zinc enzymes that play a vital role in maintaining taste and smell function. The high tropism of novel coronavirus for angiotensin-converting enzyme 2 (ACE-2) receptors expressed on neuron-supporting cells of the olfactory neuroepithelium may suggest a mechanism for disrupting both peripheric and central olfactory structures [21]. A 2021 systematic review and meta-analysis included 28 randomized controlled trials (RCTs), have shown conflicting evidence for the effects of Zn on the common cold in adults [22]. Some evidence supports that Zn might prevent acute viral respiratory infections symptoms and shorten the duration. At the end of 2021, 18 clinical trials have been performed and completed regarding the use of Zn alone or in mixture with other nutraceuticals and/or different drugs to prevent and treat COVID-19 (see ClinicalTrials.gov for ongoing studies). Different doses have been applied in studies, with a maximum amount of Zn-sulfate 220 mg (50 mg of Zn) twice daily. Currently, there is no sufficient data to recommend high-dose Zn. However, considering the direct antiviral properties and immune-modulatory effect, Zn should be helpful, especially for people with suboptimal status. Further clinical trials are needed to elucidate the potential role of Zn deficiency in COVID-19 susceptibility and determine the optimal dosage, timing and formulation before a final recommendation statement.

Selenium

Selenium is a essential trace element and component of 25 selenoproteins with a wide range of functions, including redox reactions and cell signaling; thyroid hormone metabolism; modulating the function of the immune system as well as diminishing inflammatory cytokine cascade [23]. The main dietary sources of Se are Brazil nuts, seafood, fish, eggs, poultry and beef. In foods, Se occurs in different forms, inorganic and organic, such as selenomethionine, selenocysteine, selenite and selenate [24]. The EFSA Panel on Dietetic Products, Nutrition and Allergies set an adequate daily intake for Se at 70 μg and SUL at 300 μg/day for adults [25]. There are no established reference ranges of biological marker(s) to assess Se status. Low selenium intakes are common across Europe, reflecting inadequate soil levels. The prevalence of suboptimal Se levels in the Serbian population is 50% [24]. Selenium supplementation appeared to reduce the incidence and severity of various viral infections, such as coxsackievirus B3, HIV-1, hepatitis B, hantavirus, polio, influenza [23]. Selenium, whether as particular redox-active Se species or selenoproteins, might counteract infection with SARS-CoV-2 by strengthening innate and adaptive immunity followed by moderating cytokine excess and reducing oxidative stress. The immunomodulatory properties of Se against viral infectious diseases include activation, proliferation, and differentiation of T-cells; enhancement of the lytic activity of NK cells; production and development of antibodies; preventing viral mutations as well as vasoconstriction and blood coagulation [26]. In an observational study conducted in Germany, critically ill patients received 1 mg of Se as selenite daily with combinations of different artificial nutrition [27]. During acute phase of COVID-19, high-dose Se without associated toxicity might be involved in inflammation reduction and cytotoxic immune response. These results need to be taken into consideration within the limits of a retrospective study. Moreover, Se status may influence human response to SARS-CoV-2 infection, especially in populations where its intake is suboptimal or low. However, several studies have reported inconsistent results regarding the association of the Se status with the incidence, severity, and mortality of COVID-19 [28]. The results have shown that Se status was significantly increased in COVID-19 surviving patients than deceased patients [29] and the importance of sufficient Se level for recovery from the disease [30]. Regarding the mentioned facts, Se at an appropriate dose might be useful in lowering the severity of symptoms and improving survival, but further studies are needed to clarify the clinical relevance, safety and side effects.

Omega-3 fatty acids

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) belong to the ω-3 family of fatty acids and are mainly found in high proportions in oily fish and concentrated oil preparations with fish oils, cod liver oil, or some algal oils. ω-3 FAs have been recognized as beneficial nutraceuticals in many acute and chronic diseases with elevated inflammation according to their anti-inflammatory and antioxidant properties [31]. They serve as substrates for the synthesis of signalling molecules (eicosanoids) and novel specialized pro-resolving mediators, such as protectins, resolvins, and maresins, which initiate the resolution of inflammation. Considering immune response, EPA and DHA modulate some of the functions of immune cells (i.e., macrophages, neutrophils, natural killer cells) and activate antigen-specific responses generating antibodies and long-term protection specific to repeated infection with the same invader [31]. Alongside the uncontrolled release of pro-inflammatory mediators, excessive intravascular coagulation commonly accompanies SARS-CoV-2 infection. ω-3 FAs are regarded to upregulate platelet homeostasis and decrease risks of thrombosis, which supports their promising effect in COVID-19 therapy. Higher COVID-19-related mortality has been experienced in some European countries and USA with a low omega-3 index (the sum of EPA+DHA in erythrocytes) [32]. A pilot study on 100 patients explored the correlation between the omega-3 index and COVID-19 endpoints. It was shown that patients with an omega-3 index higher than 5.7% were at about 75% lower risk for overall mortality than those below that value [33]. In a recent RCT, critically ill hospitalized patients with COVID-19 were supplemented with 400 mg EPA and 200 mg DHA daily (added to enteral feeding). Fourteen days of intervention resulted in significantly better multiple outcomes (e.g., improved parameters of respiratory and kidney functions), including a one-month survival rate compared with the control group [34]. Interestingly, results from a COVID-19 Symptom Study app using results from nearly half a million individuals indicate a moderate reduction in risk of testing positive for SARS-CoV-2 infection in those who use ω-3 FAs supplements [35]. Further clinical trials are required to confirm this evidence to establish any therapeutic recommendations for COVID-19.

α-lipoic acid

α-lipoic acid is an organosulfur compound biosynthesized by all living organisms, including humans. In addition to being cofactors of several mitochondrial enzymes, ALA, and its reduced form, dihydrolipoic acid (DHLA), act as a redox couple with unique properties. As an antioxidant, LA/DHLA acts as a scavenger of free radicals, redox-active transition metal chelator, regenerator of other endogenous antioxidants, inducer glutathione (GSH) synthesis, and modulator of signal transduction pathways [36].

ALA is present in small amounts in various foods, including red meat, organ meats, green vegetables, and potatoes. In contrast, medicinal products and food supplements contain chemical synthetized ALA in doses that are often up to several hundred-fold higher than its estimated daily dietary intake. Based on the clinical studies, oral ALA daily doses ranged from 100 to 1800 mg [37]. Besides well-established benefits in improving insulin sensitivity and management of microvascular complications of diabetes [38], due to its ability to mediate inflammatory pathways, ALA could be helpful in the prevention and treatment of cardiovascular, cognitive, neuromuscular, and many other disorders [39]. In addition, some evidence suggests the beneficial effects of ALA on both the specific and nonspecific biochemical, immunological, virological, and neurological markers related to viral infections [40]. Since SARS-CoV-2 affects other organs besides the respiratory system, including the heart, kidneys, and the CNS, ALA has attracted attention as a potential additional therapy in COVID-19 [37, 40, 41].

From a mechanistic point of view, ALA as an antioxidant might diminish oxidative stress, the SARS-CoV-2 entrance into the cellular matrix, and inflammation. Also, by enhancing GSH, ALA could indirectly boost the immune system [37]. A decrease in GSH levels is proposed as a possible risk marker for the severity of COVID-19 and lung damage upon admission, and also is the feature of aging and concomitant diseases (obesity, diabetes mellitus, and hypertension), with an influence on the development of COVID-19 severity [42]. As a glutathione-boosting nutraceutical promoting GSH synthesis, ALA may represent a valuable approach for cytokine storm syndrome caused by SARS-CoV-2 infections [43]. Additionally, ALA could play a role in preventing olfactory disorders in patients with COVID-19. The use of ALA for this purpose is based on the finding of moderate improvement in smell in patients after upper respiratory tract infection [44]. However, by the consensus of the British Rhinological Society, ALA is not suggested as a co-therapy in patients with loss of smell as an insulated symptom for more than two weeks [45].

Overall, although it considers a promising potential adjunctive therapy for COVID-19, only one study validated the clinical efficacy and safety of intravenous administration of ALA (1200 mg/day) in patients with critically ill COVID-19 [46]**.**

Quercetin

Polyphenols are secondary bioactive metabolites synthesized exclusively in plant tissues. Quercetin belongs to one of the major subclasses of flavonoids, i.e., flavonols. The highest concentrations of this bioactive compound are present in onions. Although black tea, berries, apples and wine contain low quantities of QUE, these sources are frequently consumed and may contribute to a higher intake of this compound [47]. Quercetin is available as a dietary supplement in daily recommended doses between 200-1200 mg and through functional foods/nutraceuticals (10–125 mg per serving) [48]. The bioavailability of quercetin after oral consumption is considered to be low. Nevertheless, its absorption could be increased by different delivery-food grade systems [49]. Numerous studies suggested a strong link between a QUE-rich diet and a decreased incidence of various chronic diseases [50]. Three main properties characterize quercetin: antioxidant, anti-inflammatory and immunomodulatory [49]. This bioactive compound promotes increasing antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase) and nonenzymatic antioxidants (vitamins C and E and GSH) as well as the expression of specific pro-inflammatory mediators and chemokines [51]. Quercetin is a nuclear factor erythroid-derived 2-like 2 (NRF2) agonist, and NRF2 is responsible for repealing the replication of SARS-CoV-2. It is found to repress viral replication by inhibiting 3C-like proteases inside the cells. In addition, QUE inhibits the entry of virions into the host cells by changing viral spike protein or ACE2 and inflammatory processes stimulated by interleukin-6 (IL-6) signals, nuclear factor kappa B (NF-κB), and inflammasome [52]. Therefore, QUE is recognized as the most promising alternative therapeutic/preventive anti-COVID-19 candidate.

Up to date, six clinical studies on QUE alone or in combination with other active ingredients have been performed and completed in patients with COVID-19 [53]. The interim results from one of the completed RCTs revealed that QUE supplementation partially reduced the severity of clinical symptoms and negative predictors of COVID-19 [54]. There is growing evidence that QUE, combined with vitamins C and D, may exert a synergistic antiviral activity due to overlapping immunomodulatory and antiviral properties [55, 56]. Further investigations are needed to fully exploit QUE and its potential to enrich the drug options against coronavirus infections.

Probiotics

Probiotics are live microorganisms that can positively affect the host when given an adequate dose [57]. Clinical evidence suggests that different probiotic strains may play a role in preventing certain bacterial and viral infections, including respiratory infections, gastroenteritis, and sepsis [58]. Probiotics effectively regulate the innate and adaptive immune response by regulating the functions of macrophages, dendritic cells, T and B lymphocytes and reducing inflammation [59]. Recent studies with COVID-19 patients indicate changes in the fecal microbiota composition, i.e., increasing opportunistic bacteria and decreasing the abundance of beneficial commensals such as *Lactobacillus* spp. and *Bifidobacterium* spp. [60, 61]. Additionally, literature data has proposed an association between gut microbiota composition, secondary intestinal infection, and COVID-19 disease. Furthermore, dysbiosis was significantly linked with the severity of COVID-19 [62]. Probiotics may have direct and indirect antiviral effects, including activity against different forms of coronavirus [63]. The ability of probiotics to interact with ACE2 receptors, which play a crucial role in SARS-CoV-2 pathogenesis, is also discussed [64]. A retrospective clinical study of 375 patients with COVID-19 infection showed that the addition of an oral probiotic to standard drug therapy was more efficient than drug therapy alone in terms of clinical outcomes (e.g., the shorter time required for clinical improvement, reduction in fever duration, and duration of hospital stay) [65]. In another retrospective, observational cohort study that involved 200 adult patients with severe COVID-19 pneumonia, using a commercial probiotic mixture was associated with a lower risk of death [60]. Another study, in which the same commercial probiotic combination was used, resulted in remission of diarrhea and other symptoms within 72 hours in almost all COVID-19 patients, compared to the control group [60]. A meta-analysis of RCTs involving about 2.000 patients has shown a significant benefit of probiotics in preventing ventilator-induced pneumonia [66]. However, recommendations for using oral probiotics in the treatment of high-risk patients who have COVID-19 should be more investigated. Although certain commercial probiotics have found to be effective against other coronaviruses, their efficacy in treating patients with COVID-19 has not yet been confirmed. The rationality for using probiotics in COVID-19, up to date, comes from indirect evidence. In the ClinicalTrials.gov database, 19 registered clinical trials are still ongoing and aim to explore the effectiveness of specific probiotic strains in treating COVID-19 infection. Accordingly, probiotics' preventive or medicinal role for patients with COVID-19 will be much more evident when the results of these studies become available.

CONCLUSION

Adequate nutrition is essential to support the immune system health and may associate with progression and outcomes in individuals with SARS-CoV-2 infection. Micronutrients such as vitamin C, vitamin D, Zn and Se play an important role in managing COVID-19. Based on the current evidence, ω-3 fatty acids, alpha-lipoic acid, quercetin and probiotics, have promising effects in COVID-19 therapy, although complementary studies are warranted to affirm their benefits. **Figure 2** summarizes potential beneficial effects of nutraceuticals in COVID-19 management.

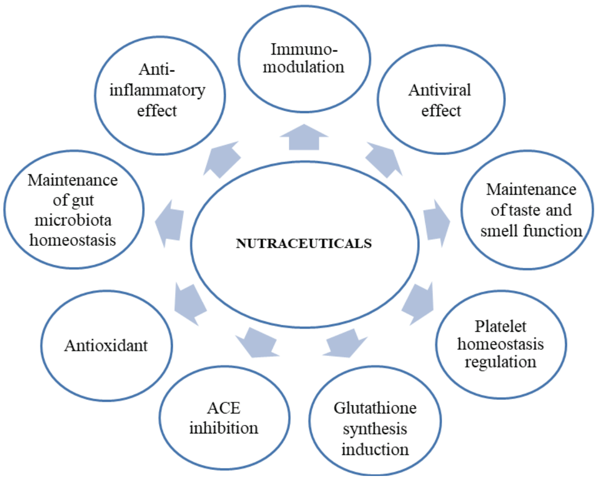

Figure 2. Nutraceuticals and therapeutic potential in COVID-19.

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Nutraceutici u prevenciji i tretmanu COVID-19

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Kratak sadržaj

Imunski sistem štiti organizam od brojnih patogena (bakterija, virusa, gljivica, parazita) uključujući veliki broj specijalizovanih tipova ćelija, komunikacionih molekula i funkcionalnih odgovora. Pojačana aktivnost imunskog sistema usled infekcija praćena je povećanim metaboličkim aktivnostima, što zahteva izvore energije, supstrate za biosintezu i regulatorne molekule. Brojni vitamini i minerali imaju ključnu ulogu u podršci imunskom sistemu i smanjenju rizika od infekcija. Ostale bioaktivne komponente kao omega-3 masne kiseline, probiotici i antioksidansi (alfa-lipoinska kiselina, kvercetin) takođe su od značaja u imunološkom odgovoru. COVID-19 karakterišu kliničke slike od blagih simptoma do teške infekcije respiratornog epitela praćene citokinskom olujom. Pokazano je da starije osobe sa hroničnim bolestima imaju smanjenu aktivnost odbrambenog sistema i neadekvatan nutritivni status, zbog čega postoji veći rizik za pojavu fatalnih ishoda. Ispitivanja ukazuju da su vitamin C, vitamin D, cink i selen posebno važni u odbrani od infekcije SARS-CoV-2. Disbioza creva je karakteristika mnogih zaraznih bolesti uključujući COVID-19, zato su dijetetski pristupi za uspostavljanje zdrave mikrobiote važni u poboljšanju imunoloških funkcija. U ovom radu prikazan je pregled literature o ulozi i potencijalnoj primeni odabranih nutraceutika u prevenciji i tretmanu COVID-19.

Ključne reči*: COVID-19; SARS-CoV-2; imuni sistem; mikronutrijenti; biološki aktivni sastojci.*