Trop J Nat Prod Res, June 2022; 6(6):836-841 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Review Article

Overview of the Potential Role of Trace Elements in COVID-19

Sara T. Ismail* and Eman A. Sulaiman

College of Pharmacy, University of Mosul, Mosul, Iraq

ARTICLE INFO

Article history:
Received 20 January 2022
Revised 05 April 2022
Accepted 01 June 2022
Published online 02 July 2022

ABSTRACT

COVID-19 is constantly evolving due to genetic mutation, and different strains have been discovered all over the world. These variants appear to be transmitted more strongly than other types, potentially contributing to an increase in cases and deaths. Currently, there are several COVID-19 vaccines on the market. Despite the availability of these commercial vaccines, the number of admitted patients continues to rise in various parts of the world. The vaccines' consistency and efficacy, in terms of variations between effects of different brands, remain ambiguous due to viral variants. Trace element deficiencies have been shown to reduce the immune response to invader pathogens and contribute to global health issues. Deficiencies in vitamins, copper, selenium, and zinc have been shown in clinical trials to alter the immune response and increase the risk of viral infections. Due to the antiviral and anti-inflammatory properties of these micronutrients, dietary supplementation of these components is likely to increase the immune response and lower the severity of COVID-19 infection. Based on existing research, therapeutic use of important trace element supplements, such as minerals (Cu, Se, and Zn) or vitamins (such as vitamins D and C), may be a preventive and consistent strategy for strengthening the immune system against the emerging pandemic COVID-19 and its novel variants.

Keywords: Copper, COVID-19, Iron, Selenium, Vitamins, Zinc.

Introduction

Coronavirus 2019, also known as "severe acute respiratory syndrome (SARS)", is a virus that causes severe respiratory illness. "Coronavirus-2 (SARS-CoV-2)" belongs to the "Beta-coronavirus genus", a coronavirus strain that has impacted the lives of billions of people around the world. It can manifest itself in a variety of ways, ranging from asymptomatic to life-threatening diseases, and it can be accompanied by a cytokine storm.[1] The pathogenesis of COVID-19 is unknown, however, it is likely complex, resulting in a systemic hyper-inflammatory response and, in severe cases, thromboembolic complications.[2] Several vitamins and nutrients may be beneficial to COVID-19 patients due to their anti-inflammatory and antioxidant characteristics.[3] Vitamins A, B, C, D, E, and folate, as well as trace minerals like iron, zinc, magnesium, selenium, and copper, are essential for the innate and adaptive immune systems.[4] According to a study, some mild to moderate cases were treated with zinc and vitamins while severe cases needed hospital admission and conservative and pharmacological therapy.[5]
The present study was aimed at conducting a comprehensive review of the roles of commonly used trace elements and important vitamins in the management of COVID-19.

*Corresponding author. E mail: seraph.taha@uomosul.edu.iq
Tel: +9647511770316

Citation: Ismail ST and Sulaiman EA. Overview of the Potential Role of Trace Elements in COVID-19. Trop J Nat Prod Res. 2022; 6(6):836-841. doi.org/10.26538/tjnpr/v6i6.2

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

Methods

The first step employed in preparing this review article involved finding articles in the online journal literature with keywords that include, “Copper, COVID-19, Iron, Selenium, Vitamins, Zinc” PubMed, NCBI, Google Scholar, and Research Gate are the databases that were used for the online search.

Results and Discussion

The roles of Vitamins in immunity and viral infections
The deaths associated with COVID-19 disease are caused by an inflammatory reaction in the body, known as a cytokine storm, which is triggered by a coronavirus. This is the body's immune defense response, in which it produces large amounts of "inflammatory mediators," also known as cytokines.[6] In a cytokine storm, the immune system is associated with an “overdrive” and this causes the immune system to attack itself.[7] Vitamin D affects the function of "white blood cells" that fight inflammation, preventing them from releasing too many cytokines and causing a cytokine storm.[8] Vitamin D does not prevent a person from contracting the virus, but it does reduce the severity of the disease and the likelihood of death.[9] This also explains why children are unaffected by coronavirus disease. Innate immunity is not yet fully developed in children, but innate immunity, which is present from birth and does not elicit cytokine storm-like overreactions, is the main defense mechanism.[9,10]
The most important vitamin is vitamin D, which has the largest impact on public health. It is a general hormone in the body that is strongly involved in health. Vitamin D regulates the functioning of the body via regulating the defense system, the circulatory system, and cell division.[11] Vitamin D is an anti-aging hormone that slows down the aging process. According to studies, problems related to aging manifest themselves a few years later when vitamin D is taken daily compared to when it is not.[12] People will have healthier life years if they maintain a suitable level of vitamin D throughout their lives, which is also an important goal for public health. Vitamin D levels are

related to northern latitudes and the fact that humans only obtain enough vitamin D from the sun for 3-4 months per year.[13]

The coronary pandemic encouraged research into dietary supplements when it was discovered that vitamin D, as well as vitamins B, C, and E, zinc, selenium, fish oil, and other dietary supplements, improve immune defense and prevent COVID-19 viral infection.[3] When inhaled, the COVID-19 virus attaches to a protein called "angiotensin-converting enzyme 2 (ACE2)" in the mucous membranes of the nose and lungs.[1,2] The virus invades cells and produces angiotensin, which constricts blood vessels in the lungs and makes the viral infection worse. Children have less ACE2 in their noses than adults, which partly explains why children have a reduced risk of infection than adults. Diabetes and related diseases (insulin resistance and metabolic syndrome) increase the onset of ACE2, predisposing diabetics to severe viral infection and death. It is also proven that the levels of vitamin D in the blood of diabetics are often lower than normal.[14] Doctoral research has discovered a new molecular mechanism that explains why diabetics and overweight people are deficient in vitamin D. Diabetes and obesity impair the body's ability to metabolize vitamin D, resulting in deficiency, which explains why diabetics are more susceptible to COVID-19.[15] When compared to normal people, diabetics have a greater need for vitamin D. The fact that overweight people have less vitamin D than people of normal weight explains why the coronavirus is more dangerous to them. Vitamin D is a fat-soluble vitamin that is stored in a large amount of adipose tissue in the body.[13] A study reveals that mortality declines to zero when serum vitamin D levels reach 85 nmol/L. Immunity is at its peak and cancer growth is inhibited when serum vitamin D levels reach 150 nmol/L or higher. Simple laboratory measurements can be used to determine vitamin D levels.[15] Fresh fruit is high in vitamins and minerals, which benefit health by improving the operation of organs in the body by acting as catalytic components in immunological, biochemical, and metabolic reactions.[3,16]

The roles of trace elements in COVID-19

COVID-19 and zinc

Zinc (Zn) is a "trace element" that is required for a variety of endogenous food-energy-production processes.[17] This chemical has an important function in antiviral immunity, as well as reducing the risk of viral infection and having anti-inflammatory properties. Zn regulates lymphocyte apoptosis by regulating the action of cytokines.[18] The recommended daily Zn intake concentration for human nutrition is 11 mg/day. For COVID-19 older patients, Zn deficiency may be common. *In vitro* Zn consumption lowers viral RNA polymerase activity and coronavirus growth.[19] When given 30 mg Zn/day, nursing home patients in the United States experienced a significant increase in T-lymphocyte multiplication.[20] Furthermore, Zn consumption reduced the number of people who had lung disease and the number of people who died from it.[21] A recent medical study found that providing 115–184 mg Zn/day for 10 to 14 days to four confirmed SARS-CoV-19 outpatients (26–63 years old) resulted in a significant improvement.[22] According to a clinical investigation, three SARS-CoV-19 patients (ages 38 to 74) recovered after receiving 220 mg of zinc for five days in combination with hydroxychloroquine (HCQ).[23,24] Unlike in an observational trial, the effects of zinc sulfate supplementation in 196 SARS-CoV-19 patients suggested that Zn had only a little impact.

The use of a zinc acetate lozenge to treat flu symptoms reduces the length of the illness by seven to four days on average.[25] The findings are based on 13 different clinical trials, 1,401 treated patients, and three extensive meta-analyses.[26] In most of these studies, the pathogens were not identified. This indicates that all of the most prevalent infections are likely to be included, with the results being averaged. As a result, old-fashioned rhino and coronavirus infections, as well as some adenovirus and influenza viral infections, are likely to be involved.[27] New types of SARS-CoV-2 coronavirus infections are unlikely to be included in the studies. Thus, it is unclear how effective zinc acetate is against certain viruses. It is still unclear how zinc acetate works against viruses. One exception is the rhinovirus, for which there is some specific information. Efficacy is good, and zinc is likely to slow down the replication of the virus in some way.[25-27] There is currently no evidence (for or against) that zinc acetate potency has a role in SARS-CoV-2 coronavirus infection. Therefore, the guidelines remain unchanged. If a person is experiencing flu-like symptoms, it is advisable to start taking zinc acetate (a CE-marked medication) right away. It may well be one of the other pathogens mentioned above. A course of treatment for SARS-CoV-2 coronavirus infection may or may not help, although there is currently no documented disadvantage. If a person becomes ill or believes the regimen is not helping, they should stop it.[28]

COVID-19 and selenium

Selenium (Se) is a cofactor for several enzymes, including glutathione peroxidase (GPX), an antioxidant enzyme that protects cells from oxidative damage (ROS).[29] For human nutrition, 55 g of selenium per day is sufficient. Increased sensitivity to influenza virus infection is associated with a low Se status.[30] The antiviral activities of selenite (Se^{+4}) are linked to the trace element's antioxidant potential.[29] Selenite inhibits virus protein disulfide isomerase (PDI) in general, which prevents virus entry into healthy human cells.[28] In the elderly, Se supplementation improves immunity against influenza and increases T lymphocyte multiplication. Non-survivors had a considerable shortfall in total serum Se levels when compared to surviving "SARS-CoV-19 patients".[31]

COVID-19 and copper

Copper (Cu) is required for the immune system to function properly. This "trace element" is linked to the normal functioning of blood immune cells such as "natural killer (Nk) and T helper (Th) cells," which are involved in the eradication of viral infections and antibody production.[32] The recommended daily intake (RDI) of Cu is 0.90 mg. Cu is a cofactor for the enzyme superoxide dismutase (SOD), which protects cells from oxidative damage. Cu's antiviral activity is through the stoppage of viral RNA replication by disrupting the RNA structure.[30] The body becomes more sensitive to viral infections in persons with Cu deficiency. Percival (1998) demonstrated that immunological dysfunction is more prevalent in patients with dietary Cu deficiency in the elderly and young age groups. Many viruses, including the bronchitis virus, poliovirus, and HIV-1, are rendered inactive by Cu supplementation. Cu deficiency in the human diet reduces "interleukin-2 (IL-2) production and IL-2 mRNA" in T-lymphocytes.[32] The active viral particles of the human influenza virus A reduced the virus population from 500,000 to 500 after 6 hours of incubation on a Cu surface. Coronavirus 229E virus morphology (envelope breakdown, surface spike disintegration, and structural backbone DNA damage) is influenced by Cu contact surfaces, rendering it dormant. In this approach, SARS-CoV-2 (COVID-19) strain is more susceptible to Cu surface contact than SARS-CoV-1. [33]

COVID-19 and magnesium

Magnesium (Mg) is a very important mineral among the others. It provides physiologically healthy functions, such as an acid-base balance in the body, as well as bioenergetics and immune responses. Furthermore, it plays a vital role in DNA replication, nucleic acid metabolism, and leukocyte activation. Magnesium modulates apoptosis and antigen adherence by monocytes and has the potential to alter both humoral and cell-mediated adaptive immunity. In addition, magnesium is also known for its ability to prevent DNA damage caused by oxidative stress. In high quantities, the generation of superoxide anion is reduced.[34,35] As the level of magnesium deficiency rises, the likelihood of infection in the upper respiratory tract increases. Due to a lack of magnesium, the production of free radicals, acute-phase proteins, and pro-inflammatory cytokines may increase, resulting in a low-grade persistent infection. When the magnesium level is maintained, the structure and function of the lungs improve. Meanwhile, the increase in respiratory complications is still associated with its lower levels. There is no study available that explores the effects and consequences of Mg to date.[36,37]

COVID-19 and other elements (manganese, iron, nickel, and lithium)

Manganese (Mn) is an essential trace element that can be found in a variety of foods as well as dietary supplements. The immune system requires several micronutrients, such as vitamins and trace minerals, to function properly and protect cells from oxidative damage. Manganese is a trace element that has immunomodulatory properties.[38] It is also a component of antioxidant enzymes that can inhibit viral replication in

host cells, making it possess antiviral properties. Iron (Fe) is also the most abundant trace element required by humans. The overall iron content of the body is about 3–5 g, with the majority of it in the blood and the rest in the liver, bone marrow, and muscles as heme. COVID-19 infection is linked to iron deficiency, which has been recognized as a risk factor.[39] Furthermore, an increase in viral infections has been associated with a high iron level. As a result, antiviral iron chelators may be employed to treat SARS-CoV-2.[40]

Nickel (Ni) is an essential trace element found in reliable concentrations in cells and tissues and is bound with DNA and RNA in physiologically significant amounts.[41] It is required for the immune system's modulation. When a low dose of nickel chloride is given, it has an immunotoxic effect. Human coronavirus is rapidly inactivated on copper and nickel alloy substrates at body temperature (21°C), leading to the production of reactive oxygen species (ROS).[42] Lithium (Li) possesses antiviral effects against the coronavirus bronchitis virus.[43] It reduces coronavirus growth and cellular entrance in Vero cells in a dose-dependent manner by lowering viral protein gene transcription. In addition, lithium has anti-inflammatory properties by suppressing COX-2, IL-1β, and TNF-α expressions, and increasing IL-2 and IL-10 levels. The activity of Li makes it a potential pharmacotherapy for COVID-19.[44,45]

The roles of Vitamins in COVID-19

Vitamin D

Vitamin D has a variety of effects on the body's immune system. These include the regulation of immunological integrity, formation of a class of small peptides, the assistance of mast cells, erythrocytes, and fibroblast functions. Furthermore, the inflection of oxidative eruptive potency, elevated stimulation in the antagonist of the receptor of IL-4, IL-6, IL-10, IL-11, IL-13, and IFN γ reserve nuclear factor κB, and different pro-inflammatory responses of adaptable defensive cells have been reported. A decrease in the potency of vitamin D increases, sinus inflammation, asthma, tuberculosis, chronic lung diseases, lung infections, and potentially COVID-19 each has heightened intensity, mortality, and fatality. Research involving an early-age sick individual who has genetic variation in the receptors for vitamin D revealed the potential effect of vitamin D in the regulation of inflammatory system with viral respiratory disease, acute lower respiratory infections (ALRI). Vitamin D has an impact on the structure, size, volume, and functioning of the lungs.[46-48] Vitamin D deficiency aggravates several lung diseases. According to a recent meta-analysis, people with sufficient vitamin D status or regular oral medication are healthier, which lowers the risk of respiratory disease. Previous research has found a risk indicator and a treatment benefit reduction, but only in people with vitamin D deficiency. With this understanding, vitamin D supplementation could be a COVID-19 variable preventative therapy for those who have a deficiency or are at risk of vitamin D deficiency.[49-51]

Vitamin C

Epidermal stability is influenced by collagen production, epithelium differentiation, fibroblast migration, and amplification. Vitamin C is required for the activities, mobility, functions, proliferation, and differentiation of essential body defensive cells. Antimicrobial processes are accelerated by vitamin C, serum supplement proteins continue to rise, and IFN production is improved.[52,53] Vitamin C is a potent antioxidant that keeps the cells under reductive-oxidative stability within the immunological reactions. It also aids in the synthesis of antibodies from plasma cells, which supports the proliferation and differentiation of T-cells. Its deficiency has been linked to the risk and severity of a variety of respiratory diseases, including pneumonic symptoms. Oral vitamin C supplementation benefits children and adolescents, despite a plethora of contradictory and unclear evidence. In the elderly, it reduces the risk of pneumonia. In mice, a combination of red ginseng and vitamin C reduced cold pathogenic viruses and pulmonary inflammation while enhancing endurance. When it comes to affordability, convenience, and care, vitamin C will always be a good option for COVID-19 control.[54,55]

Vitamin A

Vitamin A is a required trace element for the maintenance and proper growth of the epithelial tissue barrier integrity. It has anti-inflammatory properties and enhances mucosal immunological responses. Vitamin A supports various NK cell functions, including phagocyte functions and macrophage oxidative burst. It suppresses the production of IFN, interleukin-2, and TNF as pro-inflammatory cytokines by Th1 cells, allowing the generally mediated antibody and Th2 reactions to continue. Vitamin A aids the production of antibodies by B cells. Its deficiency is a significant contributor to the increased risk of lung infections caused by viruses, as well as diarrhea and measles.[52,53] Cows with vitamin A deficiency was unable to develop innate immunity to the BRSV-NP vaccine.[56] This is a nanoparticle amphiphilic polyanhydride-based vaccine containing the merging and binding of proteins from cattle respiratory tract pathogens (syncytial virus). Supplementation reduced the incidence of all-cause morbidity and mortality from infectious disease in vitamin A-deficient children aged 6 months to 5 years. Nonetheless, vitamin A supplementation reduced the risk of pneumonia vaccination, which is based on encapsulating the attachment of fusion proteins from syncytial viruses and respiratory bovine, as well as recurring lung and respiratory infections after the virus challenge. Vitamin A supplementation improves vaccination antibody titer responses. In the COVID-19 incidence, vitamin A supplementation reduces the occurrence of Mycoplasma pneumonia bacterial infection, which occurs commonly following a viral illness. Vitamin A supplementation reduced all-cause morbidity and mortality among children aged 6 months to 5 years. Despite this, vitamin A supplementation had little effect on pneumonia. In terms of the potential side effects of vitamin A, a supplement is recommended during the COVID-19 treatment for undernourished people or those who show signs of vitamin A insufficiency.[57-59]

Vitamin E

Vitamin E is a liposome antioxidant that protects cell membranes from reactive oxygen species while also maintaining the integrity of respiratory epithelial barriers. It enhances the cytotoxicity of NK cells and inhibits macrophage production of prostaglandin E2. The generation of IFN-γ and interleukin 2 regulated by vitamin E aids lymphocyte activation. Vitamin E is necessary for the activation of active immunological synapses between Th cells, as well as the optimization of how Th1 responds and the repression of Th2 responses.[52,60] Vitamin E also increases the proportion of memory T-cells that are exposed to antigen.

The deficiency of vitamin E is rare in humans. Insufficiency condition inhibits both the humoral and cell-mediated immune defense processing systems of the human body, making virus infection with more pathogenic strains, major consequences, and abnormal immune responses less likely.[59-61] Vitamin E improves the human body's overall resistance to infection and the immune system. Also, it lowers the prevalence and severity of infection in the respiratory tract, lowers the concentration of virus in the lungs' tissues, and raises antibody titers during and after adolescence. Vitamin E supplementation appears to be beneficial in the treatment of COVID-19 and also for underweight or malnourished people during the COVID-19 period.[52,59,60]

Polyphenolic compounds and COVID-19

Polyphenolic compounds are the most common phytonutrients, and they have a wide range of biological and pharmacological activities, including antiviral, antioxidant, anti-inflammatory, and antibacterial properties. They have antiviral effects against the *Coronaviridae* family of viruses.[62-65] Resveratrol inhibits the MERS virus *in vitro*. Polyphenol catenin has been grafted onto the fiber filtering membrane of antiviral gas masks and cleansing wipes.[66,67] Punicalagin, theaflavindigallate, kaempferol, Sanguine and protocatechuic acid are the six phenolic acid compounds identified by the most recent computer-based virtual screening of microstructures that specifically and firmly approach the exact proteolytic enzymes of SARS-CoV-2. The host immune response is reduced by 4-hydroxystyryl via suppressing the informational nucleocapsid proteins of the virus. Helicase, a viral replication enzyme, is inhibited by quercetin.[68,69] The remaining polyphenols, such as delphinine and epigallocatechingallate, prevent the virus from attaching to the host. Polyphenols, such as flavonoids, may have an impact on COVID-19 management. Such numerous confirmations came from extensive

research. However, they are all based on *in vitro* studies; no *in vivo* data is available at this moment. It would be premature to speculate on their clinical applications at this time.[70]

Due to its enormous impact on medical facilities and widespread use of healthcare, COVID-19 rapidly became a pandemic around the globe, posing a severe threat to the world despite its low fatality rate. Clinical respiratory symptoms include dry cough, fever, anosmia, breathing difficulties, and respiratory failure. COVID-19 cannot be treated in any way that is currently known. In addition to the antiviral approach for treatment, immune effectors and modulating immunosuppression are plausible immunomodulation strategies in COVID-19 management. Although proper nutrition and dietary habits are important for improving immunity, micronutrients appear to have a significant role in immunomodulation.[71,72]

Virus-host interaction

As the interaction between the virus and host begins, it initiates the innate immunological processes, which are supported by the micro minerals that are included in the host's continuous immune responses to the infection. A healthy immune system requires a normal healthy and energetic contribution from several micronutrients, and a single nutrient hardly manages the entire defense system of the body. A variety of nutrients, such as vitamins A, C, D, E, B6, B12, folate, copper (Cu), magnesium (Mg), iron (Fe), selenium (Se), and zinc (Zn) are beneficial to the body during the virus-host interaction.[73-78] Biochemical anomalies in the respiratory tract as well as physical obstacles to the virus, constitute first-line projections. Iron and vitamin A are required for their normal epithelial differentiation and development. The fickleness of the membrane, its integrity, intercellular connection, and tissue healing are all regulated by Zn and vitamins A, C, and D. Vitamin E inhibits the peroxidation of lipids by reactivating oxygen species. Vitamins A, C, and D, as well as their constituent elements Cu, Fe, Se, and Zn, regulate the activity of antimicrobial peptides bound to the membrane, the microbiota linked to mucosal activity, and mucosal-associated bacteria.[78] Vitamins B6, B12, and folate also modulate mucosal migration as well as defense cell synchronization.

Interferon (IFN) is an important immune system provoking factor that is involved in viral infections and maintain the phenotypes Th1 and Th2' stability of the adaptive immune system. IFN is one of the most important cytokines that act against the virus at the outer layered blockades, causing inflammation, and apoptotic cell degradation. Furthermore, Type-I IFNs enhance reactivity to TLRs and MAVS disease-causing functions.[79-83] The primary defense line is activated to prevent the infection of bronchial respiratory epithelium by SARS-CoV-2. This is achieved by moving, migrating, differentiating, proliferating, and activating to counteract the virus from replication. Cytokines and oxidative bursts cause the pro-inflammatory mile, but the virus slows and delays the activity of IFNs. Without effective counter-regulatory immunological activities, activation of adaptive immunity's Th1/Th17 phenotypes promotes hyper-inflammatory conditions and interleukin. SARS-CoV-2 explicit immunoglobulin is eventually protected by a well strengthened defensive ability, and the virus is neutralized as a result.[80-83] Vitamins A, B6, B12, C, D, E, and folate, as well as mineral components Mg, Cu, Zn, Fe, and Se, were proposed as the nutrients that trigger the entire chain of virus-host immunogenicity. They help by regulating the activities of natural immune cells such as leukocytes, white blood cells, phagocytes, and scavenger cells. They also play vital roles in anti-inflammatory interleukin production and reaction, oxidative stress, reductive arteriosclerosis, adaptive immune response (including T-cell variety, development, and working within T-cells), intuitive with the presence of viral antigens, and the generation of antiviral antibiotics. Despite synergistic contributions to hosts' pathogenic interactions and a reduction in specific nutrients, the extensive experimental investigation of infection by SARS-CoV-2 has revealed a single susceptibility. The components that can occur prior to several micronutrient deficiencies, as well as the consequences of COVID-19 intakes.[84-88]

Conclusion

The novel "acute respiratory infection (COVID-19)" is frequently linked to a weakened human immune system, which results in severe pneumonia and death. Given the aforementioned characteristics, as well as evidence of trace element antiviral and anti-inflammatory effects, selenium, zinc, and copper could be effective elements for strengthening "immunity against viral infections" such as coronavirus and its new variants.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

References

1. Ciotti M, Ciccozzi M, Terrinoni A, Jiang WC, Wang CB, Bernardini S. The COVID-19 pandemic. Crit Rev Clin Lab Sci. 2020; 57(6):365-388.
2. Hanff TC, Mohareb AM, Giri J, Cohen JB, Chirinos JA. Thrombosis in COVID-19. Am J Hematol. 2020; 95(12):1578-1589.
3. Dhok A, Butola LK, Anjankar A, Shinde AD, Kute PK, Jha RK. Role of Vitamins and Minerals in Improving Immunity during Covid-19 Pandemic-A Review. J Evol Med Dent Sci. 2020; 9(32):2296-301.
4. Merkhan MM, Abdulrazzaq GM, Al-Taii HA. Coronavirus (COVID-19): preventive measures and potential interventions. Eur J Mol Clin Med. 2021; 7(10):1388-1399.
5. Darweesh O, Abdulrazzaq GM, Al-Zidan RN, Bebane P, Merkhan M, Aldabbagh R, AlOmari N. Evaluation of the Pharmacologic Treatment of COVID-19 Pandemic in Iraq. Curr Pharmacol Rep. 2021; 7(4):171-178.
6. Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 cytokine storm; what we know so far. Front Immunol. 2020; 11:1446.
7. Mukherjee K. COVID-19 and cytokine storm. Inter J Bioinf Biol Sci. 2020; 8(1):18-26.
8. Ebadi M, Montano-Loza AJ. Perspective: improving vitamin D status in the management of COVID-19. Eur J Clin Nutr. 2020; 74(6):856-859.
9. Razdan K, Singh K, Singh D. Vitamin D levels and COVID-19 susceptibility: is there any correlation? Medicine in drug discovery. 2020; 7:100051.
10. Molloy EJ and Murphy N. Vitamin D, Covid-19, and children. Ir Med J. 2020; 113(4):64.
11. Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. Am J Clin Nutr. 2008; 88(2):491S-499S.
12. Verstuyf A, Carmeliet G, Bouillon R, Mathieu C. Vitamin D: a pleiotropic hormone. Kidney Int. 2010; 78(2):140-145.
13. Kumar R, Rathi H, Haq A, Wimalawansa SJ, Sharma A. Putative roles of vitamin D in modulating immune response and immunopathology associated with COVID-19. Virus Res. 2021; 292:198235.
14. Fosbøl EL, Butt JH, Østergaard L, Andersson C, Selmer C, Kragholm K, Schou M, Phelps M, Gislason GH, Gerds TA, Torp-Pedersen C. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. J Am Med Assoc. 2020; 324(2):168-177.
15. Bilezikian JP, Bikle D, Hewison M, Lazaretti-Castro M, Formenti AM, Gupta A, Madhavan MV, Nair N, Babalyan V, Hutchings N, Napoli N. Mechanisms in endocrinology:

vitamin D and COVID-19. Eur J Endocrinol. 2020; 183(5):R133-147.
16. Fedele D, De Francesco A, Riso S, Collo A. Obesity, malnutrition, and trace element deficiency in the coronavirus disease (COVID-19) pandemic: an overview. Nutr. 2021; 81:1-14.
17. Althanoon ZA and Merkhan MM. Effects of zinc supplementation on metabolic status in patients with metabolic syndrome. Acta Pol Pharm. 2021; 78(4):521-526.
18. Calder PC. Nutrition, immunity, and COVID-19. BMJ Nutr Prev Health. 2020; 3(1):74.
19. Pal A, Squitti R, Picozza M, Pawar A, Rongioletti M, Dutta AK, Sahoo S, Goswami K, Sharma P, Prasad R. Zinc and COVID-19: basis of current clinical trials. Biol Trace Elem Res. 2021; 199(8):2882-2892.
20. Gromova OA and Torshin IY. The importance of zinc in maintaining the activity of antiviral innate immunity proteins: analysis of publications on COVID-19. J Prev Med Pub Health. 2020; 3(23):131-139.
21. Brooks WA, Yunus M, Santosham M, Wahed MA, Nahar K, Yeasmin S, Black RE. Zinc for severe pneumonia in very young children: a double-blind placebo-controlled trial. The Lancet. 2004; 363(9422):1683-1688.
22. Ebrahimzadeh-Attari V, Panahi G, Hebert JR, Ostadrahimi A, Saghafi-Asl M, Lotfi-Yaghin N, Baradaran B. Nutritional approach for increasing public health during the pandemic of COVID-19: A comprehensive review of antiviral nutrients and nutraceuticals. Health Promot Perspect. 2021; 11(2):119.
23. Stratton CW, Tang YW, Lu H. Pathogenesis-directed therapy of 2019 novel coronavirus disease. J Med Virol. 2021; 93(3):1320-1342.
24. Nedjimi B. Can trace element supplementations (Cu, Se, and Zn) enhance human immunity against COVID-19 and its new variants?. Beni-Seuf Univ J Appl. 2021; 10(1):1-5.
25. Hemilä H, Haukka J, Alho M, Vahtera J, Kivimäki M. Zinc acetate lozenges for the treatment of the common cold: a randomized controlled trial. Br Med J Open. 2020; 10(1):e031662.
26. Jia W, Song Y, Yang L, Kong J, Boczek T, He Z, Wang Y, Zhang X, Hu H, Shao D, Tang H. The changes of serum zinc, copper, and selenium levels in epileptic patients: A systematic review and meta-analysis. Exp Rev Clin Pharmacol. 2020; 13(9):1047-1058.
27. Vogel-González M, Talló-Parra M, Herrera-Fernández V, Pérez-Vilaró G, Chillón M, Nogués X, Gómez-Zorrilla S, López-Montesinos I, Arnau-Barrés I, Sorli-Redó ML, Horcajada JP. Low zinc levels at admission associates with poor clinical outcomes in SARS-CoV-2 infection. Nutr. 2021; 13(2):562.
28. Kaye K, Paprottka F, Escudero R, Casabona G, Montes J, Fakin R, Moke L, Stasch T, Richter D, Benito-Ruiz J. Elective, non-urgent procedures, and aesthetic surgery in the wake of SARS–COVID-19: considerations regarding safety, feasibility, and impact on clinical management. Aesthetic Plast Surg. 2020; 44(3):1014-1042.
29. Kieliszek M. Selenium–fascinating microelement, properties, and sources in food. Mol. 2019; 24(7):1298.
30. Beck MA, Nelson HK, Shi Q, Van Dael P, Schiffrin EJ, Blum S, Barclay D, Levander OA. Selenium deficiency increases the pathology of an influenza virus infection. The FASEB J. 2001; 15(8):1481-1483.
31. Narota A, Puri G, Singh VP, Kumar A, Naura AS. COVID-19, and ARDS: Update on Preventive and Therapeutic Venues. Curr Mol Med. 2021; 22(4):312-324.
32. Percival SS. Copper and immunity. Am J Clin Nutr. 1998; 67(5):1064S-1068S.
33. Fooladi S, Matin S, Mahmoodpoor A. Copper as a potential adjunct therapy for critically ill COVID-19 patients. Clin Nutr ESPEN. 2020; 40:90-91.
34. Bussière FI, Mazur A, Fauquert JL, Labbe A, Rayssiguier Y, Tridon A. High magnesium concentration in vitro decreases human leukocyte activation. Magnesium Res. 2002; 15(1-2):43-48.
35. Laires MJ and Monteiro C. Exercise, magnesium, and immune function. Magnes Res. 2008; 21(2):92-96.
36. Landon RA and Young EA. Role of magnesium in the regulation of lung function. J Am Diet Assoc. 1993; 93(6):674-677.
37. Janssen R. Magnesium to counteract elastin degradation and vascular calcification in chronic obstructive pulmonary disease. Med Hyp. 2017; 107(2):74-77.
38. Son EW, Lee SR, Choi HS, Koo HJ, Huh JE, Kim MH, Pyo S. Effects of supplementation with higher levels of manganese and magnesium on immune function. Arch Pharm Res. 2007; 30(6):743-749.
39. Girelli D, Marchi G, Busti F, Vianello A. Iron metabolism in infections: Focus on COVID-19. Semin hematol. 2021; 58(3):182-187.
40. Perricone C, Bartoloni E, Bursi R, Cafaro G, Guidelli GM, Shoenfeld Y, Gerli R. COVID-19 as part of the hyperferritinemia syndromes: the role of iron depletion therapy. Immunol Res. 2020; 68(4):213–224.
41. Yu L, Peel GK, Cheema FH, Lawrence WS, Bukreyeva N, Jinks CW, Peel JE, Peterson JW, Paessler S, Hourani M, Ren Z. Catching and killing of airborne SARS-CoV-2 to control spread of COVID-19 by a heated air disinfection system. Mat today Phy. 2020; 15(1):1-5.
42. Salnikow K, Su W, Blagosklonny MV, Costa M. Carcinogenic metals induce hypoxia-inducible factor-stimulated transcription by reactive oxygen species-independent mechanism. Cancer Res. 2000; 60(13):3375-3378.
43. Rajkumar RP. Lithium as a candidate treatment for COVID-19: promises and pitfalls. Drug Dev Res. 2020; 81(7):782-785.
44. Spuch C, López-García M, Rivera-Baltanás T, Rodrígues-Amorím D, Olivares JM. Does lithium deserve a place in the treatment against COVID-19? A preliminary observational study in six patients, case report. Front Pharm. 2020; 11(2):1-8.
45. Viel T, Chinta S, Rane A, Chamoli M, Buck H, Andersen J. Microdose lithium reduces cellular senescence in human astrocytes-a potential pharmacotherapy for COVID-19?.Aging. 2020; 12(11):10035-10040.
46. Wu D, Lewis ED, Pae M, Meydani SN. Nutritional modulation of immune function: analysis of evidence, mechanisms, and clinical relevance. Front Immunol. 2019; 9(2):1-19.
47. Matsui T, Takahashi R, Nakao Y, Koizumi T, Katakami Y, Mihara K, Sugiyama T, Fujita T. 1, 25-dihydroxy vitamin D3-regulated expression of genes involved in human T-lymphocyte proliferation and differentiation. Cancer Res. 1986; 46(11):5827-5831.
48. Reichel H, Koeffler HP, Tobler A, Norman AW. 1 alpha, 25-dihydroxyvitamin D3 inhibits gamma-interferon synthesis by normal human peripheral blood lymphocytes. Proc Nat Acad Sci. 1987; 84(10):3385-3389.
49. Rigby WF, Denome S, Fanger MW. Regulation of lymphokine production and human T lymphocyte activation by 1, 25-dihydroxy vitamin D3. Specific inhibition at the level of messenger RNA. J Clin Invest. 1987; 79(6):1659-1664.
50. Zosky GR, Berry LJ, Elliot JG, James AL, Gorman S, Hart PH. Vitamin D deficiency causes deficits in lung function and alters lung structure. Am J Res Crit Care Med. 2011; 183(10):1336-1343.
51. Beyhan-Sagmen S, Baykan O, Balcan B, Ceyhan B. Association between severe vitamin D deficiency, lung function and asthma control. Arch Bronch. 2017; 53(4):186-191.
52. Maggini S, Beveridge S, Sorbara PJ, Senatore G. Feeding the immune system: the role of micronutrients in restoring resistance to infections. CAB Reviews: Perspectives in

Agriculture, Veterinary Science, Nut Nat Res. 2008; 3(098):1-21.
53. Carr NB and Melcher CP, editors. Wyoming Basin rapid ecoregional assessment. US Department of the Interior, US Geological Survey; 2017; 17(1):233-238.
54. Prentice S. They are what you eat: can nutritional factors during gestation and early infancy modulate the neonatal immune response? Front Immunol. 2017; 8(4):1-20.
55. Kim H, Jang M, Kim Y, Choi J, Jeon J, Kim J, Hwang YI, Kang JS, Lee WJ. Red ginseng and vitamin C increase immune cell activity and decrease lung inflammation induced by influenza A virus/H1N1 infection. J Pharm Pharmacol. 2016; 68(3):406-420.
56. McGill JL, Kelly SM, Guerra-Maupome M, Winkley E, Henningson J, Narasimhan B, Sacco RE. Vitamin A deficiency impairs the immune response to intranasal vaccination and RSV infection in neonatal calves. Sci Rep. 2019; 9(1):1-4.
57. Wishart K. Increased micronutrient requirements during physiologically demanding situations: a review of the current evidence. Vitam Miner. 2017; 6(166):1318-2376.
58. Pettifor JM, Zlotkin S, editors. Micronutrient deficiencies during the weaning period and the first years of life. Karger Medical and Scientific Publishers. 2004; 27(1):200-204.
59. Center MI. L.P. Institute (Ed.), Immunity In Brief, 2017; 22(1):218-222.
60. Haryanto B, Suksmasari T, Wintergerst E, Maggini SJ. Multivitamin supplementation supports immune function and ameliorates conditions triggered by reduced air quality. Vitam Miner. 2015; 4(3):1-5.
61. Traber MG and Atkinson J. Vitamin E, antioxidant and nothing more. Free Rad Bio Med. 2007; 43(1):4-15.
62. Lin SC, Ho CT, Chuo WH, Li S, Wang TT, Lin CC. Effective inhibition of MERS-CoV infection by resveratrol. BMC Inf Dis. 2017; 17(1):1-10.
63. Li YQ, Li ZL, Zhao WJ, Wen RX, Meng QW, Zeng Y. Synthesis of stilbene derivatives with inhibition of SARS coronavirus replication. Eur J Med Chem. 2006; 41(9):1084-1089.
64. Jo S, Kim H, Kim S, Shin DH, Kim MS. Characteristics of flavonoids as potent MERS-CoV 3C-like protease inhibitors. Chem Bio Drug Des. 2019; 94(6):2023-2030.
65. Park HR, Yoon H, Kim MK, Lee SD, Chong Y. Synthesis and antiviral evaluation of 7-O-aryl methyl quercetin derivatives against SARS-associated coronavirus (SCV) and hepatitis C virus (HCV). Arch Pharm Res. 2012; 35(1):77-85.
66. Lin SC, Ho CT, Chuo WH, Li S, Wang TT, Lin CC. Effective inhibition of MERS-CoV infection by resveratrol. BMC Infect Dis. 2017; 17:136-144.
67. Bhatia S, Giri S, Lal AF, Singh S. Identification of potential inhibitors of dietary polyphenols for SARS-CoV-2 M protease: An in silico study. One Health Bull. 2020; 1:21-9.
68. Nguyen TT, Woo HJ, Kang HK, Nguyen VD, Kim YM, Kim DW, Ahn SA, Xia Y, Kim D. Flavonoid-mediated inhibition of SARS coronavirus 3C-like protease expressed in Pichia pastoris. Biotech Lett. 2012; 34(5):831-838.
69. Pár A, Rőth E, Miseta A, Hegedüs G, Pár G, Hunyady B, Vincze Á. Effects of silymarin supplementation in chronic hepatitis C patients treated with peg-interferon+ ribavirin. A placebo-controlled double-blind study. OrvosiHetilap. 2009; 150(2):73-79.
70. Vázquez-Calvo Á, Jiménez de Oya N, Martín-Acebes MA, Garcia-Moruno E, Saiz JC. Antiviral properties of the natural polyphenols delphinidin and epigallocatechingallate against the flaviviruses West Nile virus, Zika virus, and dengue virus. Front Microbiol. 2017; 8(3):1-8.
71. Sokmen M, Angelova M, Krumova E, Pashova S, Ivancheva S, Sokmen A, Serkedjieva J. In vitro antioxidant activity of polyphenol extracts with antiviral properties from *Geranium sanguineum* L. Life Sci. 2005; 76(25):2981-2993.
72. Iyer M, Jayaramayya K, Subramaniam MD, Lee SB, Dayem AA, Cho SG, Vellingiri B. COVID-19: an update on diagnostic and therapeutic approaches. BMB Rep. 2020; 53(4):191.
73. Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system–working in harmony to reduce the risk of infection. Nutr. 2020; 12(1):1-28.
74. Sun J and De Vos P. Immunomodulatory functions of nutritional ingredients in health and disease. Front Immunol. 2019; 10:1-3.
75. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol. 2020; 38(1):1-9.
76. Saeed F, Nadeem M, Ahmed RS, Tahir Nadeem M, Arshad MS, 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):205-229.
77. Alpert PT. The role of vitamins and minerals on the immune system. Health Care Manag Prac. 2017; 29(3):199-202.
78. Zoroddu MA, Aaseth J, Crisponi G, Medici S, Peana M, Nurchi VM. The essential metals for humans: a brief overview. J Inorg Biochem. 2019; 195(6):120-129.
79. Chew BP and Park JS. Carotenoid action on the immune response. J Nut. 2004; 134(1):257S-61S.
80. Yin Z, Pintea V, Lin Y, Hammock BD, Watsky MA. Vitamin D enhances corneal epithelial barrier function. Invest Ophthvis Sci. 2011; 52(10):7359-7364.
81. Hemilä H. Vitamin C and infections. Nutr. 2017; 9(4):1-28.
82. Lin PH, Sermersheim M, Li H, Lee PH, Steinberg SM, Ma J. Zinc in wound healing modulation. Nutr. 2017; 10(1):1-16.
83. Biesalski HK. Nutrition meets the microbiome: micronutrients and the microbiota. Annthe New York Acad Sci. 2016; 1372(1):53-64.
84. 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(6):48-56.
85. Zhou JH, Wang YN, Chang QY, Ma P, Hu Y, Cao X. Type III interferons in viral infection and antiviral immunity. Cell Physiol Biochem. 2018; 51(1):173-185.
86. Lee SH, Kim SY, Jung K, Cho ML. Interferon-gamma regulates inflammatory cell death by targeting necroptosis in experimental autoimmune arthritis. Sci Rep. 2017; 7(1):1-9.
87. McCarty MF and Di Nicolantonio JJ. Nutraceuticals have the potential for boosting the type 1 interferon response to RNA viruses including influenza and coronavirus. Prog Card Dis. 2020; 63(3):383.
88. Pae M, Meydani SN, Wu D. The role of nutrition in enhancing immunity in aging. Aging Dis. 2012; 3(1):91-129.