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Review Article

A Review on Dietary Additive, Food Supplement and Exercise Effects on the Prevention of Covid-19

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ABSTRACT

Due to the lack of definite therapy and prevention protocols for Covid-19, nutrition and exercise are considered preventative measures in dealing with the epidemic. Healthy diets, dietary supplements and exercises boost the immune system. These factors can be effective in improving functions of the immune system. The current study investigated immune-enhancing characteristics of exercises, dietary supplements (proteins, vitamins, minerals, oils, coenzyme Q10 (CoQ10), probiotics, ginseng, antioxidants and *Chlorella vulgaris*) and food additives (titanium dioxide, sodium nitrite, monosodium glutamate, tartrazine, sweeteners and emulsifiers). The current study investigated functions of dietary supplements and exercises in strengthening the immune system, as well as assessing roles of food additives in illness prevention, particularly Covid-19, when combined with a balanced nutrition strategy. Light exercises, healthy lifestyles and nutritional supplements have been shown to boost the immune system.

Keywords: Covid-19, Dietary Supplement, Exercise, Food additive, Immune System

Introduction

In December 2019, the World Health Organization (WHO) received a report of a novel disease, Covid-19. Director-General of the WHO has announced the emergence of a novel disease spreading through the globe (1). The most common Covid-19 symptoms include fever and cough, muscle weakness and fatigue, respectively (2). The disease major symptoms include acute respiratory distress syndrome, which affects the lungs as the major organs. Symptoms occur approximately nine days after the onset of the infection. In addition, the virus causes damages to other body organs such as heart, kidneys, liver, eyes and central nervous system (CNS) (3). Neurological consequences of the coronavirus infection include confusion, amnesia, anosmia, nerve pain, seizure and stroke (4). The current emergence and prevalence of this disease are considered as emergent dangerous conditions for the public health at international levels (5). The immune system includes chemicals, cells, tissues and organs that combat unwanted intruders such as bacteria, viruses and fungi, as well as stopping cancer cells (6). The body first line of defense is anatomical defense (skin and mucous membranes), physiological conditions (low pH, temperature and chemical mediators) and cellular defense (macrophages, multinucleated leukocytes and dendritic cells), followed by natural killer cells (NK), inflammatory components (cytokines, interferons, supplements, defensins, leukotrienes, acute phase proteins and prostaglandins), macrophages and neutrophils, which are responsible for providing innate immunity in the fight against infiltrating agents to the body (7).

Researchers should investigate use of treatment regimens in similar illness patterns since antiviral treatments and vaccinations, which are regarded fast

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countermeasures, are not still fully available worldwide and are still clinically studied (8, 9). Healthy diets, dietary supplementations and physical workloads, especially exercise activities, can affect components and functions of the immune system (10). Exercises, in general, play essential roles in illness prevention as well as growth and enhancement of physiological and hormonal systems. The immune system is closely linked to cardiovascular, nervous, respiratory and muscular systems and therefore affected by exercises and appropriate diets (11). Exercises can create beneficial changes in the immune system; thus, they are considered as psychological and physiological stresses. Exercises promote B cells (B lymphocytes) generation and secretion by increasing the activity of metabolic factors, which increase serum immunoglobulins (12).

Studies have reported increases in serum immunoglobulins after physical activities, regular exercises and nutritional supplements, which are linked to the sympathetic system increased activities (11). Another study reported that immunoglobulin levels were higher in people who were more involved in physical activities than those who were less involved in physical activities since serum immunoglobulin A (IgA) levels increase in people with higher physical activity, which is likely due to the entry of immunoglobulins into the bloodstream from their previous locations (11). Nutrition plays vital roles in athletes' success and returning to the original state after exercises. By the advancements in science of exercise physiology, metabolism and nutrition, it has been verified that diet and nutritional intake affect athletic performance. Since greater calorie consumptions are significant and general signals in all athletes compared to the general population, there is a growing focus on nutrition, particularly supplements (13). Exercises and dietary supplements are tightly connected together, used for their beneficial and substantial effects on life quality. These supplements include favorable effects on the consumer immune system, health condition, vigor and energy. Considering their roles in increasing health status, quality of life, immunity, working hour and physical strength, such supplements are increasingly used by ordinary people. Therefore, the major aims of the current study were to investigate relationships between healthy diets, dietary supplementations and exercises as well as combined effects of these factors in increasing the body immunity against diseases, especially Covid-19.

Effects of exercises on Covid-19

In response to the spread of Covid-19, WHO urges individuals to improve their physical and mental health whenever possible. Alternatively, people should continue to improve public health and safety in their communities (14, 15). Cross-sectional human studies have shown that exercises can profoundly affect the immune system (16). It is shown that improving physical fitness and immunity through moderate-intensity exercises could improve immune responses to vaccination, decrease chronic inflammations and improve immune markers against various diseases, including cancers, HIV, cardiovascular diseases (CVDs), diabetes, cognitive impairments and obesity (17). However, these immune system mechanisms depend on the intensity, duration and type of exercises (15). As shown in Figure 1, results of these studies on exercise immunology have shown that regular moderate-intensity short exercises (up to 45 min) boost the immune system, while repetitive, prolonged high-intensity exercises (more than 2 h) can suppress the immune system (18).

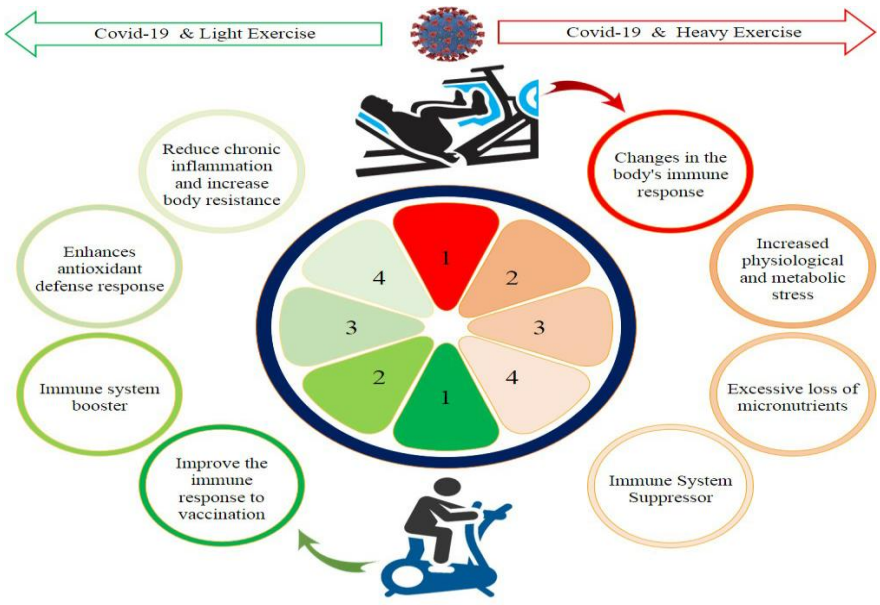


Figure 1. Comparison between the effects of light and heavy exercises on immune system

Numerous studies have reported that multiple immune system activities are temporarily disturbed as a result of acute, long-term acute assaults and chronic exercises since they affect the body immune response and may lead to the loss of essential micronutrients in the body (19). Studies have revealed that daily exercises boost antioxidant defense responses (20), which may improve immune system functions against diseases such as Covid-19. Other studies have demonstrated that modified exercises include anti-inflammatory effects on the immune system and can help fight diseases (21). However, in professional athletes, the immune system changes as a result of prolonged activities and hard trainings do not result in similar decreases in immunity as others do (22). Therefore, ways to increase the immune system potency to counteract strenuous exercises in people can include dietary supplements, adequate rests and healthy foods.

Effects of dietary supplements on Covid-19

Proteins

Proteins are essential as sources of energy and essential amino acids (EAAs). In addition to their nutritional roles, dietary proteins can positively affect health by releasing biologically active peptides. In recent years, clinical and experimental studies on the hydrolysis of proteins or biologically active peptides to generate value-added meals have been interested by the scientists and the food businesses worldwide (23). Generally, bioactive peptides are oligopeptides that are inactive in the protein molecule sequences but are released through enzymatic hydrolysis, fermentation and digestion in the gastrointestinal tract (GIT), developing a dynamic nature (24). Compared to other proteins, whey protein (WP) and branched-chain amino acids (BCAAs) are more effective in physiological systems and include active ingredients and fast digestibility and absorption. Therefore, to increase nutritional value, they are used in various foods such as ice cream, bread and milk in food industries. Furthermore, athletes are benefitted from these compounds during exercise and recovery periods (25). Whey peptides are useful molecules derived from amino acids (AAs) removed from higher WP sources. These isolated whey peptides provide benefits such as increased secretion of insulin-like growth factor, overall improvement of endocrine hormone response, increased nitrogen use, increased intracellular glutathione and improved performance of anti-aging antioxidants as well as improving immune functions by improving gastrointestinal health functions, increasing muscle growth rates and increasing body abilities to fight diseases (26).

Decreases in the most important secretory immunoglobulins such as salivary immunoglobulin A cause upper respiratory tract infection (URTI). The immunoglobulin is a protein in nature, preventing and resisting respiratory tract infections (RTIs), which is closely linked to symptoms of the Covid-19 epidemic (27). Glutamine supplements are used by the athletes to increase efficiency during training and accelerate recovery (28). A study on glutamine supplementation and immune system responses in athletes showed that glutamine supplementation significantly increased the IgA level, leading to the prevention of RTIs, one of the most common symptoms of Covid-19 (Table 1) (29). The α-lactalbumin and immunoglobulin G (IgG) are present in whey and milk, providing beneficial effects to the immune system (30). Previous studies revealed that cow milk could modulate the immune response in humans (31). These factors lead to further preventions, increasing the immune system ability to fight diseases such as Covid-19 (32). Studies have shown that proteins, especially WP, may include further comprehensive uses as functional foods in prevention and control of diseases such as cancers, hepatitis B disease, human immunodeficiency virus (HIV) infection, CVDs, osteoporosis and chronic stress (33). The WP may help prevent allergies as well (34).

In HIV, patients usually include low glutathione levels (GSH). Glutathione is a potent antioxidant that protects important cellular components from reacting with oxygenated functional groups such as free radicals and peroxides. Several studies have assessed whether WP could include beneficial effects on GSH levels in HIV-positive patients. For example, 18 participants were randomly selected to receive WP (45 g daily) from two various products over six months (Table 1). Results showed that only one product significantly increased GSH levels, preventing and fighting diseases, especially viral diseases (35). As shown in Table 1, studies have reported that use of BCAAs strengthens the immune system against inflammation and infection and these AAs are able to regulate immune responses optimally (36).

Table 1. Effects of dietary supplements and their ingredients on immune responses

Nutrients	Types	Main Effects	Ref
Proteins	WP	Significantly increases GSH levels, which could prevent and fight diseases, wildly viral diseases.	(35)
	Glutamine	Showed that glutamine supplementation significantly increased the IgA level.	(29)
	BCAAs	Strengthens the immune system against inflammation and infection.	(36)
Vitamins	D	Decreases the risk of viral infections.	(41)
	E	One of the essential and main elements of the antioxidant defense.	(44)
	C	Vitamin C is essential for the production of white blood cells.	(40)
	A	An immune system booster against diseases, especially infectious disease.	(50)
	K	Growth suppression and apoptosis	(50)
Minerals	Zn	Decrease the incidence of pneumonia	(39, 54)
	Fe	Effect on red blood cells	(56)
	Cu	Breakdown of the viral envelope and scattering of the virus surface structure.	(58)
CoQ10	-	Decrease the inflammatory effects of viral diseases.	(85)
Probiotic	-	Decreased the bacterial load in the lungs as well as lung damage and systemic inflammation.	(94)
Ginseng	RGE	Consumption of the RGE improves the survival of immune cells.	(95)
	Ginsenoside	PT-type ginsenosides protect the immune system against viruses.	(100)
Antioxidants	-	Antioxidants regulate the production of proinflammatory cytokines and sepsis associated with Covid-19-induced ARDS.	(107)
Chlorella vulgaris	-	The nASX includes positive effects in decreasing cytokine storm, acute lung injury, acute respiratory syndrome, etc.	(8, 107, 121)
Food additive	Titanium Dioxide	Decrease the immunity of the lungs.	(121)
	Sweeteners	Lead to symptoms such as inflammation of the intestines, chronic fatigue, obesity and cancer.	(125)
	Saccharin	Decreases the secretion of peptide 1 such as glucagon (GLP-1).	(129)
	Emulsifiers	Increased pro-inflammatory potentials and causing metabolic disorders.	(132)
	Sodium nitrite	Production of H2O2, which can cause tissue damage and inflammation.	(134)
	MSG	MSG includes a direct toxic effect on neutrophils.	(136)
	Tartrazine	Tartrazine causes severe allergic reactions in people with asthma.	(136)
Oils	Omega 3	Anti-inflammatory characteristics. The EPA and DHA supplementation in Covid-19 patients includes a potentially beneficial effect in managing a "cytokine storm."	(69, 74)
	Omega 6	Derivatives omega 6 (HODEs, Oxo-HODEs, epoxy – HODEs) cause LA inflammation and affect the immune system.	(75)
	Omega 9	Decreases pro-inflammatory cytokines and increases bacterial clearance.	(72, 73)
	SFA	Increased risk of atherosclerosis, coronary heart disease, obesity and metabolic syndrome.	(76)

Vitamins

Extensive advertisements have not only increased access to vitamins but significantly increased their high popularities within the people. Most people use multiple vitamins daily to treat or prevent chronic diseases and specifically athletes use vitamins to increase their performance and recovery. Multiple vitamins, especially vitamin C, include high consumption rates in athletes as well as general publics. A study showed that vitamin C supplementation significantly increased the IgA level which could prevent RTIs, including positive effects such as increased immunity and resistance to diseases such as Covid-19 (37). Other studies of vitamin C supplementation on soccer players have shown that vitamin C intake and exercise can increase IgA levels (38). The authors' studies have shown that vitamin C can boost the immune system, decrease the risk of infectious diseases, significantly decrease cortisol, improve immune system indicators and be a barrier to infectious diseases by increasing IgA and IgG levels (39). Vitamin C is essential for producing white blood cells (WBCs) and includes positive effects in preventing URTI. Driel et al. (2019) reported that vitamin C decreased the occurrence of URTI and production of

immunosuppressive hormones such as cortisol and adrenaline. Technically, URTIs include effects similar to those of Covid-19 (Table 1) (40).

Studies of vitamin D have shown that this vitamin includes immunomodulatory characteristics as vitamin D has been considered a substance that decreases the risk of viral infections in several studies (41). Vitamin D (Table 1) decreases risks of microbial infections through a variety of mechanisms. One of these mechanisms is the activation of antimicrobial systems. Recent studies have verified effects of vitamins in the treatment and prevention of Covid-19 (42). A clinical trial reported that vitamin D supplementation (4,000 IU/d) per month decreased effects of dengue virus infections (43). Mansueto et al. (2015) showed that the prevalence of vitamin D deficiency in HIV-infected patients ranged 70–85% (44). Vitamin E is a fat-soluble antioxidant and one of the essential and primary antioxidants (45). Epidemiological studies have shown that vitamin E deficiency increases viral pathogenicity and decreases efficient immune responses. Studies on animal and human nutrition models have shown that vitamin E deficiency damages humoral and cell immune functions, especially in T cells (46). Vitamin E supplementation may include simultaneous effects on increasing immunity and decreasing inflammation caused by viral diseases, which can include beneficial effects on strengthening the immune system and preventing diseases, especially Covid-19 (47).

Previous studies have demonstrated the relevance of vitamin A to immunological functions and infection preventions. Based on these studies, vitamin A insufficiency is a serious public health concern in developing and occasionally wealthy nations (48). Vitamin A plays roles in promoting the immune system and its deficiency is associated with viral diseases such as measles and viral diarrhea. Vitamin A as a dietary supplement improves disease prevention and decreases mortality rates in people with malaria, lung disease and HIV (48). Therefore, the vitamin can be referred to as an immune system booster against diseases, especially infectious diseases. Recent studies have demonstrated roles of vitamin K in regulating immune responses as well as possible links between its deficiency and inflammatory diseases and some cancers (49). Over the past years, studies have reported anti-proliferative effects of vitamin K (K1, K2 and K3) on cancer cells. Vitamin K2 includes antitumor effects (growth suppression and apoptosis) on lungs, ovaries, liver, prostate and bone marrow cancers, which can help Covid-19 patients improving immunity of lungs (Table 1) (50).

Minerals

Although minerals do not produce energy, they are active through the body and affect the body organ functions. For example, their presence in tissues and fluids is essential for the body, maintaining physicochemical processes (51). Antiviral mechanisms of zinc (Zn) against viral diseases are realized majorly through physical barriers such as uptake of viruses, decrease of infections and inhibition of viral enzymes such as proteases (52). Zinc has been reported to effectively inhibit the RNA synthesis activity of nidoviruses, including coronavirus (SARS-CoV), *in vitro* (53). Furthermore, Zn helps regulate thymulin activity, increase T cell count, increase normal immune cell cytotoxicity, decrease infections in children, decrease pneumonia and decrease duration and severity of cold symptoms (39, 54). Risks of diseases such as bacterial, viral and fungal infections (especially diarrhea), pneumonia, diarrhea and respiratory diseases increase in Zn deficiency (Table 1) (55).

Anemia can be resulted from functional changes in iron (Fe) mechanisms and their effects on red blood cells (RBCs). These changes may be associated to the entry of viruses such as coronaviruses into the body (Table 1) (56). Anemia decreases the tissue oxygen supply, it can play essential roles in causing organ failure, it is essential to understand relationships between the anemia, Fe metabolism and progression of Covid-19, whether these relationships differ in terms of age, sex and presence of chronic conditions (57). Taneri *et al.* reported several concerns regarding Fe supplementation to prevent and treat Covid-19 and addressed necessity of further studies (57). Another element, copper (Cu), includes the potential to neutralize infectious viruses such as bronchitis, polio and HIV-1 viruses as well as other enveloped and non-enveloped viruses with single or double-stranded DNA or RNA (58). Copper exposure to human coronavirus 229E destroyed the viral genomes. Changes included breakdown of the viral envelope and scattering of the virus surface structure (Figure 2) (58). Coronavirus has been reported to be highly sensitive to Cu ions (59).

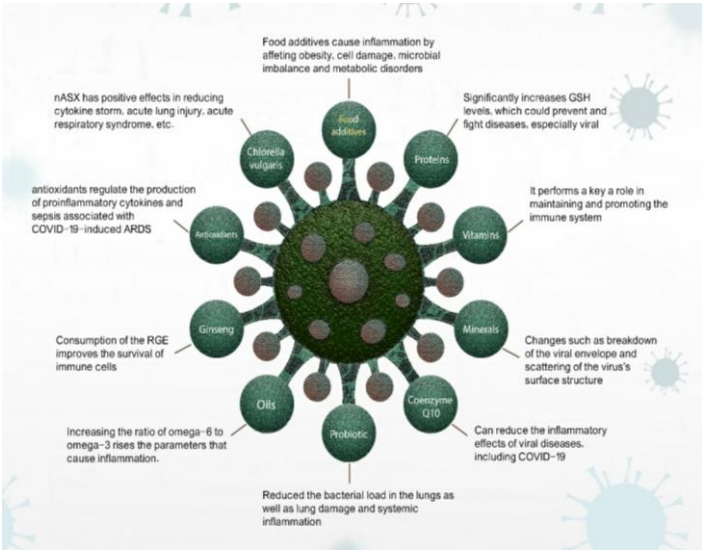


Figure 2. A summary of the function and effects of dietary supplements and food additives

Oils

Omega-3 unsaturated fatty acids (UFA) are a group of long-chain fatty acids (LCFAs) that benefit human health such as improving immune system parameters and regulating blood lipids and neuromuscular functions (60). Ergogenic aids may help athletes improve their performance or help prevent injury during strenuous exercises and post-workout muscle recoveries (61). Omega 3 has recently been considered as an ergogenic supplement. While it decreases exercise-induced inflammation, the compound contributes to muscle health, energy availability and increased immunity (62, 63). Studies have been carried out on effects of dietary polyunsaturated fatty acids (PUFA) on the immune system functions and results have demonstrated that omega-3 derived metabolites include significant effects on the regulation of immune system (64). These metabolites are generally known as metabolic mediators and can be classified into various groups such as prostaglandins, leukotrienes, thromboxanes, maresins and resolvins (65). Evidence for the anti-inflammatory effects of omega-3 fatty acids (FA) in macrophages demonstrates that omega-3 FAs are absorbed into macrophage cell membrane phospholipids, increasing their phagocytic ability. Based on the available data, it seems that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplementations in Covid-19 patients include potentially beneficial effects in managing cytokine storms (Figure 2) (66).

Cytokines are small proteins that modulate the immune response to traumas, infections and conditions such as cancers. Other functions of cytokines include inflammation activation, which is a part of the healing process (67). However, sometimes body produces too much cytokines, leading to severe inflammations and tissue damages, common symptoms in Covid-19 and omega-3 can help modulate these effects. It strengthens the immune system against diseases with effects similar to those of Covid-19 (68). Therefore, use of EPA and DHA supplementations should be considered as a supportive treatment and a prevention strategy in SARS-Cov-2 infection (69). The EPA and DHA supplements can alter biological pathways that may include direct effects on Covid-19 outcomes (69, 70). Overall, decreasing expression of excessive proinflammatory cytokines and modulating their secretion may include beneficial effects on boosting the immune system, decreasing effects of Covid-19 and improving disease prevention. In addition to omega-3 supplements used by the athletes and public people, substances such as saturated fatty acids (SFA), omega 9, omega 6 and omega 3 can be essential in disease prevention, improving the immune system. Clinical studies have shown that the location and organization of FAs within cellular fats directly affect behaviors of the proteins involved in the activation of immune cells such as the production of proteins associated to T cell responses, antigens and FA derived from inflammatory mediators (71). Based on Table 1, omega 3 and omega 9 include positive effects on increasing strength of the immune system. In a study on the effects of omega 9, this oil decreased pro-inflammatory cytokines, increased bacterial clearance and modulated sepsis and inflammation effects (72). consuming oils rich in oleic acid such as olives can positively boost the immune system (73). Omega 6 includes a favorable proportion in the diet due to its presence in oils consumed by the people, especially in corn oil. Intakes of omega 6 and omega 3 are important and should be consumed in the right balance. Excessive omega-6 intake in diets can lead to inflammatory responses (Figure 2) (74).

Omega-6 UFAs are the most important PUFAs in the membranes of cells involved in inflammation. Studies have shown that high omega-6 intakes can decrease omega-3 anti-inflammatory characteristics (Table 1) (74). Linoleic acid (LA) is metabolized by lipooxygenase (LOX) to produce derivatives such as hydroxyctadecadinoic acids (HODEs) (e.g., 9 and 13-HODE), mostly oxo-HODEs (e.g., 9-oxo-HODE and 13-oxo-HODE) and epoxy-HODEs. These derivatives cause inflammation by LA, affecting the immune system (75). Compared to the functions of omega 3 and omega 6, omega 3 includes anti-inflammatory characteristics. It is suggested that omega-6, especially LA and its derivatives, can decrease anti-inflammatory characteristics and lead to inflammation by replacing the cell membrane with omega 3. It is noteworthy that omega 3 and omega 6 include direct effects on each other and their derivatives include competitive effects on each other characteristics. Furthermore, LA has been shown to limit EPA synthesis of alpha-linolenic acid in humans (76). The SFAs such as palmitic acid (PA) (C16: 0), lauric acid (LA) (C12:0), myristic acid (MA) (C14:0) and stearic acid (STA) (C18:0) can include negative effects on the immune system (76).

Increased SFA intakes from the processed foods are associated to increased risks of atherosclerosis, coronary heart disease, obesity and metabolic syndrome (Table 1) (76, 77). During the recovery period for diseases, especially coronavirus disease, health of organs such as heart can significantly increase the rapid healing power. In general, there should be a balance in consumption between the SFAs and UFAs to modulate the immune system. In absence of this balance, SFAs can activate pre-inflammatory factors and cause inflammation (Table 1) (78). The SFA-rich diets (HFD-S) have been shown to interfere neutrophil and granulocyte functions, decrease their survivals and increase bacterial proliferations (76). Unbalanced omega-6 intake and excessive intake of SFAs can increase inflammations and risks of diseases. It is noteworthy that studies have

reported decreases in the number of neutrophils due to the use of SFAs, which can be due to the efficacy of this substance in the treatment of illnesses, especially coronavirus (76, 79). In general, it is suggested that consumption of healthy foods becomes further popular to prevent diseases and increase the immune system strength. To limit intakes of processed meals, ready-to-eat foods and quick foods, further education is needed (79, 80). People involvement in Covid-19 and paying more attention to health and increasing the body immunity have led to medical and nutritional recommendations. Therefore, it can be predicted that further attention is paid to the consumption of dietary supplements in the future. As presented in Figure 2, dietary supplements and healthy nutrition with no industrial food additives include beneficial effects that increase the body immune system in preventing diseases as much as possible.

Health benefits of other supplements

Coenzyme Q10

The CoQ10 is essential for transferring electrons from the electron transport chain to produce ATPs. The reduced form of the biochemical (ubiquinol) acts as an essential antioxidant in the body. Regarding these functions, CoQ10 supplementation includes beneficial effects on human health (81). Although researches have shown that moderate-intensity exercises are good for the immune system, strenuous exercises for the elite athletes can damage the immune system, making them further susceptible to infections. Oral intakes of compounds that decrease these components can decrease muscle damages and therefore consumption of such supplements is useful for the athletes (82). Further studies on CoQ10 deficiency and its effects on immune system functions are necessary. However, mitochondrial dysfunction associated with increases in risks of infections and possibly immunodeficiency due to CoQ10 deficiency has been reported in previous studies (83). Diagnosis of CoQ10 deficiency should be considered in patients with recurrent infections and symptoms of metabolic diseases. The CoQ10 levels decrease in acute and chronic diseases, leading to decreased cellular energy production, increased free radicals and weaken immune system. Moreover, this decrease causes further damages to mitochondria and affects their functions (84). It has been hypothesized that CoQ10 levels decrease in acute influenza infections and reported that approximately 50% of the patients exposed to influenza had lower CoQ10 levels during the recovery, compared to that the healthy people had (85). The CoQ10 levels have been reported to be inversely linked to inflammatory factors in patients with influenza. In these patients, CoQ10 levels are significantly associated to several biological and inflammatory parameters and thus the biochemical presence can decrease inflammatory effects of the viral diseases, including Covid-19 (Table 1) (86).

Probiotics

Taking probiotic-based supplements is a way to enhance performances of the people internal organs such as stomach, intestines and heart (86). Probiotics are "active and living microorganisms that produce effective health benefits if taken in moderation". Lactic acid bacteria (LAB) such as *Bifidobacteria* spp., *Pediococcus* spp., *Leuconostoc* spp., *Streptococcus* spp., *Saccharomyces* spp., *Bacillus* spp. and *Enterococcus* spp. are probiotic strains commonly used in these supplements (87). Previous studies have reported that probiotics include positive effects on public health and increase athletic performance. Examples of these effects include losing weight, lowering cholesterol levels and having anti-inflammatory and bacterial effects (88). Other studies have reported that probiotics can produce ATP by increasing carbohydrate metabolism (89). Moreover, studies have demonstrated that probiotic supplements can effectively improve athletic performance and help athletes during their recovery (90). Regarding immunity, probiotics are useful in fighting various diseases, including viral infections. Evidence for the antiviral activity of probiotic strains against common respiratory viruses, including influenza, rhinovirus and respiratory syncytial virus (RSV), have been collected from clinical and experimental studies that may help cure and prevent the Covid-19 epidemic (91). While none of these effects or mechanisms have been assessed on the novel SARS-CoV-2 virus, this should not be ruled out considering the results of studies and probiotic mechanisms of action, especially when studies have reported effects of probiotics against other coronaviruses (92). Probiotics have been reported to decrease diarrhea severity in preclinical trials and help treat viral hepatitis (93). Furthermore, patients infected with the virus may experience secondary bacterial infections. A recent mice study showed that oral *Lactobacillus acidophilus* CMCC878 administration decreased the bacterial loads in the lungs as well as decreasing lung damages and systemic inflammations, 24 h after pulmonary inoculation of *Pseudomonas aeruginosa* and *Staphylococcus aureus*; as suggested for human Covid-19 (Table 1) (94).

Ginseng

Korean ginseng (Panax ginseng) is one of the most popular medicinal plants used in traditional medicine in East Asian countries, including South Korea. Ginseng contains various nutrients with medicinal characteristics such as ginsenosides, polysaccharides, polystyrenes, phytosterols and essential oils; from which, ginsenosides are the most important bioactive compounds. This is why this substance is used in dietary supplements for exercise

(95). Recent studies have reported that caffeine (5 mg/kg) and ginseng (200 mg, Panax) supplementation one hour before the exercise include positive effects on physiological parameters and improve running (96, 97). Recent studies on the immune-boosting and disease control characteristics of ginseng reported that Korean red ginseng extract (RGE) was used to treat HIV, meaning that RGE may be another treatment for HIV-1 patients (97). Specific studies have been carried out to demonstrate the antiviral activity of RGE and its pure ginseng compounds on influenza A virus infection *in vitro* and *in vivo*. The RGE-based treatment of influenza A virus improves the survival of immune cells, resulting in decreased cytokine secretion from the virus, which can strengthen the immune system against Covid-19 (Figure 2) (95).

Hepatitis B virus (HBV) is a double-stranded DNA virus belonging to Hepadnaviridae family. There are various studies on the antiviral effects of ginsenoside Rg3 on HBV. Ginsenoside Rg3 extensively controls the secretion of HBsAg, HBeAg and viral particles in HBV-infected HepG2.2.15 cells (95, 98). Rhinovirus is the leading cause of common colds with symptoms similar to those of Covid-19. Rhinovirus is a virus that spreads from person to person by direct contacts and infects the URT (99). Song et al. (100) investigated the antiviral effects of protopanaxatriol ginsenosides (PPT) and protopanaxadiol ginsenosides (PPD) on rhinoviruses. They reported that PT-type ginsenosides protected the immune system against viruses and increased their performance (Table 1) (100). Norovirus is a single-stranded RNA virus that causes symptoms of nausea, vomiting, abdominal pain and diarrhea in humans. The active pure ginseng substances include beneficial effects in treating diseases caused by this virus (46, 101). In one study, RGE and ginsenosides were shown to cause secretion of antiviral proteins in Crandell Reese feline kidney (CRFK) cells infected with feline calicivirus (FCV). The induced protein included a significant antiviral activity and increased the body immunity against diseases, decreasing the viral propagation and cell penetration capabilities (95). Coxsackievirus is a single-stranded RNA virus with symptoms similar to symptoms of Covid-19. The (S)-protopanaxtriol is one of the major triterpenes derived from *Panax notoginseng*, which includes significant antiviral effects and fights coxsackievirus (102). Considering high potencies of the active ingredients in ginseng and the herbal ability to prevent and treat viral diseases, this functional food can be considered as an adequate food in prevention and treatment of Covid-19.

Antioxidants

Antioxidants modulate and inhibit oxidation processes against oxygen, peroxide or free radicals. The common antioxidants include carotenoids, beta-carotene, lycopene, vitamin C and vitamin E (103). Antioxidants include capabilities to boost the immune system during exercises to fight oxidative stresses. Despite the fact that natural antioxidants include great nutritional values in diets, they are more commonly used as dietary and workout supplements because of their additional benefits (84). Researchers have concluded that antioxidant supplements are preventive and effective measures to decrease oxidative stresses and muscle damages, a useful immune-boosting characteristic on physical activities of the athletes (104). Concerning disease prevention and fight, antioxidants improve occurrence of the diseases caused by coronaviruses. This protective effect occurs by decreasing oxidative stress, cerebral lipid peroxidation and inflammation regulation, preserving apolipoprotein D (ApoD) of the lipocalin family. Apolipoproteins naturally play neuroprotective roles (104). Antioxidants such as N-acetyl-L-cysteine (NAC) and pyrrolidine dithiocarbamate (PDTC) significantly inhibit coronavirus-induced apoptosis and include therapeutic and prophylactic effects (106). Considering its anti-inflammatory and antioxidant characteristics, melatonin decreases acute oxidative damages to the lungs, suggesting it as a complementary compound in treatment and prevention of Covid-19 (107). Results of a study on the treatment of Covid-19 showed that antioxidants regulated production of proinflammatory cytokines and sepsis associated to Covid-19 induced acute respiratory distress syndrome (ARDS), which can be a promising strategy for the prevention and treatment of Covid-19 (Table 1) (107). Green tea includes a high antioxidant capacity due to its high catechin content and strengthening the immune system in preventing diseases, especially infectious diseases (108). High-dose ascorbic acid destroys superoxide anions, which helps decrease inflammation and therefore includes direct relationships to antiviral activity and prevents spread of influenza virus, expression of viral antigens and increases of viral loads (109). Studies have shown that ascorbic acid includes positive therapeutic and prophylactic effects in patients with acute viral infections, including human coronavirus 229E (HCoV-229E), which modulates the immune system and increases the immune system cell production in the prevention of viral infections based on its several physiological characteristics (18).

Chlorella *vulgaris*

Chlorella vulgaris is a dietary supplement belonged to the family of freshwater unicellular microalgae with beneficial effects on immune system functions (110). Extensive studies have been carried out on eefects of *C. pyrenoidosa*, as a dietary supplement, on immune function. Therefore, microalga includes various nutrients such as AAs (e.g., BCAAs and arginine), carbohydrates, vitamins and minerals. The BCAAs and arginine can increase

aerobic endurance performance and exercise safety in people with no nutritional deficiencies (111). In another study, Leen et al. stated that *Chlorella* supplementation improved anaerobic exercise capacity and decreased post-workout muscle damages following dehydration and exercise stress (105). The *C. vulgaris* derived natural astaxanthin (nASX) is a ketocarotenoid with effective antioxidant and anti-inflammatory activities known as a dietary supplement (112). Based on the clinical studies, nASX includes excellent safety benefits, preventing oxidative DNA damages and controlling other inflammation biomarkers (112). Previous studies have reported that nASX includes positive effects in decreasing cytokine storm, acute lung injury and acute respiratory syndrome. Based on the highlighted studies, it can be concluded that the compound is useful in preventing and treating Covid-19. There is strong evidence for the antioxidant effects of nASX, revealing it as a potent anti-inflammatory and antioxidant compound and supporting its use in treatment and prevention of Covid-19 (Figure 2) (8, 107). In animals, *Chlorella* has been reported to improve host defense against viral infections and tumors (113). In humans, *Chlorella* supplementation has been shown to increase antibody titers after immunization against influenza (114). Studies have demonstrated potential antiviral activity of nASX against other viruses, including influenza virus and hepatitis C virus (115).

Food additives

Eating healthy foods and avoiding processed foods, fast foods and foods high in SFAs and high sugars can boost the immune system functions. This is due to the fact that foods containing harmful additives such as salts, saturated oils, industrial emulsifiers, high-fructose corn syrup (HFCS) and other substances include negative effects on the immune functions, whereas additives are known to include effective technological characteristics such as dyeing characteristics, texture enhancement and shelf life development (116, 117, 118, 119). For example, aspects of additive E171 (titanium dioxide) have been studied to improve the color characteristics of foods and their relationships to the body immunity (120). In animal feed, consumption of this substance decreases immunity of the lungs and causes lung tumors, which its involvement is one of the common symptoms of coronavirus (121). The International Agency for Research on Cancer (IARC) and the European Chemical Agency (ECHA) Risk Assessment Committee (RAC) for Human Inhalation have introduced this substance in the category of carcinogens and immunosuppressants (Table 1) (122). TiO_2 has been reported as a human carcinogen in a study by Bischoff et al. to destroy the immune system and gastrointestinal functions (123). At high doses, it causes problems in phagocyte function and increases cytokine production, effectively preventing coronavirus (124).

Based on Figure 2, recent studies have shown that sweeteners and food emulsifiers can cause inflammation and disease in the body by altering the intestinal microbial flora (125). Sweeteners such as HFCS, which play essential roles in producing beverages and sweets, can cause inflammation and affect the body immunity by acting on bacteria in the gut (126, 127). Consumption of substances such as saccharin, sucralose, maltodextrin (MDX) and aspartame can result in dysbacteriosis, leading to symptoms such as inflammation of the intestines, chronic fatigue, obesity and cancer (127). Saccharin decreases secretion of glucagon-like peptide-1 (GLP-1) and incretin hormones, which regulate various physiological processes such as food intake, blood sugar control and cardiovascular protection (128). Long-term uses of saccharin and other artificial sweeteners can increase complications such as diabetes, CVDs and stroke, consistent with steady decreases in GLP-1 levels (129). Emulsifiers are materials used in food industries as stabilizers, foams, tissue modifiers and product life enhancers (130). Commonly used types include lecithin, carboxymethylcellulose (CMC), polysorbate-80 (P80), polyglycerol ester (PGE), sorbitan ester (SOE), glycerol monostearate-DMG 90, poly glycerol poly ricinoleate (PGPR) and sodium stearoyl lactylate (SSL) (131). Clinical studies have shown that emulsifiers affect the immune system, including dysbiosis, movement of bacteria through the mucosal barrier and increased pro-inflammatory potentials that make people vulnerable to diseases such as Covid-19 (132). In addition, it has been shown that emulsifiers can increase fasting blood sugar (FBS), body weight and fat; thus, causing metabolic disorders. For example, it has been observed that emulsifiers are associated to twice the consumption of foods in mice, which has led to obesity and linked diseases (Figure 2) (132).

Sodium nitrite inhibits development of pathogenic microorganisms in meat products. Another characteristic of sodium nitrite includes salty flavor and increases in reddish-pink color that characterize processed meats (133). Clinical studies have shown that sodium nitrite causes abnormal cell production, leading to the production of H_2O_2 which can cause tissue damages and inflammation (134). Monosodium glutamate (E621) (MSG) is used to enhance the flavor of food products, canned vegetables, soups and processed meats (135). Based on Table 1, MSG can kill nerve cells and may cause cancers, DNA damages and fetal abnormalities in animals. It is associated to increased hyperactivity. MSG includes direct toxic effects on neutrophils in the blood and is unfavorable, decreasing the body immunity against infectious diseases (135). Tartrazine provides yellow color and is found in green and blue candies (137). Food and Drug Administration (FDA) is asked to ban the consumption of tartrazine from foods. Tartrazine causes severe allergic reactions in people with

asthma, which include symptoms common to coronavirus and exacerbate the symptoms (Figure 2) (136). As highlighted, industrial food additives include significant effects on the immune system and can interfere with the prevention and treatment of Covid-19. Therefore, it is recommended that people use healthy foods with no additives and avoid high consumption of processed and fast foods. Furthermore, adequate consumption of bioactive macronutrients such as prebiotics, FAs, proteins and BCCAs may result in antiviral reactions and inhibition of microbial organism growth. Bioactive macronutrients may help development of immune responses and acceleration of recovery from Covid-19 (138).

Conclusion

For non-athletes, synergistic effects of nutritional supplements and balanced exercises can boost the immune system. Immune system is strengthened to combat sickness and help avoid infections if the highlighted methods are used in planned synchronous manners. Combined effects of dietary supplements and exercises are not limited to preventing illnesses and can increase physical strength during recovery. Based on studies, ginseng includes the greatest effects in boosting the immune system and preventing viral infections, compared to other supplements. Combination of ginseng with exercise may offer novel options for boosting the immune system ability to fight viral infections such as Covid-19. Therefore, it can be concluded that eating nutritious meals free of industrial chemicals can enhance and boost the immune system. Industrial additives include numerous uses in people routine meals; however, it is advised that these additives are consumed with caution and good nutrition is used to boost the immune system. Inflammation may occur due to the large consumption of omega-6 to omega-3 fatty foods. In addition, high intake of omega-3 and omega-9 fatty acids may have similar side effects. It is recommended to investigate effects of exercise and consumption of dietary supplements such as prebiotics, synbiotics, various microalgae, extracts of oilseeds and natural additives in future studies.

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