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REVIEW

Can vitamins and/or supplements provide hope against coronavirus?

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Abstract

Severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) quickly became a global pandemic and has been responsible, so far, for infecting 5.8 million and claiming the lives of more than 350,000. While certain medications initially garnered attention as potential treatment options, further studies failed to demonstrate great promise but did demonstrate the need to reduce the cytokine storm experienced by patients with this potentially life-threatening virus. Unfortunately, there is no cure on the horizon, but members of the medical community are beginning to evaluate the potential role of vitamins and supplements as potential treatment options or addition to other treatments. The goal of this narrative review is to evaluate current and ongoing clinical trials of vitamins and supplements, alone or in combination with each other or other therapies, for the treatment of coronavirus disease-2019 (COVID-19).

Keywords: coronavirus, COVID-19, SARS-COV-2, severe acute respiratory syndrome coronavirus, supplement, 2019-nCOV, 2019 novel coronavirus, vitamin.

Citation

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-COV-2), the cause of coronavirus disease-19 (COVID-19),[1] was first reported to the World Health Organization (WHO) on December 31, 2019,[2] and declared a global pandemic on March 11, 2020.[3] To date, there are approximately 5.8 million confirmed cases and over 350,000 deaths globally.[4] There are no Food and Drug Administration[5] or European Medicines Agency[6] approved vaccines or medications for the treatment of COVID-19. No specific therapies are recommended by the Centers for Disease Control and Prevention,[7] Infectious Diseases Society of America,[8] Society for Critical Care Medicine,[9] or WHO[10] outside of clinical trials. The National Institutes of Health (NIH)[11] guideline was recently updated to recommend remdesivir in certain patients based on preliminary evidence from clinical trials.

Despite absence of guideline-supported recommendations, several therapies thought to be effective for COVID-19 are in use around the world. However, access to these treatments is not equitable among all populations.[12] Remdesivir and chloroquine/hydroxychloroquine are drug therapies that have received the most attention.

Remdesivir was initially available through individual compassionate use requests. This pathway was halted for the majority of patients due to the overwhelming numbers of requests and the need to focus on clinical trials. Remdesivir access was then limited to these clinical trials and expanded access programs.[13] However, not all patients had the equal opportunity to enroll due to study site locations and eligibility criteria.[14,15] It was only on May 1, 2020, that the FDA granted emergency use authorization (EUA) for remdesivir. It is now available for suspected or confirmed disease in hospitalized adults and children with severe disease, which is defined as low blood oxygen levels or needing oxygen therapy or mechanical ventilation.[16] However, allocation of remdesivir through EUA has not been transparent, and fears grow as healthcare providers are faced with rationing the limited drug supply.[17,18]

Chloroquine and its metabolite hydroxychloroquine are widely prescribed for other indications. However, when reports emerged of their possible activity against SARS-COV-2, shortages quickly developed in the United States (US).[19–21] These drugs can be obtained for COVID-19 treatment through the FDA EUA, but use is reserved for only the sickest patients in certain hospitals.[22] Additionally, chloroquine and hydroxychloroquine are associated with potentially severe cardiac side effects.[23] Furthermore, an early clinical trial failed to demonstrate efficacy.[24]

Another potential therapy showing promise is the 14-day combination of lopinavir, 400 mg, and ritonavir, 100 mg orally

every 12 h, ribavirin, 400 mg orally every 12 h, and three doses of 8 million international units of interferon beta-1b on alternate days when compared to 14 days of lopinavir, 400 mg, and ritonavir, 100 mg, every 12 h. This multicenter, prospective, open-label, randomized, phase 2 trial conducted at six sites in Hong Kong demonstrated that the triple antiviral therapy was safe and superior to lopinavir and ritonavir alone.[25]

Due to concerns over equitable access and adverse events of notable experimental treatments, we aimed to investigate potential alternative agents for treatment of COVID-19 that may have better availability and side effect profiles. Vitamins and essential nutrients are well known for their overall tolerability and requisite role in immune function. Thus, they were a natural choice for our investigation. This narrative review summarizes current and ongoing clinical trials of high-dose vitamins and supplements, alone or in combination with each other or other therapies, for the treatment of COVID-19. While not the focus of this review, vitamins and supplements may have an additional benefit in COVID-19 prevention, with a number of clinical trials planned to investigate this hypothesis. If shown to be safe and effective, vitamins and supplements may provide the much-needed answer to the COVID-19 pandemic.

Methods

The authors searched the NIH US Library of Medicine Clinical Trials Database (www.clinicaltrials.gov) and the WHO's International Clinical Trials Registry Platform (WHO ICTRP) via the NIH (https://clinicaltrials.gov/ct2/who_table). Prospective interventional trials of vitamins and/or supplements, excluding Chinese traditional medicine (CTM), for the treatment of COVID-19 posted on or before May 4, 2020, were included. Synonyms for COVID-19 were SARS-COV-2, 2019-nCOV, 2019 novel coronavirus, and SARS-COV-2. Additional search terms of 'vitamin' and 'supplement' were used to narrow search results. Traditionally, indexed literature and abstracts would have been added to the search methodology, but given the novelty of the subject, Medline and Embase searches for interventional studies yielded no results. This manuscript was exempted from ethics review as it did not involve human subjects.

Results

In the NIH COVID-19 database, the additional search terms of 'vitamin' yielded 28 studies and 'supplement' yielded 115 additional studies. Of these 143 studies, 18 met inclusion criteria from this database (Figure 1). Reasons for study exclusion were: erroneous search result (n=103); vitamin/supplement given as placebo, control, or standard of care (n=9), CTM (n=4); prevention study (n=5); diet plan as intervention (n=2; Ayurveda and ketogenic); and methodology (n=2; retrospective design and COVID-19 not required for inclusion).

Filtering the NIH's WHO ICTRP COVID-19 study table using the terms 'vitamin' yielded 27 studies. Filtering by 'supplement' yielded 36 additional studies. Of those 63 studies, 12 met inclusion criteria from this database. Reasons for study exclusion were: erroneous search result (n=37), diagnostic study (n=3), cancelled by investigator (n=3), CTM (n=2), prevention study (n=4), retrospective design (n=1), and vitamin/supplement given as placebo, control, or standard of care (n=1). One trial was dual registered in the American and European databases, leaving 11 unique studies.

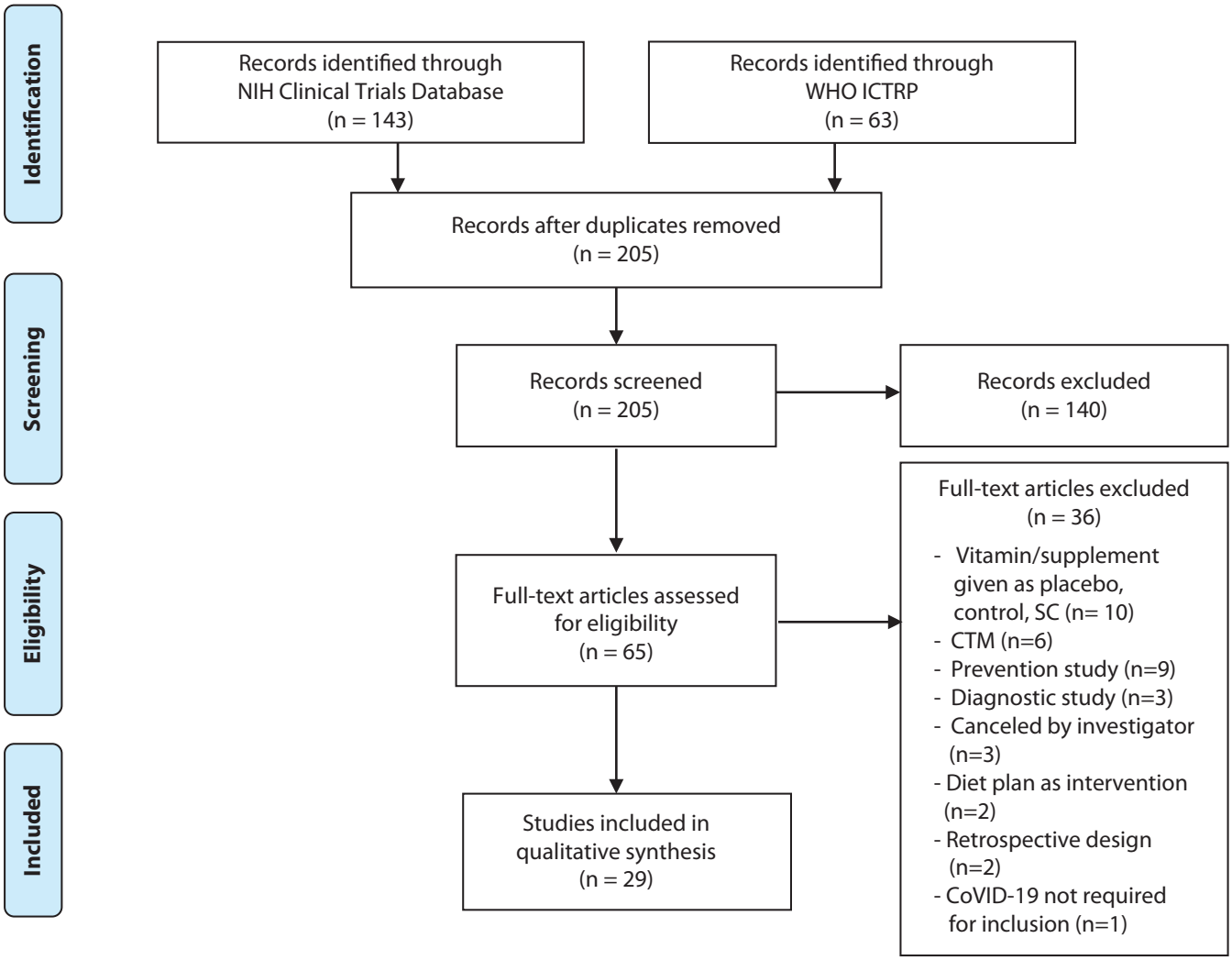
Of the two clinical trial registries searched, a total of 29 studies met inclusion for evaluation and focused on the role of fatty acids, honey, medicinal plant extracts, probiotics, vitamins A, B, C, and D, and zinc (Table 1). Although these studies are ongoing and enrolling subjects, it is important to understand the potential role of these supplements and vitamins (Table 2).

The vitamins and supplements are under investigation in these trials largely as a result of their anti-inflammatory and antioxidant properties.[26–54] It is postulated that honey also has antiviral properties.[34,35] Table 1 highlights the mechanism of action, commercial availability, common uses, considerations for adverse events and drug–drug interactions, and proposed use in COVID-19 for the vitamins and supplements.

Twelve studies in six countries seek to evaluate nutritional supplementation or supplements for the treatment of COVID-19.[55–66] Agents evaluated in these studies are α-lipoic acid (ALA) (n=2),[55,56] curcumin (n=1),[57] *Chlorella vulgaris* (green algae) with a herbal tea blend (n=1),[58] escin (n=1),[59] honey (n=1),[60] Imfluna (=1),[61] n-acetyl cysteine (NAC) (n=2)[62,63], fatty-acid/antioxidant-enriched oral supplement (n=1),[64] probiotics (n=1),[65] and resistant starch (n=1).[66] Nineteen studies in eight countries seek to evaluate vitamins and minerals for the treatment of COVID-19.[67–83] Agents evaluated in these studies are: vitamin A (n=3),[67–69] vitamin B (n=2),[69,70] vitamin C (n=10),[69,71–78] vitamin D (n=8),[64,69,77,79–83] and zinc (n=3).[77,78] The sum of studies here is more than 29, as multiple agents are investigated in some trials. For each study, Table 2 provides the trial location, design, treatment arms, requirements for treatment, status, planned end date, and endpoints.

The majority of vitamin supplements in these trials are administered orally, although some are parenteral. ALA is administered parenterally in both studies,[55,56] escin is administered parenterally in one arm of its study,[59] NAC[62] and vitamin B[69] are administered parenterally in one study each, and vitamin C is administered parentally[71–78] in all studies except one.[69] Intervention and comparator arms vary across the trials.[55–83] The intervention arms call for the study agent to be given alone, in combination with other study agents, or with standard of care. Comparator arms include other study agents (e.g. adalimumab), standard of care, and/or placebo. Standard of care is not described in all trails. It may only be defined as such or specific antivirals (e.g. hydroxychloroquine and azithromycin) may be listed. Study agents investigated in

Figure 1. Selection of studies.[98]



CoVID-19 = coronavirus disease; CTM = Chinese Traditional Medicine; NIH = National Institutes of Health; SC = standard of care; WHO ICTRP: World Health Organization's International Clinical Trials Registry Platform

combination in at least one arm of one study are: methylene blue plus vitamin C plus NAC,[62] vitamin D plus NAC,[63] and oxygen–ozone therapy plus probiotics,[65] vitamins A, B, C, D, plus E,[69] quintuple therapy of vitamins C and D plus zinc plus hydroxychloroquine and azithromycin,[77] vitamin C plus zinc,[78] vitamin D plus aspirin,[81] and vitamin D plus zinc[83] (n=1 for all).

There are a wide range of planned primary and secondary outcomes among the studies.[55–83] Notable planned outcomes include disease progression or recovery, adverse events, mortality, change in symptoms, vitals, radiology, and/or laboratory inflammatory markers, and rate of, length of, or time to hospitalization or mechanical ventilation. The study expected to have peer-reviewed results earliest is of ALA plus standard of care in critically ill patients with COVID-19.[56] The majority of the other trials are recruiting (n=15). This is followed by not yet recruiting (n=11), enrolling (n=1), and recruitment compete (n=1).[55,57–83]

Discussion

Although the full potential of vitamins and herbal supplements have not been elucidated, various studies are underway to assess these agents as potential treatment options and/or additive therapies to current treatment choices that vary around the world as there is no definitive treatment at this point in time. Depending on the formulation, vitamins and herbal supplements are relatively affordable and accessible. Availability in certain markets may be limited as this novel virus has caused patients and providers to stockpile medications, vitamins, and supplements for later use without proven efficacy and unknown safety profiles at higher than normal doses,

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Table 1. Characteristics of vitamins and supplements under investigation for SARS-CoV-2.

Name	MOA	Commercial product	Most common use(s)	Considerations and usual dose	Proposed use in COVID-19[55–83]
Nutritional supplementation or supplements					
Alpha-lipoic acid[26,27]	Antioxidant	Yes	–Aging skin –Cognitive impairment/dementia –Diabetes –Diabetic neuropathy –Dyslipidemia –Multiple sclerosis –Weight loss	AE: allergic reaction, hypoglycemia, changes in vision DDI: chemotherapy, antidiabetics Usual daily dose: 150–1800 mg	Antioxidant effects Dosing: 1200 mg/d IV
Curcumin[28,29]	Antioxidant, anti-inflammatory; active polyphenol of *Curcuma longa* (turmeric)	Yes	–Inflammatory conditions	AE: GI complaints DDI: no major; caution with: alkylating agents, anticoagulants, antiplatelets, antidiabetics Usual daily dose: 180 mg–2.5 g	Symptom improvement Specific product under investigation: SinaCurcumin Dosing: 40 mg PO BID × 2 wks, then daily
Chlorella vulgaris (Freshwater green algae)[30,31]	Nutrient and antioxidant	Yes	–Cancer –Liver disease –Infections –Skin ulcerations –Toxicity (lead, mercury) –Aging	AE: GI complaints, fatigue, photosensitivity, thrombocytopenia DDI: warfarin (high in vitamin K) Usual daily dose: 600 mg–2 g	Symptom improvement Dosing: 300 mg PO QID with herbal tea blend
Escin[32,33]	Anti-inflammatory and vasoconstrictor; triterpene saponin (active compound) in *Aesculus hippocastanum* (horse chestnut); part of plant dictates use	Yes	–CVI –Other venous conditions –IBS –Malaria –Eczema –Skin ulcers	AE: dizziness, GI complaints, headache, pruritus, calf spasms; bark can be nephrotoxic DDI: no major; caution with anticoagulants, antiplatelets, antidiabetics Usual daily dose, CVI: 100–150 mg	Reduce cytokine-mediated lung damage Dosing: 40 mg PO TID
Natural honey[34,35,96]	Antiviral, antitussive, and antimicrobial (due to high osmolarity and concentration of H2O2)	Yes	–Antimicrobial agent (antibacterial, antifungal, antiviral, antimycobacterial) –Cough caused by URI –Topical wound treatment[a]	AE: abdominal pain, nausea, vomiting, hyperglycemia with large doses, botulism (do not use in children < 1 yo) DDI: none DRI, added sugars: ≤25% of total energy	Possible antiviral effects and acute cough Dosing: 1 gram/kg/day split into 2–3 doses

(Continued)

Table 1. (*Continued*)

Name	MOA	Commercial product	Most common use(s)	Considerations and usual dose	Proposed use in COVID-19[55–83]
Imfluna[36]	Not reported	Not available in US	Not reported	NR	Mixture of medicinal plant extract powder manufactured by HomaPharmed Pharmaceutical Company; proposed MOA not reported Dosing: 500 mg capsule × 3 PO TID AC
N-acetyl cystine (NAC)[37,38]	Antioxidant	Yes	–APAP poisoning[a] –Lung diseases[a] –Contrast-induced nephropathy prevention	AE: GI complaints (> with PO), CNS effects; IV: rash, hypersensitivity DDI: nitroglycerine (major), use caution: ACE-I, anticoagulants, antiplatelets, chloroquine[b] Lab: decreased PT Usual dose, APAP poisoning: 1220 mg/kg PO over 72 h or 200 mg/kg IV over 21 h	Antioxidant effects by supporting the synthesis of glutathione Dose: 600 mg PO daily; dose not provided IV
Oral nutritional supplements (ONS)[39,40,96]	Anti-inflammatory and antioxidant	Yes	–Nutrition –Weight gain	AE: diarrhea, nausea, bloating, exhaustion, increased pulse DDI: fluoroquinolones RDA: Protein: 56 g (M), 46 g (F) Fat: ND Carbohydrate: 130 g (M or F) Fatty acids (AI): 1.6 g (M), 1.1 g (F) Selenium: 55 µg (M or F) Also see other table entries UL: Protein: NR Fat: NR Carbohydrate: NR Fatty acids: 3 g (M or F) Selenium: 400 µg (M or F) Also see other table entries	May reduce the severity of COVID-19 by preserving nutritional status High doses of n3-fatty acids and antioxidant vitamins may act as an anti-inflammatory agent to modulate cytokine production and reduce damage to the lungs from the associated cytokine storm Specific product under investigation: Oxepa (Abbott Nutrition, Abbott Laboratories); 14.8 g protein, 22.2 g fat, 25 g carbohydrate, 355 kcal, 1.1 g EPA, 450 mg DHA, 950 mg GLA, 2840 IU vitamin A as 1.2 mg β-carotene, 205 mg Vitamin C, 75 IU vitamin E, 18 ug Selenium, and 5.7 mg Zinc Dose: 8 oz PO every AM separated from meals

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Table 1. (*Continued*)

Name	MOA	Commercial product	Most common use(s)	Considerations and usual dose	Proposed use in COVID-19[55–83]
Probiotics[41,42]	Interfere with pathogenic bacteria growth (competition), improve barrier function of epithelium, and immunomodulation	Yes	–GI disorders –Mood disorders	AE: GI upset, infection DDI: no concerns Usual daily dose, Sivomixx: 1–2 sachets	Restore microbial flora Specific product under investigation: Sivomixx (Streptococcus *thermophilus* DSM 322245, *Bifidobacterium lactis* DSM 32246, *Bifidobacterium lactis* DSM 32247, *Lactobacillus acidophilus* DSM 32241, *Lactobacillus helveticus* DSM 32242, *Lactobacillus paracasei* DSM 32243, *Lactobacillus plantarum* DSM 32244, *Lactobacillus brevis* DSM 27961) Dose: 6 sachets PO BID
Resistant starch[43,44,96]	Increase butyrate production in the colon; type determines specific properties	Yes	–Improve gut health/microbiota –Improve serum inflammatory biomarkers	AE: flatulence DDI: no concerns AI, fiber: 38 g (M or F) UL: NR	Anti-inflammatory effects Dose: 2 tbsp (~20 g) PO daily × 3 d, then BID
Vitamins & minerals					
Vitamin A[45,46,96]	Essential fat-soluble micronutrient	Yes	–Deficiency –Vision conditions –Infection –Wound healing	AE: hypervitaminosis with high doses, chronic use DDI: no concerns at usual doses RDA: 900 µg (M), 700 (F) µg[c] UL: 3000 µg (M or F)[c]	Supplementation for reduced levels during infection Dose: 25,000-50,000 IU PO daily
Vitamin B[47,48,96]	Essential water-soluble vitamin; each has own specific properties	Yes	–Deficiency –Mood disorders –Energy –Cell growth	AE: no major DDI: no concerns RDA: Thiamin: 1.2 mg (M), 1.1 mg (F) Riboflavin: 1.3 mg (M), 1.1 mg (F) Niacin: 16 mg (M), 14 mg (F) Pyridoxine: 1.3 mg (M or F) Pantothenate (AI): 5 mg (M or F) Biotin (AI): 30 µg (M or F) Folic acid: 400 µg (M or F)	Anti-inflammatory effects Specific products under investigation: Nicotinamide (vitamin B3) Dose: 1000 mg PO daily Soluvit (thiamine 3.1 mg, riboflavin 4.9 mg, nicotinamide 40 mg, pyridoxine 4.9 mg, pantothenate 16.5 mg, ascorbate 113 mg, biotin 60 mcg, folic acid 400 mcg, cyanocobalamin 5 mcg)

(Continued)

Table 1. (*Continued*)

Name	MOA	Commercial product	Most common use(s)	Considerations and usual dose	Proposed use in COVID-19[55–83]
Vitamin B[47,48,96] (continued)				UL: Thiamin: ND Riboflavin: ND Niacin: 35 mg (M or F) Pyridoxine: 100 mg (M or F) Pantothenate: ND Biotin: ND Folic acid: 1000 µg (M or F)	Dose: 1 ampule PO daily
Vitamin C (ascorbic acid)[49,50,96]	Antioxidant and enzymatic cofactor	Yes	–Deficiency/nutrition[a] –Cancer prevention[d] –URI –Aging skin –Sepsis –Wound healing	AE: osmotic diarrhea, GI upset (high PO doses), hemolytic anemia if G6PD deficient DDI: no major; use caution: estrogens, antihyperlipidemics Lab: false BG elevation RDA: 90 mg (M), 75 mg (F) UL: 2000 mg (M or F)	Stimulates IFN production, which supplies lymphocyte proliferation and enhances neutrophil phagocytic capability Dose: wide range, given either IV and PO (Table 2)
Vitamin D (calciferol)[50,51,96]	Essential fat-soluble vitamin	Yes	–Deficiency –Hypoparathyroidism –Osteomalacia –Osteoporosis –Osteoporosis prevention[d] –Psoriasis	AE: intoxication with excessive doses DDI: no major; use caution: CYP P450 3A4 substrates RDA: 15 µg (M or F)[e] UL: 100 µg (M or F)[e]	Immunomodulatory and induces secretion of antimicrobial peptides Dose: 25,000–400,000 IU PO daily
Vitamin E (tocopherol)[52,53,96]	Fat-soluble vitamin	Yes	–Deficiency –CVD –Diabetes –Diabetic complications –Cancer prevention –Infections	AE: GI upset, headache, blurred vision DDI: no major; use caution: alkylating agents, anticoagulants, antiplatelets, CYP P450 3A4 substrates, warfarin RDA: 15 mg (M or F)[f] UL: 1000 mg (M or F)[f]	Antioxidant and immunomodulatory effects Dose: 300 IU PO daily

(Continued)

Table 1. (*Continued*)

Name	MOA	Commercial product	Most common use(s)	Considerations and usual dose	Proposed use in COVID-19[55–83]
Zinc[50,54,96]	Essential mineral	Yes	–Deficiency –AMD –Infections –Wound healing	AE: GI upset, metallic taste DDI: no major; use caution: antidiabetics, drugs susceptible to chelation in the gut RDA: 11 mg (M), 8 mg (F) UL: 40 mg (M or F)	Antiviral properties and essential for immune function Dose: 15–30 mg PO daily

[a]FDA approved indication; [b]Decreased effect; special caution as this is a proposed CoVID-19 treatment; [c]1 IU = 0.15 µg as RAEs for β-carotene supplement[97]; [d]FDA approved qualified health claim; [e]1 IU = 0.025 µg[97]; [f]1 IU = 0.69 µ g for natural and 0.45 µg for synthetic[97].

AC, after meals; AE, adverse event; AI, adequate intake (used when insufficient evidence to calculate RDA); AMD, age-related macular degeneration; BG, blood glucose; BID, twice daily; CNS, central nervous system; CVD, chronic vascular disease; CVI, chronic venous insufficiency; CYP, cytochrome; d, days; DDI, drug-drug interaction; DRI, dietary reference intake; F, female; FDA, US Food and Drug Administration; GI, gastrointestinal; GLA, gamma-linolenic acid; H2O2, hydrogen peroxide; hrs, hours; HSV-1, herpes simplex virus 1; IBS, irritable bowel syndrome; IM, intramuscular; IV, intravenous; kg, kilogram; M, male; MOA, mechanism of action; ND, not determinable; NICE, National Institute for Health and Care Excellence; NOS, nitric oxide synthase; NR, not reported; Oz, ounces; PHE, Public Health England; PO, oral; PT, prothrombin time; QID, four times daily; RAE, retinol activity equivalents; RDA, recommended dietary allowance (non-pregnant adults 19-50 yo); TID, three times daily; UL, tolerable upper intake level; URI, upper respiratory infection; US, United States; VZV, varicella zoster virus; wks, weeks; yo, years old.

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Table 2. Clinical trials of vitamins and supplements under investigation for SARS-CoV-2.

Trial ID and title	Location	Study design	Treatment arms (n)	Requirements for treatment (inclusion/ exclusion)	Status; study end date	Planned endpoints (primary/secondary)
Nutritional supplementation or supplements and honey						
ChiCTR2000030471[55] Efficacy and safety of lipoic acid injection in reducing the risk of progression in common patients with novel coronavirus pneumonia (COVID-19)	China	Randomized, single-blind, multicenter	α-Lipoic acid (ALA) injection, dose not provided (n=197) Routine therapy (adalimumab) + placebo (n=197)	Inclusion • 18 to 75 yo • Mild patients with confirmed COVID-19 Exclusion • Pregnancy or lactation • Allergy or intolerance to study drugs • Enrolled in other COVID-19 clinical trials Other foods or drugs with antioxidant effect (e.g. vitamin C, vitamin E) • Other serious life-threatening diseases (e.g. cancer)	Recruiting; 4/30/20	Primary • Progression from mild to critical/severe Secondary • NEWS Score • Hospitalization • 30-d all-cause mortality • Levels of inflammatory factors and oxidative stress
ChiCTR2000029851[56] A randomized, single-blind, group sequential, active-controlled study to evaluate the clinical efficacy and safety of α-Lipoic acid for critically ill patients with coronavirus disease 2019	China	Randomized, single-blind, single center	SC + α-Lipoic acid 1200 mg/d IV x 7 d (n=8) SC + placebo (equal volume saline infusion) x 7 d (n=9)	Inclusion • Critical illness of diagnosed COVID-19 Exclusion • Participation in other clinical trials • Pregnant or breastfeeding • Life-threatening diseases (e.g. cancer) • Expected survival time < 24 h • Allergy or intolerance to study drug • History of immune system or immune-related diseases	Completed; results pending	Primary • SOFA score Secondary • 30-d all-cause mortality
IRCT20200408046990N1[57] Evaluation of SinaCurcumin as a complementary therapy in mild-to-moderate COVID-19: An open label non-randomized clinical trial	Iran	Non-randomized, open label, parallel group	Sinacurcumin 40 mg 2 capsules PO BID x 2 wks then 1 capsule PO daily x 2 wks (n=30) SC (n=30)	Inclusion • Mild-to-moderate COVID-19 by laboratory, radiologic, or clinical diagnosis • 18–65 yo Exclusion • < 7 d from symptom start • Pregnancy or lactation • Allergy to study drug • Concomitant bacterial infection • SpO2 < 90% • < 5 cigarettes/d • Selected past medical diseases	Not yet recruiting; 9/20/20	Primary • Treatment response (fever, symptoms, radiologic) • AEs Secondary • LOS hospital • Clinical outcomes

(Continued)

Table 2. (*Continued*)

Trial ID and title	Location	Study design	Treatment arms (n)	Requirements for treatment (inclusion/exclusion)	Status; study end date	Planned endpoints (primary/secondary)
IRCT20151228025732N51[58] Effect of Algomed, *Menta longifolia*, Chamomile, *Althaea rosea*, *Malva sylvestris*, and *Lepidium sativum* supplements on the severity and consequences of coronavirus 19 disease (COVID-19)	Iran	Non-randomized, parallel control group, single center	SC + *C. vulgaris* 300 mg supplemented with herbal tea (2 g Pennyroyal; 2 g Chamomile, 1.4 g Hollyhocks, and 0.6 g Mallow) PO QID (n=30)	Exclusion • Malignant diseases • Severe renal, liver, and heart failure • Anticoagulants • Pregnancy or lactating	Recruiting; 6/16/20	Primary • Clinical symptoms
			SC (n=30)			Secondary • None reported
NCT04322344[59] Efficacy and safety of escin as add-on treatment in COVID-19 infected patients	Italy	Non-randomized, double-blind, parallel assignment	SC (antiviral therapy) + Escin tablet 40 mg PO TID x 12 d (n=40)	Inclusion • 18–75 yo • COVID-19 positive screening test in molecular biology • In escin group: low response to standard treatment	Recruiting; 6/30/20	Primary • All-cause mortality • Clinical status
			SC (antiviral therapy) + sodium escinate 20 mg IV/d x 12 d (n=40)	Exclusion • Pregnant or breastfeeding • Allergy/ contraindication to escin • Any condition inappropriate for study per investigators • Unable to take oral medications		Secondary • Differences in O2 intake methods • LOS in hospital and/or ICU • Pulmonary function
			SC (antiviral therapy) (n=40)			
NCT04323345[60] The efficacy of natural honey in patients infected with novel coronavirus (COVID-19): A randomized, controlled, single masked, investigator initiated, multi-center trial	Egypt	Randomized, multicenter, controlled, phase 3	Honey 1 g/kg/d PO or NGT divided into 2–3 doses x 14 d + SC (supportive measures and LPV/r, umifenovir, chloroquine, hydroxychloroquine, or oseltamivir w/ or w/o azithromycin) (n=500)	Inclusion • Diagnosis of COVID-19 (clinically or confirmed by swab) • 5–75 yo	Recruiting; 12/15/20	Primary • 14-d recovery from positive to negative swabs • 14-d fever recovery • 30-d lung CT or X-ray resolution
			SC (see above) (n=500)	Exclusion • Severely ill with terminal disease • NPO patients with contraindication to NGT feeding		Secondary • 30-d mortality • Time to negative swab (30 d)

(Continued)

Table 2. (*Continued*)

Trial ID and title	Location	Study design	Treatment arms (n)	Requirements for treatment (inclusion/exclusion)	Status; study end date	Planned endpoints (primary/secondary)
IRCT20080901001157N16[61] Evaluation of the effect of IMFLUNA herbal compound on the improvement of COVID-19 pneumonia symptoms in patients referred to Baqiyatallah Hospital	Iran	Randomized, double-blind, phase 2, placebo-controlled, clinical trial	500 mg capsules x 2 of herbal compound (mixture of medicinal plant extract powder manufactured by HomaPharmed Pharmaceutical Company) PO TID AC x 2 wks + SC (n=30)	Inclusion • Symptomatic COVID-19 pneumonia confirmed with chest CT and PCR • 20–70 yo • Able to take oral medication	Recruiting; 6/14/20	Primary • SpO2 • Respiratory rate • Lung inflammation (CT scan)
			SC + placebo (n=30)	Exclusion • Severe dyspnea or respiratory failure requiring mechanical ventilation or hospitalization in ICUs • Treatment-resistant hypoxemia or those with severe underlying disease • Reduced level of consciousness or need of hospitalization in ICUs • Swallowing disorders or possible aspiration • Unable to take oral medications • Organ transplantation • Malignant disease • Corticosteroid or chemotherapy treatment • Uncontrolled blood pressure, uncontrolled diabetes, cardiovascular disease and underlying respiratory disease • Pregnant women		Secondary • Laboratory inflammatory markers • Cough and fever
NCT04323228[64] Anti-inflammatory/ antioxidant oral nutrition supplementation in COVID-19 (ONSCOVID19)	Saudi Arabia	Double-blind, prospective, single center, randomized controlled trial	Oxepa (EPA, GLA, antioxidant ONS) 8 oz PO daily in AM separated from meals (n=15)	Inclusion • Confirmed SARS-CoV-2 infection • COVID-19 patient in stable condition (i.e. not requiring ICU admission) • 18–65 yo	Not yet recruiting; 10/1/20	Primary • Laboratory inflammatory and nutritional markers

(*Continued*)

Table 2. (*Continued*)

Trial ID and title	Location	Study design	Treatment arms (n)	Requirements for treatment (inclusion/exclusion)	Status; study end date	Planned endpoints (primary/secondary)
			Isocaloric-isonitrogenous placebo (n=15) Same manufacturer, macronutrient composition, and calorie density, and normal concentrations of vitamin A, C, E, selenium and zinc	Exclusion • Tube feeding or PN • Pregnant or lactating • Admission to ICU > 24 hrs • Participation in another study including any supplementation or disease specific ONS		Secondary • Anthropometrics • Temperature • SpO2 • WBC counts
NCT04366089[65] Oxygen–ozone as adjuvant treatment in early control of COVID-19 progression and modulation of the gut microbial flora (PROBIOZOVID)	Italy	Interventional, open-label, randomized, parallel assignment	Oxygen-ozone therapy BID + SivoMixx (200 billion) probiotic supplementation, 6 sachets BID x 7 d + SC (azithromycin + hydroxychloroquine) (n=76)	Inclusion • > 18 yo • Nasopharyngeal swab COVID-19 positive • COVID-19 stages I-II-III • Hospitalized (non-ICU)	Recruiting; 12/31/20	Primary • Intubation
			SC (azithromycin + hydroxychloroquine) (n=76)	Exclusion • COVID-19 stages IV-V-VI • ICU • Pregnancy • G6PD deficiency • Contraindications to therapy • Hyper-homocysteinemia • Favism or thyroiditis • Coagulopathies • Neurovegetative diseases • Angina		Secondary • Mortality • LOS hospital • Laboratory inflammatory markers
NCT04342689[66] The role of resistant starch in COVID-19 infection	United States	Multicenter, randomized, blinded, phase 3	Resistant starch 2 tbsp (~ 20 g) PO daily x 3 d then PO BID through 14 d (n=750)	Inclusion • Age > 18 years • COVID-positive status • Monitored in an outpatient setting at a study institution	Not yet recruiting; 5/1/21	Primary • Hospitalization for COVID-19 complication

(*Continued*)

Table 2. (*Continued*)

Trial ID and title	Location	Study design	Treatment arms (n)	Requirements for treatment (inclusion/exclusion)	Status; study end date	Planned endpoints (primary/secondary)
			Placebo starch 2 tbsp (~ 20 g) PO daily x 3 d then PO BID through 14 d (n=750)	Exclusion • IBD • History of gastric bypass surgery • Active CDI • Active participation in another COVID-19 interventional trial • Condition that would pose unacceptable risk to the patient or raise concern for compliance • Starch allergy • Difficulty swallowing • Currently taking any IL-6 inhibitors		Secondary • Time to clinical recovery • Symptom severity score
Vitamin A						
IRCT20170117032004N3[67] Evaluation of the effect of vitamin A on respiratory signs and hospitalization in patients with COVID-19	Iran	Two arm, parallel group randomized, controlled	SC + vitamin A 50,000 IU daily x 2 wks (n=15)	Inclusion • > 18 yo • Confirmed diagnosis of COVID-19 with RT-PCR • Hospitalized, ventilator-independent patients	Recruiting; 7/20/20	Primary • LOS hospitalization
			SC x 2 wks (n=15)	Exclusion • Pregnant or lactating • High-dose vitamin A use in last mo		Secondary • Respiratory signs
IRCT20180520039738N2[68] Comparison of the effectiveness of standard treatment with standard treatment plus vitamin A in treatment in COVID-19 patients	Iran	Randomized, controlled, double-blinded	SC + vitamin A 25,000 IU/d x 10 d (n=70)	Inclusion • 1–75 yo • COVID-19 diagnosis	Recruitment complete; results pending	Primary • Vital signs • Laboratory inflammatory markers
			SC + placebo (n=70)	Exclusion • Pregnant or lactating women • Autoimmune diseases (lupus, MS, etc.) • Hepatitis B or C • Use of vitamin A • Chronic renal, liver, or heart failure • COPD		Secondary • None reported

(Continued)

Table 2. (*Continued*)

Trial ID and title	Location	Study design	Treatment arms (n)	Requirements for treatment (inclusion/exclusion)	Status; study end date	Planned endpoints (primary/secondary)
Vitamin B						
DRKS00021214[70] Improvement of the nutritional status regarding nicotinamide (vitamin B3) and the course of COVID-19 disease (COVit)	Germany	Randomized, parallel group, blinded, placebo-controlled, single-center	Nicotinamide 1000 mg (500 mg x 2 tablets) PO daily x 4 wks (n=650) Placebo silica 245 mg PO daily x 4 wks (n=650)	Inclusion • > 18 yo • Confirmed SARS-CoV-2 infection • Respiratory symptoms	Recruitment planned; not provided	Primary • Hospitalization w/ continuous O2 requirement > 24 h Secondary • Ventilation • Mortality • ER visits • ICU stays • Resolution of symptoms • Severity improvement
Vitamin C						
NCT04264533[71] Vitamin C Infusion for the treatment of severe 2019-nCoV infected pneumonia	China	Randomized, parallel-assignment, blinded, placebo-controlled, single-center	Vitamin C 12 g IV BID x 7 d (infusion rate 12 mL/hr) (n=70) Placebo sterile water 50 mL IV BID x 7 d (infusion rate 12 mL/hr) (n=70)	Inclusion • > 18 yo • Diagnosed with serious or critical COVID-19 • Receiving treatment in ICU Exclusion • Vitamin C allergy • Dyspnea due to cardiogenic pulmonary edema • Pregnant or breastfeeding • Life expectancy <24 h • Tracheotomy or home O2 therapy requirement • Previously complicated with end-stage lung disease, end-stage malignancy, G6PD, diabetic ketoacidosis, and active kidney stone disease • Simultaneous participation in another clinical trial	Recruiting; 9/30/20	Primary • Ventilator-free d Secondary • 28-d mortality • LOS ICU • Need for CPR • Vasopressor days • Ventilator parameters • APACHE II and SOFA scores

(Continued)

Table 2. (*Continued*)

Trial ID and title	Location	Study design	Treatment arms (n)	Requirements for treatment (inclusion/exclusion)	Status; study end date	Planned endpoints (primary/secondary)
NCT04323514[72] Use of ascorbic acid in patients with COVID 19	Italy	Open label, longitudinal	Vitamin C 10 g IV + SC (n=500)	Inclusion • In case of doubt of interstitial pneumonia with indications for intubation • Positive swab test of SARS-CoV-2 • Interstitial pneumonia	Recruiting; 3/13/21	Primary • In-hospital mortality
				Exclusion • Negative swab for SARS-CoV-2		Secondary • PCR levels • Lactate • LOS hospital • Symptoms and resolution of symptoms (fever, cough, shortness of breath, or difficulty breathing) • Positive COVID-19 swab • Duration of positive COVID-19 swab • Tomography imaging
NCT04344184[73] Early infusion of vitamin C for treatment of novel coronavirus acute lung injury (EVICT-CORONA-ALI)	United States	Phase II, randomized, blinded, placebo-controlled	L-ascorbic acid 100 mg/kg IV q8 hrs x 72 hrs max (n=100)	Inclusion • >18 yo • Hospitalized patients diagnosed with COVID-19 based on positive RT-PCR with hypoxemia • New SpO2 <93% on room air or new requirement of supplemental O2 • Any increase in requirement of supplemental O2 in patients requiring home O2	Not yet recruiting; May 2021	Primary • Number of ventilator-free days
			Placebo dextrose 5% water IV (n=100)	Exclusion • Vitamin C allergy • Presence of diabetic ketoacidosis • Active kidney stones • Pregnant • Incarcerated		Secondary • All-cause-mortality • Acute inflammation-free days • Organ-failure-free days

(Continued)

Table 2. (*Continued*)

Trial ID and title	Location	Study design	Treatment arms (n)	Requirements for treatment (inclusion/ exclusion)	Status; study end date	Planned endpoints (primary/secondary)
NCT04357782[74] Administration of intravenous vitamin C in novel coronavirus infection and decreased oxygenation (AVoCaDO): A phase I/II safety, tolerability, and efficacy clinical trial	United States	Single-center, open-label	L-ascorbic acid 50 mg/kg IV q6 hrs x 4 d (16 doses) (n=20)	Inclusion • 18–99 yo • Hospitalized patients diagnosed with COVID-19 based on positive RT-PCR • Mild deoxygenation S/F ratio decreased by 25% from baseline on admission, or SpO2 <95% on room air • Non-childbearing potential or childbearing potential with a negative pregnancy test at screening, and using a reliable method of contraception	Recruiting; 8/1/20	Primary • Incidence of adverse events • Incidence of serious adverse events • Incidence of adverse reactions
				Exclusion • Vitamin C allergy • Stage IV or above CKD • Presence of diabetic ketoacidosis, use of insulin infusion, or frequent need for point-of-care glucose monitoring (>6 times/24 hr period) as determined by treating physician • G6PD deficiency • Kidney stone history • Pregnancy • Enrolled in another COVID-19 trial that does not allow concomitant study drugs		Secondary • Ventilator-free days • ICU-free days • Hospital-free days • All-cause mortality • Change in SpO2/FiO2 ratio during HDVIC infusion • Change in CRP, LDH, D-dimer, lymphocyte count, NLR, serum ferritin from baseline to d 7
NCT04363216[75] Pharmacologic ascorbic acid as an activator of lymphocyte signaling for COVID-19 treatment	United States	single-center, prospective, randomized, open-label, phase II clinical trial	Ascorbic acid solution (Ascor®, McGuff Pharmaceuticals, Ltd.) 1 g/L sterile water (+ 1 g/L magnesium chloride to reduce burning sensation) IV over 2 hrs at doses below q 24 hrs (+4) x 5 days (n=66)	Inclusion • Male or non-pregnant female • > 18 yo • Confirmed SARS-CoV-2 infection • Disease severity necessitating hospitalization • Currently taking supplemental O2 • No anticipated need (within 24 hrs) for mechanical ventilation, defined as: (1) positive clinical response to O2 supplementation w/ improvement in hypoxia or (2) hypoxia improvement with bronchospasm therapy if bronchospasm present	Not yet recruiting; May 2021	Primary • Clinical improvement

(Continued)

Table 2. (*Continued*)

Trial ID and title	Location	Study design	Treatment arms (n)	Requirements for treatment (inclusion/exclusion)	Status; study end date	Planned endpoints (primary/secondary)
			D 0 (enrollment day)- 0.3 g/kg; D 1- 0.6 g/kg; D 2- 0.9 g/kg; D 3- 0.9 g/kg; D 4- 0.9 g/kg; D 5- 0.9 g/kg			
			SC (n=22)	Exclusion • eGFR < 50 • G6PD deficiency • Anticipated need for mechanical ventilation within 24 hrs • Pregnant or breastfeeding • Requires home O2 for any reason		Secondary • Patient care escalated to ICU • O2 supplementation • Days with fever • Days to discharge • Serious AE related to treatment
ChiCTR2000032400[76] The efficacy and safety of high dose intravenous vitamin C in the treatment of novel coronavirus pneumonia (COVID-19): A prospective, randomize, controlled trial	China	Prospective, randomized, controlled, cohort	High dose IV Vitamin C 100 mg/kg/d (n=60)	Inclusion • Fever, respiratory tract and other symptoms • Imaging consistent with pneumonia	Recruiting; 6/1/20	Primary • CRP, ESR • SIRS
			Placebo normal saline (n=60)	Exclusion • < 18 yo • Treatment for tumor • Pregnant or lactating • Known kidney stone(s) • Vitamin C allergy • Other clinical trial involvement		Secondary • CD4+ lymphocyte count, lymphocyte count, PaO2/FiO2 indicator, total bilirubin, cTNI, APPT, D-dimer, LDH, CK, ratio of turning to severe virus, and crystalluria
Vitamin D						
NCT04334005[79] Effect of vitamin D administration on prevention and treatment of mild forms of suspected COVID-19	Spain	Randomized, parallel assignment, double-blind	Vitamin D 25,000 IU PO daily (in AM w/ toast + olive oil to facilitate absorption) + NSAIDs, ACE2 inhibitor, ARB, or TZDs based on investigator (n=100)	Inclusion • 40–70 yo • Non-severe symptomatic patients presenting with cough, fever, nasal congestion, GI symptoms, fatigue, anosmia, ageusia, or alternative signs of respiratory infections	Not yet recruiting; 6/30/20	Primary • Composite of cumulative death for all causes and specific causes

(Continued)

Table 2. (*Continued*)

Trial ID and title	Location	Study design	Treatment arms (n)	Requirements for treatment (inclusion/ exclusion)	Status; study end date	Planned endpoints (primary/secondary)
			Usual care (NSAIDs, ACE2 inhibitor, ARB, or TZDs based on investigator) (n=100)	Exclusion • Severe respiratory and/or multisystemic symptoms suggesting advanced COVID-19 and intercurrent acute or severe chronic diseases (cancers)		Secondary • Need for (non)invasive ventilation • ICU or PACU or hospital admission • Medical consultation • Home care and isolation time • Bedrest time • Duration of symptoms and recovery
NCT04344041[80] COVID-19 and vitamin D supplementation: a multicenter randomized controlled trial of high dose versus standard dose vitamin D3 in high-risk COVID-19 patients (CoVitTrial)	France	Multicenter, randomized, parallel assignment	High dose vitamin D 400,000 IU PO daily (n=130)	Inclusion • ≥ 70 yo • Diagnosis of COVID-19 by RT-PCR SARS-CoV-2 or CT scan suggesting viral pneumonia • Diagnosed within the preceding 3 d • At least 2 risk factors for complications: (1) ≥ 75 yo, (2) SpO2 ≤ 94% on room air or a PaO2 to FiO2 ratio ≤ 300 mmHg • Social security recipient	Recruiting; July 2020	Primary • Number of deaths from any cause during the 14 d following the inclusion and intervention
			Standard dose vitamin D 50,000 IU PO daily (n=130)	Exclusion • Organ failure requiring admission to a resuscitation or high dependency unit • Life-threatening comorbidity with short-term life expectancy (<3 mos life) • Any reason that makes follow-up at D 28 impossible • Vitamin D supplementation in the previous mo (exception of < 800 IU of vitamin D/d) • Contraindication for vitamin D supplementation • Participation in another simultaneous trial • Persons deprived of liberty, under psychiatric care under duress, subject to legal protection • SpO2 ≤ 92% in spite of an O2 therapy > 5 L/min		Secondary • Overall and by 25-OHD level at defined time points • Mortality • Change in WHO OSCI for COVID-19 Severe AE • 14-d mortality, compared to French hospital geriatric units

(Continued)

Table 2. (*Continued*)

Trial ID and title	Location	Study design	Treatment arms (n)	Requirements for treatment (inclusion/exclusion)	Status; study end date	Planned endpoints (primary/secondary)
NCT04363840[81] The LEAD COVID-19 trial: low-risk, early aspirin and vitamin D to reduce COVID-19 hospitalizations	United States	Phase II, multicenter, prospective, randomized, controlled	Aspirin 81 mg PO daily x 14 d (n=360)	Inclusion • > 18 yo • COVID-19 diagnosis in the past 24 h	Not yet recruiting; 12/2020	Primary • Hospitalization
			Aspirin 81 mg PO daily + vitamin D 50,000 IU PO daily x 14 d (n=360)	Exclusion • Pregnant patients • Prisoners • History of GI bleed, PUD, spontaneous bleeds, thrombocytopenia, CKD • Concurrent NSAID or steroid use • Hypervitaminosis D and associated risk factors (renal failure, liver failure, hyperparathyroidism, sarcoidosis, histoplasmosis)		Secondary • None reported
			No intervention (n=360)			
NCT04366908[82] Prevention and treatment with calcifediol of COVID-19 coronavirus-induced acute respiratory syndrome (SARS)	Spain	Randomized, open-label, parallel assignment	Best available therapy (BAT) + calcifediol 266 mcg x 2 capsules PO once on D 1 then x 1 capsule on D 3, 7, 14, 21, and 28 (n=504)	Inclusion • 18–90 yo • PCR confirmed diagnosis of COVID-19 • Radiological image with inflammatory pleuropulmonary exudate	Not yet recruiting; 8/28/20	Primary • Admission to ICU • Death
			BAT combination therapy as defined by the Ministry of Health and/or complementary notes issued by the Spanish Agency of Medicines and Health Products (n=504)	Exclusion • Treatment with calcifediol or cholecalciferol • Intolerance or allergy to calcifediol or its components • Pregnancy		Secondary • Time to discharge • ICU: time to admission, time mechanical ventilation is removed • Laboratory inflammatory markers • Vitamin D metabolites • SpO2 and SatO2/FiO2 • Dyspnea • Radiologic findings • AEs • Hemorrhagic or thrombotic phenomena

(Continued)

Table 2. (*Continued*)

Trial ID and title	Location	Study design	Treatment arms (n)	Requirements for treatment (inclusion/ exclusion)	Status; study end date	Planned endpoints (primary/secondary)
Multiple agents studied						
NCT04334512[77] A study of quintuple therapy to treat COVID-19 infection (HAZDpaC)	United States	Phase II, randomized, double-blind, placebo-controlled	Hydroxychloroquine, Azithromycin, Vitamin C, Vitamin D, + Zinc x 10 d (n=300)	Inclusion • 18–55 yo • > 2 highly effective birth control method • Diagnosis of COVID-19 by RT-PCR	Not yet recruiting; 4/2021	Primary • Successful treatment: negative test and resolution of symptoms • Safety Tolerability
			Matching placebo (n=300)	Exclusion • Screening test negative for COVID-19 by RT-PCR • Diarrhea (prior to infection) • Any comorbidities the investigator constitutes a health risk for the subject		Secondary • None reported
NCT04342728[78] Coronavirus disease 2019-using ascorbic acid and zinc supplementation (COVIDAtoZ)	United States	Randomized, single-center, prospective, open label four arm	Vitamin C 8000 mg PO divided into 2–3 doses/d w/ food (n=130)	Inclusion • >18 yo • Outpatient • Positive test for COVID-19 • Non-pregnant	Enrolling by invitation; 4/30/21	Primary • Symptom reduction
			Zinc gluconate 50 mg PO at bedtime (n=130)			
			Vitamin C + Zinc gluconate (dosing as above) (n=130)	Exclusion • Positive for COVID-19 in hospital or ER • Patients living outside of Ohio • Pregnant or lactating • End-stage CKD • Advanced liver disease awaiting transplantation • History of kidney stones		Secondary • Resolution of fever, cough, shortness of breath, and fatigue • Symptoms at D 5 • Hospitalizations • Severity of symptoms • Adjunctive medications • AEs
			SC (n=130)			
NCT04351490[83] Impact of zinc and vitamin D3 supplementation on the survival of institutionalized aged patients infected with COVID-19	France	Randomized, parallel assignment, open label	Zinc gluconate capsule 15 mg x 2/d + 25-OH cholecalciferol drinkable solution 10 drops (2000 IU) /d x 2 mos (n=1570)	Inclusion • > 60 yo • Hospitalized	Not yet recruiting; July 2020	Primary • Survival rate in asymptomatic subjects

(*Continued*)

Table 2. (*Continued*)

Trial ID and title	Location	Study design	Treatment arms (n)	Requirements for treatment (inclusion/exclusion)	Status; study end date	Planned endpoints (primary/secondary)
			SC (n=1570)	Exclusion • Life expectancy < 1 mo independent of COVID-19 infection • Hypercalcemia • Renal lithiasis		Secondary • Survival rate • COVID-19 incidence in asymptomatic subjects at inclusion
NCT04370288[62] The clinical trial of application of methylene blue vial for treatment of COVID-19 patients	Iran	Phase I, randomized, parallel assignment, single center	MCN (Methylene blue, vitamin C, N-acetyl cysteine) (n=10)	Inclusion • 18–90 yo • Confirmed case of COVID-19 (by RT-PCR, HRCT) • Admission to ICU • Need for intubation and mechanical ventilation (PaO2/FiO2 < 100–200)	Recruiting; 9/20/20	Primary • Free from mechanical ventilation in both groups
			SC (n=10)	Exclusion • Pregnancy and breastfeeding • G6PD deficiency • Preadmission anticoagulation • Renal or hepatic disease • Allergy to methylene blue • Immunosuppressive agents • Use of other investigational drugs at inclusion		Secondary • Mortality • Improvement in Pa02/Fi02 ratio • LOS hospital • LOS ICU • Dialysis-free days • CRP • WBC
IRCT20200319046819N1[69] Impact of vitamin B, A, D, E, and C supplementation on improvement and mortality rate in patients with COVID-19 admitted in intensive care unit	Iran	Randomized, single-blinded, parallel	Vitamin A 25,000 IU PO daily + vitamin D 600,000 IU PO x 1 + vitamin E 300 IU PO BID + vitamin C 500 mg PO QID + vitamin B (Soluvit) 1 ampule daily x 1 wk (n=30)	Inclusion: • 20–60 yo • COVID-19 clinical or definitive diagnosis • BMI 18.5–30 • No liver or kidney disorders	Recruiting; not provided	Primary • Inflammatory makers • Pulmonary involvement (CT) • Mortality
			SC (n=30)	Exclusion: • Rare viral diseases • Chemotherapy in prior mo • Any other specific condition		Secondary • BMI • LOS • SpO2

(Continued)

Table 2. (*Continued*)

Trial ID and title	Location	Study design	Treatment arms (n)	Requirements for treatment (inclusion/ exclusion)	Status; study end date	Planned endpoints (primary/secondary)
IRCT20200324046850N1[63] Comparison of vitamin D3 and N-acetylcysteine prescription in COVID-19 patients and their effect on recovery process	Iran	Randomized, single-blinded, factorial trial	SC w/ national drugs (n=25)	Inclusion • COVID-19 positive based on chest CT with severe symptoms (fever, muscle pain, SOB, dry cough, sore throat, runny nose) • Confirmation of COVID-19 by an infectious disease physician	Recruiting; 5/21/20	Primary • SOB, cough, chills, night sweats
			SC w/ national drugs + vitamin D3 50,000 IU once a wk (n=25)			
			SC w/ national drugs + n-acetylcysteine (NAC) 600 mg PO daily (n=25)	Exclusion • Taking medications other than the ones mentioned in this study • Pregnant and lactating women • Taking losartan or captopril • History of intestinal ulcers or GI bleed		Secondary • None reported
			SC w/ national drugs + vitamin D3 50,000 IU + NAC 600 mg PO once a wk (n=25)			

25-OHD, calcifediol; ACE2, Angiotensin-converting enzyme 2; AE, adverse event; AM, morning; APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; APPT, activated partial thromboplastin time; ARB, Angiotensin II receptor blockers; BID, twice daily; BMI, body mass index; CDI: *Clostridium difficile* infection; CK, creatine kinase; CKD, chronic kidney disease; cm, centimeter; COPD, chronic obstructive pulmonary disorder; CPR, cardiopulmonary resuscitation; CRP, c-reactive protein; CT, computerized tomography; cTNI, cardiac troponin I; d, day; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ER, emergency room; ESR, erythrocyte sedimentation rate; g, gram; G6PD, glucose-6-phosphate dehydrogenase; GI, gastrointestinal; GLA, gamma-linolenic acid; HDVIC, high dose IV vitamin C; HIV, Human Immunodeficiency Virus; HCV, Hepatitis C Virus; hr(s), hour(s); IBD, inflammatory bowel disease; ICU, intensive care unit; IL-6, interleukin-6; IU, international unit; IV, intravenous; kg, kilogram; L, liter; LDH, lactate dehydrogenase; LOS, length of stay; LPV/r, lopinavir/ritonavir; mcg, microgram; mg, milligram; mL, milliliter; mmHg, millimeter of mercury; mo(s), month(s); MS, multiple sclerosis; n= number; NEWS, national early warning score; NLR, neutrophil-lymphocyte ratio; NGT, nasogastric tube; NPO, nil per os; NSAID(s), Nonsteroidal anti-inflammatory drugs; O2, oxygen; ONS, oral nutritional supplements; OSCI, Ordinal Scale for Clinical Improvement (0 to 8; higher score, poorer outcome); PACU, post-anesthesia care unit; PaO2/FiO2, partial pressure of oxygen/ fraction of inspired oxygen; ,PN, parenteral nutrition; PO, oral; PUD, peptic ulcer disease; QID, four times daily; RT-PCR, reverse transcriptase polymerase chain reaction; SIRS, Systemic inflammatory response syndrome; SOB, shortness of breath; SOFA, sequential organ failure estimate; SC, standard of care; SpO2, oxygen saturation; SpO2/FiO2, oxygen saturation/fraction of inspired oxygen; tbsp, tablespoon; TID, three times daily; TZDs, thiazolidinediones; w/, with; WBC, white blood cell; w/o, without; y, yo (age).

leading to imposing limitations on the quantity that can be purchased.[84]

Although the use of remdesivir has been expanded in the United States, its role in the fight of COVID-19 has not provided patients and providers with the relief they expected. Although no difference in clinical outcomes was observed between 5 and 10 days of remdesivir treatment, a study conducted in Hubei, China, failed to demonstrate clinical improvements in adults with severe COVID-19 in the remdesivir arm.[85,86] Interestingly, time to clinical improvement in patients treated earlier was observed but needs confirmation in larger studies.[85] In an exploratory analysis, the sponsor of remdesivir, Gilead Sciences, Inc., found that patients who received remdesivir within 10 days of symptoms onset had improved outcomes compared with those treated after more than 10 days of symptoms. Additionally, when data were pooled across treatment arms, by Day 14, 62% of patients treated early were discharged from the hospital compared to those who were treated late; yet statistical analysis was not performed.[86] Furthermore, notable exclusion criteria in these moderate-to-severe COVID-19 patients included mechanical ventilation at screening as well as patients receiving mechanical ventilation > 5 days or extracorporeal membrane oxygenation, alanine aminotransferase or aspartate aminotransferase > 5 X upper limit of normal (ULN), and creatinine clearance (CrCL) < 50 mL/min.[14,15] Therefore, the true potential and efficacy of remdesivir therapy require expanded investigation into additional populations.

Although doses of vitamins in these ongoing clinical trials are higher than normal, use of vitamins at higher doses compared to recommended dietary allowance is safe, and upper limits for the use are defined. In addition, the use of vitamins and herbal supplements likely has more benign side effects when compared to self-medicating with unproven remedies lacking adequate investigations for use. In the instance of chloroquine phosphate and its derivative hydroxychloroquine, a wife and husband ingested chloroquine phosphate in the United States in March 2020, after hearing from a press conference that this medication was likely a very promising treatment option. The couple consumed hydroxychloroquine based on the intended use for their aquarium because they feared contracting the virus, and it was easily accessible. They were both hospitalized shorty after ingesting the product, and the husband ultimately died.[87] Meanwhile, hundreds in Iran died after drinking neat alcohol in early 2020, which was publicized on social media as a cure/prevention for COVID.[88] It is not clear how many of these deaths can be directly tied to social media misinformation, as a larger problem of contaminated bootleg alcohol was revealed.

The most studied supplement in the acute care setting has been vitamin C, where it has been used as treatment for multiple conditions, including sepsis, acute bronchitis, cardiovascular disease, postoperative infection, and prevention of contrast-induced nephropathy. A meta-analysis published in 2019, reviewed 18 trials to evaluate the effect of vitamin C on intensive care unit (ICU) length of stay and duration of mechanical ventilation. The most commonly studied populations were patients undergoing cardiac surgery, followed by sepsis, lung contusions, and burn patients. Of 12 trials containing 1766 patients, intravenously administered vitamin C reduced the length of ICU stay by 7.8% (95% confidence interval [CI]: 4.2–11.2; p=0.00003). Orally administered vitamin C in doses of 1–3 g/day was evaluated in 6 studies and was associated with reduced length of ICU stay by 8.6% (p=0.003). Of the 3 studies evaluating patients requiring mechanical ventilation for >24 h, vitamin C reduced the duration of mechanical ventilation by 18.2% (95% CI: 7.7–27; p=0.001).[89]

These authors also performed a meta-regression analysis in critically ill patients receiving mechanical ventilation and found that in 5 studies consisting of 471 patients, vitamin C (1–6 g/day) was most beneficial in reducing ventilation time by an average of 25% (p<0.0001) in patients requiring more than 10 h of mechanical ventilation.[90] These findings can serve as a foundation for analyzing the role of vitamin C in potentially reducing the time spent on mechanical ventilation in patients with COVID-19.

Vitamin C Infusion for Treatment in Sepsis Induced Acute Lung Injury (CITRIS-ALI), a randomized, double-blind, placebo-controlled, multicenter trial conducted in 7 medical ICUs in the USA evaluated the effects of vitamin C infusion in 167 patients and its role in organ failure along with biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure. Patients were assigned to receive either an infusion of vitamin C, 50 mg/kg, or placebo dextrose, 5% in water, every 6 h for 96 h. Although this study failed to improve organ dysfunction scores or alter markers of inflammation and vascular injury, vitamin C was associated with a significant reduction in 28-day all-cause mortality as well as significantly increased ICU-free days to day 28 and hospital-free days to day 60.[91] These findings also suggest that further research may be warranted to determine whether vitamin C has a role in the care of patients with sepsis and acute respiratory distress syndrome (ARDS), which has been associated with COVID-19.

Vitamin D is currently under evaluation for its role in COVID-19 for its immunomodulatory effects. A trial conducted in Guinea-Bissau investigated vitamin D as supplementary treatment for tuberculosis in 365 patients. The intervention was 100,000 IU of cholecalciferol or placebo at inclusion and again at 5 and 8 months after the initiation of treatment. Findings from this study failed to demonstrate improvements in clinical outcomes or mortality in patients receiving vitamin D as part of tuberculosis treatment, but this may be due to the dose not being high enough or given consistently.

Additional studies evaluating the role of vitamin D supplementation in the prevention and reduction of acute respiratory infections, COPD exacerbations, and pneumonia were analyzed in the Vitamin D3 Supplementation in Patients

with Chronic Obstructive Pulmonary Disease (ViDiCO) trial. This trial investigated whether vitamin D3 supplementation would reduce the incidence of moderate or severe COPD exacerbations and upper respiratory infections in 240 patients across clinics in London. Patients received six 2-month oral doses of 3 mg of vitamin D over a 1-year period. Vitamin D3 was associated with protective effects against moderate or severe COPD exacerbations in participants with baseline serum 25-hydroxyvitamin D concentrations of less <50 nmol/L (p=0·021), but not in those with baseline concentrations > 50 nmol/L. Baseline serum 25-hydroxyvitamin D concentrations had no effect on time to first upper respiratory infection.[92]

A systematic review and meta-analysis evaluated 24 randomized, controlled trials of supplementation with vitamin D in regard to incidence of acute respiratory tract infection. Protective effects were observed in subjects receiving daily or weekly vitamin D supplementation without additional bolus doses and were stronger in those with baseline 25-hydroxyvitamin D levels <25 nmol/L. Serum 25(OH)D concentration was inversely associated with risk and severity of acute respiratory tract infection; where for each 10 nmol/L decrease in 25(OH)D concentration, the odds of acute respiratory tract infection increased by 1.02 (0.97–1.07).[93] Therefore, some protective effects of vitamin D in those with lower baseline levels have been seen. However, the role of vitamin D for the treatment of acquired infections, including COVID-19, requires further investigation especially in subjects with low baseline levels of vitamin D. This concept is currently under investigation in France.[94]

When evaluating proposed studies of vitamins and supplements throughout the world, there are notable limitations in currently available information, such as standard of care. While many of the studies report a comparator arm as standard of care, there is no definition of what that actually means as there is no widely recognized treatment for COVID-19. In addition, much like other clinical trials, key populations are excluded in many of these ongoing trials as well. This includes women, who are pregnant or lactating, as well as patients with chronic diseases (i.e. kidney disease), or patients with short life expectancies (i.e. cancers).

The greatest promise in combatting this life-threatening virus appears to be through reducing the cytokine storm associated with COVID-19.[95] This is where anti-inflammatory and antioxidant vitamins and supplements may play a potential role. Results of these ongoing clinical trials are urgently needed.

At this time, we recommend vitamins and supplements as specific COVID-19 treatment in the context of a clinical trial. This recommendation is in-line with the major organizational guidelines for potentially effective COVID-19 treatments at the time of this writing. While the vitamins and supplements under investigation for COVID-19 described in this manuscript are generally without serious adverse effects and drug interactions, no therapy is completely free of risk. Additionally, while also being generally affordable, broad recommendation and implementation of unproven treatments are likely not cost effective. That being said, vitamins and supplements with existing evidence supporting their use in conditions associated with COVID-19, such as sepsis or ARDS, can be considered when potential benefit is determined to outweigh risk.

Conclusion

With the rapidity of hypothetical treatments' data being generated for COVID-19, clinical investigations up until this point have not provided efficacious treatments in eradicating the virus. While it is important to investigate treatments with the potential to reduce the severity and consequences of COVID-19, vitamins and supplements should be continued to be evaluated to provide the much-needed evidence for possible treatment modalities. A systematic review will be conducted once results from ongoing and recruiting clinical trials are available.

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