An Exploratory Review of Potential Adjunct Therapies for the Treatment of Coronavirus Infections

Brett R. Martin, DC, MSAc, MPH, [a] and Joshua Richardson, DC [b]

Abstract

Objective: The purpose of this exploratory review was to examine vitamin D, zinc, vitamin A, elderberry (*Sambucus nigra*), garlic (*Allium sativum*), licorice (*Glycyrrhiza glabra*), stinging nettle (*Urtica dioica*), *N*-acetylcysteine, quercetin, and selenium as potential adjunct therapies for the treatment of coronavirus infections.

Methods: A search of PubMed was performed for articles published from 2005 to 2021. Keywords searched were "zinc," "vitamin A," "vitamin D," "*Sambucus nigra*," "*Allium sativum*," "*Glycyrrhiza glabra*," "*Urtica dioica*," "*N*-acetylcysteine," "quercetin," "selenium," and "coronavirus."

Results: There were 47 articles selected for this review. Findings included that vitamin D, zinc, vitamin A, *S. nigra*, *A. sativum*, *G. glabra*, *U. dioica*, *N*-acetylcysteine, quercetin, and selenium have been shown to produce antiinflammatory, immunostimulatory, or antiviral effects that may enhance the actions of standard therapeutics for the treatment of coronavirus infections. Specific to effects against COVID-19, we found research articles related to the effects of only vitamin D, zinc, *G. glabra*, quercetin, and selenium.

Conclusion: We identified nonpharmaceutical supplements (vitamin D, zinc, vitamin A, *S. nigra*, *A. sativum*, *G. glabra*, and *U. dioica)* which may have potential to provide support for those with coronavirus infections. However, rigorous clinical studies need to be performed before any clinical recommendations can be made. (J Chiropr Med 2021;20;199-217)

Key Indexing Terms: *Coronavirus; COVID-19; Vitamin D; Zinc; Vitamin A; Sambucus nigra; Garlic; Glycyrrhiza*

Introduction

The coronavirus (CoV) is a single-stranded RNA virus.[1] As it is a positive-sense virus, the RNA in its genome encodes for the sense strand, allowing it to quickly translate proteins. The CoV is a sizable, enveloped virus within the order Nidovirales, family Coronaviridae, and subfamily Coronavirinae. The CoV is categorized into the genera *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*.[2] *Alphacoronavirus* and *Betacoronavirus* species are the primary coronaviruses that infect the human population.[2,3] However, researchers have hypothesized that studying treatments for other coronaviruses, such as *Gammacoronavirus* and *Deltacoronavirus* species, may be applicable in developing therapeutic strategies for human infections.[4] Viruses from Coronavirinae are capable of infecting birds and mammals, which allows for the potential of zoonotic infections.[2,5,6] The coronavirus disease that became pandemic beginning in 2019 (COVID-19) is an example of a zoonotic infection that has majorly affected the human population[7]; it is caused by the SARS-CoV-2 virus. *Betacoronavirus* species include SARS-CoV, SARS-CoV-2, and MERS-CoV.[2]

According to the United States Centers for Disease Control and Prevention, CoV received its name based on the appearance of the virion under electron microscopy, which resembles a crown or halo.[8] The virion crown is characterized by spear-shaped projections surrounding the envelope.[9] The spiked glycoproteins, termed *S proteins*, are 1 of 4 structural proteins that the SARS-CoV-2 genome codes for.[9,10] The other 3 proteins are nucleocapsid (which protect the genetic material), envelope, and membrane proteins.

The S protein is a class I viral fusion protein.[11] Fusion proteins allow the enveloped virus to infiltrate the host cell, which is achieved through the binding of the protein to the membrane receptors. Several *Alphacoronavirus* species interact with the aminopeptidase N receptor, whereas severe acute respiratory syndrome coronaviruses, including SARS-CoV-2,use the angiotensin-converting enzyme (ACE) receptor.[9] When the S glycoprotein is bound to the host receptor, host protease enzymes cleave it into S1 and

[a] Basic Science Department, National University of Health Sciences, Pinellas Park, Florida.

[b] National University of Health Sciences, Pinellas Park, Florida.

Corresponding author: Brett R. Martin, 11699 82nd Terrace, Seminole, FL 33772.
(e-mail: *Bmartin@nuhs.edu*).

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S2.[10,12] The S1 fragment is shed and stabilizes the S2 subunit. The S2 subunit is the primary fusion protein forming a support stalk.[3] The S protein mediates the enzymatic activity of hemagglutinin esterase, which is a surface protein found on the virion. Hemagglutinin esterase interacts with sialic acid, permitting entry of the virus into the host cell, assisted by the S protein.

Replication of the RNA sequence of CoVs occurs within the cytoplasm of the infected organism through attachment to RNA polymerase, which synthesizes mRNA strands.[3] The M protein controls the replication and transcription of the virus.[13] A transmembrane protein known as the E protein promotes the formation and detachment of the virus.[3] Hemagglutinin esterase mediates viral dissemination through the mucosa.

Pathogenic viruses have the ability to infect and reproduce in a host by overwhelming the defenses of the body, resulting in disease.[14] Once cells are invaded and replication begins, the possibility ensues of both chronic and acute illnesses of the hepatic, gastrointestinal, respiratory, and neurologic systems.[11] The pathophysiological process is characterized by an increased expression of nuclear factor-κB (NF-κB),[15] which is an inflammatory transcription factor that upregulates the arachidonic cascade and eicosanoid production and release.[16] The activation of NF-κB potentiates the release of the inflammatory mediators interleukin (IL)-1, IL-6, and IL-8, monocyte chemotactic protein (MCP)-1 and tumor necrosis factor α. (TNFα.).[15,17] The IL-1 family stimulates the release of other inflammatory cytokines.[18] Interleukin-6 is the primary mediator amplifying a systemic inflammatory state.[17] Interleukin-8 is involved in the nonspecific inflammatory response by activating neutrophils and recruiting T cells to the site of inflammation.[19] Monocyte chemotactic protein-1 promotes the generation of various chemicals that intensify the inflammatory process. TNF-α activates NF-κB, potentiating the synthesis of proinflammatory eicosanoids.[20] The synthesis and release of plasminogen activator inhibitor (PAI)-1, which is a procoagulant, is correlated with a severe case of coronavirus infection.[17] Plasminogen activator inhibitor-1 is involved with the formation of a thrombus, which has been shown to be a complication of CoV infections including COVID-19.[21,22]

The primary host of SARS-CoV-2 is suspected to be animal in origin.[3] The source of the infection has not been established, but the preliminary cases were traced back to Wuhan, China.[10,23] The typical host of SARS-CoV-2 and COVID-19 is chiropterans, more commonly known as bats. Bats are capable of acting as the primary reservoir for several species of CoV. There are several characteristics of bats that could allow them to be an ideal agent for increasing the rate of transmission of coronaviruses[14]: they live in close proximity to one another, have a long life span, and are able to migrate over great distances.

Once the virus is spread from an animal reservoir to a human, it can be transmitted to other people via respiratory droplets, which come into direct or indirect contact with mucous membranes of the oral or nasal cavity.[10,23] Coronavirus can be aerosolized indoors, which potentiates its spread. The SARS-CoV-2 virus targets the ACE-2 receptor, which is expressed in the epithelial lining of the respiratory tract and the mucosa of the small intestine.[23]

As the respiratory tract and gastrointestinal lining contain ACE-2 receptors, the signs and symptoms that manifest are associated with these systems.[10] Consequently, COVID-19 is characterized by a cough, dyspnea, fever, fatigue, headache, chills, pharyngitis, myalgias, malaise, anosmia, and ageusia.[24] Diarrhea and nausea may also be present.[23] For a majority of cases, the infection is mild and transient. Complications of COVID-19 can occur due to damage to the alveoli of the lungs, increasing the individual's susceptibility to pneumonia, acute respiratory distress syndrome, or respiratory arrest. Populations that are most at risk for developing severe infection resulting in complications are people who are older, people who are immunocompromised, and people with preexisting conditions. There is a potential for excessive inflammation that can overwhelm the body, causing multiorgan failure or death.

There are several medications used for the treatment of CoVs, including SARS-CoV-2. Tocilizumab is an antirheumatic and immunosuppressant medication that has been shown to reduce the severity of CoV infections by downregulating IL-6 and PAI-1.[17,25,26] Chloroquine and hydroxychloroquine have impeded the ability of the virus to enter host cells in in vitro studies.[27] However, their clinical efficacy has been highly debated. The combination of lopinavir and ritonavir has demonstrated some benefits in in vitro studies, and a systematic review revealed a reduction in overall mortality and intubation rates. Unfortunately, these antivirals must be used within the initial replication phase to have a positive clinical outcome. Ribavirin requires a very high dose to diminish viral replication, which may increase the risk of adverse effects. To enhance its efficacy, it is recommended to use ribavirin in conjunction with other therapies. Currently, remdesivir appears to be the most effective agent for impairing the replication of the CoV. It has demonstrated potent antiviral activity in in vitro trials.[27] To date, there have been no clinical trials with remdesivir, and there are concerns related to its safety and efficacy for the treatment of human diseases.[28]

Various vaccines are currently available to combat SARS-CoV-2. The overall efficacies of the BioNTech/Pfizer, Moderna, AstraZeneca/Oxford, and Janssen vaccines are 95%, 94.1%, 66.7%, and 66.9%, respectively.[29] However, the number of cases is currently on the rise due to variations of the original virus. One study found that the Delta variant is 60% more infectious and that it is moderately resistant to vaccines, especially in people who were

administered only a single dose.[30] In addition, US citizens are hesitant to vaccinate, due to a fear of the potential side effects, a lack of trust in the government and its policies, and negative attitudes circulating on social media.[31]

Due to the absence of a highly effective antiviral medication, the formation of new viral variants, potential resistance to vaccines, and the unwillingness of some individuals to vaccinate, the use of nonpharmaceutical therapeutics as adjuncts may have the potential to improve clinical outcomes of infections. Certain natural extracts have the ability to enhance immune functioning. For example, vitamin A has been shown to regulate T-cell activation.[32] Other nutraceuticals can reduce prooxidant production and inflammation, which may improve the symptomatology associated with an infection.

However, at this time, it is unknown which nonpharmaceutical products may have an effect in those infected with a coronavirus. Therefore, the purpose of this exploratory review is to identify and discuss nonpharmaceutical products for the treatment of coronavirus infection.

Methods

We selected the following supplements: vitamin D, zinc, vitamin A, elderberry (*Sambucus nigra*), garlic (*Allium sativum*), licorice (*Glycyrrhiza glabra*), stinging nettle (*Urtica dioica)*, *N*-acetylcysteine (NAC), quercetin, and selenium. A narrative review of the literature was performed in October 2020 using the PubMed computerized database. We searched for studies published in English between 2005 and 2021. The relevant key words were "zinc," "vitamin A," "vitamin D," "*Sambucus nigra*," "*Allium sativum*," "*Glycyrrhiza glabra*," "*Urtica dioica*," "*N*-acetylcysteine," "quercetin," "selenium," and "coronavirus." The search parameters are provided in Table 1.

Table 1. *Search Results*

Keywords	Screened	Eligible	References
"Vitamin D" and "coronavirus" and "trial"	86	21	33-53
"Vitamin D" and "coronavirus" and "meta-analysis"	24	10	54-63
"Zinc" and "coronavirus" and "trial"	65	2	64, 65
"Zinc" and "coronavirus" and "meta-analysis"	2	0	None
"Vitamin A" and "coronavirus"	34	1	66
"Vitamin A" and "coronavirus"and "meta-analysis"	1	0	None
"Elderberry (*Sambucus nigra*)" and "coronavirus"	5	1	4
"Elderberry (*Sambucus nigra*)" and "coronavirus" and "meta-analysis"	0	0	None
"Garlic (*Allium sativum*)" and "coronavirus"	27	2	67, 68
"Garlic (*Allium sativum*)" and "coronavirus" and "meta-analysis"	0	0	None
"Licorice (*Glycyrrhiza glabra*)" and "coronavirus"	40	2	69, 70
"Licorice (*Glycyrrhiza glabra*)" and "coronavirus" and "meta-analysis"	0	0	None
"Stinging nettle (*Urtica dioica*)" and "coronavirus"	5	3	71-73
"Stinging nettle (*Urtica dioica*)" and "coronavirus" and "meta-analysis"	0	0	None
"*N*-acetylcysteine" and "coronavirus" and "trial"	10	0	None
"Quercetin" and "coronavirus" and "trial"	14	2	74, 75
"Selenium" and "coronavirus" and "trial"	12	3	76-78

Search parameters were a date range of January 2005 to August 2021; we excluded literature reviews, narrative reviews and commentaries, and articles not in English, as well articles using herbal formulas or supplements in combination with other supplements or drugs or intravenous administration.

Table 2. *Nutraceuticals' Effects on Proinflammatory and Antiinflammatory Mediators*

Nutraceutical	Number of Studies	NF-κB	IL-1	IL-6	IL-8	IL-10	MCP-1	TNF-α	PAI-1
Vitamin D	30	↓[79]	↓[80]	↓[80]	↓[81]	↑[82]	↓[83]	↓[80]	N/D
Zinc	2	↓[89]	↓[89]	↓[90]	↓[91]	↑[91]	↓[92]	↓[90]	N/D
Vitamin A	1	↓[95]	↓[95]	↓[96]	N/D	↑[97]	↓[99]	↓[95]	↓[100]
Elderberry (*Sambucus nigra*)	1	↓[103]	↑[105]	↑↓[106]	↑[105]	↑[105]	N/D	↓[105]	N/D
Garlic (*Allium sativum*)	2	↓[108-110]	↓[111]	↓[111]	↓[112]	↑[113]	N/D	↓[111]	↓[114]
Licorice (*Glycyrrhiza glabra*)	2	↓[116]	↓[116]	↓[116]	↓[118]	↑[120]	↓[119]	↓[117]	N/D
Stinging nettle (*Urtica dioica*)	3	↓[126]	↓↑[124,127]	↓↑[124,127]	↑[127]	N/D	N/D	↓↑[125,127]	N/D
NAC	0	↓[136]	↓[136]	↓[137]	↓[138]	↑[138]	↓[139]	↓[136]	↓[140-142]
Quercetin	2	↓[147]	↓[148]	↓[148]	↓[149]	↑[164]	↓[150]	↓[147]	↓[151]
Selenium	3	↓[155]	↓[157]	↓[157]	↓[158]	↑[159]	↓[160]	↓[156]	↓[161]

↑, enhances activity; ↓, inhibits activity; ↓↑, regulates activity; *IL*, interleukin; *MCP*, monocyte chemotactic protein; *NAC*, *N*-acetylcysteine; *N/D*, no data; *NF-κB*, nuclear factor-κB; *PAI*, plasminogen activator inhibitor; *TNF*-α, tumor necrosis factor-α.

Table 3. *Dosages and Clinical Outcomes of Supplementation in Trials*

Nutraceutical	Dosage	Clinical Outcome
Vitamin D	1000 IU, once/d	Minimal improvement in symptoms; longer duration of infection[48,53]
	5000 IU, once/d	Reduced severity and shortened duration of infection[48]
	20 000 IU, twice/wk	Reduced mortality rate[51]
	21 280 IU upon admission and 10 640 IU on days 3 and 7 and weekly until discharge	Significantly reduced ICU admission[52] Mortality rate 5%, compared to 20% with standard care[47] Mortality rate 0%, compared to 7.6% with standard care[52]
	40 000 IU, once/wk	Reduced mortality rate[51]
	50 000 IU for 5 d	Full recovery[53]
	80 000 IU upon admission	Reduced severity of symptoms[49] Mortality rate 17.5%, compared to 55.6% with standard therapy[49]
	200 000 IU at admission	ICU admission rate 15.83%, compared to 20.83% with standard care[63] Mortality rate 6.67%, compared to 5% with standard care[63]
Zinc	23 mg, three times/d	Symptoms worsened[64]
	23-46 mg each day	Symptoms worsened[64]
	115-161 mg, split into multiple doses each day	Symptoms began to decline until resolution at 10 d[64]
	138 mg, split into multiple doses each day	Symptoms began to decline until resolution at 19 d[64]
	150 mg, split into multiple doses each day	Symptoms began to decline until resolution at 14 d[64]

ICU, intensive care unit.

The only academic resource used was PubMed. The studies selected for this review evaluated the potential inhibitory activity of the therapeutics against CoV infections and were available as free full-text articles. Literature reviews, hypothetical reviews, narrative reviews, commentary articles, and studies evaluating herbal formulas or in vivo intravenously administered nutraceuticals were excluded.

Results

We selected 47 journal articles from the 325 found during our search. The results of the literature review revealed a variety of articles related to the antiviral nature of nonpharmaceuticals against CoV infections.

Discussion

Research on the effects of natural agents for treating CoV infections was limited for all nutraceuticals with the exception of vitamin D. However, the potential benefit of the antiinflammatory activity of the nutraceuticals is outlined in Table 2, and there are a few studies discussing the antiviral activity of the nutraceuticals against CoV infections. Although these vitamins, minerals, and herbs do not have an abundant amount of research supporting their use, this information may assist with further study of their effect on the pathophysiology of the infection initiated by the CoV. It is possible that use of nonpharmaceutical agents may support other mainstream therapies and ultimately improve the clinical course of the disease. Table 3 outlines the research related to the dosage of vitamin D and zinc and the clinical outcome.

Vitamin D

We considered whether vitamin D may attenuate the symptoms associated with CoV infections. Since NF-κB is activated during a CoV infection, vitamin D may downregulate the inflammatory process by inactivating the transcription factor.[79] Interleukin-6 is the primary IL associated with the inflammatory process induced by CoV infections.[17] This has been proposed as a target for therapeutic treatment.[17,25,26] Vitamin D can mitigate the levels of IL-6 and attenuate the concentration of other inflammatory mediators that may contribute to the severity of CoV infections, such as IL-1, IL-8, and TNF-α, as well as increase the production of the antiinflammatory agent IL-10.[80-82] Direct inhibition of MCP-1, which is elevated with CoV infection, by vitamin D has not been shown. However, evidence shows that vitamin D can assuage the sequela of MCP-1 activity by decreasing macrocyte migration and the expression of receptors associated with MCP-1 and chemokines, overall decreasing the inflammatory response.[83] Vitamin D can reduce the activity of procoagulants, but there is no evidence that it has a direct effect on the physiological function of PAI-1, which is secreted in greater concentrations during an infection.[17,84] As hemostatic and thrombotic complications have been observed in cases of COVID-19, and anticoagulants are administered as part of the standard therapy, the additional anticoagulant activity of vitamin D may have a positive impact on treatment outcomes.[85]

In addition, vitamin D may enhance immune functioning, increasing resistance to certain pathogens. A correlation between vitamin D deficiency and increased risk of developing an infection, especially of the upper respiratory tract, has been established.[86] In addition, people with severe infections have significantly lower levels of vitamin D. Supplementation with vitamin D may reduce susceptibility to infection by enhancing the conversion of monocytes to macrophages via regulation of gene expression.[86,87] This potentiates the phagocytosis of antigens and may aid in eliminating the pathogen.[86] In addition, vitamin D is capable of regulating the release of inflammatory mediators by lymphocytes, which may decrease the severity of an infection.

We found 10 studies that determined vitamin D status and susceptibility to infection, 7 of which found an association between a deficiency of vitamin D (in the form of 25-hydroxycholecalciferol) and potential to be infected with COVID-19.[33-42] In the 3 articles that did not find a correlation between vitamin D status and risk of infection, 1 recorded a significantly lower level of vitamin D when age and body mass index were adjusted for, which indicates that additional factors may influence the development of an infection.[40] The other 2 studies observed vitamin D users compared to nonusers. In both articles, habitual use of vitamin D was recognized as reducing the incidence of developing COVID-19.[41,42] This seems plausible, as the data collected by Cereda et al found that only 11.7% of participants with COVID-19 had supplemented with vitamin D in the past 3 months.[39] Consequently, individuals chosen for these studies may have supplemented with vitamin D in the past year but not necessarily been ingesting vitamin D on a consistent basis.

Another distinguishing factor between the studies was the measurement of vitamin D levels as 25-hydroxycholecalciferol. All 10 of the studies evaluated vitamin D levels of the participants with COVID-19. Of the 3 studies that did not find an association between vitamin D status and risk of infection, 2 considered 20 ng/mL as deficient and 1 used 10 ng/mL.[40-42] One of the studies that documented an association used 10 ng/mL as an indication of deficiency, whereas another 3 used 20 ng/mL and 2 called a severe deficiency under 5 or 10 ng/mL.[33,34,36-39] Individuals with severe deficiency had a greater potential for infection.[36,37] The discrepancy between studies may be alleviated by the statistics obtained by D'Avolio et al, who note that

participants with COVID-19 had a median vitamin D level of 22 ng/mL, signifying that those who are infected may have borderline clinical deficiency of vitamin D.[35] Consequently, the analysis of infected participants with severe vitamin D deficiency may be the critical difference in the results of the studies that did not find an association between vitamin D levels and infection risk.

The study by Meltzer et al was the only one that did not determine vitamin D status based on serum received from active participants.[33] In that study, the investigators indicated that a vitamin D deficiency was correlated with an increased incidence of infection; but it was a retrospective study based on medical records from the previous year. Individuals with deficiency, as determined by vitamin D levels < 20 ng/mL according to previous test results, had a higher potential to test positive for SARS-CoV-2 infection than those with serum vitamin D > 20 ng/mL.

Due to the absence of a consensus on the association between risk of infection and vitamin D status, we conducted a meta-analysis review. There were 8 meta-analysis studies reviewing the incidence of infection and serum vitamin D, and all 8 determined that individuals with lower levels of vitamin D had a greater susceptibility to infection.[54-61] Liu et al found that only 4 of the 10 studies analyzed reported a correlation of infection with low vitamin D, yet overall, they concluded that the data reflected a relationship between vitamin D deficiency or insufficiency and the potential to be infected.[55] The data collected by Pereira et al indicated that 3 studies recorded that participants with serum 25-hydroxycholecalciferol < 20 ng/mL had a higher potential to be infected, and in 17 studies, 39% of participants with COVID-19 were deficient in vitamin D, whereas 38% of participants in 13 studies had insufficient levels of vitamin D.[54] The meta-analysis by Petrelli et al documents that participants with vitamin D deficiency were at a 50% higher risk of being infected than those with normal levels.[58] From the quantity of evidence available, there appears to be a strong association between low serum vitamin D and susceptibility to developing an infection.

There were 6 studies analyzing vitamin D levels and severity of infection, and all six signify that a vitamin D deficiency was associated with a severe infection.[35-38,43,44] D'Avolio et al found that participants with severe infection were deficient in vitamin D, with a mean serum vitamin D value of 11.1 ng/mL, which seems consistent with the data from other trials.[35] According to Cereda et al, 54.3% of the population with a severe vitamin D deficiency had a higher probability of being admitted to the intensive care unit (ICU).[38] The data from De Smet et al are congruent, concluding that 59% of participants hospitalized were deficient in vitamin D, 30% were experiencing inflammation of the cells in the interstitial space of the lungs, and 46% experienced damage to the alveoli, with consolidation and fibrosis of the lung tissue.[43] A potential reason that individuals with a vitamin D deficiency may have a greater incidence of severe infection is a marked reduction in lymphocytes and CD8 T cells, which has been found in people with COVID-19.[45] These cells are converted into cytotoxic T cells, which minimize the spread of microbial infections.[88] Therefore, it is plausible that a vitamin D deficiency may be correlated with a severe COVID infection.

Of the 10 meta-analyses, 8 discussed vitamin D deficiency and the potential for succumbing to a serious infection. All 8 found that low levels of vitamin D were correlated with severe infection.[54,56-62] Pereira et al evaluated 25 articles and determined that 65% of participants with severe COVID-19 had a vitamin D deficiency.[54] The analysis by Munshi et al observes that individuals with insufficient levels of vitamin D were at risk of serious infection with a poor prognosis.[62]

Although all of the meta-analyses agreed that people who are deficient in vitamin D have greater potential for a severe CoV infection, there was a general lack of information, and a few discrepancies in relation to vitamin D status and the requirement for hospitalization, ventilation, or admission to the ICU. There were 3 studies included in the article by Wang et al that indicated a higher rate of hospitalizations, and 2 that showed that the duration of hospital stays was longer for individuals who were deficient in vitamin D.[57] One study in the analysis performed by Kazemi et al paralleled the conclusion of Wang et al.[59] The results of 4 studies from the data collected by Kazemi et al demonstrate a correlation between vitamin D deficiency and severe pulmonary involvement, development of acute respiratory distress, and the requirement for ventilation. However, in 4 articles, Kazemi et al do not find an association between vitamin D deficiency and the rate of ICU admission, and neither does the analysis performed by Wang et al.[57,59] The research by Teshome et al did find 1 study determining that participants with vitamin D deficiency had a greater tendency to be admitted to the ICU.[56]

There were 6 articles that evaluated vitamin D levels and the incidence of mortality. Four of them determined that there was an increased risk of death in people with vitamin D deficiency, whereas the other 2 did not find an association.[34,37-39,44,46] AlSafar et al[44] concluded that individuals with a vitamin D level < 12 ng/mL had significantly greater risk of mortality, whereas Angelidi et al[46] found a correlation between mortality rate vitamin D levels < 30 ng/mL.

Because the research related to vitamin D status and mortality is limited and inconsistent, meta-analysis studies were assessed. Of the 10 meta-analyses, 7 discussed the association between vitamin D status and risk of death. Six found a correlation between vitamin D deficiency and an increased risk of mortality, and the other found no association.[54,56-61] The meta-analyses by Pereira et al[54] and Wang et al[57] evaluated 3 and 15 studies, respectively, and found a significant risk of mortality with vitamin D deficiency; the review by Crafa et al[61] documented 9 studies that found no relation between vitamin D status and mortality. Kazemi et

al assessed 13 studies and determined that 9 correlated vitamin D deficiency with a higher potential for mortality.[59]

The research by Kazemi et al demonstrates that the degree of deficiency influenced the outcome of the infection.[59] For serum vitamin D levels < 10 ng/mL, they document a 50% chance of mortality, compared to 5% in those with serum vitamin D > 10 ng/mL had a 5% mortality rate.[59] In an article reviewed by Teshome et al, participants with vitamin D deficiency had a sevenfold increase in the incidence of death.[56] The data from Akbar et al show a 55% probability of death with lower levels of vitamin D compared to a 27% probability of death with normal vitamin D status in 6 studies, and a 29% probability of death with low serum vitamin D compared to a 12% probability of death in patients with normal vitamin D levels in 8 studies.[60]

Consequently, vitamin D status may have an impact on the survival rate of people with COVID-19, as there is a multitude of research demonstrating that people who are deficient in vitamin D have greater potential to develop a serious infection. People with a more severe infection may be more susceptible to the development of severe acute respiratory syndromes, which is documented in several articles.[35,37,59] However, other factors may have a stronger influence on mortality. There are certain individual characteristics and comorbidities that may increase susceptibility to severe infection and death. The factors that may influence the course of the infection to a greater degree than vitamin D status are age > 50 years, obesity, male gender, living in poverty, immunosuppression, and preexisting medical conditions such as a malignancy, chronic obstructive pulmonary disorder, and end-stage renal disease.[34,37,44,46]

There were 7 articles that discussed the treatment of CoV with vitamin D. All 7 document an improvement in the clinical outcome of COVID-19 infections with treatment with different dosages of vitamin D.[47-53] Only 2 of the studies were randomized clinical trials; 4 were retrospective studies, and the last was a case series. In 4 of the studies, supplementation with vitamin D reduced the severity of the infection.[48,49,52,53] Sabico et al used 1000 or 5000 IU of vitamin D in the form of cholecalciferol once a day, and found that 1000 IU was inadequate to diminish the severity of infection, whereas cough and loss of taste resolved 2.9 and 5.5 days earlier in the group receiving 5000 IU per day.[48] Annweiler et al administered 80 000 IU of vitamin D_3 in a single dose every 2-3 months and found that it decreased the severity of symptoms.[49] Entrenas Castillo et al treated participants with 21 280 IU of vitamin D as calcifediol upon admission to the hospital and 10 640 IU on days 3 and 7 and then weekly until discharge.[52] Of the participants in the control group, 50% were transferred to the ICU, whereas only 1 of the participants receiving vitamin D necessitated transfer to the ICU, accounting for 2% of the sample. The study by Ohaegbulam et al supplemented participants with either 50 000 IU of ergocalciferol or 1000 IU of cholecalciferol each day for 5 days.[53] After the fifth day of treatment, the participants given 50 000 IU of ergocalciferol fully recovered, whereas the group receiving 1000 IU of cholecalciferol experienced minimal improvement in their vitamin D status, and their symptoms steadily declined, resolving on day 13 or 14.

There were 5 articles concluding that treatment with vitamin D reduced the risk of mortality. Similar to the Entrenas Castillo et al study, Alcala-Diaz et al used dosages of 21 280 IU of vitamin D in the form of 25-hydroxyvitamin D_3 at admission and 10 640 IU on days 3 and 7 weekly until discharge for 1 group, and standard care for the control group.[47] The mortality rates were recorded at 5% for the group that received 25-hydroxyvitamin D_3 and 20% for those that received standard care. In the study by Entrenas Castillo et al, the mortality rate was 7.6% for the control group and 0% for the group receiving calcifediol.[52] Ling et al administered a treatment dose or a maintenance dose of cholecalciferol: 20 000 to 40 000 IU/d for 1 to 2 weeks; 20 000, 40 000, or 50 000 IU/wk; 20 000 IU/d twice a week; or 20 000 IU every 2 weeks.[51] The majority of participants were receiving either 40 000 IU weekly or 20 000 IU twice a week, accounting for 76.7% of the sample. The investigators deduce that supplementing with vitamin D at a high dose was positively correlated with a reduction in mortality.

There were 2 articles by Annweiler et al. In one, individuals either supplemented with 50 000 IU each month, received 80 000 to 100 000 IU of vitamin D_3 every 2 to 3 months, or did not supplement and were administered 80 000 IU within hours of a COVID-19 diagnosis.[50] The last group was the control group, which received standard care. The research indicates that consistent supplementation with vitamin D_3 occurred alongside the lowest level of mortality, at 6.9%, followed by administration of vitamin D_3 upon diagnosis, at 18.8%, and standard care (control group), at 31.3%. There was no statistical difference between morality rates for the second and third groups.[50] Consequently, the investigators surmise that supplementing with high-dose vitamin D upon admission is not adequate to prevent death. However, it should be noted that in general, symptoms were less severe and mortality was lower. From other studies, it appears that consistent supplementation with vitamin D is necessary to reduce the morality rate.

In contrast, the other study by Annweiler et al analyzed the mortality rate of participants who were administered 80 000 IU of vitamin D_3 in the week or month before the onset of COVID-19, compared to a control group that did not receive vitamin D_3.[49] Individuals in the group that received vitamin D_3 were consistently administered 80 000 IU every 2 to 3 months. The mortality rate was 55.6% for the control group and 17.5% for the treatment group. As with previous data presented by Ma et al and Meltzer et al, this study may signify that consistent supplementation with vitamin D may have a positive influence over the outcome of COVID-19.[41,42] In addition to continual ingestion of

vitamin D, the administration of a high dose at the onset of COVID-19 may further improve the course of the disease.

There were 2 meta-analysis reviews that discussed participant treatment with vitamin D; both noted that supplementation with vitamin D in the form of 25-hydroxycholecalciferol reduced the incidence of admission into the ICU.[59,63] In addition, Kazemi et al determined that the average duration of infection was shorter in participants who received vitamin D.[59] Unfortunately, a dosage range was not specified in the 4 studies analyzed. Shah et al evaluated 3 studies treating patients with COVID-19 with vitamin D.[63] The first was the study by Entrenas Castillo et al, which was already discussed. Shah et al conclude that the data from this study are relevant, with a low level of bias. The second study used a single dose of 200 000 IU upon admission to the hospital; the rate of admittance into the ICU for those who were infected was 15.83% for those who were supplemented with vitamin D and 20.83% for those who were not. However, the mortality rate for those receiving the single large dose was 6.67%, compared to 5% in the control group, which is consistent with data showing that habitual use of vitamin D is more effective for limiting mortality than a 1-time high dose at the onset of infection.[41,42,50,63] No dosage range was included in the last trial evaluated by Shah et al. That research indicated that the rate of admission to the ICU was 5.26% for participants who were administered vitamin D and 25.38% for those in the control group, yet the mortality rates for the control and supplementation groups were 10.15% and 10.53%, respectively. These data may reflect that treatment with vitamin D can have a positive impact on the severity of infection, but other factors probably have a more substantive role in determining outcomes. This is exemplified by the article published by De Smet et al.[43] Those investigators documented a stronger association between increased mortality rate and age > 50 years, obesity, male gender, living in poverty, immunosuppression, and preexisting medical conditions such as a malignancy, chronic obstructive pulmonary disorder, and end-stage renal disease.[34,37,44,46]

Zinc

We considered whether zinc may be an adjunct for the treatment of CoV infection, as it has the ability to mitigate the activity of inflammatory chemicals activated by the virus. This metal can reduce the gene expression of NF-κB, attenuating the inflammatory cascade and mitigating the production of inflammatory mediators TNF-α, IL-1, IL-6, and IL-8 and increasing IL-10.[89-91] In addition, zinc suppresses the release of MCP-1.[92] Unfortunately, there is no evidence related to the impact of zinc on PAI-1 activity.

According to Mocchegiani et al, inadequate dietary intake of zinc occurs in developing and developed countries, contributing to the potential for zinc deficiency especially in older people.[93] Zinc has an important function in establishing and maintaining immune responses controlled by the innate and adaptive immune systems. It is an essential nutrient for the synthesis of DNA and division of immune cells, and is involved in the transcription of immune proteins. Inadequate dietary intake of zinc can result in an impaired immune response.[4] From the finding by Ling et al that there is a higher mortality rate after age 74 years, low levels of serum zinc could predispose an older person to a greater risk of severe infection.[51]

The literature review revealed 2 studies assessing the activity of zinc against CoV infections, including 1 related to COVID-19. The first article was a case series with 4 patients who tested positive for COVID-19.[64] The first patient was a 63-year-old man who was prescribed 23 mg of zinc citrate 3 times the first day of his infection. He experienced a worsening of symptoms. Over the next 24 hours, in intervals of a few hours, he ingested a total of 207 mg of zinc citrate, and his symptoms began to improve. He continued to supplement with 184 mg of zinc citrate each day until resolution of his disease on day 10.

The second patient was a 57-year-old woman who ingested 23 to 46 mg of zinc citrate daily for 10 days and experienced a progressive worsening of symptoms that eventually climaxed with a severe cough, neck pain, chest pain, a headache, fever, and shortness of breath (SOB). At this point, she proceeded to ingest 23 mg of zinc citrate every hour for a 7-hour period, totaling 161 mg, which drastically improved her SOB and cough. The next day she resumed consuming 46 mg of zinc a day, and her cough began to intensify again. She then self-administered an additional 69 mg and her symptoms subsided. She continued to self-medicate with 115 mg of zinc citrate daily, and her symptoms dissipated and eventually resolved after 10 days.

The third patient was a 41-year-old woman who experienced a progressive aggravation of symptoms over the first 9 days of her disease, culminating in an intense cough, SOB, and body aches. On day 9, she began taking 23 mg of zinc citrate/zinc gluconate every 4 hours, for a total of 138 mg daily. The severity of her symptoms began to improve the next day. She continued to ingest 138 mg of zinc supplement until her symptoms resolved on day 19 of her illness.

The fourth patient was a 26-year-old woman who experienced a moderate-intensity illness for a week before developing SOB and severe fatigue in the second week. In the third week her symptoms manifested as a severe cough and fatigue with body aches. At the beginning of the fourth week of her illness, she ingested 15 mg of zinc acetate every 2 hours, which equated to 150 mg daily.[64] Twenty-four hours after supplementation, her symptoms improved until she fully recovered on day 14.

This case series provides new information related to the therapeutic value of zinc for treating CoV infections, and specifically COVID-19. In each case, low dosages of zinc were unable to reduce the severity of symptoms. However, as the patients increased the dosage and the frequency of

administration, the symptoms became less pronounced, eventually resolving in all cases. This is evident because the symptoms of each patient began to dissipate after consumption of high amounts of zinc, regardless of its form. It appears as if the optimal results were observed with the consumption of > 100 mg of zinc. The second case exemplifies the importance of the dosage, as after the patient's symptoms began to improve, she lowered the dose from 161 mg to 46 mg, and her symptoms began to intensify again. Zinc's potential medicinal properties can be noted in the fourth case as well. This patient had severe illness for several weeks, but after 24 hours of a high daily dosage of zinc her symptoms began to abate. The data collected from this study may signify that continuous low-dose supplementation accumulating to > 100 mg of zinc each day could diminish the severity of COVID-19 and promote its resolution. Additional research with a much larger sample size is necessary before accurate conclusions can be drawn.

The other article related to zinc was a double-blind, randomized clinical trial in neonatal calves infected with bovine CoV, a type of *Betacoronavirus*.[6] The primary reservoir of *Betacoronavirus* infections is bats.[5] According to the Centers for Disease Control and Prevention, COVID-19 is believed to have been spread from a bat, and it is a *Betacoronavirus*.[94] Bovine CoV targets the pulmonary system or gastrointestinal tract.[6] Since it can infect a broad spectrum of domesticated ruminant species, experts have hypothesized that there may be a potential for the development of zoonotic infections.[94] In addition, treatment of CoV in animals may provide details related to therapies that may be effective in humans.[4]

In the clinical trial, 37 calves were enrolled with neonatal enteritis from bovine CoV. They were treated with either a placebo, zinc oxide, or zinc methionine.[65] Both dosages administered were equivalent to 80 mg of zinc. The outcome revealed cure rates of 80%, 81.81%, and 90.9% for the placebo, zinc methionine, and zinc oxide groups, respectively. There was no significant difference between the groups.

Although statistical significance was not observed in this study, the cure rate in the zinc oxide group was 10.9% higher than in the placebo group, which may indicate that zinc oxide is the more proficient form to use in CoV infection. The nonsignificant results may be due to the small sample size or low dosage of zinc administered. As was observed with the case series using zinc, lower dosages were less effective. Supplementing with zinc more frequently to increase the overall daily dosage might have demonstrated a better clinical outcome in this study.

Vitamin A

We considered whether vitamin A may assist with the resolution of symptomatology associated with the CoV. This vitamin can suppress the activity of transcription factor NF-κB and has been shown to significantly reduce the production of IL-1, IL-6, and TNF-α, while increasing IL-10 secretion.[95-98] Vitamin A can downregulate the expression of MCP-1 and PAI-1, attenuating their physiologic effects.[99,100] Research indicates that vitamin A can regulate T cell activation and the response of antiviral T cells, which can lower the risk of excessive systemic inflammation and tissue injury.[32] In addition, it can activate the adaptive immune system by promoting the release of IL-2 and potentiating communication between T lymphocytes.[101] Interleukin-2 promotes the propagation of T lymphocytes and enhances cytotoxicity. Metabolites of vitamin A can increase the proliferation of B lymphocytes, which secrete antibodies to fend off invading pathogens. Reducing inflammation and upregulating the immune response, as well as acting as an anticoagulant, may improve the course of CoV infections.

One article met the inclusion criteria for the literature review. It discusses the use of vitamin A to treat the porcine epidemic diarrhea virus, which is an *Alphacoronavirus* whose primary host is piglets.[102] This is a virus that causes enteropathy, resulting in diarrhea. It has the capacity to infect a variety of different cell lines, including humans, and is believed to have the potential for cross-species transmission.

In the experiment, infected animals were placed into 4 groups: infected pigs, infected pigs with a daily dose of vitamin A, infected pregnant pigs in their third trimester, and infected pregnant pigs in their third trimester receiving daily vitamin A. The dosage used was 15 000 IU twice daily in the form of retinyl acetate. The investigators found that vitamin A supplementation reduced the rate of RNA shedding in the pigs that were not pregnant, which could signify a lower rate of infectivity to a new host.[66] The severity of diarrhea was significantly reduced in the group of nonpregnant pigs receiving vitamin A, and the mortality rate of pigs receiving vitamin A was 25.8%, compared to 44.1% in the control group. The survival rate of piglets born to infected sows was not considered significant, at 8.3% for those born to sows receiving vitamin A and 5.7% for those that born to sows that were not supplemented. The data collected from this study may demonstrate that vitamin A can reduce the potential for transmission of the virus between hosts, the severity of the infection, and the mortality rate, but it did not have a significant effect on infant survival rate.

S. nigra

The botanical *S. nigra* may provide a therapeutic benefit as an adjunct in the treatment of CoV infections. *S. nigra* can deactivate the transcription factor NF- κB.[103] Evidence exists that *S. nigra* increases the proinflammatory cytokines IL-1, IL-6, IL-8, and TNF-α and the antiinflammatory cytokine IL-10.[104,105] Investigators have proposed that the elevation of these mediators stimulates the immune response.[104] In an experiment, *S. nigra* was shown to

increase inflammatory mediators while simultaneously alleviating symptoms associated with the influenza virus.[104] However, another study found that it reduces the levels of TNF-α and IL-6.[106] This may signify that *S. nigra* has a regulatory function related to inflammatory mediators.[104-106] Additional research is required to determine its exact effects on inflammatory mediators during an infection.

One of the ways that *S. nigra* may reduce symptomatology associated with infections is by acting as an immunostimulatory agent.[107] However, evidence related to its influence on the immune system is lacking. Any improvement in symptomatology is more likely due to antiviral effects. There are no data related to the physiological effect of *S. nigra* on MCP-1 or PAI-1.

There was 1 study related to the use of *S. nigra* in treating avian infectious bronchitis virus (AIBV), which is a *Gammacoronavirus* that infects the lining of the respiratory tract in chickens. Although *Gammacoronavirus* species do not typically infect humans, the investigators believe that the data obtained from the study can help determine herbal extracts that can impede the replication of different strains of CoV.[4] The data from the study could be used to devise treatment strategies for coronaviruses that affect the human population. The plant extract, prepared with an 80% ethanol solution, generated antiviral effects inhibiting the replication of the AIBV by physically damaging the membranous envelope of the virion.

In the first part of the experiment, cells were treated with the plant extract before infection and for 24 hours after infection, and the virus was incubated with the extract for 20 minutes before induction of the infection. At low and high multiplicities of infection, *S. nigra* decreased viral titers by 6 and 4 orders of magnitude, respectively. In the second part of the experiment, cells were treated with the extract before infection, the virus was treated with the plant isolate before infection, or the cells were treated after infection. The results indicate that treating the cells with *S. nigra* after infection caused a threefold reduction in virus levels. However, the virus that was exposed to the plant extract before infection demonstrated a decrease in viral titer by 3 orders of magnitude, a more pronounced effect. Consequently, *S. nigra* may possess antiviral activity against CoVs, which could prove beneficial as a therapeutic treatment. Caution should be taken in treating severe CoV infections with *S. nigra* until more evidence is available, as the CoV can induce a severe inflammatory state, and the plant extract may increase the production of certain inflammatory mediators.

A. sativum

We considered whether the addition of *A. sativum* may enhance the therapeutic value of standard treatment for CoV infections. Multiple studies indicate that the constituents of *A. sativum* can deactivate NF-κB, downregulating the inflammatory cascade.[108-110] Its oil and organosulfur components can attenuate the production of IL-1, IL-6, IL-8, and TNF-α and stimulate the synthesis of IL-10.[111-113] An extract of *A. sativum* has been shown to inhibit the effects of PAI-1.[114] *A. sativum* can enhance immune function by increasing proliferation of T lymphocytes and natural killer cells and activating macrophages.[115] There is no research related to the impact of *A. sativum* on MCP-1. These actions demonstrate that *A. sativum* may reduce the pathophysiology of CoV infections and be an advantageous adjunct therapy.

The literature review revealed 2 studies that met the inclusion criteria, one researching AIBV. That study consisted of 7 groups of embryonic chicken eggs that were infected with 1 of 2 strains of AIBV, either Intervet4/91 or M41.[67] Treatment groups were inoculated with the virus at low, medium, moderate, and high concentrations and exposed to an extract of *A. sativum*. The Intervet4/91 strain slowed the growth of the embryos but left them otherwise unaffected. The M41 strain killed all the embryos in the groups with high and moderate concentrations of the virus within 4 days, and the medium-concentration group by day 8. *A. sativum* prevented the Intervet4/91 strain from impeding the growth of the embryos. All of the embryos treated with *A. sativum* that were exposed to high concentrations of the virus died, but only 10% of the embryos in the moderate-concentration group died, and none in the medium-concentration group.

An in vitro study incorporated a nucleotide sequence encoding SARS-CoV-2 into bacteria, which were exposed to phytochemicals extracted from *A. sativum*.[68] The investigators found that the whole herb extract at a dosage of 0.5 mg/mL completely inhibited the replication of SARS-CoV-2, with a half-maximal inhibitory concentration at 137 ± 10 μg/mL. Tannic acid, puerarin, and daidzein were isolated and used against the virus. These active constituents prevented replication of the virus, with respective half-maximal inhibitory concentrations of 9, 42 ± 2, and 56 μg/mL. There were 13 additional phytochemicals that impeded replication by over 50%. The research from these studies provides a limited amount of information requiring more investigation. However, the data may indicate that *A. sativum* possesses antiviral activity that could have a role in the treatment of mild to moderate CoV infections, although in severe cases, as represented by the high-concentration group, *A. sativum* appears not to be effective.

G. glabra

We considered *G. glabra* as an adjunct therapy to attenuate the pathophysiology of CoV infections through mitigation of inflammatory mediators generated as a result of infection. There is currently not any research on the effect of *G. glabra* on PAI-1. However, the expression of NF-κB is downregulated by *G. glabra*.[116] The inflammatory activity of TNF-α, IL-1, and IL-6 is diminished by the botanical

as well.[116,117] An active constituent of the root, known as licochalcone, has the ability to reduce secretion of IL-8 and MCP-1.[118,119] The primary antiviral component, glycyrrhizin, has been shown to enhance the synthesis of IL-10.[120]

In addition, glycyrrhizin can augment the proliferation of T lymphocytes—especially CD4, CD40, and CD86 T cells—and the production of interferon-.[116,119] Elevating CD4 and CD40 T cells may be an essential component to the treatment strategy, as individuals with COVID-19 have lower levels of CD4 T cells and higher quantities of CD40 T produced, which may indicate that CD40 T cells are involved in combating the virus.[121,122] The positive attribution of CD86 T cell activity for CoV infections is not known. However, this immunoglobulin activates T lymphocytes that can defend the host against infection.[116] CD40 T cells can potentiate the differentiation of B lymphocytes and activate monocytes and macrophages, whereas interferon-γ promotes immune function by activating T lymphocytes and natural killer cells and mobilizing white blood cells associated with the immune response.[116,120] The transcription of major histocompatibility complex II—which initiates the generation of dendritic cells, macrophages, and B lymphocytes—is increased by this botanical.[116]

Lastly, *G. glabra* may act as a weak regulator of cortisol levels.[116] Research demonstrates that it can decrease activity of 11β-hydroxysteroid dehydrogenase and 5β-reductase. These enzymes are responsible for the metabolism of cortisol. Consequently, this increases cortisol levels, which may be able to attenuate the intense inflammatory state associated with CoV infections.

Evidence exists that *G. glabra* can act as a potent antiviral for treating SARS-CoV.[123] There were 2 articles that met the inclusion criteria. One involved cells infected with SARS-CoV, that were exposed to components of *G. glabra*.[69] Of the phytochemicals tested, ribavirin and mycophenolic acid were ineffective against the virus, while 6-azauridine, pyrazofurin, and glycyrrhizin were capable of downregulating viral replication at 104, 52, and 300 mg/L, respectively. The experiment revealed that glycyrrhizin diminished the ability of the virus to attach to the host cell, which could allow it to act as a prophylactic, when administered at 300 mg/L. The mechanism of action has not been elucidated.

A similar experiment was performed using cell cultures.[70] In that study, an aqueous extract of *G. glabra* was preincubated with the virus at dosages ranging from 0.004 to 4.0 mg/mL. Inhibition of viral replication was observed at 2 mg/mL, which is lower than the traditional dose of 12.5 mg/mL found in infusions. In the second part of the experiment, glycyrrhizin mitigated the replication of SARS-CoV-2 at a dosage of 0.5 mg/mL when preincubated before cellular exposure, and at 1 mg/mL when administered after the cells were infected without producing cytotoxic effects. The mechanism of action was inhibition of the primary proteinase that controls viral replication, known as M^{pro}. This may indicate that *G. glabra* could be administered as an adjunct therapy for CoV infections, but more research is required.

U. dioica

We considered whether the administration of *U. dioica* in conjunction with standard therapy may be a treatment strategy for CoV infections. The botanical can suppress the expression of NF-κB and the activity of the proinflammatory cytokines TNF-α, IL-1, and IL-6.[124-126] There is limited information on the physiological effect of *U. dioica* on IL-8. One study in rainbow trout infected with parasites found that *U. dioica* increased the synthesis and release of TNF-α, IL-1, IL6, and IL-8 while reducing the severity of the condition and mortality rate.[127] Consequently, as with *S. nigra*, *U. dioica* may be a modulator of inflammatory cytokines, which in certain cases may be essential for the immune response. Research on the influence of the botanical on IL-10, MCP-1, or PAI-1 is not available.

Evidence has shown that *U. dioica* can act as an immunomodulator.[128] It can bolster the nonspecific and cell-mediated immune response.[129] This may be accomplished by increasing the production of neutrophils and T lymphocytes.[130,131] *U. dioica* may be an effective adjunct therapy for treating CoV infections, as it can regulate inflammation and the immune function.

There were 3 studies that met the inclusion criteria related to the effects of *U. dioica* against SARS-CoV. In the first article, the genus of the virus was not specified, but the investigators noted that it was a strain that could affect the human population.[71] The first part of the experiment used human cell cultures infected with Urbani SARS-CoV and exposed to the botanical extract. *U. dioica* agglutinin demonstrated a 90% reduction of viral replication. In addition, the extract had the ability to downregulate replication of the strains of SARS-CoV obtained from Frankfurt, Hong Kong, and Toronto by 90%.

In the second part of the experiment, mice were infected with SARS-CoV. *U. dioica* agglutinin was administered through intraperitoneal injection at a dosage of 5 to 10 mg/kg/d. The mortality rate of the virus in the mice was measured at 90% to 100%. The botanical preparation significantly reduced the severity of infection and prevented the serious weight loss observed in the placebo group. In addition, the mortality rate was 10% or lower for the mice receiving the extract.

The outcome of this study may be explained through examination of the lung tissue of infected mice. In mice given the placebo, necrotic damage was observed in the capillary walls of the alveolar cells, resulting in hemorrhages. Mice that received the plant extract showed a significant degree of protection, demonstrated by a reduction in inflammation and number of cell-surface hemorrhages.

The investigators found that pretreating the virus with the extract before introducing the virus to the cells reduced its replication by 3 times. However, injecting the botanical

into the cells 24 hours after infection produced minimal effects. The virus was inoculated into viable cell cultures and the extract used to treat the cells. Viral replication was analyzed every 2 hours for 24 hours. *U. dioica* inhibited replication in hours 1 through 12, but not after 20 hours. Consequently, *U. dioica* may be most efficacious when used as a prophylactic or in the early stages of infection to reduce replication. Although it did not have an impact on viral replication after the initial stages, the extract may still attenuate symptoms through its antiinflammatory and immunostimulating activity.

In the second study, van der Meer et al used the active constituent *N*-acetylglucosamine, extracted from *U. dioica*, and tested its antiviral capacity against a variety of strains of CoV including AIBV, transmissible gastroenteritis virus (TGEV), mouse hepatitis virus (MHV), and feline CoV.[72] Research indicates that AIBV, TGEV, and MHV share 39%, 44%, and 50% of the amino-acid sequence of the SARS-CoV that infects humans.[132] Because the amino-acid sequence shares some similarities, researchers have proposed that antiviral therapies effective against these strains could be used against human CoV strains, including SARS-CoV-2. Although there is no evidence of transmission of feline CoV to humans, a broad-spectrum antiviral drug has shown decreased antiviral activity against human and feline strains of CoV.[133] This may signify that agents capable of inhibiting the replication of feline CoV strains may have the ability to reduce the replication of species of CoV that infect humans.

Cell cultures were infected with various strains of the virus and treated with different test compounds including *N*-acetylglucosamine.[72] The data show that *N*-acetylglucosamine exhibited antiviral properties against AIBV, TGEV, MHV, and feline CoV. Replication of AIBV, TGEV, MHV, and 3 isolates of feline CoV were inhibited by 50% at, respectively, 0.05 ± 0.05, 0.08 ± 0.07, 0.53 ± 0.02, 0.023 ± 0.012, 0.24 ± 0.14, and 0.11 ± 0.03 μM. These data reflect the ability of *N*-acetylglucosamine extracted from *U. dioica* to impede the replication of a broad spectrum of strains of CoV, which may have implications for human infections.

The third study was conducted by van der Meer et al as well.[73] The investigators evaluated the inhibitory nature of *N*-acetylglucosamine extracted from *U. dioica* against strains of the CoV, specifically isolates of feline CoV and MHV. As with the previous study, the virus was used to infect cell cultures and then exposed to the botanical extract, at a dosage of 6.25 mg/L. In the first part of the experiment, *N*-acetylglucosamine was capable of significantly reducing the formation of the syncytium. The synthesis of the syncytium is initiated by the S proteins responsible for fusion that allow the virus to infiltrate the host cell.[134] Decreasing the number of syncytia produced may reduce the pathophysiology of the virus.

The second part of the experiment analyzed the action of *N*-acetylglucosamine on the M protein for MHV.[73] As discussed previously, the M protein controls the replication and transcription of the virus.[13] The phytochemical was able to interfere with the function of the M protein at 0.7 ± 0.2, 2.8 ± 2.2 mg/L, and 2.7 ± 1.3 mg/L for all 3 strains of the virus.[73] Through mitigation of the activity of the M protein, *U. dioica* may reduce the ability of the virus to replicate, decreasing the severity of infection.

The capacity of the virus to enter the host cell was evaluated. *N*-acetylglucosamine inhibited the entry of the virus into the cell after it had been attached. However, the investigators noted that the presence of *N*-acetylglucosamine during the attachment phase of the infection enhanced the virus's entry into the cell. In the final portion of the experiment, *N*-acetylglucosamine was able to downregulate the replication of the virus isolates tested.

The studies analyzed in this literature review demonstrate that *U. dioica* may act as an effective adjunct therapy for treating various CoV strains. In each of the studies analyzed, the botanical was capable of inhibiting the replication of multiple virus strains.[71,73,132] Although the reduction in reproductive capacity was seen only in the first 12 hours of the study conducted by Kumaki et al[71] and with exposure of the virus to the botanical during attachment to the host cell in the study by van der Meer et al,[73] this may be due to the use of a cell culture or, in the case of van der Meer, of only a single component of the plant. Consequently, *U. dioica* diminished replication and M protein activity, suggesting that it may be effective for controlling the spread of the virus. This is apparent in the animal study conducted by Kumaki et al, in which an attenuation of symptoms and mortality rate was observed. The mortality rate in the placebo group was 90% to 100%, but decreased to < 10% with the administration of *U. dioica*, which may indicate that the botanical could be a valuable adjunct to conventional care. Unfortunately, there have not been any clinical trials performed to evaluate the therapeutically effective dosage of *U. dioica* for the treatment of CoV infections; however, the recommended therapeutic dosage of the dried extract is between 460 and 600 mg.[135]

N-acetylcysteine

We considered whether NAC may be an effective adjunct therapy to standard care for the treatment of CoV infections. This amino-acid derivative can mitigate the expression of NF-κB.[136] Evidence demonstrates that NAC can also reduce the synthesis of IL-1, IL-6, IL-8, and TNF-α, while potentiating the production of IL-10.[136-138] This nutraceutical has the ability to downregulate the expression of MCP-1.[139] Although research does not signify that NAC has a direct effect on PAI-1, data reflect an indirect inhibition of its synthesis.[140-142]

Data also show that NAC may act as an immunostimulant.[143] It can upregulate the replication and differentiation of lymphocytes. This is exemplified by enhancement of the proliferation of $CD4^+$ and $CD8^+$ lymphocytes, amplifying the immune response. Enhancing the formation of $CD4^+$ and $CD8^+$ lymphocytes decrease the severity of an

infection, as their levels are diminished in people with COVID-19.[121] Additionally, NAC can increase the production of IL-2.[144] Interleukin-2 promotes the formation of T and B lymphocytes, optimizing immune function.[145] The culmination of the antiinflammatory and immune-upregulating activity may indicate that NAC could be an efficacious adjunct therapy for treating CoV infections.

Experts have proposed NAC as a possible treatment strategy for COVID-19.[146] It is the precursor to the antioxidant compound glutathione, which may help eliminate the high levels of oxidative damage that have been observed in COVID-19. In addition, NAC can inhibit ACE activity, which may impede the ability of the virus to infiltrate the host, potentially reducing the risk or severity of infection. Unfortunately, our literature review did not reveal any studies demonstrating this concept.

Quercetin

Quercetin may improve patient care as an adjunct to standard therapy. This flavonol has the ability to downregulate expression of NF-κB and the subsequent inflammatory cascade.[147] It can also further reduce inflammation through mitigation of TNF-α, IL-1, IL-6, and IL-8 and increased IL-10.[147-149] Research indicates that quercetin can abate levels of MCP-1 and PAI-1.[150,151] Although data are limited, quercetin can act as an immunostimulant and has antiviral properties.[152,153] It can promote the phagocytotic activity of macrophages and enhance the function of natural killer cells.[154] The combination of these effects may improve the outcome of a CoV infection.

There were 2 studies on quercetin that met the inclusion criteria. The first was a randomized trial consisting of 152 participants who tested positive for and experienced mild to moderate COVID-19.[74] The participants were all receiving standard care according to hospital guidelines, and the intervention group received 1000 mg of quercetin 2 times a day for 30 days. The investigators documented significant reductions in hospital admissions, requirement for ventilation, ICU admission, hospitalization duration, and mortality. In the group receiving standard therapy, 28.9% were hospitalized, 19.7% required ventilation, 10.5% were admitted into the ICU, and 3.9% died; whereas in the quercetin group, 9.2% and 1.3% were hospitalized or required ventilation, respectively, and none were admitted to the ICU or died. The duration of hospitalization was 6.77 $\pm$ 3.08 days in the standard-therapy group, compared to 1.57 $\pm$ 0.53 days in the quercetin group.

The investigators did note an imbalance between the 2 groups in relation to comorbidities. In the standard-therapy group, 59.2% of participants had a comorbidity, compared to 38.2% in the quercetin group. To compensate, the researchers evaluated the impact of quercetin supplementation compared to standard therapy in infected participants without comorbidities. After adjustment, the data showed that 22.6%, 12.9%, 6.5%, and 6.5% of otherwise healthy participants in the standard-therapy group were hospitalized, required oxygen, were admitted to the ICU, and died, whereas 8.5% of those in the quercetin group were admitted to the hospital and none required oxygen, were admitted to the ICU, or died. The duration of hospital stays for participants who were otherwise healthy was 5.14 $\pm$ 2.79 days for the standard-therapy group and 1.25 $\pm$ 0.5 days for the quercetin group. Consequently, after adjustment for comorbidities, quercetin remained a significantly effective adjunct therapy.

In the second study, 42 participants who were positive for COVID-19 with mild to moderate illness were randomly divided into groups to receive standard therapy according to hospital guidelines or 500 mg of quercetin 3 times a day for 7 days and 500 mg 2 times a day for an additional 7 days.[75] The demographic characteristics and comorbidities were equivalent between the groups except for age, which was on average 56.2 $\pm$ 3.3 years in the standard-therapy group and 42.5 $\pm$ 3.3 years in the treatment group. The data showed that quercetin significantly increased viral clearance, by 76% in the first week compared to 9.5% in the standard-therapy group. In the treatment group, 57% of participants experienced a complete resolution of symptoms at day 7, versus 19% in the standard-therapy group. One participant in the standard-therapy group was hospitalized, was admitted to the ICU, and died. In the group receiving quercetin, no participants were hospitalized or admitted to the ICU and none died. The results of this study are a good indication that quercetin may be an effective adjunct therapy. Additional research needs to be conducted before conclusions are made.

Selenium

We considered whether selenium may be advantageous as an adjunct to standard therapy for CoV infections, as it is an antiinflammatory and antioxidant nutraceutical. This mineral can reduce the expression of the inflammatory transcription factor NF-κB.[155] The inflammatory markers TNF-α, IL-1, IL-6, and IL-8 have been shown to decrease, and IL-10 to increase, with supplementation with selenium.[156-159] Supplementation with selenium can diminish MCP-1 and PAI-1 activity.[160,161]

Research indicates that selenium can enhance immune function and combat viral infections. It can potentiate the proliferation of T lymphocytes and the secretion of interferon-γ, which activates T lymphocytes and natural killer cells and enhances the overall immune response.[116,159] The secretion of IL-4 by T lymphocytes has been shown to be upregulated by selenium.[162] Interleukin-4 attenuates the inflammatory response during an infection.[163] In a study with cases of an upper respiratory tract infection, selenium increased antibody release, fortifying immune response.[162]

There were 3 articles on selenium that met the inclusion criteria, all related to selenium status and the potential to develop COVID-19 infection. Two of the studies found that lower levels of selenium were associated with increased rate from COVID-19.[76,77] One of them compared

cure rates and death rates of COVID-19 in different regions of China related to selenium status.[77] The investigators determined that there was a positive correlation between regions of the country with low selenium and a lower cure rate and higher death rate. The other study found that selenium status was higher over time in people who survived COVID-19 than in those who did not.[76] In the third study, there was no association between the incidence of COVID-19 and selenium deficiency.[78]

Although the data are limited, supplementing with selenium may reduce inflammation and stimulate the immune function to assist in the resolution of a CoV infection. Only a small amount of research has been conducted on the effects of selenium on CoV. However, some evidence demonstrates that individuals with low selenium status may be at increased risk. This seems probable, as impaired immune function and lower levels of immunoglobulin G and immunoglobulin M have been observed in individuals with selenium deficiency.[162] More research and clinical trials are required to determine the extent of the benefit of selenium as an adjunct therapy.

Limitations and Future Studies

There are several limitations to this exploratory review. Our goal was to consider antiinflammatory and antioxidant nutraceuticals as potential adjunctive therapies for CoV illness, not to suggest using them to replace mainstream treatments that have been proven through rigorous clinical research to be effective. Our search criteria spanned 15 years, and thus some content may have not been included. Another limitation is that several of the articles were not clinical, but were instead either cell-culture studies or animal trials. This was a necessity, as the published data related to human test subjects were minimal. Clinical trials for each nutraceutical will be necessary to determine its impact as an adjunct treatment strategy. This review assesses several different species of CoV, which are not all capable of infecting humans. However, understanding the impact of certain nutraceuticals on various strains of CoV could provide insight into possible treatment strategies for species that do infect humans. This review was limited in that it sought only to explore the topic, not to make conclusive clinical recommendations. It demonstrates that further studies are needed to consider how antiinflammatory and antioxidant nonpharmaceuticals may be used as potential adjunctive therapies for CoV infections in humans.

Conclusion

In this exploratory review, we identified nonpharmaceutical supplements (vitamin D, zinc, vitamin A, *N*-acetylcysteine, quercetin, selenium, *S. nigra*, *A. sativum*, *G. glabra*, and *U dioica*) which may have the potential to provide support for those with coronavirus infections. However, rigorous clinical studies need to be performed before any clinical recommendations can be made at this time.

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Contributorship Information

Concept development (provided idea for the research): B.R.M., J.R.
Design (planned the methods to generate the results): B.R.M., J.R.
Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): B.R.M.
Data collection/processing (responsible for experiments, patient management, organization, or reporting data): B.R.M., J.R.
Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): B.R.M.
Literature search (performed the literature search): B.R.M., J.R.
Writing (responsible for writing a substantive part of the manuscript): B.R.M., J.R.
Critical review (revised manuscript for intellectual content, this does not relate to spelling and grammar checking): B.R.M., J.R.
Other (list other specific novel contributions): B.R.M.

Practical Applications

- Vitamin D, zinc, vitamin A, elderberry (*Sambucus nigra*), garlic (*Allium sativum*), licorice (*Glycyrrhiza glabra*), and stinging nettle (*Urtica dioica*) may be effective adjunct therapies in coronavirus infection that can add additional benefits.
- This review may provide a basis for further research on elderberry (Sambucus nigra), garlic (Allium sativum), licorice (Glycyrrhiza glabra), stinging nettle (Urtica dioica), NAC and selenium.
- More research is needed to better understand the appropriate dosage to treat coronavirus infections with vitamin D and zinc.

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