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Effectiveness of nutritional supplements (vitamins, minerals, omega-3, and probiotics) in preventing and treating COVID-19 and viral respiratory infections

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ABSTRACT

Background: Viral respiratory infections (VRIs) continue to be among the most common illnesses and are known to be one of the main reasons of medical consultations worldwide.
COVID-19 remains a major public concern and a threat to global health. The current focus lies on the pivotal role of the human host's immunologic response in combating viral threats.
This critical review aims to examine the current evidence on the potential benefit of nutritional supplements in the prevention and treatment of COVID-19 and viral respiratory infections (VRIs).
Methods: The study was performed in the Google-Scholar and PubMed databases with a main emphasis on publications between January 2000 and September 2023. Consequently, a total of 202 articles were included in this literature review, distributed as follows: 62 meta-analyses and systematic reviews, 20 randomized clinical trials, 11 clinical trials, 28 observational cohorts and 81 others. Of these, 44 % were published between 2020 and 2023.
Results: The research indicates that Vitamin C may have a mitigating effect on VRIs, whereas a deficiency in Vitamin D might heighten susceptibility to COVID-19. Understanding the roles of Vitamins A, B, and E is hampered by limited data availability. Zinc supplementation and probiotics emerge as potential preventive measures for both COVID-19 and VRIs, with selenium and magnesium demonstrating promising results in treating VRIs. The recommendation for omega-3 fatty acid supplementation for COVID-19 treatment awaits further evidence.
Conclusion: Currently, there is insufficient clinical evidence to definitively establish the efficacy of vitamin, mineral, probiotic and/or omega-3 supplementation for combating COVID-19 and VRIs.

1. Introduction

Viral respiratory infections (VRIs) are among the most common illnesses globally and are a leading cause of medical consultations [1]. The World Health Organization (WHO) notes that viral diseases persistently emerge and pose significant public health threats, presenting with a broad spectrum of clinical manifestations, from asymptomatic upper respiratory infections to severe lower respiratory conditions like pneumonia [2]. VRIs notably impact quality of life and societal productivity [3]. Recently, the world faced the third major coronavirus epidemic, COVID-19, which emerged in Wuhan, China, in late 2019. Initially called 2019-nCoV, it was renamed COVID-19 by the WHO in 2020 [4]. This followed earlier coronavirus epidemics: severe acute respiratory syndrome (SARS-CoV) in 2002 [5] and Middle East Respiratory Syndrome (MERS-CoV) in 2012 [6]. These prior outbreaks, originating from animal-to-human transmission, were primarily associated with severe atypical pneumonia [7,8]. SARS-CoV-2, the virus responsible for COVID-19, is a single-stranded RNA virus that enters cells through endocytosis or membrane fusion, leading to a range of illnesses including respiratory, enteric, hepatic, and neurological diseases [9]. SARS-CoV-2 features spike glycoproteins that bind to host cell receptors, facilitating viral-cell membrane fusion. These receptors are abundant in the lungs, heart, ileum, kidneys, and bladder [10]. COVID-19 manifests in a broad spectrum, from asymptomatic cases and mild upper

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respiratory tract infections to severe pneumonia, acute respiratory distress syndrome (ARDS), and death [11]. Laboratory findings also reveal cytokine storms and sepsis in some COVID-19 patients [12]. Like other viral infections, COVID-19 poses the greatest risk to the elderly, immunocompromised individuals, and those with chronic diseases [13]. The immune response plays a crucial role in combating SARS-CoV-2 [14], and researchers stress the importance of enhancing the immune system through nutritional interventions [15,16]. Recent studies suggest that nutritional supplementation may support individuals with COVID-19 [17]. Therefore, understanding how to boost immunity is vital for COVID-19 prevention and management. Nutrition is well-documented as a key factor in immune function [18,19]. Optimal immune response requires a healthy immune system, and infections increase the demand for various nutrients, heightening the risk of deficiencies. Adequate nutrition supports energy supply, immune response development, and maintenance [20], while inadequate micronutrient intake impairs immune function, leading to increased infection susceptibility and severity [21]. A 2013 review highlighted the bidirectional relationship between nutrition, infection, and immunity: immunity influences infection characteristics, and poor nutrition diminishes immune function and increases infection risk [22]. Nutritional status can also predict the clinical outcome of infections, including COVID-19 [23]. Previous research underscores the role of vitamin supplementation in boosting immunity against VRIs and ARDS [14]. Despite the recognized importance of nutrition in immune function, evidence on routine dietary and mineral supplementation to prevent infections remains inconsistent and weak. This critical literature review aims to evaluate the evidence on the preventive and therapeutic roles of vitamins (A, B, C, D, E), minerals (zinc, selenium, iron, copper, magnesium), omega-3 fatty acids, and probiotics in combating COVID-19 and VRIs. The review also elucidates these supplements' roles in immune modulation, antioxidant activity, and antimicrobial response to viral respiratory diseases, particularly COVID-19.

2. Methods

A comprehensive search strategy was employed to identify clinical studies on the role of nutritional supplementation in combatting COVID-19 and VRIs. This search included literature from PubMed and Google Scholar databases, using search terms such as "COVID-19," "SARS-CoV-2," "Coronavirus," "Vitamins," "Respiratory Tract Infections," "Vitamin E," "Vitamin D," "Vitamin C," "Vitamin B," "Vitamin A," "Vitamin Supplements," "Dietary supplements," "Mineral supplements," "Zinc," "Copper," "Iron," "Selenium," "Magnesium," "Omega 3," "Probiotics," "Prevention," and "Treatment." Filters were applied to include only studies published in English, focusing on publications from January 2000 to September 2023. The search yielded 243 non-duplicate records, which underwent title and abstract screening. Among the 243 selected articles, 14 did not provide complete versions, 23 were not directly relevant, one was retracted due to ethical concerns, and three ongoing clinical trials were excluded. Thus, 202 articles were included in this study, comprising 62 meta-analyses and systematic reviews, 20 randomized clinical trials, 11 clinical trials, 28 observational cohorts, and 81 others. Of these, 44 % were published between 2020 and 2023. The distribution of these articles is shown in Fig. 1.

3. Results and discussion

3.1. The use of nutritional supplements in managing COVID-19 and VRIs

The pathophysiology of COVID-19 involves a cytokine storm, a fatal immune response triggered by various factors, notably infections. The

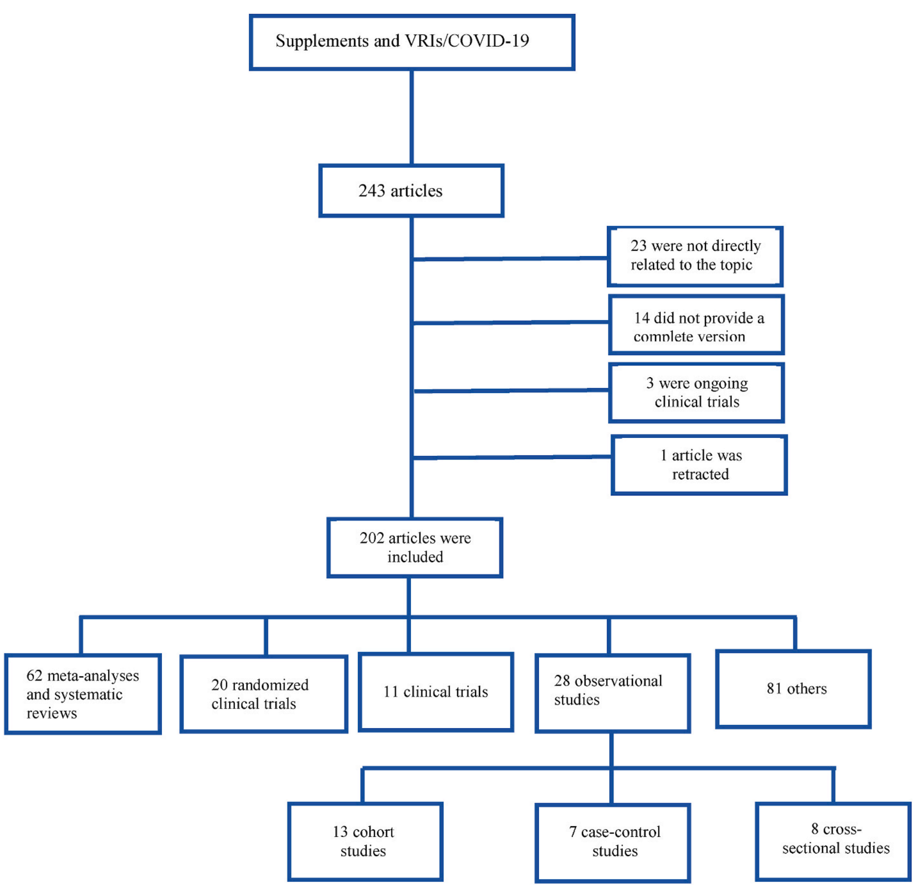

Fig. 1. Stages of studies selection.

clinical manifestations of COVID-19 are closely related to this cytokine storm and are characterized by an excessive release of pro-inflammatory cytokines [24]. Managing the cytokine storm and mitigating resultant immunogenetic damage are among the main therapeutic strategies for COVID-19 [25]. A robust immune system is crucial in combating SARS-CoV-2, with various nutrients playing a significant role in supporting immune function (Fig. 2). These nutrients enhance all three types of immunity (physical barriers, cellular immunity, and antibody production) and may offer protection against COVID-19 and other VRIs, potentially serving as adjunctive therapy for COVID-19 patients [26].

Various studies suggest that dietary supplements can provide a cost-effective immunity boost and may aid in managing COVID-19 and VRIs complications [27]. Several nutrients, including zinc, selenium, iron, copper, magnesium, omega-3 fatty acids, and probiotics, along with vitamins A, B, C, D, and E, are subjects of ongoing debate regarding their roles in the prevention and treatment of COVID-19 and other VRIs [17, 28,29].

Recent years have seen a global increase in the use of dietary supplements, evidenced by a notable sales growth of 4.4 % [30]. This surge has resulted in significant commercial activity, with estimated total expenditure of US$ 36.7 billion in the US in 2014, including US$ 14.3 billion allocated to vitamin and mineral supplements [31]. Several reports indicate a rise in supplement use among the general population of Arab countries. A 2018 study in Saudi Arabia (n = 474) revealed a prevalence of 44.6 % in vitamin and mineral supplement use [32]. Similarly, studies in the Arab region have reported increased use: in Qatar, 49.6 % of college students used supplements [33], and in the United Arab Emirates, 39 % of university students reported consuming dietary supplements [34]. In Lebanon, a 2016 study showed a rising trend in dietary supplement consumption, though it highlighted misconceptions and a need for consumer education on the efficacy and safety of these products [35].

Respiratory tract infections involve the direct invasion of the mucosal lining of the upper and lower respiratory airways by bacteria or viruses, triggering an immune response mediated by inflammatory cytokines. Individuals with suboptimal immune function are at increased risk of contracting respiratory infections and experiencing severe or prolonged disease courses. VRIs include various serotypes of viruses that replicate solely within host cells and can infect different organisms. This review will examine the impact of vitamin and mineral supplements on VRIs affecting the upper and lower respiratory tracts, including the common cold, seasonal influenza, bronchitis, and pneumonia [36].

The influenza virus, the most prevalent VRI, affects the respiratory tract by either compromising the immune system response or through direct viral infection. Pneumonia, often resulting from influenza, is a common cause of mortality in vulnerable populations such as those under 5 years old, over 65 years old, residing in nursing homes, or with chronic lung or heart diseases, a history of smoking, or immunocompromised conditions [37,38].

The common cold is an acute viral infection of the upper respiratory tract, affecting the nose, sinuses, pharynx, and larynx. It is transmitted through hand contact with secretions from an infected person or through aerosolized secretions [39,40]. Symptoms include nasal stuffiness and discharge, sneezing, sore throat, and cough [39]. Acute bronchitis is clinically diagnosed by a cough due to acute inflammation of the trachea and large airways without evidence of pneumonia and is predominantly caused by viral infections. Pneumonia is suspected in patients with tachypnea, tachycardia, dyspnea, or lung findings suggestive of the disease [41].

The SARS-CoV-2 virus, which causes COVID-19, has been a global public health concern since its emergence. Approximately 80 % of confirmed cases exhibit mild to moderate symptoms, 13.8 % have severe effects, and 6.1 % present with critical symptoms, with older adults (≥60 years) at higher risk of severe disease [42]. Pulmonary infections, including those caused by coronaviruses and certain influenza viruses, are associated with a high incidence of ARDS, a life-threatening lung injury [43]. ARDS typically develops rapidly within hours to days and may require immediate intensive care unit (ICU) treatment [44].

3.2. Effectiveness of nutritional supplements in the prevention of COVID-19 and VRIs

Currently, the most effective strategies for reducing COVID-19 transmission involve preventive measures such as physical distancing, public hygiene practices, and the use of facial masks [45]. Recent evidence suggests that nutritional supplementation, particularly with high daily doses of Vitamins D, C, E, and omega-3 fatty acids, may be beneficial for patients with COVID-19 [24,46,47]. These nutrients are recognized for their antioxidant properties and immunomodulatory effects, which can potentially reduce SARS-CoV-2 viral load and shorten hospitalization duration. Deficiencies in these vital nutrients can lead to immune dysfunction and increased susceptibility to infections, particularly in high-risk groups such as the elderly, who are more vulnerable to severe morbidity and mortality from COVID-19 [38]. Tables 1 and 2 summarize findings from various studies reviewed, highlighting the role of vitamins and mineral supplements in preventing and/or treating COVID-19 and VRIs.

3.2.1. Vitamin A

Vitamin A is a natural retinoid species predominantly obtained in its provitamin A form from beta-carotenoid, notably present in orange-colored foods like carrots and sweet potatoes [48]. The body then converts these provitamin carotenoids into retinoids [49]. Retinoids serve various functions, including maintaining vision and health [50] regulating epithelial and membrane functions, influencing bone metabolism and antioxidative properties [51] as well as modulating the immune

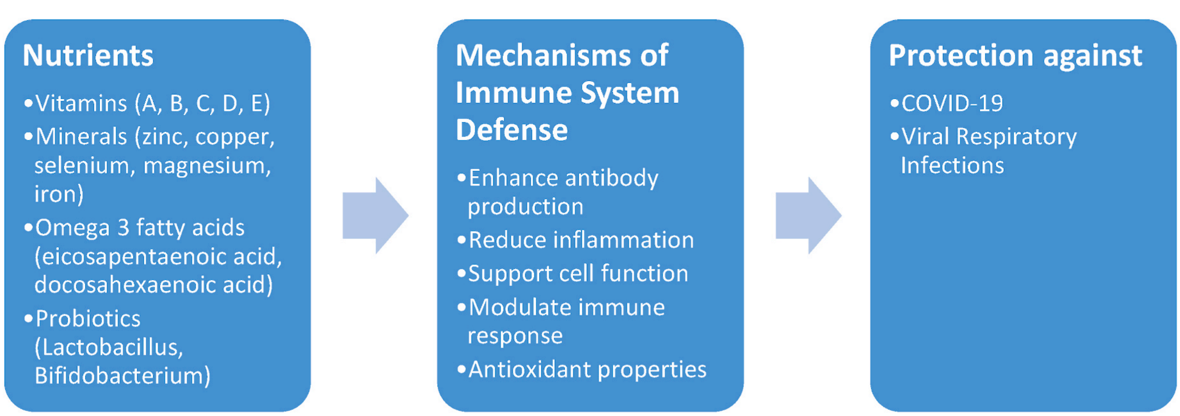

Fig. 2. Comprehensive role of nutrients in enhancing immune response against COVID-19 and viral respiratory infections.

Table 1
Vitamin supplements in the prevention and treatment of RVIs and Covid-19.

Vitamin	Function	Prevention RVIs	COVID-19	Treatment RVIs	COVID-19	Reference
D	- Has antiviral actions and immunomodulatory function on innate and adaptive immunity - Inhibits Cytokine Release Syndrome and inflammatory process. - Decreases Il-6 - Maintains functional tight junctions	**Supplementation may be effective:** Supplementation may reduce the risk of acute upper respiratory tract infections.	**Supplementation may be beneficial/Limited evidence:** Deficiency may increase the risk of COVID-19 infection.	**No available data.**	**Limited data available/ supplementation unlikely to be beneficial:** Supplementation may reduce hospitalization stay and mortality. Daily administration of vitamin D may reduce the severity of the disease and the need for ICU treatment. - Single dose administration of vitamin D_3 (200,000UI) does not significantly decrease the length of stay.	[9,25,27,38, 80,81,84–91, 93,94,96,100, 101,150,151]
C	- Antiviral and antioxidant properties - Promotes phagocytosis and chemotaxis of leucocytes - Promotes maturation and development of T-lymphocytes - Reduces Il-6 and cytokine storm.	**Limited evidence:** - Decrease in incidence, severity and duration of cold. - Slight reduction in the length and severity of colds.	**No available data**	**Inconsistent results/Limited evidence:** - Decrease duration and severity of common cold. - No effect on mortality in viral pneumonia.	**Supplementation unlikely to be effective/Limited evidence and inconsistent results:** Supplementation unlikely to be beneficial in decreasing mortality. Supplementation unlikely to decrease severity of symptoms, hospitalization, or death.	[24,47,64,66, 68–76, 140–143,145]
E	- Enhances the immune response through its anti-oxidative properties. - Increases the number of T-cells and IL-2 cytokine secretion	**Limited data available/May be beneficial:** Protects against upper respiratory tract infections and pneumonia in elderly.	**No available data**	**No available data**	**No available data**	[24,102–105]
A	- Improves adaptive immune response to pathogens by increasing T cell function. - Antioxidant properties - *Anti*-viral effects - Maintains vision & health	**Limited data:** No effect of supplementation on respiratory infections	**No available data.**	**No available data**	**No available data**	[52–54,57,58, 134]
B	- Important role in both innate and adaptive immune response: mainly Vitamins B6, B12 and folic acid.	**Unlikely to be beneficial/ Limited data:** No reduction in lower respiratory infection risk with B6 & B12 supplementation	**No available data**	**No available data**	**May be beneficial/Limited data:** Vitamins B12, D and Mg decrease clinical deterioration	[14,60,61,63, 138,139]

system [52].

Both carotenoids and retinoic acid enhance T cell function, which can improve the adaptive immune response to pathogens, such as viruses [53]. The anti-oxidative properties of vitamin A are believed to be pivotal in neonatal respiratory distress syndrome [54]. Furthermore, Vitamin A derivatives exhibit antioxidant and surfactant-mediating properties that may offer protective effects against ARDS, a severe complication of COVID-19 [53].

Vitamin A also contributes to the formation of healthy mucus layers in the respiratory tract and intestine, which is essential for mucin secretion and enhancing antigen non-specific immunity functions. As such, Vitamin A deficiency is associated with an increased risk of infection [55]. It has been highlighted in a recent review that vitamin A losses occur in infection via impaired vitamin A absorption and urinary losses [56]. However, systematic reviews and meta-analyses have indicated that vitamin A supplementation does not significantly impact the risk of lower respiratory diseases (LRD) and symptoms in children, suggesting a cautious approach to its recommendation for LRD prevention [57,58].

Despite these insights, direct clinical evidence linking vitamin A administration to enhanced resistance to infection is lacking, highlighting the need for well-controlled studies to thoroughly investigate this aspect. Similarly, no studies have suggested the role of Vitamin A supplementation for the prevention of COVID-19.

3.2.2. *Vitamin B*

B vitamins are a class of water-soluble vitamins that play a major role in cell metabolism [14]. Folic acid (B9), Cobalamin (B12), and Pyridoxine (B6) have essential roles in both the innate and adaptive immune responses [14,59]. The B vitamin complex may regulate cytokine production and facilitate interaction with immune cells participating in the inflammatory pathway [14,60]. Specifically, Vitamin B6 modulates T-lymphocyte proliferation and hinders cytokine release, making it an essential nutrient in the regulation of the immune system and antiviral activity [60,61]. Riboflavin (B2) exhibits immunomodulatory effects, and its deficiency stimulates pro-inflammatory gene expression [60]. Biotin (B7) is also recognized as an immunomodulatory vitamin capable of decreasing the production and secretion of pro-inflammatory cytokines [62]. Thiamine (B1) controls the production of cytokines and immune cells participating in pathological processes and inflammation; its deficiency leads to the overproduction of pro-inflammatory mediators such as IL-1, IL-6, and TNF–α [14]. In a 2013 randomized, double-blind, placebo-controlled trial, 1000 North Indian children aged 6–30 months received either twice the Recommended Dietary Allowance (RDA) for B9 and/or B12 or a placebo daily for 6 months. Despite this, neither of these vitamins reduced the occurrence of lower respiratory infections, indicating the necessity for further extensive randomized controlled trials (RCTs) to elucidate the complete advantages of these nutrients [63].

Table 2
Mineral and other supplements in the prevention and treatment of RVIs and Covid-19.

Supplement	Function	Prevention RVIs	COVID-19	Treatment RVIs	COVID-19	Reference
Zinc	- Maintenance of adaptive and innate immunity. - Regulation and formation of inflammatory responses. - Promotes phagocytosis, cytokine production. - Antiviral activity - Component of metalloenzyme - Gene expression. - Membrane/ Cytoskeletal stabilization	**Supplementation may be effective** - Decreases the incidence and prevalence of lower respiratory tract infections	**Limited data available/ Supplementation may be effective**	**Supplementation may be effective** - Shorter median recovery time. - Reduction in the duration of illness, respiratory rate, and improvements in oxygen saturation	**Limited data available/ Supplementation may be effective** - Shortens the duration of COVID-19 and its symptoms including cough, sore throat, and shortness of breath	[18, 107–115, 117, 158–163]
Selenium	- Antioxidant activity - Expression of inflammatory protein and cytokines - Effect on virus-host cell attachment interaction - *Anti*-inflammatory activity	**Unavailable data**	**Limited data available/ Supplement-ation may be effective**	**Limited data available/ Supplement-ation may be effective**	**Unavailable data**	[24, 119–124, 165,167]
Iron	- Regulates production of cytokines. - Improves phagocytosis. - Increases T-cell proliferation and function. - Present in Hemoglobin & myoglobin.	**Supplementation unlikely to be beneficial**	**Unavailable data**	**Unavailable data**	**Supplementation unlikely to be beneficial**	[118, 168–171, 173,175]
Copper	- Aids neutrophil phagocytosis. - Increases IL-2 and antibody production. - Increases T-cell proliferation. Improves cellular immunity by activating cytokines and chemokines.	**Unavailable data**	**Supplementation may be effective**	**Unavailable data**	**Supplementation may be effective.**	[27, 176–180]
Magnesium	- Involved in DNA replication and repair. - Role in antigen binding to macrophages. - Regulation of leukocytes activation. - Cofactor in antibody synthesis. - Anti-inflammatory, antioxidant, and bronchial smooth muscle relaxation properties	**Unavailable data**	**Unavailable data**	**Limited data available/ Supplementation unlikely to be beneficial**	**Unavailable data**	[139, 181–187]
Omega 3	- Constitutive part of the cell membrane - Signaling molecules. - Exert anti-viral effects by inhibiting influenza virus replication. - *Anti*-inflammatory properties.	**Unavailable data**	**Unavailable data**	**Unavailable data** - Insufficient positive outcomes in terms of multiple inflammatory, respiratory, and clinical measures for patients with ARDS.	**Unavailable data** - Insufficient data that Omega-3 supplementation may hold significance for critically ill COVID-19 patients	[23,28, 188–190, 193,194, 197]
Probiotic	- Gene expression. - Protein synthesis. - Signaling pathways in immune cells.	**Supplementation may be effective.** - Reduces the incidence and duration of fever,	**Unavailable data**	**Supplementation could be effective**	**Unavailable data** - Data showed promising benefits of probiotics in	[29, 129–133, 198–202]

(*continued on next page*)

Table 2 (*continued*)

Supplement	Function	Prevention RVIs COVID-19	Treatment RVIs COVID-19	Reference
	- Produces interferon which helps suppress virus-induced cytokine storms	rhinorrhea, cough and antibiotic prescription. - Reduces the number of episodes and frequencies of ARTIs.	lowering the risk of COVID-19.	

3.2.3. *Vitamin C*

Vitamin C, also known as ascorbic acid, is an essential water-soluble vitamin recognized for its role in immunity, particularly during infections. It enhances phagocytosis and chemotaxis in white blood cells and aids in the development and maturation of T-lymphocytes [64]. Speculation exists that Vitamin C may mediate the adrenocortical stress response during sepsis [65]. Previous studies suggest that vitamin C inhibits the replication of viruses such as Herpes Simplex Virus, Poliovirus, and Influenza [66,67]. Moreover, research indicates that vitamin C reduces IL-6 levels, thereby decreasing inflammation [68,69]. A recent meta-analysis confirmed that vitamin C, administered at doses of 250–1000 mg per day for less than a week, reduces IL-6 levels, regardless of the administration route [70]. Vitamin C is also suggested to prevent the common cold, with regular supplementation modestly reducing the duration and severity of colds [14,71].

A UK placebo-controlled trial with 168 participants showed that those receiving daily vitamin C (2 $\times$ 500 mg) for 60 days had a lower incidence of colds (37 vs. 50, $p = 0.05$) and shorter duration of severe symptoms (1.8 vs. 3.1 days, $p = 0.03$), with a 17 % reduction in recurrent colds (19 % vs. 2 %; $p < 0.001$) [72]. A Cochrane review of 29 placebo-controlled trials with 11,306 participants found that regular oral administration of vitamin C (200 mg daily) did not consistently reduce the incidence of colds in the general population [73,74]. However, in five trials with 598 individuals involved in skiing, military service, and marathon running, vitamin C reduced the incidence of colds by 52 % ($p < 0.0001$). These results suggest that vitamin C may enhance viral infection resistance during intense physical exertion, though mega-dose prophylaxis is not justified for general use but may be warranted under specific conditions [74].

A Cochrane systematic review demonstrated that regular administration of 1–2 g of vitamin C is cost-effective, safe, and consistently reduces the severity and duration of the common cold by 18 % in children. Trials with regular vitamin C administration showed an 8 % reduction in cold duration (3 %–12 %) in adults and by 14 % (7 %–21 %) in children, indicating a potential dose-dependent effect up to 6–8 g/day [73]. However, trials administering vitamin C only after symptom onset did not consistently demonstrate benefits [76]. Despite controversy regarding vitamin C's precise effects, administration route, and optimal dosage, its potential benefits, safety profile, and cost-effectiveness make it a potential treatment for respiratory infections.

Limited studies have investigated vitamin C status in individuals with COVID-19. Low vitamin C levels are common among critically ill, hospitalized COVID-19 patients, likely due to increased metabolic consumption [74]. An observational study of 21 critically ill COVID-19 patients admitted to the ICU showed that those who died had hypovitaminosis C, with a mean level of 15 μmol/L, compared to 29 μmol/L among survivors [77]. Another observational study in a Barcelona ICU with 18 COVID-19 patients having ARDS found that all patients had undetectable to low vitamin C levels (<9 μmol/L among 17 individuals vs. 14 μmol/L in one individual), though the study's small sample size and variations in blood sample collection days limit generalization [78].

In summary, oral vitamin C supplementation may reduce the duration and severity of cold symptoms via a dose-dependent effect. A recent review notes that symptoms associated with some coronaviruses resemble those in the early phase of SARS-CoV-2 infection, suggesting a rationale for considering vitamin C administration to reduce infection severity and duration. While vitamin Caction is not virus-specific, it may alleviate symptoms related to SARS-CoV-2. Despite being inexpensive and safe, these assertions require validation through RCTs [74].

3.2.4. *Vitamin D*

Vitamin D, a group of fat-soluble steroids, encompasses a range of biological functions, including bone formation and calcium and phosphorus homeostasis. The two main forms of vitamin D supplementation, ergocalciferol (Vitamin D2) and cholecalciferol (Vitamin D3), serve as precursors to 1,25(OH)2D3, the active form of Vitamin D. Recently discovered non-classical roles include immunomodulation, lung and muscle function, cardiovascular health, and infectious disease prevention [9].

3.2.4.1. Immunomodulatory functions of Vitamin D. Beyond its role in mineral homeostasis, Vitamin D serves as an immune system regulator. It plays a crucial role in modulating both innate and adaptive immunity, offering protection against pathogens [9]. Vitamin D exerts direct antiviral and antibacterial actions by inducing antimicrobial peptides, including human Cathelicidin (LL37). These peptides eliminate invading pathogens by disrupting their cell membranes and neutralizing endotoxins [79]. Moreover, Vitamin D acts as a modulator of adaptive immunity, enhancing the development of immune cells and their responses, which helps limit the release of pro-inflammatory cytokines, contributing to the defense against pathogens [80]. In the context of COVID-19, Vitamin D may function as an immunosuppressant by inhibiting Cytokine Release Syndrome. Specifically, it can downregulate pro-inflammatory cytokines in pulmonary infections, thereby mitigating inflammatory responses. This includes decreasing the expression of IL-6, which plays a key role in the cytokine storm associated with severe outcomes in patients with COVID-19 induced-pneumonia. This cytokine storm is linked to severe adverse outcomes, making vitamin D a possible preventive nutrient against ARDS [38]. Vitamin D also protects against COVID-19 through physical barriers composed of tightly connected cells that block the entry of pathogens, such as viruses, into susceptible tissues. While viruses can alter cell junction integrity, vitamin D plays a major role in maintaining the functionality of these junctions [81]. Given its role as a potent immune suppressor, vitamin D supplementation may inhibit abnormal immune responses, specifically the cytokine storm seen in COVID-19. Consequently, vitamin D is integral to the immune response and is needed for maintaining the health of the respiratory tract. Studies have reported that vitamin D supplementation reduces the risk of acute upper respiratory tract infections, suggesting it may play a role in the response to COVID-19 [14,27,38]. Initial reports highlighted a high prevalence of hypovitaminosis D in 85 % of COVID-19 patients [82] and showed that serum concentrations of 25-hydroxyvitamin D are lower in COVID-19 patients compared to controls [83]. However, although significant inverse correlations were observed across 20 European countries, no significant associations between vitamin D deficiency and COVID-19 were reported [84]. A meta-analysis of 25 RCTs including 10,933 participants across 14 countries showed that the administration of vitamin D reduces the risk of ARTIs (OR 0.88, 0.81 to 0.96; P for heterogeneity <0.001). Protective effects were obtained with daily or weekly doses but not with supplemental boluses. These effects were more pronounced in participants with low baseline calcifediol levels (<25 nmol/L) compared to those with levels ≥25 nmol/L [85]. A systematic review and meta-analysis including data from 11 RCTs involving 5660 participants with an average age of 16 years demonstrated a significant reduction in the risk of RTIs with vitamin D supplementation (OR 0.64, 95 % CI 0.49–0.84; p = 0.001). However, the interpretation of these findings is restricted by limited availability of patient groups, considerable heterogeneity across the studies, and indications of notable publication bias [86,87]. Further analysis showed that daily Vitamin D supplementation exhibited a protective effect (OR 0.51, 95 % CI 0.39–0.67), while vitamin D administered in bolus doses once per month or less did not yield the same result (OR 0.86, 95 % CI 0.60–1.20). A comprehensive 2013 systematic review, encompassing 39 studies (14 RCTs, 13 cohort studies, 8 case–control studies, and 4 cross-sectional studies) reported consistent associations in observational studies between low vitamin D levels and an elevated risk of ARTIs. In contrast, interventional trials within this review presented inconclusive evidence, potentially attributed to significant heterogeneity in dosing regimens and baseline vitamin D status [86]. Moreover, several subsequent RCTs have reported that Vitamin D supplementation did not lead to a reduction in the risk of ARTIs [86,88,89]. A study involving predominantly Vitamin-D deficient residents living in sheltered accommodations showed an increased risk of upper ARTI when given a high bolus dose (Hazard Ratio [HR] = 1.48, 95 % CI 1.02–2.16; p = 0.039) [86,90]. Conversely, a placebo-controlled trial with 5660 subjects demonstrated a significant reduction in the risk of respiratory tract infections with vitamin D supplementation [87]. Another review including five clinical studies reported a significantly lower risk of respiratory tract infection in patients supplemented with vitamin D compared to the control group [91]. Currently, there is insufficient evidence to support recommending vitamin D supplementation to prevent ARTIs [86]. Thus, the Scientific Advisory Committee on Nutrition (SACN) declared a statement concluding that current evidence does not justify the recommendation of vitamin D supplementation for the prevention of ARTIs, unless data from interventional studies advise otherwise [92].

3.2.4.2. Vitamin D deficiency and COVID-19. Vitamin D, a group of fat-soluble steroids, encompasses a range of biological functions, including bone formation and calcium and phosphorus homeostasis. The two main forms of vitamin D supplementation, ergocalciferol (Vitamin D2) and cholecalciferol (Vitamin D3), serve as precursors to 1,25(OH)2D3, the active form of Vitamin D. Recently discovered non-classical roles include immunomodulation, lung and muscle function, cardiovascular health, and infectious disease prevention [9]. A study conducted in the UK with 341,484 participants aged 37–73 years (2006–2010) examined baseline exposure data, including initial 25(OH) D concentration and ethnicity, in relation to COVID-19 test results. This investigation aimed to determine if vitamin D deficiency or insufficiency (defined as serum 25(OH)D < 25 and < 50 nmol/L, respectively) was associated with COVID-19-related deaths. Among participants, 203 individuals died from COVID-19 infection between March 5th and April 25th, 2020. The findings indicated that both vitamin D deficiency and lower 25(OH)D concentration were associated with a higher risk of death from COVID-19; however, no association was observed after adjusting for potential confounders such as age, sex, ethnicity, month of assessment, household income, BMI category, smoking status, diabetes, blood pressure, self-reported health rating, and long-standing illness, disability, or infirmity. A notable limitation is the 10-year gap between the baseline 25(OH)D measurement and COVID-19 infection. Additionally, in a subsample of 15,473 participants with follow-up measurements (average 4.3 years later), an 84 % concordance rate for vitamin D deficiency was observed [93].

Numerous observational studies suggest a protective effect of adequate vitamin D levels. For instance, a study of 14,000 health service members tested for COVID-19 (February 1 - April 30, 2021) found that individuals who tested negative had significantly higher mean plasma vitamin D levels compared to those who tested positive. Univariate analysis indicated an association between low plasma 25(OH)D3 levels and increased odds of COVID-19 infection (OR 1.58, 95 % CI: 1.24–2.01, $p < 0.001$) as well as hospitalization due to SARS-CoV-2 (OR 2.09, 95 % CI: 1.01–4.30, $p < 0.05$) [93,94]. In a multivariate analysis, the adjusted OR for COVID-19 infection (1.45, 95 % CI 1.08–1.95; $p < 0.001$) and hospitalization (adjusted OR 1.95, 95 % CI 0.98–4.845; p = 0.061) remained significant with low vitamin D levels, even after controlling for demographic variables and psychiatric and somatic disorders [95]. Another study with 212 COVID-19 patients found a correlation between vitamin D status and hospitalization outcomes, showing that higher vitamin D levels were associated with milder clinical outcomes [96].

The "COVID-19 rapid guideline: vitamin D″ from the National Institute for Health and Care Excellence (NICE) reviewed five studies examining the link between vitamin D status and COVID-19, with four studies suggesting an association between lower vitamin D levels and the development of COVID-19, though confounding factors were not accounted for [97]. A retrospective study in Belgium with 186 positive cases and 2717 negative controls showed significantly lower median vitamin D levels in COVID-19 patients compared to controls (p = 0.0016) [98]. Conversely, a UK study found no significant differences in vitamin D levels between COVID-19 cases and controls after adjusting for confounders [99].

While these studies demonstrate an association rather than causation, it highlights the need for further RCTs in the prevention and treatment of COVID-19 [86]. Despite a lack of clinical trials assessing the preventive role of vitamin D in COVID-19, some retrospective observational studies report a correlation between vitamin D levels and COVID-19 cases and severity, though findings are inconsistent. For example, a retrospective study in South Asia found a significant relationship between vitamin D status and clinical outcomes ($p < 0.001$) [25]. While current treatments for COVID-19 include various agents like antiviral drugs and plasma transfusion, the role of vitamin D remains under investigation with insufficient evidence to conclusively establish its impact on COVID-19 severity and mortality [100]. Although vitamin D deficiency has been linked to an increased risk of respiratory infections like COVID-19, and higher levels appear protective, there is no well-established cut-off level defining this relationship [101].

3.2.5. *Vitamin E*

Vitamin E, a fat-soluble compound, is an effective antioxidant that neutralizes free radicals and reactive oxygen species. As a major component of antioxidant defense, it may improve cell membrane integrity and enhance the adaptive immune system response to viral respiratory tract infections [14,102]. Vitamin E boosts the immune system by increasing the number of T cells, enhancing mitogenic lymphocyte responses, IL-2 cytokine secretion, and natural killer (NK) cell activity, and decreasing infection risk [24]. Its role in preventing infections, particularly influenza, has been discussed, although well-controlled human studies are lacking. A randomized, double-blind, placebo-controlled trial from April 1998 to August 2001 involving 617 individuals aged 65 or older in 33 long-term care facilities in Boston found that a daily dose of 200 IU vitamin E did not significantly affect lower respiratory tract infections but did show a protective effect against upper respiratory tract infections, such as the common cold [103]. Another randomized controlled study with 2216 smokers receiving 50 mg/d of vitamin E for 5–8 years reported a 69 % reduction in pneumonia incidence among elderly men [104]. Additionally, vitamin E supplementation has been shown to increase resistance to respiratory infections [105]. Mixed tocopherols are more effective than α-tocopherol alone due to a broader range of receptors [106]. Despite these benefits, there is limited information on the effects of vitamin E supplementation in humans with COVID-19. However, adequate intake of antioxidant nutrients through a balanced diet is currently encouraged [24].

3.2.6. *Zinc*

Zinc is an essential trace element that plays an important role in growth, development, and maintenance of the immune function [107].

As a cofactor, it is an integral component of more than 300 enzymes, exerting secondary effects on the human immune system and acting as a signaling molecule in the physiology of the immune system [108]. Studies show that zinc functions not only as an anti-inflammatory agent but also as an antioxidant stabilizing nutrient [109]. Moreover, zinc influences the survival of immune cells and affects important functions such as phagocytosis, target cell killing, and cytokine production [110]. Numerous reviews highlight the role of zinc in immunity and its impact on host susceptibility to viral infections, particularly VRIs [111–113]. Randomized clinical trials have explored the role of zinc in preventing VRIs. For instance, a 2014 study found no significant effect from 2 weeks of prophylactic zinc supplementation on the incidence of acute respiratory infections [114]. Another RCT comparing zinc gluconate 15 mg/day capsules with a corn-starch placebo showed no significant differences between groups in diagnosed cases of upper respiratory infections [115]. However, a recent study showed that daily supplementation of 5 mg of zinc over 12 months significantly decreased the incidence of respiratory infections in healthy children aged 6–12 months [116]. Likewise, another study concluded that zinc supplementation reduced the incidence and prevalence of lower respiratory tract infections in children [117]. These findings align with a 2020 meta-analysis suggesting that zinc doses of more than 75 mg/d may have promising antiviral effects against common cold viruses, including influenza [118].

3.2.7. Selenium

Selenium, a trace element, plays a crucial role in the immune system through its antioxidant and anti-inflammatory effects [119,120]. Selenoproteins K and S contribute to the regulation of immune responses. Inadequate selenium levels are linked to increased mortality risk and impaired immune function, whereas higher selenium concentrations or supplementation demonstrate antiviral effects [121]. Research has shown that selenium intake is associated with enhanced immunity, largely due to the role of dietary selenium deficiency in elevating oxidative stress, impairing immunity, and promoting genetic mutations of pathogenic viruses, such as influenza [118]. Several studies have investigated the impact of selenium supplementation on immunity in patients with VRIs, including COVID-19. Despite ongoing debate about the potential benefits and risks of selenium supplementation, there is limited research on its preventive role in VRIs. An RCT exploring the influence of selenium on influenza vaccine immunity in older adults found that the effects could be both beneficial and detrimental, depending on the selenium form and dose [123]. Currently, there is insufficient evidence to support the use of selenium supplements for preventing COVID-19 or improving its prognosis [124].

3.2.8. Iron

Numerous reviews have explored the role of iron in immunity and host susceptibility to infection. Iron deficiency affects various aspects of immune function, including respiratory burst, bacterial killing, natural killer cell activity, T lymphocyte proliferation, and T helper 1 cytokine production [125,126]. There is consensus that iron deficiency increases susceptibility to infection, underscoring the importance of maintaining optimal iron levels for an effective immune response. However, the relationship between iron deficiency and infection susceptibility is complex, and studies on the antiviral role of iron yield conflicting results. While many studies have investigated the connection between iron levels and immunity or the risk of viral infections, few have examined the impact of iron supplementation on preventing or treating COVID-19 and VRIs. A randomized, placebo-controlled clinical trial assessing daily iron supplementation found no statistically significant effects on the incidence of respiratory infections or anthropometric indices [127].

3.2.9. Copper

Copper is essential for immune function, contributing to the development and differentiation of immune cells. It exhibits antimicrobial properties and supports the activity of neutrophils, monocytes, macrophages, and natural killer cells. Additionally, copper enhances T lymphocyte responses, including proliferation and IL-2 production, aids in antibody production, maintains intracellular antioxidant balance, and protects immune cells [27]. Although no clinical studies have yet investigated copper supplementation for preventing or treating respiratory infections in humans, emerging evidence suggests its potential benefits for immunity, especially concerning COVID-19. This will be discussed further in the section "Copper in the treatment of COVID-19 and VRIs".

3.2.10. Probiotics

The United Nations Food and Agriculture Organization (FAO) and the World Health Organization (WHO) define probiotics as live microorganisms that offer health benefits to the host when administered in adequate amounts [128,129]. Probiotics are known for their impact on immunity, significantly affecting the functionality of the mucosal and systemic immune systems through the activation of multiple immune mechanisms [130]. Research has explored the association between probiotics and VRIs, with particular focus on COVID-19. A double-blind, placebo-controlled study assessing the effects of probiotic consumption on the incidence of cold and influenza-like symptoms in healthy children during the winter found that six months of daily dietary probiotic supplementation was both safe and effective in decreasing the incidence and duration of fever, rhinorrhea, and cough, as well as the reliance on antibiotic prescriptions [131]. Conversely, a systematic review of 14 RCTs demonstrated that probiotics improved the response of the immune system to the influenza virus and were more effective than placebo in reducing the number of participants experiencing episodes and frequencies of acute respiratory tract infections (ARTIs), as well as decreasing antibiotic use [132]. A separate meta-analysis including 10 RCTs with a total of 2894 participants found that probiotics had a modest but significant effect on reducing the common cold [133].

3.3. Effectiveness of nutritional supplements in the treatment of COVID-19 and VRIs

3.3.1. Vitamin A

A study aimed at identifying candidate targets, pharmacological functions, and therapeutic pathways of vitamin A against SARS-CoV-2 showed that vitamin A exhibits anti-viral, anti-inflammatory, and immunomodulatory effects through different biological processes and cell signaling pathways, and may have clinical utility in the treatment of COVID-19 [134]. However, it is important to note that no well-controlled patient-oriented study has been conducted to assess this possibility.

3.3.2. Vitamin B

The effectiveness of vitamin B12 supplementation remains debated. In Brazil, numerous hospitals treating COVID-19 patients recommend vitamin B12 supplementation or intramuscular injection, especially in cases of deficiency [135]. Pharmacological treatment with B12 typically involves high doses (1000–2000 μg/day) administered for an average of 1–3 months [136]. Vitamin B12 therapy, particularly when combined with folate, is known to reduce levels of inflammation and oxidative damage, both systemically and in the central nervous system [137], potentially alleviating COVID-19 symptoms and improving prognosis, including during or after the post-acute COVID-19 syndrome [138]. In a cohort observational study including older hospitalized COVID-19 patients aged ≥50 years, supplementation with 500 mcg/d oral vitamin B12, 1000 IU/d oral vitamin D3, and 150 mg/d oral magnesium upon admission significantly reduced the number of patients with clinical deterioration, particularly those requiring oxygen support, intensive care support, or both [139]. However, larger randomized controlled trials (RCTs) are needed to fully confirm the benefits of this combination in reducing the severity of COVID-19. Thiamin and its derivatives are proposed to synergistically act with ascorbic acid, potentially reducing anaerobic respiration and oxidative stress. This synergy may improve mortality outcomes and organ recovery in critically ill patients with septic shock. However, there is no conclusive evidence supporting vitamin B supplementation for VRIs. Additionally, there is insufficient significant data to advise group B vitamins supplementation in SARS-CoV-2 infected patients to enhance their immune response [14].

3.3.3. Vitamin C

Since its synthesis in 1933, Vitamin C supplementation has been suggested as a preventive method for respiratory infections. Although considered safe, high intravenous doses may cause adverse effects, such as oxalate kidney stone formation [14]. Some studies indicate positive effects on reducing the duration of the common cold [73], but administering Vitamin C only after symptom onset has inconsistent benefits [75]. Despite its antiviral and antioxidant properties, the effects of Vitamin C on COVID-19 remain unclear. Its safety profile supports cautious use until more data on COVID-19 is available.

Numerous studies have explored the efficacy of vitamin C in treating severe viral infections. A recent observational study showed that adjunctive intravenous Vitamin C therapy (6 g/day until ICU discharge) did not improve 28-day mortality or prognosis in patients with severe viral pneumonia and respiratory failure [140]. A large trial with high-dose intravenous Vitamin C (50 mg/kg every 6 h) for ARDS found no significant improvement in inflammation markers or organ dysfunction scores, but mortality was dramatically reduced [141]. Another meta-analysis indicated that intravenous Vitamin C in critically ill patients with sepsis and septic shock might reduce ICU stay duration and mechanical ventilation need but does not impact overall mortality [142].

Therapeutic studies on Vitamin C have shown inconsistent benefits, potentially due to factors like initiation timing and duration affecting trial outcomes [75]. During the previous SARS outbreak, Vitamin C use was suggested, and it may reduce elevated IL-6 levels seen in severe COVID-19 patients [143]. A recently published randomized clinical trial on severe COVID-19 patients found no significant differences in SpO 2 levels at discharge, ICU stay length, or mortality between those receiving daily high-dose intravenous Vitamin C (6 g) and those receiving lopinavir/ritonavir and hydroxychloroquine [144]. Similarly, a 2020 trial involving 214 SARS-CoV-2 patients found no significant differences in symptom severity, hospitalizations, or mortality among those receiving zinc gluconate, ascorbic acid, both agents, or standard care [145].

A systematic review of six RCTs indicated no reduction in mortality, ICU stay length, or mechanical ventilation need with Vitamin C supplementation [146]. In critically ill septic patients, some clinicians reported positive clinical effects with intravenous Vitamin C (3 g every 6 h) combined with steroids and anticoagulants [147]. Early administration of intravenous Vitamin C with corticosteroids and thiamine has been effective in preventing organ dysfunction and reducing mortality in severe sepsis and septic shock. However, the combination of high-dose Vitamin C, hydrocortisone, and thiamine showed similar survival impacts to intravenous hydrocortisone alone, suggesting limited additional value of Vitamin C in sepsis [148]. In a randomized trial, septic patients receiving Vitamin C (25 mg/kg intravenously every 6 h) showed a significant reduction in 28-day mortality compared to placebo (14 % vs. 64 %; $p = 0.009$) [149].

Given the ability of vitamin C to prevent IL-6 increase in severe inflammatory conditions and the crucial role of IL-6 in severe COVID-19, it is logical to consider vitamin C as a potential treatment for COVID-19 patients. However, there is currently insufficient strong evidence to support the use of vitamin C as prophylaxis or treatment for COVID-19, and ongoing clinical trials are expected to provide more definitive evidence [143]. Numerous clinical trials are underway to evaluate Vitamin C supplementation in COVID-19 patients [24].

3.3.4. Vitamin D

Information on the preventive effects of vitamin supplements on COVID-19 severity and mortality is currently limited. Several registered randomized trials are investigating the role of vitamin D in the severity of COVID-19 infections, but their results have not yet been reported [25]. The COVIT-TRIAL, an open-label, multicenter, randomized controlled superiority trial, aims to assess whether vitamin D supplementation can improve the prognosis of COVID-19 in older adults at higher risk of worsening. It compared the effects of a single oral high dose of cholecalciferol with a single oral standard dose on the 14-day all-cause mortality rate in older adults with COVID-19. Participants, aged 65 years or older with COVID-19, were randomized to receive either high-dose cholecalciferol (two 200,000 IU drinking vials at once on the day of inclusion) or standard-dose cholecalciferol (one 50,000 IU drinking vial on the day of inclusion). Results showed that providing at-risk older patients with COVID-19 an early high-dose of vitamin D3, as opposed to a standard dose, resulted in improved overall mortality at day 14 but not after 28 days [81]. A randomized clinical trial involving 240 hospitalized patients with moderate to severe COVID-19 found that a single oral dose of 200,000 IU of vitamin D3 did not significantly reduce hospital length stay compared to a placebo [150]. Another trial at Reina Sofia University Hospital in Spain, involving 76 hospitalized COVID-19 patients, showed that oral calcifediol administration significantly reduced the need for ICU admission [151]. However, larger trials are needed for a definitive conclusion on the reduction of disease severity. Two quasi-experimental studies conducted in France showed that bolus vitamin D3 supplementation, among frail elderly nursing-home residents, during or just before COVID-19 was not associated with significantly less severe COVID-19 and a better survival rate [81,152]. Consequently, there is no significant difference observed with vitamin D supplementation on major health-related outcomes in COVID-19, such as ICU admission, mortality, and mechanical ventilation. Well-designed RCTs are necessary to further investigate this topic [146]. The primary risk associated with excess vitamin D supplementation is the possibility of overdosing, although doses exceeding the recommended limit of 10 mcg (400 IU) by Public Health England can be taken safely. The Endocrine Society set an upper daily limit at 10,000 IU [153] while other authorities such as the UK's Scientific Advisory Committee on Nutrition (SACN) [154], the Institute of Medicine (IOM) [155], the European Food and Safety Authority (EFSA) [156] recommend staying below 4000 IU/day (100 μg). Large doses of vitamin D can lead to intoxication (hypervitaminosis D) with symptoms related to elevated calcium levels, including confusion, polyuria, polydipsia, anorexia, vomiting, and muscle weakness [86]. Because vitamin D is often taken as a supplement and not as a prescription, there is a risk of accidental overdose. The pandemic has influenced purchasing behaviors, potentially leading to supplement stockpiling and shortages for vulnerable groups, such as pregnant women [157]. Additionally, any potential benefits of vitamin D in reducing SARS-CoV-2 transmission must be studied in conjunction with other preventive measures such as mask-wearing, social distancing, hand hygiene, and avoiding contact, crowds, and public gatherings [86].

3.3.5. Zinc

Several randomized clinical trials have demonstrated the role of zinc in the treatment and prognosis of VRIs. A study evaluating the effectiveness of zinc gluconate supplementation over a 2-month period compared to a placebo in children with acute lower respiratory infections found that those supplemented with zinc exhibited a significantly shorter median recovery time [158]. Additionally, a study of 103 children with pneumonia showed a statistically significant clinical improvement, including a reduction in the duration of illness, respiratory rate, and improvements in oxygen saturation, in the group receiving zinc supplementation compared to the placebo group [159]. Meta-analyses and systematic reviews of various RCTs on zinc supplementation have consistently indicated that children with recurrent respiratory tract infections tend to have a shorter duration of the common cold when supplemented with zinc [112,160]. Similar findings were reported in a 2020 meta-analysis, which highlighted that administering zinc within 24 h of the onset of symptoms reduces the duration of common cold symptoms [118]. It is agreed that individuals with zinc deficiency, especially children and the elderly, are more susceptible to infectious diseases, including respiratory viral infections and increased respiratory morbidity [18,161].

Recent insights into COVID-19 emphasize the significant role of zinc in antiviral immunity, particularly its potential role as a crucial element in host defense against RNA viruses [107]. Supporting the immune-enhancing properties of zinc, a recent study suggests that zinc supplementation can alleviate the effects of COVID-19-induced diarrhea and respiratory symptoms, including cough, sore throat, and shortness of breath [162]. Another recent study revealed that supplementation with 25 mg of elemental zinc twice daily for 15 days significantly reduces the 30-day ICU admission rate and shortens the duration of COVID-19 symptoms, especially in patients aged 65 and above with comorbid conditions requiring oxygen [163]. This proposes a promising immunotherapeutic approach for the prevention and treatment of COVID-19.

3.3.6. *Selenium*

An intervention study was conducted on young children under one year, hospitalized with pneumonia or bronchiolitis caused by respiratory syncytial virus (RSV), to evaluate the therapeutic effectiveness of selenium supplementation on acute lower respiratory tract infections. Results showed that the days needed for symptom relief and recovery were fewer in the selenium supplement group than in the controls. Thus, it was concluded that selenium supplements can promote recovery from RSV infection [164]. Selenium deficiency has been linked to an increased risk of respiratory viral infections. A recent study on the correlation between selenium status, determined by selenium concentrations in hair, and the COVID-19 cure rate in a city population, showed a significant association between poor selenium status and lower cure rates in COVID-19 patients. Furthermore, critically ill patients suffering from viral diseases experienced a rapid drop in selenium levels and worse outcomes compared to those with adequate selenium levels. This has heightened the focus on selenium deficiency as a major risk factor for poor outcomes in viral diseases. A study among COVID-19 patients found that selenium status was significantly higher in survivors compared to non-survivors [165]. However, some suggest that while selenium intake is crucial in host defense against infectious diseases, dietary intake alone might not suffice in certain conditions [166]. Interestingly, a study on selenium supplementation in preventing COVID-19 concluded that only one chemical form of selenium (sodium selenite) offers true protection against COVID-19 [167]. Although selenium supplementation in selenium-deficient patients, particularly elderly individuals, may be an effective option for treating COVID-19 and mitigating its severe outcomes, more individual-level data are needed to confirm a positive effect.

3.3.7. *Iron*

While our understanding of the effects of iron in VRIs is limited, some clues could be obtained from other viral infections [168]. Iron has demonstrated inhibitory effects on various viral infections, including influenza A virus and HIV [169]. Moreover, research indicates that iron exhibits robust antiviral activity against influenza virus strain A/H1N1 by influencing RNA transcription and is proposed to enhance protection efficacy against the virus [170,171]. Conversely, another study showed that the immune-modulating effects of iron and its deficiency pose a potential risk factor for the development of recurrent respiratory tract infections [172].

Recent updates on the management of anemia in high-risk COVID-19 patients, such as pregnant women, cancer patients, or hospitalized COVID-19 patients, suggest that iron replacement therapy is a promising approach to prevent associated complications [118]. However, it has also been proposed that limiting the iron supply to COVID-19 patients inhibits viral replication and reduces the risk and severity of infections [173]. This is supported by several studies suggesting that excessive iron in the host leads to oxidative stress, which increases the risk of virus mutation [174]. In fact, RCTs have demonstrated an association between iron supplementation or overload and compromised immunity. Given iron's involvement in essential biological processes such as DNA/RNA synthesis and ATP generation, it holds significance for both the host and the pathogen. Many viruses, including those causing respiratory infections, depend on iron for replication. Evidence suggests that an excess of iron may diminish the host's immune response to the virus, leading to impaired immune system, increased inflammation, and fostering pathogen growth [173]. It is therefore a necessary approach to maintain adequate iron levels, focusing particularly on chelated ions in order to prevent the harmful responses produced as a result of excessive iron intake or supplementation [175].

3.3.8. *Copper*

A meta-analysis on the therapeutic role of copper in critically ill COVID-19 patients suggests that physicians should consider addressing copper insufficiency in their treatment strategies [176]. Additionally, a 2020 meta-analysis hypothesized that increasing plasma copper levels could enhance both innate and adaptive immunity, making it a potential preventive and therapeutic approach against COVID-19 due to its potent antiviral properties [177]. Combining copper with existing antiviral agents may offer a promising treatment strategy [178]. While copper administration is generally considered an effective and low-cost complementary strategy to help reduce the transmission of several infectious diseases [179], it is important to note that increased copper intake (7.8 mg/day) can negatively impact the immune system, as observed in a study on the Beijing strain of influenza [180]. Therefore, careful attention should be given to the dosage, severity, and duration of copper imbalance to prevent potential copper toxicity.

3.3.9. *Magnesium*

Magnesium plays an important role in controlling immune function by influencing immunoglobulin synthesis, immune cell adherence, antibody-dependent cytolysis, Immunoglobulin M lymphocyte binding, macrophage response to lymphokines, and T helper-B cell adherence. However, very few studies have demonstrated a beneficial effect of magnesium supplementation on immunity against viral infections. Previous trials indicated its potential benefits in managing acute asthma exacerbations through intravenous or inhaled magnesium routes [181]. However, studies on oral supplements have reported inconclusive findings [182,183]. A 2019 meta-analysis suggested that oral magnesium supplements, as an adjuvant to standard treatment for mild to moderate asthma, lack high-quality supporting evidence, necessitating more robust research before recommendations can be made [184].

A recent review proposed timely magnesium supplementation for COVID-19 patients with hypertension, kidney injury, diabetes, or pregnancy complications. Magnesium sulfate supplementation has shown beneficial effects in treating lung-related diseases, including asthma and pneumonia, due to its anti-inflammatory, antioxidant, and bronchial smooth muscle relaxation properties [185]. Monitoring magnesium levels in COVID-19 patients may be effective in influencing disease progression [186]. Additionally, a cohort study indicated that combining magnesium with vitamin D and vitamin B12 in critically ill older COVID-19 patients significantly reduces the need for oxygen or intensive care support [139]. Given the hypothesis that low magnesium status may contribute to the progression from mild to critical COVID-19, further epidemiological, clinical, and fundamental research is necessary to elucidate the potential role of magnesium deficiency in COVID-19 [187].

3.3.10. Omega 3

Omega-3 fatty acids are polyunsaturated fats known for their beneficial effects on immunity and inflammation [188]. Besides their structural role in cell membranes, omega-3 PUFAs and their derivatives function as signaling molecules, significantly inhibiting the replication of the influenza virus [189,190]. This suggests the potential of omega-3 as a dietary preventive and treatment for flu-like viral infections, including COVID-19. Although the European Society for Parenteral and Enteral Nutrition (ESPEN) proposes that omega-3 fatty acids may improve oxygenation in COVID-19 patients, definitive evidence is still lacking [191]. Limited studies specifically examine the impact of omega-3 supplementation on respiratory infections, but data from other research highlights its role in modulating the inflammatory response [192]. Trials on omega-3 oral supplementation or its inclusion in parenteral nutrition for ARDS patients show positive outcomes in various inflammatory, respiratory, and clinical measures [193,194]. Some reviews support omega-3 supplementation for critically ill COVID-19 patients [23,195,196], with a 2023 systematic review suggesting it may safely reduce hospitalization and mortality rates in SARS-CoV-2 patients [197]. However, caution is advised due to potential increases in oxidative stress and inflammation, possibly from enhanced membrane susceptibility to damage. A 2020 meta-analysis indicates that while omega-3 fatty acids have anti-inflammatory properties that could aid COVID-19 recovery, EPA and DHA might make cell membranes more prone to oxidation, increasing oxidative stress. Hence, further evidence is needed before recommending omega-3 supplementation, especially in high doses, for the general population [28].

3.3.11. Probiotics

Both probiotics and probiotic-derived factors exert positive health effects by modulating host immune responses, maintaining gut homeostasis, and producing interferon, which helps suppress virus-induced cytokine storms and enhance overall immunity [29]. A review of 20 RCTs found that individuals who received probiotics experienced significantly fewer days of illness, with illness episodes being shorter by almost a day compared to those who took a placebo, leading to the conclusion that probiotics may reduce the duration of illness in both healthy children and adults [198]. A meta-analysis also suggested a modest effect of probiotics in reducing the common cold, emphasizing the need to weigh the balance of benefits and harms when using probiotics for common cold prevention [133]. A 2021 review concluded that probiotic administration can boost host immunity, suggesting potential benefits in reducing symptoms associated with the novel coronavirus, in line with findings from other antiviral studies [199]. In a meta-analysis evaluating the use of probiotics and prebiotics in patients with COVID-19, data showed promising benefits of probiotics in lowering the risk of COVID-19. Specifically, probiotic supplements containing L. paracasei, L. casei, and L. fermentum significantly reduced the occurrence of influenza-like symptoms and upper respiratory infections in adults with a history of frequent colds ($\geq$4 times per year) [200]. Another recent RCT revealed that probiotic supplementation in 293 participants resulted in a significant improvement in remission rate and an increase in specific IgM and IgG against SARS-CoV-2 compared to placebo [201]. Despite these findings, the specific role of probiotics in mitigating novel COVID-19 remains unclear, and whether these supplements can prevent or alleviate COVID-19-related symptoms is not fully understood [202].

3.4. Limitations

Several limitations of this critical literature review, which differs from a systematic review in its methodology and scope, require mentioning. The heterogeneity among the included studies prevents a unified conclusion. Variability exists in the dose, route of administration, and duration of the supplemented vitamins and minerals. Additionally, diverse age groups and concurrent treatments were employed across studies. Confounders were not adjusted in all the studies, and some interventional and observational studies had small sample sizes, limiting the interpretation of causality.

4. Conclusion

In conclusion, there is currently insufficient clinical evidence from completed RCTs to demonstrate a specific role for vitamin and/or mineral supplementation in combating COVID-19 and VRIs. Certain meta-analyses and systematic reviews indicated the positive impact of vitamin C supplementation in reducing the incidence, severity, and duration of VRIs, while highlighting limited data supporting the role of vitamin D supplementation in preventing and treating COVID-19. For vitamins A, B, and E, data were markedly scarce and predominantly absent. Consequently, substantial controversy persists regarding the use of vitamin supplementation for preventing and treating viral infections and COVID-19, with variations in methodology across systematic reviews and meta-analyses contributing to the ongoing debate.

Regarding mineral supplementation, zinc was shown to be potentially effective in both the treatment and prevention of COVID-19 and VRIs, although existing data are limited and incomplete. Probiotics may be effective in preventing and treating VRI, while selenium and magnesium supplementation may only be effective in treating VRIs. Iron supplementation is unlikely to confer benefits. Nevertheless, all data were limited and even unavailable for some topics. Future studies and well-designed randomized controlled trials with standardized control groups and sub-group analyses based on severity of illness, route of administration, dose, and duration of treatment are needed to determine whether the clinical value of nutrient supplements matches the promise of their physiological properties.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviation

ARDS	Acute respiratory distress syndrome
ARTIs	Acute respiratory tract infections
BMI	Body Mass Index
COVID-19	Coronavirus Disease 2019
DHA	Docosahexaenoic acid
EFSA	European Food and Safety Authority
EPA	Eicosapentaenoic acid
ESPEN	European Society for Parenteral and Enteral Nutrition
FAO	Food and Agriculture Organization
HR	Hazard Ratio
ICU	Intensive care unit
IOM	Institute of Medicine
LRD	Lower respiratory diseases
MERS-CoV	Middle East Respiratory Syndrome
NICE	National Institute for Health and Care Excellence
RCTs	Randomized Controlled Trials
RDA	Recommended Dietary Allowance
RSV	Respiratory syncytial virus
SACN	Scientific Advisory Committee on Nutrition
SARS-CoV	Severe acute respiratory syndrome
URTI	Upper respiratory tract infection
VRIs	Viral respiratory infections
WHO	World Health Organization

References

[1] A. Anzueto, M.S. Niederman, Diagnosis and treatment of rhinovirus respiratory infections, Chest 123 (5) (2003) 1664–1672, https://doi.org/10.1378/chest.123.5.1664.

[2] W.G. Nichols, A.J. Peck Campbell, M. Boeckh, Respiratory viruses other than influenza virus: impact and therapeutic advances, Clin. Microbiol. Rev. 21 (2) (2008) 274–290, https://doi.org/10.1128/CMR.00045-07.

[3] E.B. Fragaszy, C. Warren-Gash, P.J. White, M. Zambon, W.J. Edmunds, J. S. Nguyen-Van-Tam, A.C. Hayward, Effects of seasonal and pandemic influenza on health-related quality of life, work and school absence in England: results from the Flu Watch cohort study. Influenza and Other Respiratory, Viruses 12 (1) (2018) 171–182, https://doi.org/10.1111/irv.12506.

[4] N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, X. Zhao, B. Huang, W. Shi, R. Lu, P. Niu, F. Zhan, X. Ma, D. Wang, W. Xu, G. Wu, G.F. Gao, W. Tan, China Novel Coronavirus Investigating and Research Team, A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. 382 (8) (2020) 727–733, https://doi.org/10.1056/NEJMoa2001017.

[5] N.S. Zhong, B.J. Zheng, Y.M. Li, Poon, Z.H. Xie, K.H. Chan, P.H. Li, S.Y. Tan, Q. Chang, J.P. Xie, X.Q. Liu, J. Xu, D.X. Li, K.Y. Yuen, Peiris, Y. Guan, Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003, Lancet (London, England) 362 (9393) (2003) 1353–1358, https://doi.org/10.1016/s0140-6736(03)14630-2.

[6] A. Assiri, A. McGeer, T.M. Perl, C.S. Price, A.A. Al Rabeeah, D.A. Cummings, Z. N. Alabdullatif, M. Assad, A. Almulhim, H. Makhdoom, H. Madani, R. Alhakeem, J.A. Al-Tawfiq, M. Cotten, S.J. Watson, P. Kellam, A.I. Zumla, Z.A. Memish, KSA MERS-CoV Investigation Team, Hospital outbreak of Middle East respiratory syndrome coronavirus, N. Engl. J. Med. 369 (5) (2013) 407–416, https://doi.org/10.1056/NEJMoa1306742.

[7] Z. Song, Y. Xu, L. Bao, L. Zhang, P. Yu, Y. Qu, H. Zhu, W. Zhao, Y. Han, C. Qin, From SARS to MERS, thrusting coronaviruses into the spotlight, Viruses 11 (1) (2019) 59, https://doi.org/10.3390/v11010059.

[8] Y. Yin, R.G. Wunderink, MERS, SARS and other coronaviruses as causes of pneumonia, Respirology (Carlton, Vic.) 23 (2) (2018) 130–137, https://doi.org/10.1111/resp.13196.

[9] Y. Xu, D.J. Baylink, C.S. Chen, M.E. Reeves, J. Xiao, C. Lacy, E. Lau, H. Cao, The importance of vitamin d metabolism as a potential prophylactic, immunoregulatory and neuroprotective treatment for COVID-19, J. Transl. Med. 18 (1) (2020) 322, https://doi.org/10.1186/s12967-020-02488-5.

[10] X. Zou, K. Chen, J. Zou, P. Han, J. Hao, Z. Han, Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection, Front. Med. 14 (2) (2020) 185–192, https://doi.org/10.1007/s11684-020-0754-0.

[11] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, J. Xiang, Y. Wang, B. Song, X. Gu, L. Guan, Y. Wei, H. Li, X. Wu, J. Xu, S. Tu, Y. Zhang, H. Chen, B. Cao, Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet (London, England) 395 (10229) (2020) 1054–1062, https://doi.org/10.1016/S0140-6736(20)30566-3.

[12] Y.M. Gao, G. Xu, B. Wang, B.C. Liu, Cytokine storm syndrome in coronavirus disease 2019: a narrative review, J. Intern. Med. 289 (2) (2021) 147–161, https://doi.org/10.1111/joim.13144.

[13] M.C. Grant, L. Geoghegan, M. Arbyn, Z. Mohammed, L. McGuinness, E.L. Clarke, R.G. Wade, The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): a systematic review and meta-analysis of 148 studies from 9 countries, PLoS One 15 (6) (2020) e0234765, https://doi.org/10.1371/journal.pone.0234765.

[14] T.H. Jovic, S.R. Ali, N. Ibrahim, Z.M. Jessop, S.P. Tarassoli, T.D. Dobbs, P. Holford, C.A. Thornton, I.S. Whitaker, Could vitamins help in the fight against COVID-19? Nutrients 12 (9) (2020) 2550, https://doi.org/10.3390/nu12092550.

[15] F. Aman, S. Masood, How Nutrition can help to fight against COVID-19 Pandemic, Pakistan J. Med. Sci. 36 (COVID19-S4) (2020) S121–S123, https://doi.org/10.12669/pjms.36.COVID19-S4.2776.

[16] E. Derbyshire, J. Delange, COVID-19: is there a role for immunonutrition, particularly in the over 65s? BMJ Nutri. Prevention & Health 3 (1) (2020) 100–105, https://doi.org/10.1136/bmjnph-2020-000071.

[17] S.M. Michienzi, M.E. Badowski, Can vitamins and/or supplements provide hope against coronavirus? Drugs in Context 9 (2020) 2020, https://doi.org/10.7573/dic.2020-5-7, 2025-7.

[18] S. Maggini, A. Pierre, P.C. Calder, Immune function and micronutrient requirements change over the life course, Nutrients 10 (10) (2018) 1531, https://doi.org/10.3390/nu10101531.

[19] M.J. Rytter, L. Kolte, A. Briend, H. Friis, V.B. Christensen, The immune system in children with malnutrition–a systematic review, PLoS One 9 (8) (2014) e105017, https://doi.org/10.1371/journal.pone.0105017.

[20] C.E. Childs, P.C. Calder, E.A. Miles, Diet and immune function, Nutrients 11 (8) (2019) 1933, https://doi.org/10.3390/nu11081933.

[21] P.C. Calder, A.C. Carr, A.F. Gombart, M. Eggersdorfer, Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections, Nutrients 12 (4) (2020) 1181, https://doi.org/10.3390/nu12041181.

[22] P.C. Calder, Feeding the immune system, Proc. Nutr. Soc. 72 (3) (2013) 299–309, https://doi.org/10.1017/S0029665113001286.

[23] P.C. Calder, Nutrition, immunity and COVID-19, BMJ Nutri. Prevention & Health 3 (1) (2020) 74–92, https://doi.org/10.1136/bmjnph-2020-000085.

[24] H. Shakoor, J. Feehan, A.S. Al Dhaheri, H.I. Ali, C. Platat, L.C. Ismail, V. Apostolopoulos, L. Stojanovska, Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: could they help against COVID-19? Maturitas 143 (2021) 1–9, https://doi.org/10.1016/j.maturitas.2020.08.003.

[25] N. Ali, Role of vitamin D in preventing of COVID-19 infection, progression and severity, J. Infect. Public Health 13 (10) (2020) 1373–1380, https://doi.org/10.1016/j.jiph.2020.06.021.

[26] I. Kapoor, H. Prabhakar, C. Mahajan, Vitamins as adjunctive treatment for coronavirus disease, Ann. Intensive Care 10 (1) (2020) 127, https://doi.org/10.1186/s13613-020-00748-7.

[27] R. Jayawardena, P. Sooriyaarachchi, M. Chourdakis, C. Jeewandara, P. Ranasinghe, Enhancing immunity in viral infections, with special emphasis on COVID-19: a review, Diabetes Metabol. Syndr. 14 (4) (2020) 367–382, https://doi.org/10.1016/j.dsx.2020.04.015.

[28] M.M. Rogero, M.C. Leão, T.M. Santana, M.V.M.B. Pimentel, G.C.G. Carlini, T.F. F. da Silveira, R.C. Gonçalves, I.A. Castro, Potential benefits and risks of omega-3 fatty acids supplementation to patients with COVID-19, Free Radical Biol. Med. 156 (2020) 190–199, https://doi.org/10.1016/j.freeradbiomed.2020.07.005.

[29] A. Sundararaman, M. Ray, P.V. Ravindra, P.M. Halami, Role of probiotics to combat viral infections with emphasis on COVID-19, Appl. Microbiol. Biotechnol. 104 (19) (2020) 8089–8104, https://doi.org/10.1007/s00253-020-10832-4.

[30] K.B. Comerford, Recent developments in multivitamin/mineral research, Adv. Nutrition (Bethesda, Md 4 (6) (2013) 644–656, https://doi.org/10.3945/an.113.004523.

[31] Office of Dietary Supplements—Multivitamin/mineral Supplements, 2022. https://ods.od.nih.gov/factsheets/MVMS-HealthProfessional/.

[32] W.M. Al-Johani, K.M. Al-Dawood, M.M. Abdel Wahab, H.A. Yousef, Consumption of vitamin and mineral supplements and its correlates among medical students in Eastern Province, Saudi Arabia, J. Family Commun. Med. 25 (3) (2018) 169–174, https://doi.org/10.4103/jfcm.JFCM_156_17.

[33] R. Mamtani, S. Cheema, B. MacRae, H. Alrouh, T. Lopez, M. ElHajj, Z. Mahfoud, Herbal and nutritional supplement use among college students in Qatar, East. Mediterr. Health J. 21 (1) (2015) 39–44, https://doi.org/10.26719/2015.21.1.39.

[34] F.K. Alhomoud, M. Basil, A. Bondarev, Knowledge, attitudes and practices (kap) relating to dietary supplements among health sciences and non-health sciences students in one of the universities of United Arab Emirates (UAE), J. Clin. Diagn. Res.: J. Clin. Diagn. Res. 10 (9) (2016) JC05–JC09, https://doi.org/10.7860/JCDR/2016/19300.8439.

[35] G. El Khoury, W. Ramadan, N. Zeeni, Herbal products and dietary supplements: a cross-sectional survey of use, attitudes, and knowledge among the lebanese

population, J. Community Health 41 (3) (2016) 566–573, https://doi.org/10.1007/s10900-015-0131-0.
[36] Overview of Viral Respiratory Infections—Infectious Diseases, MSD Manual Professional Edition, 2021. https://www.msdmanuals.com/professional/infectious-diseases/respiratory-viruses/overview-of-viral-respiratory-infections. Retrieved April 5, 2021.
[37] G.S. Lei, C. Zhang, B.H. Cheng, C.H. Lee, Mechanisms of action of vitamin d as supplemental therapy for pneumocystis pneumonia, Antimicrob. Agents Chemother. 61 (10) (2017) e01226, https://doi.org/10.1128/AAC.01226-17, 17.
[38] W.B. Grant, H. Lahore, S.L. McDonnell, C.A. Baggerly, C.B. French, J.L. Aliano, H. P. Bhattoa, Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths, Nutrients 12 (4) (2020) 988, https://doi.org/10.3390/nu12040988.
[39] T. Heikkinen, A. Järvinen, The common cold, Lancet (London, England) 361 (9351) (2003) 51–59, https://doi.org/10.1016/S0140-6736(03)12162-9.
[40] G.M. Allan, B. Arroll, Prevention and treatment of the common cold: making sense of the evidence, CMAJ (Can. Med. Assoc. J.): Can. Med. Assoc. J. 186 (3) (2014) 190–199, https://doi.org/10.1503/cmaj.121442.
[41] S. Kinkade, N.A. Long, Acute bronchitis, Am. Fam. Physician 94 (7) (2016) 560–565.
[42] CDC COVID-19 Response Team, Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States, February 12-March 16, 2020, MMWR. Morbidity and Mortality Weekly Report 69 (12) (2020) 343–346, https://doi.org/10.15585/mmwr.mm6912e2.
[43] T.T. Bauer, S. Ewig, A.C. Rodloff, E.E. Müller, Acute respiratory distress syndrome and pneumonia: a comprehensive review of clinical data, Clin. Infect. Dis.: an Official Publication of the Infectious Diseases Society of America 43 (6) (2006) 748–756, https://doi.org/10.1086/506430.
[44] E. Fan, D. Brodie, A.S. Slutsky, Acute respiratory distress syndrome: advances in diagnosis and treatment, J. Am. Med. Assoc. 319 (7) (2018) 698–710, https://doi.org/10.1001/jama.2017.21907.
[45] J. Wang, L. Pan, S. Tang, J.S. Ji, X. Shi, Mask use during COVID-19: a risk adjusted strategy, Environ. Pollut. 266 (Pt 1) (2020) 115099, https://doi.org/10.1016/j.envpol.2020.115099.
[46] A.F. Gombart, A. Pierre, S. Maggini, A review of micronutrients and the immune system-working in harmony to reduce the risk of infection, Nutrients 12 (1) (2020) 236, https://doi.org/10.3390/nu12010236.
[47] H. Hemilä, E. Chalker, Vitamin C can shorten the length of stay in the icu: a meta-analysis, Nutrients 11 (4) (2019) 708, https://doi.org/10.3390/nu11040708.
[48] S.A. Tanumihardjo, Vitamin A: biomarkers of nutrition for development, Am. J. Clin. Nutr. 94 (2) (2011), https://doi.org/10.3945/ajcn.110.005777, 658S–65S.
[49] G. Tang, Bioconversion of dietary provitamin A carotenoids to vitamin A in humans, Am. J. Clin. Nutr. 91 (5) (2010) 1468S–1473S, https://doi.org/10.3945/ajcn.2010.28674G.
[50] M. Zhong, R. Kawaguchi, M. Kassai, H. Sun, Retina, retinol, retinal and the natural history of vitamin A as a light sensor, Nutrients 4 (12) (2012) 2069–2096, https://doi.org/10.3390/nu4122069.
[51] J. Fiedor, K. Burda, Potential role of carotenoids as antioxidants in human health and disease, Nutrients 6 (2) (2014) 466–488, https://doi.org/10.3390/nu6020466.
[52] Z. Huang, Y. Liu, G. Qi, D. Brand, S.G. Zheng, Role of vitamin A in the immune system, J. Clin. Med. 7 (9) (2018) 258, https://doi.org/10.3390/jcm7090258.
[53] R. Caccialanza, A. Laviano, F. Lobascio, E. Montagna, R. Bruno, S. Ludovisi, A. G. Corsico, A. Di Sabatino, M. Belliato, M. Calvi, I. Iacona, G. Grugnetti, E. Bonadeo, A. Muzzi, E. Cereda, Early nutritional supplementation in non-critically ill patients hospitalized for the 2019 novel coronavirus disease (COVID-19): rationale and feasibility of a shared pragmatic protocol, Nutrition 74 (2020) 110835, https://doi.org/10.1016/j.nut.2020.110835.
[54] S. Araki, S. Kato, F. Namba, E. Ota, Vitamin A to prevent bronchopulmonary dysplasia in extremely low birth weight infants: a systematic review and meta-analysis, PLoS One 13 (11) (2018) e0207730, https://doi.org/10.1371/journal.pone.0207730.
[55] M. Iddir, A. Brito, G. Dingeo, S.S. Fernandez Del Campo, H. Samouda, M.R. La Frano, T. Bohn, Strengthening the immune system and reducing inflammation and oxidative stress through diet and nutrition: considerations during the COVID-19 crisis, Nutrients 12 (6) (2020) 1562, https://doi.org/10.3390/nu12061562.
[56] L.P. Rubin, A.C. Ross, C.B. Stephensen, T. Bohn, S.A. Tanumihardjo, Metabolic effects of inflammation on vitamin a and carotenoids in humans and animal models, Adv. Nutr. 8 (2) (2017) 197–212, https://doi.org/10.3945/an.116.014167.
[57] R. Gu, H. Chen, A. Adhikari, Y. Gu, J.S.W. Kwong, G. Li, Z. Li, Y. Pan, Vitamin A for preventing acute lower respiratory tract infections in children up to seven years of age, Cochrane Database Syst. Rev. 2021 (4) (2021) CD014847, https://doi.org/10.1002/14651858.CD014847.
[58] N. Brown, C. Roberts, Vitamin A for acute respiratory infection in developing countries: a meta-analysis, Acta Paediatr. 93 (11) (2004) 1437–1442, https://doi.org/10.1080/08035250410022143.
[59] N.C.A. Michele, N.B. Angelo, N.L. Valeria, N.M. Teresa, N. De Luca Pasquale, N. C. Giuseppe, N.M. Giovanni, N. Di Pumpo Michele, N.P. Ernestina, N.B. Mario, Vitamin supplements in the era of SARS-Cov 2 pandemic, GSC Biol. Pharm. Sci. 11 (2) (2020) 7–19, https://doi.org/10.30574/gscbps.2020.11.2.0114.
[60] E. Spinas, A. Saggini, S.K. Kritas, G. Cerulli, A. Caraffa, P. Antinolfi, A. Pantalone, A. Frydas, M. Tei, A. Speziali, R. Saggini, F. Pandolfi, P. Conti, Crosstalk between vitamin B and immunity, J. Biol. Regul. Homeost. Agents 29 (2) (2015) 283–288.
[61] K. Yoshii, K. Hosomi, K. Sawane, J. Kunisawa, Metabolism of dietary and microbial vitamin B family in the regulation of host immunity, Front. Nutr. 6 (2019) 48, https://doi.org/10.3389/fnut.2019.00048.
[62] R. Rodriguez-Melendez, J. Zempleni, Regulation of gene expression by biotin, J. Nutr. Biochem. 14 (12) (2003) 680–690, https://doi.org/10.1016/j.jnutbio.2003.07.001.
[63] S. Taneja, T.A. Strand, T. Kumar, M. Mahesh, S. Mohan, M.S. Manger, H. Refsum, C.S. Yajnik, N. Bhandari, Folic acid and vitamin B-12 supplementation and common infections in 6-30-mo-old children in India: a randomized placebo-controlled trial, Am. J. Clin. Nutr. 98 (3) (2013) 731–737, https://doi.org/10.3945/ajcn.113.059592.
[64] S.J. Padayatty, M. Levine, Vitamin C: the known and the unknown and Goldilocks, Oral Dis. 22 (6) (2016) 463–493, https://doi.org/10.1111/odi.12446.
[65] P.E. Marik, Vitamin C: an essential "stress hormone" during sepsis, J. Thorac. Dis. 12 (Suppl 1) (2020) S84–S88, https://doi.org/10.21037/jtd.2019.12.64.
[66] N. Majidi, F. Rabbani, S. Gholami, M. Gholamalizadeh, F. BourBour, S. Rastgoo, A. Hajipour, M. Shadnoosh, M.E. Akbari, B. Bahar, N. Ashoori, A. Alizadeh, F. Samipoor, A. Moslem, S. Doaei, K. Suzuki, The effect of vitamin C on pathological parameters and survival duration of critically ill coronavirus disease 2019 patients: a randomized clinical trial, Front. Immunol. 12 (2021) 717816, https://doi.org/10.3389/fimmu.2021.717816.
[67] A.C. Carr, A new clinical trial to test high-dose vitamin C in patients with COVID-19, Crit. Care 24 (1) (2020) 133, https://doi.org/10.1186/s13054-020-02851-4.
[68] Y. Chen, G. Luo, J. Yuan, Y. Wang, X. Yang, X. Wang, G. Li, Z. Liu, N. Zhong, Vitamin C mitigates oxidative stress and tumor necrosis factor-alpha in severe community-acquired pneumonia and LPS-induced macrophages, Mediat. Inflamm. 2014 (2014) 426740, https://doi.org/10.1155/2014/426740.
[69] N.C. Righi, F.B. Schuch, A.T. De Nardi, C.M. Pippi, G. de Almeida Righi, G. O. Puntel, A.M.V. da Silva, L.U. Signori, Effects of vitamin C on oxidative stress, inflammation, muscle soreness, and strength following acute exercise: meta-analyses of randomized clinical trials, Eur. J. Nutr. 59 (7) (2020) 2827–2839, https://doi.org/10.1007/s00394-020-02215-2.
[70] M. Gholizadeh, S.G. Saeedy, A. Abdi, F. Khademi, K. Lorian, C.C. Clark, K. Djafarian, Vitamin C reduces interleukin-6 plasma concentration: a systematic review and meta-analysis of randomized clinical trials, Clin. Nutri. Open Sci. 40 (2021) 1–14, https://doi.org/10.1016/j.nutos.2021.09.003.
[71] H.A. Mousa, Prevention and treatment of influenza, influenza-like illness, and common cold by herbal, complementary, and natural therapies, J. Evidence-Based Complementary Alternative Med. 22 (1) (2017) 166–174, https://doi.org/10.1177/2156587216641831.
[72] M. Van Straten, P. Josling, Preventing the common cold with a vitamin C supplement: a double-blind, placebo-controlled survey, Adv. Ther. 19 (3) (2002) 151–159, https://doi.org/10.1007/BF02850271.
[73] H. Hemilä, E. Chalker, Vitamin C for preventing and treating the common cold, Cochrane Database Syst. Rev. 2013 (1) (2013) CD000980, https://doi.org/10.1002/14651858.CD000980.pub4.
[74] P. Holford, A.C. Carr, T.H. Jovic, S.R. Ali, I.S. Whitaker, P.E. Marik, A.D. Smith, Vitamin C-an adjunctive therapy for respiratory infection, sepsis and COVID-19, Nutrients 12 (12) (2020) 3760, https://doi.org/10.3390/nu12123760.
[75] H. Hemilä, Vitamin C and infections, Nutrients 9 (4) (2017) 339, https://doi.org/10.3390/nu9040339.
[76] A. Bucher, N. White, Vitamin C in the prevention and treatment of the common cold, Am. J. Lifestyle Med. 10 (3) (2016) 181–183, https://doi.org/10.1177/1559827616629092.
[77] C. Arvinte, M. Singh, P.E. Marik, Serum levels of vitamin C and vitamin D in a cohort of critically ill COVID-19 patients of a North American community hospital intensive care unit in May 2020: a pilot study, Med. Drug Discovery 8 (2020) 100064, https://doi.org/10.1016/j.medidd.2020.100064.
[78] L. Chiscano-Camón, J.C. Ruiz-Rodriguez, A. Ruiz-Sanmartin, O. Roca, R. Ferrer, Vitamin C levels in patients with SARS-CoV-2-associated acute respiratory distress syndrome, Crit. Care 24 (1) (2020) 522, https://doi.org/10.1186/s13054-020-03249-y.
[79] J. Agier, M. Efenberger, E. Brzezińska-Błaszczyk, Cathelicidin impact on inflammatory cells, Cent.-Eur. J. Immunol. 40 (2) (2015) 225–235, https://doi.org/10.5114/ceji.2015.51359.
[80] M. Teymoori-Rad, F. Shokri, V. Salimi, S.M. Marashi, The interplay between vitamin D and viral infections, Rev. Med. Virol. 29 (2) (2019) e2032, https://doi.org/10.1002/rmv.2032.
[81] G. Annweiler, M. Corvaisier, J. Gautier, V. Dubée, E. Legrand, G. Sacco, C. Annweiler, Vitamin D supplementation associated to better survival in hospitalized frail elderly COVID-19 patients: the GERIA-COVID quasi-experimental study, Nutrients 12 (11) (2020) 3377, https://doi.org/10.3390/nu12113377.
[82] C. Annweiler, M. Beaudenon, J. Gautier, J. Gonsard, S. Boucher, G. Chapelet, A. Darsonval, B. Fougère, O. Guérin, M. Houvet, P. Ménager, C. Roubaud-Baudron, A. Tchalla, J.C. Souberbielle, J. Riou, E. Parot-Schinkel, T. Célarier, COVIT-TRIAL study group, High-dose versus standard-dose vitamin D supplementation in older adults with COVID-19 (COVIT-TRIAL): a multicenter, open-label, randomized controlled superiority trial, PLoS Med. 19 (5) (2022) e1003999, https://doi.org/10.1371/journal.pmed.1003999.
[83] A. D'Avolio, V. Avataneo, A. Manca, J. Cusato, A. De Nicolò, R. Lucchini, F. Keller, M. Cantù, 25-hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS-CoV-2, Nutrients 12 (5) (2020) 1359, https://doi.org/10.3390/nu12051359.

[84] P.C. Ilie, S. Stefanescu, L. Smith, The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality, Aging Clin. Exp. Res. 32 (7) (2020) 1195–1198, https://doi.org/10.1007/s40520-020-01570-8.
[85] A.R. Martineau, D.A. Jolliffe, R.L. Hooper, L. Greenberg, J.F. Aloia, P. Bergman, G. Dubnov-Raz, S. Esposito, D. Ganmaa, A.A. Ginde, E.C. Goodall, C.C. Grant, C. J. Griffiths, W. Janssens, I. Laaksi, S. Manaseki-Holland, D. Mauger, D. R. Murdoch, R. Neale, J.R. Rees, C.A. Camargo Jr., Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data, BMJ 356 (2017) i6583, https://doi.org/10.1136/bmj.i6583.
[86] I.T. Parsons, R.M. Gifford, M.J. Stacey, L.E. Lamb, M.K. O'Shea, D.R. Woods, Does vitamin D supplementation prevent SARS-CoV-2 infection in military personnel? Review of the evidence, BMJ Military Health 167 (4) (2021) 280–286, https://doi.org/10.1136/bmjmilitary-2020-001686.
[87] P. Bergman, A.U. Lindh, L. Björkhem-Bergman, J.D. Lindh, Vitamin D and respiratory tract infections: a systematic review and meta-analysis of randomized controlled trials, PLoS One 8 (6) (2013) e65835, https://doi.org/10.1371/journal.pone.0065835.
[88] E.C. Goodall, A.C. Granados, K. Luinstra, E. Pullenayegum, B.L. Coleman, M. Loeb, M. Smieja, Vitamin D3 and gargling for the prevention of upper respiratory tract infections: a randomized controlled trial, BMC Infect. Dis. 14 (2014) 273, https://doi.org/10.1186/1471-2334-14-273.
[89] M. Urashima, H. Mezawa, M. Noya, C.A. Camargo Jr., Effects of vitamin D supplements on influenza A illness during the 2009 H1N1 pandemic: a randomized controlled trial, Food Funct. 5 (9) (2014) 2365–2370, https://doi.org/10.1039/c4fo00371c.
[90] A.R. Martineau, Y. Hanifa, K.D. Witt, N.C. Barnes, R.L. Hooper, M. Patel, N. Stevens, Z. Enayat, Z. Balayah, A. Syed, A. Knight, D.A. Jolliffe, C.L. Greiller, D. McLaughlin, T.R. Venton, M. Rowe, P.M. Timms, D. Clark, Z. Sadique, S. M. Eldridge, C.J. Griffiths, Double-blind randomised controlled trial of vitamin D3 supplementation for the prevention of acute respiratory infection in older adults and their carers (ViDiFlu), Thorax 70 (10) (2015) 953–960, https://doi.org/10.1136/thoraxjnl-2015-206996.
[91] J. Charan, J.P. Goyal, D. Saxena, P. Yadav, Vitamin D for prevention of respiratory tract infections: a systematic review and meta-analysis, J. Pharmacol. Pharmacother. 3 (4) (2012) 300–303, https://doi.org/10.4103/0976-500X.103685.
[92] Scientific Advisory Committee on Nutrition, Rapid Review: Vitamin D and Acute Respiratory Tract Infections, Public Health England, 2020. Retrieved in September 2022 from, https://www.gov.uk/government/publications/rapid-review-vitamin-d-and-acute-respiratory-tract-infections.
[93] C.E. Hastie, J.P. Pell, N. Sattar, Vitamin D and COVID-19 infection and mortality in UK Biobank, Eur. J. Nutr. 60 (1) (2021) 545–548, https://doi.org/10.1007/s00394-020-02372-4.
[94] R. Munshi, M.H. Hussein, E.A. Toraih, R.M. Elshazli, C. Jardak, N. Sultana, M. R. Youssef, M. Omar, A.S. Attia, M.S. Fawzy, M. Killackey, E. Kandil, J. Duchesne, Vitamin D insufficiency as a potential culprit in critical COVID-19 patients, J. Med. Virol. 93 (2) (2021) 733–740, https://doi.org/10.1002/jmv.26360.
[95] E. Merzon, D. Tworowski, A. Gorohovski, S. Vinker, A. Golan Cohen, I. Green, M. Frenkel-Morgenstern, Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study, FEBS J. 287 (17) (2020) 3693–3702, https://doi.org/10.1111/febs.15495.
[96] R. Pal, M. Banerjee, S.K. Bhadada, A.J. Shetty, B. Singh, A. Vyas, Vitamin D supplementation and clinical outcomes in COVID-19: a systematic review and meta-analysis, J. Endocrinol. Invest. 45 (1) (2022) 53–68, https://doi.org/10.1007/s40618-021-01614-4.
[97] National Institute for Health and Care Excellence, COVID-19 rapid guideline: Vitamin D, Retrieved in May 2022 from, https://www.nice.org.uk/guidance/ng187, 2020.
[98] D. De Smet, K. De Smet, P. Herroelen, S. Gryspeerdt, G. Martens, Vitamin D deficiency as risk factor for severe COVID-19: a convergence of two pandemics, medRxiv (2020), https://doi.org/10.1101/2020.05.01.20079376. Retrieved in October 2022 from.
[99] C.E. Hastie, D.F. Mackay, F. Ho, C.A. Celis-Morales, S.V. Katikireddi, C. L. Niedzwiedz, B.D. Jani, P. Welsh, F.S. Mair, S.R. Gray, C.A. O'Donnell, J.M. Gill, N. Sattar, J.P. Pell, Vitamin D concentrations and COVID-19 infection in UK Biobank, Diabetes Metabol. Syndr. 14 (4) (2020) 561–565, https://doi.org/10.1016/j.dsx.2020.04.050.
[100] N. Farid, N. Rola, E.A.T. Koch, N. Nakhoul, Active vitamin D supplementation and COVID-19 infections: review, Ir. J. Med. Sci. 190 (4) (2021) 1271–1274, https://doi.org/10.1007/s11845-020-02452-8.
[101] J.L. Mansur, C. Tajer, J. Mariani, F. Inserra, L. Ferder, W. Manucha, Vitamin D high doses supplementation could represent a promising alternative to prevent or treat COVID-19 infection. El suplemento con altas dosis de vitaminaD podría representar una alternativa promisoria para prevenir o tratar la infección por COVID-19, Clín. Invest. Arterioscler. : publicacion oficial de la Sociedad Espanola de Arteriosclerosis 32 (6) (2020) 267–277, https://doi.org/10.1016/j.arteri.2020.05.003.
[102] G.Y. Lee, S.N. Han, The role of vitamin E in immunity, Nutrients 10 (11) (2018) 1614, https://doi.org/10.3390/nu10111614.
[103] S.N. Meydani, L.S. Leka, B.C. Fine, G.E. Dallal, G.T. Keusch, M.F. Singh, D. H. Hamer, Vitamin E and respiratory tract infections in elderly nursing home residents: a randomized controlled trial, J. Am. Med. Assoc. 292 (7) (2004) 828–836, https://doi.org/10.1001/jama.292.7.828.
[104] H. Hemilä, Vitamin E administration may decrease the incidence of pneumonia in elderly males, Clin. Interv. Aging 11 (2016) 1379–1385, https://doi.org/10.2147/CIA.S114515.
[105] D. Wu, S.N. Meydani, Vitamin E, immune function. And Protection against Infection, Springer eBooks, 2019, pp. 371–384, https://doi.org/10.1007/978-3-030-05315-4_26.
[106] M. Liu, R. Wallin, A. Wallmon, T. Saldeen, Mixed tocopherols have a stronger inhibitory effect on lipid peroxidation than alpha-tocopherol alone, J. Cardiovasc. Pharmacol. 39 (5) (2002) 714–721, https://doi.org/10.1097/00005344-200205000-00012.
[107] S.A. Read, S. Obeid, C. Ahlenstiel, G. Ahlenstiel, The role of zinc in antiviral immunity, Adv. Nutr. 10 (4) (2019) 696–710, https://doi.org/10.1093/advances/nmz013.
[108] S. Hojyo, T. Fukada, Roles of zinc signaling in the immune system, J. Immunology Res. 2016 (2016) 6762343, https://doi.org/10.1155/2016/6762343.
[109] A.S. Prasad, Zinc is an antioxidant and anti-inflammatory agent: its role in human health, Front. Nutr. 1 (2014) 14, https://doi.org/10.3389/fnut.2014.00014.
[110] A.S. Prasad, Zinc in human health: effect of zinc on immune cells, Mol. Med. 14 (5–6) (2008) 353–357, https://doi.org/10.2119/2008-00033.Prasad.
[111] A.V. Skalny, L. Rink, O.P. Ajsuvakova, M. Aschner, V.A. Gritsenko, S. I. Alekseenko, A.A. Svistunov, D. Petrakis, D.A. Spandidos, J. Aaseth, A. Tsatsakis, A.A. Tinkov, Zinc and respiratory tract infections: perspectives for COVID-19 (Review), Int. J. Mol. Med. 46 (1) (2020) 17–26, https://doi.org/10.3892/ijmm.2020.4575.
[112] M. Science, J. Johnstone, D.E. Roth, G. Guyatt, M. Loeb, Zinc for the treatment of the common cold: a systematic review and meta-analysis of randomized controlled trials, CMAJ (Can. Med. Assoc. J.) : Can. Med. Assoc. J. 184 (10) (2012) E551–E561, https://doi.org/10.1503/cmaj.111990.
[113] R.O. Suara, J.E. Crowe Jr., Effect of zinc salts on respiratory syncytial virus replication, Antimicrob. Agents Chemother. 48 (3) (2004) 783–790, https://doi.org/10.1128/AAC.48.3.783-790.2004.
[114] A. Malik, D.K. Taneja, N. Devasenapathy, K. Rajeshwari, Zinc supplementation for prevention of acute respiratory infections in infants: a randomized controlled trial, Indian Pediatr. 51 (10) (2014) 780–784, https://doi.org/10.1007/s13312-014-0503-z.
[115] D.V. Veverka, C. Wilson, M.A. Martinez, R. Wenger, A. Tamosuinas, Use of zinc supplements to reduce upper respiratory infections in United States Air Force Academy cadets, Compl. Ther. Clin. Pract. 15 (2) (2009) 91–95, https://doi.org/10.1016/j.ctcp.2009.02.006.
[116] N.S. Martinez-Estevez, A.N. Alvarez-Guevara, C.E. Rodriguez-Martinez, Effects of zinc supplementation in the prevention of respiratory tract infections and diarrheal disease in Colombian children: a 12-month randomised controlled trial, Allergol. Immunopathol. 44 (4) (2016) 368–375, https://doi.org/10.1016/j.aller.2015.12.006.
[117] Z.S. Lassi, A. Moin, Z.A. Bhutta, Zinc supplementation for the prevention of pneumonia in children aged 2 months to 59 months, Cochrane Database Syst. Rev. 12 (12) (2016) CD005978, https://doi.org/10.1002/14651858.CD005978.pub3.
[118] S. Akhtar, J.K. Das, T. Ismail, M. Wahid, W. Saeed, Z.A. Bhutta, Nutritional perspectives for the prevention and mitigation of COVID-19, Nutr. Rev. 79 (3) (2021) 289–300, https://doi.org/10.1093/nutrit/nuaa063.
[119] P.R. Hoffmann, M.J. Berry, The influence of selenium on immune responses, Mol. Nutr. Food Res. 52 (11) (2008) 1273–1280, https://doi.org/10.1002/mnfr.200700330.
[120] M.P. Rayman, Selenium and human health, Lancet 379 (9822) (2012) 1256–1268, https://doi.org/10.1016/S0140-6736(11)61452-9.
[121] J.C. Avery, P.R. Hoffmann, Selenium, selenoproteins, and immunity, Nutrients 10 (9) (2018) 1203, https://doi.org/10.3390/nu10091203.
[122] L. Hiffler, B. Rakotoambinina, Selenium and RNA virus interactions: potential implications for SARS-CoV-2 infection (COVID-19), Front. Nutr. 7 (2020) 164, https://doi.org/10.3389/fnut.2020.00164.
[123] K. Ivory, E. Prieto, C. Spinks, C.N. Armah, A.J. Goldson, J.R. Dainty, C. Nicoletti, Selenium supplementation has beneficial and detrimental effects on immunity to influenza vaccine in older adults, Clin. Nutr. 36 (2) (2017) 407–415, https://doi.org/10.1016/j.clnu.2015.12.003.
[124] R. Ambra, S. Melloni, E. Venneria, Could selenium supplementation prevent COVID-19? A comprehensive review of available studies, Molecules 28 (10) (2023) 4130, https://doi.org/10.3390/molecules28104130.
[125] T.H. Hassan, M.A. Badr, N.A. Karam, M. Zkaria, H.F. El Saadany, D.M. Abdel Rahman, D.A. Shahbah, S.M. Al Morshedy, M. Fathy, A.M.H. Esh, A.M. Selim, Impact of iron deficiency anemia on the function of the immune system in children, Medicine 95 (47) (2016) e5395, https://doi.org/10.1097/MD.0000000000005395.
[126] B.J. Cherayil, Iron and immunity: immunological consequences of iron deficiency and overload, Arch. Immunol. Ther. Exp. 58 (6) (2010) 407–415, https://doi.org/10.1007/s00005-010-0095-9.
[127] S.A. Richard, N. Zavaleta, L.E. Caulfield, R.E. Black, R.S. Witzig, A.H. Shankar, Zinc and iron supplementation and malaria, diarrhea, and respiratory infections in children in the Peruvian Amazon, Am. J. Trop. Med. Hyg. 75 (1) (2006) 126–132, https://doi.org/10.4269/ajtmh.2006.75.1.0750126.
[128] Food and Agriculture Organization of the United Nations, & World Health Organization, Probiotics in food: health and nutritional properties and guidelines for evaluation, Food Agric. Organization United Nations: World Health Organization 85 (2006) 1–56.

[129] L.H. Shi, K. Balakrishnan, K. Thiagarajah, N.I. Mohd Ismail, O.S. Yin, Beneficial properties of probiotics, Trop. Life Sci. Res. 27 (2) (2016) 73–90, https://doi.org/10.21315/tlsr2016.27.2.6.

[130] C. Maldonado Galdeano, S.I. Cazorla, J.M. Lemme Dumit, E. Vélez, G. Perdigón, Beneficial effects of probiotic consumption on the immune system, Ann. Nutr. Metab. 74 (2) (2019) 115–124, https://doi.org/10.1159/000496426.

[131] G.J. Leyer, S. Li, M.E. Mubasher, C. Reifer, A.C. Ouwehand, Probiotic effects on cold and influenza-like symptom incidence and duration in children, Pediatrics 124 (2) (2009) e172–e179, https://doi.org/10.1542/peds.2008-2666.

[132] Q. Hao, B.R. Dong, T. Wu, Probiotics for preventing acute upper respiratory tract infections, Cochrane Database Syst. Rev. (2) (2015) CD006895, https://doi.org/10.1002/14651858.CD006895.pub3.

[133] E.J. Kang, S.Y. Kim, I.H. Hwang, Y.J. Ji, The effect of probiotics on prevention of common cold: a meta-analysis of randomized controlled trial studies, Korean J. Family Med. 34 (1) (2013) 2–10, https://doi.org/10.4082/kjfm.2013.34.1.2.

[134] R. Li, K. Wu, Y. Li, X. Liang, W.K.F. Tse, L. Yang, K.P. Lai, Revealing the targets and mechanisms of vitamin A in the treatment of COVID-19, Aging 12 (15) (2020) 15784–15796, https://doi.org/10.18632/aging.103888.

[135] G. Ponti, M. Maccaferri, C. Ruini, A. Tomasi, T. Ozben, Biomarkers associated with COVID-19 disease progression, Crit. Rev. Clin. Lab Sci. 57 (6) (2020) 389–399, https://doi.org/10.1080/10408363.2020.1770685.

[136] A.K.H. Wee, COVID-19's toll on the elderly and those with diabetes mellitus - is vitamin B12 deficiency an accomplice? Med. Hypotheses 146 (2021) 110374 https://doi.org/10.1016/j.mehy.2020.110374.

[137] J. Guest, A. Bilgin, B. Hokin, T.A. Mori, K.D. Croft, R. Grant, Novel relationships between B12, folate and markers of inflammation, oxidative stress and NAD(H) levels, systemically and in the CNS of a healthy human cohort, Nutr. Neurosci. 18 (8) (2015) 355–364, https://doi.org/10.1179/1476830515Y.0000000041.

[138] K.S. Batista, V.M. Cintra, P.A.F. Lucena, R. Manhães-de-Castro, A.E. Toscano, L. P. Costa, M.E.B.S. Queiroz, S.M. de Andrade, O. Guzman-Quevedo, J.S. Aquino, The role of vitamin B12 in viral infections: a comprehensive review of its relationship with the muscle-gut-brain axis and implications for SARS-CoV-2 infection, Nutr. Rev. 80 (3) (2022) 561–578, https://doi.org/10.1093/nutrit/nuab092.

[139] C.W. Tan, L.P. Ho, S. Kalimuddin, B.P.Z. Cherng, Y.E. Teh, S.Y. Thien, H.M. Wong, P.J.W. Tern, M. Chandran, J.W.M. Chay, C. Nagarajan, R. Sultana, J.G.H. Low, H. J. Ng, Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B12 in combination on progression to severe outcomes in older patients with coronavirus (COVID-19), Nutrition 79–80 (2020) 111017, https://doi.org/10.1016/j.nut.2020.111017.

[140] S.I. Lee, C.M. Lim, Y. Koh, J.W. Huh, J.S. Lee, S.B. Hong, The effectiveness of vitamin C for patients with severe viral pneumonia in respiratory failure, J. Thorac. Dis. 13 (2) (2021) 632–641, https://doi.org/10.21037/jtd-20-1306.

[141] A.A. Fowler 3rd, J.D. Truwit, R.D. Hite, P.E. Morris, C. DeWilde, A. Priday, B. Fisher, L.R. Thacker 2nd, R. Natarajan, D.F. Brophy, R. Sculthorpe, R. Nanchal, A. Syed, J. Sturgill, G.S. Martin, J. Sevransky, M. Kashiouris, S. Hamman, K. F. Egan, A. Hastings, M. Halquist, Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the CITRIS-ALI randomized clinical trial, J. Am. Med. Assoc. 322 (13) (2019) 1261–1270, https://doi.org/10.1001/jama.2019.11825.

[142] M. Zhang, D.F. Jativa, Vitamin C supplementation in the critically ill: a systematic review and meta-analysis, SAGE Open Med. 6 (2018) 2050312118807615, https://doi.org/10.1177/2050312118807615.

[143] A.F. Feyaerts, W. Luyten, Vitamin C as prophylaxis and adjunctive medical treatment for COVID-19? Nutrition 79–80 (2020) 110948 https://doi.org/10.1016/j.nut.2020.110948.

[144] S. JamaliMoghadamSiahkali, B. Zarezade, S. Koolaji, S. SeyedAlinaghi, A. Zendehdel, M. Tabarestani, E. Sekhavati Moghadam, L. Abbasian, S. A. Dehghan Manshadi, M. Salehi, M. Hasannezhad, S. Ghaderkhani, M. Meidani, F. Salahshour, F. Jafari, N. Manafi, F. Ghiasvand, Safety and effectiveness of high-dose vitamin C in patients with COVID-19: a randomized open-label clinical trial, Eur. J. Med. Res. 26 (1) (2021) 20, https://doi.org/10.1186/s40001-021-00490-1.

[145] S. Thomas, D. Patel, B. Bittel, K. Wolski, Q. Wang, A. Kumar, Z.J. Il'Giovine, R. Mehra, C. McWilliams, S.E. Nissen, M.Y. Desai, Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial, J. Am. Med. Association network open 4 (2) (2021) e210369, https://doi.org/10.1001/jamanetworkopen.2021.0369.

[146] D. Rawat, A. Roy, S. Maitra, V. Shankar, P. Khanna, D.K. Baidya, Vitamin D supplementation and COVID-19 treatment: a systematic review and meta-analysis, Diabetes Metabol. Syndr. 15 (4) (2021) 102189, https://doi.org/10.1016/j.dsx.2021.102189.

[147] P.E. Marik, P. Kory, J. Varon, J. Iglesias, G.U. Meduri, MATH+ protocol for the treatment of SARS-CoV-2 infection: the scientific rationale, Expert Review of Anti-Infective Therapy 19 (2) (2021) 129–135, https://doi.org/10.1080/14787210.2020.1808462.

[148] J.J. Litwak, N. Cho, H.B. Nguyen, K. Moussavi, T. Bushell, Vitamin c, hydrocortisone, and thiamine for the treatment of severe sepsis and septic shock: a retrospective analysis of real-world application, J. Clin. Med. 8 (4) (2019) 478, https://doi.org/10.3390/jcm8040478.

[149] M.H. Zabet, M. Mohammadi, M. Ramezani, H. Khalili, Effect of high-dose Ascorbic acid on vasopressor's requirement in septic shock, J. Res. Pharm. Pract. 5 (2) (2016) 94–100, https://doi.org/10.4103/2279-042X.179569.

[150] I.H. Murai, A.L. Fernandes, L.P. Sales, A.J. Pinto, K.F. Goessler, C.S.C. Duran, C.B. R. Silva, A.S. Franco, M.B. Macedo, H.H.H. Dalmolin, J. Baggio, G.G.M. Balbi, B. Z. Reis, L. Antonangelo, V.F. Caparbo, B. Gualano, R.M.R. Pereira, Effect of a single high dose of vitamin d3 on hospital length of stay in patients with moderate to severe COVID-19: a randomized clinical trial, J. Am. Med. Assoc. 325 (11) (2021) 1053–1060, https://doi.org/10.1001/jama.2020.26848.

[151] M. Entrenas Castillo, L.M. Entrenas Costa, J.M. Vaquero Barrios, J.F. Alcalá Díaz, J. López Miranda, R. Bouillon, J.M. Quesada Gomez, Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study, J. Steroid Biochem. Mol. Biol. 203 (2020) 105751, https://doi.org/10.1016/j.jsbmb.2020.105751.

[152] C. Annweiler, B. Hanotte, C. Grandin de l'Eprevier, J.M. Sabatier, L. Lafaie, T. Célarier, Vitamin D and survival in COVID-19 patients: a quasi-experimental study, J. Steroid Biochem. Mol. Biol. 204 (2020) 105771, https://doi.org/10.1016/j.jsbmb.2020.105771.

[153] M.F. Holick, N.C. Binkley, H.A. Bischoff-Ferrari, C.M. Gordon, D.A. Hanley, R. P. Heaney, M.H. Murad, C.M. Weaver, Endocrine Society, Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline, J. Clin. Endocrinol. Metabol. 96 (7) (2011) 1911–1930, https://doi.org/10.1210/jc.2011-0385.

[154] Scientific Advisory Committee on Nutrition, Rapid Review: Vitamin D and Acute Respiratory Tract Infections, 2020. https://www.gov.uk/government/publications/sacn-rapid-review-vitamin-d-and-acute-respiratory-tract-infections.

[155] I.O. Medicine, Dietary Reference Intakes for Calcium and Vitamin D, National Academies Press eBooks, 2011, https://doi.org/10.17226/13050.

[156] European Food Safety Authority Panel on Nutrition, Novel Foods and FoodAllergens (NDA), D. Turck, T. Bohn, J. Castenmiller, S. de Henauw, K. I. Hirsch-Ernst, H.K. Knutsen, A. Maciuk, I. Mangelsdorf, H.J. McArdle, K. Pentieva, A. Siani, F. Thies, S. Tsabouri, M. Vinceti, S. Lanham-New, G. Passeri, I. Craciun, L. Fabiani, R.F. De Sousa, A. Naska, Scientific opinion on the tolerable upper intake level for vitamin D, including the derivation of a conversion factor for calcidiol monohydrate, European Food Safety Authority J. 21 (8) (2023) e08145, https://doi.org/10.2903/j.efsa.2023.8145.

[157] N. Bokharee, Y.H. Khan, T. Wasim, T.H. Mallhi, N.H. Alotaibi, M.S. Iqbal, K. Rehman, A.I. Alzarea, A. Khokhar, Daily versus stat vitamin D supplementation during pregnancy; A prospective cohort study, PLoS One 15 (4) (2020) e0231590, https://doi.org/10.1371/journal.pone.0231590.

[158] U.H. Shah, A.K. Abu-Shaheen, M.A. Malik, S. Alam, M. Riaz, M.A. Al-Tannir, The efficacy of zinc supplementation in young children with acute lower respiratory infections: a randomized double-blind controlled trial, Clin. Nutr. 32 (2) (2013) 193–199, https://doi.org/10.1016/j.clnu.2012.08.018.

[159] J.A. Acevedo-Murillo, M.L. García León, V. Firo-Reyes, J.L. Santiago-Cordova, A. P. Gonzalez-Rodriguez, R.M. Wong-Chew, Zinc supplementation promotes a Th1 response and improves clinical symptoms in fewer hours in children with pneumonia younger than 5 years old. A randomized controlled clinical trial, Front. Pediatrics 7 (2019) 431, https://doi.org/10.3389/fped.2019.00431.

[160] S. Rerksuppaphol, L. Rerksuppaphol, A randomized controlled trial of zinc supplementation in the treatment of acute respiratory tract infection in Thai children, Pediatr. Rep. 11 (2) (2019) 7954, https://doi.org/10.4081/pr.2019.7954.

[161] D.E. Roth, S.A. Richard, R.E. Black, Zinc supplementation for the prevention of acute lower respiratory infection in children in developing countries: meta-analysis and meta-regression of randomized trials, Int. J. Epidemiol. 39 (3) (2010) 795–808, https://doi.org/10.1093/ije/dyp391.

[162] I. Wessels, B. Rolles, L. Rink, The potential impact of zinc supplementation on COVID-19 pathogenesis, Front. Immunol. 11 (2020) 1712, https://doi.org/10.3389/fimmu.2020.01712.

[163] S. Ben Abdallah, Y. Mhalla, I. Trabelsi, A. Sekma, R. Youssef, K. Bel Haj Ali, H. Ben Soltane, H. Yacoubi, M.A. Msolli, N. Stambouli, K. Beltaief, M.H. Grissa, M. Khrouf, Z. Mezgar, C. Loussaief, W. Bouida, R. Razgallah, K. Hezbri, A. Belguith, N. Belkacem, S. Nouira, Twice-daily oral zinc in the treatment of patients with coronavirus disease 2019: a randomized double-blind controlled trial, Clin. Infect. Dis.: An Official Publication of the Infectious Diseases Society of America 76 (2) (2023) 185–191, https://doi.org/10.1093/cid/ciac807.

[164] X. Liu, S. Yin, G. Li, Zhonghua yu fang yi xue za zhi, Chin. J. Prev. Med. 31 (6) (1997) 358–361.

[165] A. Moghaddam, R.A. Heller, Q. Sun, J. Seelig, A. Cherkezov, L. Seibert, J. Hackler, P. Seemann, J. Diegmann, M. Pilz, M. Bachmann, W.B. Minich, L. Schomburg, Selenium deficiency is associated with mortality risk from COVID-19, Nutrients 12 (7) (2020) 2098, https://doi.org/10.3390/nu12072098.

[166] A. Gasmi, S. Noor, T. Tippairote, M. Dadar, A. Menzel, G. Bjørklund, Individual risk management strategy and potential therapeutic options for the COVID-19 pandemic, Clin. Immunol. 215 (2020) 108409, https://doi.org/10.1016/j.clim.2020.108409.

[167] M. Kieliszek, B. Lipinski, Selenium supplementation in the prevention of coronavirus infections (COVID-19), Med. Hypotheses 143 (2020) 109878, https://doi.org/10.1016/j.mehy.2020.109878.

[168] S.M. Schmidt, The role of iron in viral infections, Front. Biosci. 25 (5) (2020) 893–911, https://doi.org/10.2741/4839.

[169] H. Wang, Z. Li, J. Niu, Y. Xu, L. Ma, A. Lu, X. Wang, Z. Qian, Z. Huang, X. Jin, Q. Leng, J. Wang, J. Zhong, B. Sun, G. Meng, Antiviral effects of ferric ammonium citrate, Cell Dis. 4 (2018) 14, https://doi.org/10.1038/s41421-018-0013-6.

[170] R. Kumar, M. Nayak, G.C. Sahoo, K. Pandey, M.C. Sarkar, Y. Ansari, V.N.R. Das, R. K. Topno, Bhawna, M. Madhukar, P. Das, Iron oxide nanoparticles based antiviral activity of H1N1 influenza A virus, J. Infect. Chemother. 25 (5) (2019) 325–329, https://doi.org/10.1016/j.jiac.2018.12.006.

[171] T. Qin, R. Ma, Y. Yin, X. Miao, S. Chen, K. Fan, J. Xi, Q. Liu, Y. Gu, Y. Yin, J. Hu, X. Liu, D. Peng, L. Gao, Catalytic inactivation of influenza virus by iron oxide nanozyme, Theranostics 9 (23) (2019) 6920–6935, https://doi.org/10.7150/thno.35826.

[172] S. Mullick, U. Rusia, M. Sikka, M.A. Faridi, Impact of iron deficiency anaemia on T lymphocytes & their subsets in children, Indian J. Med. Res. 124 (6) (2006) 647–654.

[173] W. Liu, S. Zhang, S. Nekhai, S. Liu, Depriving iron supply to the virus represents a promising adjuvant therapeutic against viral survival, Curr. Clin. Microbiol. Rep. 7 (2) (2020) 13–19, https://doi.org/10.1007/s40588-020-00140-w.

[174] G. Weiss, T. Ganz, L.T. Goodnough, Anemia of inflammation, Blood 133 (1) (2019) 40–50, https://doi.org/10.1182/blood-2018-06-856500.

[175] E. Subroto, R. Indiarto, R. Andoyo, Bioavailability of iron and its potential to improve the immune system and ward off COVID-19: a review, Food Res. 7 (1) (2023) 76–92, https://doi.org/10.26656/fr.2017.7(1).701.

[176] S. Fooladi, S. Matin, A. Mahmoodpoor, Copper as a potential adjunct therapy for critically ill COVID-19 patients, Clinical Nutrition ESPEN 40 (2020) 90–91, https://doi.org/10.1016/j.clnesp.2020.09.022.

[177] S. Raha, R. Mallick, S. Basak, A.K. Duttaroy, Is copper beneficial for COVID-19 patients? Med. Hypotheses 142 (2020) 109814 https://doi.org/10.1016/j.mehy.2020.109814.

[178] A. Andreou, S. Trantza, D. Filippou, N. Sipsas, S. Tsiodras, COVID-19: the potential role of copper and N-acetylcysteine (NAC) in a combination of candidate antiviral treatments against SARS-CoV-2, In Vivo 34 (3 Suppl) (2020) 1567–1588, https://doi.org/10.21873/invivo.11946.

[179] A.A. Cortes, J.M. Zuñiga, The use of copper to help prevent transmission of SARS-coronavirus and influenza viruses. A general review, Diagn. Microbiol. Infect. Dis. 98 (4) (2020) 115176, https://doi.org/10.1016/j.diagmicrobio.2020.115176.

[180] J.R. Turnlund, R.A. Jacob, C.L. Keen, J.J. Strain, D.S. Kelley, J.M. Domek, W. R. Keyes, J.L. Ensunsa, J. Lykkesfeldt, J. Coulter, Long-term high copper intake: effects on indexes of copper status, antioxidant status, and immune function in young men, Am. J. Clin. Nutr. 79 (6) (2004) 1037–1044, https://doi.org/10.1093/ajcn/79.6.1037.

[181] W.J. Song, Y.S. Chang, Magnesium sulfate for acute asthma in adults: a systematic literature review, Asia Pacific Allergy 2 (1) (2012) 76–85, https://doi.org/10.5415/apallergy.2012.2.1.76.

[182] A.G. Kazaks, J.Y. Uriu-Adams, T.E. Albertson, S.F. Shenoy, J.S. Stern, Effect of oral magnesium supplementation on measures of airway resistance and subjective assessment of asthma control and quality of life in men and women with mild to moderate asthma: a randomized placebo controlled trial, J. Asthma 47 (1) (2010) 83–92, https://doi.org/10.3109/02770900903331127.

[183] A. Fogarty, S.A. Lewis, S.L. Scrivener, M. Antoniak, S. Pacey, M. Pringle, J. Britton, Oral magnesium and vitamin C supplements in asthma: a parallel group randomized placebo-controlled trial, Clin. Exp. Allergy 33 (10) (2003) 1355–1359, https://doi.org/10.1046/j.1365-2222.2003.01777.x.

[184] F. Abuabat, A. AlAlwan, E. Masuadi, M.H. Murad, H.A. Jahdali, M.S. Ferwana, The role of oral magnesium supplements for the management of stable bronchial asthma: a systematic review and meta-analysis, NPJ Primary Care Res. Med. 29 (1) (2019) 4, https://doi.org/10.1038/s41533-019-0116-z.

[185] C.F. Tang, H. Ding, R.Q. Jiao, X.X. Wu, L.D. Kong, Possibility of magnesium supplementation for supportive treatment in patients with COVID-19, Eur. J. Pharmacol. 886 (2020) 173546, https://doi.org/10.1016/j.ejphar.2020.173546.

[186] T.C. Wallace, Combating COVID-19 and building immune resilience: a potential role for magnesium nutrition? J. Am. Coll. Nutr. 39 (8) (2020) 685–693, https://doi.org/10.1080/07315724.2020.1785971.

[187] S. Iotti, F. Wolf, A. Mazur, J.A. Maier, The COVID-19 pandemic: is there a role for magnesium? Hypotheses and perspectives, Magnes. Res. 33 (2) (2020) 21–27, https://doi.org/10.1684/mrh.2020.0465.

[188] S. Gutiérrez, S.L. Svahn, M.E. Johansson, Effects of omega-3 fatty acids on immune cells, Int. J. Mol. Sci. 20 (20) (2019) 5028, https://doi.org/10.3390/ijms20205028.

[189] M. Morita, K. Kuba, A. Ichikawa, M. Nakayama, J. Katahira, R. Iwamoto, T. Watanebe, S. Sakabe, T. Daidoji, S. Nakamura, A. Kadowaki, T. Ohto, H. Nakanishi, R. Taguchi, T. Nakaya, M. Murakami, Y. Yoneda, H. Arai, Y. Kawaoka, J.M. Penninger, Y. Imai, The lipid mediator protectin D1 inhibits influenza virus replication and improves severe influenza, Cell 153 (1) (2013) 112–125, https://doi.org/10.1016/j.cell.2013.02.027.

[190] Y. Imai, Role of omega-3 PUFA-derived mediators, the protectins, in influenza virus infection, Biochim. Biophys. Acta 1851 (4) (2015) 496–502, https://doi.org/10.1016/j.bbalip.2015.01.006.

[191] R. Barazzoni, S.C. Bischoff, J. Breda, K. Wickramasinghe, Z. Krznaric, D. Nitzan, M. Pirlich, P. Singer, endorsed by the ESPEN Council, ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection, Clin. Nutr. 39 (6) (2020) 1631–1638, https://doi.org/10.1016/j.clnu.2020.03.022.

[192] R.D. Stapleton, J.M. Martin, K. Mayer, Fish oil in critical illness: mechanisms and clinical applications, Crit. Care Clin. 26 (3) (2010) 501–ix, https://doi.org/10.1016/j.ccc.2010.04.009.

[193] P. Singer, M. Theilla, H. Fisher, L. Gibstein, E. Grozovski, J. Cohen, Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury, Crit. Care Med. 34 (4) (2006) 1033–1038, https://doi.org/10.1097/01.CCM.0000206111.23629.0A.

[194] K. Shirai, S. Yoshida, N. Matsumaru, I. Toyoda, S. Ogura, Effect of enteral diet enriched with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with sepsis-induced acute respiratory distress syndrome, J. Intensive Care 3 (1) (2015) 24, https://doi.org/10.1186/s40560-015-0087-2.

[195] R.S. Torrinhas, P.C. Calder, G.O. Lemos, D.L. Waitzberg, Parenteral fish oil: an adjuvant pharmacotherapy for coronavirus disease 2019? Nutrition 81 (2021) 110900 https://doi.org/10.1016/j.nut.2020.110900.

[196] G. Messina, R. Polito, V. Monda, L. Cipolloni, N. Di Nunno, G. Di Mizio, P. Murabito, M. Carotenuto, A. Messina, D. Pisanelli, A. Valenzano, G. Cibelli, A. Scarinci, M. Monda, F. Sessa, Functional role of dietary intervention to improve the outcome of COVID-19: a hypothesis of work, Int. J. Mol. Sci. 21 (9) (2020) 3104, https://doi.org/10.3390/ijms21093104.

[197] H.Y. Yue, J. Zeng, Y. Wang, M.J. Deng, W. Peng, X. Tan, H. Jiang, Efficacy of omega-3 fatty acids for hospitalized COVID-19 patients: a systematic review and meta-analysis of randomized controlled trials, Asia Pac. J. Clin. Nutr. 32 (3) (2023) 308–320, https://doi.org/10.6133/apjcn.202309_32(3).0002.

[198] S. King, J. Glanville, M.E. Sanders, A. Fitzgerald, D. Varley, Effectiveness of probiotics on the duration of illness in healthy children and adults who develop common acute respiratory infectious conditions: a systematic review and meta-analysis, Br. J. Nutr. 112 (1) (2014) 41–54, https://doi.org/10.1017/S0007114514000075.

[199] K. Gohil, R. Samson, S. Dastager, M. Dharne, Probiotics in the prophylaxis of COVID-19: something is better than nothing, Biotec 11 (1) (2021) 1, https://doi.org/10.1007/s13205-020-02554-1.

[200] A.N. Olaimat, I. Aolymat, M. Al-Holy, M. Ayyash, M. Abu Ghoush, A.A. Al-Nabulsi, T. Osaili, V. Apostolopoulos, S.Q. Liu, N.P. Shah, The potential application of probiotics and prebiotics for the prevention and treatment of COVID-19, NPJ Sci. Food 4 (2020) 17, https://doi.org/10.1038/s41538-020-00078-9.

[201] P. Gutiérrez-Castrellón, T. Gandara-Martí, A.T. Abreu Y Abreu, C.D. Nieto-Rufino, E. López-Orduña, I. Jiménez-Escobar, C. Jiménez-Gutiérrez, G. López-Velazquez, J. Espadaler-Mazo, Probiotic improves symptomatic and viral clearance in Covid 19 outpatients: a randomized, quadruple-blinded, placebo-controlled trial, Gut Microb. 14 (1) (2022) 2018899, https://doi.org/10.1080/19490976.2021.2018899.

[202] A. Akour, Probiotics and COVID-19: is there any link? Lett. Appl. Microbiol. 71 (3) (2020) 229–234, https://doi.org/10.1111/lam.13334.