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Review Article

SARS-CoV-2: Micronutrient Optimization in Supporting Host Immunocompetence

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Abstract

The novel 2019 coronavirus (SARS-CoV-2) has become an international pandemic. The lack of targeted treatment for SARS-CoV-2 has necessitated the need to evaluate all potential modalities to enhance host immune response. This article reviews the role essential micronutrients play in the risk reduction and treatment of COVID-19. While literature supporting the risk and severity reduction of COVID-19 infections through exogenous supplementation is limited, micronutrient optimization is essential in maintaining host immunocompetence, and deficits may critically impair host defense. The immune supportive mechanisms and physiologic effects of various micronutrients are multifaceted, including the reduction of viral replication, inhibition of polymerase function, augmentation of innate and acquired immune responses, enhancement of anti-inflammatory immune responses, and the reduction of pro-inflammatory responses.

Keywords: COVID-19; immunocompetence; micronutrients; SARS-CoV-2; coronavirus

Host Immune Response

Micronutrient optimization is critical in maintaining host immunocompetence [4]. Micronutrient deficiencies may predispose the host to viral infection acquisition [4]. Severe cases of SARS-CoV-2 can trigger an uncontrolled inflammatory immune response characterized by lymphopenia, reduced natural killer cells, CD4+, CD8+, T lymphocytes, B lymphocytes, basophils, monocytes, and eosinophils [68]. SARS-CoV-2 induced cytokine storm triggers the excessive production of pro-inflammatory cytokines [68]. Clinical laboratory findings include lymphopenia, elevated CRP, elevated LDH, elevated D-dimer and increased ferritin levels [68]. Cytokine storm precipitates neutrophil and macrophage sequestration, infiltration, pulmonary hyaline membrane formation and diffuse alveolar wall thickening [68]. Subsequently, multiple organ dysfunction may ensue [68].

The immune system response consists of innate and adaptive immunity [4]. Innate immunity includes physiological barrier mechanisms of the respiratory and GI tract, and general non-specific immune responses such as inflammation. This includes leukocyte activity (phagocytes, macrophages, mast cells, neutrophils, eosinophils, natural killer cells and dendritic cells) and complement system activity (opsonisation, cell lysis, agglutination, chemotaxis) [4].

Adaptive, acquired immune responses are antigen-specific, consisting of B and T lymphocyte responses [4]. B lymphocytes contribute to the humoral immune response, are highly specific, and bind directly to antigens [4]. T lymphocytes contribute to the cellular-mediated immune response through the expression of T cell receptors, and CD4+ or CD8+ cells, that recognize antigens bound to class I or II major histocompatibility complexes (MHC) [4].

Vitamin D (1,25-dihydroxyvitamin D_3)

Vitamin D (1,25-dihydroxyvitamin D_3) reduces the risk of host viral respiratory infection acquisition [1,5-13] 1,25-dihydroxyvitamin D_3 can be acquired exogenously or endogenously through the synthesis of steroid hormone, cholecalciferol, when the host is exposed to ultraviolet light [36,44,47] Physiologically, vitamin D_3 undergoes hepatic conversion to 25(OH)D with subsequent renal conversion to its active form, 1,25-dihydroxyvitamin D_3 (1,25(OH)2D) [1]. This hormonal metabolite, also known as calcitrol, directly targets genome sequences, inducing genetic and epigenetic transcription modifications [1].

1,25-dihydroxyvitamin D_3 functions to promote bone mineralization by regulating serum levels of phosphorus and calcium [36]. Increased levels of serum 1,25-dihydroxyvitamin D_3 provides enhanced innate immunity barrier support through the maintenance of gap, tight and adherens junctions [13]. 1,25-dihydroxyvitamin D_3 reduces pro-inflammatory cytokines TNF-α and INF-γ and increase anti-inflammatory cytokine expression [12,14,15]. 1,25-dihydroxyvitamin D_3 elicits antimicrobial peptides, cathelicidins and defensins, which are found to reduce the rate of viral replication and reducing pro-inflammatory cytokine concentrations [1,21]. Observational studies suggest a serum 1,25-

dihydroxyvitamin D_3 therapeutic goal of ≥ 40–60 ng/mL (100–150 nmol/L) in the reduction of hospital-acquired viral infections 16-18].

Supra-therapeutic dosages of 1,25-dihydroxyvitamin D_3 have been shown to reduce the duration of hospitalization in ventilated critical care patients from a hospital stay of 36 (SD=19) to a duration of 18 (SD=11) days in patients receiving treatments of 500,000 IU 1,25-dihydroxyvitamin D_3 [19]. Moreover, 1,25-dihydroxyvitamin D_3 has been clinically shown to increase levels of hemoglobin, enhance the metabolism of iron, and improve host oxygen carrying capacity [19,20].

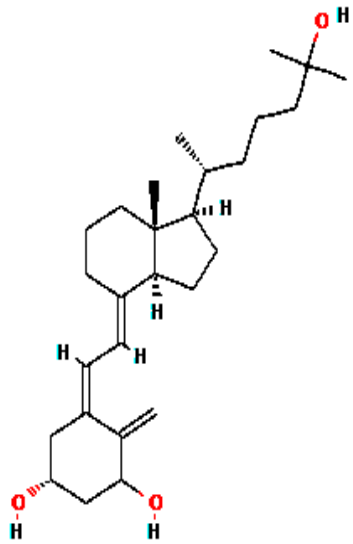

Figure 1: 1,25-dihydroxyvitamin D3
Retrieved from: *National Center for Biotechnology PubChem Compound Database [36]*
Vitamin C (l-ascorbic acid)

Ascorbic acid, a water-soluble form of vitamin C, functions as a potent antioxidant and detoxifier [40], Pro-inflammatory cytokines contribute to the severe inflammation of the lungs as observed in severe cases of SARS-CoV-2 [1,3]. Scavengers of reactive oxygen species, such as vitamin C, may play an influential role in minimizing cytokine storm and alleviating tissue damage [3,25]. Antioxidants found in vitamin C enhance T lymphocyte response, natural killer cell activity, and interleukin-2 production [28,29]. Vitamin C supports the maintenance of gap, tight and adherens junctions in epithelial barriers, increases serum antibody levels, and increases lymphocyte production and differentiation [22,23]. Vitamin C has also been shown to have anti-histamine properties [44,52].

Vitamin C deficiency has been linked to the development of viral and bacterial pneumonia [24,32,53]. Two randomized controlled trials identified a dose-dependent relationship between levels of vitamin C and the duration of symptomatic respiratory infections with vitamin C doses of 6-8g/day [24].

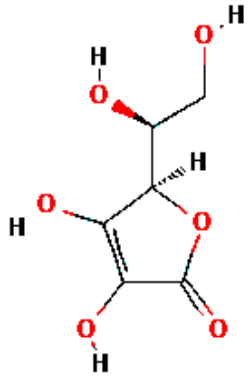

Figure 2: l-ascorbic acid
Retrieved from: *National Center for Biotechnology PubChem Compound Database [40] Vitamin E (α-tocopherol)*

Vitamin E is a fat-soluble vitamin and anti-oxidant bioavailable in the form of α-tocopherol [39]. α-tocopherol is a scavenger of reactive oxygen species, neutralizing free radicals, and influential in minimizing cytokine storm and tissue damage [3,25]. α-tocopherol prevents protein oxidation,

lipid perioxidation, and inhibits protein kinase C (PKC) mediated pathways [39]. Antioxidants found in α-tocopherol enhance T lymphocyte response, natural killer cell activity and interleukin-2 production [28,29].

α-tocopherol inhibits platelet aggregation, promotes vasodilation, stabilizes membranes, and inhibits angiogenesis [39].

Deficiency of α-tocopherol reduces adaptive immune response, hindering B and T lymphocyte function [4]. The utilization of exogenous vitamin E supplementation is controversial and may increase all-cause mortality [37]. It should be noted that simultaneous vitamin C and vitamin E supplementation has been shown to increase pneumonia and tuberculosis risk when compared to vitamin C supplementation alone [26,27].

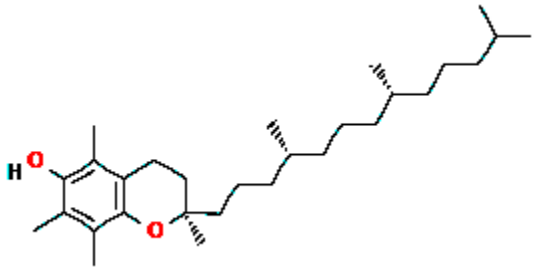

Figure 3: α-tocopherol
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Vitamin A (β-carotene)

β-carotene is a naturally occurring retinol, pro-vitamin A [41,46]. β-carotene has antineoplastic properties and is a scavenger of reactive oxygen species [3,25,41]. Antioxidants found in β-carotene also enhance T lymphocyte response, natural killer cell activity and interleukin-2 production [28,29]. Vitamin A has been shown to reduce the overall severity and consequent fatalities associated with HIV, malaria, and measles [48]. An animal model study linked increased rates of infectious bronchitis coronavirus in chickens with vitamin A deficiency [44,49]

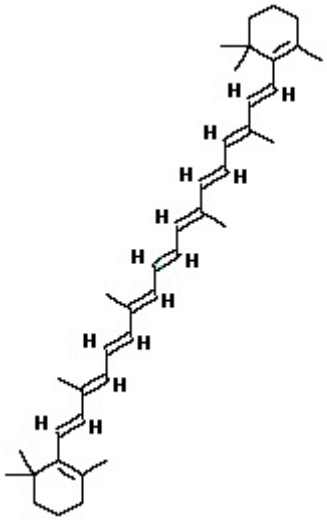

Figure 4: *β-carotene*
Retrieved from: *National Center for Biotechnology PubChem Compound Database [41]*

Vitamin B2 (riboflavin)

Vitamin B2 (riboflavin) is a water-soluble precursor to flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) [57]. FMN and FAD are essential in respiration, metabolism of fats, proteins, carbohydrates, and in detoxification mediated by glutathione reductase [57]. Riboflavin and UV light has been shown to reduce human plasma viral titer levels of MERS- CoV [44,50].

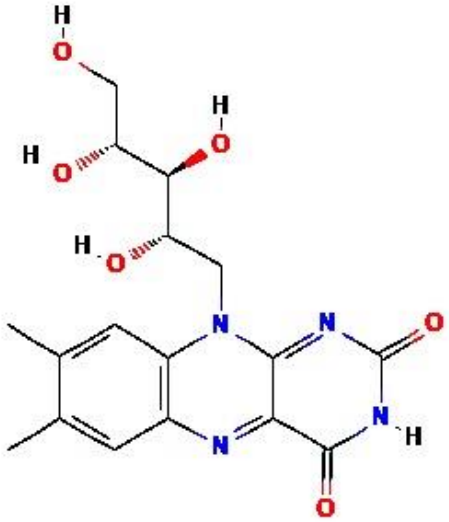

Figure 5: Riboflavin
Retrieved from: *National Center for Biotechnology PubChem Compound Database [57]*
Vitamin B3 (nicotinic acid)

Vitamin B3 (Nicotinic acid), also called nicotinamide or niacin, is a water-soluble vitamin that promotes DNA repair, energy metabolism, vasodilation, and reduced serum lipids [58]. Nicotinic acid lowers low density lipoprotein cholesterol and raises high density lipoprotein cholesterol [58]. Nicotinic acid has anti-inflammatory properties and has been shown to inhibit pulmonary neutrophil infiltration in cases of ventilator- induced pulmonary injury, albeit, increasing overall hypoxia [44,51]. Serum aminotransferase levels must be monitored with the administration of chronic or high dose nicotinic acid [58].

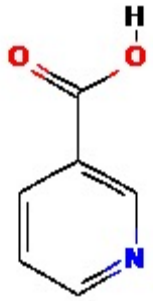

Figure 6: Nicotinic Acid
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Vitamin B6 (pyridoxine)

Pyridoxine is the 4-methanol form of vitamin B6, a water soluble vitamin that acts as a coenzyme in amino acid and neurotransmitter synthesis [63]. Large dose (50-100 mg/day) pyridoxine administration has been shown to increase T lymphocyte production and activity [61,62].

Figure 7: Pyridoxine
Retrieved from: *National Center for Biotechnology PubChem Compound Database [63]*

Vitamin B12 (cyanocobalamin)

Vitamin B12 (cyanocobalamin) is an immunomodulator for cellular immunity [62]. Cyanocobalamin functions to support the hematopoietic, nervous and immune systems [59,60]. Exogenous cyanocobalamin is necessary in the myelin synthesis, cellular growth, cellular reproduction, and erythropoiesis [59, 61]. Cyanocobalamin deficiency may lead to megaloblastic anemia, disruption of neuron myelin sheath integrity, and reduced protective immune response [12]. Methyl-B12 administration has been shown to increase leukocyte, lymphocyte, CD8+ cell, and natural killer cell production ($P < 0.05$) [62]. Vitamin B12 deficiencies lead to CD8+ and natural killer cell suppression [62]. Restoration and augmentation of cyanocobalamin levels can be achieved in patients with COVID-19 with methyl-B12 administration [62].

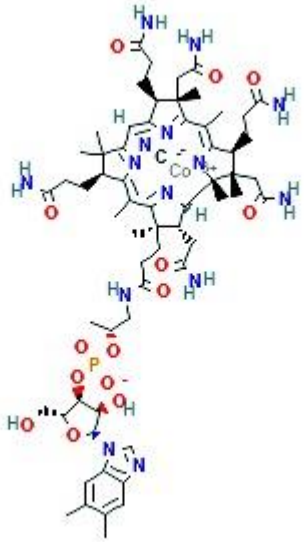

Figure 8: Cyanocobalamin
Retrieved from: *National Center for Biotechnology PubChem Compound Database [59]*

Zinc

Zinc supports both innate and acquired immune responses [44]. Zinc supplementation has been shown in several randomized controlled trials and in a meta-analysis to reduce the incidence and the duration of acute respiratory infections by 35% and 2 days, respectively. This effect has not been found to be dose dependent [30,31]. Zinc has been shown in vitro to inhibit SARS-CoV RNA polymerase activity and viral replication [2]. Zinc lozenges are shown to reduce viral respiratory infection duration and severity if utilized within 24 hours of the onset of respiratory symptoms [30]. Zinc lozenges may reduce the binding efficacy of the SARS-CoV-2 virus to the host oral mucosa [30,34,35].

Iron

Iron deficiency is a contributor to the development of lower respiratory tract infections [52]. Excess iron, however, can lead to oxidative damage

and viral mutation [44,52]. Iron deficiency should be avoided in the prevention of SARS-CoV-2 acquisition. In patients with diagnosed SARS-CoV-2, elevated serum ferritin levels are observed in patients with SARS-CoV-2 induced cytokine storm [42]. One hemoglobin molecule is comprised 2-α and 2-β subunits. Each subunit has one iron-bound heme complex [42]. Elevated serum ferritin suggests that excessive iron levels accumulating due to SARS-CoV-2 interfering with the iron-bound heme complex [42]. Thus, supplementation of iron should be avoided in patients with diagnosed SARS-CoV-2 infection.

Selenium

Selenium deficiency may induce viral genome mutation of RNA viruses. These mutations may amplify virulence in the host, creating increasing the magnitude and severity of the resultant infection [44]. Selenium, synergistically with vitamin E, acts as a scavenger of reactive oxygen species, also influential in minimizing cytokine storm and tissue damage [3,25,42].

Omega- 3 Long- chain Polyunsaturated Fatty Acids

Omega- 3 polyunsaturated fatty acids promote anti- inflammatory effects and are precursors to protectins and resolvins [44]. Omega- 6 polyunsaturated fatty acids promote pro- inflammatory effects and are precursors to prostaglandins and leukotrienes [44]. A delicate balance of omega-3 and omega-6 polyunsaturated fatty acids must be maintained to minimize pro- inflammatory effects. Protectin D1 is an omega- 3 polyunsaturated fatty acid derived lipid mediator shown to reduce influenza viral replication, reduce influenza mortality in animal models, and have been shown to target hepatitis C viral replication [44,55,56].

Micronutrient	Sources	Selected Physiologic Effects
Vitamin D (1,25dihydroxyvitamin D_3)	Green vegetables, legumes, egg yolks, cheese, beef, tuna, mackerel, soy [67]	↓Pro-inflammatory cytokines TNF-α and INF-γ ↑Anti-inflammatory cytokines Epithelial barrier support ↑O_2 carrying capacity
Vitamin C (l-ascorbic acid)	Green vegetables, citrus fruits [40]	Epithelial barrier support Antioxidant Anti-histamine ↑Antibody production ↑Lymphocyte production and differentiation ↓Pro-inflammatory cytokines TNF-α and INF-γ Dose dependent effect
Vitamin B2 (riboflavin)	Eggs, leafy greens, liver, kidney, heart, milk, malted barley, yeast [57]	FMN and FAD production Respiration Metabolism of macronutrients Detoxification
Vitamin B3 (Nicotinic acid)	Tuna, salmon, legumes, coffee, vegetables, poultry [67]	DNA repair Energy metabolism Vasodilation ↓ LDL ↑ HDL
Vitamin B6 (pyroxidine)	Eggs, vegetables, meats, liver [67]	↑lymphocyte production

Vitamin B12 (cyanocobalamin)	Salmon, egg, clams, liver, canned tuna, trout, beef [67]	↑ leukocyte production ↑ lymphocyte production ↑ CD8+ cell production ↑ Natural killer cell production
Vitamin E (α-tocopherol)	Plant-based oils, nuts, seeds, grains, nuts, fruits, vegetables[38]	Epithelial barrier support Antioxidant ↓Pro-inflammatory cytokines TNF-α and INF-γ ↑Lymphocyte activity ↑Natural killer cell activity ↑IL-2 production ↓Platelet aggregation Vasodilation ↑Membrane stabilization ↓Angiogenesis
Vitamin A (β-carotene)	Orange, yellow and green leafy vegetables and fruits[41]	Antioxidant Antineoplastic ↑Lymphocyte activity ↑Natural killer cell activity ↑IL-2 production
Iron	Beans, lentils, tofu, potatoes, whole grain bread, dark leafy greens [67]	Essential in O_2 carrying capacity ↑Serum iron levels observed in SARS-CoV-2 induced cytokine storm
Zinc	Oysters, whole grains, milk, beans, chickpeas, nuts, poultry[67]	↓SARS-CoV RNA polymerase activity ↓Viral replication of SARS-CoV
Selenium	Brazil nuts, sunflower seeds, egg, spinach, tofu, brown rice[67]	Antioxidant
Omega-3 Fatty Acids	Fish oil, walnuts, pumpkin seeds, sesame seeds, vegetable oils, durum wheat [44,67]	Anti- inflammatory effects

Table 1: Micronutrient Optimization in Maintaining Host Immunocompetenc

Discussion

Anti-aging gene Sirtuin 1 (SIRT1)

Maintaining adequate micronutrient intake to optimize host immune response is indicated in both the prevention and treatment of SARS-CoV-2. Malnutrition is linked to insufficient plasma protein level of anti-aging gene Sirtuin 1 (SIRT1) [70,71]. SARS-CoV-2 deactivates and represses SIRT1 [69]. SIRT1, dependent on nicotinamide dinucleotide (NAD+) for deacetylation, contributes to the prevention and reversal of chronic diseases that impair the host immune response, such as NAFLD, diabetes, neurodegenerative diseases and obesity [69,70]. SIRT1 functions in global DNA reparation, fat differentiation, insulin sensitivity, neurogenesis, inflammation, genetic stability and reduces pro-inflammatory cytokines [69,70]. SIRT1 deactivation and repression observed in the SARS-CoV-2 infection may contribute to varying levels of disease severity [69]. Micronutrient optimization in the SARS-CoV-2 infected host is necessary in the optimization for plasma protein SIRT1 levels and in the mitigation of anti-aging gene SIRT1 inactivation [71].

Exogenous vitamin D increases plasma protein levels of SIRT1 [73]. Exogenous vitamin E has also been shown to influence plasma protein levels of SIRT1 [73]. NAD+, essential for SIRT1 deacetylation, is synthesized from its precursor, vitamin B3 (nicotinic acid) [73].

Angiotensin-converting enzyme-2 (ACE2)

Angiotensin-converting enzyme-2 (ACE2), a physiologic enzyme of the renin-angiotensin-aldosterone system (RAAS), is the receptor for the SARS-CoV-2 virus [74]. Levels of the enzyme ACE2 has been speculated as a contributor to varying degrees of the 2019 coronavirus infection severity [74]. Binding of SARS-CoV-2 virus to the ACE2 receptor results in ACE2 down-regulation, precipitating neutrophil sequestration, an exaggerated pro-inflammatory response, and a hypoxia induced release of renin [76,77].

Vitamin D (1,25-dihydroxyvitamin D_3) is a known modulator of RAAS, thus exogenous vitamin D may reduce RAAS activity through the reduction of renin expression [75,77]. 1,25-dihydroxyvitamin D_3 can be acquired exogenously or endogenously through the synthesis of steroid hormone, cholecalciferol, when the host is exposed to ultraviolet light [36.44.47].

Micronutrient Optimization

Vitamin D (1,25-dihydroxyvitamin D_3) has been shown to reduce the risk of host viral respiratory infection acquisition [1,5-13]. 1,25-dihydroxyvitamin D_3 reduces pro-inflammatory cytokines, increases anti-inflammatory cytokines, enhances epithelial barrier support, reduces the rate of viral replication, reduces RAAS activity through the reduction of renin expression, and increases host oxygen carrying capacity [1,13-21]. Exogenous vitamin D should be evaluated as an adjuvant therapy in the prevention and treatment of SARS-CoV-2.

Vitamin C (l-ascorbic acid) is a potent antioxidant that may play an important role in mitigating cytokine storm and alleviating tissue damage [3,25,40]. L-ascorbic acid enhances epithelial barrier support, increases lymphocyte production and differentiation, and reduces pro-inflammatory cytokines [22,23,28,29]. Vitamin E (α-tocopherol) is a potent antioxidant that may also play a significant role in alleviating cellular damage, enhancing T lymphocyte response, promoting natural killer cell activity, increasing interleukin-2 production, and mitigating host cytokine storm [3,25,28,29]. The utilization of exogenous vitamin E supplementation is controversial and may increase all-cause mortality [37]. Concurrent exogenous vitamin C and vitamin E supplementation should also be avoided [26,27].

Vitamin A (β-carotene) is a potent antioxidant and scavenger of reactive oxygen species shown to enhance T lymphocyte response, natural killer cell activity and interleukin-2 production [3,25,28,29,41]. Increased rates of infectious bronchitis coronavirus in chickens has been linked to vitamin A deficiency [44,49]. Exogenous vitamins D, A, and C should be evaluated as adjuvant therapies in the prevention and treatment of SARS-CoV-2.

B vitamins also play a critical role in maintaining host immunocompetence. Vitamin B2 (riboflavin) has been shown to shown to reduce human plasma viral titer levels of MERS- CoV [44,50]. Vitamin B3 (Nicotinic acid) is essential for SIRT1 deacetylation [73]. Nicotinic acid has anti-inflammatory properties and has been shown to inhibit pulmonary neutrophil infiltration in cases of ventilator- induced pulmonary injury, albeit, increasing overall hypoxia [44,51]. Large dose (50-100 mg/day) vitamin B6 (pyridoxine) administration has been shown to increase T lymphocyte production and activity [61,62]. Methyl-B12 administration has been shown to increase leukocyte, lymphocyte, CD8+ cell, and natural killer cell production ($P < 0.05$) [62]. Vitamin B12 deficiencies lead to CD8+ and natural killer cell suppression [62]. Restoration and augmentation of cyanocobalamin levels can be achieved in patients with COVID-19 with methyl-B12 administration [62].

Zinc has been shown in vitro to inhibit SARS-CoV RNA polymerase activity and viral replication [2]. Zinc lozenges may reduce the binding efficacy of the SARS-CoV-2 virus to host oral mucosa [30,34,35]. The utilization of exogenous zinc should be evaluated for use in SARS-CoV-2 infections and initiated within 24 hours of the onset of respiratory symptoms [30].

Elevated serum ferritin in severe SARS-CoV-2 infections, suggest that excessive plasma iron levels accumulate in this state due to SARS-CoV-2 interfering with the iron-bound heme complex [42]. Exogenous iron should be avoided in these patients. Selenium, synergistically with vitamin E, acts as a scavenger of reactive oxygen species, also influential in minimizing cytokine storm and tissue damage [3,25,44]. A delicate balance of omega-3 and omega-6 polyunsaturated fatty acids must be maintained to minimize pro- inflammatory effects. Protectin D1, an omega- 3 polyunsaturated fatty acid, should be evaluated as an adjuvant therapy in the reduction of cytokine induced pro-inflammatory effects and as a potential inhibitor of SARS-CoV-2 viral replication [44,55,56].

Conclusion

The immune supportive mechanisms and physiologic effects of various micronutrients are multifaceted. Micronutrient optimization is critical in maintaining host immunocompetence. Maintaining adequate micronutrient intake to optimize host immune response is indicated in both the prevention and treatment of SARS-CoV-2. Further investigations should be performed to evaluate the utilization of exogenous micronutrient therapies as an adjunct to the treatment of SARS-CoV-2. Vigilance should be paid to maintaining adequate micronutrient intake to optimize host immune response in both the prevention and treatment of SARS-CoV-2.

Ethical Declarations

The author declares that no conflicts of interest exist.

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