COVID19-HealthProfessional

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Dietary Supplements in the Time of COVID-19  
Fact Sheet for Health Professionals  
  
  
Data are insufficient to support recommendations for or against the use of any vitamin, mineral, herb or other botanical, fatty acid, or other dietary supplement ingredient to prevent or treat COVID-19.  
  
Introduction  
COVID-19, the disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in 2019 and has infected more than 650 million people worldwide as of January 1, 2023 [1]. Common initial signs and symptoms include cough, fever, fatigue, headache, muscle aches and pain, and diarrhea [2]. Some individuals with COVID-19 become severely ill, usually starting about 1 week after symptom onset; severe COVID-19 often involves progressive respiratory failure and may also result in life-threatening pneumonia, multiorgan failure, and death [2,3]. In addition, many individuals who have had COVID-19 report symptoms of long COVID (including breathlessness, cough, fatigue, muscle aches and weakness, sleep difficulties, and cognitive dysfunction) for several weeks, months, or longer after the acute stage of illness has passed [4-8]. Risk of long COVID appears to be higher in people who are hospitalized following SARS-CoV-2 infection as well as those who are not vaccinated against COVID-19 [4].  
  
Currently, data are insufficient to support recommendations for or against the use of any vitamin, mineral, herb or other botanical, fatty acid, or other dietary supplement ingredient to prevent or treat COVID-19. And by law, dietary supplements are not allowed to be marketed as a treatment, prevention, or cure for any disease; only drugs can legally make such claims [9]. Nevertheless, sales of dietary supplements marketed for immune health increased after the emergence of COVID-19 because many people hoped that these products might provide some protection from SARS-CoV-2 infection and, for those who develop COVID-19, help reduce disease severity [10-13].  
  
The immune system defends the body from pathogens that cause disease and is comprised of innate responses, which are the first line of defense, and adaptive responses, which become engaged later [14-16].  
  
The innate immune system includes physical barriers, such as the skin and gut epithelium, that help prevent pathogen entry. It also includes leukocytes (white blood cells) such as neutrophils, macrophages (which release cytokines), and natural killer cells that attempt to find and eliminate foreign pathogens. However, these components are nonspecific, meaning that unlike the adaptive immune system, they do not recognize and respond to specific pathogens [14,15].  
  
The adaptive immune system consists of B lymphocytes (B cells) that secrete antibodies into the blood and tissues (a process known as humoral immunity) and T lymphocytes (T cells; a process known as cell-mediated immunity), both of which are pathogen specific [16]. The adaptive response takes several days or weeks to develop, but it generates immunological memory; as a result, a subsequent exposure to the same pathogen leads to a vigorous and rapid immune response [14,16]. Vaccinations target the adaptive immune system, protecting the body from exposures to the same pathogen in the future [15].  
  
The body s immune response to pathogens leads to inflammation, causing redness, swelling, heat, pain, and loss of tissue function [17]. Inflammation helps eliminate the pathogen and initiate the healing process, but it is also a cause of symptoms and severe pathologies [17,18]. For example, activation of CD8 T cells as part of the adaptive immune response can increase inflammation and cause pulmonary damage. This process can lead to acute respiratory distress syndrome, which has occurred in some patients with COVID-19 [18]. Other signs of inflammation, including elevated levels of C-reactive protein and interleukin-6, sometimes develop in patients with severe COVID-19 [2]. Some patients with COVID-19 experience a cytokine storm, a critical condition caused by excessive production of inflammatory cytokines, including tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6 [3,19]. This condition increases disease severity and risk of death, so tempering the body s inflammatory response is an important component of COVID-19 management.  
  
People require several vitamins and minerals including vitamin C, vitamin D, and zinc for proper immune function, and clinical deficiencies of these nutrients can increase susceptibility to infections [15,20]. Other dietary supplement ingredients, such as botanicals and probiotics, do not have essential roles in the body but might affect immune function.  
  
Measuring the impact on the immune system of vitamins, minerals, and other dietary supplement ingredients is difficult because the immune system is a complex network of organs, tissues, and cells. No single, straightforward measure of immune system function and resistance to disease exists. Indirectly, immune function can be assessed by examining a person s risk of infectious diseases and severity of symptoms.  
  
COVID-19 vaccines are safe and highly effective at reducing the risk of disease, including the risk of severe illness [21,22]. Pharmacologic treatments are also available, but no cure for COVID-19 exists. Thus, interest in dietary supplement ingredients that might enhance immune function and reduce inflammation to help prevent COVID-19 or manage its signs and symptoms remains high. Many of these ingredients have not been studied in people with COVID-19, but research suggests that they might improve immune function and help prevent or reduce symptoms of the common cold, influenza, and other respiratory tract infections. Therefore, some scientists believe that they might hold promise for COVID-19, although the strength of the evidence supporting these speculations varies widely. For example, many studies have examined associations between serum or plasma concentrations of vitamins or minerals and risk of COVID-19 infection or disease severity. However, serum or plasma nutrient concentrations might not reflect body stores. Furthermore, the onset of disease can cause low (or sometimes high) nutrient concentrations; it cannot be assumed that the nutrient concentrations observed in these studies contributed to the onset of COVID-19 or its severity. In addition, many clinical trials in patients with COVID-19 had small samples, were not randomized or placebo controlled, and measured multiple outcomes, complicating the interpretation of their results.  
  
This fact sheet summarizes the state of the science on the safety and efficacy of these dietary supplements. Ingredients are presented in alphabetical order. Citations to published research and in-process clinical trials throughout the world from the ClinicalTrials.gov databaseexternal link disclaimer are provided; unless otherwise stated, these trials are being conducted in the United States. In addition, this fact sheet briefly discusses interactions between dietary supplement ingredients and medications. However, especially for botanicals, this information is often based on individual case reports and theoretical interactions derived from animal studies, cellular assays, or other indirect evidence. In most cases, potential interactions have not been adequately evaluated in clinical settings [23,24].  
  
The content of this fact sheet is current as of the publication date, but because this is an evolving area of research, additional evidence might have become available since that time.  
  
Andrographis  
Andrographis paniculata, also known as Chu n X n Li n, is an herb that is native to subtropical and Southeast Asia [25]. Its leaves and other aerial (above ground) parts are used in traditional Ayurvedic, Chinese, and Thai medicine for relieving symptoms of the common cold, influenza, and other respiratory tract infections [26-29]. The active constituents of andrographis are believed to be andrographolide and its derivatives, which are diterpene lactones that might have antiviral, anti-inflammatory, and immune-stimulating effects [25,27,29-34].  
  
Efficacy  
Studies conducted before the emergence of COVID-19 suggest that andrographis supplementation might reduce the severity of respiratory tract infections [27,28,35,36]. Because of these findings, some scientists believe that andrographis could help treat the symptoms of COVID-19, but studies have not thoroughly assessed use of this herb for this purpose [31,33,34,37].  
  
A few in vitro studies suggest that andrographolide isolated from andrographis might bind the main protease of SARS-CoV-2, thereby inhibiting its replication, transcription, and host cell recognition [32,33,37,38]. In a small clinical trial in Thailand, researchers examined the effects of 60 mg or 100 mg andrographis extract (called Fah Talai Jone in Thailand), given three times per day in 12 people with mild to moderate COVID-19 symptoms [39-41]. COVID-19 symptoms, especially cough, improved within a few days after patients started taking the low dose (60 mg) andrographis, and all patients recovered after 3 weeks [42]. No information was provided on the effects of the 100 mg andrographis dose.  
  
On the basis of these findings, a larger placebo-controlled trial was conducted among 60 participants, and Thailand s health ministry subsequently approved a pilot program to use Fah Talai Jone for individuals age 18 to 60 with minor symptoms within 72 hours of a COVID-19 diagnosis [39,43]. Andrographis is commonly used in Thailand in patients with mild COVID-19 [44], but its effects have been mixed. A retrospective study of 605 hospitalized patients (mostly unvaccinated) in Thailand with mild COVID-19 who took andrographis (total daily dose of 180 mg andrographolide) or received only standard of care for 5 days found that the use of andrographis was not significantly associated with risk of pneumonia [44].  
  
A clinical trial in Tbilisi, Georgia, randomized 86 hospitalized patients with mild to moderate COVID-19 (mean age 45 to 50 years, vaccination status not specified) into two groups where 34 took 6 capsules daily of a product called Kan Jang/Nergecov (containing andrographis and Eluetherococcus senticosus for a total daily dose of 90 mg andrographolides) and 52 took a placebo for 14 days [45]. Of the 71 patients who completed the study, 10% of those who took Kan Jang/Nergecov progressed to severe disease compared with 24% who took placebo. Kan Jang/Nergecov also appeared to relieve the severity of sore throat, muscle pain, and nasal discharge but not severity of cough, duration of hospitalization, time to viral clearance, or fever.  
  
A clinical trialexternal link disclaimer in progress in Thailand is comparing the effects of andrographis (three capsules, three times per day for a total daily dose of 180 mg andrographolide) with an extract of Boesenbergia rotunda (a plant in the ginger family) or standard supportive treatment for 5 days in 3,060 adults with asymptomatic COVID-19 infection.  
  
Safety  
The safety of andrographis has not been well studied, but no safety concerns have been reported when typical doses of the herb (340 to 1,200 mg/day) have been used for several days or weeks [28,29,46]. Clinical trials have found minor adverse effects, including nausea, vomiting, vertigo, skin rashes, diarrhea, and fatigue [27,29,35]. Allergic reactions might also occur [29,34]. Findings from some animal studies suggest that andrographis might adversely affect fertility, so experts recommend against its use by pregnant women and by men and women during the preconception period [26,28,29].  
  
According to animal and laboratory studies, andrographis might decrease blood pressure and inhibit platelet aggregation, so it could interact with antihypertensive and anticoagulant medications by enhancing their effects [46-48]. Because of its potential immune-stimulating effects, andrographis might also reduce the effectiveness of immunosuppressants [30,46]. Whether the potential immunostimulatory effect of andrographis might worsen the cytokine storm associated with COVID-19 is not known [34].  
  
Echinacea  
Echinacea, commonly known as purple coneflower, is an herb that grows in North America and Europe [49]. Although the genus Echinacea has many species, extracts of E. purpurea, E. angustifolia, and E. pallida are the most frequently used in dietary supplements. The echinacea supplements on the market in the United States often contain extracts from multiple species and plant parts [23].  
  
Echinacea contains volatile terpenes, polysaccharides, polyacetylenes, alkamides, phenolic compounds, caffeic acid esters, and glycoproteins [23,49,50]. However, echinacea s purported active constituents are not well defined [50], and the chemical composition of various echinacea species differs [23].  
  
Echinacea might have antioxidant and antibacterial activities, stimulate monocytes and natural killer cells, and inhibit viruses from binding to host cells [16,49]. It might also reduce inflammation by inhibiting the inflammatory cytokines interleukin-6, interleukin-8, and tumor necrosis factor and increasing levels of the anti-inflammatory cytokine interleukin-10 [16,51]. Most studies of echinacea have assessed whether it helps prevent and treat the common cold and other upper respiratory illnesses, but it has also been used in traditional medicine to promote wound healing [49,50].  
  
Efficacy  
Several studies suggest that echinacea offers limited benefits for preventing the common cold [52,53], so some researchers have suggested that echinacea might have similar effects on COVID-19 [16,34,54,55].  
  
A preliminary in vitro study found that Echinaforce, an E. purpurea preparation, inactivated SARS-CoV-2 [56]. However, results have been mixed from the few clinical trials that have examined whether echinacea reduces the risk of SARS-CoV-2 infection or severity of disease. In a clinical trial in Iran conducted before the availability of COVID-19 vaccines, 100 adults (mean age 45 47 years) with suspected COVID-19 based on chest computed tomography (CT) scan or x-ray and clinical symptoms who were not hospitalized took either echinacea (species and dose not specified) plus ginger (Zingiber officinale, dose not specified) and hydroxychloroquine for 7 days or hydroxychloroquine alone [57]. Coughing, muscle pain, and shortness of breath were alleviated in 91% to 98% of individuals who took the combination of echinacea, ginger, and hydroxychloroquine, whereas only 69% to 79% of individuals who took hydroxychloroquine alone experienced these benefits. However, the combination treatment did not reduce severity of fever or sore throat or the rate of hospitalization for COVID-19.  
  
Another clinical trial in Bulgaria included 120 healthy participants age 18 to 75 years [58]. Half of the participants took 2,400 mg Echinaforce daily over three periods of 2 months, 2 months, and 1 month with washouts of 1 week between each period; the other half served as a control group (there was no placebo). All participants were unvaccinated against COVID-19 at the start of the trial. Several became partially or fully vaccinated during the trial, but there was no significant difference in vaccination rates between groups. Participants were followed to determine if they had a positive test result for COVID-19 or developed another acute respiratory tract infection. During the trial, participants in the echinacea group who had COVID-19 or another respiratory tract infection were treated with 4,000 mg/day Echinaforce for up to 10 days; all participants also received concomitant treatments. Participants who took Echinaforce were less likely to have a positive test result for COVID-19 than those in the control group, but there were no differences between groups in the number of symptomatic episodes of COVID-19. In addition, treatment with Echinaforce reduced SARS-CoV-2 viral load but did not affect the number of days it took to achieve SARS-CoV-2 viral clearance. According to ClinicalTrials.govexternal link disclaimer, a few other clinical trials are assessing the effects of echinacea on COVID-19. For example, one trialexternal link disclaimer in Bulgaria will examine whether Echinaforce supplements at doses of 1,200 to 2,800 mg/day reduce SARS-CoV-2 viral shedding and transmission in about 75 children and adults age 12 to 75 with COVID-19. Another trialexternal link disclaimer in Spain will examine whether echinacea (dose not specified) for 10 days improves symptoms severity in about 230 nonhospitalized adults with mild COVID-19.  
  
Because echinacea might have immunostimulatory effects, some investigators have suggested that it might worsen the cytokine storm that can develop in patients with COVID-19 [54]. However, limited evidence from clinical trials suggests that the use of echinacea decreases not increases levels of proinflammatory cytokines [54].  
  
Safety  
Echinacea appears to be safe. The most common of echinacea s few adverse effects are gastrointestinal upset such as diarrhea, sleeplessness, and skin rashes [50,59,60]. Isolated reports of elevated liver enzymes and liver injury have been associated with its use, but these events could have been caused by a contaminant or the product s preparation. In rare cases, echinacea can cause allergic reactions [50].  
  
The safety of echinacea during pregnancy is not known, so experts recommend against the use of echinacea supplements by pregnant women [61].  
  
Echinacea might interact with several medications. For example, echinacea might increase cytochrome P450 activity, thereby reducing levels of some drugs metabolized by these enzymes [62]. In addition, echinacea might reduce the effectiveness of immunosuppressants due to its potential immunostimulatory activity [63].  
  
Elderberry (European Elder)  
Elder berry (usually written elderberry) is the fruit of a small deciduous tree, Sambucus nigra (also known as European elder or black elder), that grows in North America, Europe, and parts of Africa and Asia [64,65]. Elderberry contains many compounds including anthocyanins, flavonols, and phenolic acids that might have antioxidant, anti-inflammatory, antiviral, antimicrobial, and immune-stimulating effects [16,65-69]. Studies of the effects of elderberry have primarily used elderberry extracts, not the berries themselves [65].  
  
Efficacy  
Sales of elderberry supplements more than doubled shortly after the COVID-19 pandemic began in the United States [70], and some researchers have recommended studying the use of elderberry to treat COVID-19 symptoms [16,67,71,72].  
  
The interest in elderberry is based on preliminary laboratory and animal research suggesting that constituents of elderberry might help prevent upper respiratory tract infections by inhibiting viruses from binding to host cells and by stimulating the immune system [65]. Elderberry s effects on the common cold and influenza have been examined in a few small clinical trials with promising results [66]. A 2021 systematic review of five clinical trials of elderberry to prevent or treat viral respiratory illnesses found beneficial effects on some outcomes [73]. The authors found that elderberry supplementation for 2 to 16 days might reduce the severity and duration of the common cold and the duration of flu but does not appear to reduce the risk of the common cold [73]. However, the authors noted that the evidence is uncertain because the studies were small, heterogeneous, and of poor quality.  
  
According to ClinicalTrials.govexternal link disclaimer, a few clinical trials are examining whether elderberry helps prevent or treat COVID-19. For example, one trialexternal link disclaimer will examine whether 600 milligrams (mg) elderberry extract (ElderCraft) daily for 13 weeks reduces the incidence, duration, and severity of upper respiratory infections, including COVID-19, in 420 participants age 20 to 65 years. Another trialexternal link disclaimer in the United Kingdom is assessing whether an elderberry supplement (Sambucol; 15 mL four times per day) for 14 days reduces symptom severity and rates of hospital admission in 204 adults with mild or moderate COVID-19.  
  
Safety  
Elderberry flowers and ripe fruit appear to be safe for consumption. However, the bark, leaves, seeds, and raw or unripe fruit of S. nigra contain a cyanogenic glycoside that is potentially toxic and can cause nausea, vomiting, diarrhea, dehydration due to diuresis, and cyanide poisoning [65,70,74]. The heat from cooking destroys this toxin, so cooked elderberry fruit and properly processed commercial products do not pose this safety concern [16,65,67,70,74]. Elderberry might affect insulin and glucose metabolism, so according to experts, people with diabetes should use it with caution [70]. The safety of elderberry during pregnancy is not known, so experts recommend against the use of elderberry supplements by pregnant women [61,65].  
  
Recent analyses suggest that some elderberry supplements have been adulterated because they are highly diluted or contain a cheaper ingredient, such as black rice extract, instead of elderberry [64].  
  
Due to its potential immunostimulatory activity, elderberry might reduce the effectiveness of immunosuppressant medications [75].  
  
Ginseng  
Ginseng is the common name of several species of the genus Panax, most commonly Panax ginseng (also called Asian ginseng or Korean ginseng) and Panax quinquefolius (American ginseng) [76,77]. Asian ginseng grows mainly in China and Korea, whereas American ginseng grows in the United States and Canada [76].  
  
Triterpene glycosides, also known as ginsenosides, are some of the main purported active constituents of ginseng [76,78]. Although ginseng contains numerous ginsenosides, research has focused on the Rb1 ginsenoside and compound K, a bioactive substance formed when the intestinal microbiota metabolize ginsenosides [76,78]. Both the product s preparation method and variations in people s intestinal microbiota can affect the type and quantity of ginseng s bioactive compounds in the body [78].  
  
Animal and laboratory studies suggest that ginseng stimulates B-lymphocyte proliferation and increases production of some interleukins and interferon-gamma [76]; these cytokines affect immune activation and modulation [14]. Ginseng might also inhibit virus replication and have anti-inflammatory activity. However, whether ginseng has a clinically meaningful effect on immune function in humans is not clear [76,79].  
  
Another botanical, eleuthero (Eleutherococus senticosus), is sometimes confused with true ginseng. Eleuthero used to be called Siberian ginseng, but it comes from the Eleutherococcus genus of plants, not the Panax genus, and it does not contain ginsenosides [76].  
  
Efficacy  
Several clinical trials have examined whether ginseng helps prevent upper respiratory tract infections, such as the common cold and flu, but results have been mixed and none of the trials addressed COVID-19 [78,80]. Based on this limited evidence of ginseng s effects on immune function and treatment of upper respiratory tract infections, some researchers recommend studying the use of ginseng as an adjuvant therapy for COVID-19 [81-83].  
  
According to ClinicalTrials.govexternal link disclaimer, a few clinical trials are examining whether ginseng helps reduce the duration and severity of COVID-19 symptoms. For example, one clinical trialexternal link disclaimer in Hong Kong aims to determine whether ginseng and other ingredients, as part of individually tailored traditional Chinese medicine, will help about 150 children and adults with COVID-19 recover more quickly after hospital discharge [84]. Another trialexternal link disclaimer in Vietnam will examine whether a combination product containing ginseng combined with standard of care for 10 days reduces the duration and severity of symptoms in 300 adults with mild to moderate COVID-19.  
  
Safety  
Ginseng appears to be safe. Most of its adverse effects, including headache, sleep difficulty, and gastrointestinal symptoms, are minor [78-80]. However, doses of more than 2.5 g/day might cause insomnia, tachyarrhythmias, hypertension, and nervousness [76,78].  
  
A few case reports of vaginal bleeding and mastalgia (breast pain) in the 1970s and 1980s from the use of ginseng preparations raised concerns about the safety of ginseng. As a result, some scientists concluded that ginseng has estrogenic effects [85-88]. However, one of these case reports involved use of Rumanian ginseng [87], and whether this was true ginseng is not clear. In addition, eleuthero was often referred to, incorrectly, as ginseng at that time because it was called Siberian ginseng. So, it is unclear whether these case reports reflected the effects of true ginseng. Nevertheless, some experts caution that ginseng might not be safe for use during pregnancy [78,89,90].  
  
Ginseng might interact with many medications. For example, it might increase the risk of hypoglycemia if taken with antidiabetes medications, increase the risk of adverse effects if taken with stimulants, and reduce the effectiveness of immunosuppressants [90,91].  
  
Magnesium  
Magnesium is an essential mineral that is present in many foods, including green leafy vegetables, nuts, seeds, and whole grains. The Recommended Dietary Allowance (RDA, average daily level of intake sufficient to meet the nutrient requirement of 97% 98% healthy individuals) ranges from 30 to 410 mg for infants and children, depending on age, and from 310 to 420 mg for adults [92].  
  
Magnesium is a cofactor for more than 600 enzymatic reactions and plays a role in both innate and adaptive immunity as well as blood pressure regulation and normal heart rhythm [15,93-96]. Magnesium also has antithrombotic and bronchodilation effects and is required for the activation of vitamin D [93,96-100]. Because of these effects in the body, magnesium supplementation may be beneficial for people with some respiratory disorders, such as asthma and pneumonia [101,102].  
  
Healthy people do not routinely develop overt signs of magnesium deficiency, but many people do not consume recommended amounts of magnesium [94,103]. Low magnesium status is associated with decreased immune cell activity, increased oxidative stress, and increased inflammation, including increased levels of some inflammatory cytokines, such as interleukin-6 [93,97,104-107]. Low magnesium intakes or status are also associated with hypertension, impaired pulmonary function, cardiovascular disease, type 2 diabetes, and obesity [94,100,108]. These conditions are associated with poorer COVID-19 outcomes.  
  
Efficacy  
Data are insufficient to support a recommendation for or against the use of magnesium supplements to prevent or treat COVID-19. However, many researchers believe that ensuring adequate magnesium status is important in the management of COVID-19 because of magnesium s effects on immunity, inflammation, and the cardiovascular system [93,96-98,100,101,104,105,109-112].  
  
A few studies have found that people who have COVID-19 develop dysmagnesemia (abnormally low or high blood levels of magnesium) [113-115]. For example, in an analysis of serum magnesium levels of 300 patients (mean age 66.7 years) admitted to the hospital with COVID-19 in France, 48% had abnormally low magnesium levels (less than 0.75 mmol/L) and 9.6% had abnormally high magnesium levels (0.95 mmol/L or higher) [115]. In addition, an observational study in Iran among 459 patients with COVID-19 (mean age 61.8 years) found that those who died from the disease had lower magnesium levels than those who survived, although the mean magnesium levels for both groups were within the normal range [113]. However, hypomagnesemia is common in critically ill patients, regardless of their COVID-19 status [100]. Furthermore, renal failure, other health conditions, and use of certain medications, which might apply to many people with COVID-19, can also cause both hypomagnesemia and hypermagnesemia [116]. Finally, serum magnesium levels might not reflect total body magnesium stores, and hypoalbuminemia might cause spuriously low magnesium levels because about 25% of magnesium is bound to albumin [94,117]. Therefore, the presence of dysmagnesemia among patients with COVID-19 does not necessarily mean that magnesium intakes affect the risk of the disease or its severity. In addition, like other critical illnesses, COVID-19 might cause dysmagnesemia.  
  
A few observational studies have examined the effects of magnesium supplementation in patients with COVID-19. In a retrospective study in Singapore among 43 hospitalized patients age 50 years or older with COVID-19, those who received daily supplementation with 150 mg magnesium, 1,000 international units (IU) (25 mcg) vitamin D3, and 500 mcg vitamin B12 for a median of 5 days, starting within the first day of hospitalization for most patients, were less likely to need oxygen therapy, intensive care support, or both than those who did not receive the supplementation [99].  
  
Another small study in Serbia in five hospitalized patients with COVID-19 (mean age 39.6 years), difficulty breathing, and oxygen saturation at or below 95% found that taking a supplement providing 200 mg magnesium, 1,200 mg potassium, 50 mg zinc, and 1,000 mg citric acid every 4 hours for 48 hours increased oxygen saturation by a mean of 3.6 points [118]. However, with studies that use combination treatments, the potential contribution of one component is impossible to determine.  
  
Clinicaltrials.gov lists a few trialsexternal link disclaimer that are examining the use of combinations of magnesium with other ingredients in patients with COVID-19. For example, one trialexternal link disclaimer in China is investigating whether a nutritional supplement containing 400 mg magnesium, vitamins and other minerals, probiotics, L-arginine, methionine, glutamine, and other ingredients twice daily for 14 days improves outcomes in 145 adults age 60 to 90 years with mild to moderate COVID-19. Another trialexternal link disclaimer in Mexico aims to determine whether 350 mg magnesium and 4,000 IU (100 mcg) vitamin D per day for four months improves signs and symptoms of long COVID in about 200 adults with this condition.  
  
Safety  
Magnesium in foods is considered safe at any intake. Supplemental magnesium from dietary supplements or medications that contain magnesium, such as some laxatives, is safe at intakes up to 65 to 350 mg/day for children, depending on age, and up to 350 mg/day for adults [92]. These upper limits, however, do not apply to individuals receiving magnesium treatment under the care of a physician. Intakes that are higher than the upper limits can cause diarrhea, nausea, and abdominal cramping. Magnesium toxicity, which usually develops after serum concentrations exceed 1.74 2.61 mmol/L, can cause hypotension, nausea, vomiting, facial flushing, urine retention, ileus, depression, and lethargy and patients can ultimately develop muscle weakness, difficulty breathing, extreme hypotension, irregular heartbeat, and cardiac arrest or even die.  
  
Magnesium supplementation can interact with several medications. For example, it can decrease the absorption of bisphosphonates and form insoluble complexes with antibiotics. In addition, the use of loop diuretics, thiazide diuretics, or proton pump inhibitors can deplete magnesium levels [119-122].  
  
More information on magnesium is available in the Office of Dietary Supplements (ODS) health professional fact sheet on magnesium.  
  
Melatonin  
Melatonin is a hormone produced by the pineal gland in the brain, mainly during the night, that helps regulate circadian rhythms [123,124]. Its levels decrease with aging [124]. Most melatonin supplementation studies have evaluated its ability to control sleep and wake cycles, promote sleep, and reduce jet lag [124]. Studies have also examined the use of melatonin supplements for reducing blood pressure [125].  
  
Laboratory and animal studies suggest that melatonin enhances immune response by increasing the proliferation and maturation of natural killer cells, T and B lymphocytes, granulocytes, and monocytes [31,126,127]. Melatonin also appears to have anti-inflammatory and antioxidant effects [31,123,124,126-128]. However, whether these properties have a clinically significant effect on immunity in humans is not clear. Melatonin supplementation also appears to improve some markers of oxidative stress and cardio-metabolic risk in individuals with type 2 diabetes and coronary heart disease [129].  
  
Efficacy  
No evidence shows that melatonin helps prevent or treat COVID-19. However, some researchers recommend studying melatonin s effects on COVID-19 because of its reported anti-inflammatory, antioxidant, and immune-enhancing properties [31,126-128,130].  
  
One study found that among 26,779 people tested for COVID-19, those who reported using melatonin supplements were less likely to have the disease [131]. A small clinical trial in Mexico examined the effects of 50 mg melatonin every 12 hours for 5 days plus the drug pentoxifylline in 22 hospitalized adults (mean age 57.9 years) with pneumonia that resulted from COVID-19 [132]. Another group of 22 patients received pentoxifylline alone. Patients who received melatonin and pentoxifylline had a significantly lower lipid peroxidation index (a measure of oxidative stress) than at baseline, whereas those who received pentoxifylline alone did not. Both treatments significantly increased nitrite levels (suggesting higher oxygen levels) from baseline values and reduced levels of the inflammatory marker C-reactive protein. Neither treatment affected total antioxidant capacity or levels of the inflammatory markers interleukin-6 and procalcitonin.  
  
Other clinical trial evidence suggests that melatonin might help attenuate cytokine levels in people with diabetes, multiple sclerosis, and other health conditions [127]. Therefore, some researchers believe that melatonin supplements might help modulate the cytokine storm that can develop in COVID-19 [127], but studies have not tested this hypothesis.  
  
According to ClinicalTrials.govexternal link disclaimer, several other trials are underway in people with COVID-19, including a small trialexternal link disclaimer examining the effects of 10 mg melatonin supplementation three times daily for 14 days in about 30 adults age 18 years and older with COVID-19 who are not hospitalized [133]. Another trialexternal link disclaimer is investigating the effects of 10 mg melatonin plus 1,000 mg vitamin C daily on the symptoms and outcomes of about 150 adults age 50 years and older with COVID-19 who have not been hospitalized [134].  
  
Safety  
Typical doses of 1 10 mg/day melatonin appear to be safe for short-term use [31,135]. Reported side effects, which are usually minor, include dizziness, headache, nausea, upset stomach, rash, and sleepiness [124,135]. However, some reports have linked high blood levels of melatonin with delayed puberty and hypogonadism [124].  
  
Studies have not evaluated melatonin supplementation during pregnancy and breastfeeding, but some research suggests that these supplements might inhibit ovarian function [136]. Therefore, some experts recommend that women who are pregnant or breastfeeding avoid taking melatonin [135].  
  
Melatonin might interact with several medications. For example, melatonin might have anticoagulant effects, so it might increase the risk of bleeding if used with anticoagulants. It also might reduce the effects of both anticonvulsants and immunosuppressants [137-139].  
  
N-acetylcysteine  
N-acetylcysteine (NAC) is a derivative of the amino acid cysteine. It is an antioxidant and increases glutathione levels in the body [140,141]. NAC has mucolytic activity, so it helps reduce respiratory mucus levels [140,142]. Laboratory research suggests that NAC might affect immune system function and suppress viral replication [142]. NAC also decreases levels of interleukin-6 and has other anti-inflammatory effects [140,141].  
  
Much of the research on NAC has used an inhaled, liquid form of this compound. This form which is classified as a drug, not a dietary supplement is approved by the U.S. Food and Drug Administration (FDA) as a mucolytic agent and for decreasing respiratory secretion viscosity [143]. Products containing NAC are also sold as dietary supplements [144].  
  
Efficacy  
Data are insufficient to support a recommendation for or against the use of NAC supplements to prevent or treat COVID-19. However, studies have evaluated the use of oral NAC to treat bronchopulmonary diseases, such as bronchitis and chronic obstructive pulmonary disease (COPD) with some promising results in reducing numbers of episodes and symptom severity [145,146].  
  
The results from two studies suggest that NAC might benefit patients with COVID-19. In a retrospective study in Greece of 82 patients (mean age 61 64 years) hospitalized with moderate or severe COVID-19 pneumonia, 600 mg NAC twice daily for 14 days in addition to standard of care reduced the risk of progression to severe respiratory failure with the need for mechanical ventilation [147]. NAC also reduced 14- and 28-day mortality rates; at 14 days, 10 of 40 patients in the control group and 0 of 42 in the NAC group had died, and 12 of the patients in the control group and 2 in the NAC group had died at 28 days.  
  
A small clinical trial in Mexico examined the effects of 600 mg NAC every 12 hours for 5 days plus the drug pentoxifylline in 22 hospitalized adults (mean age 57.9 years) with pneumonia that resulted from COVID-19 [132]. Another group of 22 patients received pentoxifylline alone. Patients who received NAC and pentoxifylline had a significantly lower lipid peroxidation index (a measure of oxidative stress) as well as lower levels of the inflammatory markers interleukin-6 and procalcitonin than at baseline, whereas those who received pentoxifylline alone did not. NAC plus pentoxifylline also significantly increased total antioxidant capacity, whereas pentoxifylline alone did not. Both treatments significantly reduced levels of the inflammatory marker C-reactive protein and increased plasma nitrite levels (suggesting higher oxygen levels).  
  
A clinical trial in Brazil examined the effects of intravenous NAC (which is classified as a drug) in 135 hospitalized patients (median age 58 59 years) with confirmed or suspected COVID-19 [148]. Patients received either 21 g NAC, administered intravenously over 20 hours, or placebo, in addition to standard of care. NAC had no effect on the need for or duration of mechanical ventilation or admission to the intensive care unit (ICU), time in the ICU, or mortality.  
  
Because of these findings; NAC s potential antioxidant, anti-inflammatory, and antiviral effects; and its mucolytic activity, some researchers believe that using NAC as an adjuvant treatment might improve outcomes in patients with COVID-19 [140-142]. Several additional clinical trialsexternal link disclaimer are examining this possibility. For example, one trialexternal link disclaimer will evaluate the effects of 600, 1,200 or 1,800 mg NAC three times daily with or without the drug famotidine for 3 months in 42 adults who have COVID-19 and are not hospitalized [149]. Another trialexternal link disclaimer is examining whether NAC combined with glycine for 2 weeks improves outcomes in about 64 hospitalized adults age 55 to 85 years who have COVID-19 [150].  
  
Safety  
As an FDA-approved drug, the safety profile of NAC has been evaluated [143]. Reported side effects of oral NAC include nausea, vomiting, abdominal pain, diarrhea, indigestion, and epigastric discomfort [146]. No safety concerns have been reported for products labeled as dietary supplements that contain NAC.  
  
NAC might have anticoagulant effects and might reduce blood pressure so it could have additive effects if taken with anticoagulants and antihypertensive medications [151]. The combination of NAC and nitroglycerine (a medication used to treat angina) can cause hypotension and severe headaches [152,153].  
  
Omega-3 fatty acids  
Omega-3 fatty acids (omega-3s) are polyunsaturated fatty acids that are present in certain foods, such as flaxseed and fatty fish, as well as dietary supplements, such as those containing fish oil. Several different omega-3s exist, including alpha linolenic acid (ALA), but most scientific research focuses on the long-chain omega-3s, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The main food sources of EPA and DHA are fatty fish and fish oil.  
  
The Food and Nutrition Board (FNB) of the National Academies of Sciences, Engineering, and Medicine established an Adequate Intake (AI; intake assumed to ensure nutritional adequacy) for omega-3s that ranges from 0.5 to 1.6 g per day for infants and children, depending on age, and from 1.1 to 1.6 g per day for adults [154]. The FNB has not established intake recommendations for EPA and DHA specifically because they are not essential nutrients; only ALA, which our bodies cannot synthesize, is essential. Our bodies can then convert ALA into EPA and DHA.  
  
Omega-3s play important roles as components of the phospholipids that form the structures of cell membranes [154]. Omega-3s also form eicosanoids; these signaling molecules affect the body s cardiovascular, pulmonary, immune, and endocrine systems [154,155]. Omega-6 fatty acids, the other major class of polyunsaturated fatty acids, also form eicosanoids, and these eicosanoids are generally more potent mediators of inflammation, vasoconstriction, and platelet aggregation than those made from omega-3s. Thus, higher concentrations of omega-3s than of omega-6s tip the eicosanoid balance toward less inflammatory activity [156,157].  
  
Higher intakes and blood levels of EPA and DHA are associated with lower levels of inflammatory cytokines [156,158]. Omega-3s might also affect immune function by upregulating the activity of macrophages, neutrophils, T cells, B cells, natural killer cells, and other immune cells.  
  
A deficiency of omega-3s can cause rough, scaly skin and dermatitis [154]. However, researchers have not identified cut-off concentrations of DHA or EPA below which functional endpoints, such as for visual or neural function or for immune response, are impaired. Almost everyone in the United States obtains sufficient amounts of omega-3s to avoid a deficiency, but many people might benefit from higher intakes of EPA and DHA, particularly to maintain or improve cardiovascular health [159].  
  
Efficacy  
Whether higher intakes or blood levels of omega-3s reduce the risk or severity of COVID-19 is not known. However, self-reported use of omega-3 supplements (dose not reported) more than three times per week for at least 3 months among 372,720 U.K. residents age 16 to 90 years was associated with a 12% lower risk of SARS-CoV-2 infection after adjustment for potential confounders [160]. Findings were similar for 45,757 individuals in the United States and for 27,373 participants in Sweden.  
  
Because of these findings and the potential anti-inflammatory and immune-stimulating effects of omega-3s, several researchers believe that omega-3s might benefit patients with COVID-19 [15,96,106,156,158,161-164]. An analysis of red blood cell levels of EPA plus DHA among 100 hospitalized patients with COVID-19 (mean age 72.5 years) did not find a difference in the risk of death among quartiles of EPA plus DHA levels [158]. In a clinical trial in Iran, 42 of 128 critically ill patients with COVID-19 (mean age 64 to 66 years) received a 1,000 mg omega-3 supplement containing 400 mg EPA and 200 mg DHA for 14 days [165]. Patients receiving the supplement had a significantly higher 1-month survival rate compared with those who were not supplemented. The omega-3 supplement also improved several measures of respiratory and renal function, including arterial pH, blood urea nitrogen, and creatinine levels, but it did not affect other measures including oxygen saturation or white blood cell count.  
  
A few other clinical trialsexternal link disclaimer are examining whether omega-3 supplements help reduce the risk of COVID-19 or help lower levels of inflammation. For example, one trialexternal link disclaimer in about 100 healthy adults age 30 to 66 years in Jordan is investigating whether a wild salmon and fish oil complex providing 300 mg of omega-3s daily for 2 months affects levels of interleukin-1 beta, interleukin-6, and tumor necrosis factor; these cytokines are involved in the cytokine storm [166]. Another trialexternal link disclaimer in Norway is examining whether a daily cod liver oil supplement providing a total of 1,200 mg of long-chain omega-3s (mainly EPA and DHA) for 6 months reduces the risk of developing COVID-19 and reduces the severity of disease in about 80,000 healthy adults age 18 to 75 years [167].  
  
Safety  
The FNB did not establish a Tolerable Upper Intake Level (UL; maximum daily intake unlikely to cause adverse health effects) for omega-3s, although it noted that high doses of DHA and/or EPA (900 mg/day EPA plus 600 mg/day DHA or more for several weeks) might reduce immune function by suppressing inflammatory responses [154].  
  
Doses of 2 15 g/day EPA and/or DHA might also increase bleeding time by reducing platelet aggregation [154]. However, according to the European Food Safety Authority (EFSA), long-term consumption of EPA and DHA supplements at combined doses of up to about 5 g/day appears to be safe for adults [168]. EFSA noted that these doses have not been shown to cause bleeding problems or affect immune function, glucose homeostasis, or lipid peroxidation. Similarly, FDA has concluded that dietary supplements providing no more than 5 g/day EPA and DHA are safe when used as recommended [169].  
  
Commonly reported side effects of omega-3 supplements including unpleasant taste, bad breath, heartburn, nausea, gastrointestinal discomfort, diarrhea, headache, and odoriferous sweat are usually mild [170,171]. Because of their antiplatelet effects at high doses, omega-3s might interact with anticoagulants [172]. However, according to the FDA-approved package inserts for omega-3 pharmaceutical preparations, studies with omega-3s have not found that these medications result in clinically significant bleeding episodes [173]. Omega-3s might also interact with other medications. For example, omega-3s might increase the risk of hypotension if taken with antihypertensive agents and might increase levels of cyclosporine (an immunosuppressant drug) [174-176].  
  
More information on omega-3s is available in the ODS health professional fact sheet on omega-3s.  
  
Probiotics  
Probiotics are live microorganisms that confer a health benefit on the host when administered in adequate amounts [177]. They include certain bacteria (e.g., Lactobacillus acidophilus, Lactobacillus rhamnosus, and Bifidobacterium longum) and yeasts (e.g., Saccharomyces boulardii). Probiotics are naturally present in some fermented foods, added to some food products, and available as dietary supplements.  
  
Probiotics are identified by their strain, which includes the genus, species, subspecies (if applicable), and an alphanumeric strain designation [178]. Their amounts are measured in colony-forming units (CFUs), which indicate the number of viable cells. Common amounts used are 1 x 109 (1 billion CFU; commonly designated as 109 CFU) and 1 x 1010 (10 billion CFU or 1010 CFU).  
  
Probiotics act mainly in the gastrointestinal tract [18]. They might improve immune function in several ways, including enhancing gut barrier function, increasing immunoglobulin production, inhibiting viral replication, and enhancing the phagocytic activity of white blood cells. However, the mechanisms of their potential effects on immune function are unclear [18,179,180]. In addition, research findings for one probiotic strain cannot be extrapolated to others [18,181].  
  
Efficacy  
Several systematic reviews and meta-analyses published before the emergence of COVID-19 evaluated probiotic use to prevent or treat respiratory tract infections in children and adults. All of these studies found that probiotics have beneficial effects on some, but not all, outcomes [180,182-185]. Several studies have also suggested that probiotics improve outcomes in patients who have ventilator-associated pneumonia and other infections, although the evidence is of low quality and high heterogeneity [186,187]. In addition, self-reported use of probiotic supplements more than three times per week for at least 3 months among 372,720 U.K. residents age 16 to 90 years was associated with a 14% lower risk of SARS-CoV-2 infection after adjustment for potential confounders [160]. Findings were similar for 45,757 individuals in the United States and for 27,373 participants in Sweden.  
  
Probiotics might also help reduce inflammation. A meta-analysis of 42 randomized clinical trials in 2,258 participants found that probiotic supplementation with lactobacillus, bifidobacteria, saccharomyces, or combinations of strains for 1 to 52 weeks significantly reduced serum levels of some proinflammatory cytokines, including C-reactive protein, tumor necrosis alpha, interleukin-2, and interleukin-6 [188]. However, probiotic administration had no effect on other proinflammatory cytokines, including interleukin-8 and interleukin-17.  
  
Because of these findings, many researchers believe that probiotics could be useful adjuvant therapies to treat COVID-19 [164,189-196]. This possibility was examined in a clinical trial in Italy among 70 patients (median age 59 years) hospitalized with COVID-19 [197]. All patients received hydroxychloroquine, antibiotics, and tocilizumab (a monoclonal antibody), alone or in combination. In addition, 28 of the 70 patients also took a probiotic (Sivomixx) containing a mixture of Streptococcus, Lactobacillus, and Bifidobacterium strains three times daily for a total daily dose of 2,400 billion bacteria for 14 days. Signs and symptoms including diarrhea, fever, asthenia (weakness), headaches, myalgia (muscle pain), and dyspnea (difficulty breathing) were significantly lower within 7 days in patients taking the probiotic than in those who did not. Probiotic administration also reduced the risk of mortality, transfer to ICU, and respiratory failure.  
  
Another clinical trial examined the effects of an enzyme and probiotic combination in 200 adults (mean age 41 years) with post-COVID fatigue and muscle weakness who had received a negative COVID-19 test result 3 weeks before, on average [198].The supplements used were capsules containing 500 mg of ImmunoSEB and 5 billion CFU of ProbioSEB CSC3. Participants took two capsules in the morning and two in the evening on an empty stomach, plus two capsules with lunch. The investigators measured fatigue using questions about such issues as tiredness, difficulty starting tasks, lack of energy or muscle strength, difficulty concentrating, and memory. After 14 days of treatment, fatigue resolved in 91% of individuals who took the enzyme and probiotic supplement and only 15% of individuals who took the placebo.  
  
Several additional clinical trialsexternal link disclaimer are underway. For example, one trialexternal link disclaimer in Canada plans to investigate whether probiotic administration for up to 25 days reduces the duration and severity of symptoms of COVID-19 in about 84 adults age 18 years and older with moderate forms of the disease who are not hospitalized [199]. Another trialexternal link disclaimer is examining the effects of Lactobacillus rhamnosus GG supplementation for 28 days on the microbiome of 182 children and adults age 1 year and older with a household exposure to someone diagnosed with COVID-19 but who do not have any COVID-19 symptoms [200].  
  
Safety  
Probiotics, such as strains of Lactobacillus, Bifidobacterium, and Propionibacterium, have a long history of use in food and are often present in the normal gastrointestinal microbiota, indicating that probiotic supplements are safe for most people [179]. Side effects, which are usually minor, include gastrointestinal symptoms, such as gas [18,180]. However, potential safety concerns can include systemic infections, especially in individuals who are immunocompromised [179]. For example, in a few cases (mainly in individuals who were severely ill or immunocompromised), the use of probiotics was linked to bacteremia, fungemia (fungi in the blood), or infections that resulted in severe illness [201,202].  
  
Probiotics are not known to interact with medications. However, antibiotic and antifungal medications might decrease the effectiveness of some probiotics [203,204].  
  
More information on probiotics is available in the ODS health professional fact sheet on probiotics.  
  
Quercetin  
Quercetin is a flavonol (a polyphenolic compound) present in many fruits, vegetables, spices, and beverages, including citrus fruits, apples, onions, berries, broccoli, cilantro, dill, tea, and red wine [205-209]. Research suggests that quercetin might have antioxidant, antiviral, anti-inflammatory, and immunomodulatory effects [206-212]. It might also inhibit platelet aggregation [206,212]. Quercetin has very low oral bioavailability, ranging from 3% to 17% [207], but combining it with sunflower lecithin increases its bioavailability by as much as 20 times [206,208].  
  
Efficacy  
Results have been mixed in a few clinical trials examining the effects of 500 and 1,000 mg/day quercetin (sometimes in combination with vitamin C or niacin) on the risk of upper respiratory tract infections and the severity of symptoms of these infections [213,214]. Because of its molecular structure and pharmacological properties, some researchers believe quercetin might inhibit the SARS-CoV-2 virus so they recommend studying its use to reduce the risk of COVID-19 [206,208,209,211,215] Quercetin might also reduce inflammation and organ damage, such as acute kidney injury, that occurs in some critically ill patients with COVID-19 [207,210,216]. Others recommend studying the combination of quercetin with vitamin C because these substances might have antioxidant synergy [212]. However, at this time, only a couple of preliminary clinical trials have examined the use of quercetin supplementation in patients with COVID-19.  
  
In an open-label clinical trial in Pakistan, 152 adults age 18 to 80 with COVID-19 who had mild to moderate symptoms and were not hospitalized were divided into two groups. The first group received Quevir, a supplement containing 200 mg quercetin with sunflower lecithin (Quercetin Phytosome), twice daily plus standard of care (analgesics, fever-reducing medications, oral steroids, and antibiotics) or standard of care only for 30 days [217]. Individuals receiving quercetin supplements were significantly less likely to require hospitalization than those who did not receive quercetin supplements. Among patients who required hospitalization, stays were shorter if they received the quercetin supplements. Quercetin supplementation also reduced the need for oxygen therapy. A follow-up open-label study by the same researchers compared the effects of supplementation with Quevir (three times daily for a total dose of 600 mg/day quercetin for 7 days, followed by 400 mg/day for 7 more days) with the effects of standard of care in 42 adults with mild to moderate COVID-19 who were not hospitalized [218]. Of 21 individuals who received quercetin and standard of care, 16 had negative SARS-CoV-2 test results after 1 week of treatment, whereas only 2 of 21 patients in the standard-of-care group had negative test results. After 2 weeks of treatment, all patients who received quercetin and standard of care had negative SARS-CoV-2 test results, as did 19 of 21 patients in the standard-of-care group. A confounding factor in this study, however, was that patients in the standard-of-care group were significantly older (mean of 56.2 years) than those in the quercetin group (42.5 years).  
  
Several additional clinical trialsexternal link disclaimer are underway. For example, one trialexternal link disclaimer in Turkey is examining whether 500 mg/day quercetin for 3 months reduces the risk of COVID-19 in healthy adults and whether 1,000 mg/day for 3 months improves outcomes in adults with COVID-19 [219]. Another trialexternal link disclaimer in Pakistan is comparing the effect of 400 mg/day quercetin (Quercetin Phytosome) for 30 days to that of standard of care on COVID-19 disease progression in 152 adults with COVID-19 who are not hospitalized [220].  
  
Safety  
According to FDA, up to 500 mg quercetin per serving is generally recognized as safe (GRAS) as an ingredient in foods and beverages, including grain products, pastas, processed fruits, fruit juices and soft candies [221]. Less is known about quercetin supplements, but no serious adverse effects have been reported in clinical trials that used up to 1,000 mg/day for up to 12 weeks [205,213,217,218,222]. Reported side effects from one clinical trial that administered 200 mg quercetin twice daily for 30 days included gastric pain and reflux, constipation, diarrhea, flatulence, and sleep disorders, but the rate of these effects was similar in the treatment and control groups [217].  
  
Quercetin might affect drug-metabolizing enzymes, such as CYP3A4, which could increase the bioavailability of cyclosporine, pravastatin (used to treat high cholesterol), and fexofenadine (an antihistamine) [222]. In addition, quercetin might reduce blood pressure in people with hypertension [223], so it could potentiate the effects of antihypertensive medications.  
  
Selenium  
Selenium is an essential mineral contained in many foods, including Brazil nuts, seafood, meat, poultry, eggs, and dairy products as well as bread, cereals, and other grain products. The RDA for selenium ranges from 15 to 70 mcg for infants and children, depending on age, and from 55 to 70 mcg for adults [224].  
  
Selenium helps support both the innate and adaptive immune systems through its role in T-cell maturation and function and in natural killer cell activity. It also reduces the risk of infections [15,106,225-230]. As an antioxidant, selenium might also help reduce the systemic inflammatory response that can lead to acute respiratory distress syndrome and organ failure [226,228,231].  
  
Low selenium status in humans has been associated with lower natural killer cell activity, increased risk of some bacterial infections, and increased virulence of certain viruses [15,227,230-232]. In addition, some research suggests that 100 to 300 mcg/day selenium supplements improve immune function and that doses of 50 or 100 mcg/day enhance the immune response to poliovirus vaccine [227].  
  
Selenium status varies by geographic region because of differences in the amounts of selenium in soil and in local foods consumed [224,233]. Selenium deficiency is very rare in the United States and Canada, but low selenium status is common in some areas of the world, such as parts of Europe and China [229,234].  
  
Efficacy  
Data are insufficient to support a recommendation for or against the use of selenium supplements to prevent or treat COVID-19. However, many researchers recommend studying selenium as an adjuvant therapy for COVID-19 because of its antiviral, anti-inflammatory, and immune-enhancing effects [106,225-227,229-231,234-238].  
  
Before the emergence of COVID-19, a Cochrane Review of 16 clinical trials with a total of 2,084 critically ill patients (because of burns, head injury, brain hemorrhage, cerebrovascular accident, or elective major surgery) found that intravenous selenium supplementation (which is classified as a drug) for 5 to 28 days or until discharged (length of treatment not specified) reduced overall mortality rates by 18% but did not affect 28-day or 90-day mortality rates [228]. Intravenous selenium also had no effect on duration of ICU stay or hospital stay or on number of days on a ventilator. However, the authors note that these findings should be viewed with caution because the evidence was of very low quality.  
  
Some research shows that patients hospitalized with COVID-19 have low selenium status at admission, and this low status might adversely affect the body s immune response [236,237,239]. In addition, selenium deficiency might increase the risk of mortality from COVID-19 [230]. For example, in a small study in Germany, the mean serum selenium level of 33 patients with COVID-19 (50.8 mcg/L) was significantly lower than the mean value from a healthy cross-sectional study of 1,915 European residents (84.4 mcg/L) [237]. A value of 80 mcg/L is typically considered adequate. In addition, the 27 patients who survived COVID-19 had a significantly higher mean serum selenium level (53.3 mcg/L) than the six who did not (40.8 mcg/L) [237]. Similarly, a retrospective analysis in China of data from about 70,000 people with COVID-19 found significantly higher survival rates in those living in areas where average selenium status was higher than in those living in areas where average selenium status was lower, based on hair selenium levels in the various regions [234]. However, selenium status can be assessed in multiple ways and because 37% of selenium is bound to albumin in the blood [240], selenium measurements can be confounded if not adjusted for albumin levels in severe illness.  
  
No clinical trials of selenium supplementation in patients with COVID-19 have been published, but several trialsexternal link disclaimer are underway. For example, one trialexternal link disclaimer in Spain is investigating whether daily micronutrient supplementation with 110 mcg selenium along with 10 other vitamins and minerals for 14 days in 300 adults with COVID-19 reduces the need for hospitalization due to the disease [241]. Another trialexternal link disclaimer is examining the effects of 2,000 mcg selenium (as a selenious acid infusion) on day 1 followed by 1,000 mcg on days 2 14 plus standard-of-care therapy in 100 hospitalized adults with moderate, severe, or critical COVID-19 [242].  
  
Safety  
Up to 45 to 400 mcg/day selenium from foods and dietary supplements is safe for infants and children, depending on age, and up to 400 mcg/day is safe for adults [224]. These upper limits, however, do not apply to individuals receiving selenium under the care of a physician. Higher intakes can cause garlic odor in the breath and a metallic taste in the mouth as well as hair and nail loss or brittleness. Other signs and symptoms of excess selenium intakes include nausea, diarrhea, skin rashes, mottled teeth, fatigue, irritability, and nervous system abnormalities.  
  
Cisplatin, a chemotherapy agent used to treat ovarian, bladder, lung, and other cancers can reduce selenium levels in hair, plasma, and serum [243,244]. Some studies have examined whether selenium supplementation helps reduce the side effects of cisplatin and other chemotherapy agents, but the evidence is uncertain [244,245].  
  
More information on selenium is available in the ODS health professional fact sheet on selenium.  
  
Vitamin C  
Vitamin C, also called ascorbic acid, is an essential nutrient found in many fruits and vegetables, including citrus fruits, tomatoes, potatoes, red and green peppers, kiwi fruit, broccoli, strawberries, brussels sprouts, and cantaloupe. The RDA ranges from 15 to 115 mg for infants and children, depending on age, and from 75 to 120 mg for nonsmoking adults; people who smoke need 35 mg more per day [224].  
  
Vitamin C plays an important role in both innate and adaptive immunity, probably because of its antioxidant effects, antimicrobial and antiviral actions, and effects on immune system modulators [59,246-249]. Vitamin C helps maintain epithelial integrity, enhance the differentiation and proliferation of B cells and T cells, enhance phagocytosis, normalize cytokine production, and decrease histamine levels [247]. It might also inhibit viral replication [250].  
  
Vitamin C deficiency impairs immune function and increases susceptibility to infections [247]. Some research suggests that supplemental vitamin C enhances immune function [251], but its effects might vary depending on an individual s vitamin C status [252].  
  
Vitamin C deficiency is uncommon in the United States, affecting only about 7% of individuals age 6 years and older [253]. People who smoke and those whose diets include a limited variety of foods (such as some older adults and people with alcohol or drug use disorders) are more likely than others to obtain insufficient amounts of vitamin C [248,251].  
  
Efficacy  
Currently, data are insufficient to support a recommendation either for or against the use of vitamin C supplements to prevent or treat COVID-19. However, many researchers recommend studying vitamin C as an adjuvant therapy for COVID-19, including its possible ability to reduce inflammation and vascular injury in these patients [106,128,164,246,249,254-257].  
  
Interest in the use of vitamin C supplements to treat COVID-19 comes from research showing that taking 200 mg/day or more vitamin C supplements on a regular basis helps reduce the duration of the common cold and the severity of its symptoms [246,250]. Vitamin C supplements also appear to reduce the risk of developing a cold in people exposed to extreme physical stress including marathon runners, skiers, and soldiers in subarctic areas [250]. In addition, vitamin C supplementation might benefit people with pneumonia who have low vitamin C levels [258] as well as people with viral infections, including Epstein-Barr and herpes zoster [251]. Vitamin C s antioxidant action might also help reduce oxidative stress during infections [246,250]. People with low vitamin C status might benefit more from vitamin C supplementation than those who already obtain sufficient vitamin C [252].  
  
A few observational studies have examined the effects of vitamin C supplementation on mortality rates in patients with COVID-19 and have had mixed findings [257]. For example, a retrospective chart review of 102 patients (median age 63 years) with COVID-19 who were receiving intensive care included 73 patients who received vitamin C plus zinc (doses not specified); the other patients did not receive these supplements [259]. Vitamin C and zinc supplementation did not affect mortality. Another retrospective chart review included 152 patients with COVID-19 (median age 68 years) who were on mechanical ventilation [260]. The 79 patients who received vitamin C supplements (doses not specified) had a significantly lower mortality rate than those who did not receive vitamin C supplements. In addition, self-reported use of vitamin C supplements (doses not reported) more than three times per week for at least 3 months among 372,720 U.K. residents age 16 to 90 years, 45,757 individuals in the United States, and 27,373 individuals in Sweden was not associated with higher or lower risk of SARS-CoV-2 infection [160].  
  
A small clinical trial in Mexico examined the effects of 1,000 mg vitamin C every 12 hours for 5 days plus the drug pentoxifylline in 22 hospitalized adults (mean age 57.9 years) with pneumonia that resulted from COVID-19 [132]. Patients who received vitamin C and pentoxifylline had significantly lower levels of the inflammatory markers interleukin-6 and procalcitonin than at baseline, whereas those who received pentoxifylline alone did not. Vitamin C plus pentoxifylline also significantly increased total antioxidant capacity, but pentoxifylline alone did not. Both treatments significantly increased nitrite levels (suggesting higher oxygen levels) from baseline values and reduced levels of the inflammatory marker C-reactive protein, but neither treatment affected the lipid peroxidation index. The COVID A to Z trial compared the effects of daily supplementation with 8,000 mg ascorbic acid, 50 mg zinc (as zinc gluconate), or both for 10 days with standard of care in 214 adults (mean age 45.2 years) with COVID-19 who were not hospitalized [261]. None of the supplements shortened symptom duration.  
  
Studies have also examined the effects of vitamin C administered intravenously. Intravenous administration of vitamin C can produce plasma concentrations that are much higher than those produced by oral doses [262]. FDA classifies intravenous forms of vitamin C as drugs; only oral forms can be classified as dietary supplements. According to some case reports from China, for example, high-dose intravenous vitamin C (10 20 g per day administered over 8 to 10 hours) increased the oxygenation index in 50 patients with moderate to severe COVID-19; all patients eventually recovered [263]. In a pilot trial in China, 56 patients with COVID-19 (mean age 66.7 years) in ICU received either intravenous vitamin C (12 g twice daily) or placebo for 7 days or until ICU discharge or death [264]. Vitamin C administration did not affect 28-day mortality rates. In another trial of 60 patients with severe COVID-19 infection (mean age 58 to 61 years) and receiving oral lopinavir/ritonavir and hydroxychloroquine, 30 patients were also given intravenous vitamin C (1.5 g four times daily) for 5 days [265]. Vitamin C administration did not affect mortality, length of ICU stay, or oxygen saturation at discharge.  
  
The National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel notes that in patients who do not have COVID-19, intravenous vitamin C alone or in combination with other nutrients and medications improves some but not all outcomes in critically ill patients with sepsis, acute respiratory distress syndrome, or pneumonia [249]. However, the Panel concludes that data are insufficient to support a recommendation for or against the use of vitamin C to treat COVID-19 [249].  
  
Several other clinical trialsexternal link disclaimer are examining whether vitamin C (administered intravenously or as a dietary supplement) in combination with other dietary supplement ingredients, medications, or both helps prevent or treat COVID-19. For example, one trialexternal link disclaimer in Italy is investigating intravenous administration of 10 g ascorbic acid in addition to conventional therapy in about 500 children and adults who are hospitalized with COVID-19 pneumonia [266]. Another trialexternal link disclaimer is evaluating whether daily supplementation with 1,000 mg ascorbic acid plus 10 mg melatonin for 14 days affects the symptoms and outcomes of COVID-19 in about 150 adults aged 50 years and older who are not hospitalized [134].  
  
Safety  
Vitamin C in foods and dietary supplements is safe at intakes up to 400 to 1,800 mg/day for children, depending on age, and up to 2,000 mg/day for adults [224]. These upper limits, however, do not apply to individuals receiving vitamin C treatment under the care of a physician. Higher intakes can cause diarrhea, nausea, and abdominal cramps. High vitamin C doses might also cause falsely high or low readings on some blood glucose meters that are used to monitor glucose levels in people with diabetes [267-269]. In people with hemochromatosis, high doses of vitamin C could exacerbate iron overload and damage body tissues [224,248]. The FNB recommends that these individuals be cautious about consuming vitamin C doses above the RDA [224].  
  
Vitamin C supplementation might interact with some medications. For example, it might reduce the effectiveness of radiation therapy and chemotherapy by protecting tumor cells from the action of these agents [270].  
  
More information on vitamin C is available in the ODS health professional fact sheet on vitamin C.  
  
Vitamin D  
Vitamin D, whose forms are vitamin D2 and vitamin D3, is an essential nutrient that is naturally present in only a few foods, such as fatty fish (including salmon and tuna) and fish liver oils, and in small amounts in beef liver, cheese, and egg yolks. Fortified foods, especially fortified milk, provide most of the vitamin D in American diets. The RDA for vitamin D ranges from 10 to 15 mcg (400 IU to 600 IU) for children, depending on age, and from 15 to 20 mcg (600 to 800 IU) for adults [271]. The body can also synthesize vitamin D from sun exposure.  
  
Vitamin D obtained from sun exposure, foods, and supplements is biologically inert and must undergo two hydroxylations in the body for activation. The first hydroxylation, which occurs in the liver, converts vitamin D to 25-hydroxyvitamin D [25(OH)D]. The second hydroxylation occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [1,25(OH)2D]. Serum concentration of 25(OH)D is currently the main indicator of vitamin D status [271]. Although researchers have not definitively identified serum concentrations of 25(OH)D associated with deficiency and adequacy, the FNB advises that levels below 30 nmol/L (12 ng/mL) are associated with vitamin D deficiency, and levels of 50 nmol/L (20 ng/mL) or more are considered adequate for bone and overall health in most people [271]. However, 25(OH)D levels defined as deficient or adequate vary from study to study.  
  
In addition to its well-known effects on calcium absorption and bone health, vitamin D plays a role in immunity [272]. Vitamin D appears to lower viral replication rates, suppress inflammation, and increase levels of T-regulatory cells and their activity [128,255,273-277]. In addition, immune cells (e.g., B lymphocytes and T lymphocytes) express the vitamin D receptor, and some immune cells (e.g., macrophages and dendritic cells) can convert 25(OH)D into the active 1,25(OH)2D. This ability suggests that vitamin D might modulate both innate and adaptive immune responses [255,274,276,277].  
  
Vitamin D deficiency affects the body s susceptibility to infection and has been associated with influenza, hepatitis C, human immunodeficiency virus (HIV) and other viral diseases [278,279]. Surveys indicate that most people in the United States consume less than recommended amounts of vitamin D [280]. Nevertheless, according to a 2011 2014 analysis of serum 25(OH)D concentrations, most people in the United States age 1 year and older had adequate vitamin D status [281]. Sun exposure, which increases serum 25(OH)D levels, is one of the reasons serum 25(OH)D levels are usually higher than would be predicted on the basis of dietary vitamin D intakes alone [271].  
  
Efficacy  
Currently, data are insufficient to support a recommendation for or against the use of vitamin D supplementation to prevent or treat COVID-19. However, some evidence suggests that vitamin D supplementation helps prevent respiratory tract infections, particularly in people with 25(OH)D levels less than 25 nmol/L (10 ng/mL) [282]. Scientists are therefore actively studying whether vitamin D might also be helpful for preventing or treating COVID-19.  
  
Some studies link lower vitamin D status with a higher incidence of COVID-19 and more severe disease [239,283-291] but others do not [292-296]. For example, a comparison of serum 25(OH)D levels in 335 patients with COVID-19 in China with levels in 560 age- and sex-matched healthy participants found significantly lower 25(OH)D concentrations (median of 26.5 nmol/L [10.6 ng/mL]) in patients with COVID-19 than healthy participants (median of 32.5 nmol/L [13 ng/mL]) [284]. In addition, the prevalence of vitamin D deficiency [defined as serum 25(OH)D less than 30 nmol/L (12 ng/mL)] was significantly higher in patients with COVID-19 than healthy participants, and vitamin D deficiency was associated with more severe COVID-19. Another study from Spain also found lower 25(OH)D levels as well as higher rates of vitamin D deficiency in 216 hospitalized patients with COVID-19 than in 197 healthy individuals, although it did not find any relationship between disease severity and vitamin D levels or deficiency status [285]. Similarly, a study of 120 patients (mean age 62.3 years) hospitalized in Algeria with severe COVID-19 found a linear inverse association between vitamin D status and mortality rates; patients with adequate 25(OH)D levels (higher than 78 nmol/L [30 ng/mL]) had a 13.3% mortality rate, whereas those with severe deficiency [25(OH)D lower than 26 nmol/L (10 ng/mL)] had a 46.9% mortality rate [286]. A systematic review and meta-analysis of 31 observational studies (including some of those described above) did not find significant associations between serum 25(OH)D levels below 50 nmol/L (20 ng/ml) and incidence of COVID-19, risk of mortality, ICU admission, or need for ventilation among COVID-19 patients [297]. However, mean 25(OH)D levels were significantly lower in COVID-19 patients than healthy individuals, based on the results from five studies that examined this outcome.  
  
Other studies found that people with vitamin D deficiency were more likely to have COVID-19 and a poorer prognosis than those who were vitamin D sufficient [239,298-302] and that people who regularly took vitamin D supplements (amounts not specified) were less likely to develop COVID-19 than those who did not [303]. A retrospective study of 4,638 individuals (mean age 52.8 years) who were tested for COVID-19 examined associations between vitamin D levels (measured during the previous year but not within 14 days of COVID-19 testing) and COVID-19 test results [304]. Black individuals with 25(OH)D levels below 100 nmol/L (40 ng/mL) had higher risk of COVID-19 than those with higher levels, but the results showed no associations between vitamin D levels and COVID-19 risk among White individuals. Another study in 235 patients (mean age 58.7 years) hospitalized with COVID-19 found that those with vitamin D sufficiency had less severe disease [305]. In this study, people with vitamin D sufficiency [defined as 25(OH)D levels higher than 75 nmol/L (30 ng/mL)] also had lower levels of C-reactive protein and higher lymphocyte percentages than those with vitamin D insufficiency. These changes might have reduced the risk of the cytokine storm [275,305].  
  
Some of these investigators did not consider confounders, such as obesity and race. Many people with obesity, for example, have lower vitamin D status and more severe COVID-19 than individuals with a healthy weight [271,306]. An analysis of 348,598 U.K. Biobank participants (median age 49 years), of whom 449 had COVID-19, did not find a link between 25(OH)D concentrations and risk of SARS-CoV-2 infection after adjusting for confounders including ethnicity, body mass index (BMI) category, age at assessment, and sex [296].  
  
A systematic review and meta-analysis of 39 studies from around the world (primarily in adults) that examined associations between 25(OH)D levels and SARS-CoV-2 infection rates and COVID-19 severity found that participants with vitamin D deficiency [defined as 25(OH)D levels <25 nmol/L to 75 nmol/L (<10 ng/mL to 30 ng/mL) depending on the study] had a higher risk of SARS-CoV-2 infection and more severe COVID-19 disease than those with adequate vitamin D levels [307]. However, associations between vitamin D deficiency and ICU admission, pulmonary complications, hospitalization, inflammation, and mortality were inconsistent. Other systematic reviews and meta-analyses have found that patients with COVID-19 who have vitamin D deficiency or lower vitamin D status or who do not take vitamin D supplements have more severe disease and higher mortality rates than others [308-310]. However, these reviews found inconsistent associations between vitamin D status and risk of SARS-CoV-2 infection. A study in Ireland that examined 25(OH)D levels in 149 patients (mean age 48 years) at a median of 79 days after the onset of COVID-19 illness found no relationship between 25(OH)D levels and fatigue or exercise tolerance, both of which are common symptoms of long COVID [311].  
  
Although many observational studies suggest a link between low vitamin D status and higher incidence of COVID-19 and more severe disease, vitamin D status measurements after disease onset might not reflect preinfection vitamin D status. In a small study in nine healthy men (median age 22 years), administration of a lipopolysaccharide to induce systemic inflammation significantly reduced 25(OH)D levels within hours [312]. Because COVID-19 induces an inflammatory response, some of the associations between low 25(OH)D concentrations and COVID-19 might be explained by reverse causality [i.e., the disease might have caused the low 25(OH)D concentrations].  
  
Some evidence suggests that vitamin D supplementation might reduce COVID-19 severity. Self-reported use of vitamin D supplements (dose not reported) more than three times per week for at least 3 months among 372,720 U.K. residents age 16 to 90 years was associated with a 9% lower risk of SARS-CoV-2 infection after adjustment for potential confounders [160]. Findings were similar for 45,757 individuals in the United States and 27,373 individuals in Sweden.  
  
An analysis of data on 77 hospitalized adults in France (where vitamin D supplementation is routinely recommended for those over 65 years of age) with COVID-19 (mean age 88 years) found that those who had received bolus oral doses of 1,250 mcg (50,000 IU) vitamin D3 per month or 2,000 mcg (80,000 IU) or 2,500 mcg (100,000 IU) vitamin D3 every 2 or 3 months throughout the preceding year had less severe disease and lower mortality rates than those who did not receive vitamin D supplementation [313]. In addition, a nonrandomized retrospective study in Spain of 537 patients hospitalized with COVID-19 (median age 70 years) found that the 79 patients who received calcifediol (25-OHD3, 532 mcg on the first day and 266 mcg on days 3, 7, 14, 21, and 28) combined with medications had a lower mortality rate during the first 30 days of hospitalization than those who received medications without calcifediol [314].  
  
An observational study in the United Kingdom found that of 444 hospitalized patients (median age 74 years) with COVID-19, those who received various vitamin D3 regimens with doses of 500 to 1,250 mcg (20,000 to 50,000 IU) daily to biweekly for 7 days to 7 weeks had a lower risk of death from the disease [315]. This finding was replicated in another cohort of 542 hospitalized patients, some of whom received similar doses of vitamin D3 supplements [315]. Similarly, an observational study in Singapore found that the 17 of 43 hospitalized patients aged 50 years or older with COVID-19 who received 25 mcg (1,000 IU) vitamin D3, 150 mg magnesium, and 500 mcg vitamin B12 daily for a median of 5 days (initiated within the first day of hospitalization for most patients) were less likely to need oxygen therapy, intensive care support, or both than those who did not receive the supplementation [99].  
  
Because of these findings, many researchers recommend additional research on whether higher vitamin D intakes or vitamin D supplementation can reduce the risk and severity of COVID-19 [96,97,106,128,164,239,255,273,275,276,284,298,299,305,316-322].  
  
In an open letter, more than 200 scientists and doctors recommended that adults increase vitamin D intakes from all sources to achieve serum 25(OH)D levels above 75 nmol/L (30 ng/mL) to prevent COVID-19 or reduce its symptoms [323]. They also recommended that adults whose 25(OH)D levels are not tested achieve a daily vitamin D intake of 50 to 100 mcg daily (2,000 4,000 IU); individuals at increased risk of vitamin D deficiency (e.g., those who have obesity, have dark skin, or live in care facilities) might need even larger amounts. These scientists and doctors also recommended that hospitals measure the serum 25(OH)D levels of all patients hospitalized for COVID-19 and that patients with levels below 75 nmol/L (30 ng/mL) receive vitamin D supplementation.  
  
This open letter is not an official guidance document, however. The NIH COVID-19 Treatment Guidelines Panel states that data are currently insufficient to support a recommendation for or against the use of vitamin D to prevent or treat COVID-19 [277]. Guidelines on vitamin D and COVID-19 from the National Institute for Health and Care Excellence (NICE) in the United Kingdom state that individuals older than 4 years should consider taking 10 mcg (400 IU) of vitamin D daily between October and early March to maintain bone and muscle health [324]. However, the United Kingdom does not fortify milk with vitamin D [325]. In addition, NICE does not recommend that people take vitamin D supplements solely to prevent or treat COVID-19, except as part of a clinical trial [324].  
  
A clinical trial in 240 hospitalized patients (mean age 56.2 years) with moderate to severe COVID-19 compared the effects of a single oral dose of 5,000 mcg (200,000 IU) vitamin D3 administered about 10 days after symptom onset with placebo [326]. The mean baseline 25(OH)D level among participants was 52.3 nmol/L (20.9 ng/mL). Vitamin D treatment did not significantly reduce the length of hospitalization or risk of mortality while hospitalized, ICU admission, or need for mechanical ventilation, even among the 115 patients with vitamin D deficiency at baseline [defined as 25(OH)D below 50 nmol/L (20 ng/mL)]. Another clinical trial in Saudi Arabia compared the effects of 125 mcg (5,000 IU) vitamin D3 daily for 14 days with the effects of 25 mcg (1,000 IU) vitamin D3 in 69 adults (mean age 49.8 years) who were hospitalized with mild to moderate COVID-19 [327]. Patients receiving 125 mcg vitamin D had shorter duration of coughing (mean of 6.2 days vs. 9.1 days) and loss of taste (mean of 11.4 days vs. 16.9 days) than those receiving 25 mcg, but the duration of other symptoms including fever, fatigue, headache, sore throat, body aches, and chills did not differ between groups.  
  
Many additional clinical trialsexternal link disclaimer are examining whether vitamin D supplementation, alone or in combination with other treatments, helps prevent COVID-19 or reduce its severity. For example, the CORONAVIT trialexternal link disclaimer is comparing the impact of 20 mcg (800 IU) or 80 mcg (3,200 IU) daily vitamin D3 supplementation with U.K. standard of care (10 mcg vitamin D3 [400 IU]) for 6 months on risk and severity of COVID-19 in 6,200 healthy U.K. residents age 16 years and older [328]. Another trialexternal link disclaimer is examining whether vitamin D3 supplementation for 28 days (240 mcg [9,600 IU] on days 1 and 2, followed by 80 mcg [3,200 IU] on days 3 through 28) in about 2,700 adults age 30 years and older who were recently diagnosed with COVID-19 helps reduce the severity of disease and risk of transmission to household members [329].  
  
Safety  
Daily intakes of up to 25 100 mcg (1,000 IU 4,000 IU) vitamin D in foods and dietary supplements are safe for infants and children, depending on age, and up to 100 mcg (4,000 IU) are safe for adults [271]. These upper limits, however, do not apply to individuals receiving vitamin D treatment under the care of a physician. Higher intakes (usually from supplements) can lead to nausea, vomiting, muscle weakness, confusion, pain, loss of appetite, dehydration, excessive urination and thirst, and kidney stones. In extreme cases, vitamin D toxicity causes renal failure, calcification of soft tissues throughout the body (including in coronary vessels and heart valves), cardiac arrhythmias, and even death [330-332].  
  
Several types of medications might interact with vitamin D. For example, orlistat, statins, and steroids can reduce vitamin D levels [333,334]. In addition, taking vitamin D supplements with thiazide diuretics might lead to hypercalcemia [333].  
  
More information on vitamin D is available in the ODS health professional fact sheet on vitamin D.  
  
Vitamin E  
Vitamin E, also called alpha-tocopherol, is an essential nutrient that is present in several foods, including nuts, seeds, vegetable oils, and green leafy vegetables. The RDA for vitamin E is 4 to 15 mg for infants and children, depending on age, and 15 to 19 mg for adults [224].  
  
Vitamin E is an antioxidant that plays an important role in immune function by helping to maintain cell membrane integrity and by enhancing antibody production, lymphocyte proliferation, and natural killer cell activity [106,227,272,335,336]. Vitamin E has also been shown to limit inflammation by inhibiting the production of proinflammatory cytokines [337]. Vitamin E deficiency impairs both humoral and cell-mediated immunity and increases susceptibility to infections [227,336,338]. Some studies suggest that high-dose vitamin E supplements (60 to 800 mg/day) for 1 to 8 months enhance lymphocyte proliferation, interleukin-2 production, and natural killer cell activity in adults age 60 or older [339-341].  
  
Frank vitamin E deficiency is rare, except in individuals with intestinal malabsorption disorders [224,272]. For this reason, research on the ability of vitamin E to improve immune function tends to use supplemental vitamin E rather than simply ensuring that study participants achieve adequate vitamin E status [336].  
  
Efficacy  
The effects of vitamin E supplementation on infectious diseases, such as respiratory tract infections, in studies are mixed [338,342]. In one clinical trial, 90 mg (200 IU) vitamin E supplements (as DL-alpha-tocopherol) daily for 1 year reduced the risk of upper respiratory tract infections, particularly the common cold, by 16% in 617 adults age 65 or older but not lower respiratory tract infections [343]. Supplementation with 50 mg/day vitamin E (as DL-alpha tocopheryl acetate) for 5 8 years also reduced the risk of pneumonia by 69% in 2,216 men age 50 69 years who smoked 5 19 cigarettes per day and exercised, but it did not affect the risk of pneumonia in another 5,253 men who smoked more than 19 cigarettes per day or did not exercise [344]. In another clinical trial in 652 adults age 60 years or older, 200 mg vitamin E supplements (as alpha-tocopheryl acetate) for about 14 months did not affect the incidence of acute respiratory tract infections and actually increased illness severity [345]. For example, rates of fever were 37% in individuals receiving vitamin E and 25% in those receiving placebo; illness duration was also significantly longer, at 19 days, for those receiving vitamin E than for the others, whose average illness duration was 14 days.  
  
Data are insufficient to support a recommendation for or against the use of vitamin E supplements to prevent or treat COVID-19. However, because of its effects on immune function, many researchers recommend studying vitamin E to see if it reduces the risk of COVID-19 or reduces symptoms of the disease [106,227,235,238,272,336-338,346].  
  
A small clinical trial in Mexico examined the effects of 800 mg vitamin E (as alpha-tocopheryl acetate) every 12 hours for 5 days plus the drug pentoxifylline in 22 hospitalized adults (mean age 57.9 years) with pneumonia that resulted from COVID-19 [132]. Another group of 22 patients received pentoxifylline alone. Patients who received vitamin E and pentoxifylline had significantly lower levels of the inflammatory markers interleukin-6 and procalcitonin than at baseline, whereas those who received pentoxifylline alone did not. Vitamin E plus pentoxifylline also significantly decreased the lipid peroxidation index (a measure of oxidative stress), but pentoxifylline alone did not. Both treatments significantly increased nitrite levels (suggesting higher oxygen levels) and reduced levels of the inflammatory marker C-reactive protein, but neither treatment affected total antioxidant capacity.  
  
Clinicaltrials.govexternal link disclaimer does not list any other trials investigating vitamin E alone in patients with COVID-19, but studies are using vitamin E in combination with other ingredients. For example, a clinical trialexternal link disclaimer in Spain is investigating whether a micronutrient supplement containing 45 mg vitamin E (as alpha-tocopherol) and 10 other vitamins and minerals for 14 days reduces the need for hospitalization in 300 outpatient adults with COVID-19 [241]. Another trialexternal link disclaimer in Saudi Arabia is examining whether taking a dietary supplement containing 90 mg vitamin E (form not specified) plus 1,500 mcg vitamin A (as beta-carotene), 250 mg vitamin C, 15 mcg selenium, and 7.5 mg zinc for 14 days affects the progression of disease and the risk of cytokine storm in 40 adults with COVID-19 [347].  
  
Safety  
All intake levels of vitamin E in foods are considered safe. Up to 200 mg to 800 mg/day supplemental vitamin E is safe for children, depending on age, and up to 1,000 mg/day is safe for adults [224]. These upper limits, however, do not apply to individuals receiving vitamin E under the care of a physician. Higher vitamin E intakes can increase the risk of bleeding because of the vitamin s anticoagulant effect and can cause hemorrhagic stroke.  
  
Vitamin E supplementation might interact with certain medications, including anticoagulant and antiplatelet medications. It might also reduce the effectiveness of radiation therapy and chemotherapy by protecting tumor cells from the action of these agents [270,348,349].  
  
More information on vitamin E is available in the ODS health professional fact sheet on vitamin E.  
  
Zinc  
A wide variety of foods contain zinc, an essential nutrient. These foods include oysters, crab, lobster, beef, pork, poultry, beans, nuts, whole grains, and dairy products. The RDA for zinc is 2 13 mg for infants and children, depending on age, and 8 12 mg for adults [350].  
  
Zinc is involved in numerous aspects of cellular metabolism. Zinc is necessary for the catalytic activity of approximately 100 enzymes, and it plays a role in many body processes, including both the innate and adaptive immune systems [15,350-353]. Zinc also has antiviral and anti-inflammatory properties, and it helps maintain the integrity of tissue barriers, such as the respiratory epithelia [128,354,355]. In addition, zinc is required for sense of taste and smell.  
  
Zinc deficiency adversely affects immune function by impairing the formation, activation, and maturation of lymphocytes. In addition, zinc deficiency decreases ratios of helper and suppressor T cells, production of interleukin-2, and activity of natural killer cells and cytotoxic T cells [15,231,351,353,356]. Furthermore, zinc deficiency is associated with elevated levels of proinflammatory mediators [354]. These effects on immune response probably increase susceptibility to infections [357] and inflammatory diseases, especially those affecting the lungs [354].  
  
Studies have found associations between low zinc status and increased risk of viral infections [272], and people with zinc deficiency have a higher risk of diarrhea and respiratory diseases [15]. Poor zinc status is also common among individuals with HIV and hepatitis C and is a risk factor for pneumonia in older adults [231,355,358,359].  
  
Although zinc deficiency is not common in the United States, 15% of the U.S. population might obtain marginal amounts of zinc [360]. Older adults are among the groups most likely to have low intakes.  
  
Efficacy  
Currently, data are insufficient to support recommendations for or against the use of zinc to prevent or treat COVID-19. However, because of zinc s role in the immune system and in maintaining epithelial integrity, its antiviral activities, and its anti-inflammatory effects, some researchers believe that adequate zinc intakes might reduce the risk of COVID-19 and its severity [96,106,128,140,164,231,255,354,361-363]. Evidence that zinc lozenges might help shorten the duration of the common cold [364] has also spurred interest in zinc supplementation to help treat COVID-19. In addition, some researchers believe that zinc supplements might help reduce the severity of some of the symptoms of COVID-19, including diarrhea and a loss of taste and smell [365-367].  
  
An observational study of 249 patients (median age 65 years) with COVID-19 admitted to a hospital in Spain found that patients with serum zinc levels lower than 50 mcg/dL had more severe disease at admission, took longer to recover (median of 25 vs. 8 days), and had higher mortality rates (21% vs. 5%) than those with higher zinc levels [368]. A similar study in India found that 47 hospitalized patients with COVID-19 (median age 34 years) had lower median serum zinc levels at admission (74.5 mcg/dL) than 45 randomly selected healthy individuals who were not hospitalized and were used as a control group (median age 32 years; 105.8 mcg/dL), although both of these median values would be considered normal [369]. In addition, patients with COVID-19 who had zinc levels below 80 mcg/dL had higher rates of complications than those with higher levels. Mean serum zinc concentrations were also lower (71.7 mcg/dL) in 35 hospitalized patients (median age 77 years) with COVID-19 in Germany, especially in the six patients who did not survive the disease, than a group of randomly chosen healthy individuals who were used as control group (97.6 mcg/dL) [370]. However, hypozincemia is part of the acute-phase response during infection, and zinc concentrations can also decline substantially as a result of acute physiological stress [371].  
  
In another study, self-reported use of zinc supplements (dose not reported) more than three times per week for at least 3 months among 372,720 U.K. residents age 16 to 90 years as well as 45,757 individuals in the United States and 27,373 individuals in Sweden was not associated with higher or lower risk of SARS-CoV-2 infection [160].  
  
In a case report from the United States, four patients age 26 63 years with COVID-19 were treated with high-dose zinc citrate, zinc gluconate, or zinc acetate lozenges every 2 to 4 hours for a total dose of 115 to 184 mg of zinc per day for 10 to 14 days [372]. The symptoms including fever, cough, headache, shortness of breath, body aches, and fatigue of all four patients began to decline within 24 hours of starting the zinc treatment, and all ultimately recovered. However, case studies such as these that do not have a placebo control arm cannot show whether the treatment was responsible for the outcomes.  
  
A retrospective study included 932 patients (average age of 62 63 years) hospitalized with COVID-19 between March and April 2020 [373]. All patients were treated with hydroxychloroquine and azithromycin, and 411 also received 50 mg zinc (as zinc sulfate) twice daily for 5 days; the other 521 patients did not receive the zinc supplements. Zinc supplementation did not affect the length of time the patients remained in the hospital, on a ventilator, or in the ICU. However, among patients who did not require intensive care, those receiving zinc had a lower rate of mortality or transfer to a hospice and a higher likelihood of being discharged to their homes. Another retrospective study compared mortality rates among 242 patients hospitalized with COVID-19; 196 patients (median age 65 years) received supplementation with 100 mg/day zinc (as zinc sulfate), and 46 patients (median age 71 years) received no supplements [374]. Zinc supplementation did not affect mortality rates.  
  
In a clinical trial in Egypt, 191 patients (mean age 43 years) with COVID-19 received either 50 mg zinc (as zinc sulfate) twice daily plus hydroxychloroquine or hydroxychloroquine only for 5 days [375]. The numbers of patients who recovered within 28 days, needed mechanical ventilation, or died was not significantly different between groups.  
  
The COVID A to Z trial compared the effects of daily supplementation with 50 mg zinc (as zinc gluconate), 8,000 mg ascorbic acid, or both for 10 days with standard of care in 214 adults (mean age 45.2 years) who had COVID-19 and were not hospitalized [261]. Zinc, ascorbic acid, and the combination did not shorten the duration of symptoms.  
  
According to NIH treatment guidelines, data are insufficient to recommend for or against the use of zinc supplements to treat COVID-19 [376]. In addition, the guidelines recommend against doses of zinc supplements above the RDA to prevent COVID-19, except in a clinical trial.  
  
Several other clinical trialsexternal link disclaimer of zinc supplementation, mostly in combination with other dietary supplement ingredients and/or medications, to help prevent or treat COVID-19 are underway. For example, one trialexternal link disclaimer is examining the effects of 50 mg/day zinc (as zinc sulfate) in adults age 60 years or older or age 30 to 59 years with an underlying health condition with COVID-19 who are not hospitalized but have a high risk of complications due to their age or underlying health conditions [377]. Another trialexternal link disclaimer is investigating whether supplementation with zinc, vitamin C, vitamin D (doses not specified), and hydroxychloroquine for 24 weeks helps prevent COVID-19 in about 600 medical workers aged 18 years and older [378].  
  
Safety  
Intakes up to 4 34 mg/day zinc in foods and dietary supplements for infants and children, depending on age, and up to 40 mg/day for adults are safe [350]. These upper limits, however, do not apply to individuals receiving zinc treatment under the care of a physician. Higher intakes can cause nausea, vomiting, loss of appetite, abdominal cramps, diarrhea, and headaches [59,350]. Chronic consumption of 150 450 mg/day can cause low copper status, reduced immune function, and reduced levels of high-density lipoproteins [379]. In clinical trials among children, zinc supplementation to treat diarrhea increased the risk of vomiting more than placebo [380,381].  
  
Zinc supplementation might interact with several types of medications. For example, zinc can reduce the absorption of some types of antibiotics as well as penicillamine, a drug used to treat rheumatoid arthritis [382,383]. In addition, some medications, such as thiazide diuretics and certain antibiotics, can reduce zinc absorption [384,385].  
  
More information on zinc is available in the ODS health professional fact sheet on zinc.  
  
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