Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19?

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ABSTRACT

The world is currently in the grips of the coronavirus disease (COVID-19) pandemic, caused by the SARS-CoV-2 virus, which has mutated to allow human-to-human spread. Infection can cause fever, dry cough, fatigue, severe pneumonia, respiratory distress syndrome and in some instances death. COVID-19 affects the immune system by producing a systemic inflammatory response, or cytokine release syndrome. Patients with COVID-19 have shown a high level of pro-inflammatory cytokines and chemokines. There are currently no effective anti-SARS-CoV-2 viral drugs or vaccines. COVID-19 disproportionately affects the elderly, both directly, and through a number of significant age-related comorbidities. Undoubtedly, nutrition is a key determinant of maintaining good health. Key dietary components such as vitamins C, D, E, zinc, selenium and the omega 3 fatty acids have well-established immunomodulatory effects, with benefits in infectious disease. Some of these nutrients have also been shown to have a potential role in the management of COVID-19. In this paper, evidence surrounding the role of these dietary components in immunity as well as their specific effect in COVID-19 patients are discussed. In addition, how supplementation of these nutrients may be used as therapeutic modalities potentially to decrease the morbidity and mortality rates of patients with COVID-19 is discussed.

1. Introduction

Coronavirus disease (COVID-19) is a global public health concern caused by the novel coronavirus SARS-CoV-2 and represents a significant threat to healthcare worldwide. It was first identified in a cluster of patients with pneumonia symptoms in Wuhan city, China, in late 2019. Initially, it was referred to as 2019 nCoV but was later renamed as COVID-19 by the World Health Organization. It is considered to be similar to the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) viruses. The virus can be transferred from human to human through respiratory droplets, contact and fomites. SARS-CoV-2 has two principal strains: 'L type' (70 %) and 'S' (30 %), with the L type being the more aggressive and contagious [1,2]. Symptoms of COVID-19 vary from asymptomatic, to severe, and include fever, dry cough, pneumonia, malaise, acute respiratory distress syndrome [3]. Approximately 80 % of confirmed cases have mild or moderate symptoms, 13.8 % having severe effects and 6.1 % showing critical symptoms, with older adults (≥ 60 years) at higher risk of developing severe disease [4]. According to worldometer as of 29 July 2020, SARS-CoV-2 virus has affected over 20 million people worldwide, with more than 732,000 deaths. By the time this paper is published these values will be doubled. These figures are also likely to be significant underestimations, due to lack of testing, reporting, and other factors.

Currently, there are no approved treatments for COVID-19 but prevention strategies such as social distancing, public hygiene and wearing facial masks are the best current approaches to reduce COVID-19. Recent evidence has highlighted that nutritional supplementation could play a supportive role in COVID-19 patients. Administration of higher than recommended daily doses of nutrients such as vitamins D, C, E, Zinc and omega-3 fatty acids might have a beneficial effect, potentially reducing SARS-CoV-2 viral load and length of hospitalization [5–8]. These nutrients are well-known for their antioxidant properties

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and immunomodulatory effects. Deficiencies in these nutrients can result in immune dysfunction, and increase susceptibility to pathological infection. In fact, dietary insufficiency of vitamins and minerals has been observed in high-risk groups of COVID-19 patients, such as the elderly, increasing the morbidity and risk of mortality [9]. It is well known that the elderly are more likely to be nutrient deficient and to have compromised immunity via immuno-senescence, significantly increasing their risk of poor outcomes from COVID-19, and making adequate nutrition doubly important. The role of vitamins D, C, E, Zinc, selenium and omega-3 fatty acids in immunity, their status in patient infected by SARS-CoV-2 and their potential therapeutic role are discussed.

2. Methodology

The searches carried out in this review were performed as described in Fig. 1 on July 27, 2020. To identify COVID-19, specific literature, title/abstract searches were conducted in the 'PubMed,' 'Google Scholar' and 'Science Direct' databases. Search terms included 'COVID-19', 'SARS-CoV-2', 'coronavirus', 'nutrient', 'vitamin', and 'mineral', with filters identifying only studies published since 2020. 211 non-duplicate records were identified and underwent title and abstract screening. A total of 35 relevant studies specifically on COVID-19 and nutrition or diet components were identified. Studies were excluded based on relevance to the topic, with letters to the editor and commentaries also removed. Four published pre-prints are also discussed where relevant and are specifically identified in the manuscript. Included papers with relevant data are summarized in Table 1.

3. COVID-19 dysregulation of the immune system

On entry, SARS-CoV-2 virus binds to human alveolar epithelial cells, activating the innate and adaptive immune systems, resulting in the onset of cytokine release syndrome. This systemic cytokine barrage dysregulates host immune responses, leading to the development of acute respiratory distress syndrome (ARDS) [10]. This is particularly relevant in the vulnerable elderly, who are at greater risk of cytokine storm, and more likely to be significantly impacted by it. COVID-19 patients have a high level of interleukin (IL)-6, which is a critical inflammatory mediator involved in respiratory failure, shock and multi-organ dysfunction, and the similar SARS and MERS viruses are known to cause hyper-activation of cytotoxic T cells. Likewise, patients with severe COVID-19 symptoms and pneumonia, admitted to intensive care units, have been shown to have high levels of circulating pro-inflammatory cytokines such as IL-2, IL-7, G-CSF, and TNFα [11,12]. This elevation of cytokines leads to hyper-inflammation and a severe hyper-cytokinemic state of inflammation. COVID-19 infection results in elevated levels of IL-6 and is associated with higher mortality. COVID-19 patients with severe symptoms have also been shown to have dysfunctional immune signaling, particularly in the human major histocompatibility complex II, particularly the HLA-DR allele, with a significant reduction in T- and B-lymphocytes and natural killer (NK) cells [13].

4. Immunomodulatory role of vitamin D

Vitamin D is a fat-soluble steroid hormone precursor that arises from ultraviolet B (UVB) radiation exposure of 7-dehydrocholesterol (7-DHC) in the epidermis of the skin, where it is transformed into the circulating precursor cholecalciferol. In the liver, cholecalciferol is hydroxylated to form 25-hydroxyvitamin D, which is transformed into the active hormone 1,25-hydroxyvitamin D ($1,25(OH)_2D$) in the kidneys. Vitamin D has roles in a wide range of body systems, including in both innate and adaptive immune responses as shown in Fig. 2. Vitamin D enhances innate cellular immunity through stimulation of expression of antimicrobial peptides, such as cathelicidin and defensins. Defensins maintain tight and gap junctions, adherens and enhance the expression of anti-oxidative genes. Viruses such as influenza are known to significantly damage the integrity of epithelial tight junctions increasing the risk of infection and pulmonary oedema. Vitamin D is known to maintain the integrity of these junctions [14]; with low levels of vitamin D receptor expression leading to increased expression of claudin-2 and inflammation. Vitamin D also promotes the differentiation of monocytes to macrophages whilst increasing superoxide production, phagocytosis and bacterial destruction. In addition, vitamin D is able to modulate the adaptive immune response, by suppressing T helper type-1 (Th1) cell function and decreasing the production of pro-inflammatory cytokines

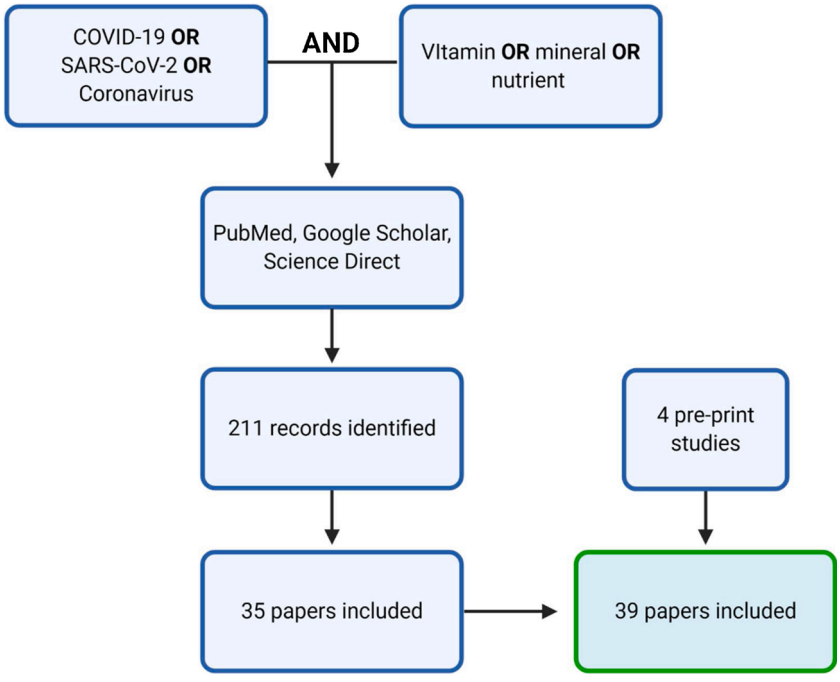

Fig. 1. Summary of search strategy and paper exclusion.

Table 1
Summary of included studies on COVID-19.

Reference	Design/study type	Risk of Bias	Finding
Epidemiological background			
Guo et al. [1]	Report/review	n/a	Epidemiological data on SARS-CoV-2
Tang et al. [2]	Genetic study	Low	Describes the evolution of the two principle strains of SARS-CoV-2
Wang et al. [3]	Review	n/a	Describes the clinical characteristics of COVID-19 globally
Grant et al. [9]	Review	n/a	Provides justification for the hypothesis of poorer outcomes in vitamin D deficient COVID-19 patients
Li et al. [10]	Review	n/a	Describes coronavirus mediated immune dysfunction and relates back to outcomes seen in COVID-19
Huang et al. [11]	Observational – prospective cohort	Low	Describes the first cohort of COVID-19 patients and their symptomatology in Wuhan, China
Rothan et al. [12]	Review	n/a	Describes epidemiology and clinical findings of COVID-19
Giamarellos-Bourboulis et al. [13]	Cohort Study	Low	Compares outcomes and immune response in SARS-CoV-2 infection and bacterial pneumonia
Vitamin D			
D'Avolio et al. [16]	Cohort Study	Moderate – recruitment unclear, no identification or adjustment of confounders. Baseline not described	Correlation between SARS-CoV-2 infection and vitamin D levels.
Merzon et al [17]	Pre-print population study	Moderate – results not peer reviewed, but large cohort, clear design and adequate confounder adjustment	Correlation between vitamin D levels and SARS-CoV-2 infection
Meltzer et al. [18]	Preprint observational study	High – results no peer-reviewed, indirect estimations of vitamin D.	Correlation between vitamin D deficiency and rates of SARS-CoV-2 infection.
Hastie et al. [19]	Cross-sectional biobank study	Low – Very large sample, strong statistical approach	Univariable correlation between Vitamin D and COVID-19, but relationship lost when adjusted for significant confounders
Raisi-Estabragh et al. [20]	Cross-sectional biobank study	Low – strong design, well reported	Racial disparities in COVID-19 infection rates not explained by vitamin D levels
Braiman et al. [21]	Review/report	n/a	Describes epidemiological data on mortality and latitude in light of vitamin D deficiency
Kara et al. [22]	Epidemiological	Moderate – Correlational data based on risk factors	Describes vitamin D deficiency against regional rates COVID-19 mortality
Daneshkhah et al. [23]	Pre-print Epidemiological modelling	Moderate – indirect assessment of vitamin D deficiency, Inability to adjust for all confounding variables, results yet to be peer-reviewed	Modelled relationship between Vitamin D and CRP, relevant to COVID-19 cytokine storm
Lau et al. [24]	Pre-print cross sectional study	Moderate – small sample, observational data, results yet to pass peer-review	Correlation between vitamin D insufficiency and COVID-19 outcomes
Panagiotou et al. [25]	Retrospective cohort study	Moderate – Small sample of local clinical care pathway, little adjustment for confounding factors	Correlation between severe COVID-19 outcomes and vitamin D deficiency
Razdan et al. [27]	Review	n/a	Discusses vitamin D and the cytokine storm, in light of COVID-19
Vitamin C			
Hiedra et al. [33]	Single centre observational study	Moderate – Small sample, no evaluation of confounding factors	Improved outcomes with Vitamin C administration in COVID-19 patients
Waqas Khan et al, [34]	Case Study	High – Singe case, adjunct treatment, subjective assessment of improvement rate	Patient receiving vitamin C improved faster than deemed normal
Cheng [35]	Perspective	High – unverified data, opinion based on little data	50 COVID-19 patients had clinical improvements after vitamin C administration
Zinc			
Rahman et al. [40]	Review	n/a	Describes biological hypothesis for zinc as a complementary adjunct to anti-viral therapies
Finzi [41]	Case series	High – case series, small sample, subjective assessment of improvement	Four patients had clinical improvement after treatment with zinc
Barazzoni et al. [43]	Clinical guideline	Moderate – based on expert opinion in the absence of data	Recommends omega-3 supplementation in COVID-19
Rogereo et al. [44]	Review	n/a	Discusses both potential benefits, but also risks of omega-3 supplementation in COVID-19
Selenium			
Zhang et al. [45]	Epidemiological study	Moderate – association study based on regional characteristics	Relationship between selenium status and COVID-19 recovery rate
Magnesium			
Wallace [50]	Review	n/a	Provides background theory on a role for

(*continued on next page*)

Table 1 (*continued*)

Reference	Design/study type	Risk of Bias	Finding
			magnesium in COVID-19
Iotti et al. [51]	Perspective	n/a	Suggests a role for magnesium in COVID-19
Vitamin A			
De Andrade et al. [52]	Review	n/a	Suggests a role for vitamin A deficiency in COVID-19

IL-2 and interferon-gamma (INF-γ). Vitamin D also promotes anti-inflammatory cytokines by Th2 cells and indirectly suppressing Th1 cells diverting pro-inflammatory cells to an anti-inflammatory phenotype as well as stimulating suppressive regulatory T cells [15].

Deficiency in vitamin D has been suggested to increase incidence and severity of COVID-19 infection. COVID-19 patients have been repeatedly shown to have lower levels of vitamin D, with mean plasma concentrations half that of controls [16], though the selection of the study cohort was unclear, and unadjusted relative to important confounders, leaving their conclusions unclear. Therefore, supplementation of vitamin D is suggested to boost immunity against COVID-19 and reduce human mortality; however this hypothesis needs to be tested in human trials. It has also been suggested that adequate vitamin D levels may help to protect the respiratory epithelium from pathogenic invasion, decreasing risk of infection. A pre-print population study in Israel also found that vitamin D correlated with disease incidence, even after adjustment for sociodemographic and comorbidity variables [17]. This finding is also supported in an additional pre-print study, currently under review [18], however these results must be corroborated. However, large biobank studies concluded that vitamin D deficiency was not related to incidence of COVID-19, nor did it explain differences in demographic variation of infection rates [19,20]. It appears that associations with vitamin D and COVID-19 rely heavily on univariate analysis and do not remain consistent after adjustment for important confounding variables, such as comorbidity and sociodemographic factors. While it is unclear whether vitamin D status affects infection rates, there is evidence to suggest a role in mitigating disease severity. The mortality rates related to COVID-19 vary from country to country, and in the southern hemisphere the mortality rates are lower than in the northern hemisphere [21]. One hypothesis explaining this pattern is that people in the northern hemisphere classically have more prevalent vitamin D deficiency, due to lack of sun exposure in winter as compared to summer period in the southern hemisphere during peak pandemic months (January-May) [21]. It has also been shown that countries with higher prevalence of vitamin D deficiency tend to have a higher burden of COVID-19 morbidity and mortality [22]. Spain and Italy have high prevalence of vitamin D deficiency, which is linked with other important health factors including, hypertension, diabetes, obesity and ethnicity, which appear to be associated with an increased risk of severe COVID-19 infection. Evidence has shown directly that mortality rate is higher in COVID-19 patients with vitamin D deficiency and the mortality rate is lower in Nordic countries (Norway, Sweden, Iceland, Finland, Greenland and Denmark) [21] possibly because of the rarity of vitamin D deficiency due to widespread supplement use. In addition, C-reactive protein (CRP), a marker of inflammation and surrogate marker for cytokine storm, was highly expressed in patients with severe COVID-19 symptoms and correlated with vitamin D deficiency [23]. Likewise, a pre-print retrospective study of twenty COVID-19 patients, showed a link between vitamin D insufficiency and severe COVID-19. The participants with vitamin D inefficiency were more likely to have coagulopathy and suppressed immune function [24]. in another study patients with deficiency were more likely to require intensive care admission in 134 inpatients [25] While mechanistic understanding of the role of

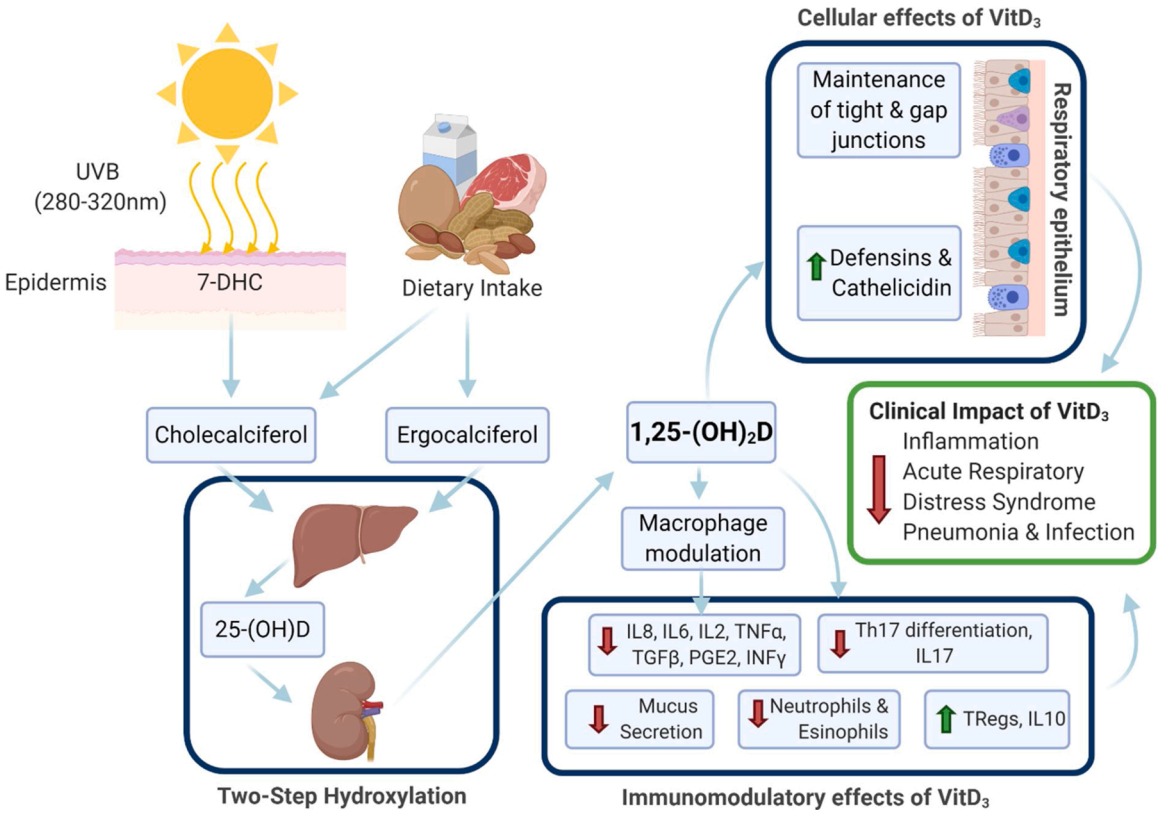

Fig. 2. Immunomodulatory actions of vitamin D.IL: interleukin; TNF: Tumor necrosis factor; IFN: Interferon; Th: T-Helper; 7-DHC: 7-Dehydrocholesterol; PGE2: Prostaglandin E2.

vitamin D in COVID-19 is lacking, genetic studies of the SARS-CoV-2 virus have identified a number of protein targets likely regulated by it, however no definitive evidence has been found. However, with the evidence currently available, many agencies are beginning to review whether supplementation should be broadly recommended.

4.1. Vitamin D deficiency and COVID-19 associated risk factors

Vitamin D is strongly linked to a range of COVID-19 risk factors. Vitamin D insufficiency is linked with advanced age, obesity, male sex, hypertension, concentration in northern climates, and coagulopathy, all of which are associated with poorer outcomes. With increased age, concentrations of active vitamin D decrease due to less sunlight exposure and reduced production of 7-DHC in the skin. This may also partly explain why the mortality rate of COVID-19 is higher in older adults. There is also a well-documented shift in the immune system towards a pro-inflammatory state in older adults (known as 'inflamm-aging') which leads to chronic low-grade inflammation, a steady accumulation of biological injury, and eventually progression of chronic disease [26]. It has been shown that vitamin D is associated with increased anti-inflammatory and decreased pro-inflammatory cytokines in older adults. The positive influence of vitamin D on the immune system is helpful during cytokine storm, relevant to COVID-19 patients with ARDS [27]. In a systematic review and meta-analysis of eight observational studies involving 20,966 subjects it was noted that those with low levels of vitamin D had an increased risk of pneumonia [28].

4.2. Protective role of vitamin D in viral infection

Vitamin D supplements are known to aid in reducing the incidence and severity of viral infection and there is an inverse relationship between upper respiratory tract infection and serum 25-hydroxyvitamin D levels. While the effect of vitamin D against SARS-CoV-2 infection has not yet been shown, supplementation could potentially reduce pro-inflammatory cytokines and subsequently limit acute respiratory distress syndrome associated mortality in COVID-19 patients. A number of human clinical trials have been registered to determine the effect of vitamin D supplementation in COVID-19 patients (Table 2).

5. Immunomodulatory role of vitamin C

Vitamin C, or ascorbic acid, is a water-soluble nutrient that cannot be synthesized by humans. Vitamin C acts as an anti-oxidant that can scavenge reactive oxygen species (ROS), thereby, protecting biomolecules such as proteins, lipids and nucleotides from oxidative damage and dysfunction. Vitamin C accumulates in leukocytes, in concentrations of 50−100-fold higher than in the plasma. During infection, vitamin C that is present in leukocytes is rapidly utilized. Disturbance of the balance between antioxidant defenses and oxidant generation can alter multiple signaling pathways involving pro-inflammatory transcription factors, such as nuclear factor κB (NF-κB). Increasing levels of oxidants lead to activation of NF-κB, triggering a signaling cascade, with the end result of further production of oxidative species and inflammatory mediators. NF-κB is involved in inflammatory responses, the pathogenesis of certain diseases and viral infection. Inhibition of NF-κB can be a therapeutic mode against viral infections [29].

Vitamin C is well known to confer a protective benefit in infectious disease. Indeed, supplementation is known to support respiratory defense mechanisms, preventing viral infections, and reducing their

Table 2
Registered trials of vitamin D in patients with COVID-19.

Trial Number	Study design	Intervention	Participants	Primary outcomes	Country
NCT04334005	Randomized, Parallel, Double blinded	One dose of 25,000 IU of vitamin D	200 non-severely symptomatic patients	Number of deaths of any cause	Spain
NCT04344041	Randomized,, Parallel, Open Label	One oral dose of 400,000 or 500,000 IU vitamin D.	260 subjects ≥ 70 years old with COVID-19	Number of deaths of any cause within 14 days	France
NCT04335084	Randomized, Double-Blind, Placebo-Controlled Phase 2a	Vit D, C, Zinc and drug hydroxychloroquine	600 subjects ≥18 years at high risk	Prevention of COVID-19 symptoms	USA
NCT04385940	Phase 3 RCT	50,000 IU Vitamin D	64 patients with COVID19	Biochemical and clinical outcomes	USA
NCT04449718	Interventional trial	200,000IU vitamin D	200 COVID-19 Patients	Length of hospitalization	Brazil
NCT04483635	Phase 3 placebo controlled RCT	100,000IU followed by 16 weeks of a 1000IU supplementation	2414 Healthy patients working in high-risk locations for SARS-CoV-2 infection	Incidence of new COVID-19 infection	Canada
NCT04482673	Interventional Phase 4	6000IU daily, with or without a 20000IU bolus dose	140 participants with or without COVID-19	SARS-CoV-2 Ab titres, serum vitamin D	USA
NCT04407286	Phase 1 interventional RCT	10000−15,000IU Vit D/day for 2−5 weeks until >50 nm/mL	100 COVID-19 patients	Symptom severity	USA
NCT04411446	Phase 4 interventional RCT	500,000 IU dose vitamin D	1265 patients with COVID-19	Symptom severity	Argentina
NCT04459247	Interventional RCT	60,000 IU dose of vitamin D	30 participants with COVID-19	Inflammation and COVID-19 status	India
NCT04363840	Phase 2 RCT	Weekly 50,000IU vitamin D for 2 weeks plus 81 mg of aspirin	1080 Patients with COVID-19 diagnosis	Hospitalization rate	USA
NCT04351490	Interventional RCT	2000IU vit D daily for 2 months	3140 COVID-19 patients over 60	Survival rate	France
NCT04344041	Phase 3 interventional RCT	200,000 or 50,000IU vitamin D	260 COVID-19 patients over 70	All cause and COVID-19 mortality, symptom severity	France
NCT04334512	Phase 2 interventional study	Unspecified dose of vitamin D, alongside hydroxychloroquine, azithomyosin, vitamin C and zinc	600 COVID-19 patients	Recovery rate, symptom severity	USA
NCT04476680	Interventional RCT	1000IU vitamin D daily	4400 healthy volunteers	Rate of COVID-19 infection	UK
NCT04386850	Phase 2/3 interventional RCT	25mcg Vitamin D daily	1500 participants – COVID-19 positive, alongside negative testing healthcare workers and family members of COVID-19 patients	Rate of infection Severity of disease Hospitalization Duration of disease Mortality Ventilation	Iran

duration and severity as well as having anti-histamine properties that can improve flu-like symptoms. Interestingly, patients with acute respiratory infections such as, pneumonia or tuberculosis have decreased plasma vitamin C concentrations and, vitamin C administration reduces the severity and duration of pneumonia in elderly patients [30]. This key protective action against respiratory infection makes it a target of interest in COVID-19 (Fig.3).

5.1. Vitamin C and immune responses in COVID-19

Cytokine storm during COVID-19 infection escalates as disease progresses, and vitamin C has been suggested as a counter to this. For instance, the pro-inflammatory cytokines, IL-1β and TNF-α increase rapidly after infection, and the acute response triggered by this stimulates further secretion of IL-6 and IL-8 promoting an ongoing pro-inflammatory state. TNF-α is currently under investigation in facilitating entry of SARS-CoV-2 into host cells [31]. Vitamin C is known to reduce the levels of pro-inflammatory cytokines including TNF-α and increase anti-inflammatory cytokines (IL-10). Clinical studies have demonstrated that intake of 1 g/day of vitamin C increases IL-10 secretion by peripheral blood mononuclear cells. IL-10 works as a negative feedback mechanism with IL-6 and controls inflammation, critical in COVID-19. Older people are more susceptible to infection because of low immune cell function and immuno-senescence [32]. Data shows that COVID-19 patients are at a higher risk of pneumonia. in another small trial improvements in inflammatory biomarkers and some respiratory parameters were noted following intravenous administration of vitamin C [33]. A case study of a patient treated with high-dose vitamin C after development of ARDS was able to be removed from ventilation after 5 days which was deemed unusually early, however it should be noted that she also received anti-viral medications [34]. Vitamin C has also been shown to have a role in sepsis secondary to pneumonia, also seen in COVID-19. There is unpublished data suggesting beneficial effects of high dose vitamin C supplementation in 50 Chinese patients with severe symptoms, though this requires substantiation [35]. Therefore, vitamin C supplementation is a sensible option in micronutrient deficient individuals that are at risk of COVID-19 infection to assist with the prevention and support of immune responses. To this end, several clinical trials are evaluating Vitamin C supplementation in COVID-19 patients (Table 3).

6. Immunomodulatory role of zinc

Zinc is a key trace mineral, involved in many biological processes including immunity and it is vital in both the innate and acquired responses to viral infection. Zinc deficiency significantly increases pro-inflammatory cytokines and remodeling of lung tissue is noted, an effect which was partially countered by zinc supplements [36]. Furthermore, zinc deficiency results in an alteration of cell barrier function in lung epithelial tissues, via up-regulation of IFN-γ, TNF-α and Fas receptor signaling as well as apoptosis *in vitro*. Zinc is purported to be a vital mineral during COVID-19 infection because of its dual immunomodulatory and anti-viral properties [37,38].

6.1. Immunomodulatory and anti-viral properties of zinc

Zinc plays a significant role in the recruitment of neutrophil granulocytes and chemotactic activity and has positive effects on NK cells, phagocytosis, generation of oxidative burst, and CD4+ and CD8 + T cells. Zinc deficiency reduces lymphocyte counts and impairs their function; in fact, zinc supplementation increases the number of T cells and NK cells and increases IL-2 and soluble IL-2 receptor expression. Zinc has been shown to inhibit the synthesis, replication and transcription complex of coronaviruses [39]. It can also interfere directly with viral replication and protein synthesis, providing beneficial and therapeutic effects against viral infections [37].

6.2. Zinc and COVID-19

Due to the immunomodulatory and anti-viral properties of zinc, it has the potential to be a supportive treatment in COVID-19 patients (Fig. 3). It has been suggested that zinc supplementation may increase the efficacy of other treatments currently under investigation such as hydroxychloroquine [40]. A case series of four COVID-19 patients treated with high-dose zinc also showed both clinical symptomatic improvements [41]. Studies have shown that zinc supplementation is able to decrease COVID-19 related symptoms such as lower respiratory tract infection. These effects have been suggested to be due to inhibition of viral uncoating, binding and replication, and may be relevant to COVID-19. A clinical trial registered in Australia will determine the use of intravenous zinc administration COVID-19 positive individuals [42].

7. Immunomodulatory role of omega-3 fatty acids

Omega-3 fatty acids are polyunsaturated fatty acids and include eicosapentaenoic and docosahexaenoic fatty acids, and are well known to have favorable effects on immunity and inflammation. Of interest, omega-3 fatty acids exert anti-viral effects by inhibiting influenza virus replication. According to the European Society for Parenteral and Enteral Nutrition expert statement, the use of omega-3 fatty acids may improve oxygenation in COVID-19 patients, although firm evidence is still missing [43]. Others however have suggested caution in the use of the omega-3 s in COVID-19 patients, citing evidence showing a counter-intuitive increase in oxidative stress and inflammation due to increased susceptibility of cellular membranes to damage [44]. Until there is validated trial data, supplementation, particularly in high doses, must be performed with care in this population.

Table 3
Registered clinical trials of vitamin C in patients with COVID-19.

Trial Number	Study design	Intervention	Eligibility criteria	Primary outcomes	Country
NCT04264533	Randomized, triple blinded, parallel design. Phase 2	24 g/day vitamin C for 7 days	COVID 19 in ICU patients, ≥ 18 years old. Diagnosed as serious or critical SARI	Ventilation free days	China
NCT04323514	Uncontrolled longitudinal, open-label, single-group study	10 g intravenous vitamin C in addition to conventional therapy	500 participants of all ages with the indication of incubation, positive COVID 19 and interstitial pneumonia	In-hospital mortality	Italy
NCT03680274	Randomized, quadruple blinded, phase 3, parallel study	200 mg/kg/day and 16 doses of vitamin C intravenously	800 patients ≥ 18 years old; with COVID-19 in ICU. Treated with a continuous intravenous infusion of vasopressors	Decreased death rate and dependency on mechanical ventilation	Canada
NCT04395768	Phase 2 interventional study	50 mg/kg vitamin C every 6 h day 1, 100 mg/kg/6 h for next 7 days	200 patients with a COVID-19 diagnosis	Symptom severity, length of hospital stay, ventilation requirement	Australia

COVID-19, coronavirus disease-19; ICU, intensive care unit; SARI, Severe Acute Respiratory Infection.

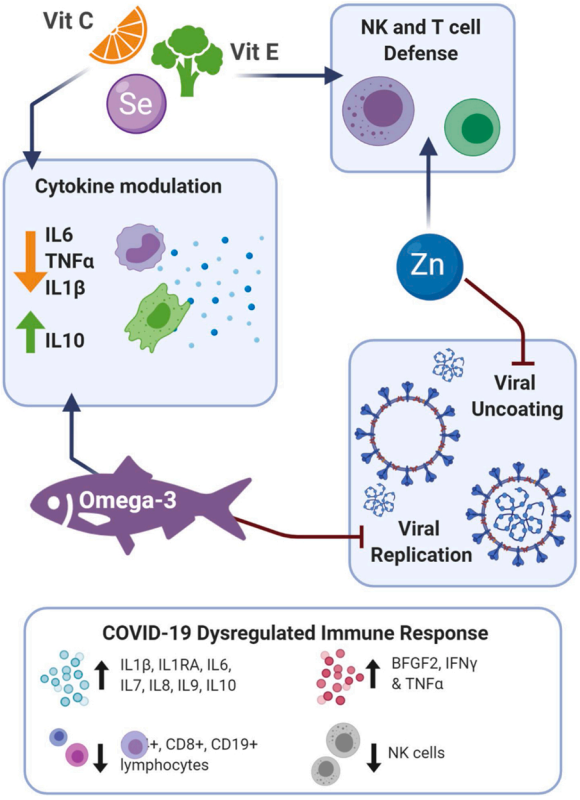

Fig. 3. COVID19 protective actions of vitamin C, E zinc, selenium and omega-3 fatty acids. IL: interleukin; NK: Natural Killer; BFGF2: Basic Fibroblast Growth Factor 2; TNF: Tumor necrosis factor; IFN: Interferon.

8. Immunomodulatory role of other nutrients

The anti-oxidant Vitamin E, and trace element selenium, are major components of anti-oxidant defense. Epidemiological studies demonstrate that deficiencies in either of these nutrients alters immune responses and viral pathogenicity. It has been noted, that there is a correlation between geographic selenium levels and COVID-19 cure rates in different Chinese provinces [45]. Vitamin E and selenium both act through anti-oxidant pathways to increase the number of T cells, enhance mitogenic lymphocyte responses, increase IL-2 cytokine secretion, enhances NK cell activity, and, decreases the risk of infection (Fig. 3). Selenium and vitamin E supplementation has also been shown to increase resistance to respiratory infections [46,47]. It is worthy to note that mixed tocopherols are more effective than α-tocopherol alone, due to the range of receptors for these nutrients [48].Despite these beneficial roles in immunity, there is limited information on the effects of vitamin E or selenium supplementation in humans with COVID-19 infection, though patients are encouraged to have adequate intakes of these antioxidant nutrients.

Other nutrients have been proposed to have a potential role in the management of COVID-19, including magnesium and vitamin A. While the mechanisms are still unclear, magnesium deficiency has been shown to have a range of effects on the immune system. Magnesium deficiency is associated with decreased immune cell activity and increased inflammation, including of IL-6, central to the pathology of the cytokine storm associated with COVID-19 [5]. Magnesium is also known to have a relationship to vitamin D physiology, as it has been shown to regulate the levels of the hormone in vivo [49]. This may suggest magnesium as playing some role in the beneficial relationship between vitamin D and COVID-19 outcomes. These relationships have led a number of authors and commentators to suggest that magnesium might be used to combat the symptoms of COVID-19, however concrete data of efficacy in prevention, or treatment is currently lacking [50,51]. Similarly, vitamin A is known to have beneficial roles in respiratory infections, again leading to speculation about a potential protective role in COVID-19 [52]. While these nutrients are likely to have value in general health both in and out of the SARS-CoV-2 setting, there is no experimental data to support a specific role in the disease.

9. The role of nutritional supplementation in COVID-19

Adequate levels of vitamins C, D and E are crucial during COVID-19 to reduce symptom burden and lessen the duration of respiratory infection. Research also supports a role for minerals such as zinc as they have antiviral effects and may improve immune responses and suppress viral replication. Therefore, the consumption of adequate amounts of vitamins and minerals through diet is essential to ensure the proper functioning of the immune system. Fruits, vegetables, meat, fish, poultry and dairy products are good source of these vitamins and minerals (Table 4). To support immune function during COVID-19 disease higher dietary intakes of vitamins D, C and E, zinc and omega-3 fatty acids could be beneficial [5]. It is worth noting however, that much of the evidence surrounding the use of these nutrients in COVID-19 patients, utilize doses too high to come solely from diet. Supplementation with higher doses of these nutrients during COVID-19 infection, have shown positive outcomes, and given their low risk profile are a sensible addition to patient care. However, further research needs to be undertaken to define the effective dosage of vitamins C, D, E, zinc and omega-3 fatty acids to protect individuals or alleviate symptoms against COVID-19.

10. Conclusion and future prospects

The effects of vitamins C, D, E, zinc, selenium and omega-3 fatty acids on the immune system and the possible benefits to those suffering from COVID-19 are presented. These are particularly pertinent in the vulnerable elderly population, who represent a disproportionate burden of morbidity and mortality in these times. All of the nutrients mentioned have a feasible role in the support of COVID-19 patients. Supplementation of higher dosage of vitamins D, C and zinc may have a positive effect during COVID-19 infection. However, clinical trials based on the associations of diet and COVID-19 are lacking. Some clinical studies have been registered and are currently being conducted to determine the effectiveness of certain nutrients in patients with COVID-19. Hopefully, the results of these trials will clarify the use of micronutrients during SARS-CoV-2 infection. It is also important to investigate other important immunomodulatory micronutrients such as vitamin B in COVID-19, to further explore the role of nutrition in disease outcomes [53,54]. On balance, given the negligible risk profile of supervised nutritional supplementation, weighed against the known and possible benefits, it appears pertinent to ensure adequate, if not elevated intake of these key vitamins and minerals in people both at risk of, and suffering from COVID-19.

Contributors

Hira Shakoor drafted the original manuscript and contributed to the editing and review of the article.

Jack Feehan drafted the original manuscript and contributed to the editing and review of the article.

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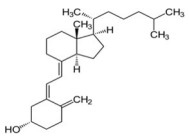
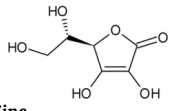
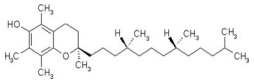
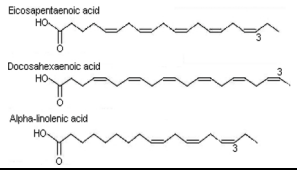
Lily Stojanovska drafted the original manuscript and contributed to

Table 4
Sources and daily requirement of vitamins D, C, E, zinc, omega-3 fatty acids.

Nutrients	Plant sources	Animal Sources	RDI/day	Effective dosage/ day
Vitamin D 	Wild mushroom, fortified orange juice, fungi	Milk, eggs, margarine, fortified cheese, yogurt, bread	5–15 μg	20–50 μg [55]
Vitamin C 	Citrus fruits (i.e. orange, grapefruit, lime, mandarin), strawberries, kiwi, pineapple, tomato, broccoli, cabbage, kale, spinach	Chicken, beef liver, oysters, milk	40–85mg	6000–8000 mg/ day [56]
Zinc Zn^{2+}	Beans, nuts, whole grains, fortified breakfast cereals	Poultry, red meat, crab, Oysters, lobster, dairy products	8–14 mg	30–50 mg [57]
Vitamin E 	Nuts (hazelnut, almonds, peanuts), seeds, vegetable oils, green leafy vegetables, mango, avocado, fortified cereals	Salmon, trout, crayfish, lobster	7–10mg	50–200 mg [58]
Selenium Se^{2-}	Nuts, whole grains, cereals, mushrooms	Dairy products Poultry, red meat, seafood	60–70 μg	Yet to be determined
Omega-3 fatty acids 	Flaxseed, chia seed, walnuts	Eggs, fish (salmon, sardine, mackerel), lobster	90–160mg	1000–3000 mg [59]

AI, adequate intake; Effective dosage, effective dose of supplements during infection and respiratory diseases; RDA, recommended dietary intake, based on Australia and New Zealand recommendations [60].

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Conflict of interest

The authors declare that they have no conflict of interest.

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