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Boosting the immune system with functional compounds during the Covid-19 pandemic: A Review

Parisa Rasolabadi[1], Masoud Rasolabadi[2], Himan Nourbakhsh[1]

1 Department of Food Science and Engineering, Faculty of Agriculture, University of Kurdistan, Sanandaj, Kurdistan, Iran
2 Vice Chancellor for Research and Technology, Kurdistan University of Medical Sciences, Sanandaj, Iran

Review Article

Abstract

BACKGROUND: More than 1 year has passed since the outbreak of the COVID-19 pandemic. Nutrition and its role in boosting the immune system have been a hot topic during the previous year in the light of the COVID-19 pandemic. An effective medicine for COVID-19 has not been introduced and public vaccination has not gained an acceptable speed in the world; therefore, preventive measures, protocols adherence, and a robust immune system are crucial. The aim of this study was to evaluate the role of food in boosting the immune system during the Covid-19 pandemic.

METHODS: In this scoping review, we searched and collected data related to food and its role in strengthening the immune system and COVID-19 in 4 leading databases including PubMed, Scopus, Web of sciences, and ScienceDirect. Findings were analyzed and combined using thematic analysis.

RESULTS: People with weak immune systems have been more affected by the coronavirus. Vitamins D, A, and E, zinc, selenium, copper, prebiotics, probiotics, lactoferrin, and omega-3 fatty acids have been shown to minimize SARS-CoV-2 viral load and shorten hospital stay. The dietary sources that can provide such functional compounds and boost the immune system are fish, milk and cheese, eggs, meat, fruits, beans, nuts and seeds, liver, and vegetable oils.

CONCLUSION: Due to the high demand for and limited availability of successful vaccines around the world, developing and low-income countries should be cautious about personal health problems and use food supplements to improve the immune system until public vaccination can be made available.

KEYWORDS: Antiviral agents, Coronavirus; Dietary supplements; Immunity

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Introduction

Viruses are responsible for a large proportion of worldwide illness and mortality, and viral outbreaks like the new coronavirus are no exception (COVID-19). COVID-19 is currently generating a global health disaster. In order to limit the transmission of diseases in the short term and medium term, a range of preventative public health strategies are used, such as hand washing, cough covering, lockdown, and social distancing. Although the human experience in controlling this infection has increased and vaccines have been introduced one after another by companies and pharmaceutical institutes in different countries, health experts believe that in addition to observing health protocols, following a healthy and balanced diet is essential to combat COVID-19.[1-5] Nutrition compounds and their roles in boosting the immune system has been a hot topic in light of the COVID-19 pandemic during the previous year. Although more than a year has passed, the COVID-19 pandemic is still the world's

Corresponding Author:
Himan Nourbakhsh; Department of Food Science and Engineering, Faculty of Agriculture, University of Kurdistan, Sanandaj, Kurdistan, Iran
Email: h.nourbakhsh@uok.ac.ir

most serious threat.

The virus which is responsible for the COVID-19 pandemic is a new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[6] Coronaviruses are a broad genus of single-stranded RNA viruses that cause respiratory and, less frequently, gastrointestinal illnesses in mammals and birds.[7] SARS-CoV-2 is transmitted through respiratory droplets from coughing and sneezing, which are then inhaled into the nasal system, where it replicates.[8] While the respiratory tract is affected by all coronaviruses, SARS-CoV-2 virus, in addition to the respiratory tract, also affects the gastrointestinal system, heart, kidney, liver, and the central nervous system, thus leading to multi-organ failure.[9,10] The COVID-19 incubation period is 1-14 days, but might extend to up to 24 days.[11,12] Although the signs and symptoms of COVID-19 disease differ from patient to patient, the most common clinical symptoms of COVID-19 are varied, ranging from typical cold-like or mild influenza-like signs to severe pneumonia. The common clinical symptoms are fever, cough, sore throat, headache, fatigue, and breathlessness.[13,14]

To date, there is no real therapy for COVID-19. Therefore, the key management of COVID-19 patients included early diagnosis, immediate patient isolation, and protective conditions to prevent the infection. Typical treatment for COVID-19 disease included general supportive care, respiratory support, and nutritional support.[15] Coronavirus mostly affects people with weak immune systems and underlying diseases. The role of the immune system is to shield the host from harmful environmental pathogens, which may be in the form of bacteria, viruses, fungi, or parasites.[16] To function optimally, the immune system must be supported by a sufficient supply of a variety of nutrients.[17] The nutritional status of the human body is important in developing an effective and balanced immune response to pathogenic viruses.[18] The immune system is the body's primary defense mechanism, and it is responsible for responding to foreign entities such as viruses. The innate immune response consists of a group of cells that protect the body against any foreign attacking material by releasing chemicals that finally kill the foreign agent.[19] Therefore, one of the sustainable ways to survive in the present state is to strengthen the immune system.

Hence, a healthy immune system is essential for survival.[13] To strengthen the immune system, the diet should be full of beneficial nutriments. Nutrition that supports the operations of immune cells and allows them to launch effective responses against infections is considered optimal for the best immunological response. To strengthen the immune system, the diet should be full of beneficial nutriments. An optimal nutrition for the best immunological response is a nutrition which supports the functions of immune cells, allowing them to initiate effective responses against pathogens.[20] In particular, it is important understand how functional meals, nutraceuticals, and physical activity behaviors, whether alone or in combination, may be used to improve antiviral immune defense capability. Functional foods and nutraceuticals can help to boost the immune system and guard against pathogenic viral infections in a safe and cost-effective manner. For example, maximizing a well-functioning immune system has been shown to reduce the burden of virulent strain diseases, such as lower and upper respiratory tract infections. However, little is known regarding the effect of functional foods on communicable illnesses, particularly, when it comes to the immune system's protection against viral infections like COVID. Because of their natural abundance of nutraceuticals such as polyphenols, terpenoids, flavonoids, alkaloids, sterols, pigments, and unsaturated fatty acids, fruits, vegetables, oily fish, olive oil, nuts, and legumes

are all considered functional foods.[16-20]

As mentioned in previous studies, it is crucial to take preventive measures, keep ourselves healthy, follow the protocols, and strengthen the immune system until the release of approved drugs and vaccines that are effective on the coronavirus. [1,2,4,10-20] Due to the high demand and low supply of effective vaccines in the world, it seems that developing and low-income countries should be careful to observe personal health issues as well as strengthen the immune system by using food supplements until public vaccination. Therefore, the aim of this study was to evaluate the role of food in boosting the immune system during the Covid-19 pandemic.

Methods

PubMed, Web of Science, Scopus, and ScienceDirect were the main databases we searched and used. In the identification phase, a total of 471 articles were retrieved. We analyzed a set of database to find articles with the search terms in the title. The titles of all retrieved articles were evaluated. Duplicated articles were removed. To detect the duplicates, we used the Microsoft Word compare function. A total of 403 articles remained. Through reading the titles and browsing the abstracts, we excluded papers which were not related to our subject; therefore, based on the inclusion criteria, the articles that were not related to our topic, their full text was not available, books, dissertations, letters to the editor, and notes were excluded from the study. We read the full text of the remaining articles, and after eligibility assessing, finally, 15 articles were considered suitable for inclusion in the qualitative synthesis. In table 1, the number of retrieved articles from used databases and our search phrase in each is presented.

In this review we searched and collected data related to food and its role in the strengthening of the immune system and COVID-19. The search terms we used were "food"," COVID-19", "immune system", "boosting OR strengthening", and "coronavirus". Our final search phrase was the same for all used databases [(Food) AND (strengthening OR boosting) AND (immune system) AND (Covid-19)]. Since the time of the COVID-19 outbreak was late 2019, the duration of the research was limited to 2019-2021. A search strategy was developed and used. The main inclusion criteria were articles about food and its effect on the immune system during the COVID-19 pandemic, access to the full text, and no time and language limitations. The articles that were not related to our topic, their full text was not available, and books, dissertations, letters to the editor, and notes were excluded from the study.

In this study, we also evaluated the findings and main focused points of the articles. The mechanism of effect was not evaluated and reported. Current literature on food and its role in the strengthening of the immune system and COVID-19 were reviewed and summarized. From among the retrieved articles, a total of 15 articles that were more closely related to our topic were selected and analyzed. The PRISMA flowchart for extracting the target papers is presented in figure 1.

Table 1. The number of retrieved articles from used databases

Row	Database	Number of retrieved articles	Search strategy
1	PubMed	40	"(Food) AND (strengthening OR boosting) AND (immune system) AND (Covid-19)"
2	Web of Science	26	Food AND strengthening OR boosting AND immune system AND Covid-19
3	Scopus	16	Food AND strengthening OR boosting AND immune system AND Covid-19
4	ScienceDirect	389	(Food AND strengthening OR boosting AND immune system AND Covid-19)
Total		471	

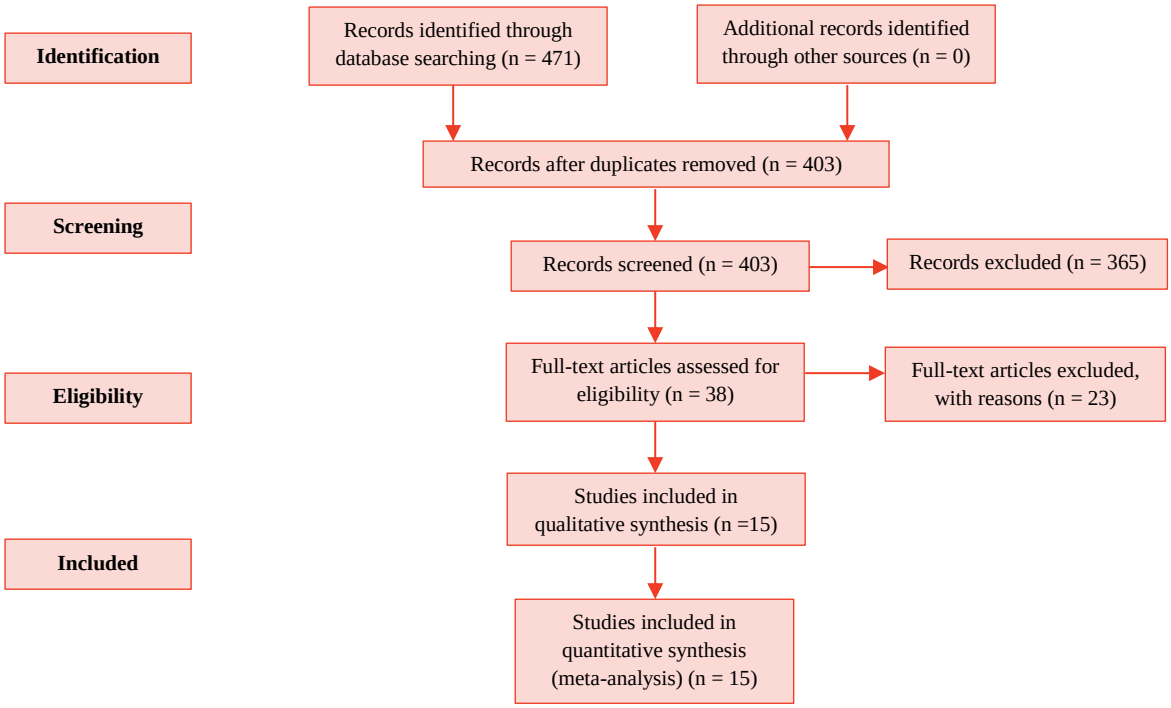

Figure 1: Flow diagram of searching

This study is a scoping review and the quality of the studies was not evaluated. Thematic analysis method was used to extract concepts related to the research question and to combine the qualitative findings of the study.

Results

As mentioned before, 15 articles published during 2019-2021 were selected and analyzed in this study. Details and findings of the articles included in the study are presented in table 2.

Discussion

In this section, most functional foods that may optimize the immune system's antiviral defense have been discussed. Although these natural chemicals do not engage in the direct inhibitory response against coronavirus, full immunity is critical for COVID-19 prevention. These functional elements will be discussed in more detail in the following sections.

Minerals

Micronutrients, such as vitamins and minerals, are biological or biochemical substances that are required in trace amounts or in small quantities for participation in metabolic processes and important biochemical pathways. Selenium supplementation has long been recognized to have an immune-stimulant impact, including increased activity of activated T cells (cytotoxic lymphocytes). The richest dietary sources of selenium include nuts, shellfish, and organ meats. Muscle meats, cereals and other grains, and dairy products are other good sources. In most geographic locations, the quantity of selenium in drinking water is not nutritionally noteworthy. Breads, cereals, meat, poultry, fish, and eggs are the main sources of selenium in the Iranian diet.[21-24]

Zinc is required for the induction of the immune system (cytokine release and natural killer cell activity) as well as the generation of antibodies. Zinc affects the function of macrophages, neutrophils, T cells, and B cells, among other immune cells.

Table 2. Details and findings of the articles included in the study

Author	Article subject	Findings
Mishra and Patel[2]	Role of Nutrition on Immune System During Covid-19 Pandemic	Micronutrients are considered to help an ideal immune system. Vitamins A, B, C, D, and E, folate, zinc, iron, copper, and selenium are all essential for a healthy immune system.
Calder[3]	Nutrition, immunity and COVID-19	The role of vitamins (A, B6, B12, folate, C, D, and E) and trace elements (zinc, copper, selenium, and iron) in supporting the human immune system and reducing the risk of infections. Each of the above nutrients has roles in supporting antibacterial and antiviral defense, but zinc and selenium are the most important.
Lockyer[5]	Effects of diets, foods and nutrients on Immunity: Implications for COVID-19?	The immune system is a complicated system made up of many different cells each of which performs a different function. Although no single food or supplement has been found to prevent COVID-19 infection, specific roles have been established for a number of micronutrients, including vitamins A, B6, B12, C, and D, copper, folate, iron, and zinc, and their effects on specific aspects of immune function have been documented.
Singh et al.[23]	Potential Inhibitors for SARS-CoV-2 and Functional Food Components as Nutritional Supplement for COVID-19: A Review	As a dietary supplement, functional food components assist the improvement of the immune system and prevent COVID-19.
Shakoor et al.[24]	Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19?	The immune-boosting role of vitamins C, D, and E, zinc, selenium, and omega 3 fatty acids is discussed and confirmed. In addition, the potential role of some of these nutrients has been shown in the management of COVID-19.
Han and Hoang[26]	Opinions on the current pandemic of COVID-19: Use functional food to boost our immune functions	Healthy behaviors and consuming functional foods and nutritional agents is a rational strategy to minimizing the damages caused by viruses.
François et al.29	Coronavirus and Nutrition: An Approach for Boosting Immune System: A Review	Vitamins A, B6, B12, C, D, and E, and folic acid, as well as trace elements such as zinc, iron, selenium, magnesium, copper, and omega-3 fatty acids, such as EPA and DHA, strengthen and enhance the immune system.
Arshad et al.[32]	Coronavirus disease (COVID-19) and immunity booster greenfoods: A mini review	Plant-based meals raised the number of intestinal beneficial bacteria, which are good bacteria that make up 85% of the immune system and are essential for improving the immune system and controlling COVID-19 infection.
Celik et al.[33]	Can food and food supplements be deployed in the fight against the COVID 19 pandemic?	Based on literature and clinical findings curcumin, zinc, and zinc-ionophores are potentially effective on viral infections; therefore, these food supplements can be used as complementary supplements in the treatment of COVID-19. However, food supplement-drug interactions should be considered.

Table 2. Details and findings of the articles included in the study (continue)

Author	Article subject	Findings
Hu et al.[36]	Probiotics, prebiotics and dietary approaches during COVID-19 pandemic	Probiotics were found to have antiviral properties against different types of coronavirus and to be able to strengthen the immune system of the host during the Covi-19 pandemic.
Galanakis et al.[39]	Food Ingredients and Active Compounds against the Coronavirus Disease (COVID-19) Pandemic: A Comprehensive Review	Drinking enough of water, eating foods high in minerals like magnesium and zinc, as well as vitamins C, D, and E, and leading a healthier lifestyle will all help you stay healthy throughout the Covid-19 pandemic. It has also been suggested that beta-glucan be used to treat COVID-19.
Mrityunjaya et al.[41]	Immune-Boosting, Antioxidant and Anti-inflammatory Food Supplements Targeting Pathogenesis of COVID-19	Zn, vitamin D, vitamin C, curcumin, cinnamaldehyde, probiotics, selenium, lactoferrin, and quercetin were among the nutraceuticals with immune-boosting, antiviral, antioxidant, and anti-inflammatory properties.
Kannamreddy et al.[45]	Immunity boosters to combat COVID-19 pandemic	Apart from a normal healthy diet containing more proteins, vitamins, and minerals, consuming herbal extracts of medicinal crops helps to maintain immunity and good function of the body.
Alkhatib[46]	Antiviral Functional Foods and Exercise Lifestyle Prevention of Coronavirus	Consumption of appropriate dietary and functional foods in combination with exercise reduces viral risk and enhances sleep quality, and consequently, strengthens the immune system.
Panyod et al.[48]	Dietary therapy and herbal medicine for COVID-19 prevention: A review and perspective	This study clearly supports food therapy and herbal medicine as potentially effective antiviral and COVID-19 prevention therapies against SARS-CoV-2.

Proteases and polymerases, for example, are antiviral enzymes that include zinc. Chelation of zinc by immunological processes disrupts zinc homeostasis in oral gustatory cells. Taste disorders caused by zinc deficiency may be the result of this process. As a result, zinc supplementation might be beneficial in the prevention and treatment of COVID-19. Zinc is found in a wide range of foods. Oysters have the highest zinc content of any item, yet red meat and poultry account for the bulk of zinc. Beans, nuts, some types of seafood (such as crab and lobster), whole grains, fortified breakfast cereals, and dairy products are all rich sources of zinc.[23,25-27]

For a long time, copper has been utilized as a disinfectant, antibacterial, and antiviral agent. Because of the unpaired free electron in its outer orbitals, the copper ion can participate in oxidation-reduction processes. The ion causes holes in the viral membranes, causing free radicals to form, which can destroy the genetic information. Copper was found to be effective against a variety of viruses, including influenza and noroviruses. Copper is required for the activity of superoxide dismutase, a powerful antioxidant enzyme that fights cellular defenses. Shellfish, seeds and nuts, organ meats, wheat-bran cereals, whole-grain cereals, and chocolate are the best sources of copper in the diet. The quantity of copper in the food has a significant impact on copper absorption; bioavailability of dietary copper ranges from 75% (when the diet includes only 400 mcg/day) to 12% (when the diet contains 7.5 mg/day).[26,28-30]

Lipids

Viruses need fatty acids to replicate in the host cell during infections. Some fatty acids, on the other hand, can inactivate microorganisms (directly or indirectly) and boost the body's defenses. The essential family of omega 3 fatty acids abundantly present in fish oil, for example, can act as endogenous molecules to boost immunity against COVID-19 infections.[31] According to Das, polyunsaturated fatty acids (PUFA) can directly target the microbial cell wall, causing membrane leakage and lysis, and thus, increasing the production of bioactive metabolites such as prostaglandins which limit viral replication.[31] PUFAs have antiviral activity against chronic hepatitis C virus (HCV) as well as normal physiological function. Alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are the three major omega-3 fatty acids (DHA). Plant oils such as flaxseed, soybean, and canola oils are high in ALA. In fish and other seafood, DHA and EPA are present.[32-34]

Prebiotic and probiotics

These products decrease stress levels in the body and boost the immune system's reaction. These functional food components, probiotics, and micronutrient supplements keep the gut healthy by keeping the microflora and bacterial colonies in check, and they are reported to have immune-boosting effects. Previous studies have identified many prebiotic and probiotic products as natural candidates for boosting the immune response. Prebiotics are dietary supplements that include oligosaccharides that are not digested by the host and are used to stimulate the growth and activity of the gut microbiota selectively. Probiotics interact with the host system and provide strength and resistance in the body through a commensal connection with the microbiota that live in our bodies. Probiotic bacteria can interact with our gut microbiota to strengthen our immune system, boost immune response, and promote particular immunological signaling that has a variety of physiological and clinical implications.[35-37]

The role of probiotics in the enhancement of the immune system has been discussed in a study by Al-Ansari et al.[35] They concluded that regular physical exercise, a healthy lifestyle, and probiotics supplementation can induce immunity. They also pointed to the specific

role of probiotics in the enhancement of natural killer cells' function, IgA antibodies stimulation, and mucosal barrier inflammation control, and in turn, the enhancement of immunity against COVID-19 viruses. Probiotics and dietary approaches during the COVID-19 pandemic were the main topic of interest and were discussed in a review by Hu et al.[36] They summarized alterations of gut microbiota in patients with COVID-19 including the impact of specific bacteria on disease severity and the role of probiotics in the prevention of and reduction of disease susceptibility.[36,37]

Vitamins

Vitamins are necessary for good health, immunity, and energy generation, as well as performing certain important activities in the body. Vitamins are necessary micronutrients that the body cannot generate on its own (with the exception of Vitamin D) and must be obtained from diet. Vitamins are widely known for their involvement in the treatment of a variety of illnesses. Vitamin A is a fat-soluble vitamin that is essential for healthy growth, development, eyesight, and immunity. Vitamin A comes in various active forms, including retinol, retinal, and retinoic acid. Retinoic acid has the most bioactive structure of all the vitamin A derivatives. Retinoic acid can boost the synthesis of anti-inflammatory cytokines and antibodies, especially IgA, which assists the defense against viral infections. Some rich sources of vitamin A are sweet potato, carrot, kale, tomato, lettuce, and spinach.[23,26,38]

Vitamin E is a powerful antioxidant that, like vitamin C, can boost immunity. This tocotrienol molecule maintains suitable immunological function by acting as a free radical scavenger in cellular membranes. Vitamin E's antioxidant properties are based on the chromanol ring, which can stop PUFAs from oxidizing. Gasmi et al. emphasized the antioxidant and anti-inflammatory properties of certain vitamins, such as C and E, and suggested that they be used to treat COVID-19.[38] Some rich sources of vitamin E are wheat germ oil, sunflower oil seeds, almonds, hazel nut oil, and avocado.[26] Vitamin D is a fat-soluble vitamin that may be found naturally in some foods, and taken as a supplement. Ultraviolet (UV) rays from the sun impact the skin and induce vitamin D production, but it is also generated endogenously. Vitamin D aids calcium absorption in the stomach and keeps blood calcium and phosphate levels in check, allowing for appropriate bone mineralization. Vitamin D has other functions in the body, such as reducing inflammation and modulating cell development, neuromuscular and immunological function, and glucose metabolism. Salmon, tuna, and egg are good food sources of vitamin D.[26, 39,40]

Proteins

Proteins with antiviral characteristics, such as lectin and lactoferrin, interfere with viral reproduction. They can identify the virus and attach to the sugars in an irreversible manner through their binding sites. HIV, influenza, hepatitis C, and coronaviruses are all affected by lectins. In this regard, the majority of mannose-binding lectins were shown to have antiviral properties against coronaviruses (SARS-CoV).[41] Lactoferrin, often known as the red protein of milk, is an enthusiastic iron-binding protein present in the milk of animals. Lactoferrin content varies from milk to milk and is mostly determined by the lactation stage. Lactoferrin aids innate immunity and is thought to be the initial line of defense against a variety of illnesses. Lactoferrin protects newborns by acting as an antibacterial, anti-inflammatory, and immunomodulating agent. Adenovirus, rotavirus, poliovirus, HSV, HIV, influenza virus, and hepatitis viruses have all been shown to be resistant to lactoferrin.[42-44]

Moreover, non-nutrient components, notably phytochemicals like polyphenols, flavonoids, alkaloids, thiophenes, terpenoids, tannins, lignins, and others, have

demonstrated antiviral activity. The antioxidant, antiviral, anticarcinogenic, and anti-inflammatory properties of flavonoids render them useful. Polyphenols like epigallocatechin gallate, a phytochemical derived from green tea, have been shown to have potent antiviral properties against a variety of viruses. Furthermore, due to their high concentration of phytochemicals and other minor health-related substances, fruits and vegetables may have antiviral effects.[45-47] Alberca et al. investigated the effects of naringenin, a flavonoid present in citrus, on COVID-19.[47] They confirmed the antiviral and anti-inflammatory effects of naringenin and suggested that it is better that naringenin be applied as a prophylactic intervention at the onset of SARS-CoV-2 infection.[47,48]

Many studies have clearly claimed that there is no individual food or supplement that can prevent infection with COVID-19, but have mentioned the immune-boosting, antiviral, antioxidant, and anti-inflammatory effects of nutraceuticals, including Zn, vitamin D, vitamin E, probiotics, selenium, and lactoferrin, on the enhancement of the immune system against COVID-19.

Conclusion

The COVID-19 pandemic spread quickly throughout the world, resulting in an unparalleled public health disaster. In order to combat the present epidemic, efforts must be made to reduce infection and transmission from person to person. Another approach to combating this condition is to improve one's immune system. Micronutrients and functional dietary components can be called natural immune booster meals. The immune system is boosted by these immune-boosting functional meals enriched with bioactive substances and antioxidants.

Moreover, despite the large number of antiviral medicines now accessible for use, in the search for an acceptable treatment, the rapid development of new virus strains makes it difficult to deliver effective drugs or cures in a timely manner. As a result, the best method to prevent transmissible diseases is to practice self-sanitation, maintain social distance, and boost immunity to certain viruses. Individuals' immunity may be boosted by a well-balanced and nutritious diet. Foods with more nutrients, such as vitamins, minerals, fatty acids, proteins, and a few polysaccharides, as well as non-nutrients (i.e., polyphenols) with therapeutic activities might be highly useful in this respect. These chemicals have the ability to either directly attack viruses or to enhance the body's protection against viruses.

Conflict of Interests

Authors have no conflict of interests.

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