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An overview on role of nutrition on COVID-19 immunity: Accumulative review from available studies

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SUMMARY

The novel coronavirus infection (COVID-19) conveys a serious global threat to health and economy. A common predisposing factor for development to serious progressive disease is presence of a low-grade inflammation, e.g., as seen in diabetes, metabolic syndrome, and heart failure. Micronutrient deficiencies may also contribute to the development of this state. Therefore, the aim of the present study is to explore the role of the nutrition to relieve progression of COVID-19. According PRISMA protocol, we conducted an online databases search including Scopus, PubMed, Google Scholar and web of science for published literatures in the era of COVID-19 Outbreak regarding to the status of nutrition and COVID-19 until December 2021. There were available studies (80 studies) providing direct evidence regarding the associations between the status of nutrition and COVID-19 infection. Adequate
Introduction

COVID-19 is a novel infectious disease due to infection by SARS-CoV-2 (Severe Acute Respiratory Syndrome - coronavirus-2), a newly identified coronavirus, which spreads primarily between human hosts through respiratory droplets during close contacts. Besides, it could also develop after touching a contaminated surface with subsequent facial contact [1]. SARS-CoV-2 is a single positive-stranded RNA enveloped virus containing ~30kb with a nucleocapsid that undergoes membrane fusion or endocytosis for its entrance into the infected cells with subsequent development of enteric, respiratory, neurological and hepatic diseases in different species such as human being [2]. In severe cases, excessive activation of innate immune system, progressive inflammation and cytokine storm particularly in airways occurs leading to the development of cytokine release syndrome [3,4]. The contribution of clinical and subclinical micronutrient deficiencies to development of diminished immune function is suggested in patients with COVID-19 infection [5]. The role of nutritional management is suggested to be essential to diminish risk of severe infection [6]. Considering scant data on therapeutic and/or preventive efficiency of dietetics and nutrition in COVID-19 cases, in this narrative review we are going to discuss recently published data on the role of nutrition on immune system competency in COVID-19 patients.

Methods

Beast on PRISMA protocol [7], we did a literature search for the period COVID-19 Outbreak on Web of Science, PubMed, Scopus, Google scholar and Science Direct, and Medline with the keywords COVID 19, zinc, selenium, vitamins, mineral, deity, and nutrition until December, 2021 (Fig. 1). No restriction was considered for the time and language of publications. Papers evaluating nutrition status in cases with COVID-19 were eligible for inclusion. In this study, letters, comments, and short communications were excluded from the current study. Based on the information retrieved, we here discussed the role of the status of nutrition in the perspective of principles for implementing preventive measures against COVID-19.

The status of nutrition and COVID-19

Subclinical or clinical micronutrient deficiencies, such as vitamins and minerals deficiencies which often occurs in elder population, contribute to the development of age-related diseases including hypertension, diabetes, and coronary heart disease [8–10]. These highly interacting metabolic diseases [11] are characterized by the presence of systemic low-grade inflammation [12]. Pre-infectious signs of underlying inflammation, such as elevated plasma levels of C-reactive protein (CRP) in COVID-19
indicate to a common aggravating factor [13]. Nutrients adequacy is vital for proper immune competence and their deficiency could be associated with inflammatory aggravation (Table 1). Dietary advice may not be alone enough to guarantee adequacy in some populations, including in elder subjects [14] implying to seeking for supplementation in some populations.

**Vitamins**

**Vitamin A**

Vitamin A impacts on cellular immunity in different ways. Vitamin A has shown to exert a central function in the process of development and differentiation of dendritic cells (DCs) which are potent antigen-presenting cells activating T-cells. DCs express three isotypes of retinoic acid receptors and, therefore, directly respond to vitamin A status [15]. DCs drive differentiation of T-cells into either pro-inflammatory effector T-cells or anti-inflammatory regulating T-cells (Treg) following receptor activation to maintain homeostasis between pro-inflammatory and anti-inflammatory stimuli [16]. Vitamin A is involved in migration of effector T-cells to inflammatory sites during infective processes through induction of leukocyte-homing receptors such as α4β7 integrin and CCR9 [17]. It also initiates production of pro-inflammatory cytokines such as interferon-gamma in order to resolve viral infection [18]. Vitamin A drives humoral immune responses which crucially promotes maturation of B-cells with subsequent antibody responses during viral clearance [19,20]. Vitamin A promotes differentiation of anti-inflammatory Treg cells and their extravasation into the inflammation site so as to limit pro-inflammatory stimuli [21]. Taken together, both anti-inflammatory and pro-inflammatory cellular immune responses could be promoted using vitamin A [22].
| Vitamin type | Sample size | Outcome | Country | Reference |
|--------------|-------------|---------|---------|-----------|
| Vitamin A (research article) | 40 hospitalized patients and 47 age-matched convalescent as the control group | Reduced plasma levels of vitamin A correlated significantly with higher levels of inflammatory markers (ferritin, C-reactive protein (CRP)) and markers of acute SARS-CoV-2 infection (reduced LDH, lymphocyte count). Significantly lower Vitamin A levels were observed in hospitalized patients compared with convalescent persons. Among critically ill patients, vitamin A levels were observed in critically ill patients than moderately ill patients. Plasma level of vitamin A below 0.2 mg/L was shown to be significantly related with the development of mortality and acute respiratory distress syndrome (ARDS). | Germany | Tepasse et al. 2021 [22] |
| Vitamin A (bioinformatics study) | 393 SARS-CoV-2-associated genes and 122 VA-pharmacological action genes. | Mechanisms of action related with vitamin A functions against SARS-CoV-2 based on bioinformatics findings include inhibition of inflammatory reaction, enrichment of immunoreaction and biological processes associated with reactive oxygen species. Besides, seven core targets of vitamin A against COVID-19, including IL10, MAPK1, EGFR, MAPK14, ICAM1, PRKCB and CAT were identified. Based on this bioinformatics-based report, mechanisms of vitamin A and functions of anti-SARS-CoV-2 suggest vitamin A as a potent therapeutic option for COVID-19. | UAE | Li et al. 2020 [162] |
| Vitamin B (review) | | Vitamin B helps in building and maintenance of healthy immune system, prevention or reduction of COVID-19 symptoms and treatment of SARS-CoV-2 infection. Poornutritional status is a predisposing factor getting infections more easily. Thus, a balanced diet is essential for immuno-competence. Seeking for cost-effective and safe adjunct or therapeutic strategies to act as anti-thrombotic agents and suppress aberrant immune activation with its subsequent cytokine storm is essential. Adequate vitamin intake is fundamental for proper body function and also strengthening of immune system. Vitamin B particularly modulates immune response through downregulation of inflammation and pro-inflammatory cytokines, reduction of breathing difficulties and gastrointestinal discomforts, prevention of hypercoagulability, improvement of outcomes and reduction of hospital length of stay in COVID-19 patients. | UAE | Shakoor et al. 2021 [23] |
| Vitamin C (review) | 21 studies | Vitamin C has potent anti-inflammatory and anti-oxidant effects which diminishes chance of tissue damage related to oxidative stress and suppress significant inflammatory responses recognized as cytokine storm. By stimulating lymphocyte proliferation and increasing production of interferon, vitamin C is able to improve host antiviral immune responses. Vitamin C consumption in critically ill patients and those with severe COVID-19 and sepsis was associated with reduced mortality both in multi-center and univariate analyses, respectively. Vitamin C consumption was associated with reduced mortality and ameliorated clinical course in patients with severe COVID-19 in a recent multinational, retrospective study. High-dose intravenous (IV) vitamin C has demonstrated promising results in the United States and China. However, a large randomized controlled trial is still needed to confirm these promising results. The effectiveness of vitamin C as an antioxidant is still not statistically significant. In our preliminary analysis on 31 peer-reviewed observational studies, a positive trend was observed between serum 25(OH)D level < 20 ng/ml and mortality. | UK | Abobaker et al. 2020 [164] |
| Vitamin D (Systematic review) | | | China | Liu et al. 2020 [43] |
| Nutrition type                          | Sample size | Outcome                                                                 | Country     | Reference                  |
|----------------------------------------|-------------|--------------------------------------------------------------------------|-------------|----------------------------|
| Vitamin D (Systematic review)          | 9 studies   | significant enhanced risk of ICU admission, invasive or non-invasive ventilation, mortality, or SARS-CoV-2 positivity. In COVID-19 positive cases, mean 25(OH)D levels were 5.9 ng/ml significantly lower compared to COVID-19 negative patients, albeit there was very low certainty of the evidence. Only 32 clinical trial protocols were identified in which just three of them have published data to-date. The trials administer vitamin D doses of 357 to 60,000 IU/day, from one week to 12 months. Eight mega trials evaluate the efficacy of vitamin D in outpatient cases. A significant reduction in ICU admission using calcifediols vs. placebo revealed through a pilot trial with an unclear certainty of the evidence. Supplementation with daily cholecalciferol (60,000 IU) showed by another small trial to decrease fibrinogen levels without having any impact on CRP, D-dimer and procalcitonin levels compared to placebo. The third trial did not show any impact of supplementation with vitamin D on COVID-19 related outcomes. | Ethiopia    | Yisak et al. 2021 [166]                                                  |
| Vitamins and mineral (review)          |             | Of nine reviewed studies, seven (77.8%) demonstrated the correlation between vitamin D status and COVID-19 prognosis and mortality. Most articles demonstrated that plasma vitamin D status could determine the possibility of catching coronavirus and its mortality and severity. Thus, maintained of appropriate plasma levels of vitamin D through its supplementation or sunshine exposure is recommended to cope with the pandemic. | Norwegian   | Alexander et al. 2020 [167]                                              |
| Vitamin D (review and correlation study) | 12 studies  | There were a few investigations which provide direct evidence regarding associations between vitamin D, selenium, zinc and COVID-19. Adequate supply of selenium, zinc, and vitamin D is necessary to resist other viral infections, to improve immune function, and reduce inflammation. Nutrition intervention securing an adequate status has been stated to protect against the novel coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome - coronavirus-2) and mitigate the disease course of COVID-19 infection. | Bangladesh  | Ali et al 2020 [56]                                                      |
| Vitamin D (review)                     |             | There was a significant negative correlation ($P = 0.033$) between COVID-19 cases per one million populations and mean vitamin D levels in European countries. However, in these countries the correlation between vitamin D and COVID-19 related death was not significant. There was an observed correlation between vitamin D and COVID-19 related severity and mortality in some retrospective studies, while other investigations observed no correlation after adjustment of other confounding variables. Several studies indicated to the roles of vitamin D in reducing the risk of pneumonia and acute viral respiratory tract infections including direct inhibition of viral replication or through anti-inflammatory or immunomodulatory approaches. Therefore, high risk patients for vitamin D deficiency during this global pandemic should be supplemented with vitamin D to maintain optimal levels of circulating 25(OH)D (75–125 nmol/L). Conclusively, there is not enough evidence regarding association between severity and mortality of COVID-19 infection and vitamin D levels. Thus, further cohort studies and randomized control trials are needed to test this hypothesis. | USA         | Bilezikian et al. 2020 [168]                                             |
| Vitamin D (review)                     | 47 studies  | Pervasive actions of vitamin D on different organ systems raised different probable interactions between it and mechanisms by which SARS-CoV-2 virus infects humans. By the way, for getting more conclusive results, further research is yet needed. | USA         | Grant et al. 2020 [169]                                                  |
5000 IU/d is recommended. The goal should be to raise 25(OH) D concentrations above 40–60 ng/mL (100–150 nmol/L). For treatment of infected people with COVID-19, higher doses of vitamin D3 might be useful.

Large population studies and randomized controlled trials should be conducted to assess these recommendations.

Vitamin D (review) Vitamin D, a key regulator of renin-angiotensin system, is exploited by SARS-CoV-2 for its entrance into host cells. Furthermore, it modulates numerous immune mechanisms to contain virus including dampening SARS-CoV-2 entrance and replication, reduction of concentration of pro-inflammatory cytokines and enhancement of anti-inflammatory cytokines, increasing production of natural antimicrobial peptide and activating defensive cells such as macrophages, with the ability to destroy SARS-CoV-2. Hill’s criteria for causality in a biological system, namely, consistency, strength of association, biological gradient, plausibility (e.g., mechanisms), temporality, and coherence despite of lacking experimental verification. There is enough strong evidence of usage of vitamin D supplements to prevent or treat COVID-19 outcomes. Role of vitamin D in COVID-19 could be twofold by reducing inflammatory responses and supporting production of antimicrobial peptides in respiratory epithelium which makes development of COVID-19 symptoms less likely. Deregulation of inflammatory responses, especially renin-angiotensin system is the main feature of COVID-19 and over activation brings poorer prognosis. Vitamin D is able to interact with a protein in ACE-2 pathway which is also exploited by SARS-CoV-2 as an entry receptor. While ACE-2 expression is downregulated by SARS-CoV-2, vitamin D promotes its expression.

It has been hypothesized that vitamin D supplementation could help in maintenance of sufficient vitamin D levels in COVID-19 patients as guideline recommended. This could be done by adjusting dietary intake of vitamin D or by vitamin D supplementation. Monitoring of serum calcium level is recommended and its mitigation using hydration or adjustment of the dose of applied vitamin D supplement is essential in the case of significant hypercalcemia.

Vitamin D (review) A growing body of circumstantial evidence links vitamin D status and COVID-19 outcomes. Role of vitamin D in COVID-19 could be twofold by reducing inflammatory responses and supporting production of antimicrobial peptides in respiratory epithelium which makes development of COVID-19 symptoms less likely. Deregulation of inflammatory responses, especially renin-angiotensin system is the main feature of COVID-19 and over activation brings poorer prognosis. Vitamin D is able to interact with a protein in ACE-2 pathway which is also exploited by SARS-CoV-2 as an entry receptor. While ACE-2 expression is downregulated by SARS-CoV-2, vitamin D promotes its expression.

Vitamin E (review) Lipid hydroperoxides will be formed due to reaction of oxygen with the cell membrane lipids using lipoxygenase with the help of peroxyl radicals. In order to prevent formation of hydroperoxides, vitamin E reacts with peroxyl radicals. Afterward, oxidized lipids will be detoxified by GPX4, glutathione, and other enzymes.

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antioxidant agents to prohibit triggering of ferroptosis. Besides, vitamin E is able to compensate for detoxification induced by GPOX deficiency. Indeed, induced neurodegeneration in the setting of vitamin E deficiency is said to be related to ferroptosis. Neural damage in COVID-19 cases might be partly inhibited using consumption of vitamin E through prohibition of peroxyl and lipoxygenase radicals. Furthermore, vitamin E has a role in the prevention of oxidative stress, DNA damage, and the development of cancer progression in the setting of certain cytokines. Multiple organ damages including gut, kidney, heart, lung, and nervous system could also lead to a heart attack and inflammation through modulation of T cells.

| Nutrition type | Sample size | Outcome | Country |
|----------------|-------------|---------|---------|
| Vitamin E (research article) | 60 pregnant women with COVID-19 infection and 36 age-matched pregnant women without any defined risk factors. | A correlation analysis on pregnant women showed reduced vitamin E levels in the COVID-19 group for all trimesters. Increased Afamin levels and lower vitamin E levels were observed in the COVID-19 group for all trimesters, albeit this association was statistically non-significant for Afamin levels, which could support the role of enhanced oxidative-stress in pathogenesis of COVID-19 infection and its relationship with the development of adverse perinatal outcomes. The values in the ROC curves with the best balance of sensitivity/specificity for vitamin E and afamin were 3.150 mg/ml and 0.424 mg/l, respectively. A positive moderate statistically significant correlation was observed between Afamin and vitamin E levels. | Turkey |
| Vitamin E (in vitro and in vivo) | 138 COVID-19 patients and 138 population controls. Plasma levels of dephosphorylated-uncarboxylated Matrix Gla Protein (dp-ucMGP) were significantly different between survivors vs. non-survivors. Patients had significantly decreased dp-ucMGP levels in correlation with vitamin K status reflecting higher mortality risk based on Cox regression survival analysis. After adjustment for co-morbidities, the association became attenuated and statistically insignificant. Low vitamin K status was found to be associated with mortality in COVID-19 patients in age- and sex-adjusted analyses, but not in analyses with additional adjustment for co-morbidities. Indeed, we identified no impact associated with vitamin K status for mortality. | USA | 
| Vitamin E (research article) | 1270 | There was a similar risk of death in VKA and DOAC groups. In the VKA cohort, there was a 43% higher risk at any 30-day event-free survival including all-cause mortality, ICH/gastrointestinal bleeding and ICU admission/MV necessity in VKA-treated patients compared to patients on DOACs. | Denmark |

Table 1 (continued)
| Vitamin E (research article) | sixty-two COVID-19 positive patients | Vitamin K deficiency is suggested to be frequently observed in COVID-19 cases with more prevalence in males vs. females. Vitamin K deficiency in male patients is associated with greater circulatory levels of IL-6. Vitamin K deficiency is able to support both cytokine storm. Through enhancement of proinflammatory cytokines including IL-6 which is involved in build-up of recruitment of inflammatory responses that recruit both humoral and cellular components. Moreover, it also contributes to events involved in vascular calcification associated with thrombosis and disseminate intravascular coagulation (DIC) as features of microvascular injury seen in COVID patients. These data introduce Vitamin K as a probable modifiable risk factor for development of a severe course of COVID-19 infection. | Italy | Anastasi et al. 2020 [177] |
|---|---|---|---|---|
| Vitamin E (research article) | 135 hospitalized COVID-19 patients were compared with 184 historical controls. | Elevated Dp-ucMGP was observed in COVID-19 cases compared to controls, with higher dp-ucMGP in infected cases with poor outcomes. In 82.1% of cases, prothrombin (PIVKA-II) was normal. There was a correlation between Dp-ucMGP and desmosines and scores of thoracic aorta and coronary artery calcification. | Netherlands | Dofferhoff et al. 2020 [79] |
| Vitamin E (review) | Covid-19 results in significant extrahepatic vitamin K insufficiency leading to the development of impairment in activation of extrahepatic proteins such as endothelial anticoagulant protein S in the setting of normal hepatic procoagulant activity. This indicates to enhanced thrombogenicity in the setting of severe Covid-19 infection. VKA inhibits vitamin K recycling and exerts a greater impact on procoagulant activity during SARS-CoV-2 infections rather than activation of extrahepatic vitamin K-dependent proteins. A genetic polymorphism in vitamin K epoxide reductase complex 1 which is known as Vitamin K epoxide reductase complex subunit 1 (VKORC1) – 1639A, which is associated with low rates of vitamin K recycling is especially prevalent in East Asia. Allele carriage could be considered as being bioequivalent to consumption of low-dose VKA. VKORC1 – 1639A is speculated to confer protection against development of thrombotic complications related to Covid-19. Variations in its allele frequency could be partly responsible for differences in Covid-19 severity among East and West. Disparity in COVID-19 related morbidity and mortality between East and West that could be partly explained by variations in allelic distribution of a VKORC1 polymorphism involved in determination of vitamin K recycling rate. Since VKORC1 – 1639A allele has been demonstrated to be associated with reduced risk of thrombotic complications and/or death, it could support the important role of vitamin K metabolism in determination of COVID-19-related disease severity. | Netherlands | Janssen et al. 2020 [178] |
| Vitamin E (review) | The vitamin K-dependent factors protein S (PROS1) and growth-arrest-specific gene 6 (GAS6) and their tyrosine kinase receptors TYRO3, MERKTK, AXL and the TAM subfamily of receptor tyrosine kinases (RTK) are known as key regulators of vascular response to injury and inflammatory processes. The important role of the TAM receptor family is being recognized during SARS-CoV-2 infection and progression of COVID-19 disease. Altered serum levels of sAXL, sGAS6, sMERTK or sPROS1 have been previously associated with progression of inflammatory diseases and fibrosis in lung, heart and liver. Changes of specific components in COVID-19 patients seems to be associated with clinical complications and disease severity. Thus, COVID-19 could be possibly benefited from TAM targeting. | Spain | Tutusaus et al. 2020 [179] |

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| Nutrition type            | Sample size | Outcome                                                                                                                                                                                                 | Country | Reference                |
|--------------------------|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|--------------------------|
| Calcium (systematic review) | 25 studies  | Clinical data derived from 12 articles demonstrated hypocalcemia in 59% of COVID-19 patients. The results of meta-analysis demonstrated significant association between hypocalcemia and disease severity, mortality, admission to intensive care unit and number of hospitalization days. Indeed, a direct association was observed between low serum calcium levels and decreasing lymphocyte counts and increasing D-dimer levels. | Iran    | Alemzadeh et al. 2020 [82] |
| Calcium (review)          | 20 studies  | Evidence have indicated reduced mortality of COVID-19 through consumption of calcium channel blockers (CCBs), especially nifedipine and amiodipine. Indeed, hypocalcemia had strong positive association with severity of COVID-19. Effectiveness of CCBs as antiviral therapeutic approach and positive relationship between hypocalcemia and mortality have been shown for various viruses as well. It has been hypothesized that hypocalcemia indicates a host defense. In addition, hypocalcemia might include antiviral properties as the same with CCBs through its interference with metabolism of calcium in virus-infected cells. Calcium ions are central to replication of coronavirus and possible interference of hypocalcemia and CCBs with viral replication through reduction of intracellular calcium level has been suggested. | USA     | Crespi et al. 2021 [180]  |
| Calcium (review)          |              | Calcium supplementation during SARS CoV-2 associated hyperactive stage of CaSR might induce injury to cardio-renal system. Besides, CaSR inhibition is also able to regulate enhanced levels of intracellular calcium, proinflammatory mechanisms, oxidative stress and cardio-renal cellular apoptosis with their subsequent adverse induction of high cytokine levels during COVID-19 infection. | India   | Singh et al. 2021 [181]  |
| Zinc (review)             | 15 studies  | Zinc should be prescribed as a preventative measure against COVID-19 infection and generally for support of immune health. Zinc should be considered as an adjunct therapy for COVID-19 based on its limited drug interactions and known safety. It also should be supplemented in the setting of acquired zinc deficiency during a viral infection and its related host immune response. | USA     | Joachimiak et al. 2021 [182] |
| Zinc (review)             |              | Zinc is a well-tolerated element with antiviral, anti-inflammatory, antioxidant and immunomodulatory properties. Its anti-viral properties are possibly mediated through inhibition of RNA virus RdRp which protects cells and tissues against oxidative damage and viral infection. Thus, zinc could be supplemented safely in COVID-19 cases. | India   | Pal et al. 2021 [85]     |
| Zinc (review)             |              | Zinc could reduce risk of infection and optimize immune functions as an anti-inflammatory agent. Zinc supplementation could be a useful supplementation in order to diminish the global burden of infection in elderly patients. | Brazil  | Almeida Brasiel et al. 2020 [183] |
| Zinc (review)             |              | Improvement of zinc status in COVID-19 patients could conquer the infection and subsequently bolster their recovery. By adoption of this health restoration strategy, other nutrients are also needed to be applied. | Australia | Butters et al. 2020 [184] |
| Zinc and vitamins (review) |              | Deficiency of one or more of vitamins C, D and zinc compromises immune responses, which makes persons prone to viral infections and a worse disease prognosis. Therefore, adequate intake of vitamin C, D and zinc during the COVID-19 pandemic could represent a promising approach based on high demands of these nutrients in cases with contact to the virus and those who are at the onset of inflammatory process. | Brazil  | Name et al. 2020 [185]    |
| Zinc (review)             |              | Chloroquine is able to induce zinc uptake into cell cytosol which enables inhibition of RNA-dependent RNA polymerase and ultimate halting of coronavirus replication in host cells. Chloroquine is widely prescribed as an anti-malarial agent without any doubt in its safety. | USA     | Shittu et al. 2020 [186]  |
Zinc (review)

Certain indications implicate modulation of zinc status could be beneficial in COVID-19. In vitro experiments indicate antiviral properties of Zn2+ through inhibition of SARS-CoV RNA polymerase. This effect might indicate to the therapeutic efficiency of chloroquine which functions as zinc ionophore. Decreased activity of ACE2 which is known as SARS-CoV-2 receptor by Zn2+ is demonstrated through indirect evidence. Zinc could also improve antiviral immunity through up-regulated production of interferon α and enhancement of its antiviral properties. Zinc exert anti-inflammatory activity through modulation of regulatory T-cell functions and inhibition of NF-κB signaling that might limit cytokine storm in COVID-19. Improved Zinc status is also able to diminish the risk of bacterial co-infection through improvement of mucociliary clearance and respiratory epithelial barrier function and possessing antibacterial effects. Zinc is tightly associated with risk factors of severe COVID-19 including immune deficiency, ageing, obesity, atherosclerosis and diabetes which are recognized risk groups for zinc deficiency. Thus, Zinc could have protective effects such as adjuvant and preventive therapeutic measure of COVID-19 through reduction of inflammation, prevention of ventilator-induced lung damage, modulation of antibacterial and antiviral immunity and improvement of mucociliary clearance.

Russia
Skalny et al. 2020 [187]

Several lines of evidence indicate to the benefits of supplementation with zinc. Zinc supplementation is associated with improved mucociliary clearance, preserved antiviral immunity, strengthened epithelial integrity, decreased viral replication, attenuated risk of hyper-inflammation, possessing anti-oxidative effects, minimized secondary infections and reduced lung damage. Patients with underlying chronic diseases, elder subjects, and most of the remaining COVID-19 risk groups would most likely be benefited. However, more investigation is required to test the impacts of zinc as a therapeutic option for the established disease. Indeed, preventive supplementation of cases from risk groups should be initiated due to the cost effectiveness, having little or no side effects, global availability and simple application of zinc.

Germany
Wessels et al. 2020 [188]

Iron (review)

During COVID-19 infection, enhanced plasma iron levels is associated with higher amounts of generated reactive oxygen species which subsequently lead to oxidative stress and lung injury followed by declined lung function and lung fibrosis. Iron overload enhances viral replication and exert a fundamental role in severity of infection. Iron chelating agents such as Deferoxamine and Lactoferrin could diminish iron availability in serum and body tissues which could prevent lung injury and fibrosis related to COVID-19 infection. Indeed, recent nominate compounds with a potential as protease inhibition seems to be novel candidates for treatment of SARS-CoV-2 infection.

Italy
Carota et al. 2021 [189]

Iron (review)

Iron is an important player ensuring adequate immune responses and a number of interesting intersections have been highlighted from surveys on iron metabolism in COVID-19. While the functional implications of the action of iron in facing certain parasites, bacteria and the host have been established, this scenario is less clarified during viral infections. Furthermore, specific patterns related to hepcidin and iron regulation occur during various viral infections. Severe COVID-19 is characterized by significant functional iron deficiency and high hepcidin levels, the former is possibly associated with impaired response to lymphocyte function and hypoxia.

Italy
Girelli et al. 2021 [190]

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Iron overload is implicated as a contributor in pathogenesis of COVID-19. Besides, several manifestations of COVID-19, such as hypercoagulation, immune dysfunction, inflammation and hyperferritinemia are reminiscent of iron overload. Although iron is vital for alive cells, free unbound iron which leads to iron dysregulation and overload is significantly reactive with potential toxic properties due to generation of reactive oxygen species (ROS). ROS react with and damage nucleic acids, cellular lipids and proteins which consequently activates either acute or chronic inflammatory processes during multiple clinical conditions. Furthermore, iron catalyzes lipid injury events a direct causative impact on the newly identified nonapoptotic cell death pathway recognized as ferroptosis, which is immunogenic unlike apoptosis. It not only results in amplification of cell death but also promotes occurrence of reactions related to inflammation. Generally, iron-chelator are safe and able to protect patients in the clinical conditions induced by iron overload. Iron chelators also exert anti-inflammatory activities. Lactoferrin, as a naturally occurring iron chelator, possess immunomodulatory and anti-inflammatory properties which binds to the receptors in demand of coronaviruses to block their entry into host cells. Thus, iron chelators could be with high therapeutic value during this current COVID-19 pandemic.

Endolysosomal function could be considered as a target in COVID-19. Based on recent clinical data, patients on lysosomotropic drugs for the treatment of their underlying conditions would also be benefited from this therapeutic strategy to prevent SARS-CoV-2 infection and its transition to COVID-19. In these cellular settings, there are some obvious alterations in iron metabolism. Enhanced iron levels and/or dysregulated homeostasis of iron occur in various lung diseases such as pulmonary fibrosis and chronic obstructive pulmonary disease (COPD). Bracken and Declercq function in experimental and clinical development of bleomycin-induced pulmonary fibrosis. Indeed, increased iron accumulation is observed in lung sections obtained from cases with idiopathic pulmonary fibrosis.

Current antioxidant compounds of interest include enzymes (superoxide dismutases and GPXs), quercetin, minerals, melatonin, GSH, N-acetylcysteine, selenium, curcumin, vitamins B6, D, E, and C and natural polyphenols.
The beneficial impacts of iron chelation therapy on inflammation and on fibrogenesis occur in the lungs indicate that iron chelation could improve the survival and long-term outcomes in critically ill COVID-19 patients.

**Iron (review)**

Hydroxychloroquine (HCQ) and chloroquine (CQ) possible have: [1] a direct antiviral property; [2] a possible ability to attenuate progression of COVID-19 to the development of severe forms by inflammatory mechanisms; [3] a potential anti-thrombotic effect. Due to their minimal toxicity and complex action, we suggest treatment with CQ/HCQ CQ beyond 5–10 days in patients with COVID-19 based on the hypothesis that their application could be extended after ending high replication phase of Sars-CoV-2 and considering the possibility of infection reactivation.

Italy Roldan et al. 2020 [194]

**Selenium (review)**

Oxidative stress is a unique feature of COVID-19 disease which is associated with immunopathological disorder seen in cases with severe COVID-19. Selenium deficiency is associated with hyperinflammation and oxidative stress observed in critical and severe COVID-19 illness.

Australia Khattriwada et al. 2021 [195]

**Selenium (review)**

Selenium is an essential trace element for proper functioning of immune system. Impaired immune responses and predisposition to autoimmune disease (AID) especially for thyroid gland could be induced by severe Selenium deficits. Active immune system by elevated cytokine levels suppresses biosynthesis of hepatic selenoprotein and secretion of selenoprotein P into the circulation leading to diminished metabolism of Selenium and suppressed Selenium status. An acute or chronic severe Selenium deficiency perturbs immune system irrespective of its cause (e.g., infection, poor nutrition, pregnancy, cancer, trauma, surgery). Clinical settings with low Selenium status are overlapping with known triggers of AID indicating to the presence of a direct causal interrelation. Benefits of supplemental Selenium are recognized for the thyroid but not yet for the other prevalent AID, such as type 1 diabetes mellitus or rheumatoid arthritis. Avoidance of severe Selenium deficiency might diminish risks of AID that alleviate symptoms of disease, both for prevention and treatment. Therefore, substitution of selenium is recommended strongly for acute or chronic deficiency, while supplementation of healthy persons by sufficiently high baseline levels is not a warranty.

Germany Schomburg et al. 2021 [196]

**Selenium (review)**

Disrupted antioxidant defense is shown in severe acute respiratory syndrome caused by SARSCoV infection. Selenium exerts a fundamental role in reduction of produced ROS in response to different viral infections. Selenoprotein enzymes are important for fighting against oxidative stress due to excessive production of ROS. Selenium also plays a role in inhibition of NF-κB activation which alleviates inflammation. Selenoproteins could inhibit responses related to type I interferon during viral infections which modulates oxidative burst in macrophages and proliferation of T cells with subsequent inhibition of viral transcriptional activators. Potential virally encoded selenoproteins have been recognized through computational analysis performed in various viral genomes such as Japanese encephalitis virus, HIV-1 and hepatitis C virus. The relationship between these potential virally encoded selenoproteins with different disease phenotypes highlights their biological role in pathogenesis of COVID-19. It could also help in better understanding impacts of an apparent selenium deficiency in the host cell through over translation of viral selenoproteins on host cell defense mechanisms against COVID-19 infection. Trials on

India Tomo et al. 2021 [197]
### Table 1 (continued)

| Nutrition type   | Sample size | Outcome                                                                 | Country   | Reference          |
|------------------|-------------|--------------------------------------------------------------------------|-----------|--------------------|
| Selenium (review)| 36 studies  | Environments with selenium deficiency favor replication, virulence and mutation of RNA viruses. Selenium status could influence SARS-CoV-2 like other RNA viruses. Selenium induces activity of antioxidant selenoenzymes that possibly rebalance host responses. Selenium plays a role as a NF-κB inhibitor in progression of COVID-19 and functions as an anti-inflammatory and immunomodulatory micronutrient. Besides, it could reduce impacts of SARS-CoV-2 on vascular endothelial cells and platelet aggregation. Oxidative state is a common feature of COVID-19 especially in obese and elder patients who are at risk for the development of severe outcomes. Selenium has an important roles to play by reduction of oxidative stress. | France    | Hifler et al. 2020 [96] |
| Selenium (review)|             | There is a long story behind selenium in reduction of incidence and severity of different viral infections. Significantly higher selenium level was observed in serum samples of survivors vs. non-survivors of COVID-19 infection. Indeed, there was a significant positive linear relationship between the cure rate of COVID-19 in Chinese people and regional selenium status. Furthermore, the cure rate raised to beyond the selenium intake needed for optimization of selenoproteins which suggest that possibly selenoproteins are not the whole story. Significant reduction in expression level of a number of selenoproteins that control ER stress and increase in IL-6 expression was observed in SARS-CoV-2 infected cells in culture suggesting a potential association between the reduced expression of selenoprotein and COVID-19-related inflammation. The synthetic redox-active selenium compound, ebselen, could strongly inhibit main SARS-CoV-2 protease which enables maturation of viruses within host cells. This observation indicates that formed redox-active selenium species at high selenium intake could possibly inhibit SARS-CoV-2 proteases. Through interference with human selenoprotein system, SARS-CoV-2 could evade an adequate host response. | China     | Zhang et al. 2020 [198] |
| Amino acids (review) | 30 control and 112 COVID-19 patients | There was a significant difference regarding 20 amino acids when compared to the control group in COVID-19 patient groups with different levels of severity. Branched-chain amino acids showed alteration in correlation with each other, and L-phenylalanine and L-2-aminobutyric acid were suggested to be potential biomarkers for COVID-19. Thus, L-2-aminobutyric acid could afford prognostic information regarding disease course. | Turkey    | Atila et al. 2021 [115] |
| Amino acids (research article) | 46 severe and 19 mild COVID-19 patients and 27 controls | In hypoxic conditions, there was an association between modified metabolic profiles and altered amino acid catabolism. Besides, there was an increase in three α-hydroxy acids of amino acid origin with disease severity in correlation with clinical markers of lung injury and changed oxygen saturation levels. We speculate maintenance NAD recycling through enzymatic conversion of α-keto-acids to α-hydroxy-α-keto-acids in the setting of altered oxygen levels indicating to the potential relevance of supplementation with amino acids during SARS-CoV-2 infection. | Mexico    | Páez-Franco et al. 2021 [199] |
| Amino acids (review) |             | Overnutrition/excess serum amino acid profile during obesity has been associated with inflammation and reprogramming of translational machinery through hyperactivation of amino acid sensor mammalian target of rapamycin (mTOR), which is exploited by SARS-CoV-2 for its replication. Indeed, activation of general control non-repressible 2 (GCN2) dependent amino acid starvation sensing pathway prevents intestinal inflammation through suppressing production of interleukin-1 | India     | Philips et al. 2021 [200] |
beta and reactive oxygen species (ROS). While activation of GCN2 is able to mitigate susceptibility to dengue infection, enhanced GCN2 deficiency is associated with viremia and inflammation-related pathologies. These findings display role of amino acid sensing pathway in controlling viral infections and inflammation. The current fact is aggravated COVID-19 infection through activation of obesity/excess amino acids/mTOR pathway and activation of amino acid starvation sensor GCN2 could possibly have an opposite effect.

Amino acids (review) Impaired angiotensin-converting enzyme-2 (ACE2) which is cellular anchor of SARS-CoV-2 results in GI disturbance. During infection it is postulated to be internalized to dwindle expression of sodium-dependent neutral amino acid transporter (B$_{0}$AT1) in intestinal cells (Nisoli et al., 2020). Hartnup disorder, an inherited defect in B$_{0}$AT1 amino acid transporter, which is encoded by mutated SLC6A19 gene shares numerous psychiatric symptoms with COVID-19 (Nisoli et al., 2020). Impaired uptake of amino acid reduces neurotransmitter levels which could invite psychiatric symptoms. Tryptophan catabolites (TRYCATs) exerts pleiotropic effects during physiological and psychiatric health. It also regulates presentations of depressive disorders (Rao et al., 2008); which postulates a link for psychoneuroimmunomodulation in COVID-19 (Soni et al., 2020b). Precursor amino acid therapy was associated with huge success in management of pain and management of psychosomatic disorders (Rao et al., 2008). Attempts made for management of COVID-19 encompass both physiological and mental well-being (Tandon, 2020). Thus, psychiatric symptoms in COVID-19 infected cases are contributing to physiological injuries triggered by SARS-CoV-2-infection. Nutritional deficiency mainly at the level and ratio of amino acids might change the neurotransmitters balance in provoking depression, anxiety, and mood alterations in COVID-19 patients. A supplementation with conditional amino acids could improve mental well-being, immunity and therapeutic outcomes of COVID-19.

Coenzyme Q10 (review) Modulated mitochondrial dynamics and metabolism with lower levels of Coenzyme Q10 (CoQ10) in viral infections highlights dysfunction in mitochondrial bioenergetics with CoQ10 deficit as the main pathobiochemical impacts of SARS-Cov-2 virus resulting in reduction in its endogenous biosynthesis. The mechanism could pass through virus induced oxidative stress leading to mutation of one or more of the nine COQ genes resulting in the development of primary CoQ10 deficiency.

omega-3 (review) Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have immunomodulation effects and are also able to improve mood disorders. Strengthening baseline immunity could facilitate prevention of psychiatric sequelae and fatal outcomes in COVID-19 infected cases or prevent relapse of pre-pandemic psychiatric disorders. Therefore, a balanced healthy diet might be what is required for improvement of our immunity and it is needed to evaluate if n-3 PUFAs are possible nutraceutical for maintenance of our mental.

omega-3 (review) Omega-3 fatty acids (FA) has several benefits and taking it as a supplement could prevent viral entry through altered composition of fat component in cellular bilipid membrane. Omega-3 FAs, such as Docosahexaenoic Acid (DHA) and Eicosapentaenoic Acid (EPA) and exert their functions by their incorporation in cell membrane and

(continued on next page)
| **Nutrition type** | **Sample size** | **Outcome** | **Country** | **Reference** |
|-------------------|----------------|-------------|-------------|--------------|
| Omega-3 (review)  | 46 studies     | Probiotic (research article) | Iran       | Taghinezhad-S et al. 2021 [207] |
|                   |                | Probiotic (review) | Iran       | Behbahani et al. 2021 [209] |
|                   |                | Omega-3 (review) | France      | Well et al. 2020 [205] |
|                   |                | Omega-3 (review) | Brazil      | Rogers et al. 2020 [204] |

Although documented in vivo and in vitro assays demonstrated benefits of omega-3 fatty acids to decrease severity of COVID-19, the risk of high supplementation doses previous or during infection with SARS-CoV-2 must be investigated. Regarding consequences of oxidative stress, cytokines storm, and antiviral drugs on progression of cardiovascular diseases, more investigations on supplementation with omega-3 fatty acids should be performed on survivors of SARS-CoV-2 infection, since health status of these individuals could be improved using proper and controlled supplementation.

Omega-3 LC-PUFAs are able to play a central role to prevent cytokine storm at least through reduction of the intensity of inflammation and mortality risk in patients with Covid-19. For general population and primary prevention, at least nutritional recommendation is 500 mg/day for EPA+ DHA and 2.2 g/day for a-linolenic acid (ALA). For secondary prevention, and for symptomatic cases or those with positive Covid-19 infection, the optimal doses for both omega-3 LC-PUFAs and ALA are yet unknown. It is also crucial to meet nutritional recommendation of 2.2g/day of ALA. Regarding omega-3 LC-PUFAs, EPA and DHA should be prescribed in Covid-19 cases at the highest amounts of omega-3 LC-PUFAs. Higher amounts of LC-PUFAs are known to be beneficial for synthesis of pro-resolution mediator. ALA is the initial precursor of these LC-PUFAs by successive desaturation and elongation. Although the overall ALA to DHA conversion is weak, ALA might exert its own impact on resolution of inflammation. Plants and microorganisms are known to have affinity for l-lactic acid (L-ala). Manipulation of their sequences are associated with elimination of side effects. In these two discovered drugs seem to be optimal for treatment of COVID-19 infection.
neutralize and eradicate infections. Application of probiotics as live delivery vectors, promotes prospective investigations to evaluate efficacy of genetically modified probiotics against SARS-CoV-2 infection. New emerging horizons in development of vaccine technology re-emphasizes into the contribution of adjuvants accompanied by optimization of codon usage during designing a synthetic gene, expression level, and inoculation dose in order to elicit potent and specific protective immune responses. Mucosal immunization, mainly through nasal route using a probiotic-based vaccine might strongly prohibit SARS-CoV-2 infection.

Probiotic (research article) 200 frontline medical staff China Wang et al. 2021 [208]

Our data indicates significantly diminished the incidence of respiratory tract infections by about 64.8%, shortened work absent days by 95.5%, reduced time being under medication, reduced time experiencing symptoms of respiratory tract infection and oral ulcer by 78% using administration of oropharyngeal probiotic while no history of antibiotic and anti-viral medicine consumption in the probiotic group. Medical staff under treatment by Bactobis demonstrated sustained protection against respiratory tract infections with extremely low incidence rate of being suffered from respiratory tract infections at 10th day of administrated probiotic.

Probiotic (review) Saudi Arabia Al-Ansari et al. 2020 [137]

The nutritional and immunity enhancing probiotics which operate gut homeostasis must be paid more research attention. A healthy lifestyle, regular physical exercise, and probiotics supplementation are prominent players for induction of immunity. The specific probiotics roles for stimulation of IgA antibodies, enhancement of natural killer cells function, and control of mucosal barrier inflammation made a big interest in generation of novel probiotics for strengthening of immunity to fight against COVID-19 viruses.

Probiotic (research article) Saudi Arabia Anwar et al. 2020 [209]

Binding energies for Plantaricin W for residual binding protein (RBP), polymerase and ACE2 were -11.1, -14.64, and -12.68, respectively comparatively very high with other compounds. Plantaricin W, D, and JLA-9 were able to block the residues (THR556, ALA558) surrounding the deep groove catalytic site (VAL557) of RdRp making them more therapeutically active for COVID-19. Molecular dynamics studies would strengthen the stability of the complexes of plantaricin w and SARS-CoV-2 RdRp enzyme, RBD of spike protein, and human ACE2 receptor.

Diet (review) Italy Gangitano et al. 2021 [210]

Administration of very low-calorie ketogenic diet could be considered in severely obese cases as an effective adjuvant treatment or preventive measure for both rapid weight loss and also rehabilitation during COVID-19 infection. Administration of high fat ketogenic diet (HFKD) in hospitalization period or delicate cases such as cases after positive ventilation and intensive care unit is a challenging hypothesis. Limiting intake of carbohydrate and promotion of ketone formation could lead to amelioration of respiratory parameters. Moreover, HFKDs have strong anti-inflammatory properties and could be helpful in reduction of viral replication. However, numerous studies are old with small sample size without specific addressing of ketosis which highlights the importance of novel clinical trials.

Diet (review) Poland Jabczyk et al. 2021 [211]

Diet, prebiotics and probiotics are primary modulators to maintain gut biodiversity and to support immune responses. Nutritional strategies with the aim to restore a beneficial gut microbiome might facilitate suppression of viral infection in elders and those with underlying comorbidities. Besides, large-scale international randomized clinical trials are required to identify an association between dietary probiotic remedies, gut microbiome, predisposition to SARS-CoV-2 infection, and severity of COVID-19 infection.

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Table 1 (continued)

| Nutrition type | Sample size | Outcome | Country | Reference |
|----------------|-------------|---------|---------|-----------|
| Diet (review)  | 23 studies  | A diet with positive impacts on immune function should have adequate protein levels especially arginine, glutamine, and branched-chain amino acids; high fiber content such as whole grains, high amounts of micronutrients including vitamin A, C, D, B and K, iron, selenium, zinc and phytochemicals, high levels of omega-3 vs. lower saturated, trans fat, and omega-6 fatty acids and low amounts of refined sugars. However, as shown well for dietary fiber, an excessive anti-inflammatory response may also reduce the immune response and increase susceptibility to infection. There are controversial reports about vitamin A, in which supplementation with carotenoid might be merely detrimental for asbestos-exposed workers and smokers. Supplementation with selenium should also be considered carefully due to its narrow therapeutic window and its possible side-effects particularly in diabetic cases. While anti-inflammatory constituents of diet could be beneficial during hyper-inflammation phase such as cytokine storm of COVID-19, too strong suppression of immune system and inflammation using high doses of antioxidants and or isolated anti-inflammatory compounds during healthier conditions seems dangerous. Strengthening of immune system during COVID-19 crisis is the output of reduced oxidative stress and inflammation. This topic is highly complex and indicates to seeking for simultaneous determination of individual marker and a nutrient signature in different ways such as using nutrigenomics tools (i.e., metabolomics fingerprinting). This approach might clarify unnoticed associations between nutrients, their metabolites inflammation, oxidative stress, and the immune system. Besides, confounding factors such as environmental pollutants and medication should also be taken into account. It is also of great importance of control low-grade inflammation associated with chronic diseases such as obesity, auto-immune, diabetes, and cardiovascular diseases (CVD) possibly through management of nutritional deficiencies and promotion of appropriate nutritional status, which could improve immune response during infection phases. | Luxembourg | Iddir et al. 2020 [213] |
| Diet (review)  | A healthy and well-balanced diet exert beneficial impacts on conditions predisposing patients to COVID-19 and its complications. A diet with high antioxidant, immunomodulatory and anti-inflammatory potential might prophylactically mitigate severity of COVID-19. Thus, more investigations are required to evaluate specific components of diet to prevent COVID-19 and also improve infection parameters during illness. In the case of hospitalized COVID-19 patients, cases in intensive care units and in critical condition, assessment of their nutritional status and implementation of rapid and proper nutritional care is recommended. Nutritional support requires adequate intake of all essential nutrients particularly n-3 fatty acids, proteins, microelements (zinc and selenium) and vitamins especially C and D and caloric value based on patient’s requirements. | Poland | Skrajnowska et al. 2021 [212] |
| Diet (review)  | Different players are involved in extension and severity of COVID-19 infection including early and fast education, public preparedness for pandemics, trained immunity of population, public hygiene and rapid adaptation and organization of the hospital. Diet is only one of the possible causes of the COVID-19 Which still requires further assessment. | Germany | Bousqu et al. 2020 [148] |
| Diet (review)  | 23 studies  | Adequate management of metabolic disorders is essential to reduce risk of severe COVID-19. We should seek for avoidance of deleterious consequences of and positive energy balance physical inactivity through maintenance of exercise levels and physical activity in a safe home environment and applying a healthy diet. It is also beneficial for people without metabolic disorders to prevent deleterious impacts of positive energy balance and physical inactivity, which could lead to the development of metabolic syndrome and its related comorbidities. Avoidance of overeating | Spain | Martinez-Ferran et al. 2020 [214] |
through applying a healthy balanced diet based on carbohydrates with a low glycemic index such as legumes, healthy fats, vegetables or fruits, protein enriched foods with lower fat percentage is of great value. Besides, restricted calorie intake in the setting of diminished activity or physical inactivity is beneficial. These nutritional recommendations should be accompanied by appropriate daily physical activity program advised by sports science specialists to prohibit metabolic-related health issues. The items need to be considered in this program include coordination, mobility, resistance, and balance and aerobic. The training frequency is recommended to be performed 5–7 days per week with at least 2–3 days with resistance training. The signs and symptoms of respiratory infections due to COVID-19 could be categorized in the field of Zato al-rieh that can mainly be matched with pneumonia. Some medicinal materia medica and nutrients have been introduced based on the described criteria for the treatment of acute respiratory infections including Rosa Damas Cena, Honey, Cydonia oblonga, Raisin, Citrus sinensis, Malus domestica, D.Carota, Crocus sativus, Citrus medica, Camellia Sinensis, Punica granatum, Anethum graveolens dhi, Coriandrum sativum, Urtica dioica, Petroselinum Crispum, Sesamum indicum, Allium sativum.

Diet (review) 57 studies

The signs and symptoms of respiratory infections due to COVID-19 could be categorized in the field of Zato al-rieh that can mainly be matched with pneumonia. Some medicinal materia medica and nutrients have been introduced based on the described criteria for the treatment of acute respiratory infections including Rosa Damas Cena, Honey, Cydonia oblonga, Raisin, Citrus sinensis, Malus domestica, D.Carota, Crocus sativus, Citrus medica, Camellia Sinensis, Punica granatum, Anethum graveolens dhi, Coriandrum sativum, Urtica dioica, Petroselinum Crispum, Sesamum indicum, Allium sativum.

Diet (review) Iran Moslemifard et al. 2020 [215]

Multiple mechanisms exist which highlight the impacts of ketone bodies during significant viral infections such as COVID-19. Administration of exogenous ketones into critical patients to target complications respiratory viruses could be considered as a possible therapy. In order to prevent infection by Sars-Cov 2 infection and its adverse outcomes in obese cases, especially in this current prolonged pandemic emergency, ketogenic diet (KD)-induced increased endogenous ketone bodies might represent a valuable strategy. Furthermore, prevention and or modification of risk status associated with serious COVID-19 including hyperglycemia, obesity, high glycemic variability, hypertension and insulin resistance is mandatory considering novel infection routes in the absence of vaccination and functional pharmacological therapies. This could be achieved using a nutritional strategy aimed to diminish systemic and hepatic insulin resistance and chronic inflammation, improve cardiovascular health, nutritional status, glucose homeostasis, immune response and blood pressure control and induce fat mass loss. Adoption of a personalized and well-structured KD regimen could help a progressive rehabilitation and nutritional education in obese cases which provides an effective strategy to modify lifestyle behavior, support a long-term management of body weight and reduce risk factors for the development of potentially severe complications associated with Sars-Cov2 infection. Well-designed multicentric investigations on the incidence of severe COVID-19 among obese cases who followed or not a planned protocol of KD might help in confirmation of such hypothesis.

Diet (review) India Paoli et al. 2020 [216]

Large body of evidence support the role of commensal microbiota in human health. Diet plays a crucial role in modulation of gut microbiota resulting in the development of symbiosis or dysbiosis. People should be informed about the benefits of daily consumption of a balanced diet that could be prescribed or improved by food industries or nutritional biologists. A balanced diet like those prepared by dieticians in hotels and hospitals of educational institutions could also be defined for general public, migrants and economically weaker subpopulation of society in order to prevent malnutrition. Besides, intermittent fasting or a fasting-mimicking diet could also be an important advisory, for restoration of beneficial gut microbiota and promotion of overall health.

Diet (review) India Rishi et al. 2020 [217]

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Nutrition is an important determining factor for immune responses. Good nutrition is essential for supporting immune responses. Immunity could be impaired in elders especially obese, malnourished and frail ones and those who use low amounts of micronutrients. These immune impairments due to nutritional inadequacy leads to susceptibility to infection which allows infections to get more severe and or even fatal. Nutritional inadequacy facilitates dysregulated oxidative stress and inflammation contributing to the development of frailty and poor outcome following infection. Adverse impacts of poor nutrition on immune system and its inflammatory component could explain partly higher risk of poor outcomes following infection with SARS-CoV-2 as observed in elders and those who lose obesity. The role of good nutrition in promotion of diverse gut microbiota which supports immune system should also be considered. Good nutrition ensuring good responses to vaccination, too. Therefore, attention should be paid on addressing current nutritional inadequacies which are widespread in general population for better supporting of immune responses.

**UK Calder et al. 2021 [218]**

The COVID-19 lockdown resulted in unhealthy dietary alterations and increased body weight of the population which implies to physical inactivity and obesity as risk factors for COVID-19. Indeed, hospitalized COVID-19 patients manifested malnutrition and deficiencies in selenium, omega-3, iron, medium and long-chain fatty acids and vitamin C, B12 which highlights the potential health impacts of vitamin D and C interventions.

**Spain Clemente-Suarez et al. 2021 [219]**

The COVID-19 pandemic resulted in alterations in food supply. In many countries, special programs are currently implemented to increase food safety and availability. This altered food availability due to the pandemic is a worldwide phenomenon and its severity is dependent of the economic status and influence of that country. It induces serious implications especially in third world countries due to delayed food delivery, impaired food access, income losses to purchase food. This has acute serious health implications and considering deleterious impacts of past pandemics on human health and growth, prediction of current COVID-19 pandemic is reasonable which will induce global nutritional deficiencies with long-lasting negative impacts on human health. There is no evidence regarding transmission of COVID-19 virus through foods or food packages. The importance of appropriate precautionary equipment in the food industry and application of appropriate personal protective measures; disinfectant and hand hygiene are not negligible. Personal nutritional status could modulate positively or negatively in inflammatory processes and infectious disease through alteration of immune system. Malnutrition in elderly and disadvantaged populations leaves these populations predisposed to COVID-19 infections with severe clinical symptoms and poorer outcomes. Although severity of clinical symptoms and infectivity rate of a coronavirus infection could be modulated, strong viral transmission could likely be fully prevented through following a healthy diet and supplementation of diet with nutraceuticals. The impact of zinc, and vitamin D status in COVID-19 patients on viral transmission and its related clinical symptoms is still unclear and needs further research. COVID-19 has a significant impact on some populations through changed eating behaviors. The impact of lockdowns and social isolation on eating habits during the COVID-19 pandemic era should not be underestimated since it has acute effects with possible long-term deleterious impacts on population health. Poor nutritional choices over extended periods of time could have enhanced plasma risk factors for the development of diabetes, cardio-vascular disease and cancer.
Nutritional risk is a highly prevalent event in hospitalized COVID-19 cases with a multifactorial etiology which is likely due to affliction of older patient population and higher prevalence of comorbidities and altered energy intake due to enhanced requirement of energy and protein due to hypermetabolism, mechanical ventilation, fever, muscle mass loss, weight and diminished nutrient intake related to reduced appetite, mechanical ventilation, dyspnea and gastrointestinal intolerance. Thus, screening or assessing nutritional risk in hospitalized COVID-19 cases through validated screening/assessment tools is recommended by most expert guidance. Since the preferred route of feeding is oral intake, parenteral Nutrition (PN) or enteral Nutrition (EN) should be prescribed soon after ICU admission within 12–48 h, based on the source of expert guidance in the case of contraindications. Furthermore, hospitalized patients might not be able to receive timely nutritional interventions due to uncontrolled hypoxemia, uncontrollable shock needing vasopressor support, uncontrollable hypoxemia, acidosis or hypercapnia, feeding contraindications such as significant gastrointestinal symptoms and difficulty in assessment of patient’s nutritional risks which all could lead to the development of poor outcomes. In order to prevent potential exposure to SARS-CoV-2 cluster care is recommended and screening of underlying malnutrition by other family, healthcare professionals and/or caregivers is essential. In the case of experiencing contraindications to nutrition such as enhanced vasopressor support or gastrointestinal intolerance, prioritizing patient stabilization is important while considering PN or enteral trophic feeding. After patient stabilization, trophic EN could be initiated by slow progression to the goal nutritional requirements. A standard, protein enriched, polymeric isosmotic EN formula is advised by ASPEN/SCCM; although a higher protein formula may be more appropriate to meet protein requirements in this population. In critically ill hospitalized COVID-19 cases, formulas enriched with DHA and EPA may beneficial through exertion of immunomodulatory effects. Despite lack of clinical evidence providing specific recommendations for nutritional interventions in COVID-19 cases, experience derived from guidelines and clinicians associated with similar disease states could be beneficial until availability of more clinical data. By emerging more data derived from this population, specific guidelines and recommendations can be updated. Recent publications demonstrate higher nutritional risk in critically and severely COVID-19 patients who are hospitalized or admitted to ICU. Poorer clinical outcomes are seen in cases with increased nutritional risk in these populations. Therefore, rapid assessment, recognition and treatment of poor nutritional status is fundamental to improve clinical outcomes in critically and severely ill COVID-19 patients.

No miracle food, cure or supplement to treat or prevent COVID-19 is yet available. During the pandemic, application of healthy eating habits is the most appropriate nutritional recommendation.

The impacts of selenium, zinc, omega-3 fatty acids and vitamins D, C, E on the immune system and their possible benefits for suffered COVID-19 cases are presented, especially in vulnerable elder population with a disproportionate burden of related morbidity and mortality. All of the above-mentioned nutrients have a feasible role to support COVID-19 patients. Consumption of higher dosage of zinc and vitamins C and D could exert positive effects during COVID-19 infection. Given the negligible risk of supervised nutritional supplementation which weighs against its possible benefits, ensuring adequate intake of these minerals and key vitamins in both at risk of, and or suffered from COVID-19 patients.
Vitamin B1
Thiamine could improve functioning of immune system and diminish the risk of kidney disease, cardiovascular disease, type-2 diabetes, aging-related disorders, mental disorders, cancer, and neurodegenerative disorders [23]. Thiamine deficiency impacts on cardiovascular system leading to the development of neuro-inflammation, increasing general inflammation and aberrant antibody responses [24]. Since T-cells and antibodies are required for elimination of SARS-CoV-2 virus, thiamine deficiency is potentially able to result in development of inadequate antibody responses with subsequent development of severe COVID-19 symptoms. Indeed, thiamine acts as an inhibitor of anhydrase isoenzyme [25]. High-doses of thiamine is potentially able to limit hypoxia and reduce following hospitalization at early stages of COVID-19. By the way, further research is needed to determine if high-doses of thiamine could improve COVID-19 control [23].

Vitamin B2
Riboflavin in association with UV light result in irreversible injury to nucleic acids such as RNA and DNA pathogens disabling replication of microbial pathogens. Riboflavin and UV light are effective against the MERS-CoV virus indicating to their efficacy against SARS-CoV-2 [26]. Thus, riboflavin-UV reduces SARS-CoV-2 infectious titer below the detection limit in human blood [23], and plasma and platelet products [27]. Vitamin B2 could diminish transmission of COVID-19 and other pathogens in blood products of critically ill COVID-19 cases [23].

Vitamin B3
Niacin functions as a building block for NAD and NADP, two essential elements during chronic systemic inflammation [28]. NAD+ acts as a coenzyme in different metabolic pathways in which its enhanced levels are needed for treatment of various pathophysiologial conditions. At early stages if inflammation NAD+ is released providing immunomodulatory properties in order to diminish pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α [23]. Recently, it has been advocated that IL-6 reduction could relieve the inflammatory storm in the setting of COVID-19 infection [29]. Besides niacin diminishes neutrophil infiltration with subsequent anti-inflammatory properties incases with ventilator-induced lung damage. Nicotinamide and niacin administration were associated with prohibited lung injury in hamsters [30]. Moreover, nicotinamide decreased viral replication (human immunodeficiency virus, vaccinia virus, hepatitis B virus and enteroviruses) with subsequent enforcement of defense mechanisms. Considering the immune strengthening and lung protective roles of niacin, it could be prescribed as an adjunct treatment in COVID-19 patients [31,32].

Vitamin B5
Pantothenic acid has various properties including triglyceride and cholesterol-lowering properties and are involved in different processes such as wound healing, improvement of mental health and decreasing inflammation [24]. Even though the available studies regarding the impacts of pantothenic acid on the immune system are scant, this field of investigation is open for further studies [23].

Vitamin B6
Pyridoxal 5’-phosphate (PLP), active form of pyridoxine, is an essential cofactor in various inflammatory pathways [23]. There is an inverse relationship between PLP and plasma TNF-α and IL-6 in chronic inflammatory conditions. Enhanced utilization of PLP during inflammation leads to B6 depletion, indicating to the possible B6 deficiency in COVID-19 cases with high inflammation [23]. In elderly, cases with cardiovascular diseases and type-2 diabetes who are at higher risk for COVID-19 infection with poor outcomes, low PLP levels have been observed [23,33]). Enhanced risk of coagulopathy and dysregulation of immune responses have also been observed in COVID-19 infected patients [23]. In a recent study, modulated COVID-19 symptoms have been observed using PLP supplementation through decreasing pro-inflammatory cytokines, regulating immune responses, preventing hypercoagulability and maintaining endothelial integrity [34]. In fact, PLP diminishes abnormalities in platelet aggregation and clot formation [35]. Recently, it has been revealed upregulated IL-10 as a powerful immunosuppressive and anti-inflammatory cytokine using vitamin B6 (as well as B2 and B9), which is able to deactivate monocytes and macrophages and monocytes and prohibit T cells and antigen-
presenting cells [36]. Excessive secretion of pro-inflammatory cytokines and exaggerated T cell responses are common in COVID-19 patients. Possible contribution of PLP in dampening inflammation and cytokine storm in some COVID-19 patients [23].

Vitamin B9

Folate is vital for protein and DNA synthesis and is fundamental for adaptive immune response. Furin is an enzyme related to viral and bacterial infections and is considered as a promising target for infection treatment. Recently, furin inhibition by folic acid with subsequent prevention of binding by SARS-CoV-2 spike protein and prohibited cell entry and following virus turnover has been noted. Thus, folic acid could be applied for earlier management of COVID-19-related respiratory disease [37]. Stable and strong binding affinities against the SARS-CoV-2 by folic acid and its derivatives 5-methyl tetrahydrofolic acid and tetrahydrofolic acid have been illustrated using structure-based molecular docking [38]. Thus, folic acid might be applied as a therapeutic approach for management of COVID-19.

Vitamin B12

Vitamin B12 is fundamental for myelin synthesis, cellular growth, red blood cell synthesis, and rapid synthesis of DNA. Active vitamin B12 forms are adenosyl-, hydroxo-, and methylcobalamin. Vitamin B12 acts as regulator of gut microbiota and its low levels elevates homocysteine, and methylmalonic acid leading to enhanced production of reactive oxygen species, oxidative stress and inflammation [39]. Hyperhomocysteinemia is associated with activated platelet and coagulation cascades, endothelial dysfunction, megaloblastic anemia, decreased immune responses and disruption of myelin sheath integrity [23,40]. SARS-CoV-2 is able to interfere with vitamin B12 metabolism which could impair proliferation of intestinal microbes. Thus, symptoms of vitamin B12 deficiency such as elevated lactate dehydrogenase and oxidative stress, coagulation cascade activation, hyperhomocysteinemia, vasoconstriction and pulmonary and renal vasculopathy are possibly close to COVID-19 infection [23]. Besides, B12 deficiency can lead to gastrointestinal, respiratory, and central nervous system disorders [30]. Recently, methylcobalamin supplements have demonstrated to potentially diminish COVID-19-related organ damages [41]. COVID-19 patients who received supplemental vitamin B12, vitamin D and magnesium showed reduced severity of COVID-19 symptoms and diminished intensive care support and need for oxygen [42].

Vitamin C

Vitamin C (VC), is a common necessary nutrient with antioxidant properties. Despite its role in metabolism of human body including collagen biosynthesis and repair, iron absorption, energy transformation, adrenal catecholamine and steroid production [43], it also has antimicrobial properties and immunomodulatory functions especially in high concentrations [44]. Its role in immunomodulation passes through prohibition of nuclear factor kappa-B (NFκB) activation as a primary proinflammatory transcription factor playing a fundamental role in overall immunity, including genetic regulation of cytokines, chemokines, inflammatory mediators, adhesion molecules, and apoptosis inhibitors [45]. Vitamin C is able to inhibit production of tumor necrosis factor alpha (TNF-α) and IL-6 through a dose dependent manner [43]. It also diminishes GM-CSF signaling responses [46], acts as a regulator of cytokine redox-signal transduction in host defense cells and possibly have a role in controlling inflammatory responses. Besides, vitamin C at high doses could regulate proliferation and functioning of B cells, T cells and natural killer (NK) cells [43]. It might facilitate progression of cytokine storm and improve the host’s immunity. Moreover, vitamin C could inhibit oxidative stress with fundamental role in innate immune response against viral respiratory infection and contribute to the development of barrier dysfunction and lung injury [43]. Oxidative stress could also be involved in pathogenesis of COVID-19 [47]. Furthermore, vitamin C is able to repair oxidative damage in human bronchial epithelium through modulating regeneration of reactive oxygen species (ROS) and inflammatory expression with subsequent prevention of ROS-induced lung damage [43]. Vitamin C could indeed regulate clearance of alveolar fluid by enhancement of lung epithelial barrier functioning through transcriptional and epigenetic enhancement of protein channels which regulates alveolar fluid clearance [48,49]. Vitamin C might reduce symptoms related to acute respiratory distress syndrome (ARDS) which improves respiratory function. The antiviral effects of vitamin C passes through
inhibition of replication of poliovirus type 1, herpes simplex virus 1, and influenza A virus [50]. Intravenous vitamin C (IVC) achieves higher plasma concentration compared to oral vitamin C attributed to losses during tissue transport, intestinal absorption and renal reabsorption [51]. The safety and efficacy of intravenous high-dose vitamin C (HIVC) in critically ill cases have been evaluated through several clinical trials. A recent meta-analysis on cardiac surgery trials demonstrated shortened duration of mechanical ventilation in ICU patients and ICU length of stay after using vitamin C [52]. Indeed, vitamin C effects were significantly greater in patients with more severe illness [43]. Vitamin C significantly reduced levels of circulating injury biomarkers and scores of multi-organ failure in patients with ARDS or sepsis in a phase I trial using IVC [53]. The impacts were greater in high–dose group (200 mg/kg) vs. low–dose group (50 mg/kg). Moreover, no difference was reported regarding primary outcome of inflammation biomarkers and organ failure scores in a study conducted on patients with ARDS and sepsis, while a significant reduction in both 28-day mortality and long–term prognosis were also observed using 50 mg/kg IVC at patients undergoing mechanical ventilation. In a case report [54], administration of HIVC (200 mg/kg) was showed to successfully treat virus-induced ARDS in patients experienced a rapid recovery without any long–term sequelae after being on extracorporeal membrane oxygenation [43].

**Vitamin D**

Vitamin D, a steroid hormone which is endogenously produced by ultraviolet radiation on skin or exogenously from food or dietary supplements. Its insufficiency is a public health issue affecting over a billion people worldwide at all life stages [55]. There is a potential link between vitamin D deficiency and numerous diseases such as systemic infection [56]. Since vitamin D has an immune modulatory role, its insufficiency affects immune functions [57]. Vitamin D increases innate immunity through secretion of antiviral peptides [58,59] with the ability to improve mucosal defenses. In clinical studies, low serum levels of vitamin D were associated with development of acute respiratory tract infections such as epidemic influenza [56]. A recent meta-analysis on eight observational studies demonstrated a 64% enhanced risk of community-acquired pneumonia in cases with a serum vitamin D concentration <50 nmol/l [60]. Vitamin D insufficiency has been hypothesized to diminish respiratory immune function with subsequent increased risk of COVID-19 severity and mortality. Correlation between vitamin D levels and COVID-19 mortality and severity has been determined through some retrospective studies [56]. Antiviral effects of vitamin D with the ability to directly hinder viral replication besides its immunomodulatory and anti-inflammatory properties have been demonstrated recently [61]. In some patients, SARS-CoV-2 seems to primarily apply immune evasion process followed by cytokine storm and hyper reaction [62], as a known pathogenic process involved in development of acute respiratory disease syndrome (ARDS) [63]. SARS-CoV-2 applies angiotensin converting enzyme 2 as host receptor for its entrance into intestinal and alveolar epithelial cells [64]. Subsequent dysregulation of renin–angiotensin system might result in excessive cytokine production leading to prospective fatal ARDS [63]. Nutrient such as vitamin D demonstrated substantial roles in immune function. However, scant data are available regarding the role of vitamin D in prevention of COVID-19 infection and fatality [56].

**Vitamin E**

Vitamin E is a lipophilic antioxidant [65,66] which amplifies immune system and supplies integrity of T-cell membranes. It also diminishes the course of influenza virus infection [67]. The glutathione preserves membrane integrity through elimination of electrophiles derived from lipid peroxidation and inhibits protein cysteine oxidation. The main underlying mechanism related to antiferroptosis effect of vitamin E is reduction of ferric iron center in 15-lipoxygenase to inactive ferrous (Fe2+) leading to 15-lipoxygenase inhibition [68]. Lipoxygenase result in formation of lipid hydroperoxides using peroxyl radicals, while reaction of vitamin E with peroxyl radicals leads to prevention of lipid hydroperoxides formation. Afterward, GPX4, glutathione and other antioxidant agents are involved in detoxification of lipids to prohibit triggering of ferroptosis. Besides, vitamin E compensates for detoxification made by GPX4 in its deficiency. Indeed, alpha-tocopherol hydroquinone is a more potent antioxidant compared to alpha-tocopherol [69]. Furthermore, neurodegeneration due to vitamin E deficiency is associated with ferroptosis. The neural damages in COVID-19 patients might be partly
prohibited using vitamin E through an anti-ferroptosis mechanism. Thus, vitamin E is able to prevent toxic mechanisms behind iron serum levels such as ferroptosis through prohibition of peroxyl and lipoxygenase radicals. High doses of vitamin E (500 mg/kg) might act as a therapeutic medicine to inhibit ferroptosis and reduce ferroptosis injury to multiple organ such as liver, lung, heart, gut, nervous system and kidney in COVID-19 cases. It also leads to ablation of inflammation and viral clearance through modulation of T cells [68].

**Vitamin K**

Recently, anti-inflammatory actions of vitamin K, mediated through reduction of COX2, PGE2, and IL-6, have been focused [70]. Inflammatory cytokines, including C-reactive protein and IL-6 are increased in the setting of vitamin K deficiency due to intestinal malabsorption or interaction with medicines such as prolonged antibiotic therapy or anticoagulant. Besides anti-inflammatory actions, diminished coronary calcification and reduced risk of cardiovascular diseases have been reported to be associated with high intake of vitamin K [71]. Furthermore, vitamin K supplementation in experimental animal models was associated with a 50% reduction in rate of atherosclerotic calcification due activation of a specific matrix Gla protein (MGP) with the ability to remove abnormal accumulation from the arteries [72]. Vitamin K deficiency is clinically a frequent complication observed in admitted patients in adult intensive care units (ICU) with an incidence as high as 25% [73]. Low vitamin K status in COVID-19 patients was associated with poor disease outcome. Moreover, increased blood levels of desmosines, a biomarker of degradation of elastic fibers in the lung, was seen in the setting of low vitamin K status [74], indicative to the enhanced rate of elastic fiber degradation possibly due to low vitamin K status during severe COVID-19. Over degradation of lung’s elastic fibers could be related to lack of activated MGP, which is recognized to prevent calcification and following degradation of extracellular matrix proteins including elastic fibers [75]. MGP is known as the strongest inhibitor of calcification in arterial vessel walls that subsequently inhibit arterial calcification [74]. MGP is highly expressed in the lungs [76]. Degraded lung’s elastic fibers stimulate their calcification [77]. Local synthesis of MGP is stimulated by rising calcium level of extracellular matrix which prevents calcification of elastic fibers [75]. MGP is synthesized as dp-ucMGP which requires activation through vitamin K-dependent carboxylation to protect elastic fibers in extracellular matrix from calcification. These processes create or facilitate a pre-morbid vitamin K deficiency during severe disease course with enhanced vitamin K demands. Vitamin K is also required for carboxylation of antithrombotic proteins such as protein C and S in addition to carboxylation of prothrombotic proteins [78]. Protein C and prothrombotic proteins are exclusively hepatic proteins, while about half of protein S is synthesized extrahepatically and subsequently activated by vitamin K. Indeed, synthesis and activation of MPG is primarily extrahepatically [76]. During vitamin K deficiency such as acute illness with enhanced vitamin K usage, vitamin K is used primarily for hepatic carboxylation of prothrombotic coagulation factors and to a lesser extent for extrahepatic carboxylation of vitamin K-dependent proteins such as antithrombotic protein S and MGP [79]. This could induces a prothrombotic state with enhanced blood clotting in peripheral tissues as could be observed in COVID-19 patients [80].

**Minerals**

**Calcium**

Calcium is a vital ion for cellular processes and metabolic and signaling pathways playing a fundamental role in viral survival and virulence [81]. Hypocalcemia is prominent in COVID-19 patients with a direct relationship with enhanced likelihood of hospitalization, ventilation, admission to ICU, longer hospitalizations, increased D-dimer levels, disease severity and increased mortality in COVID-19 patients [82]. Since there are some limitations in published surveys in this regards [83], a
comprehensive study is essential in this area. Therefore, development of hypocalcemia during SARS-CoV-2 infection with severe clinical course, is not unexpected. Thus, degree of hypocalcemia could be a robust indicator of disease intensity and should be considered by physicians during the treatment process [82].

**Zinc**

Zinc, as the second most abundant trace element after iron in human body, is a common element for both prophylactic and curative applications in COVID-19 clinical studies. Zinc is fundamental for multiple cellular purposes such as maintenance of immune health. In fact, “Zinc proteome” is believed to possess around 3000 proteins [84] including about 750 Zinc finger transcription factors which are deeply implicated in inflammation and homeostasis. The history of zinc deficiency identification in human goes back to more than 56 years ago. Zinc deficiency has been associated to hypogonadism, immune dysfunction, growth retardation, and cognitive impairment [85]. Zinc also plays a fundamental role in antiviral immunity [86,87]. There are specialized reviews regarding essential role of zinc in both human health maintenance (including zinc transporters and homeostasis) and in nonviral/viral diseases [85]. Although abundant clinical trials are going on against COVID-19 pandemic, there is still scientific curiosity about these trials [88].

**Iron**

COVID-19 is manifested by various complications as well as biochemical and physiological alterations. These include hemoglobin damage, hyper coagulation state and dysregulation of iron homeostasis including iron overload that is likely a key factor in pathogenesis of COVID-19 [89,90]. Liu et al. (2020) indicated hemoglobin attack as the key pathogenic molecular step in COVID-19 leading to porphyrin dissociation from iron and subsequent releasing of iron into the circulation [89]. Therefore, hemoglobin loses its oxygen binding capacity which hinders its delivery to major organs that subsequently is coupled with development of rapid multi-organ failures. Besides, the released free iron into circulation might lead to iron overload resulting in oxidative damage to the lung and other organs. Iron overload could lead to inflammation and dysfunction of immune system [91,92]. These dictate enhanced uptake and storage of iron in iron-binding proteins. Moreover, it is supported by enhanced ferritin level in COVID-19 patients [89]. Iron overload results in blood hyper viscosity with diffuse and recurrent micro and macro circulatory thrombosis that could explain unexpected deterioration and subsequent death in some instances [89,93].

**Selenium**

Selenium (Se) exerts a fundamental and complex role in the immune system, especially in oxidative stress processes via NADPH, Thioredoxin, and TrxR [94,95]. Furthermore, Se deficiency is associated with susceptibility to viral RNA infections and poor outcomes. In addition, obesity (BMI > 30 kg/m2) is now identified as major risk factors for severe COVID-19 [96]. This important risk factor could contribute to the development of uncontrolled epidemic in Mexico and USA where 30% and 42% of the population are obese, respectively [97,98] with a relatively younger average age of hospital admission due to COVID-19 infection compared to European cohorts [99]. Worse outcomes of COVID-19 [100] are characterized to oxidative stress and an underlying low-grade inflammation such as metabolic syndrome and obesity [96]. Adipose tissue, a distinct endocrine organ, is capable of synthesizing enormous cytokines such as TNF-alpha, IL-6 and IL-8 [101]. Obesity is characterized by enhanced infiltration of macrophages in adipose tissue as a SARS-Cov-2 reservoir [102]. These macrophages can be locally activated by the virus resulting in production of deleterious reactive oxygen/nitrogen species if not counterbalanced by redox homeostasis [96]. Notably, Se attenuates expression of pro-inflammatory genes in the macrophages [103]. The miR-185-5p which is a Se sensitive microRNA was recognized to control feedback expression of selenoproteins in obese cases through regulation of six of eight
Glutathione Peroxidase [104]. Indeed, obesity is associated with reduction of Glutathione Peroxidase 3 (GPx 3) activity in adipose tissue [105]. Hauffe et al. demonstrated enhanced GPx3 activity and insulin receptors/sensitivity in adipose tissue of obese mice following sodium selenite supplementation [106]. Furthermore, obesity is usually accompanied by impaired cardiovascular functioning including arterial stiffness and endothelial cell dysfunction favoring endothelial infection by SARS-CoV-2 [107]. Besides, cardiac changes and prothrombotic propensity in obesity are parallel with enhanced rate of cardiovascular events in COVID-10 cases admitted in intensive care unit [96]. These pathologies exhibit inflammation and oxidative stress along with low Se level and endothelial dysfunction [96,108], and the above mentioned relationships between RNA viruses and Se suggest a possible joint between Se and SARS-CoV-2 infection. Indeed, older subjects are consistently more vulnerable to COVID-19 infection with atypical clinical manifestations and enhanced risk of significant complications and mortality compared to healthy adults [109,110]. Average case fatality ratio for subjects older than 60 years driven from international data is reported to be of 4–5%, and this value for subjects > 80 years is probably up to 14.8% [96,111]. Numerous factors could explain this including aging related frailty, multiple chronic co-morbidities and blunted immune response along with a degree of malnutrition [96]. Furthermore, senescent fibroblasts are four times more prone to oxidative stress compared to young cells and use more Se [112]. Indeed, addition of high concentration of Se to these cells is associated with over activity of Glutathione Peroxidase and reduced amounts of reactive oxygen species [112]. Low or borderline levels of Se in old ages influences longevity and mortality rate [96]. Se deficiency was reported in 71% of Sweden elders admitted to Intensive Care Unit [113]. Se supplementation was associated with significantly reduced infection in institutionalized elderly subjects [114]. Besides, Se supplementation for 4 years in Swedish elderly peoples diminished risk of cardiovascular mortality by more than 40%, the long-lasting effect even 12 years later [96].

**Amino acids**

Amino acids are essential for synthesis of numerous important molecules such as hormones and neurotransmitters which ensure proper metabolic functioning and immune responses against diseases through being used in cellular redox status, lymphocyte proliferation, gene expression, production of lymphokines, cytokines, antibodies and cytotoxic substances and activation of natural killer cells, B and T lymphocytes, and macrophages; various diseases including malignancies (hepatocellular, breast, lung and colon cancer, cervical squamous epithelium cell carcinoma, cervical intraepithelial neoplasia and renal cell carcinoma), kidney diseases, metabolic diseases (metabolic syndrome, diabetes mellitus, nasal polyposis, and sepsis [115]. Insufficient data is available regarding the way that serum amino acid profile through which plays a significant role in making immune responses in SARS-CoV-2 infection. Increase and decrease in amino acid levels could be a possible significant prognostic factors in some diseases [115,116]. Clinical healing could develop through replacement of decreased amino acids in significant diseases as demonstrated in some clinical studies [115]. Detection of both cytokines and amino acid profiles might be beneficial for estimation of possible organ damages and development of diverse therapeutic strategies [115,117]. Previous studies have also focused on the importance of serum amino acids during infections such as COVID-19 [115]. Determining amino acid profile in such acute conditions is fundamental for both patient diagnosis and supplementation [118]. Thus, new investigations focusing on serum amino acid profile and its alterations are required [115].

**Coenzyme Q10**

Frederick Loring Crane discovered Coenzyme Q10 (CoQ10) in 1957. CoQ10 is located within the inner membrane of mitochondria and is an integral part of mitochondrial respiratory chain transporting electrons from complex I and complex II to complex III. It is also the key part of ATP production in mitochondria. FL Crane demonstrated its effects through a plasma membrane to autism [119,120]. CoQ10 is primarily synthetized endogenously from tyrosine in the endoplasmic reticulum by
mevalonate pathway using vitamins C, B2, B6, B9, and B12 and transported into plasma by low-density lipoproteins [119]. Since now, there are nine known genes to be involved in endogenous biosynthesis of CoQ10 known as “COQ genes” of coenzyme Q2-polyprenyltransferase (COQ2), coenzyme Q4 (COQ4), coenzyme Q6–monooxygenase (COQ6), coenzyme Q7–hydroxylase (COQ7), coenzyme Q8A (COQ8A), coenzyme Q8B (COQ8B), coenzyme Q9 (COQ9), prenyl diphosphate synthase, subunit 1 and 2 (PDSS1, PDSS2). Biosynthesis of CoQ10 involves several metabolic reactions including decarboxylation, methylation and hydroxylation [121]. Its low levels might be due to impaired endogenous synthesis of CoQ10 or mutation of one or more COQ genes or its over utilization. Significantly lower serum levels of CoQ10 were observed in cases with chronic kidney disease, acute influenza infection, infertile men, in patients with cardiomyopathy and in endomyocardial biopsies of post heart transplantation samples [119,122]. CoQ10 has the potential to reduce fatigue and pain in fibromyalgia patients [123]. There is a significant association observed between CoQ10, IL-2 and TNF-alpha in patients with septic shock [124]. Lower levels of CoQ10 due to statin therapy may also induce mitochondrial dysfunction, myopathy, fatigue and myalgia [119]. Suggested roles of CoQ10 in cardiovascular disease have been discovered by another research group [119,125]. Targeted therapy with CoQ10 for mitochondrial disturbances has also documented [126]. Beneficial impacts of CoQ10 pass through its antioxidant activity, and its impacts on production of cytokine by human peripheral blood mononuclear cells (PMBC) could modulate human immune functions. Incubation of PMBC with variable dosages of CoQ10 for 24 hours was associated with reduced secretion of TNF-alpha and IL-2 in those cells [127]. Therefore, CoQ10 diminishes inflammatory cytokines and biomarkers [128].

**Omega-3**

Polyunsaturated fatty acids (PUFA) are substrates for anti-inflammatory, pro-inflammatory, and specialized pro-resolving lipid mediators (SPM) [129]. Omega-6 PUFA arachidonic acid (AA) is substrate for cyclooxygenase and lipooxygenase pathways leading to generation of leukotrienes and prostaglandins, respectively, which all called as eicosanoids. In contrast, docosahexaenoic acid (DHA) and omega-3 PUFA eicosapentaenoic acid (EPA) act as substrate for pro-resolving SPM. PUFA can also be metabolized into respective epoxides by cytochrome (CYP) P450 epoxygenases which regulate inflammatory reaction. Decreased omega-6 PUFA and enhanced omega-3 PUFA represent a probable mean to skew immune response toward modulation of inflammation [130]. Thus, AA is able to give rise to pro-resolving lipoxins favored by CYP450-derived AA epoxides [131]. Indeed, anti-inflammatory actions of adrenic acid which is another omega-6 PUFA has been recently ascribed [132]. A general nutritional state in favor of inflammation is made in the setting of low omega-3 to omega-6 ratio [130] and ratios of respective lipid mediators such as resolvin to leukotriene ratio [133]. Omega-3 PUFA reduces relative availability of AA for synthesis of pro-inflammatory eicosanoid and formation of leukotriene [134] which all results in diminished eicosanoid storm in COVID-19 [130].

**Probiotics**

Entry point of SARS-CoV-2 is often the respiratory passage, leading to significant acute respiratory illness. Its impacts on gastrointestinal system are well known. Affinity of SARS-CoV-2 to the respiratory and gastrointestinal epithelium is due to the receptor angiotensin-converting enzyme-2 (ACE-2) in lungs alveolar epithelial type II cells and brush border of gut enterocytes [135]. Presence of SARS-CoV-2 viral RNA in fecal samples of COVID-19 cases [136] is a clue toward their gut inhabitation. Gut co-infection impairs gut physiology that eliminates “Good bacteria” to make an imbalance between good and bad bacteria (dysbiosis) [137]. Further complications might shoot up, unless this gut dysbiosis induced by COVID-19 is set by probiotic supplementation [138]. The entrance of SARSCoV-2 into the gut along with respiratory tract invasion infects gut epithelium which impacts on its integrity and gut microbiome [139]. The sentinel cells, dendritic cells, mast cells and macrophages promote first-line defense following viral entry. Viruses bind with sentinel cells’ receptors through specific receptor
binding molecules also known as pathogen-associated molecular pattern [PAMPs]. Since PAMPs are virus specific, their receptors in sentinel cells need to be complimentary [137]. Masked PAMPs in the setting of COVID-19 infection leads to escape of viruses from surveillance of sentinel cells. Besides, virus recognizing lymphocytes [B-cells, T-cells and natural killer (NK) cells] which secret antibodies against viruses are diminished sharply and affect immunity [140]. However, probiotics are able to stimulate cytokines and other factors with the capacity to trigger innate and adaptive immunity (Anwar et al., 2020). Macrophages and T helper cells initiate uncontrolled release of cytokines due to SARS-CoV-2 infection. Cytokine storm results in heavy inflammation-associated acute respiratory distress syndrome, which is most often fatal [141]. Probiotic supplementation might be useful due to the ability to induce Th1 and Th2 cells and promote anti-inflammatory actions and subsequently diminishes lungs' viral load [142]. Moreover, supplementation with probiotics along with zinc and vitamin D diminishes Th1/Th17 T cells and production of pro-inflammatory cytokines, such as TNFa, IFNc, IL-1, IL-6 and IL-8 induced by Th2 cells and inflammation in ling and gut in the setting of COVID-19 infection [143]. The gut probiotics consortium is often low among the older and immune-compromised patients and those cases enduring severe impact of COVID-19 disease [144]. Probiotic anti-inflammatory properties could regulate the above mentioned inflammatory reactions through co-supplementation of personalized functional foods with probiotics [145]. As a therapeutic solution for COVID-19, attention is mainly focused on appliance of effective nutritional therapy. Probiotics are highlighted by several recent reviews as an adjunct alternative among other available therapies for the treatment of this novel coronavirus [137]. Besides, some probiotics weaken viral replication through playing role in purine management that could help in treatment of COVID-19 [146]. Secretion of protein p40 by probiotic L. rhamnosus GG has been proved by several experimental studies, which reduces IFNc, IL-6, TNF, and chemoattractant preventing inflammation in gut epithelium [147]. A cocktail, f L. casei L. reuteri, L. acidophilus, and other probiotics stimulated dendritic cell and down-regulated Th1 cells, Th2 cells and other factors inducing gut and lung inflammation through gut-lung axis link [140]. Since development of COVID-19 vaccines takes time, alternative measures including immunity-boosting nutritional strategies including probiotics and prebiotics seems beneficial. Probiotics regulate gut-lung axis and produce numerous antiviral offensive and defensive mechanisms through innate and adaptive immunity [138]. A review of gastrointestinal disorders in COVID-19 cases emphasizes requirements for glorify gut using probiotics to resolve gut dysbiosis as a major impact of COVID-19 [137].

Diet
Nutrition might play a role in immune defense against COVID-19. Differences in dietary status in European countries could explain partly some of the differences observed in COVID-19 across Europe [148]. Foods containing potent antioxidants are mainly consumed in low-death rate regions including European countries, Taiwan and Korea [148]. Another considered factor could be food availability. Alterations in food availability has particularly changed alimentary habits—promoting sugar-enriched, vitamin deficient foods—and has become one of the reasons led to obesity epidemic. These foods came from centralized farms located in selected world’s areas are distributed around planet and elongate the supply chain of food. Enhanced rate of insulin resistance and metabolic syndrome are health outcomes of long supply chain of food [149]. Thus, short supply of food is more common in rural areas which have lower death toll and better toleration of COVID-19 pandemic. These considerations could partly explain lower death rates in Southern Italy vs. Northern parts [148].

Nutrition
Nutritional intervention for COVID-19 has been recently discussed extensively. Possible therapeutic impacts of certain food properties with the ability to treat COVID-19 have been discussed. Most available data are derived from case studies, observational studies, reviews, systematic reviews, clinical trials, laboratory diagnosis, and general nutritional guidelines [150]. Presently, no definite
recommendations are available in terms of nutritional therapeutic and medical guidelines to treat COVID-19. The public shared nutrition remedies for prevention or treatment of this virus are without any support from evidence-based studies. Most worldwide dietitian association societies have emphasized on getting healthy eating habits and there are general guidelines for preparation and storage of foods. No specific food has been noted by the American, Canada and Australia Dietetics Association to prevent and cure COVID-19 infection. These guidelines specify good hygiene throughout lockdown and quarantine periods. UNICEF [150] and WHO [151] encourage healthy eating guidelines throughout lockdown and quarantine period of COVID-19. The Food and Drug Association (FDA) has also noticed that COVID-19 is not foodborne. For critically ill patients, ESPEN and ASPEN provided nutrition recommendations derived from convincing evidence-based guidelines [150]. Medical nutrition therapy focuses mainly on the malnutrition pre- and post- COVID-19 diagnosis. Thus, being aware of personal nutritional habits and following balanced and healthy dietary habits containing high amounts of vitamins, antioxidants and minerals is essential during this period. Several investigations showed the boosting of immune functions using micronutrients with antioxidant properties derived from vegetables and fruits such as beta-carotene, vitamin C and vitamin E. This pandemic has emphasized on getting healthy life and good nutrition and a healthy life as the key element for strengthening immunity [150]. Although consumption of a well-balanced diet could ensure normal functioning of immune system, no specific food, nutrient or supplement will ‘boost’ it beyond its average level. Thus, prevention and minimization of symptoms during severe illness phases is more effective than its treatments [150].

**Impact of nutrition on the susceptibility of COVID-19 and its long-term consequences**

Sufficient intake of vitamins is an essential factor COVID-19 patients. Vitamins have diverse properties including immune-modulatory, anti-microbial, antioxidant and anti-inflammatory properties which could be useful for the prevention of diseases and infections (mainly viral infections). Although their anti-inflammatory and immunomodulatory properties are noticeable, some unique antiviral mechanisms [152]. Vitamin D is supposed to develop (IFN)-based therapy and CD8+ T cells’ responses against viral infections [1]. The vitamin is leading to the synthesis of antimicrobial peptides, induction of autophagy, blockage of viral entrance, suppression of Toll-like receptors and induction of virus specific CD8+ T cells. Sufficient vitamin D level results in under expression of dipeptidyl peptidase 4 (DPP-4 or CD26) which interacts with the S1 domain of spike glycoprotein taking part in adhesion of SARS-CoV-2 to epithelial cells [152]. Another important fact is inhibitory role of SARS-CoV-2 by its prominent binding to spike protein. B9 and B12 directly prevent pathogenicity of SARS-CoV-2 by binding to non-structural protein 3 (NSP3) and furin, respectively. Furin-mediated cleavage of viral spike is essential for its entry into the host cell. Viral NSP3 encodes; NTPase, N-terminal proteinase (in charge of polyprotein cleavage), and C-terminal helicase [153,154]. Antiviral activity of E, C, and A vitamins have been proved against respiratory viruses, passing through immunomodulatory mechanisms [152].

Trace elements are another noteworthy nutritional factor with antiviral properties. The major function responsible for this property is their immunomodulatory properties. Some trace elements exert a fundamental role in induction of long-term consequences SARS-CoV-2 infection [155]. Survivors of SARS-CoV-2 might develop lung fibrosis. Release of TGF-β is reduced by Mg supplementation which consequently result in collagen deposition and the development of lung fibrosis [156]. Several lines of evidence suggest significant suppression of systemic inflammatory responses against SARS-CoV-2 infection using selenium supplementation which could diminish the risk of formation of blood clot in covid-19 cases [157]. Zn is another trace element which prohibit SARS-CoV-2 through reduction of viral entry following prevention of virus into the host cell membrane. In other word, RNA dependent RNA polymerase (RdRp) is inhibited by Zn [155].

Fatty acids exert potent immunomodulatory that could be beneficial for covid-19 infection. Omega-3 fatty acid, a natural product, is recognized by their anti-inflammatory effects. Sufficient levels of omega-3 reduction of CRP as well as inflammatory markers. Anti-inflammatory effects related to omega-3 are able to prevent pro-inflammatory cytokine storm of covid-19 [158]. Omega-3 and -6
polyunsaturated fatty acids are supposed to not only mount immune responses but also prohibit the development of inhibition and subsequent tissue damage [159].

Coenzyme Q10 (CoQ10) represents anti-platelet and antioxidant properties which makes it a potential candidate for the treatment of covid-19. Wang et al. observed enhanced in vitro ROS level and platelet aggregation by SARS-CoV-2 spike proteins. CoQ10 was able to reduce ROS level and aggregation of platelets induced by viral spike protein [160]. TNF-α, CRP, IL-6, and other inflammatory cytokines are modulated by this potent anti-inflammatory compound. It is also able to pass through Brain Blood Barrier (BBB) and might attenuate BBB damage and CNS inflammation. Indeed, long-term consequences of covid-19 infection could be prevented using Coenzyme Q10 supplementation [161]. Diverse natural and nutritional compounds could mount host immune responses and prevent COVID-19 infection in different steps. They are also able to prevent the development of comorbidities and deleterious consequences induced by COVID-19.

Different natural and nutritional compounds may prevent covid-19 through two ways. First, they can demonstrate antiviral activity with mounting host immune response and inhibition of covid-19 in various steps (entrance, replication, and etc.). They also may prevent the COVID19-induced morbidities with a protective activity against the deleterious consequences of the disease.

Limitations

It was obligatory to limit the scope of our study to the most important nutritional elements. Indeed, this is incomplete, and the role of gut microbiota is another relevant area of interest. Shortage of sufficient cohort studies is another important issue. Estimated attributable risks could potentially change during time with the prevailing SARS-CoV-2 infection rate. Besides, it was not possible for us to thoroughly cover all factors with the ability to impact the relationship between nutritional state and disease progression. Interpretation of eligible literature is obligatory limited to the context of the original studies. In addition, a wide range of factors preclude extrapolation to the wider population. Thus, factors such as genetic polymorphisms, their frequency and their impact in different populations, age, gender, environment, access to health care, hemoglobinopathies, and other underlying political and economic factors which determine nutritional vulnerability should be considered. The last but not least, most chosen studies were at a high risk for bias due to the selection of hospital-based samples in their conducted studies and taking data related to patients records from secondary recordings. Presence of confounding factors such as gender, age and underlying comorbidities which were not applied in most of the studies, is also of great importance. These factors are determinant of the severity of COVID-19.

Conclusion

This article provides comprehensive focal point of evidence on nutritional recommendations to defeat COVID-19. We highlighted fundamental facts in this field from our perspectives in this scoping review. There is considerable information regarding food and nutrition reducing risk of COVID-19 which also helps patient recovery. Moreover, evidence derived from most of these recommendations should be evaluated in detail. Indeed, health care professionals should be cautious when advising this information to the public. It is highly unlikely that an individual nutrient or food had immune boosting capability or being able to prevent COVID-19 infection. The best strategy during COVID-19 era, is healthy eating habits based on the principles of moderation, balance and variety.

Conflict of interest

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Authors’ contributions

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