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Natural Supplements for COVID19—Background, Rationale, and Clinical Trials

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Abstract

Worldwide, the turmoil of the SARS-CoV-2 (COVID-19) pandemic has generated a burst of research efforts in search of effective prevention and treatment modalities. Current recommendations on natural supplements arise from mostly anecdotal evidence in other viral infections and expert opinion, and many clinical trials are ongoing. Here the authors review the evidence and rationale for the use of natural supplements for prevention and treatment of COVID-19, including those with potential benefit and those with potential harms. Specifically, the authors review probiotics, dietary patterns, micronutrients, antioxidants, polyphenols, melatonin, and cannabinoids. Authors critically evaluated and summarized the biomedical literature published in peer-reviewed journals, preprint servers, and current guidelines recommended by expert scientific governing bodies. Ongoing and future trials registered on clinicaltrials.gov were also recorded, appraised, and considered in conjunction with the literature findings. In light of the controversial issues surrounding the manufacturing and marketing of natural supplements and limited scientific evidence available, the authors assessed the available data and present this review to equip clinicians with the necessary information regarding the evidence for and potential harms of usage to promote open discussions with patients who are considering dietary supplements to prevent and treat COVID-19.

Keywords

ascorbic acid, micronutrients, niacinamide

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Background

We are in an era that needs no introduction. The emergence of a novel coronavirus from Wuhan, China, at the end of 2019 has now become a worldwide pandemic, leading to significant research efforts in search of effective prevention and treatment modalities. Recently, remdesivir became the first approved treatment for severe COVID-19 infection[1] and several vaccines were approved for emergency use, and are rapidly being deployed to protect vulnerable populations.[2,3] Many medical therapies are being evaluated as treatment modalities for COVID-19; however, deliberative study of biochemical pathways, clinical efficacy, and safety profiles of various potential therapies cannot match the urgency of the ongoing pandemic. Additionally, prevention of COVID-19 thus far has focused on public health efforts such as handwashing and mask-wearing as well as vaccination, and therapies are lacking.

In the meantime, patients have turned their attention to natural supplements in search of preventive and therapeutic options.[4,5] Nutritional and dietary supplements (nutraceuticals) are utilized regularly by approximately half of the US population and intermittently used by an estimated 3-quarters of the US population.[4] Despite this statistic, only a third of patients disclose the use of nutraceuticals in clinical encounters.[6] The COVID-19 pandemic has heralded a surge in sales of certain supplements by over 400%, in spite of a dearth of studies

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Table 1. Probiotics and COVID-19.

	Mechanism of action and potential benefits	Potential harms or adverse reactions	Association with COVID-19 infection	Ongoing registered clinical trials related to COVID-19
Probiotics	• Prevents gut dysbiosis and intestinal inflammation • Contributes to reduction in systemic inflammatory response • Improves outcomes in upper respiratory and lower respiratory infection • Modulates antiviral activity via stimulation of native immunity in the gut	• May theoretically cause the following side effects in at risk patients with weakened immune system, gut dysbiosis and/or impaired intestinal barrier.	• Downregulates ACE2 receptors, altering gut microbiota • Upregulates pro-inflammatory chemokines and cytokines, including fecal calprotectin and serum interleukin-6 • Microbial dysbiosis with decreased Lactobacillus and Bifidobacterium species in patients with COVID-19	• There are 9 ongoing registered clinical trials related to probiotics and COVID19 on clinicaltrials.gov

examining supplements and COVID-19.[5] The majority of evidence supporting use of natural supplements for COVID-19 is presumptive based on previous research into other viral conditions such as coronaviruses and respiratory complications seen in COVID-19. Additionally, variability in product quality underscores the important of safety and regulation of supplements purported to prevent or treat COVID-19, for which many resources are available but underutilized.[7-10]

This review examines current literature and registered clinical trials to determine which supplements have promise for treatment and prevention of COVID-19 and which supplements are potentially harmful. The authors do not explicitly encourage use of any individual nutraceutical for COVID-19 prevention or treatment; rather, this review serves to inform practitioners interested in recommending or prescribing these supplements.

Materials and Methods

This comprehensive review encompasses original research articles, viewpoints, critiques, proposals, guidelines, and registered trials in which vitamins and supplements are discussed in the context of the novel coronavirus (SARS-CoV-2) that causes COVID-19. From March 15th, 2020, through March 3rd, 2021, the authors conducted weekly environmental scans, critically evaluated, and summarized the biomedical literature published in peer-reviewed journals, preprint servers, and current guidelines recommended by expert scientific governing bodies. Ongoing and future trials registered on clinicaltrials.gov, the official clinical research study registry run by the United States National Library of Medicine and National Institutes of Health, were also recorded, appraised, and considered in conjunction with the literature findings.

Microbial Dysbiosis and Probiotics

Much attention has been paid to the role of the microbiome on immune health, and the therapeutic effects of probiotic supplementation (Table 1). Microbial dysbiosis combined with a pro-inflammatory diet, such as the standard Western diet, can lead to a breakdown of gut integrity and subsequent translocation of commensal bacteria and their metabolites into the peripheral circulation. Consequently, this leads to systemic inflammation and impairs adaptive immunity while potentiating innate immunity.[11-13] Thus, microbial dysbiosis has impacts on immune health beyond the gut. As a result, probiotics have been extensively studied for their role in local as well as systemic immunity. Various strains of probiotics show promise for protecting against *Clostridium difficile* infection as well as ICU-related microbial dysbiosis.[14,15] Moreover, probiotics modulate systemic immunity to reduce the inflammatory response while upregulating antiviral actions via stimulation of native immunity in the gut, thereby contributing to improved outcomes in upper respiratory and lower respiratory infection.[16,17] Prior studies have shown probiotics to shorten the duration of respiratory infections and reduce the frequency of ventilator-associated pneumonia.[18-20] *Lactobacillus plantarum* in particular reduces upper respiratory infection symptoms and duration via an upregulation of immune cytokines and cellular response.[16]

Given the broad effects of probiotics on inflammation, probiotics may prove useful in reducing the systemic inflammatory response in COVID-19. Recent publications suggest that COVID-19 may contribute to gut inflammation and subsequently microbial dysbiosis.[21] This is evidenced by elevated levels of fecal calprotectin and serum IL-6, often seen in patients presenting clinically with diarrhea.[22] COVID-19 also substantially detriments microbial flora by down-regulating ACE2 expression in infected cells.[23,24] A small case series from China revealed microbial dysbiosis with decreased *Lactobacillus* and *Bifidobacterium* species in patients with COVID-19, and prior coronaviruses have also been associated with microbial dysbiosis.[25] Together, these findings suggest that probiotics, particularly *Lactobacillus* species, may reduce both local gut inflammation and systemic inflammation seen in COVID-19.

Table 2. Dietary Patterns and COVID-19.

	Mechanism of action and potential benefits	Potential harms or adverse reactions	Association with COVID-19 infection	Ongoing registered clinical trials related to COVID-19
Mediterranean diet pattern	• Western diet is pro-inflammatory by impairing adaptive immunity and host defense against viral infection • Mediterranean diet is rich in antioxidant functional foods, which help to support the systemic immune response • Low protein intake contributes to increased infection risk, and higher protein intake is associated with lesser inflammatory state • Greater dietary fiber intake is associated with reduced risk of death from respiratory or infectious causes • Adiponectin, an anti-inflammatory chemokine, is higher in those consuming and adherent to Mediterranean diet	• Overemphasis on the benefits of healthy diet may limit emphasis on exercise and the important social aspects of the Mediterranean diet	• Worsened outcomes in obese patients • COVID-19 quarantine measures worsen food intake quality and leads to weight gain in general population • Malnutrition is highly prevalent in elderly patients with COVID-19 and patients should be screened	• There are 5 registered clinical trials related to+Mediterranean diet and COVID19 on clinicaltrials.gov
Omega-3 FA supplementation	• Reduces pro-inflammatory cytokines • Enhances antiviral immune response • Omega-3 FAs attenuate inflammatory response in ARDS mouse and human models, though meta-analysis of human studies with nonsignificant effect	• Potential risk of increased bleeding • Association with atrial arrhythmias • Oxidation of Omega-3 FAs by reactive oxygen species may increase oxidative stress; co-treatment with antioxidants may mitigate this effect	• May improve clinical outcomes for patients with acute respiratory distress syndrome, a complication of COVID-19 infection	• There are 10 registered clinical trials related to omega-3 fatty acid supplementation and COVID19 on clinicaltrials.gov

There are currently 9 registered clinical trials exploring the use of probiotics as a therapeutic agent for COVID-19. In particular, one study is utilizing probiotics in healthcare workers to determine if they can decrease the incidence of healthcare-associated infections and gastrointestinal symptoms in patients with COVID-19.[26] Other studies are using probiotics in combination with therapies (oxygen-ozone treatment, micronutrients) to potentially reduce the rate of intubation and length of hospitalization in patients with COVID-19.[27] Caution is advised when administering probiotics to patients with immunosuppression or an impaired intestinal barrier due to chronic gastrointestinal illness such as inflammatory bowel disease. In patients with a weakened immune system, probiotics may be associated with systemic infections, altered metabolic function, excessive systemic immune response, and gene transfer.[28,29] Otherwise, probiotics are generally well tolerated.

Dietary Effects on COVID-19

The therapeutic effect of food cannot be understated when discussing COVID-19 prevention and treatment (Table 2). Appropriate nutrition is essential for a fully functional immune system and impacts infection risk from an early age.[30-32] Both malnutrition from underconsumption or starvation and from

excess intake of foods of poor nutritional quality contribute to increased risk of infection. Inadequate protein and fiber intake contribute to risk of infection,[33-35] as do micronutrient and antioxidant deficiencies. Moreover, malnutrition is highly prevalent in elderly patients with COVID-19.[36] On the other hand, the Western diet, rich in fat and low in fiber and micronutrients, impairs the immune response to viral infection and may worsen risk of COVID-19.[11,21,23,37] Obese patients who get COVID-19 are at higher risk for complications of the disease and may have higher mortality rates as well. Contributing to obesity is the weight gain and unhealthy eating patterns that have occurred as a consequence of the pandemic's impact on daily life.[38] Choosing a healthy diet, such as the Mediterranean diet, may help with reducing risk of infection via reducing inflammation and supporting immune system health.[39-41] For example, adiponectin, an anti-inflammatory chemokine, is higher in those consuming and adherent to the Mediterranean diet.[41] Multiple micronutrients and antioxidant compounds emphasized in this diet show promise for improving outcomes in COVID-19, and will be individually discussed below.

There are currently 5 registered trials looking at dietary patterns, including Mediterranean diet, and COVID-19. Adherence to a healthy diet is a significant barrier for some patients to achieve the proposed benefits, and effective counseling to help motivate patients is essential.[41] Healthy diet is but one part of lifestyle management, and incorporation of dietary intervention into a comprehensive lifestyle intervention that addresses other aspects such as physical activity, mental health, social support, and healthcare access are essential for care of patients with COVID-19.

Omega-3 Fatty Acids

Omega-3 fatty acids function as active or precursor molecules on the anti-inflammatory cytokine production pathway. Omega-3 fatty acids have been associated with antioxidant and anti-inflammatory functions and may enhance antiviral responses via modulation of systemic immunity.[42-44] In human and animal models of ARDS, inhaled lipid emulsions of omega-3 fatty acids attenuate pro-inflammatory cytokine production and immune cell response.[45] Meanwhile, a meta-analysis examining enteral omega-3 fatty acids for treating ARDS was inconclusive.[46]

Patients with COVID-19 infection are vulnerable to the development of ARDS, and omega-3 fatty acids may serve as a useful preventive and therapeutic agent for ARDS in COVID-19.[47] Investigation into the role of omega-3 fatty acids in COVID-19 is ongoing, with 10 currently registered trials in clinicaltrials.gov. Concerns about fish oils contributing to arrhythmia and bleeding risk are debated.[48] Omega-3 fatty acid oral supplementation can cause mild gastrointestinal discomfort, and therefore should generally be taken with meals. Oxidation of omega-3 fatty acids is pro-inflammatory, and therefore combining omega-3 fatty acid with other antioxidants may reduce oxidative damage to the supplement.[47]

Micronutrient and Antioxidant Support

While micronutrients have pluripotent effects, those micronutrients that have been studied in relation to COVID-19 have primarily antioxidant and anti-inflammatory effects (Tables 3 and 4). Emerging research on COVID-19 has examined the inflammatory cascade and endothelial dysfunction as a major contributor to clinical pathology, and insufficiency or deficiency of selected micronutrients has been associated with higher likelihood of infection and/or complications related to COVID-19.[49,50] We discuss several of the most commonly utilized micronutrient and antioxidant strategies below.

Intravenous High-Dose Ascorbic Acid (Vitamin C)

Vitamin C is an essential antioxidant and enzyme cofactor to several vital biochemical pathways. When given intravenously in high doses (50 mg/kg up to 100 grams or higher, daily), vitamin C may improve clinical outcomes in patients with sepsis and several cancers, though research is ongoing.[51] Poor outcomes in sepsis are associated with significantly reduced plasma vitamin C concentrations. In sepsis, there is increased consumption of vitamin C by somatic cells combined with high leukocyte turnover, triggered by an overwhelming state of oxidative stress that then contributes to higher levels of reactive oxygen species (ROS).[52] At high serum concentrations, only attainable by intravenous administration (millimolar [mM] range), vitamin C seems to elicit a dual response with both antioxidant and pro-oxidant properties depending on cell type.[51,53]

Activated immune cells with high turnover rates rely on accelerated glycolysis (the "Warburg effect")[54] while others such as lung epithelial cells rely on oxidative phosphorylation for energy production. High doses of vitamin C can overwhelm the redox pathways in highly glycolytic cells leading to elevated endogenous ROS. Increased oxidative stress, together with inhibition of ATP production from high levels of ROS, leads to a cellular energy crisis and cell death.[51] This may provide a mechanism of immunosuppression by preventing myeloid and lymphoid cells' hyperactivation, yet still providing antioxidant protection to lung epithelial cells.[53]

Prior trials utilizing high-dose vitamin C for conditions such as sepsis demonstrate mixed results.[55,56] More recent studies show a potential mortality benefit with high-dose vitamin C given intravenously combined with steroids for patients with sepsis complicated by acute respiratory distress syndrome (ARDS).[57,58] These findings and many others related to vitamin C have led to numerous clinical trials evaluating this strategy's effectiveness in critically-ill patients with COVID-19.[59,60] In addition, vitamin C is being examined in conjunction with other supplements to regulate oxidative effects at lower doses, such as with quercetin.[61] At the time of this publication, there are currently 32 registered clinical trials utilizing vitamin C in various dosing strategies (including oral supplementation) and in combination with other therapies

Table 3. Micronutrients and COVID-19.

Supplement	Mechanism of action and potential benefits	Potential harms or adverse reactions	Association with COVID-19 infection	Ongoing registered clinical trials related to COVID-19
Ascorbic acid (Vitamin C)	• Antioxidant and enzyme cofactor • May limit pro-oxidant effects when given in conjunction with other supplements • Pro-oxidant properties at higher doses when given IV which may inhibit hyperactivation of over-stimulated myeloid and lymphoid cells	• Oral: abdominal pain, diarrhea • IV (high-dose): hemolytic anemia in patients with G6PD-deficiency; glucose	• Vitamin C levels are depleted during the acute stage of infection due to increased metabolic demands • Many patients with severe COVID-19 have elevated levels of the mediators interleukin-6 and endothelin-1 which may explain the propensity of COVID19 pneumonia for elderly, male, obese, hypertensive patients, as well as of persons of color and smokers. Vitamin C in high doses can reduce these mediators	• There are 53 registered clinical trials related to Vitamin C and COVID19 on clinicaltrials.gov
Cholecalciferol (Vitamin D3)	• Supports both innate and adaptive immune mechanisms • Inhibition of T cell proliferation, production of cytokines, antibody synthesis by B lymphocytes • Stimulate surfactant synthesis in alveolar cells	• Hypercalcemia which can lead to gastric distress, muscle weakness, neuropsychiatric disturbances, dehydration, polyuria, nephrolithiasis, and fatal cardiac arrhythmias	• Vitamin D deficiency has been correlated with poor outcomes in COVID-19 • Vitamin D supplementation along with magnesium and Vitamin B12 mitigated clinical deterioration in elderly patients with COVID-19 infection	• There are 73 registered clinical trials related to vitamin D supplementation and COVID19 on clinicaltrials.gov
Zinc	• Preserves natural tissue barriers such as the respiratory epithelium, improves mucociliary clearance, decreases viral replication, attenuates inflammation, and minimizes secondary respiratory infections	• If large doses of zinc (10-15 times higher than the RDA) are taken by mouth even for a short time, stomach cramps, nausea, and vomiting may occur. Ingesting high levels of zinc for several months may cause anemia, damage the pancreas, and decrease levels of high-density lipoprotein (HDL) cholesterol.	• COVID-19 infection and survival associated with zinc deficiency • Both zinc deficiency and early COVID-19 infection are uniquely associated with loss of taste • Zinc supplementation reduced time to recovery of smell and/or taste • Zinc deficiency is common in patients at risk for COVID-19; screening for zinc deficiency may be helpful are at the same time groups that are associated with zinc deficiency	• There are 46 registered clinical trials related to zinc supplementation and COVID19 on clinicaltrials.gov

(continued)

Table 3. (continued)

Supplement	Mechanism of action and potential benefits	Potential harms or adverse reactions	Association with COVID-19 infection	Ongoing registered clinical trials related to COVID-19
Nicotinamide riboside (Vitamin B3)	• Restoration and balance of cellular energy function and stabilization of oxidation/ reduction pathways • May potentiate interferon activity and help mitigate viral replication	• No significant adverse effects reported. Mild gastrointestinal symptoms	• SARS-CoV-2 must exploit host functions, including nucleic acid and protein synthesis, to assemble more viruses. Both viruses and hosts rely on nicotinamide adenine dinucleotide derivatives, as these coenzymes accept and donate electrons in numerous essential biological processes • SARS-CoV-2 infection in cell lines and humans appears to down-regulate synthesis of NAD from tryptophan and niacin while upregulating synthesis capacity from nicotinamide and nicotinamide riboside (NR).	• There are 2 registered clinical trials related to nicotinamide riboside supplementation and COVID19 on clinicaltrials.gov

as a treatment strategy for various stages of COVID-19 severity. Due to inhibition of glycolytic pathways, individuals must be tested for glucose-6-phosphate dehydrogenase deficiency before receiving high-dose vitamin C, as this can lead to hemolytic anemia from increased oxidative stress in enzyme-deficient erythrocytes. Otherwise, excess vitamin C is cleared renally and is generally well tolerated.

Cholecalciferol (Vitamin D3)

Emerging research indicates vitamin D may have an essential role in the function and regulation of innate and adaptive immunity.[62] Vitamin D deficiency contributes to increases in seasonal respiratory viral infections, and disproportionately impacts those likely to be deficient, including individuals who are older, obese, smokers, have dark skin tone, live in more northern latitudes and in individuals with genetic variants impeding vitamin D status.[63] This particularly alarming for African-Americans, who experience high rates of vitamin D deficiency and suffer a 3-fold higher rate of COVID-19 infection and a 6-fold higher death rate due to COVID-19 as compared to Caucasians.[64] Thus, vitamin D status may significantly impact vulnerability to infection from COVID-19.

There are roughly 2 dozen RCTs and 10 observational studies exploring vitamin D supplementation as an adjunct treatment for COVID-19 infection. Cross-sectional observational studies have shown that vitamin D deficiency is associated with risk of COVID-19 infection and worse disease severity.[65,66] In 1 observational study, supplementation with cholecalciferol combined with magnesium and B12 showed less clinical deterioration and reduced the need for intensive care in elderly patients with COVID-19.[67] Researchers are using both high- and standard-dose vitamin D combined with various other agents, including hydroxychloroquine, azithromycin, vitamin C, zinc, and aspirin as a potential treatment.[68-71] Given the ethnic variation in vitamin D production, some observational studies underway will hopefully clarify these discrepancies as it relates to those affected by COVID-19.[72,73] Vitamin D supplementation has minimal side effects, however vitamin D toxicity is associated with kidney stones and hypercalcemia and should be avoided.

Zinc

Zinc has multiple effects on protecting the respiratory system from viral infection, including preserving respiratory epithelial linings, improving mucociliary clearance, decreasing viral replication, attenuating local inflammation, and minimizing secondary respiratory infections.[74] Zinc deficiency is underrecognized and undertreated, and affects up to one-third of the world population.[75] The WHO asserts that roughly 1 in 6 deep respiratory infections worldwide can be attributed to zinc deficiency, with a preponderance toward children in developing countries.

Early data suggests a role of zinc in the manifestation of COVID-19 symptoms. Both zinc deficiency and early

Table 4. Antioxidants and COVID-19.

Supplement	Mechanism of action and potential benefits	Potential harms or adverse reactions	Association with COVID-19 infection	Ongoing registered clinical trials related to COVID-19
Glutathione	• Antioxidant involved in metabolic regulation and promoting cellular homeostasis	• Gastric cramping, nausea, abdominal bloating, and allergic reactions have been reported. • Chronic supplementation linked to low serum zinc concentrations. • Inhaled glutathione reported to trigger asthma attacks. • FDA has warned that glutathione powders used to prepare injectable forms may contain endotoxins that can cause myalgia, arthralgia, nausea, vomiting, and hypotension.	• May help to mitigate ARDS response to COVID-19 infection	• There are 5 registered clinical trials related to glutathione supplementation and COVID19 on clinicaltrials.gov
N-acetylcysteine	• Antioxidant in the extracellular environment to increase intracellular penetration of glutathione • Increases pulmonary defense mechanisms through its natural antioxidant properties and its indirect role in glutathione synthesis • Has been shown to thin mucus buildup in the lungs of elderly individuals with influenza • Has been shown to reduce levels of toxic hydrogen peroxide concentration in exhaled air condensate,	• As noted above for glutathione	• May help to mitigate ARDS response to COVID-19 infection	• There are 14 registered clinical trials related to glutathione supplementation and COVID19 on clinicaltrials.gov
Quercetin	• Anti-carcinogenic, anti-inflammatory, antiviral, antioxidant, and psychostimulant activities • Ability to inhibit lipid peroxidation, platelet aggregation and capillary permeability, and to stimulate mitochondrial biogenesis	• Prior studies demonstrated that quercetin unexpectedly depleted intracellular glutathione, causing pro-oxidant effects. • Potentially harmful interactions with statins, cyclosporine, and fexofenadine have been reported	• May alter the expression of human genes encoding protein targets of SARS-CoV-2	• There are 4 registered clinical trials related to quercetin supplementation and COVID19 on clinicaltrials.gov

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Table 4. (continued)

Supplement	Mechanism of action and potential benefits	Potential harms or adverse reactions	Association with COVID-19 infection	Ongoing registered clinical trials related to COVID-19
Curcumin	• Anti-inflammatory, antioxidant • Potentially binds to both the ACE2 receptor and receptor-binding domain of the SARS-CoV-2 spike protein (blocking viral entry)	• Cardiotoxicity from binding hERG channels	• May inhibit COVID-19 binding of spike protein, thereby reducing viral infectivity	• There is 1 registered clinical trial related to curcumin and COVID19 on clinicaltrials.gov
Melatonin	• Anti-inflammatory, antioxidant • Inhibition of the NLRP3 inflammasome • May reduce vessel permeability, alleviate anxiety, and improve sleep quality	• Alters sleep cycles, which may contribute to poor sleeping patterns and insomnia • May cause headache, confusion, dizziness, somnolence, and nausea	• COVID-19 may attack the melatonin synthetic pathway • Melatonin may reduce vessel permeability, alleviate anxiety, and improve sleep quality in COVID19 patients	• There are 8 registered clinical trials related to melatonin and COVID19 on clinicaltrials.gov
Cannabidiol (CBD)	• Interferes with ACE2-mediated viral entry into cells • Anti-inflammatory	• Risk of anxiety, psychosis, and euphoria in products containing THC • Lung damage and inflammation from smoking or vaping marijuana products	• Downregulation of inflammatory cytokines including TNFa and IL-6, major contributors to progression to ARDS in COVID-19	• There are 8 registered clinical trials related to cannabinoids and COVID19 on clinicaltrials.gov

COVID-19 infection are uniquely associated with loss of smell and taste, and zinc supplementation may reduce time to recovery of smell and/or taste.[76] Additionally, both conditions overlap in terms of demographic and risk factor profiles.[74] This suggests a common pathway to smell and taste alteration for which zinc may prove useful as a therapeutic agent. Zinc serum levels may also predict survival when combined with selenium levels, and further investigation of the mechanism of this relationship is needed.[77] There are currently 46 registered clinical trials related to zinc supplementation and COVID-19 on clinicaltrials.gov. Registered clinical trials are investigating zinc largely in combination with vitamins C and D to reduce disease severity and lessen duration of COVID-19 infection.[73,78,79] Zinc is also being investigated as an adjunct treatment to hydroxychloroquine in addition to other nutraceuticals.[71] Zinc supplementation is fairly harmless, but zinc toxicity on the order of >10 times the recommended daily allowance can result in gastrointestinal upset and over time result in anemia, pancreatic injury, and reductions in high-density lipoprotein cholesterol.[80]

Nicotinamide Adenine Dinucleotide and Its Precursors, Nicotinamide Riboside

Nicotinamide adenine dinucleotide (NAD) serves essential biochemical functions in metabolic pathways and also contributes heavily to cellular immunity.[81] NAD assists in the function of interferon-inducible proteins such as ADP-ribosyltransferases (PARPs), which perform a wide range of cellular and immune functions. Some of these functions include suppression of cellular protein synthesis and cellular metabolism, all of which result in suppression of viral replication in infected cells.[82,83] This mechanism allows for the innate immune response to counter viral infections and preserve cellular function and health. Additionally, NAD has been associated with better glycemic control and neuroprotective effects via its involvement in catabolic pathways, and has demonstrated cardioprotective effects via lipid metabolism and relief of oxidative stress.[81,84,85]

Early studies of the COVID-19 virus have revealed similar actions to other viruses in the suppression of innate immunity and the development of metabolic derangements that contribute to comorbidity of disease. A conserved ADP-ribosylhydrolase domain on the COVID-19 virus induces overexpression of PARPs, contributing to consumption of NAD and impaired resistance to the hijacking of cellular machinery for viral replication.[82] Indeed, COVID-19 infection *in vitro* was seen to suppress synthesis of NAD from amino acids, causing cells to derive their NAD production from other forms of NAD, including nicotinamide and nicotinamide riboside.[82] These other forms of NAD enzymatically support the production of NAD, and therefore depletion of these forms can further diminish the cell's capacity to maintain physiologic

levels of NAD.[81] Supplementation with NAD can therefore be achieved with supplementation with nicotinamide riboside, which will enhance NAD production in the body. There are currently 2 ongoing clinical trials investigating whether 1 gram of nicotinamide riboside given orally for 14 days can reduce COVID-19 infection severity in elderly patients.[86] The supplement is very well tolerated, and it should be noted that flushing is not seen with ingestion of nicotinamide, unlike niacin for which this side effect is well documented and often difficult to tolerate.

Glutathione, N-Acetylcysteine, and Synthetic Organoselenium (Ebselen)

Glutathione (GSH), and its precursor N-acetylcysteine (NAC), are potent antioxidants which may be vital in host defense against COVID-19.[87] Clinical trials are exploring antioxidant therapy in COVID-19 with GSH, NAC, and Ebselen, a synthetic organoselenium that biologically mimics glutathione peroxidase.[88,89]

GSH is an essential and complex detoxification agent involved in metabolic regulation and promotes cellular homeostasis. Although GSH poorly penetrates cells, its precursor, NAC, works as an antioxidant in the extracellular environment to increase intracellular penetration of GSH.[90] While NAC by itself has antioxidant properties to protect respiratory epithelium from injury, NAC indirectly increases availability of GSH intracellularly for cellular health.[90] In small clinical trials, NAC reduces hydrogen peroxide in exhaled air of patients with COPD, demonstrating the antioxidant effects of NAC supplementation.[91]

Multiple mechanisms have been proposed in support of antioxidant therapy for COVID-19. With a broad range of antioxidant and anti-inflammatory mechanisms, NAC may increase glutathione and further attenuate the risk of severe complications from COVID-19, as previously demonstrated for influenza and other respiratory illnesses.[92] There are 5 registered clinical trials related to glutathione supplementation and COVID-19 and 14 registered clinical trials related to NAC supplementation and COVID-19 on clinicaltrials.gov. A phase 3 randomized placebo-controlled trial is currently underway to assess NAC's efficacy in preventing COVID-19 progression in severity.[93] Moreover, high-dose intravenous NAC is also being studied in clinical trials as an adjuvant in treating severe cases of COVID-19.[94]

Risks associated with glutathione supplementation including gastric cramping, nausea, abdominal bloating, and allergic reactions have been reported. Chronic supplementation has been linked to low serum zinc concentrations, and inhaled glutathione has been reported to trigger asthma attacks. The FDA has warned that glutathione powders used to prepare injectable forms may contain endotoxins that can cause myalgia, arthralgia, nausea, vomiting, and hypotension.[95] Therefore, inhaled forms of glutathione should be avoided.

Polyphenolic Compounds

Quercetin

Abundant in foods such as onions, juniper berries and many other fruits and vegetables,[96] quercetin is a type of flavonoid, a class of antioxidant compounds that has been studied extensively for anti-inflammatory and antiviral actions, among other potential benefits. Quercetin inhibits lipid peroxidation via antioxidant actions, and supports mitochondrial health via its role in the protecting against ROS production.[96,97] Quercetin can also demonstrate pro-oxidant effects. In a prior study unrelated to COVID-19, quercetin unexpectedly depleted intracellular glutathione, a vital antioxidant involved in ROS scavenging system. It is reasonable to consider that this seemingly pro-oxidant effect may be similar to that of high dose vitamin C by helping to suppress overstimulated immune effector cells during viral infection, thereby mediating the inflammatory response.[98]

These findings show that quercetin may demonstrate complex mediation of oxidation to quell viral infections such as COVID-19. Quercetin effectively inhibits the hyperinflammatory response triggered by COVID-19 infection through the inflammasome pathway, which results in an exaggerated release of proinflammatory cytokines, IL-6 and IL-1β.[99,100] Quercetin may have epigenetic effects as well, altering the expression of COVID-19 viral proteins in human cells.[98] It has been proposed that combining quercetin with vitamin C takes advantage of quercetin's effect on COVID-19 viral protein function while limiting degree of pro-oxidant effects to prevent toxicity.[61] Current open-label trials are evaluating quercetin both for prophylaxis and treatment of COVID-19,[101] which will help identify the most effective and safe regimen. There are 4 registered clinical trials related to quercetin supplementation and COVID-19 on clinicaltrials.gov. Flavanoid supplementation is generally well tolerated, and quercetin is no exception.

Curcumin

Traditionally used in Asian countries as a medical herb, curcumin (diferuloylmethane) has reported antioxidant, anti-inflammatory, antimicrobial and anti-cancer properties.[101] Curcumin has previously demonstrated several anti-inflammatory as well as antiviral properties through inhibition of various proinflammatory cytokines.[102,103] Potentially binding to both the ACE2 receptor in addition to the receptor-binding domain of the SARS-CoV-2 protein, some studies suggest curcumin may act as an inhibitory agent by blocking viral host interaction at entry sites in human cells.[104] Notably, curcumin accelerated endothelial cell restoration and endothelium recovery, which may be beneficial in tempering the overwhelming endothelial damage associated with severe cases of COVID-19.[105]

Despite several potential benefits and overall favorable safety profile of curcumin, poor oral absorption in conjunction with rapid metabolism of curcumin result in overall low bioavailability. However, heat extraction techniques and curcumin

nanocarriers have improved bioavailability with increased cellular uptake in some studies.[105] Although serious side effects are rare, curcumin has reported activity against several human enzymes linked to compound toxicity, including hERG channels (leading to cardiotoxicity).[106] The NCCIH warns that no conclusions have been reached on curcumin's ability to provide any benefit for human medical conditions.[107] There is 1 registered clinical trial related to curcumin and COVID-19 on clinicaltrials.gov. Researchers are currently investigating a combination of curcumin, artemisinin, frankincense, and vitamin C as a possible strategy to promote clinical improvement in patients with COVID-19.

Melatonin

Melatonin, an antioxidant and anti-inflammatory agent, has demonstrated clinical benefit in sepsis and many viral infections.[108] Researchers are exploring its use for COVID-19 by focusing on melatonin's capacity to reduce vessel permeability, alleviate anxiety, and increase sleeping quality to improve clinical outcomes.[109-111] As a modulator of the cytokine storm, melatonin can ameliorate activation of the nucleotide-binding domain, leucine-rich repeat, and pyrin domain-containing receptor 3 (NLRP3) inflammasome.[111] This intracellular component secretes proinflammatory chemicals in response to infection.[112] Adverse reactions include, altered sleep cycles, which may contribute to poor sleeping patterns and insomnia and potential headache, confusion, dizziness, somnolence, and nausea.

There are currently 8 registered RCTs evaluating melatonin (or its agonist, ramelteon) to reduce symptom severity or prevent COVID-19.[112] A current clinical trial is evaluating the therapeutic effects of melatonin via inhibition of the NLRP3 inflammasome in patients hospitalized with COVID-19 infection.[112] Some hypotheses have suggested that COVID-19 may attack the melatonin synthetic pathway, thereby reducing melatonin levels, and the presence of the virus in neural tissue may explain the reduced physiological levels of melatonin.[113] Moreover, investigation of melatonin supplementation in exposed healthcare workers to prevent infection with SARS-CoV2 is ongoing.[114]

Cannabinoids

Utilization of cannabis terpenes and cannabis-derived cannabidiol (CBD) as adjunct anti-inflammatory treatments for COVID-19 infection is under investigation.[115] Cannabinoids, specifically, the non-psychotropic portion cannabidiol (CBD), has previously demonstrated efficacious reduction of inflammation in preclinical models of numerous diseases.[116] Recently, researchers discovered at least 13 high-potency CBD cannabis strains which can affect ACE2 pathways, concluding that hemp extracts rich in CBD may interfere with the ability of SARS-CoV-2 to enter host cells.[117]

CBD inhibits the production of several proinflammatory cytokines primarily through inhibition of toll like receptor-4 (TLR4) activity, which is corroborated in humans who consume cannabis.[118] Tissue models have previously demonstrated marked inhibition of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-a) using various Sativa strains of cannabis that also contain high amounts of CBD.[119] Given the vast distribution of the endocannabinoid system in the human body,[118] it is plausible that CBD may be beneficial in treating inflammatory conditions, including those associated with COVID-19.

Current trials are investigating high-concentration CBD tablets in conjunction with steroids or antiviral medications for COVID-19.[120] There are 8 registered clinical trials associated with cannabinoids and COVID-19 on www.clinicaltrials.gov. In particular, 1 RCT is evaluating a 14 course of CBD in reducing viral load and inflammatory cytokines while improving the quality of life in patients with COVID-19.[121] Additionally, CBD has been shown to reduce depression, anxiety, and stress—potentially enhancing the human body's innate ability to fight infection by lessening the deleterious effects of psychological stress on immune function. There is a single-arm study evaluating CBD for burnout prevention in frontline healthcare workers dealing with SARS-CoV-2 exposure.[122] Despite the promising potential of CBD, products that contain THC may lead to anxiety, psychosis, and euphoria.[123] Moreover, smoking or vaping should be strongly discouraged to patients. This may damage lung endothelial cells and the ciliary network, potentially increasing susceptibility to respiratory pathogens.[124]

Special Mention of Supplements Which Should be Considered With Caution

The COVID-19 pandemic has generated a spike in interest regarding natural therapies for this disease, driving up sales of certain supplements by over 400% (Table 5).[125] Unfortunately, some disingenuous business have seized on the opportunity to advertise COVID-19 treatments with minimal peer-reviewed evidence for benefit, and for some, significant potential harms. Nevertheless, these supplements have gained attention in the public domain, mostly from non-peer-reviewed sources including online health forums, political leaders, and news outlets. Thus far, the FDA has sent over 40 warning letters to companies and a preliminary injunction to a company refusing to remove from the market its "Miracle Mineral Solution" found to be a chlorine dioxide product, equivalent to industrial bleach.[126] Additional products are described below as well as in Table 5.

Elderberry *(Sambucus)* may potentiate the COVID-19 cytokine storm by increasing levels of IL-6 and TNF-a; while it is generally considered low risk, some integrative health experts advise discontinuation of elderberry for above stated reason if one contracts COVID-19.[127] Currently, there are no registered clinical trials exploring elderberry as a therapeutic or preventive agent in coronavirus. Most recommendations for its use come from anecdotal evidence gleaned from studies with viral infections such as influenza.[128-130] We urge caution

Table 5. Potential Harmful Substances Related to COVID-19.

Supplement	Mechanism of action and potential benefits	Potential harms or adverse reactions	Ongoing registered clinical trials related to COVID-19
Elderberry (*Sambucus*)	• Antiviral activity, especially in context of influenza pneumonia	• May increase TNFa and IL-6 levels, exacerbating cytokine storm contributing to ARDS in COVID-19	• There are zero registered clinical trials related to elderberry and COVID19 on clinicaltrials.gov
Colloidal silver	• Antibacterial and potentially antiviral properties when administered topically	• May cause peripheral neuropathy or argyria with oral high doses	• There is 1 registered clinical trial related to colloidal silver and COVID19 on clinicaltrials.gov
Licorice (*Glycyrrhiza glabra)*	• Herbal medicine with purported benefits for cough or febrile illness	May cause pseudoaldosteronism with hypertension and possibly death	There are 2 registered clinical trial related to licorice and COVID19 on clinicaltrials.gov
Oleander (*Nerium oleander*)	• Herbal medicine with unclear medicinal value	• Cardiac glycoside action may cause arrhythmias and possibly sudden cardiac death	• There is 1 registered clinical trial related to oleander and COVID19 on clinicaltrials.gov

before recommending this to patients until elderberry is studied specifically in the context of COVID-19 infection.

Colloidal silver can cause significant adverse effects if used inappropriately or at high doses including peripheral neuropathy and argyria—a bluish-gray, potentially permanent discoloration of the skin.[131] The National Center for Complementary and Integrative Health (NCCIH) affirms that colloidal silver has "no known function or benefits when taken by mouth." To our knowledge, there are no registered trials exploring the use of colloidal silver for the treatment of COVID-19. Unfortunately, a variety of supplement companies have advertised purported benefits of colloidal silver for treatment of COVID-19, prompting FDA warning letters.[132] Given the potential harms and lack of evidence for benefit, practitioners are discouraged from using this supplement until further evidence is available.

Licorice extract *(Glycyrrhiza glabra)* is being evaluated in 2 registered clinical trials[133,134] to determine if it has any impact on disease severity or can speed recovery from COVID-19,[133,134] but misuse of this product may result in pseudoaldosteronism with hypertension and possibly death.[135] Therefore, practitioners are discouraged from utilizing licorice as a treatment or preventative strategy in COVID-19 until trial data can verify its safety and efficacy.

Oleander extract *(Nerium oleander)* is undergoing a feasibility trial[136] for COVID-19, however, due to potential cardiotoxicity,[137] practitioners should inform patients of the potential dangers associated with this natural cardiac glycoside and recommend against its use until well-validated clinical trials evaluate safety and efficacy for COVID-19.[138]

Conclusion

Grappling to calm the ubiquitous turmoil of a worldwide pandemic, investigators have been galvanized into an expedient growth of research and ongoing clinical trials searching for effective strategies to prevent and treat COVID-19. Considering limited treatment options for COVID-19, patients and clinicians alike are increasingly turning to natural supplements in the hopes of finding effective therapeutics and adjuncts to regular care to promote immune function, diminish infectivity, and reduce the severity and duration of illness. Here the authors present a mélange of the scientific evidence and rationale for ongoing trials utilizing natural supplements in the setting of COVID-19. Natural supplements including micronutrients (vitamin C, vitamin D; zinc, NAD), probiotics, antioxidants (GSH and NAC), as well as melatonin and cannabis are being clinically investigated as an adjunct in therapy for COVID-19. Several natural supplements popular with patients, however, are not being investigated in rigorous clinical trials or are inherent with potential harms. Awaiting the results from such trials, the authors' objective is to arm clinicians with the necessary knowledge and background scientific evidence to appropriately guide patients in their selection of alternative and complementary supplements for COVID-19 prophylaxis and treatment undergoing current clinical trials.

Authors' Note

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