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Immunomodulation strategies against COVID-19 evidence: key nutrients and dietary approaches

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Abstract

The novel coronavirus disease-2019 (COVID-19) has created a major public health crisis. Various dietary factors may enhance immunological activity against COVID-19 and serve as a method to combat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The dietary factors that are responsible for boosting immunity may provide a therapeutic advantage in patients with COVID-19. Investigators have demonstrated that vitamins B6, B12, C, D, E, and K, and trace elements like zinc, copper, selenium, and iron may serve as important tools for immunomodulation. Herein this is a review the peer-reviewed literature pertaining to dietary immunomodulation strategies against COVID-19. This review is intended to better define the evidence that dietary modifications and supplementation could positively influence the proinflammatory state in patients with COVID-19 and improve clinical outcomes. With appropriate insight, therapeutic interventions are discussed and directed to potentially modulate host immunity to mitigate the disease mechanisms of COVID-19.

Keywords

Coronavirus disease-2019, immunity, diet, fasting, dietary supplements, probiotics

Introduction

The global outbreak of the novel coronavirus disease-2019 (COVID-19) and the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created a major public health issue. With expanded attempts to withstand the coronavirus disease, food items that offer health benefits, in addition

to conventional preventative measures, have been investigated as adjunctive and preventive therapy beyond only nutritional value, to improve the body's immunity. Environmental factors such as dietary antigens can modulate components of the host immune system beneficially and enhance host defenses against pathogens, such as bacteria, viruses, parasites, and fungi [1].

A multitude of macronutrients, micronutrients, and certain dietary strategies can exert a multitude of beneficial effects on the cellular functions of both the innate and adaptive immune systems [2]. Conversely, a diet lacking in nutrients can adversely affect immune function. Recent research has shown that dietary nutrients such as antioxidants like vitamins C and E, and also trace elements, may be effective in patients with COVID-19 [3]. This review serves to examine the role of dietary nutrients and nutritional patterns as well as the role of innate and adaptive immunity against COVID-19. Prospects demonstrate the potential for dietary therapy against COVID-19 as the complex web of interactions between pathogens, the host immune system, and dietary antigens are better understood.

Methodology

All authors performed an extensive literature search utilizing PubMed and Google Scholar search for any clinical case reports, randomized control trials, systemic reviews, and meta-analyses from peer-reviewed sources published from January 2019 to August 2022 pertaining to dietary immunomodulation strategies against COVID-19. Literature included prior to January 2019 was incorporated for reference and not inclusive of COVID-19 trials. Examples of keywords utilized in the search process included "COVID-19", "immunity", "diet", and "dietary supplements". All authors also reviewed and reported new cases and updates on prior COVID-19 cases from journals within the time period specified. With the initial search utilizing the keywords listed and, in the timeline, specified above, the search resulted in 70 articles. Duplicate articles were removed. The review focused on publications specifying new diets, dietary immunomodulation strategies, herbal supplements, and nutrients investigated against COVID-19. Articles that were not written in the English language or did not demonstrate high-quality data were removed. The review yielded 70 articles that were included and summarized in the review. The goal was to include articles published in journals with an impact factor of > 1, however, not all journals of the reviewed articles reported an impact factor but were felt to be of clinical significance.

Components of the immune system

Innate immunity

The immune system has evolved to protect the host from inflammatory and infectious pathogens. The system is multifaceted and comprised of both innate and adaptive immunity. Innate or "non-specific" immunity is the host's first line of defense against pathogens or antigens. The responses of the innate system are not specific to a particular pathogen or antigen. It is comprised of physical barriers such as skin and other epithelial surfaces, antimicrobial peptides, and phagocytes. Nearly all cells can contribute to innate immunity by releasing cytokines. However, the main immune cellular components of the innate immune system are monocytes, macrophages, neutrophils, natural killer (NK) cells, and dendritic cells (DCs) [4]. In an inflammatory response to an antigen or pathogen, a variety of signaling molecules, such as cytokines, chemokines, and prostaglandins, activate signaling cascades. The inflammatory response can induce the activation of macrophages and the attraction of monocytes and DCs. The DCs phagocytize, process, and present antigens to lymphocytes, hence activating the adaptive immune system. Adaptive or antigen-specific immune responses are pathogen-specific and the host's second line of defense.

Adaptive immunity

Adaptive or "antigen-specific" immune responses are pathogen-specific. The main immune cellular components of the adaptive response are T and B lymphocytes. Activated T lymphocytes differentiate into helper and cytotoxic subsets. Phagocytic cells process and present antigens to CD4+ T helper (Th) lymphocytes. The lymphocytes proliferate and produce cytokines that trigger inflammatory signaling and activate transcription factors and B lymphocytes. The activated B lymphocytes, also known as plasma

cells, possess immunoglobulin surface receptors (antibodies). Antibodies bind to pathogens, including free viruses, opsonizing, or neutralizing the antigen. In summary, lymphocytes undergo expansion, and differentiation, which is regulated by regulatory lymphocytes and ultimately stored in memory lymphocytes for future encounters with the same antigen or pathogen.

Cytokine "storm"

It is important to note that the same inflammatory cascades that are imperative for host defense can also have deleterious effects on the host itself. The systemic release of proinflammatory reactive oxygen species, inflammatory chemokines, and cytokines can damage the host, known as a cytokine storm. This cytokine storm is a key element in COVID-19 infections as it contributes directly to pulmonary tissue damage and respiratory failure [5]. Evidence suggests that the proinflammatory state the cytokine storm induces can suppress adaptive immunity [6]. The pro-inflammatory and pro-oxidative cascade provides many potential therapeutic targets for various antioxidant and anti-inflammatory nutrients such as vitamins, minerals, and trace elements.

Role of specific dietary nutrients in immunomodulation in COVID-19: macromolecules

Carbohydrates

Carbohydrates and their effects on immunomodulation are closely related to dietary effects with high sugar and obesity. In population-based data, there is a linear relationship between national sugar consumption per capita and the COVID-19 mortality rate. The data also demonstrates that countries with low national daily calory intake and less sugar consumption had lower mortality counts [7]. The ketogenic diet, which focuses on reducing carbohydrate oral intake, enables the production of ketones and as a downstream effect holds anti-inflammatory and immunomodulating roles [8]. Specifically, a ketogenic diet inhibits aerobic glycolysis and prevents inflammatory cell differentiation and functions [8]. In addition, the ketone body β-hydroxybutyrate inhibits nucleotide-binding domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation which is one of the key drivers for the proinflammatory state in critical viral illness such as COVID-19 [8].

In addition to the relationship between the consumption of carbohydrates and immune function, there are also underlying clinical effects of glucose level and COVID-19. A recent meta-analysis of 35 studies demonstrated that high admission fasting blood glucose was an independent predictor of COVID-19 outcomes [9]. The study involved 14,502 patients who were admitted to the hospital for COVID-19 admission and showed that each 1 mmol/L increase in fasting blood glucose increased the risk of developing severe COVID-19 infection by 33%. There is limited data on specific dietary consumption of carbohydrates and COVID-19 to investigate the underlying pathophysiology. There appears to be a relationship between the average dietary carbohydrate consumption and the risk of metabolic derangements which determine the severity of COVID-19 infection. However, the immunomodulation effect of carbohydrates in COVID-19 still needs further research.

Proteins: amino acids

Macromolecules, including proteins, carbohydrates, and lipids, are important determinants of immune function and can serve as key actors in immunomodulation against COVID-19. Amino acids are the building blocks of protein. Amino acids such as arginine are building blocks of polyamines, which regulate DNA replication and cell division. In addition, its levels correlate with antibody production and dietary supplementation has been shown to increase T-cell function [10]. Particularly, L-arginine, a substrate of nitrate oxide production, shows potential benefits in COVID-19 infection. In an interim report of a randomized, double-blinded, placebo-controlled study by Fiorentino et al. [11], patients hospitalized for severe COVID-19 who received L-arginine supplementation (1.66 g twice daily) significantly decreased the length of hospitalization and reduced the respiratory support at 10 days after starting therapy.

Glutamine is the most abundant amino acid in the body and has many roles including serving as a precursor to other amino acids, proteins, nucleotides, glutathione (antioxidant), and fueling immune

cells [12]. Among many roles, its effectiveness as an immunomodulator has been an active area of research. A case-control study demonstrated that patients with COVID-19 who consumed glutamine (10 g powder three times daily for 5 days) had significantly reduced interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and high-sensitivity (hs)-C-reactive protein (CRP) [13]. Another study investigated the effect of oral L-glutamine supplementation in COVID-19-infected patients [14]. The study demonstrated that patients without the L-glutamine supplementation had longer hospitalization time (8.9 ± 1.8 days, $P = 0.005$) and 4 patients required intensive care unit (ICU) stay while the group with the supplementation had no ICU stay ($P = 0.038$) [14]. From these studies, it can be deduced that certain amino acids with an antioxidant role or as a precursor to a molecule with antioxidant properties can provide benefits in the immunomodulation of COVID-19.

Lipids: fatty acids

Fatty acids are integral building blocks of lipids and can be classified as unsaturated or saturated based on their carbon bonds. Dietary fatty acids such as arachidonic acids (or omega-6 fatty acids), eicosapentaenoic acid, and docosahexaenoic acid (or omega-3 fatty acids) are well-known examples of immunomodulation. Omega-6 polyunsaturated fatty acids are precursors to membrane phospholipids to inflammatory cells and pro-inflammatory cytokines [15]. Importantly, the Western diet is composed of high omega-6 to omega-3 essential fatty acid ratios, which promote the pathogenesis of chronic cardiovascular and autoimmune diseases and cancer [16]. Omega-3 fatty acids have anti-inflammatory and antioxidative effects and achieve coagulopathy homeostasis [17]. These particular effects of omega-3 fatty acids make a good potential dietary supplement for COVID-19 infection where patients are in a pro-inflammatory, pro-oxidative, and coagulopathic state.

A recent double-blinded, randomized clinical trial studied the effect of omega-3 fatty acid supplementation on critically ill patients with COVID-19 [18]. The study included 101 critically ill patients with COVID-19, and the intervention group received 1,000 mg of omega-3 fatty acids daily which contained 400 mg of eicosapentaenoic acid and 200 mg of docosahexaenoic acid. The study demonstrated that the intervention group had a significantly higher 1-month survival rate and improved kidney functions [represented with blood urea nitrogen (BUN) and chromium (Cr)] and metabolic and respiratory acidosis. These effects are thought to be due to improvements in endothelial function and microcirculation. This study showed that omega-3 fatty acid supplementation has immunomodulating and organ-protecting effects. In addition, 1-month survival is an important clinical marker that highlights the benefits of omega-3 fatty acids as supplements.

Role of specific dietary nutrients in immunomodulation in COVID-19: micronutrients

Vitamins B

The B vitamins are water-soluble vitamins that act as coenzymes in molecular synthesis reactions. In addition, many B vitamins have been implicated in immune response regulation and are currently being studied in patients with COVID-19. Thiamine, also known as vitamin B1, has been shown to have significant anti-inflammatory effects in murine studies. Mice that were injected with B1 shots demonstrated reduced ear edema promptly after injection [19]. In another study, mice with thiamine deficiency were more likely to exhibit death from oxidative stress [20]. Many B vitamins, including thiamine, riboflavin (B2), and folate (B9) have also been implicated in T cell function regulation [21].

A study investigating the Middle East respiratory syndrome coronavirus demonstrated that ultraviolet (UV) light and vitamin B2 therapy reduced viral titer, leading to decreased infection transmission [22]. Niacin, or vitamin B3, supplementation was associated with a lower risk of death and decreased need for renal replacement therapy in patients with COVID-19-related acute kidney injury (AKI) [23]. Niacin has also been shown to have lung-protective properties by decreasing neutrophil infiltration and exhibiting anti-inflammatory effects in patients with ventilator-associated lung damage [24].

Vitamins B5 and B6, also known as pantothenic acid and pyroxidine respectively, have been implicated in decreased production of antibody-forming cells after antigen stimulation [25]. This finding suggests

a possible immunosuppressive and therapeutic potential for both of these vitamins given that patients who develop severe COVID-19 symptoms do so as a result of an upregulated inflammatory response. In addition, patients who are vulnerable to severe COVID-19 infection have been found to have low levels of pyroxidine. Further, supplemental vitamin B6 levels improved platelet and clot aggregation, which are known to be dysregulated in patients with COVID-19 [26]. Vitamin B6 has also been linked to increased production of IL-10, which is a powerful anti-inflammatory cytokine that decreases severe symptomatic COVID-19 response [24, 27].

Folate, or vitamin B9, has been shown to bind to furin and prevent activation of various precursor proteins involved in viral and bacterial infection progression [28]. A study done in 2021 on folate levels in patients hospitalized with coronavirus showed decreased levels of folic acid but no significant difference in the incidence of AKI, hypoxemia, invasive ventilation, length of hospital stays, or mortality between these patients [29]. Another study showed that folate can bind to the spike glycoprotein on the coronavirus membrane and decrease host cell immune response [30]. Given this knowledge, further research could yield a therapeutic folate treatment for severe immune dysregulation due to COVID-19 infection.

Patients with previous COVID-19 infections were also found to have vitamin B12 deficiencies, suggesting depletion of B12 may facilitate pathogenesis [31]. This finding suggests that severe infection might necessitate early B12 supplementation to prevent neurological, psychological, and gastrointestinal symptoms of B12 deficiency. Older patients with COVID-19 treated with a combination of vitamin D, magnesium, and vitamin B12 showed a statistically significant decrease in ICU and respiratory support needs [32]. It is unclear however at present if low B12 predisposes to COVID-19 infection. A recent study suggested that B12 deficiency could predispose to increased susceptibility to pathogens and related infections [33].

Vitamin C

Vitamin C is a heavily researched micronutrient with its relation to immunomodulation, particularly with the rise of COVID-19. However, there have been many conflicting results from these studies. In general, studies have found that critically ill patients, especially those in septic shock, were found to have severely depleted vitamin C levels despite standard ICU nutrition [34]. One study found that 82% of critically ill patients were found to have low vitamin C values [35]. A meta-analysis showed that orally administered vitamin C reduced ICU length of stay by 8% [36]. On the other hand, a Mendelian randomization study using single nucleotide polymorphisms associated with plasma vitamin C in patients with severe COVID-19 found that there was no association between genetically predisposed low levels of vitamin C and the severity of COVID-19 [37]. Another trial testing the effect of high-dose intravenous (IV) vitamin C on critical COVID-19 patients showed no difference in invasive mechanical ventilation need within 28 days of symptom onset but did show a possible benefit in oxygenation [38]. A recent study done on sepsis patients in the ICU receiving vasopressors even showed that patients who received IV vitamin C had a higher risk of death or continued organ dysfunction [39].

Despite a few studies showing a neutral or negative effect of vitamin C, most research shows a beneficial correlation between vitamin C and ill patients. One study found that chick tracheal organ cultures showed resistance to coronavirus infection after exposure to ascorbate [40]. A recent case series of 17 patients showed that patients who received IV vitamin C had a significant decrease in inflammatory markers of ferritin and D-dimer with a decreased fraction of inspired oxygen (FiO_2) requirements [41]. However, this discrepancy illustrates the need for further understanding of vitamin C's role in critically ill patients. Currently, there are several trials underway with regard to COVID-19 patients receiving vitamin C supplementation.

Vitamin D

Vitamin D is a fat-soluble vitamin primarily associated with calcium regulation and bone health. However, many immune cells have also been shown to have vitamin D receptors that are involved in autocrine signaling [42]. One paracrine/autocrine loop that was studied showed that vitamin D can decrease interferon-γ

(IFN-γ) and increase IL-10 response by altering key transcription factors to suppress Th1 cell inflammatory response [43]. Another randomized control trial showed that a high dose of vitamin D decreased CD4+ T-cell activation which often exacerbates symptomatic viral infections [44]. Low vitamin D has also been implicated in an increased risk of thrombosis due to its role in endothelial cell activation [45]. These studies demonstrate the potential use of vitamin D to decrease the hyper-inflammatory T-cell response in severe COVID-19 infection.

Certain studies have also looked into the role of vitamin D related to COVID-19. One study conducted on 20 patients with COVID-19 demonstrated that 75% of patients overall had vitamin D deficiency and 85% of those deficient patients required ICU care [46]. Multiple observational studies illustrated that vitamin D deficiency increased patient susceptibility to severe COVID-19 infections [47–49]. One randomized control study on patients with severe COVID-19 who were given a one-time dose of vitamin D showed that it was safe to give vitamin D supplementation but it did not change the hospital length of stay or ventilation requirement [50]. However, many of the current randomized control studies that have been published, including the study done by Murai et al. [50], on vitamin D supplementation in patients with COVID-19 have not been peer-reviewed, emphasizing the need for further research.

Vitamin E

Vitamin E is an antioxidant that participates in many immune system functions involving neutrophils, lymphocytes, and NK cells [51]. It acts as an immunomodulator to decrease oxidative stress responses from nuclear factor-kappa B (NF-κB), which has been shown to cause severe acute respiratory syndrome (SARS) [52, 53]. A combination of vitamins A, B, C, D, and E given to ICU-admitted COVID-19 patients showed significant decreases in inflammatory markers such as CRP, IL-6, erythrocyte sedimentation rate (ESR), and TNF-α and decreased prolonged length of hospital stay [54]. However, another study found that supplementing patients with both vitamins C and E had no immune-boosting effect in COVID-19 patients [55]. Like other vitamins, vitamin E with regard to COVID-19 has not been heavily studied in randomized controlled trials and requires further testing to understand its immunomodulatory effects on COVID-19.

Vitamin K

Vitamin K plays a role in both the coagulation cascade and inflammatory pathways. One such inflammatory response is the growth arrest specific 6 (GAS6)/TYRO3-AXL-MERTK [tumor-associated macrophages (TAMs)] signaling pathway, which has been thought to be involved in SARS-CoV-2 infection progression as a vascular signaling mechanism for thrombosis [56]. Further studies are necessary to understand the full extent of TAM's contribution to disease severity among infected patients. However, this is a promising signaling mechanism to regulate the prothrombotic state caused by COVID-19 infection.

One randomized control trial on functional vitamin K status found that there is an association between low functional vitamin K levels and increased mortality in patients with severe COVID-19 symptoms [57]. However, the association was no longer significant when adjusted for comorbidities. Extrahepatic vitamin K insufficiency has also been related to poor outcomes in COVID-19. This is because decreased vitamin K causes accelerated elastic fiber damage and thrombosis due to impaired activation of matrix Gla protein (MGP) which usually protects against pulmonary and vascular elastic fiber damage and endothelial protein S [58]. Given these findings, it is reasonable to pursue further randomized controlled studies to determine the effects of vitamin K supplementation on disease severity.

Minerals

Several key nutrients such as iron, folic acid, zinc, and selenium have well-established immunomodulatory effects and have shown benefits in various infectious diseases although their benefit in COVID-19 infection is still being investigated [59]. Effective supplementation may help modulate immune function, reduce the risk of infection, and ensure the proper function of physical barriers and immune cells [60].

Zinc

Zinc is a key trace mineral involved in innate and acquired responses to viral infection. Studies investigating lung pathology have shown that zinc deficiency is associated with increased pro-inflammatory cytokines and results in alterations of cell barrier functions in epithelial tissues by upregulating IFN-γ, TNF-α, Fas receptor signaling as well as apoptosis *in vitro* [61]. Studies investigating zinc and bacterial and viral infections have shown a direct influence of the mineral in immunomodulation. Adequate levels of zinc are required for the normal recruitment of neutrophil granulocytes and have a positive effect on NK cells, phagocytosis, generation of the oxidative burst, and CD4 and CD8 cell function. This contrasts with zinc deficiency which is associated with reduced lymphocyte counts and impaired function. Studies have shown that supplementation of zinc increases the number of T-cells and NK cells and increases IL-2 and soluble IL-2 receptor expression. Specifically, zinc has been shown to inhibit the synthesis, replication, and transcription of coronaviruses (SARS-CoV-2) [62].

As studies shift focus to COVID-19 (SARS-CoV-2) disease, zinc appears to have the potential to be a therapeutic option for COVID-19. An early case series showed patients treated with high-dose zinc had clinical symptomatic improvement, although further studies are needed to identify consistent results [63]. Early studies are investigating how high-dose zinc may reduce lower respiratory infections by inhibiting viral uncoating, binding, and replication [64]. A public health study looking at vitamin D, calcium, and zinc levels in patients with COVID-19 compared to a control group showed lower levels of these vitamins and nutrients compared to the control group and suggested supplementation would be a low-cost measure to help reduce the burden of COVID-19 even if the full mechanistic effect has not been elucidated [65].

Selenium

Selenium is a known major component of antioxidant defense and deficiency may be a risk factor for COVID-19 mortality. An early cross-sectional study of COVID-19-positive patients showed that the serum selenium was significantly higher in surviving patients compared to the deceased [66]. A separate early study noted a correlation between geographic selenium levels and COVID-19 cure rates in different Chinese provinces [67].

Selenium has been known to affect many different immunomodulation pathways. First, it has been shown to increase CD4+ T-cell activation, proliferation, and differentiation and induce the Th1 cell phenotype [68]. It also has been shown to enhance cytotoxic cells by increasing CD8+ T-cells and the lytic activity of NK cells [69]. It also plays a large role in maintaining T cell maturation and functions, including T-cell-dependent antibody production [70]. Together, these mechanisms provide a robust immune response and decrease the risk of and severity of infection. Selenium has also been shown to increase resistance to coronavirus respiratory infections [71]. Despite these beneficial roles in immunity, there is limited information available on the consistent effects of selenium supplementation specifically with COVID-19. Further research is forthcoming and may elicit specific mechanisms at play with COVID-19.

Iron

Iron is an important nutrient for the human body as it has a role in several immune processes. It is highly regulated throughout the body and is involved in activating immune cells, but it should be noted that excessive levels can produce free radicals and contribute to cellular toxicity. For example, one study showed that increased cell iron loading triggers the expression of monocyte polarization markers of macrophage 2 (M2)-like phenotype in resting macrophages and dampens pro-inflammatory immune responses, while iron deficiency has the opposite effect [72].

Iron deficiency has been associated with a wide range of pulmonary diseases through cascades as mentioned above, however, information on iron status in COVID-19 is still emerging. One study by Zhao et al. [73] showed COVID-19 severity and mortality were closely correlated with serum iron levels. Specifically, a low serum iron concentration was an independent risk factor for death in COVID-19 patients [73].

Folic acid

Opposed to the other vitamins and minerals with potential therapeutic benefits, folic acid supplementation may play a negative role in COVID-19 outcomes. Folate, a vitamin B, carries out critical roles in the transfer of one-carbon units in intermediary metabolism. Folate forms are involved in numerous reactions, including the synthesis of methionine from homocysteine, and are also used in purine and pyrimidine metabolism for DNA and RNA synthesis. To generate purines, SARS-CoV-2 post-transcriptionally remodels host folate metabolism and has been shown to be sensitive to folate inhibitors such as methotrexate [74]. Thus, methotrexate has been postulated as a potential therapy to prevent the progression of COVID-19, however, since folic acid is routinely included with methotrexate to prevent methotrexate-related toxicity, such putative beneficial effect of methotrexate on viral proliferation and hence on COVID-19 outcomes may be negated by folic acid supplementation [75].

Role of specific dietary nutrients in immunomodulation in COVID-19: prebiotics and probiotics

Prebiotics and probiotics

The commensal microbiome is an important regulator of the immune system. Dysbiosis, or a state of altered microbial composition, has been implicated in several disease states. While there is a significant inter-individual variation in microbial composition, groups of flora play similar roles in gut-immune crosstalk, and changes in the ratio of a number of floras lead to altered luminal metabolism and subsequent effects on the host. Various therapies have been utilized with the aim of restoration of a "normal" microbiome. Of these, pre-biotics are food components or supplements that induce microbiome changes with beneficial downstream effects. Pro-biotics are microorganism-containing products that are ingested with the goal of promoting eubiosis.

Probiotics

Among the colonic microbiome changes seen in SARS-CoV-2 infection, an increase in *Clostridium* spp. and a decrease in *Bacteroides* and *Bifidobacterium* spp. has been observed [76]. The decrease in fiber-fermenting flora has downstream effects on short-chain-fatty acids (SCFAs) production as described in the previous section. Probiotic consumption has been theorized as a potential adjunct to anti-inflammatory treatments, as data suggest a decrease in COVID-19 severity with high fermented vegetable intake [77]. Given the high prevalence of fermented milk products containing *Lactobacillus* spp. and *Bifidobacterium* spp., several clinical trials have investigated the intake of this flora as probiotics and their effect on disease severity. One investigation using a formulation with multiple florae as an adjunct to standard COVID-19 therapy, notably *Lactobacillus* spp. and *Bifidobacterium* spp., found a decreased risk of respiratory failure and decreased reported-symptom severity in the treatment group [78]. Another trial demonstrated a shortening of symptom severity and polymerase chain reaction (PCR) positivity with a probiotic product containing *Lactiplantibacillus* spp. and *Pediococcus* spp. [79]. With myriad factors affecting the severity of the disease, including the extent and nature of dysbiosis, it is unclear if probiotic products have a direct effect on the inflammatory response, and more data are needed to evaluate their utility.

Phytochemicals

Phytochemicals are plant-derived compounds with investigational uses for health purposes. Among the subtypes of phytochemicals with demonstrated health effects relating to SARS-CoV-2 are polyphenols and carotenoids [80]. Several polyphenols have demonstrated anti-coronavirus activity *in vitro*, including quecertin and reservatrol, among others [81–83]. Hesperidin, another polyphenol, has demonstrated a blockade of SARS binding to angiotensin-converting enzyme-2 (ACE2) receptors [84]. Alkaloids, another group of phytochemicals have also demonstrated direct antiviral activity and RNA-dependent RNA polymerase activity [85, 86].

In addition to antiviral effects, phytochemical consumption may play a role in mitigating the severity of COVID-19. Alkaloids have been demonstrated to inhibit the systemic inflammatory cascade through toll-like receptor (TLR) and IL suppression and may play a role in inhibiting the severe inflammatory

response during acute SARS-CoV-2 infection [80]. Coumarins have anti-oxidant activity and play a role in the inhibition of the lipopolysaccharide (LPS)-TLR cascade, by downregulating mitogen-activated protein kinases (MAPKs) and NF-κB [80]. Polyphenols, including flavonoids, have several systemic effects, including the downregulation of NF-κB, inducible nitric oxide synthase (iNOS), and MAPKs [80, 87]. Leafy vegetable, legume, and tea-derived flavonoids, including quecertin, myricetin, and kaempferol demonstrated a reduction in the severity of acute lung injury [80, 88, 89].

Role of diet in immunomodulation in COVID-19: fasting and plant-based diets

Plant-based diets

Dietary habits and patterns have long been known to affect overall health via modulation of the immune system, and recent theories have suspected an effect with regard to COVID-19 infection as well. Dietary patterns based on nutritional intakes, such as plant-based diets, and patterns based on fasting, such as intermittent fasting (IF), have been studied recently with an emphasis on improved outcomes such as infection and subsequent severity of COVID-19.

Plant-based diets are defined as dietary patterns that are majority vegetables and plant proteins such as legumes and nuts, and low in animal products such as poultry, red meat, and processed meat. It is hypothesized that plant-based diets, given their rich abundance of nutrients including phytochemicals, vitamins A, C, and E, and minerals such as iron and magnesium, could result in improved outcomes following COVID-19 infection [90].

One recent study examined the quality of diet with regard to the risk and severity of COVID-19. Using the COVID-19 smartphone symptom study based in the UK and US, nearly 600,000 cases were analyzed between March and December 2020, with 31,815 cases of COVID-19 documented [91]. Participants filled out the Leeds Short-Form Food Frequency Questionnaire, collecting data about the frequency of intake of 27 different food items per day. This data was then analyzed to create a healthful plant-based diet index (hPDI), with scores ranging from 14 to 70, with higher scores indicating a healthier diet. In models fully adjusted for confounding variables, those who scored highly resulted in a 9% lower risk of COVID-19 compared to lower scorers, and a 41% lower risk of severe COVID-19.

One recent population-based, case-control study examined plant-based and pescatarian diets and COVID-19 [92]. Thousands of healthcare workers across six countries were included in the study, with 568 workers infected with COVID-19 and symptomatic. Of these 568 workers, 430 had very mild to mild infection meaning fever < 38°C with or without cough, and 138 had moderate to severe infection, meaning fever and/or respiratory symptoms ranging from respiratory distress or hypoxia. After adjusting for basic demographics, medical specialty, and lifestyle behaviors such as smoking and exercise, cases were divided based on self-reported diets. After initially providing 11 different dietary options, several were combined to increase the sample size, and participants were to report if they followed one of three dietary options over the past year prior to the pandemic: plant-based diets, plant-based or pescatarian diet, or low carbohydrate and high protein diet.

In the study, participants who followed plant-based diets had 73% lower odds of moderate-to-severe COVID-19, and participants who followed plant-based or pescatarian diets had 59% lower odds of moderate-to-severe COVID-19 compared to those who did not follow these diets [92]. These associations remained significant when body mass index (BMI) and the presence of medical conditions were adjusted. Additionally, following a low carbohydrate, high protein diet was associated with 48% greater odds of moderate-to-severe COVID-19, however, it is worth noting this association was not statistically significant in models which adjusted for BMI or the presence of a medical condition. No significant association was observed between any of the diets and the odds of COVID-19 illness or duration of COVID-19. Another suggested mechanism by which plant-based diets create their significant impact is through increased dietary fiber, which will be discussed herein.

Plant-based diets: fiber

Research suggests that SARS-CoV-2 infection can cause alterations in the gut microbiome and metabolome [93]. The dysbiotic microbiota changes have been suggested to be linked to compromised intestinal barrier function [94]. Non-digestible carbohydrates, or dietary fibers, provide a key protective role in gut barrier function and integrity [95]. Although insoluble fibers resist digestion, they provide energy through fermentation. Fiber is fermented into SCFAs by microbiota to produce carbon and energy. The main SCFAs produced by microbiota are acetate, propionate, and butyrate. SCFAs have local anti-inflammatory local effects, including the promotion of optimal intestinal barrier function and integrity [96].

A recent study suggests that SARS-CoV-2 infection decreases SCFA-producing bacteria, thus compromising intestinal integrity [97]. A recent study investigating the effect of SCFAs on SARS-CoV-2 infection was conducted in Brazil [98]. The study examined the colon tissue samples of 11 patients without COVID-19. The tissue cells were then infected with SARS-CoV-2 and treated with a mixture of SCFAs. The treatment did not alter viral load however there was a reduction in the expression of a gene that plays a key role in viral cell entry. Further study is needed as the study was *in vitro* and SCFAs can also have systemic effects which need to be explored in different contexts as discussed herein.

SCFAs have been shown to promote an anti-inflammatory state via G-protein-coupled receptors (GPRs) and IL-10, which leads to the repression of pro-inflammatory cytokines such as TNF-α and IL-1 [99]. Fiber has been shown to increase the concentration of probiotics such as *Lactobacillus* and *Bifidobacterium*, both of which have been shown to not only decrease mucosal inflammation and reduce the risk of colorectal carcinoma, but also decrease the concentration of pro-inflammatory organisms such as *Fusoabcterium nucleatum* [100]. Fiber, via the production of SCFAs, has also been shown to decrease the *Firmicutes* to *Bacteroidetes* ratio, of which elevated levels have been associated with chronic inflammation and obesity [101].

Given the impact of dietary fiber and SCFAs on the immune system, recent studies have examined their effect with regard to viral infection risk, specifically COVID-19 infection. Butyrate has been shown to have a significant impact on the risk of COVID-19 infection via the upregulation of TLRs and antiviral pathways and the downregulation of genes required for COVID-19 infection [102]. Evidence suggests increased dietary fiber may be a key reason why plant-based diets result in a lower risk of COVID-19 infection, as well as decreased disease severity [102]. An additional study examined the effect of COVID-19 infection on SCFAs and the immunomodulator L-isoleucine [103]. After the viral infection, fecal levels of SCFAs and L-isoleucine were significantly higher in patients with COVID-19. Further, the insult persisted for 30 days post-infection. Additionally, the decreased levels of SCFAs and L-isoleucine coincided with an increase in disease severity, though no causation has been evidenced thus far. The decrease in fecal SCFAs, specifically butyrate, was also noted to coincide with increased plasma levels of pro-inflammatory cytokine IL-10 and chemokine (C-X-C motif) ligand-10 (CXCL-10). These findings are particularly significant as many Americans are deficient in dietary fiber, consuming roughly 40–60% of the recommended values of 25 g and 38 g for women and men, respectively, and studies have shown that an increase in as little as 5 g can increase SCFA levels [99].

These studies illustrate that plant-based diets, high in vitamins, minerals, and nutrients such as arachidonic and linoleic fatty acids, have played a role in the infection and severity of COVID-19. Identifying the potential mechanisms of the therapeutic effects enables the application of these dietary habits to create clinical change in the COVID-19 pandemic as well as general viral protection. Additionally, plant-based diets have been shown to improve outcomes in patients with comorbidities such as type 2 diabetes mellitus (T2DM), obesity, and cardiovascular disease, all of which in turn improve COVID-19 outcomes beyond the direct role plant-based diets have [104].

Fasting

One additional dietary habit newly considered to have therapeutic advantages to COVID-19 infection is IF. IF may take many forms, including water-only fasting for 18 h with a 6 h intake period, a 1,200-kcal calorie-restricted fast two days per week, and one 24 h fast day per week. IF has been shown to play a large

role in the regulation of inflammation as well as boosting host immunity and defense mechanisms, notably by increasing the protein galectin-3. Galectin-3 plays a large role in immune support with one specific impact via increasing the expression of antiviral proteins and inhibiting viral replication [105]. It is suspected this protein would play a large role in the suspected protection IF provides against COVID-19.

Recently, a study examined the role of water only one day per month fast and its effect on COVID-19 [106]. Using the Intermountain Healthcare Biological Samples Collection Project and Investigational (INSPIRE) Registry of over 8,600 participants who had undergone cardiac catheterization, 5,795 patients who enrolled in the registry between February 2013 and March 2020 were cross-referenced with patients who were PCR tested for COVID-19 at Intermountain. Of these 5,795 subjects, 1,682 of them were tested between March 2020 and February 21, with 1,457 testing negative and 225 testing positive. These patients were then screened via two survey questions, inquiring about whether they engage in periodic fasting, where period fasting is defined as routine fasting for 5 years or more, and how many years they have engaged in routine fasting during their lifetime. Participants (158 persons) were then excluded for having a prior history of fasting for more than 5 years but reporting no periodic fasting. The remaining participants were studied with a primary end point of all-cause mortality and hospitalization for COVID-19.

In the 205 patients who tested positive for COVID-19, 11% of fasting participants and 28.8% of non-fasters were hospitalized or had mortality [106]. Periodic fasting was also found to have a hazard ratio of 0.61 when associated with the primary endpoint. When examining the association between fasting and infection of COVID-19, however, no significant improvement was found in rates of infection.

While there are many studies detailing the benefits of IF, these studies provide evidence of the significant impacts IF provides with regard to COVID-19 infection as well as provides additional evidence of the role dietary habits play in immunoregulation.

Conclusions

Adequate nutrition is a key factor in maintaining bodily homeostasis and maintaining good health. Diverse macronutrients, micronutrients, and diets can exert beneficial effects on the immune system, support immune competence, and augment the ability to combat diseases such as COVID-19 and SARS-CoV-2. There are sparse reports on the effects of different micronutrients on disease activity in COVID-19. Further study with systematic approaches is warranted to better understand how dietary treatments can be used as adjunctive treatment with preventative or disease-directed pharmacotherapy against COVID-19.

Abbreviations

COVID-19: coronavirus disease-2019

DCs: dendritic cells

ICU: intensive care unit

IF: intermittent fasting

IL-1β: interleukin-1β

IV: intravenous

NF-κB: nuclear factor-kappa B

NK: natural killer

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SCFAs: short-chain-fatty acids

Th: T helper

TLR: toll-like receptor

TNF-α: tumor necrosis factor-α

Declarations

Author contributions

LC and DJ: Conceptualization, Investigation, Writing—original draft, Writing—review & editing, Validation. MV, MS, KH, BSY, and SDS: Writing—original draft, Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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