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Review

The Role of Diet and Supplements in the Prevention and Progression of COVID-19: Current Knowledge and Open Issues

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ABSTRACT: A healthy diet and dietary supplements have gained attention as potential co-adjuvants in managing and preventing coronavirus disease 2019 (COVID-19). This paper critically reviews the current evidence regarding the impact of diet and supplements on the prevention and progression of COVID-19. According to available data, a healthy diet and normal weight are considered protective factors. Regarding dietary supplementation, the most robust results from human studies are for vitamin C, which appears to decrease inflammatory markers and suppress cytokine storm. A small, randomized trial showed that a high dose of vitamin D significantly reduced the need for intensive care unit treatment of patients requiring hospitalization for COVID-19. According to retrospective human studies, there is limited evidence for vitamin E and selenium supplements. Animal studies have investigated the effects of green tea and curcumin. Xanthohumol and probiotics, interesting for their antiviral, anti-inflammatory, and immunoregulatory properties, need formal clinical study. In summary, there is promising evidence supporting the role of diet and supplements as co-adjuvants in the treatment of COVID-19. Further studies and properly designed clinical trials are necessary to draw more robust conclusions; however, it is not unreasonable to take a pragmatic approach and promote the use of appropriate diet and supplements to counter the effects of COVID-19, ideally with a mechanism to assess outcomes.

Keywords: COVID-19, diet, dietary factors, nutrition, supplements

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), belonging to the family Coronaviridae, is responsible for the highly contagious coronavirus disease 2019 (COVID-19) outbreak, which first emerged in China in December 2019 spread across the globe and determined a pandemic (Huang et al., 2020); by October 2021, SARS-CoV-2 had infected more than 180 million of the world's population, killing more than 3.5 million, with an approximate 2% mortality rate worldwide (Dong et al., 2020). Thus, COVID-19 has become our generation's most serious public health crisis, profoundly impacting the global economy and geopolitics.

COVID-19 is a multi-system, multi-organ disorder whose clinical scenario may range from asymptomatic cases to severe pneumonia resulting in acute respiratory distress syndrome (ARDS) to death. Although all age groups are susceptible to the virus, the coexistence of advanced age and co-morbidities, including arterial hypertension, chronic renal insufficiency, diabetes, hyperlipidemia, and obesity, has been associated with a worse prognosis (Guan et al., 2020).

No agent has yet to receive approval from the United States Food and Drug Administration to treat severe COVID-19, but randomized trials of many therapeutic candidates are ongoing. Available treatment options include steroids such as dexamethasone, which exert an anti-inflammatory effect, and antivirals that target viral replication. Currently, only remdesivir has been reported to be effective in shortening the time to recovery of hospitalized patients with COVID-19 (Beigel et al., 2020). There was initial publicity surrounding hydroxychloroquine (often in association with macrolides) targeting vi-

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ral entry by endocytosis; however observational data and randomized clinical trials lacked compelling clinical evidence of efficacy (Chorin et al., 2020). Further trials analyzing the potential therapeutic effect of hydroxychloroquine are ongoing. In some patients, especially with severe forms of COVID-19, there are increasing levels of inflammatory biomarkers resulting in hyperinflammation due to cytokine release syndrome. Cytokines, particularly interleukin (IL)-1 and IL-6, appear to contribute to such systemic hyperinflammation. Consequently, anti-cytokine therapies may offer an important treatment option for patients with COVID-19 (Buckley et al., 2020). Compared to other coronaviruses and respiratory viruses, SARS-CoV-2 induces a weak type I, II, and III interferon (IFN) response and strong activation of the IL-1/IL-6 pathway, which the direct activation of pro-inflammatory routes might explain. The exuberant IL-1/IL-6 response to SARS-CoV-2 appears to contribute to symptoms and outcomes. Based on these observations, prospective randomized trials evaluating different anti-cytokine therapies in adults with COVID-19 are underway.

Extraordinary efforts have led to the development of vaccines, and by July 2021, 3,282,358,034 vaccine doses have been administered (Dong et al., 2020). Vaccines to prevent SARS-CoV-2 infection are considered the most important approach to fighting the pandemic. By the end of 2020, several vaccines had become available for use in different parts of the world, including over 40 candidate vaccines in human trials and over 150 in preclinical trials. Although phase III clinical trials have been completed and others are ongoing, issues remain unsolved, including how long the vaccine-derived immunity might last, whether there is a need for additional booster doses, their timing, and if vaccines will be effective against variant forms of the virus. Finally, the impact on community transmission remains unclear.

In addition to the development of drugs targeting different aspects of the viral disease, the pharmacological properties of natural compounds and dietary supplements have gained increasing attention as potential co-adjuvant therapeutic approaches. Oxidative stress and impairment of the immune system, in addition to existing co-morbidities, contribute to many of the complications associated with COVID-19 infection. Natural compounds have been shown to exert antiviral, antifibrotic, antioxidant, anti-inflammatory, and immunomodulatory actions, which might synergize as prophylactic or supportive agents to reduce some typical COVID-19 symptoms (Thota et al., 2020). Furthermore, a healthy nutritional status has been reported to support immune function and prevent the onset of severe infection. This suggests the potential role of a healthy diet together with dietary supplements as co-adjuvants in treating COVID-19 and possibly even in the prevention of severe forms of the disease. However, evidence in the literature supporting this hypothesis is inconclusive.

Here, we aimed to critically review the current evidence related to the impact of diet and different dietary components on the prevention and progression of COVID-19.

HEALTHY DIET

A diet rich in fruits and vegetables and low in refined sugar and calorie-dense processed foods is essential to health (Belanger et al., 2020). The overall prevalence of obesity among American adults is 42.4%, resulting from a poor diet, low fiber, high fat, salt, and sugar. Healthy diet disparities are often the consequence of socioeconomic, educational, and environmental disadvantages. Lower socioeconomic conditions may necessitate utilizing cheaper energy-dense processed foods, increasing the risk of being overweight or obese, which are both associated with a dismal prognosis for COVID-19 (Bhoori et al., 2020; Gao et al., 2020a; Guan et al., 2020). The coexistence of advanced age and co-morbidities, including arterial hypertension, chronic renal insufficiency, diabetes, hyperlipidemia, and obesity, has been associated with a severe disease course and, consequently, a worse prognosis (Guan et al., 2020).

Obesity is also linked to many chronic illnesses, including cardiovascular disease and diabetes, which significantly contribute to mortality associated with COVID-19. It is pertinent that obesity is a state of chronic, though low-grade, systemic inflammation that may predispose patients to a “cytokine storm”. Moreover, adipose tissue may serve as a reservoir for SARS-CoV-2, according to Ryan and Caplice (2020). They provided a theoretical framework whereby systemic viral spread, entry, and prolonged viral shedding in inflamed adipose tissue may increase immune responses with cytokine cascade amplification. Adipose tissue might represent a relevant source for local and systemic enrichment of cytokines, which could be responsible for increased COVID-19 mortality.

Based on these observations, it is clear that a healthy diet and normal weight are generally associated with a better disease course. Therefore, as a general rule to boost immune function, individuals might be recommended to consume high amounts of fiber, whole grains, unsaturated fats, and antioxidants rather than foods rich in saturated fats and refined sugar.

SUPPLEMENTS

Natural compounds with respect to dietary supplements have gained increasing attention as an alternative and co-adjuvant therapeutic approach to several diseases. This

information may support a potential role for these compounds in COVID-19; however, evidence is preliminary, and only a few clinical studies specific to SARS-CoV-2 infection are available.

Vitamins

***Vitamin C*:** Vitamin C is a water-soluble vitamin that acts as both an antioxidant and a cofactor for regulatory enzymes through the production of cortisol, catecholamines, and vasopressin. Vitamin C plays a key role in both the innate and the adaptive immune systems and has been reported to exert antioxidant functions. In fact, vitamin C detoxifies exogenous radical species that have entered cells or arisen within cells due to excess superoxide (O_2^-) generation via mitochondrial metabolism, nicotinamide adenine dinucleotide hydrate oxidase, xanthine oxidase, or uncoupled nitric oxide (NO) synthase (May and Harrison, 2013).

In humans, supplementation with vitamin C improves the immune system and reduces the risk, severity, and duration of different infectious diseases, including the common cold, pneumonia, and tetanus. However, the actual clinical relevance and optimally efficacious dose of vitamin C for preventing and treating infections are still unknown. Intravenous treatment with high dose vitamin C (more than 1 g/kg) has shown beneficial effects on sepsis and septic shock (Marik et al., 2017; Fowler et al., 2019). Literature data showed that combining vitamin C, hydrocortisone, and thiamine prevented organ dysfunction and reduced the mortality rate associated with sepsis and severe pneumonia (Marik et al., 2017; Kim et al., 2018b). Furthermore, vitamin C has been reported to exert antiviral effects, and its supplementation is generally recommended against the common cold (Ran et al., 2018). The proposed mechanisms underlying these antiviral effects include the increased production of antiviral cytokines (IFN-α/β), free radical formation, or direct inhibition of virus binding to cells (Bae and Kim, 2020).

In the absence of a specific therapeutic protocol, it has been hypothesized that vitamin C could attenuate excessive immune responses in patients with COVID-19. Those affected by COVID-19 have an increased inflammatory status with consequent higher levels of molecules related to inflammation, such as NO, NO_3, C-reactive protein, and lactate dehydrogenase, in the blood compared to healthy individuals (Buckley et al., 2020). COVID-19 infection appears to be responsible for activating macrophages, which produce a considerable amount of inflammatory molecules and NO. Oxidative stress and NO contribute to the establishment of an inflammatory cascade that can be responsible for patient mortality. In a recent study (Alamdari et al., 2020), the oral or intravenous administration of vitamin C with methylene blue and N-acetyl cysteine was associated with a significant decrease in the blood levels of NO_3, methemoglobin, C-reactive protein, and lactate dehydrogenase in four out of five patients as well as improved survival. Based on these preliminary findings, a larger clinical trial has been designed and is currently ongoing (NCT04370288). According to another study (Hiedra et al., 2020), vitamin C treatment was associated with decreased inflammatory markers, such as ferritin and D-dimer, and a trend toward decreasing oxygen requirements. In this study, 17 patients with a severe disease course requiring a 30% or more fraction of inspired oxygen received intravenous vitamin C 1 g every 8 h for 3 days. The inpatient mortality rate in this series was 12%, with a 17.6% intubation and mechanical ventilation rate.

In an open-label clinical trial (Thomas et al., 2021), outpatients with SARS-CoV-2 infection were randomized to receive either 10 days of oral ascorbic acid 8,000 mg, Zn gluconate 50 mg, both agents, or standard of care. Those who received the standard of care achieved a 50% reduction in symptom severity scores at a mean of 6.7 days compared with 5.5 days for the ascorbic acid arm, 5.9 days for the Zn gluconate arm, and 5.5 days for the arm that received both agents. No serious adverse effects were associated with the administration of the supplements. However, this study is limited by the small sample size (214 patients) and the lack of a placebo control.

A Chinese clinical trial (Zhang et al., 2021) was conducted to investigate whether intravenous vitamin C (24 g/d) could suppress cytokine storms caused by COVID-19, improve pulmonary function, and reduce the risk of ARDS in COVID-19. The study found no differences between arms for mortality, the duration of mechanical ventilation, or the change in median sequential organ failure assessment scores. However, statistically significant improvements in oxygenation from baseline to day 7 in the treatment arm were reported.

Despite promising clinical studies, further clinical trials are needed to fully delineate the effects of vitamin C on COVID-19 infection and recommend its supplementation. Thus far, based on the lack of clinical data, the United States National Institute of Health has been unable to recommend vitamin C to treat COVID-19 in critically and non-critically ill patients.

***Vitamin D*:** Vitamin D is a steroid hormone produced endogenously with the effect of ultraviolet radiation on the skin or available from exogenous food sources and dietary supplements. In addition to its well-known role in bone metabolism, low vitamin D has been associated with an increased risk of developing various pathologies, including cancer, infectious diseases, immune dysfunction, and depression (Thacher and Clarke, 2011).

After binding its nuclear receptor, the active metabolite of vitamin D [i.e., 1,25-dihydroxyvitamin D (1,25 (OH)2D)3 or calcitriol] influences gene transcription, ex-

erting several effects on the immune and inflammatory response. Antigen-presenting cells, such as macrophages and dendritic cells, synthesize the active form of vitamin D, 1,25(OH)2D, from its precursor 25-hydroxyvitamin D (25-OHD) via the enzyme 1α-hydroxylase (CYP27B1). In addition, the epithelium, the main barrier between the environment and the body, expresses CYP27B1. In the case of vitamin D deficiency, immune responses are impaired as less 25-OHD is available for synthesizing 1,25(OH)2D, leading to the impairment of innate immune functions (Hewison, 2010). Vitamin D has been reported to exert antimicrobial activity through both the generation of NO (Gough et al., 2017) and O_2^- (Hübel et al., 1991) and the expression of the antimicrobial proteins cathelicidin and β-defensin 2, which both stimulate the expression of antiviral cytokines and chemokines, including IFN-β, IFN-γ, myxovirus resistance protein A, double-stranded RNA-activated protein kinase, RNase L, and nucleotide-binding and oligomerization domain-2, involved in the recruitment of monocytes/macrophages, natural killer cells, neutrophils, and T cells (Kim et al., 2018a). Vitamin D also modulates helper T cell responses as it reduces T helper type 1 (Th1) immune responses and induces Th2 responses (Boonstra et al., 2001).

Levels of 25-OHD reportedly inversely correlate with acute respiratory infections (Monlezun et al., 2015). Conversely, adequate levels of 25-OHD are associated with a reduced risk of acute respiratory tract infections in adults (Sabetta et al., 2010). Of note, according to a recent meta-analysis including 5,660 patients, vitamin D supplementation (average dose 1,600 IU/d with a dosing interval between 24 h and 3 months) significantly reduced the risk of respiratory tract infections (Bergman et al., 2013). The immunomodulatory effects of vitamin D may be responsible for these findings (Bertoldi et al., 2020).

The possible relationship between vitamin D deficiency and COVID-19 has been investigated in several studies. According to a recent meta-analysis, vitamin D supplementation might be associated with improved clinical outcomes, especially when administered after the diagnosis of COVID-19 (Pal et al., 2022). Whether there is an association between low vitamin D levels and mortality is unclear (Hastie et al., 2020; Darling et al., 2021).

Some registered randomized trials are evaluating the role of vitamin D in COVID-19, but the results are not yet available. According to a small cohort observational study (Tan et al., 2020), including 42 COVID-19 positive patients, treatment with a combination of vitamin D, magnesium, and vitamin B12 showed significant protective effects against clinical deterioration.

Based on published data, vitamin D supplementation up to 250 μg/d for a month, followed by a maintenance dose of 100 μg/d, may increase 25(OH)D serum levels into the optimal range between 75 and 125 nmol/L with no side effects (Vieth et al., 2004; Bischoff-Ferrari et al., 2010). Furthermore, a previous study suggests that vitamin D supplementation effectively prevents acute respiratory tract infections (Martineau et al., 2017). As vitamin D deficiency is a worldwide issue (Amrein et al., 2020), the need for vitamin D supplements may represent a hot topic in COVID-19 pandemic times, especially in the most vulnerable population groups (Hadizadeh, 2021). Data from European countries show general nutritional deficiency of vitamin D, but with huge variation between countries. Finland has a relative genetic deficiency of vitamin D, which is, however, well compensated for with optimal intake and is associated with favorable COVID-19 epidemiological indicators. Conversely, Spain (followed by France and Italy) shows the highest genetic risk of vitamin D deficiency, not compensated for by intake, which coincides with a high incidence of COVID-19 (Galmés et al., 2020).

In a small randomized controlled trial of vitamin D, 76 consecutive patients hospitalized with COVID-19 infection received a combination of hydroxychloroquine and azithromycin with eligible patients allocated on the day of admission to take oral calcifediol or not. Administration of a high dose of calcifediol or 25-OHD (soft capsules, 0.532 mg) significantly reduced the need for intensive care unit treatment of patients requiring hospitalization for COVID-19. However, whether these results would also apply to patients at an earlier stage of the disease and whether baseline vitamin D status modifies these results is unclear (Entrenas Castillo et al., 2020). A trial (COVIDIOL) (NCT04366908) involving 15 Spanish hospitals is ongoing to address these issues.

According to the United Kingdom National Institute for Health and Care Excellence, during the COVID-19 pandemic, vitamin D supplementation should be encouraged to maintain bone and muscle health during the autumn and winter months. While taking vitamin D is considered harmless, there is insufficient evidence to suggest using vitamin D specifically to prevent COVID-19 infection.

***Vitamin E*:** Vitamin E is a fat-soluble antioxidant that includes molecules such as tocopherols and tocotrienols. Vitamin E may exert its immune-enhancing effects by reducing oxidative stress and inducing anti-inflammatory effects (Singh et al., 2005), which is why it has been hypothesized that vitamin E supplementation might be beneficial against COVID-19. Vitamin E has been reported to decrease lipid peroxidation and O_2^- production and decrease the release of pro-inflammatory cytokines and chemokine IL-8 and plasminogen activator inhibitor-1 levels, as well as decrease the adhesion of monocytes to the endothelium. In addition, vitamin E has been shown to decrease C-reactive protein levels and is responsible for inhibiting protein kinase C, 5-lipoxygenase, tyrosine

kinase, and cyclooxygenase-2. Although it has been suggested that supplementation with both vitamins C and E may be useful as antioxidant therapy to reduce the risk of cardiac complications in COVID-19 (Wang et al., 2020), evidence of the utility of vitamin E as a prophylactic or therapeutic agent against COVID-19 is very limited to date, and supplementation is not currently recommended.

Minerals

***Zinc (Zn)*:** Zn is a trace mineral known to be a regulator of immunity. *In vivo*, Zn deficiency alters the number and function of neutrophil granulocytes, monocytes, natural killer cells, and T and B cells (Haase and Rink, 2014). Particularly, T cell functions and balance between the different subsets are especially susceptible to changes in Zn status (Haase and Rink, 2014). Consequently, alteration of Zn status results in increased susceptibility to inflammatory and infectious diseases, including acquired immune deficiency syndrome, measles, malaria, tuberculosis, and pneumonia (Gammoh and Rink, 2017). Furthermore, Zn status is reported to be associated with the prevalence of respiratory tract infections in both children and adults (Walker et al., 2013).

Zn may play a role in COVID-19 treatment as it has been shown to inhibit SARS-coronavirus RNA polymerase activity by decreasing its replication (te Velthuis et al., 2010). Furthermore, chloroquine, which some have proposed as an antiviral agent, is a Zn ionophore that increases Zn^{2+} flux into the cell (Xue et al., 2014). SARS-CoV-2, similarly to SARS-CoV, requires angiotensin-converting enzyme 2 (ACE2) for entry into target cells (Hoffmann et al., 2020), and Zn exposure (100 μM) was shown to reduce recombinant human ACE-2 activity in rat lungs (Speth et al., 2014). Other proposed antiviral effects of Zn, although hypothetical, need substantiation (Chilvers et al., 2001). Finally, Zn supplementation was reported to improve nCoV-2019-induced mucociliary clearance dysfunction by increasing ciliary length in the bronchial epithelium of Zn-deficient rats (Darma et al., 2020) as well as ciliary beat frequency *in vitro* (Woodworth et al., 2010). Overall, Zn appears to play a key role in improving barrier functions essential for preventing respiratory distress. Zn was shown to modulate viral particle entry, fusion, replication, viral protein translation, and further release for several viruses, including those involved in human respiratory system pathology (Ishida, 2019; Read et al., 2019). According to a systematic review (Singh and Das, 2013) published in the Cochrane database, a significant reduction in common cold duration and the incidence rate ratio of developing the common cold was observed in response to Zn supplementation, with a dose of >75 mg/d being significantly associated with a reduced duration of the common cold (Hemilä, 2017).

Elderly people are often characterized by Zn deficiency (Haase et al., 2006), which might be considered a risk factor for pneumonia development in this fragile population (Bhat et al., 2016). Intake of at least 75 mg/d of Zn was associated with reduced pneumonia symptom duration but not severity, with the response being more pronounced in adults than in children (Saigal and Hanekom, 2020). Zn deficiency has also been associated with ventilator-induced injury (Boudreault et al., 2017) and sepsis (Hoeger et al., 2017).

Zn has also been reported to exert anti-inflammatory effects (Gammoh and Rink, 2017), which might represent a relevant aspect in COVID-19 pathogenesis at both local (pneumonia) and systemic levels. Of note, Zn deficiency was found to be related to inflammatory alterations of the lung extracellular matrix leading to fibrosis (Biaggio et al., 2012) and an increased risk of developing systemic inflammation and sepsis-induced organ damage, including the lungs (Knoell et al., 2009).

Direct data on anti-COVID-19 effects of Zn are scanty to date, even as there is growing evidence that Zn status may act as adjuvant therapy in the management of COVID-19. Several ongoing or proposed clinical trials in the United States for COVID-19 involve Zn. According to a case series, four consecutive outpatients with COVID-19 were treated with high dose Zn salt oral lozenges, and all of them experienced significant improvement in the clinical course, suggesting that Zn therapy might play a role in recovery (Finzi, 2020). The patients were started on Zn therapy at different times in their disease course depending on when they were referred for treatment. Patients 1 and 2 were treated with Zn citrate lozenges (23 mg of elemental Zn), patient 3 with Zn citrate/Zn gluconate (23 mg), and patient 4 with Zn acetate (15 mg). They were told to take lozenges every 2 to 4 h but not exceed 200 mg. No side effects from Zn therapy were reported. In a recent retrospective observational study (Carlucci et al., 2020), the outcomes of hospitalized patients with COVID-19 treated with hydroxychloroquine and azithromycin plus Zn sulfate were compared to patients treated with hydroxychloroquine and azithromycin alone. The authors observed that the supplementation with Zn sulfate (Zn sulfate 220 mg orally twice a day along with hydroxychloroquine 400 mg once followed by 200 mg orally twice a day with azithromycin 500 mg once daily) increased the frequency of patients being discharged home and decreased the need for ventilation, admission to the intensive care unit, and mortality.

Another prospective study (Jothimani et al., 2020) found that a significant number of patients with COVID-19 were Zn deficient. These patients also developed more complications, and Zn deficiency status was associated with a prolonged hospital stay and increased mortality.

Further studies are warranted to clarify the potential

role of Zn deficiency in COVID-19, the encouraging effects of Zn supplementation, and the underlying mechanisms involved.

***Selenium (Se)*:** Se is a unique trace element of high importance for human health and particularly for a well-balanced immune response. Supplementation with Se reportedly exerted a beneficial role in several viral infections (Steinbrenner et al., 2015). As the mortality risk from severe diseases such as sepsis or polytrauma is inversely related to Se status, there is growing speculation that this might also apply to COVID-19 scenarios.

In the specific setting of COVID-19, it was notable that, among several Chinese cities characterized by different Se intake rates, the cure rate was much higher where the Se intake was known to be higher, and the death rate was significantly higher in the provinces with a low Se intake (Zhang et al., 2020a). Furthermore, countries with the highest reported COVID-19 case-fatality rates, i.e., Italy, France, Spain, and the United Kingdom, correspond to those where suboptimal Se status has previously been documented (Stoffaneller and Morse, 2015), as compared to the United States, Canada, and Japan where the Se status is considered adequate.

In a German study, serum samples from 33 patients with COVID-19 were collected consecutively and analyzed for total Se by X-ray fluorescence and selenoprotein P (SELENOP) with a validated ELISA. The patients showed a pronounced deficit in total serum Se and SELENOP concentrations. Notably, the Se status was significantly higher in samples from surviving patients with COVID-19 than from non-survivors (Moghaddam et al., 2020).

The mechanisms underlying this possible association, however, are not fully understood. Se supplementation has been reported to stimulate T cell proliferation and enhance innate immune system functions (Huang et al., 2019) by favoring a predominant Th1 phenotype (Huang et al., 2012), which is also associated with many of the cytokines that correlate with COVID-19 severity (Romagnani, 2000). It is well known that the COVID-19 cytokine storm represents a pathogenic mechanism for the deterioration of critically ill patients (Huang et al., 2020), with a predominant role exerted by IL-1β and IL-6 (Conti et al., 2020). Se has been reported to exert antioxidant effects (Zhang et al., 2020b) and down-regulate the IL-6 response (Martitz et al., 2015). Se deficiency has been associated with higher levels of IL-6 in the elderly (Tseng et al., 2013), which may be clinically relevant.

In the context of COVID-19, an association between a more-than-adequate Se intake/status and a higher cure rate has been reported (Zhang et al., 2020b), with a low risk of toxicity in patients with COVID-19.

While further studies are needed, from a pragmatic point of view, considering the lack of toxicity associated with Se supplementation and the fact that blood levels can be easily checked, Se supplementation might be suggested.

***Iron (Fe)*:** Fe is an essential trace element that plays a role in systemic oxygen transfer and acts as an electron donor or acceptor in many biological functions. Excess intracellular Fe interacts with molecular oxygen, generating reactive oxygen species (ROS), which might be responsible for the oxidative damage of cellular components of different organs. Ferroptosis is the process of programmed cell death mediated by Fe-dependent peroxidation mechanisms (Ursini and Maiorino, 2020) implicated in inflammatory pathologies involving multiple organs, including the lungs. Ferroptosis has been reported to be linked to neurological disturbances, including ageusia and anosmia, which are common manifestations of COVID-19 (Vaira et al., 2020). It is well known that coagulopathy is a hallmark of Fe toxicity and, in patients with COVID-19, reflects an inflammatory status related to an increased risk of mortality (Giannis et al., 2020; Lodigiani et al., 2020). Hyperferritinemia observed in patients with COVID-19 may be induced in response to inflammation and might be associated with Fe toxicity due to increased ferritin leakage from damaged tissue releasing free Fe in the process. Hyperferritinemia is generally associated with viral replication, ROS generation, ferroptosis, mitochondria dysfunction, microbiota dysbiosis, and hypercoagulopathy (Edeas et al., 2020). Based on these observations, it might be advisable, in addition to treating the inflammatory state, to assess Fe chelators, ferroptosis inhibitors, hepcidin modulators, and erythropoietin as potential therapeutic options (Edeas et al., 2020).

Phytochemicals

***Epigallocatechin-3-gallate (EGCG)*:** EGCG, the most abundant (approximately 50%) and active catechin present in green tea extract (GTE), is characterized by a wide range of beneficial properties, including anti-inflammatory, anticarcinogenic, antimicrobial, and immune-modulating effects. Several studies have shown the antiviral effects of EGCG (Mhatre et al., 2021).

In the case of COVID-19, there are many binding sites present on SARS-CoV-2 that might be potential targets. In particular, there is some evidence that EGCG might be responsible for inhibiting 3-chymotrypsin-like protease, an important enzyme found in SARS-CoV responsible for proteolytic function in the maturation stage of the virus (Khaerunnisa et al., 2020; Mhatre et al., 2021). In addition, EGCG and GTE have been reported as potential Janus kinase (JAK)/signal transducer and activator of transcription inhibitors (Menegazzi et al., 2020). EGCG/GTE exerted inhibitory effects toward JAK2-elicited STAT1 phosphorylation, leading to inflammatory cascade blockade (Menegazzi et al., 2001; Tedeschi et al., 2004; Menegazzi et al., 2014).

Another point to consider is progressive lung fibrosis in severe COVID-19, including ARDS development. SARS-CoV-2 infection induces a massive neutrophil infiltration increase into the lungs, with the production and activation of transforming growth factor-β and other inflammatory cytokines (Chen, 2020), including tumor necrosis factor (TNF)-α, IL-6, and IL-1β. According to animal studies, EGCG and GTE are considered potent antifibrotic agents (Sriram et al., 2009; Sriram et al., 2015). Considering the beneficial properties and the safety profile of EGCG and GTE in humans, one might speculate that GTE supplementation could help control the hallmark inflammation damage associated with SARS-CoV-2 infection. Undoubtedly, further clinical trial data are needed; however, taking a pragmatic approach, advising drinking green tea (perhaps preferable to taking supplements) could be an appropriate lifestyle recommendation.

***Xanthohumol (Xn)*:** Xn is a prenylated flavonoid found in hops with various medicinal properties (Zanoli and Zavatti, 2008). There is growing evidence supporting the role of Xn in exerting anti-inflammatory effects against lipopolysaccharide-induced acute lung injury and ischemia-reperfusion-induced liver injury in mice (Ge et al., 2017; Lv et al., 2017), as well as antiviral activities against human immunodeficiency virus, bovine viral diarrhea virus, herpes simplex viruses 1 and 2 (Buckwold et al., 2004; Cos et al., 2008), and hepatitis C virus (Lou et al., 2014). Another beneficial effect of Xn is against porcine reproductive and respiratory syndrome (PRRS), which causes lung inflammation similar to COVID-19 and is an endemic infectious disease of pigs with a high mortality rate. Xn has been reported to both inhibit PRRS virus (PRRSV) proliferation and alleviate oxidative stress induced by PRRSV (Liu et al., 2019a). Furthermore, Xn could inhibit infection with different PRRSV sub-genotype strains with a low 50% inhibitory concentration (IC_{50}) and significantly decrease the inflammatory responses in porcine primary alveolar macrophages (Liu et al., 2019b). PRRSV-infected piglets exhibited increased expression levels of IL-1β, IL-6, IL-8, and TNF-α, which were attenuated in a dose-dependent manner after treatment with Xn.

Additionally, Xn plays a beneficial role in treating hyperlipidemia, obesity, and type 2 diabetes mellitus, according to *in vitro* and *in vivo* study results (Rossi et al., 2019). This is of great relevance in the setting of COVID-19, which generally has dismal outcomes in the presence of metabolic co-morbidities including obesity, diabetes, and dyslipidemia, thus suggesting a potential benefit for Xn in this setting. In a recent study, plasma lipidome levels were monitored over the course of COVID-19, and triacylglycerol was identified as the dominant lipid class present in SARS-CoV-2-induced metabolic dysregulation. The lipid droplet formation enzyme diacylglycerol acyltransferase (DGAT) and the lipid droplet stabilizer adipocyte differentiation-related protein were found to be fundamental host factors for SARS-CoV-2 replication, thus becoming a potential therapeutic target. This is of great relevance as Xn, which is known to be a DGAT1/2 inhibitor with both antiviral and anti-inflammatory properties, might indeed be an orally available treatment option for COVID-19 (Yuan et al., 2021).

While there are no clinical trials as yet, these hypotheses should be explored to assess Xn as a viable supplement in patients with COVID-19.

***Curcumin*:** Curcumin, an active constituent of rhizomes of *Curcuma longa* (turmeric), is a hydrophobic polyphenol characterized by several pharmacological properties, including antioxidant, anticancer, antibacterial, antiviral, and antidiabetic effects (Moghadamtousi et al., 2014; Fan et al., 2015; Zhu et al., 2017), as well as anti-inflammatory activity (Cheng et al., 2018). Curcumin has been observed to exert antiviral activities against a broad spectrum of viruses, including immunodeficiency virus, herpes simplex viruses 2, papilloma viruses, influenza virus, Zika virus, hepatitis virus, and adenovirus (Praditya et al., 2019). There is evidence that curcumin might act as an antiviral specifically directed against COVID-19. It has been proposed that curcumin could serve as a potential inhibitory agent antagonizing the entry of SARS-CoV-2 viral protein by binding to the receptor-binding domain of viral S protein and the viral attachment sites ACE2 receptor (Das et al., 2021). Interestingly, an emulsion form of a topical application of curcumin may effectively prevent SARS-CoV-2 infection in humans, as the viral entry site of ACE2 receptor is mainly located at the nasal cells and the mucosal surface of the respiratory tract and eyes (Pang et al., 2015). A role for curcumin in modulating the immune system has also been described in association with a significant decrease in the level of pro-inflammatory cytokines TNF-α, IL-6, and ROS (Pang et al., 2015). Furthermore, animal studies have studied the protective effects of curcumin in several pulmonary diseases, including ARDS, pulmonary fibrosis, and asthma (Lelli et al., 2017). Curcumin has been reported to antagonize pulmonary fibrosis development. In animal studies (Subhashini et al., 2013), curcumin reduced bronchoconstriction, and as a matter of fact, it is recommended as an add-on therapy for bronchial asthma (Abidi et al., 2014).

Curcumin up to 8,000 mg/d is safe and effective in humans; however, higher doses are characterized by toxicity (Kunnumakkara et al., 2019). Several clinical trials showed high efficacy of curcumin or turmeric against several diseases (Kunnumakkara et al., 2019), and according to recent evidence, the encapsulation of curcumin into a specific nano-carrier might improve its therapeutic efficacy (Moballegh Nasery et al., 2020). In an open, non-randomized clinical trial of the effectiveness of an oral cur-

cumin nanosystem (SinaCurcumin®) (Moballegh Nasery et al., 2020) in hospitalized patients with COVID-19, most symptoms quickly improved in the group treated with SinaCurcumin®. In a randomized, double-blind, placebo-controlled study (Valizadeh et al., 2020), the effects of 40 mg of SinaCurcumin® were evaluated on the modulation of inflammatory cytokines in patients with COVID-19, and it was observed to modulate the expression of IL-1β and IL-6 mRNA. Another study (Tahmasebi et al., 2021) investigated the therapeutic effects of SinaCurcumin® on the frequency and responses of Th17 cells (T helper cells) in patients with mild and severe COVID-19 and reported that SinaCurcumin® was able to reduce the frequency of Th17 cells and the related inflammatory factors in this setting. Furthermore, there is a registered protocol (Hassaniazad et al., 2020) for a prospective placebo-controlled clinical trial evaluating the effectiveness of nanomicelles containing curcumin and their effects on immune responses after treatment. Further large-scale clinical trials with high-absorbable curcumin are warranted to understand the potential utility of this supplement as supportive therapy in treating COVID-19. Again, pragmatically from a lifestyle perspective, it is not unreasonable to recommend turmeric in the diet and for the many people who take a supplement to ensure that it is a high-absorbable form.

Probiotics

SARS-CoV-2 RNA has been detected in the stool of patients with COVID-19 (Gu et al., 2020; Holshue et al., 2020). Furthermore, the presence of the viral host receptor ACE2 was demonstrated in the cytoplasm of gastrointestinal epithelial cells, whereas the viral nucleocapsid protein was visualized in the cytoplasm of rectum, duodenal, and gastric epithelial cells (Xiao et al., 2020). Based on these findings, one might speculate that, even if the respiratory tract is the main transmission route, the intestine could play a relevant role, both in disease pathogenic evolution and as a possible route of infection. Viral replication in the intestine could be responsible for a loss of barrier integrity with an imbalance in the microbial flora and its metabolites, potentially leading to strong production of cytokines leading to ARDS and multiple organ failure (Infusino et al., 2020).

The term "microbiota" refers to the complex community of microorganisms that colonize the mucosal surfaces of the human body. The term "eubiosis" refers to a balanced state within the microbial communities. In contrast, the term "dysbiosis" refers to any perturbations of such a condition that might lead to the dysregulation of the normal functions generally provided by the microbiota, potentially favoring both infectious and non-infectious diseases (Clemente et al., 2012). Viral infections, including those sustained by influenza viruses, are known to alter the commensal microbiota in both the gastrointestinal and the airway tracts of the host (Edouard et al., 2018) through the altered delivery of cytokines and the induction of a Th17-mediated immune response (Wang et al., 2014). Even if very little is known regarding the association between COVID-19 and microbial dysbiosis in both the gut and the respiratory tract, the possible occurrence of diarrhea, nausea, vomiting, and abdominal discomfort with this disease, as well as the determined tropism of SARS-CoV-2 for enterocytes (Gu et al., 2020; Wu et al., 2020), suggests a possible interaction between this new coronavirus and the gut microbiota.

With this in mind, probiotics consisting of live organisms could represent a promising, supplementary treatment against viral infections, comprising those responsible for colds and flu, as suggested by some studies (Rautava et al., 2009; Sanders et al., 2013; Sanders et al., 2019). According to a recent Cochrane meta-analysis, the number of acute upper respiratory tract infections, the mean duration of disease, antibiotic administration, and cold-related school absences were all decreased by the administration of probiotics when compared to a placebo (Hao et al., 2015). The mechanisms underlying the possible protective role of probiotics against viral infections may include improvement in the mucosal innate immune response, decreased intestinal permeability, and alteration of the systemic acquired immune response as a consequence of regulatory and anti-inflammatory effects.

Lactobacilli, as well as other probiotics, administered both orally or through the nasal route, exerted an immunomodulatory and protective effect against virus infections by enhancing cytokine antiviral responses in respiratory and immune cells as well as in the intestinal mucosa (Weiss et al., 2010; Biliavska et al., 2019; Infusino et al., 2020). Even if robust evidence is lacking, probiotic supplementation has been suggested as a complementary treatment for gastrointestinal symptoms, particularly diarrhea, which may occur in COVID-19, and to reduce the risk of secondary infections due to microbial translocation in severe COVID-19 cases (Gao et al., 2020b).

Another interesting application of probiotic supplementation might be as a preventive tool in high risk patients (i.e., elderly patients with co-morbidities) or subjects at high risk of being in contact with a COVID-19-positive patient (i.e., health care professionals). This hypothesis is based on the ability of probiotics to preserve a healthy status in the gut-associated lymphoid tissue as well as eubiosis to avoid virus entry into gut cells (Didari et al., 2014).

Despite representing a potential attractive complementary tool, further evidence is needed to better understand the possible role of probiotics in COVID-19 and select a specific population whose administration might be helpful with no side effects.

DISCUSSION

The current pandemic has dramatically impacted lifestyle, economy, and politics worldwide, with many victims, like the well-known Spanish-flu pandemic of 1918. With the recent advent of vaccines, there is hope that we can win this battle and go back to everyday life. Meanwhile, available therapeutic options are limited, and growing attention is being directed toward widely available supplements with no relevant side effects that may help treat this challenging disease. Co-morbidities including overweight/obesity, arterial hypertension, diabetes, and renal insufficiency, proven to be associated with poor outcomes in this specific setting, must be actively addressed. A healthy diet and lifestyle and consequent normal weight are considered protective factors. There are currently very little trial data to support the role of dietary supplements as potential adjuvant therapy in COVID-19 (Table 1). It may be difficult to run large-scale trials of generic (non-pharma-associated) products. The most significant results from human studies are available for vitamin C, which appears to decrease inflammatory markers and suppress cytokine storms. Of note, two clinical trials that focused on vitamin C's role in this setting have been undertaken. One study is still ongoing, and the other is waiting for the results to be published. A small, randomized trial showed that a high dose of vitamin D significantly reduced the need for intensive care unit treatment of patients requiring hospitalization for COVID-19. However, it is not known whether similar findings would also apply to patients with an earlier stage of the disease and whether baseline vitamin D status would modify these results. For other supplements, there is interesting theoretical evidence for Se and Zn. However, limited clinical trial evidence exists, with even less evidence for vitamin E. Foodstuffs, such as green tea and curcumin, can be easily included in the diet as supplements with no significant toxicities. Xn is also of interest for its antiviral and anti-inflammatory properties, in addition to benefits in sugar and fat metabolism, but it needs formal clinical study. Probiotics stimulating the gut immune system also have interesting properties needing further evaluation. The mechanisms underlying the potential benefits of these supplements are mainly linked to their ability to regulate the immune system, modulating the cytokine cascade, which is primarily responsible for the development of ARDS and organ failure leading to death in the most severe cases of COVID-19.

Obviously, further studies and properly designed clinical trials are warranted to draw more robust conclusions. Still, while we await such studies, it may not be inappropriate to follow a pragmatic approach advising dietary recommendations and supplementation, ideally with a mechanism to assess outcome.

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Table 1. Summary of the current evidence on the potential role of dietary supplements in the management of COVID-19

Dietary supplement	Potential role	Available evidence
Vitamin C	Decreases NO_3, methemoglobin, C-reactive protein, and lactate dehydrogenaselevels	Retrospective human study, ongoing clinical trial (NCT04370288)
	Suppresses cytokine storms, improves pulmonary function, and decreases the risk of ARDS in COVID-19	Randomized clinical trial
Vitamin D	Immunomodulatory effects	Retrospective human studies, inconsistent results
	Low levels associated with dismal outcomes and mortality	
	Supplementation might reduce the risk of severe disease	Randomized clinical trial, ongoing trial (COVIDIOL, NCT04366908)
Vitamin E	Antioxidant effects in combination with vitamin C	Single retrospective study
Zinc	Improves barrier functions and modulates viral particle entry, fusion, replication, viral protein translation, and anti-inflammatory effects	Human studies, ongoing trials
Selenium	Stimulates T cell proliferation and enhances innate immune system functions	Retrospective human studies
	Down-regulates the IL-6 response and antioxidant effects	
Epigallocatechin-3-gallate	Antiviral and antifibrotic effects	*In vitro* and animal studies
Xanthohumol	DGAT1/2 inhibitor with both antiviral and anti-inflammatory properties	Animal study
Curcumin	Inhibitory agent antagonizes the entry of SARS-CoV-2 viral protein by binding to receptor-binding domain site of viral S protein and viral attachment sites of angiotensin-converting enzyme 2 receptor	*In vitro* and *in vivo* studies, one registered clinical trial
Probiotics	Improve the mucosal innate immune response, decrease intestinal permeability, and anti-inflammatory effect	No direct clinical evidence associated with COVID-19

AUTHOR DISCLOSURE STATEMENT

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

MEC planned the project. RER searched for relevant literature and wrote the draft paper. MEC and JC made critical revisions related to important intellectual content. RER wrote the final manuscript. Finally, all the authors read and approved the final manuscript.

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