NKMJ
Namık Kemal Tıp Dergisi
Namık Kemal Medical Journal

Review Article/ Derleme
Doi: https://doi.org/10.37696/nkmj.739985
e-ISSN: 2587-0262

# ENHANCEMENT OF IMMUNE SYSTEM IN ADDITION TO MEDICAL THERAPY FOR COUNTERACTING COVID-19: THE IMPORTANCE OF MICRONUTRIENTS

## COVID-19 ile Mücadelede Tıbbi Tedaviye ek olarak İmmün Sistemin Güçlendirilmesi: Mikrobesinlerin Önemi

Mustafa Metin DONMA[1], Orkide DONMA[2]

[1]Tekirdağ Namik Kemal University, Faculty of Medicine, Department of Pediatrics, Tekirdağ, TURKEY.
[2]Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Department of Medical Biochemistry, İstanbul, TURKEY.

**Abstract**

Immune responses in patients with Coronavirus Disease 2019 infection have been dysregulated. Decreased T cells, natural killer cells, monocytes/macrophages and increased proinflammatory cytokines are observed. Immunological status of the body is greatly affected by the nutrition. Micronutrients are required for the optimum performance of macronutrients. Vitamin and trace element deficiencies are generally associated with altered immune responses, which lead to increased susceptibility to infections. Supplementation with micronutrients generally reverses many impaired immune responses. In this study, close associations between the regulation of immune processes and some vitamins, trace elements as well as phytochemicals have been pointed out. In addition to a proper diet as well as a medical therapy, supplementation of vitamins A, B6, B9, B12, C, D, E and zinc, copper, selenium may be beneficial for both prevention and treatment of viral infections including this new extraordinary coronavirus disease. The investigations on phytochemicals are also underway. In individuals with a powerful immune system, the recovery from this disease is either without symptoms or with a mild clinical picture. Therefore, it is plausible to apply natural integrative approaches comprising some vitamins, minerals and phytochemicals as preventive measures or as supplements in addition to the present medical treatment. This approach will favor the enhancement of the immune system. Such an integrative treatment reduces morbidity and mortality rates in patients, who have been contaminated with this virus. Micronutrients, within the scope of immune system, may be conceivable as the expedient to find some solutions for the prevention and/or treatment of this disease.

**Keywords:** Covid-19, immune system, micronutrients, trace elements, vitamins.

**Öz**

Koronavirüs 2019'lu hastalarda immün cevapların düzenlenmesi bozulmaktadır. Azalmış T hücreleri, doğal öldürücü hücreler, monositler/makrofajlar ve artmış proinflamatuvar sitokinler gözlenmektedir. Vücudun bağışıklık durumu beslenmeden büyük ölçüde etkilenir. Mikrobesinler, makrobesinlerin optimum performansı için gereklidir. Vitamin ve eser element eksiklikleri sırasında genel olarak immün cevaplar değişir. Bu da enfeksiyonlara eğilimin artmasına yol açar. Mikrobesin desteği genellikle birçok bozulmuş immün cevabın geriye çevrilmesini sağlar. Bu çalışmada, immün işleyişin düzenlenmesi ile bazı vitamin, eser element ve fitokimyasallar arasındaki yakın beraberliklere dikkat çekilmiştir. Uygun bir diyetin yanısıra tıbbı tedaviye ek olarak A, B6, B9, B12, C, D, E vitaminleri ile çinko, bakır, selenyum destekleri bu yeni sıradışı koronavirüs hastalığını da içine alan viral enfeksiyonların önlenmesi ve tedavisi için yararlı olabilir. Fitokimyasallar ile ilgili çalışmalar da sürdürülmektedir. Güçlü bir immün sistemi olan hastalarda iyileşme ya semptomsuz ya da hafif bir klinik tablo beraberliğinde gerçekleşmektedir. Bu nedenle, uygulanmakta olan tıbbi tedaviye ek olarak ya da koruyucu önlem olarak, vitaminleri, mineralleri ve fitokimyasalları da içine alan doğal bütünleyici yaklaşımların uygulanması kabul edilebilir. Bu yaklaşım immün sistemin iyileştirilmesine yardımcı olacaktır. Bu tip bir bütünleyici tedavi, bu virüs ile kontamine olmuş hastalarda morbidite ve mortalite oranlarını önemli ölçüde azaltır. Mikrobesinler, immün sistem kapsamında, bu hastalığın önlenmesi ve/veya tedavisi için bazı çözümler bulunması konusunda önlem olarak düşünülebilir.

**Anahtar Kelimeler:** Covid-19, eser elementler, immün sistem, mikrobesinler, vitaminler.

## INTRODUCTION

Under the light of clinical and laboratory investigations, an effective and adequate treatment protocol against COVID-19 has not been developed yet. Laboratory and experimental studies concerning the development of the vaccine are underway. Nevertheless, due to the fact that this novel virus undergoes mutation in a continuous manner, these attempts appear to take a long time to attain success. In the meantime, individuals with

**Corresponding Author / Sorumlu Yazar:**

Mustafa Metin DONMA
**Adres:** Tekirdağ Namik Kemal University, Faculty of Medicine, Department of Pediatrics, Tekirdağ/TÜRKİYE
**E-posta:** mdonma@nku.edu.tr

**Article History / Makale Geçmişi:**

Date Received / Geliş Tarihi: 19.05.2020
Date Accepted / Kabul Tarihi: 23.10.2020

a strong immune system recover from this disease without any related signs or symptoms. However, in individuals with a weakened immune system, in the elderly, and in patients with chronic diseases, this disease becomes life-threatening problem. This information confirmed that the performance of the immune system is extremely important during the course of the disease. Micronutrients including vitamins, minerals and phytochemicals may be evaluated within the scope of natural integrative medical approaches. The use of these nutritional elements in addition to the present pharmacological therapies constitute a very important topic.

**Micronutrients, COVID-19 Infection and Immune System**

Immunological status of the human body is greatly affected by the nutrition. Micronutrients are required for the optimum performance of macronutrients. Most of them play critical roles on immune functions. Dietary deficiencies of some micronutrients may be caused by socioeconomic, sociocultural, psychosocial, dental and some drug-related problems. Vitamin and trace element deficiencies are generally associated with altered immune responses, which lead to increased susceptibility to infections[1-5].

Cells in the immune system communicate with one another by cytokines considered as hormonal messengers. Cytokines may also be divided into two main groups in terms of their relevance to oxidative stress and inflammation: Proinflammatory and antiinflammatory[1,6].

T lymphocytes are the major sources of cytokines. Two main subsets of T lymphocytes are CD8+ and CD4+. They are known as cytotoxic (TC) and helper (TH) T cells, respectively. TC cells kill infected cells. TH1 cells promote cell-mediated immunity by facilitating macrophage and TC cell responses. TH1-type cytokines produce proinflammatory responses. They produce mainly interferon- γ (IFN-γ), interleukin-2 (IL-2) and tumor necrosis factor-α (TNF-α). TH2 cells promote humoral immunity via stimulating antibody production by B cells. TH2-type cytokines produce essentially antiinflammatory responses. They include IL-4, IL-5, IL-10, IL-13. The balance between TH1 and TH2 responses is critical. These cytokines work harmoniously to keep everyting in balance. Regulatory T cells (TREG cells) mediate suppression of immune responses [1,6,7].

Micronutrients found in fruits and vegetables can boost immune functions. This may be due to their antioxidative nature as in vitamin E, vitamin C and betacarotene. Antioxidants increase the number of T cell subsets, enhance lymphocyte response to mitogen, increase IL-2 production, potentiate natural killer (NK) cell activity and increase response to influenza virus vaccine[8,9].

Dietary zinc and selenium are important nutritional elements for the immune response to protect against the development of age-related diseases. These two physiologically essential trace elements interact in many biochemical processes. One of inorganic selenium species, selenates couple with the reduced-to-oxidized glutathione and metallothionein-to-thionein redox pairs to release or bind zinc metal [10,11].

The immune responses in patients with COVID-19 infection have been dysregulated. Clinical and immunologic features in severe and moderate Coronavirus Disease 2019 have been investigated. So far, decreased TREG cells, TC and TH cells, NK cells, monocytes/macrophages have been reported. Also, the increased concentrations of proinflammatory cytokines were noted[12-14].

Supplementation with micronutrients generally reverses many impaired immune responses. In this study, close associations between the regulation of immune processes and some vitamins, trace elements as well as phytochemicals have been pointed out.

## VITAMINS

### Vitamin A

Treating CD4+ Foxp3+ TREG cells with all-trans retinoic acid (atRA), the active derivative of vitamin A, may represent a novel treatment strategy to control immune-mediated inflammatory diseases. Vitamin A possesses an antiinflammatory nature. The addition of atRA inhibits the synthesis of IFN-γ and enhances the development of CD4+ TH cells. Vitamin A is required for CD4+ TH lymphocyte stimulation of B cells to produce an appropriate antibody response to an antigen. Retinoic acid possesses important roles in lymphocyte proliferation. Retinoic acid enhances T-cell-independent production of Ig A antibodies. Vitamin A is known for its protective roles against infections. This may be largely due to its ability to enhance Ig A antibody responses in mucosal tissues [15-21].

Vitamin A deficiency impairs innate immunity because of the failure of the epithelial tissue regeneration. Cell-mediated and humoral antibody responses are also impaired because TH1 response as well as the secretion of proinflammatory cytokines IL-6, IL-12 and TNF-α are increased, TH2 antiinflammatory response is suppressed. Therefore, deficiency of this vitamin induces inflammation [15-21].

The immune-supporting roles of vitamin A include the promotion of mucins and keratins, lymphopoiesis, apoptosis, cytokine expression, antibody production, and the enhanced functions of neutrophils, NK cells, monocytes/macrophages, T cells, and B cells [22-24].

Vitamin A deficiency alters integrity of mucosal epithelium, impairs innate immunity, affects neutrophil and eosinophil functions, reduces number and killing activity of NK cells, impairs ability of macrophages to phagocytose pathogens, diminishes oxidative burst activity of macrophages, increases production of TNF-α, induces inflammation and potentiates existing inflammatory conditions, decreases number and distribution of T cells, alters TH1/TH2 balance, decreasing TH2 response, exerts adverse effects on growth and differentiation of B cells, impairs antibody-mediated immunity [2, 25- 29].

The mechanisms by which vitamin A inhibits the replication of measles virus upregulate elements of the innate immune response. Therefore, vitamin A could be a promising agent for the treatment of this novel coronavirus and the prevention of lung infection [30,31].

### B complex vitamins

Vitamin B6, vitamin B9 and vitamin B12 are water-soluble vitamins participating in the transsulfuration reactions of the body. Deficiencies of these vitamins may weaken host immune response and increase the infection risk. Supplementation of them will enhance the immune system of virus-infected patients, Therefore, B vitamins could be chosen as a basic option for the treatment of COVID-19 [1,31].

### Vitamin B6

Vitamin B6 enhances NK cell activity. This vitamin is required in the synthesis and metabolism of amino acids, building blocks of cytokines and antibodies, helps to regulate inflammation, is involved in lymphocyte proliferation, differentiation, maturation, and activity; maintains TH1 immune response. Vitamin B6 deficiency may cause general deficiencies in cell-mediated immunity, lowered antibody responses, reduced responses to mitogens, impaired lymphocyte maturation and growth [2, 3,27-29, 32-37].

**Vitamin B9**

Folate enhances NK cell cytotoxic activity. It affects TH1-mediated immune response. This vitamin is important for sufficient antibody production, metabolism and response. Impaired NK cytotoxicity, depressed T-cell proliferation, inhibited proliferation of Tc cells, impaired thymidine as well as purine synthesis and immunoglobulin secretion, decreased antibody response are the abnormalities observed during folate deficiency [2,3,27,28,32,33,37-40].

**Vitamin B12**

Vitamin B12 may act as immunomodulator for cellular immunity. It facilitates production of T cells, such as cytotoxic T cells; helps to regulate ratio between TH and TC cells. This vitamin is involved in antibody production and metabolism, via folate mechanism. Suppressed NK cell activity, depressed T-cell proliferation, decreased number of lymphocytes, impaired antibody response, abnormal TH/TC ratio may be observed during vitamin B12 deficiency [2,27,28,33,36,37,39,41,42].

**Vitamin C**

Vitamin C is highly concentrated in leukocytes and used rapidly during infections to prevent the damage caused by oxidative stress. Vitamin C deficiency impairs leukocyte functions, decreases NK cell activity and lymphocyte proliferation[1,43].

Vitamin C supplementation appears to support immune responses in individuals at risk for COVID-19 infection. These patients commonly suffer from lung damage, vitamin C may be introduced as a preventive agent during this process. It was reported that vitamin C might prevent the susceptibility to lower respiratory tract infections. The COVID-19 was reported to cause lower respiratory tract infection, therefore, this vitamin could be effective during the treatment of COVID-19 [22,31,43-45].

**Vitamin D**

Aside from regulating calcium and phosphorus homeostasis as the main function of vitamin D, its effects on the immune system are also noteworthy. Vitamin D may exert effects on the proliferation, differentiation and function of immune cells such as dendritic cells (DC), macrophages, T cells and B cells [46-52].

Vitamin D stimulates response to infection by increasing macrophage differentiation as well as phagocytosis and the production of cathelicidine, a potent anti-microbial peptide. It reduces TH1 cell proliferation and TH1 cytokine response. Also, it decreases TH17 differentiation, TH17 response, IL-17 production and thus, inflammation. Proinflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-23 are decreased. This vitamin supports TH2 response. Antiinflammatory IL-10 production is increased. TREG cells are induced [46-52].

The risk of viral infections can be reduced by vitamin D. The related mechanisms are the stimulation of antimicrobial peptides (cathelicidins and defensins), which decreases the replication of virus and increases antiinflammatory cytokines, as well as the reduction in pro-inflammatory cytokines, which induce inflammation-related pneumonia. Vitamin D deficiency is globally prevalent, particularly in the elderly. The virus-infected people generally had insufficient vitamin D levels. Much lower concentrations of vitamin D have been reported in severe cases. This is the supportive data for the effective role of vitamin D in decreasing risk of COVID-19 infection. Therefore, vitamin D may be suggested for the prevention and treatment of this novel disease [22,31,53].

Vitamin D has antifibrotic, antiinflammatory and immunomodulatory properties. The role of vitamin D in reducing the risk of respiratory tract infections caused by this new coronavirus, SARS- Cov-2 has been pointed out. This vitamin protects respiratory tract preserving tight junctions, killing enveloped viruses through the induction of antimicrobial peptides that can reduce viral replication rate and inhibiting the production and secretion of proinflammatory cytokines [9,44,54,55].

Vitamin D deficiency is associated with inflammation, impairs both natural and adaptive immunity and thus increases the risk of infectious and inflammatory diseases. This vitamin also causes reduction in the number of lymphocytes, impaired immune capabilities of macrophages [2,37,56,57].

**Vitamin E**

Free radical formation and lipid peroxidation are immunosuppressive processes. Vitamin E possesses protective antioxidant action as well as immunostimulatory effect. Vitamin E deficiency leads to suppression of TH1 and promotion of TH2 responses [58-61].

Experimental studies have reported immunomodulatory effects of vitamin E. It is proposed that vitamin E can enhance T cell-mediated function by directly promoting membrane integrity and positively modulating the signaling events in T cells while also protecting T cell function indirectly by reducing production of T cell-suppressing factors such as prostaglandins from macrophages. Vitamin E can reverse the age-associated reduction in activation-induced T cell expansion and IL-2 production in naive T cells [58-61].

Vitamin E deficiency impairs humoral and cell-mediated aspects of adaptive immunity, including B and T cell function, reduces T cell maturation [2,27,33].

## TRACE ELEMENTS

### Zinc

Zinc plays a critical role in the immune system. Its effects may vary from those on the skin as a physical barrier to the regulation of gene expression in lymphocytes. It is an essential element for normal function and development of cells regulating immunity, NK cell activity, generation of oxidative bursts, cytokine production, complement activity, immune and antioxidative responses, phagocytosis, apoptosis, and mental health. Zinc is the main structural component of most transcription factors. An optimal intake of zinc restores the normal immune response and reduces the risk of infection [1,54,62- 66].

Zinc induces TREG cells, supresses pro-inflammatory TH17 and TH9 cell differentiation. Since the elderly is more likely to have zinc deficiency and aging is associated with impaired immune functions and increased risk of infections, zinc supplementation has been identified as a part of potential solution for the immunosenescence[58,67-70].

A balanced zinc homeostasis is crucial, because both zinc deficiency and excess cause impairment of immune functions. Zinc can be considered as a gatekeeper of the immune system, since the functions of almost all immune cells is zinc-dependent [71].

Zinc inhibits the replication of various RNA viruses such as SARS-CoV-2. When the inhibiting action of zinc in the replication of coronavirus is considered, it is possible that zinc may have beneficial effects also on COVID-19 infection [9,31,44,72].

Zinc also plays role in the regulation of appetite. Zinc deficiency is associated with decreased appetite. The loss of sense of smell and taste in COVID-19 patients have been reported. Zinc deficiency may be associated with these symptoms in such patients. Zinc administration may be used to treat taste disorders[44, 73-76].

Zinc deficiency impairs both innate and cell-mediated immunity. Impaired survival, proliferation and maturation of monocytes, NK cells, T and B cells, impaired NK cell activity, impaired phagocytosis by macrophages and neutrophils, altered cytokine production, contributing to greater oxidative stress and inflammation, impaired generation of oxidative burst, decreased lymphocyte proliferation and function, particularly T cells, altered expression of genes related to proliferation, survival, and response of T-cells, decreased production of TH1 cytokines, imbalance in TH1/TH2 ratio, impaired antibody response to T cell-dependent antigens may be observed during zinc deficiency [2,27,28,77-80].

**Copper**

Copper plays a crucial role in immunity, because it participates in the development and differentiation of immune cells. In vitro studies have shown that copper demonstrates antiviral properties [81-83].

Copper is capable of killing some infectious viruses such as influenza viruses, poliovirus, human immunodeficiency virus, other enveloped or nonenveloped, single- or double-stranded DNA and RNA viruses. This physiologically essential metal can disrupt the lytic cycle of the Coccolithovirus, EhV86 by increasing the production of reactive oxygen species [84].

It has been hypothesized that enrichment of plasma copper levels will boost both the innate and adaptive immunity. Moreover, owing to its potent antiviral activities, copper may also act as a preventive and therapeutic regime against COVID-19 infection [8]).

In case of copper deficiency, abnormally low neutrophil levels and reduced phagocytic ability, decreased T-cell proliferation, ineffective immune response to infections, increased viral virulence may be observed [2,27,28,33,86].

**Selenium**

Selenium is the integral part of glutathione peroxidases and thioredoxin reductases. This physiologically essential trace element has an important role in defensive mechanisms fighting against viral infections through its antioxidant function and its contribution to redox signaling. Therefore, selenium intake affects many types of immune responses, which emphasize the effective role of selenium supplementation in viral diseases [22,81,87].

In an experimental study, it has been shown that selenium upregulates the expression of Foxp3 mRNA and increases the percentage of TREG [CD4(+) CD25(+)] cells [88].

In case of selenium deficiency, increased oxidative stress, suppression of immune functions, diminished NK-cell cytotoxicity, impaired humoral and cell-mediated immunity, impaired antibody production, increased viral virulence, increased proinflammatory chemokines may be detected [2, 27,28,37,89].

In concert with vitamin E, selenium acting as the integral part of a group of enzymes, work to prevent oxidative damage to cells and tissues. Therefore, selenium supplementation could be an effective choice for the treatment of this novel virus of COVID-19 infection [31,90].

**Phytochemicals**

In the current emergency state, there are some suggestions related to the use of all available therapeutic tools and the potential antiretroviral activity of hesperidin as well as rutin as co-treatment or as preventive measure in patients with COVID-19 infection [91].

Green tea contains high content of catechins. Green tea and its most abundant and also the most biologically active constituent epigallocatechin-3-gallate have been reported to be effective in modulating multiple aspects of innate and adaptive immunity [58,92].

Garlic supplementation causes significant increases in CD4+ and CD8+ cells. This plant also stimulates NK cells. Decreased leptin, leptin receptor, IL-6 concentrations were also detected. Garlic is a selenium accumulator plant. Therefore, it may be used to accumulate selenium to be more beneficial for the patients [93-97].

**Conclusive Remarks**

Links between micronutrients and immune system are widely investigated, because diseases are closely related with nutrition and immune system parameters. Prior to the emergence of this novel coronavirus infection, obesity, a low-grade inflammatory disease, was being considered as the disease of the age. There are investigations reflecting the associations between obesity development and some immune system elements as well as micronutrients[98,99]. At present, all countries try to find a solution for a very contagious and severe infectious disease problem. The association between micronutrients and immune system has also been recognized as the expedient to find some solutions for the prevention and/or treatment of this disease.

In individuals with a powerful immune system, the recovery from this disease is either without symptoms or with a mild clinical picture. Therefore, it is plausible to apply natural integrative approaches comprising some vitamins, minerals and phytochemicals as supplements in addition to the present medical treatment. Besides, it may be suggested that such an integrative approach will also be useful in individuals, who have not met with this viral agent yet. This approach will favor the medical approach by the enhancement of the immune system. We foresight that the sustainment of the immune system with the help of the above mentioned natural elements is going to be a protective measure for individuals, who have not been infected yet and reduce morbidity and mortality rates significantly in patients, who have already been contaminated with this virus. In addition to a proper diet as well as a medical therapy, supplementation of vitamins A, B6, B9, B12, C, D, E and zinc, copper, selenium may be beneficial for both prevention and treatment of viral infections including COVID-19.

**References**


1. Donma MM, Donma O, Michalke B, Halbach S, Nischwitz V: Vitamins, Minerals, and Metabolic Pathways in Health and Diseases with a Special Chapter on Speciation (1st ed). Istanbul: Istanbul University Publishing House, 2012; 7-12.
2. Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system- Working in harmony to reduce the risk of infection. Nutrients. 2020;12(1), pii: E236.
3. Maggini S, Pierre A, Calder PC. Immune function and micronutrient requirements change over the life course. Nutrients. 2018;10(10), pii: E1531.
4. Castellani ML, Shaik-Dasthagirisaheb YB, Tripodi D, Anogeianaki A, Felaco P, Toniato E, et al. Interrelationship between vitamins and cytokines in immunity. J Biol Regul Homeost Agents. 2010;24(4):385-90.
5. Chandra RK. Nutrition and immune system: an introduction. Am J Clin Nutr.1997;66(2):460S-3S.
6. Santos-Rosa M, Bienvenu J, Whicher J: Cytokines. In: Burtis CA, Ashwood ER (eds), TIETZ Textbook of Clinical Chemistry. USA: W B Saunders, 1999; 541-616.
7. Berger A. Science commentary: Th1 and Th2 responses: what are they? BMJ.2000;321(7258): 424.
8. Chandra RK. Effect of vitamin and trace-element supplementation on immune responses and infection in elderly subjects. Lancet. 1992;340(8828):1124–7.

9. Muscogiuri G, Barrea L, Savastano S, Colao A, et al. Nutritional recommendations for CoVID-19 quarantine. Eur J Clin Nutr. 2020;74(6):850-1.
10. Maret W. Cellular zinc and redox states converge in the metallothionein/thionein pair. J Nutr.2003;133(5 Suppl 1):1460S–2S.
11. Mocchegiani E, Malavolta M. Role of zinc and selenium in oxidative stress and immunosenescence: Implications for healthy aging and longevity. Handbook of immunosenescence: Basic understanding and clinical implications. 2019; 2539–73.
12. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020;71(15):762-8.
13. Wang F, Nie J, Wang H, Zhao Q, Xiong Y, Deng L, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. J Infect Dis. 2020; 221(11):1762-9.
14. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunologic features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130(5):2620-9.
15. Zhou X, Kong N, Wang J, Fan H, Zou H, Horwitz D, et al. Cutting edge: All-trans retinoic acid sustains the stability and function of natural regulatory T cells in an inflammatory milieu. J Immunol. 2010; 185(5): 2675-9.
16. Russell RM. Vitamin A spectrum: from deficiency to toxicity. Am J Clin Nutr. 2000; 71(4): 878-84.
17. Iwata M. The roles of retinoic acid in lymphocyte differentiation. Sem Immunol. 2009; 21(1):1.
18. Hoag KA, Nashold FE, Goverman J,Hayes CE. Retinoic acid enhances the T helper 2 cell development that is essential for robust antibody responses through its action on antigen-presenting cells. J Nutr. 2002; 132(12): 3736-9.
19. Duriancik DM, Lackey DE, Hoag KA. Vitamin A as a regulator of antigen presenting cells. J Nutr. 2010; 140(8): 1395-9.
20. Dawson HD, Collins G, Pyle R, Key M, Taub DD. The retinoic acid receptor-alpha mediates human T-cell activation and Th2 cytokine and chemokine production. BMC Immunol. 2008; 9:16.
21. Cantorna MT, Nashold FE, Chun TY, Hayes CE. Vitamin A down-regulation of IFN-gamma synthesis in cloned mouse Th1 lymphocytes depends on the CD28 costimulatory pathway. J Immunol. 1996; 156(8):2674-9.
22. Gasmi A, Noor S, Tippairote T, Dadar M, Menzel A, Bjørklund G. Individual risk management strategy and potential therapeutic options for the COVID-19 pandemic. Clin Immunol. 2020;215:108409.
23. Jee J, Hoet AE, Azevedo MP, Vlasova AN, Loerch SC, Pickworth CL, et al. Effects of dietary vitamin A content on antibody responses of feedlot calves inoculated intramuscularly with an inactivated bovine coronavirus vaccine, Am J Vet Res. 2013; 74(10):1353-62.
24. Kańtoch M, Litwińska B, Szkoda M, Siennicka J. Importance of vitamin A deficiency in pathology and immunology of viral infections. Rocz Panst Zakl Hig. 2002;53(4):385-92.
25. Calder PC. Feeding the immune system. Proc Nutr Soc. 2013; 72(3): 299–309.
26. Villamor E, Fawzi WW. Effects of vitamin a supplementation on immune responses and correlation with clinical outcomes. Clin Microbiol Rev. 2005; 18(3): 446–64.
27. Micronutrient Information Center. Immunity in Depth. Linus Pauling Institute. 2016. Available online: http://lpi.oregonstate.edu/mic/health-disease/immunity (accessed on 10 May 2019).
28. Maggini S, Beveridge S, Sorbara JP, Senatore G. Feeding the immune system: The role of micronutrients in restoring resistance to infections. CAB Rev. 2008; 3(098): 1–21.
29. Wishart K. Increased micronutrient requirements during physiologically demanding situations: Review of the current evidence. Vitam Miner. 2017; 6(2): 1–16.
30. Trottier C, Colombo M, Mann KK, Miller WH Jr, Ward BJ. Retinoids inhibit measles virus through a type I IFNγ dependent bystander effect. FASEB J. 2009;23(9):3203-12.
31. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. J Med Virol. 2020;92(5):479–90.
32. Wu D, Lewis ED, Pae M, Meydani SN. Nutritional modulation of immune function: Analysis of evidence, mechanisms, and clinical relevance. Front Immunol. 2019; 9: 3160.
33. Saeed F, Nadeem M, Ahmed RS, Nadeem MT, Arshad S,Ullah A. Studying the impact of nutritional immunology underlying the modulation of immune responses by nutritional compounds—A review. Food Agric Immunol. 2016; 27(2): 205–29.
34. Sakakeeny L, Roubenoff R, Obin M, Fontes JD, Benjamin EJ, Bujanover Y, et al. Plasma pyridoxal-5-phosphate is inversely associated with systemic markers of inflammation in a population of U.S. adults. J Nutr. 2012;142(7): 1280–5.
35. Ueland PM, McCann A, Midttun O, Ulvik A. Inflammation, vitamin B6 and related pathways.Mol Asp Med. 2017; 53: 10–27.
36. Haryanto B, Suksmasari T, Wintergerst E, Maggini S. Multivitamin supplementation supports immune function and ameliorates conditions triggered by reduced air quality. Vitam Miner. 2015;4(2):1-15.
37. Calder P, Prescott S, Caplan M: Scientific Review: The Role of Nutrients in Immune Function of Infants and Young Children Emerging Evidence for Long-Chain Polyunsaturated Fatty Acids. Illinois: Mead Johnson & Company: Glenview, 2007.
38. Troen AM, Mitchell B, Sorensen B, Wener MH, Johnston A, Wood B, et al. Unmetabolized folic acid in plasma is associated with reduced natural killer cell cytotoxicity among postmenopausal women. J Nutr. 2006; 136(1): 189–94.
39. Yoshii K, Hosomi K, Sawane K, Kunisawa J. Metabolism of dietary and microbial vitamin B family in the regulation of host immunity. Front Nutr. 2019; 6: 48.
40. Selhub J. Folate, vitamin B12 and vitamin B6 and one carbon metabolism. J Nutr Health Aging. 2002; 6(1): 39–42.
41. Tamura J, Kubota K, Murakami H, Sawamura M, Matsushima T, Tamura T, et al. Immunomodulation by vitamin B12: Augmentation of CD8+ T lymphocytes and natural killer (NK) cell activity in vitamin B12-deficient patients by methyl-B12 treatment. Clin Exp Immunol. 1999; 116(1): 28–32.
42. Maggini S, Wintergerst E, Beveridge S, Hornig DH. Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses. Br J Nutr. 2007; 98(Suppl 1): S29–S35.
43. Wintergerst ES, Maggini S Hornig DH. Immune-enhancing role of vitamin C and zinc and effect on clinical conditions. Ann Nutr Metab. 2006;50(2): 85-94.
44. Zhang J, Xie B, Hashimoto K. Current status of potential therapeutic candidates for the COVID-19 crisis. Brain Behav Immun. 2020;87:59-73.
45. Hemila H. Vitamin C intake and susceptibility to pneumonia. Pediatr Infect Dis J.1997;16(9):836-7.
46. Bikle DD. Nonclassic actions of vitamin D. J Clin Endocrinol Metab. 2009; 94(1):26-34.
47. Bruce D, Yu S, Ooi JH, Cantorna MT. Converging pathways lead to overproduction of IL-17 in the absence of vitamin D signaling. Int Immunol. 2011; 23(8): 519-28.
48. Guillot X, Semerano L, Saidenberg-Kermanac'h N, Falgarone G, Boissier MC. Vitamin D and inflammation. Joint Bone Spine. 2010; 77(6): 552-7.
49. Hewison M. Vitamin D and the immune system. New perspectives on an old theme. Endocrinol Metab Clin North Am. 2010; 39(2): 365-79.
50. Smolders J, Thewissen M, Peelen E, Menheere P, Tervaert JW, Damoiseaux J, et al.Vitamin D status is positively correlated with regulatory T cell function in

patients with multiple sclerosis. PLoS One. 2009; 4(8): e6635.
51. Thurnham DI. Plasma 25-hydroxy-cholecalciferol (vitamin D) is depressed by inflammation: Implications and parallels with other micronutrients. Sight & Life. 2011; 25:38-47.
52. Vanoirbeek E, Krishnan A, Eelen G, Verlinden L, Bouillon R, Feldman D, et al. The anti- cancer and anti-inflammatory actions of 1,25(OH)2 D3. Best Pract Res Clin Endocrinol Metab. 2011; 25(4):593-604.
53. Duchateau J, Servais G, Vreyens R, Delespesse G, Bolla K. Modulation of immune response in aged humans through different administration modes of thymopentin. Surv Immunol Res. 1985;4(suppl 1):94-101.
54. Gupta S, Read SA, Shackel NA, Hebbard L, George J, Ahlenstiel G. The role of micronutrients in the infection and subsequent response to Hepatitis C virus.Cells. 2019;8(6):603.
55. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 2020;12(4):988.
56. Meghil MM, Hutchens L, Raed A, Multani NA, Rajendran M, Zhu H, et al. The influence of vitamin D supplementation on local and systemic inflammatory markers in periodontitis patients: A pilot study. Oral Dis. 2019; 25(5): 1403–13.
57. Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, et al. Epidemic influenza and vitamin D. Epidemiol Infect. 2006; 134(6):1129–40.
58. Wu D, Lewis ED, Pae M, Meydani SN. Nutritional modulation of immune function: Analysis of evidence, mechanisms, and clinical relevance. Front Immunol. 2019; 9:3160.
59. Meydani SN, Han SN, Wu D. Vitamin E and immune response in the aged: Molecular mechanisms and clinical implications. Immunol Rev. 2005; 205(1): 269-84.
60. Wu D, Meydani SN. Age-associated changes in immune and inflammatory responses: impact of vitamin E intervention. J Leukoc Biol. 2008; 84(4):900–14.
61. Adolfsson O, Huber BT, Meydani SN. Vitamin E-enhanced IL-2 production in old mice: naive but not memory T cells show increased cell division cycling and IL-2-producing capacity. J Immunol. 2001;167(7):3809–17.
62. Skrajnowska D, Bobrowska-Korczak B. Role of zinc in immune system and anti-cancer defense mechanisms. Nutrients. 2019; 11(10): 2273.
63. Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. Am J Clin Nutr. 1998; 68 (2 suppl.): 447S-63S.
64. Fraker PJ, King LE, Laakko T, Vollmer TL. The dynamic link between the integrity of the immune system and zinc status. J Nutr. 2000; 130(5S Suppl): 1399S–406S.
65. Sangthawan D, Phungrassami T, Sinkitjarurnchai W. Effects of zinc sulfate supplementation on cell-mediated immune response in head and neck cancer patients treated with radiation therapy. Nutr Cancer. 2015; 67(3): 449–56.
66. Tergaonkar V. NF-κB pathway: A good signaling paradigm and therapeutic target. Int J Biochem Cell Biol. 2006; 38(10): 1647–53.
67. Rosenkranz E, Maywald M, Hilgers RD, Brieger A, Clarner T, Kipp M, et al. Induction of regulatory T cells in Th1-/Th17-driven experimental autoimmune encephalomyelitis by zinc administration. J Nutr Biochem. 2016; 29:116–23.
68. Rosenkranz E, Metz CH, Maywald M, Hilgers RD, Weßels I, Senff T, et al. Zinc supplementation induces regulatory T cells by inhibition of Sirt-1 deacetylase in mixed lymphocyte cultures. Mol Nutr Food Res. 2016; 60(3):661–71.
69. Kitabayashi C, Fukada T, Kanamoto M, Ohashi W, Hojyo S, Atsumi T, et al. Zinc suppresses Th17 development via inhibition of STAT3 activation. Int Immunol. 2010; 22(5):375–86.
70. Maywald M, Wang F, Rink L. Zinc supplementation plays a crucial role in T helper 9 differentiation in allogeneic immune reactions and non-activated T cells. J Trace Elem Med Biol. 2018; 50:482–8.
71. Wessels I, Maywald M, Rink L. Zinc as a gatekeeper of immune function. Nutrients. 2017; 9(12): 1286.
72. te Velthuis AJW, van den Worm SHE, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLOS Pathog. 2010;6(11):e1001176.
73. Baltaci AK, Mogulkoc R. Leptin and zinc relation: In regulation of food intake and immunity. Indian J Endocrinol Metab. 2012;16(Suppl 3):S611-S6.
74. Keyhan SO, Fallahi HR, Cheshmi B. Dysosmia and dysgeusia due to the 2019 novel coronavirus; a hypothesis that needs further investigation. Maxillofac Plast Reconstr Surg. 2020;42(1): 9.
75. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al.Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol. 2020; 277(8):2251-61.
76. Yagi T, Asakawa A, Ueda H, Ikeda S, Miyawaki S, Inui A. The role of zinc in the treatment of taste disorders. Recent Pat Food Nutr Agric. 2013; 5(1): 44–51.
77. Moore JB, Blanchard RK, McCormack WT, Cousins RJ. cDNA array analysis identifies thymic LCK as upregulated in moderate murine zinc deficiency before T-lymphocyte population changes. J Nutr. 2001; 131(12): 3189–96.
78. Maywald M, Wessels I, Rink L. Zinc signals and immunity. Int J Mol Sci. 2017; 18(10): 2222.
79. Sandström B, Cederblad A, Lindblad BS, Lönnerdal B. Acrodermatitis enteropathica, zinc metabolism, copper status, and immune function. Arch Pediatr Adolesc Med. 1994; 148(9): 980–5.
80. Bonaventura P, Benedetti G, Albarede F, Miossec P. Zinc and its role in immunity and inflammation. Autoimmun Rev. 2015; 14(4): 277–85.
81. Jayawardena R, Sooriyaarachchi P, Chourdakis M, Jeewandara C, Ranasinghe P. Enhancing immunity in viral infections, with special emphasis on COVID-19: A review. Diabetes Metab Syndr. 2020; 14(4): 367-82.
82. Li C, Li Y, Ding C. The role of copper homeostasis at the host-pathogen axis: From bacteria to fungi. Int J Mol Sci. 2019; 20(1): 175.
83. Miyamoto, D., Kusagaya Y, Endo N, Sometani A, Takeo S, Suzuki T, et al. Thujaplicin- copper chelates inhibit replication of human influenza viruses. Antiviral Res. 1998;39(2):89-100.
84. Sagripanti JL, Routson LB, Lytle CD. Virus inactivation by copper or iron ions alone and in the presence of peroxide. Appl Environ Microbiol. 1993; 59(12): 4374-6.
85. Raha S, Mallick R, Basak S, Duttaroy AK. Is copper beneficial for COVID-19 patients? Med Hypotheses. 2020; 142: 109814.
86. Percival SS. Copper and immunity. Am J Clin Nutr. 1998; 67(5 Suppl): 1064s–8s.
87. Guillin OM, Vindry C, Ohlmann T, Chavatte L. Selenium, selenoproteins and viral infection.Nutrients. 2019;11(9): 2101.
88. Xue H, Wang W, Li Y, Shan Z, Li Y, Teng X, et al. Selenium upregulates CD4(+)CD25(+) regulatory T cells in iodine-induced autoimmune thyroiditis model of NOD.H-2(h4) mice. Endocr J. 2010; 57(7):595–601.
89. Prentice S. They are what you eat: Can nutritional factors during gestation and early infancy modulate the neonatal immune response? Front Immunol. 2017; 8: 1641.
90. Harthill M. Review: micronutrient selenium deficiency influences evolution of some viral infectious diseases. Biol Trace Elem Res. 2011; 143(3):1325-36.
91. Coppola M, Mondola R. Phytotherapeutics and SARS-CoV-2 infection: Potential role of bioflavonoids. Med Hypotheses. 2020; 140:109766.
92. Pae M, Wu D. Immunomodulating effects of epigallocatechin-3-gallate from green tea: mechanisms and applications. Food Funct. 2013; 4(9):1287–303.

93. Arreola R, Quintero-Fabián S, López-Roa RI, Flores-Gutiérrez EO, Reyes-Grajeda JP, Carrera-Quintanar L, et al. Immunomodulation and anti-inflammatory effects of garlic compounds. J Immunol Res. 2015; 2015: 401630.
94. Beni MA, Omidi M. Effect of short-term garlic supplementation on CD4 and CD8 factors in young karate athletes after intense exercise session. CMJA 2018; 7: 2041-51.
95. Sánchez-Sánchez MA, Zepeda-Morales ASM, Carrera-Quintanar L, Viveros-Paredes JM, Franco-Arroyo NN, Godínez-Rubí M, et al. Alliin, an Allium sativum nutraceutical, reduces metaflammation markers in DIO mice. Nutrients. 2020; 12(3): E624.
96. Amor S, González-Hedström D, Martín-Carro B, Almodóvar P, Prodanov M, García-Villalón AL, et al. Beneficial effects of an aged black garlic extract in the metabolic and vascular alterations induced by a high fat/sucrose diet in male rats. Nutrients. 2019; 11(1): 153.
97. Ogra Y, Ogihara Y, Anan Y. Comparison of the metabolism of inorganic and organic selenium species between two selenium accumulator plants, garlic and Indian mustard. Metallomics. 2017;9(1):61-8.
98. Donma M, Karasu E, Ozdilek B, Turgut B, Topcu B, Nalbantoglu B, et al. CD4(+), CD25(+), FOXP3 (+) T regulatory cell levels in obese, asthmatic, asthmatic obese and healthy children. Inflammation. 2015; 38(4): 1473-8.
99. Donma MM, Donma O. Trace elements and physical activity in children and adolescents with depression. Turkish J Med Sci. 2010; 40(3): 323-33.