



Myth Busters: Dietary Supplements and COVID-19

Annals of Pharmacotherapy
2020, Vol. 54(8) 820–826
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DOI: 10.1177/1060028020928052
journals.sagepub.com/home/aop



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Abstract

News and social media platforms have implicated dietary supplements in the treatment and prevention of coronavirus disease 2019 (COVID-19). During this pandemic when information quickly evolves in the presence of contradicting messages and misinformation, the role of the pharmacist is essential. Here, we review theoretical mechanisms and evidence related to efficacy and safety of select supplements in the setting of COVID-19, including vitamin C, vitamin D, zinc, elderberry, and silver. Evidence evaluating these supplements in COVID-19 patients is lacking, and providers and patients should not rely on dietary supplements to prevent or treat COVID-19. Rather, reference to evidence-based guidelines should guide treatment decisions.

Keywords

coronavirus, dietary supplements, vitamin C, vitamin D, zinc, elderberry and silver

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the coronavirus disease 2019 (COVID-19) pandemic gripping the globe in 2020.¹ During this difficult time, when health care systems and providers are constantly strained, the public is more likely to seek medical information from online sources. Prominent medical entertainment personalities have been featured on television programs and across social media platforms touting the use of certain dietary supplements to both protect individuals from contracting COVID-19 and aid in its acute treatment. In fact, sales of dietary supplements such as elderberry and zinc have significantly increased by as much as 255% and 415%, respectively, in the single-week period ending March 8, 2020.² The US Food and Drug Administration (FDA) actively monitors for false marketing claims and has issued warning letters to multiple companies selling products with false claims for prevention and treatment of COVID-19, but more needs to be done.³ It is paramount that pharmacists, who are often on the front lines of this pandemic, be aware of the data supporting or refuting dietary supplement use to help patients make informed decisions during this time of information overload and confusion. Here, we review select supplements that have been most frequently touted within social media and news outlets for COVID-19 prevention and/or treatment, including vitamin C, vitamin D, zinc, elderberry, and silver.

Vitamin C

Vitamin C (ie, ascorbic acid) has several physiological properties that make it an attractive option to both prevent viral infections and treat the resulting severe illness. These include, but are not limited to, scavenging oxygen free radicals, decreasing the gene expression of proinflammatory cytokines, and enhancing microbial killing in certain cell types.^{4,5} Despite these theoretical benefits, evidence does not support the routine use of vitamin C for prevention of viral infections, including the common cold.⁶ Meta-analyses of clinical trial data does suggest a shortening in common cold duration by a modest 8% with regular vitamin C intake (amounts varying across studies).⁶ Whereas the common cold can be caused by a human coronavirus, COVID-19 is caused by a novel coronavirus with a different genome sequence.⁷ It cannot be assumed, therefore, that outcomes of vitamin C from the management of the common cold will translate to the management of COVID-19.

Some of the distinguishing features of a more severe COVID-19 infection course include development of acute respiratory distress syndrome (ARDS), secondary infection

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Table 1. Evidence-Based Resources for COVID-19 and Dietary Supplements.

Resource	Weblink
Centers for Disease Control and Prevention, Coronavirus (COVID-19)	https://www.cdc.gov/coronavirus/2019-ncov/index.html
ClinicalTrials.gov, listed clinical studies related to COVID-19	https://clinicaltrials.gov/ct2/results?cond=COVID-19
Infectious Diseases Society of America, COVID-19 Resource Center	https://www.idsociety.org/public-health/COVID-19-Resource-Center/
National Institutes of Health, Coronavirus (COVID-19)	https://www.nih.gov/health-information/coronavirus
National Institutes of Health, Office of Dietary Supplements	https://ods.od.nih.gov/
Natural Medicines ^a	https://naturalmedicines.therapeuticresearch.com/

^aSubscription required.

(eg, bacterial pneumonia), and severe sepsis.⁷ Recently published clinical trials have investigated vitamin C use as part of a management strategy for ARDS⁸ and septic shock.⁹ The CITRIS-ALI trial showed that giving intravenous (IV) vitamin C 50 mg/kg every 6 hours for 96 hours did not significantly alter disease severity scores, C-reactive protein levels, or thrombomodulin levels compared with placebo in patients with sepsis and ARDS, although 28-day all-cause mortality was significantly lowered and ICU-free days was significantly shorter with vitamin C use.⁸ Similarly, the VITAMINS trial showed that a combination of IV vitamin C, hydrocortisone, and thiamine did not improve duration of time alive or free from vasopressor administration compared with hydrocortisone alone in a population with septic shock.⁹

Physicians from China have stated on various media outlets that they have successfully treated more than 50 patients with moderate to severe COVID-19 with large doses of IV vitamin C (10 000-20 000 mg/d), leading to a shorter mean hospital length of stay compared with untreated patients with COVID-19 and no incidences of death.¹⁰ Details of this evidence are unavailable because these findings have not (at the time of this writing) been published in either preprint or peer-reviewed journals. It is also important to note that the high doses used in this study are not obtainable when using orally available over-the-counter versions of vitamin C. Moreover, the gastrointestinal adverse events (nausea, vomiting, heartburn, abdominal cramps) could be dose limiting, and pharmacists should advise patients against attempting to take that much daily supplement. High doses of vitamin C may be associated with formation of kidney stones, particularly in those with high oxalate levels to begin with.¹¹ Randomized controlled trials of vitamin C are currently registered on the National Institutes of Health ClinicalTrials.gov website examining monotherapy (NCT04264533, NCT04344184, NCT03680274, NCT04357782) for acute COVID-19 treatment, in combination with hydroxychloroquine to treat (NCT04328961) or prevent (NCT04326725, NCT04335084) COVID-19 and with other supplements for prevention (NCT04342728). The dosing of vitamin C in these trials varies widely, ranging from 250 to 500 mg orally daily to 24 g IV daily. Overall, it is important for pharmacists

to highlight the lack of evidence that vitamin C can be taken to prevent or treat COVID-19. Instead, patients should consult with trusted resources (Table 1) or their physician regarding the most effective way to avoid COVID-19.

Vitamin D

Vitamin D is a fat-soluble vitamin and is found in supplements and foods as vitamin D₂ (ergocalciferol) and D₃ (cholecalciferol), both of which require further metabolism into the active form, calcitriol.¹² Vitamin D is the proposed driver of the “seasonal stimulus” hypothesis that emerged from epidemiological observations of the influenza A epidemics.¹³ This idea suggests that coinciding with peak influenza cases in the winter is a reduced exposure to the sun, leading to reduced synthesis and serum levels of vitamin D, which in turn affects immune function.¹³ The complex mechanisms by which vitamin D supports immune function have been reviewed extensively.¹³⁻¹⁶ To summarize, vitamin D activity contributes to the maintenance of cell physical barrier integrity, enhanced antimicrobial peptide expression, enhanced activity of our innate immunity through macrophages and monocytes, and shifting response of cells involved with innate and adaptive immunity, such as dendritic and T-cells, toward a more tolerable and anti-inflammatory behavior.

Observational data consistently associate low vitamin D levels with acute respiratory tract infections.¹⁷ Patients may also be at risk of ARDS with low vitamin D levels.¹⁸ Trial evidence is less consistent, perhaps because of heterogeneity in baseline vitamin D levels or the regimens studied.^{13,19} The largest evaluation to date, an individual patient data meta-analysis, included more than 10 000 individuals from 25 high-quality trials.¹⁹ Investigators concluded that oral vitamin D₃ supplementation reduced the risk of acute respiratory tract infections (number needed to treat [NNT] = 33; range = 20 to 101). Effects were stronger when baseline 25-hydroxyvitamin D levels were <25 nmol/L (NNT = 8; range = 5 to 21) and with daily (vitamin D₃ oral doses ranging from 400 to 4000 IU) or weekly dosing versus regimens with bolus doses. No signals of serious adverse events were

identified; renal stones (0.2%) and hypercalcemia (0.5%) were rare overall and balanced between treatment arms.¹⁹

This prior knowledge currently underlies internet reports speculating a role for vitamin D in the COVID-19 pandemic. The former director of the Centers for Disease Control and Prevention (CDC)²⁰ and faculty from the University of Turin in Italy have both suggested that ensuring adequate vitamin D levels through safe sun exposure, food, or vitamin D supplementation may have a role in COVID-19 management.²¹ The report from Italy takes it further to suggest a possible role of IV calcitriol in patients with COVID-19 and compromised respiratory function and claims a “very high prevalence of hypovitaminosis D” in patients with COVID-19 in Turin. Data were not published at the time of writing this review. A single sample of 20 patients hospitalized with COVID-19 and with available vitamin D levels suggests that vitamin D insufficiency is prevalent.²² Ongoing studies aim to evaluate the relationship between vitamin D levels and prognosis in patients with COVID-19 as well as efficacy of vitamin D supplementation as part of treatment.^{23,24}

Without studies specific to COVID-19, whether taking daily vitamin D improves outcomes associated with COVID-19 is unknown. For the purpose of overall general health and in the setting of a high prevalence of vitamin D deficiency in America,²⁵ patients should continue to follow recommendations for daily vitamin D consumption consistent with the recommended daily allowance and tolerable upper intake level. For adults, this is within the range of 600 or 800 IU to 4000 IU.¹² Until scientific evidence emerges, patients should avoid excessive doses of vitamin D in hopes of preventing or treating COVID-19. Long-term consumption of vitamin D in excess of 4000 IU is considered possibly unsafe and could lead to hypercalcemia.²⁶

Zinc

Zinc is a trace mineral that has been hypothesized to inhibit viral replication and attachment to the nasopharyngeal mucous, and through this mechanism, has been implicated in the management of the common cold.^{27,28} In vitro studies suggest that zinc modifies effects of several respiratory pathogens, including rhinovirus, respiratory syncytial virus, and SARS-COV.²⁹⁻³¹

Results from clinical trials evaluating zinc supplements for the common cold have conflicted, and many suffer from methodological flaws.²⁸ Similarly, conclusions of multiple meta-analyses vary in whether zinc significantly affects cold duration and to what extent patient and regimen characteristics modify treatment effects.³²⁻³⁵ One comprehensive systematic review with broad inclusion of studies found moderate quality evidence that zinc supplementation reduces common cold duration by 1.65 days.³² Considerable

heterogeneity was found and partially explained by age, zinc dose, and salt form. Adverse events were more common with zinc compared with placebo.

News reports are starting to emerge with claims that zinc may have a role in COVID-19 management, and this may be a result of prior knowledge that some coronaviruses can cause the common cold.³⁶⁻³⁸ A physician in New York is claiming to have near perfect clinical response to prescribing his patients a combination of hydroxychloroquine, azithromycin, and zinc, although data supporting these claims have not been published.³⁹

There are no studies evaluating zinc for COVID-19 management to date, although a few trials are currently registered to test zinc as part of a regimen to treat COVID-19.⁴⁰ Some patients may choose to take zinc during this pandemic, but reputable data are lacking. Oral zinc supplementation is likely to be safe up to 40 mg/d in adults, but safety is less certain with greater doses that are implicated in common cold management.⁴¹ Adverse effects include, but are not limited, to nausea, vomiting, and changes in taste. The nasal preparation should not be used because of reports of the permanent loss of the sense of smell.

Elderberry

Elderberry (*Sambucus nigra*) is hypothesized to have antiviral properties because of its ability to modulate inflammatory cytokines⁴² and has been tested both in vitro⁴³⁻⁴⁷ and in vivo against varying viruses.⁴⁸⁻⁵² At the time of writing, there are no published studies evaluating the use of elderberry and COVID-19. Although elderberry and its phenolic acid components exhibit antiviral activity against human coronavirus HCoV-NL63 in vitro,⁴⁴ this cannot be extrapolated to COVID-19 as previously mentioned.⁷

Randomized, double-blind, placebo-controlled trials evaluating elderberry for treatment of influenza have suggested that elderberry may reduce symptom duration.⁴⁸⁻⁵⁰ The utility of these findings is unclear because of the small sample size, lack of objective outcomes, omission of intention-to-treat analysis, and lack of adverse event reporting.⁴⁸⁻⁵⁰ The trials do not align with standard of care because patients who received the annual influenza vaccine were excluded.⁴⁸⁻⁵⁰ In these trials, 1 tablespoon of elderberry oral solution was administered 4 times daily for 3 to 5 days within 24 to 48 hours of initial symptoms.^{48,49} Elderberry 175-mg lozenges were administered 4 times daily for 2 days within 24 hours of symptoms.⁵⁰

The results of a randomized, double-blind, placebo-controlled trial evaluating elderberry in air travelers suggested that elderberry may reduce cold symptom duration and severity.⁵¹ Elderberry capsules were initiated at 600 mg daily 10 days prior to travel. One day prior to travel, the dose was increased to 900 mg daily and continued for 4 to 5 days after

arrival.⁵¹ Patients with chronic respiratory diseases such as asthma, chronic obstructive pulmonary disease, and cystic fibrosis were excluded. Half of the participants reported using additional symptom-relief medications for an average of 1.5 days during the trial, limiting the application of these findings.⁵¹

Elderberry is likely safe when cooked and consumed in moderation.⁴² It is dangerous to consume uncooked elderberry, bark, root, leaves, and unripe berries because of the risk of cyanide toxicity.⁴² Elderberry should be used with caution in patients with diabetes because of its ability to stimulate insulin and promote glucose metabolism.⁴² Other potential adverse effects of elderberry include nausea, vomiting, diarrhea, tachycardia, hypotension, hypokalemia, and dehydration resulting from diuresis.³⁸ Elderberry may have the ability to stimulate cytokines⁵³ and, thus, may interfere with immunosuppressant therapy. Additionally, elderberry may alter theophylline levels.⁴²

Although there exists a hypothetical benefit of elderberry for the treatment of viral infections, conclusive evidence from high-quality clinical trials is lacking, and data addressing elderberry's role with COVID-19 are absent.

Silver

Colloidal silver has been used for medicinal purposes throughout history because of its proposed antibacterial⁵⁴ and antiviral properties.^{55,56} Colloidal silver describes silver particles suspended in liquid.⁵⁷ It is heavily marketed despite discouraging safety and efficacy data.^{58,59} Silver toothpaste and silver solution were recently promoted by social media personalities as potential cures for COVID-19.^{60,61}

In 1999, the FDA declared that over-the-counter products containing silver were not recognized as safe or effective and that any colloidal silver product marketed for a medical purpose was misbranded.⁵⁹ Extensively documented in the literature, the most common side effect of silver exposure is argyria, an irreversible gray or blue-gray skin discoloration.^{59,62,63} Systemic silver exposure may have additional harmful effects on the gastrointestinal system, liver, kidney, and other major organs.⁶² Long-term ingestion of silver has resulted in reports of neurotoxicity, seizure, acute psychosis, acute myeloid leukemia,⁶³ and leukocytoclastic vasculitis.⁶⁴

Despite the FDA's warning, colloidal silver is still readily available and advertised to the public.^{58,59} Until new evidence supports safety and efficacy, patients should not consume over-the-counter colloidal silver products.

Viewpoint

Pharmacists are an accessible drug information resource who have the ability to provide real-time data-driven

education to patients and providers. News and social media reports should not be the sole source for evidence-based information. During this pandemic when information quickly evolves in the presence of contradicting messages and misinformation, the role of the pharmacist is essential.

Patients and providers should not rely on dietary supplements to prevent or cure COVID-19.⁶⁵ Current guidelines for the treatment of COVID-19 do not comment on dietary supplements and, currently, do not recommend any pharmacological interventions widely with the exception of use through clinical trials.⁶⁶⁻⁶⁸ Pharmacists have the responsibility to ensure that patients have accurate information regarding the current lack of data supporting efficacy of these supplements in COVID-19. On the other hand, patients may choose to self-treat with these supplements because they are easily accessible and may provide a sense of security. This practice can be dangerous as seen in the death of a man who ingested chloroquine phosphate, a fish tank cleaner, to prevent COVID-19.⁶⁹ In these cases, pharmacists have the responsibility to ensure patient safety regardless of whether they agree with the patient's choice to self-treat. This is possible by screening for contraindications and drug or disease state interactions that are known to exist for the specific dietary supplement. In addition, pharmacists should educate patients on the potential harms and monitoring parameters known for these supplements. Resources such as the Natural Medicine Database or the National Institute of Health Office of Dietary Supplements website provide clinician- and consumer-directed information that is evidence based.⁷⁰

The best method to prevent spread of COVID-19 is to avoid being exposed.⁷¹ Currently, the CDC recommends to avoid touching the face with unwashed hands, wearing a cloth face cover over the nose and mouth in public, and covering the mouth and nose when coughing or sneezing.⁷¹ It is recommended to wash hands with soap and water for at least 20 s to prevent transmission.⁷¹ When soap and water are unavailable, hand sanitizer containing at least 60% alcohol may be used instead.⁷¹ The CDC recommends avoiding contact with others who are sick and to practice social distancing measures. Finally, highly touched surfaces should be cleaned and disinfected daily. Patients, providers, and pharmacists should refer to the CDC website for regular updates regarding prevention strategies and recommendations.


Declaration of Conflicting Interests


The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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