

Vitamins for the Prevention and/or Treatment of COVID-19: An Umbrella Review



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ABSTRACT

Objective: This umbrella review synthesizes the existing literature on the role of vitamins for COVID-19 prevention and management. The objective is to elucidate potential preventive and therapeutic dimensions of these vitamins, highlight clinical applicability, and identify avenues for future research.

Methods: A systematic search was conducted using PubMed and Google Scholar, with predefined key words for each vitamin combined with COVID-19-related terms. Narrative and systematic reviews were included, following Cochrane guidelines. AMSTAR scoring was used to assess systematic review quality, while SANRA guidelines were used to evaluate narrative reviews. Data extraction, synthesis, and reference overlap were conducted.

Findings: Narrative reviews ($n=14$) revealed preclinical benefits of vitamins A, B group, C, D, and E (no research on vitamin K found) in COVID-19 management, with potential for immune modulation and anti-inflammatory responses. Of the systematic reviews ($n=44$), none included vitamins A or E. Some B vitamins exhibited potential, with significant associations between vitamin C supplementation and reduced COVID-19 severity. Many significant findings were also found between vitamin D deficiency and heightened COVID-19 risks, as well as promising effects of vitamin D supplementation.

Conclusion: Vitamins A, B group, C, D, and E hold mechanistic rationale for combating COVID-19, as suggested by narrative reviews. In systematic reviews, vitamin D deficiency underscores its role in COVID-19 severity, while vitamin C and D supplementation show potential benefits as adjunct therapies. This umbrella review highlights the comprehensive research on the efficacy of vitamins in addressing COVID-19, with challenges that warrant further investigation.

Key Words Umbrella review, naturopathic medicine, complementary and alternative medicine, SARS-CoV-2, nutrients

INTRODUCTION

Coronavirus disease (COVID-19; see Appendix 1 for a glossary of terms and acronyms used in this manuscript), instigated by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, ushered in a global crisis. The World Health Organization's (WHO's) proclamation of COVID-19 as a public health emergency of international concern in January 2020, swiftly followed by its characterization as a pandemic in March 2020, underscored the gravity of the situation.¹ With almost 700,000,000 cases and close to 7,000,000 fatalities reported worldwide within 2 years,² COVID-19's impact on global health is profound. Its symptoms encompass fever, cough, fatigue, headache, diarrhea, arthromyalgias, and serious interstitial pneumonia, among others, which can culminate in acute respiratory distress syndrome, sepsis-induced coagulopathy, and multi-organ dysfunction.³ The disease's progression incites a cytokine storm,⁴⁻⁶ marked by an overproduction of pro-inflammatory cytokines, further contributing to its complexity.⁷⁻⁹

Due to the severity of the pandemic, various nutrients and natural therapies were investigated to determine their potential benefits in preventing and treating COVID-19 as part of naturopathic treatment. Among these, vitamins are essential micronutrients with wide accessibility, safety, and affordability that garnered special focus. Vitamin supplementation is known for offering a feasible avenue for bolstering immune responses,¹⁰ particularly for vulnerable populations. The safety of vitamins is well established, with low instances of adverse effects when consumed within recommended limits.¹¹ These factors collectively contribute to the potential of vitamins as a holistic approach to addressing the challenges posed by COVID-19. Despite this, controversy and misinformation about natural treatments, including vitamins, were widely discussed in the early days of the pandemic.¹²⁻¹⁴

Prior to the pandemic, the significance of vitamins was already established through their physiological roles in immune and overall health. Vitamin A bolsters interferon-based defenses against RNA viruses, impeding viral replication, and thus maintains immune

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homeostasis and boosts innate responses.¹⁵⁻¹⁷ Vitamin B, integral to cellular function, energy metabolism, and immune activation, has potential to fortify immune competence.^{18,19} Vitamin C contributes to chemotaxis, phagocytosis, and tissue repair. Vitamin D's functions in immune regulation²⁰⁻²³ have been associated with decreased risk of acute respiratory tract infections. Lastly, Vitamin E's antioxidants potentially heighten adaptive immunity against viruses.^{24,25} Such mechanisms of action were also shown to be beneficial in a number of rapid reviews specifically for COVID-19.²⁶ The previously published interim report²⁷ (see the methods section) on various naturopathic interventions in the prevention and treatment of COVID-19 did not find narrative and systematic reviews using vitamin K as an intervention, and therefore it was not included in this review.

Considering the controversy and misinformation about the potential role vitamins can play in preventing and treating COVID-19, the objective of this umbrella review is to compile synthesized literature on the role of vitamins vis-a-vis COVID-19, thus elucidating the state of evidence on preventive and therapeutic dimensions and clinical applicability. Peer-reviewed insights are distilled, informing the feasibility of naturopathic treatments. We aim to pinpoint avenues for future research and clinical application, enriching the arsenal against COVID-19.

METHODS

Design

This study commenced as a continuous, high-level monitoring effort involving systematic reviews on natural health products (NHPs) and natural treatments for COVID-19 prevention and management, including post-COVID conditions. To capture new significant evidence in this emerging domain, monthly searches were conducted for over a year, starting in May 2022. Results were published in an interim report.²⁷ Adhering to Cochrane Guidelines,²⁸ monthly meetings ensured refinement of research design, search terms, and inclusion/exclusion criteria, following the principles of living systematic reviews.

Upon completion of the data collection process as fully outlined in the interim report,²⁷ the methodology transitioned into an umbrella review design.^{29,30} An umbrella review methodically synthesizes evidence from multiple systematic reviews, permitting a comprehensive evaluation of the available evidence's quality and consistency across different interventions.

Search Strategy

Following the Cochrane guidelines for a living systematic review, PubMed and Google Scholar databases were searched using keywords "natur*," "nutraceutical," "prevention," "prophylaxis," "COVID," "Coronavirus," "SARS-CoV-2," combined with vitamin-specific terms for each of the vitamins:

Vitamin A: Vitamin A, retinol, retinoid, carotene, alpha carotene, beta carotene, carotenoid

Vitamin B group: Vitamin B1, thiamine, vitamin b2, riboflavin, vitamin b3, niacin, vitamin B5, pantothenic acid, vitamin b6,

pyridoxine, vitamin b7, biotin, vitamin b9, folate, folic acid, vitamin b12, cobalamin

Vitamin C: Vitamin C, ascorbic acid, ascorbate

Vitamin D: Vitamin D, cholecalciferol, hydroxycalciferol

Vitamin E: Vitamin E, tocopherol

Vitamin K: Vitamin K, vitamin K1, phyloquinone, phytonadione, vitamin K2, menaquinone, vitamin K3, menaphthone, menadione

Inclusion and Exclusion Criteria

Encompassing reviews without language restrictions, the study targeted structured database searches, transparent methodological criteria, and cumulative outcome conclusions. Additionally, relevant narrative reviews were collected if their reporting was similar to a systematic review with only some missing criteria for inclusion.

PICO eligibility criteria requirements for study inclusion were as follows:

Population: Clinical/observational (humans of any age/gender, any setting), in vivo (including animals), in vitro, or in silico studies.

Intervention: Vitamins A, B group, C, D, E and K.

Comparison: No comparator limitation.

Outcome: Symptoms, biological markers, diagnostic criteria, or viral traits related to severe acute respiratory syndrome, viral respiratory tract infections, or COVID-19.

Secondary analyses, literature reviews, editorial discussions, best practice guidelines, book chapters, and publications referring to COVID but using data prior to 2019 were excluded.

Data Mining

To truly address the objective of highlighting the preventive and therapeutic roles of vitamins with their clinical applicability, narrative reviews were included to extract therapeutic considerations and medicinal properties of vitamins, their relationship to other natural health products or pathways, and doses used. However, narrative reviews were excluded if they did not actually review studies directly related to COVID-19, but only hypothesized therapeutic applications.

Systematic reviews and meta-analyses were examined for the types of interventions and populations included, outcome measures and statistically significant results as well as their clinical relevance. Systematic reviews that did not examine studies on COVID-19 but other similar respiratory conditions or viral infections were excluded.

Data extraction and summarization of systematic and narrative reviews were conducted by eight trained independent volunteers

(doctors/researchers in naturopathic medicine), following specified data mining criteria. Only statistically significant results with outcomes relevant to NHPs and COVID-19 prevention and management were included. Finally, a reference overlap analysis was conducted to identify common citations across systematic and narrative reviews.

Data Analysis

Narrative reviews were assessed by two independent reviewers based on the Scale for the Assessment of Narrative Review Articles (SANRA). Individuals providing data extraction were blind to the quality assessment criteria for inclusion / exclusion. Reviews were excluded if they did not have a scientific reasoning score of 1 or 2 AND an overall total sum >5.

Systematic reviews were assessed for risk of bias and quality grading using A MeaSurement Tool to Assess systematic Reviews (AMSTAR) and were reviewed by two individuals for accuracy.

Discrepancies were addressed by a third reviewer. Volunteers were blind to the quality assessment criteria for inclusion/exclusion. Reviews were excluded if they did not get full marks in question 9 and question 13.

Microsoft Excel was used to collate the data using a pre-tested, revised template tailored to the two review types.

RESULTS

Study Selection

Figure 1 shows the study selection and screening results.

Narrative Reviews

Narrative reviews were included in this project to provide a broader perspective and complement the systematic reviews, facilitating a comprehensive exploration of the landscape of vitamins for COVID-19 prevention and management.

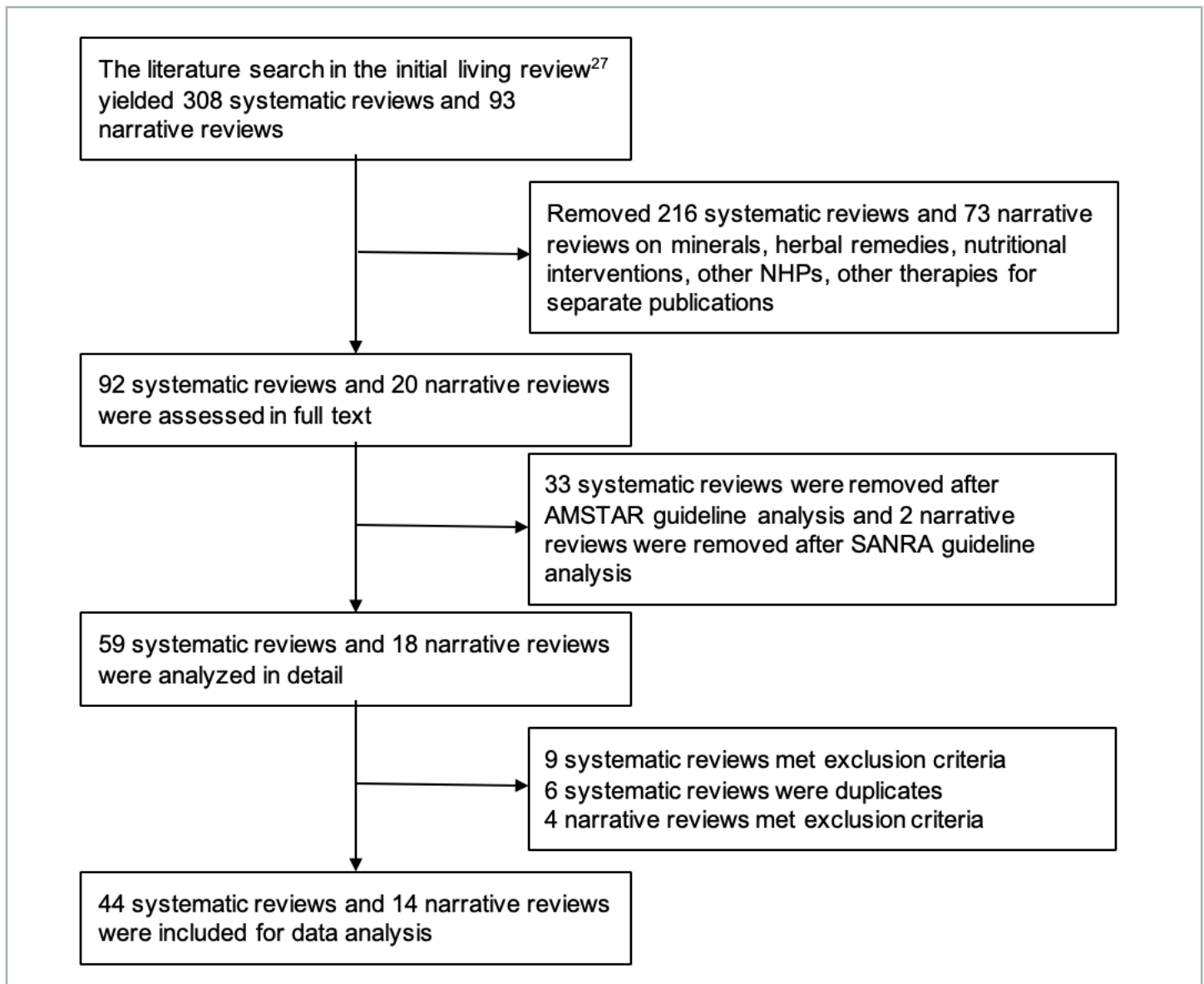


FIGURE 1 Study Selection and Screening against Inclusion/Exclusion

Of the 20 narrative reviews initially included, 18 (90%) remained for data extraction, and 14 (70%) remained for the final umbrella review after removing all reviews that met exclusion criteria (see Table 1).³¹⁻⁴⁴ Based on WHO regions of the country of residence of the first author, four of these reviews were from the Americas (AMR), four were from the European region (EUR), and two each were from the Eastern Mediterranean Region (EMR), the Western Pacific region (WPR) and South-East Asian region (SEA). With regard to the narrative reviews on vitamins, six were on vitamin A, four on the group of B vitamins, eight on vitamin C, 12 on vitamin D and four on vitamin E. As previously mentioned, vitamin K did not have relevant narrative reviews for this study. Considering most narrative reviews covered multiple NHPs, the total number of papers on vitamins ($n=34$) exceeds the number of papers reviewed ($n=14$).

Systematic Reviews

Of the 92 systematic reviews initially included, 59 (64%) remained for data extraction after the AMSTAR analysis. Of those, 44 (48%) were included in the umbrella review after removing all that met

TABLE 1 Narrative Reviews Included in the Umbrella Review

Narrative Review	Country	Region	SANRA Score	Vitamins
Base Medicine Task Force (2020) ³¹	USA	AMR	11	Vitamin C Vitamin E
Pisoschi et al. (2022) ³²	Romania	EMR	6	Vitamin A Vitamin D
Ahvanooei et al. (2022) ³³	Iran	EMR	8	Vitamin A Vitamin B Vitamin C Vitamin D Vitamin E
Michael et al. (2022) ³⁴	USA	AMR	10.5	Vitamin D
Paudel et al. (2022) ³⁵	Australia	WPR	7	Vitamin C Vitamin D
Djordjevic et al. (2022) ³⁶	Serbia	EUR	9.5	Vitamin A Vitamin B Vitamin C Vitamin D
Bahat et al. (2021) ³⁷	Turkey	EUR	8	Vitamin D
Inchingolo et al. (2021) ³⁸	Italy	EUR	7	Vitamin D
Bell et al. (2023) ³⁹	USA	AMR	7	Vitamin A Vitamin C Vitamin D Vitamin E
Stafford et al. (2023) ⁴⁰	USA	AMR	6	Vitamin D
Park et al. (2023) ⁴¹	Korea	SEA	10	Vitamin A Vitamin B Vitamin C Vitamin D Vitamin E
Huang et al. (2023) ⁴²	Singapore	WPR	12	Vitamin B Vitamin C
Chatterjee et al. (2022) ⁴³	India	SEA	8	Vitamin A Vitamin C Vitamin D
Del Giudice et al. (2022) ⁴⁴	Italy	EUR	7	Vitamin D

AMR = region of the Americas; EMR = Eastern Mediterranean region; EU = European region; SANRA = Scale for the Assessment of Narrative Review Articles; SEA = South-East Asian region; WPR = Western Pacific region.

exclusion criteria and duplicates (see Table 2).⁴⁵⁻⁸⁸ Based on WHO regions, 17 of the systematic reviews were from the European region (EUR), eight were from the South-East Asian region (SEA), seven were from the region of the Americas (AMR), eight were from the Western Pacific region (WPR), three were from the Emirates (EM) and one was from the African continent (AFR). There were no eligible systematic reviews on vitamin A, vitamin E, or vitamin K. Three systematic reviews were included for the group of B vitamins, 11 for vitamin C, and 33 for vitamin D. Due to systematic reviews covering multiple vitamins, the total number of papers on vitamins ($n=47$) exceeds the number of papers reviewed ($n=44$).

Vitamin A

Of the six narrative reviews that mentioned vitamin A, only two discussed its potential benefits and properties.^{33,36} These reviews referred to vitamin A's pulmonary, immunomodulatory, antimicrobial, and anti-inflammatory effects. This is mainly as a result of proliferating T lymphocytes by increasing interleukin-2 (IL-2). One narrative review focused more on carotenoids, with specific reference to their antioxidant, anti-inflammatory, and immunomodulatory potential.³²

Since none of the systematic reviews on vitamin A specifically addressed its direct effects on COVID-19, no conclusions can be drawn.

Vitamin B

Three of the narrative reviews examined the effects of B vitamins in relationship to COVID-19. Discussing the role of B vitamins in regulating cell function, energy metabolism, and immune functions, B12 was highlighted for its benefits to patients requiring oxygen support (when combined with other interventions),³⁶ and B9 (folate) for its antiviral ability to inhibit furin protease and inactivate 3C-like protease.⁴¹

One systematic review that included vitamin B in its search found a single case-control study on 200 participants who may have had more severe symptoms due to vitamin B6 or B9 deficiency ($\leq 5 \mu\text{g/L}$ and $\leq 4 \mu\text{g/L}$, respectively).⁵⁴ Another review on the prognostic role of micronutrients included only one retrospective study on B12 with no clinically helpful results.⁶¹ A third systematic review looked at any pharmaceutical and complementary intervention on the psychological wellbeing of people with long COVID, finding one study on 100 participants receiving a daily dose of 2000 mg nicotinamide mononucleotide (vitamin B3) for 22 weeks, but this study is ongoing.⁸⁸

All other B vitamins do not have adequate research to draw any conclusions regarding their potential benefits for COVID prevention, its treatment, or on long-COVID management. The group of B vitamins, therefore, do not have sufficient evidence to support their supplementation in COVID-19 cases. However, ensuring nutritional adequacy may theoretically prevent disease severity.

Vitamin C

Of the eight narrative reviews that covered the effects of vitamin C in relation to COVID-19, four discussed its antioxidant potential,^{31,33,35,42} six reviewed its anti-inflammatory

TABLE 2 (Part 1 of 6) Systematic Reviews Included in the Umbrella Review

Study	Country	Study Designs Included	Risk of Bias Tools and Heterogeneity	Vitamins Studied and Doses	Primary Outcomes	# of Studies (Total Participants)	Age and Sex of Participants	Findings
Liu et al. (2021) ⁴⁵	China	Observational studies	Newcastle-Ottawa scale I^2 : 64.9%–93.6%	Vit D: serum levels	Incidence	10 (376,596)	Age range: >50 years Male: 25.2%–54.3% (not reported = 2)	Increased risk of COVID-19 associated with vitamin D deficiency or sufficiency (OR=1.43, 95% CI 1.00–2.05); Average vitamin D level was lower in COVID-19–positive patients (serum 25(OH)D: -0.37, 95% CI -0.52 to -0.21); nmol/L: -7.90, 95% CI -13.41 to -2.38)
Pereira et al. (2022) ⁴⁶	Brazil	Observational studies	Research Triangle Institute Item Bank (RTI – Item Bank) I^2 : 35.7%	Vit D: serum levels	Symptom severity, LOS, mortality	27 (372,332)	Mean age: 35.58 years (not reported = 1) Female: 26%–65% (not reported = 1)	Severe cases of COVID-19 present more with vitamin D deficiency than mild cases 65% (OR=1.65, 95% CI 1.30–2.09). Vitamin D insufficiency below 75 nmol/L increased hospitalization (OR=1.81, 95% CI 1.41–2.21) and mortality from COVID-19 (OR=1.82, 95% CI 1.06–2.58).
Bassatne et al. (2021) ⁴⁷	Lebanon	Observational studies and RCTs	Newcastle-Ottawa scale I^2 : 94%	Vit D: 357 IU/day to 60,000 IU/day, from one week to 12 months	Mortality	34 (19,080)	Age range: 42–81 years Female: 20%–67% (not reported = 2)	Mean serum 25(OH)D levels were 5.9 ng/mL significantly lower in COVID-19 positive, compared with negative patients (MD=-5.9, 95% CI -9.5 to -2.3)
Munshi et al. (2020) ⁴⁸	USA	Observational studies	Not reported	Vit D: serum levels	Disease severity, ICU admission, mortality	6 (1,368)	Mean age: 63.8 years Male: 58.6%	Patients with poor prognosis (N=150) had an adjusted standardized mean difference of -0.58 (95% CI -0.83 to -0.34, $p < .001$) serum 25(OH)D levels compared with those with good prognosis (N=161); Larger differences between ICU and floor admission (SMD=-0.84, 95% CI 1.32 to -0.36, $p = .001$); Larger differences by severity (SMD=-0.50, 95% CI -0.78 to -0.22, $p < .001$)
Teshome et al. (2021) ⁴⁹	Ethiopia	Observational studies	JBI, GRADE I^2 : 79.1%	Vit D: serum levels	Incidence	14 (91,120)	Not reported	Serum 25(OH)D deficiency was associated with an 80% increased risk of COVID-19 infection (OR=1.80, 95% CI 1.72–1.88)
Szarpak et al. (2021) ⁵⁰	Poland	Observational studies	Cochrane RoB 2 tool I^2 : 99%	Vit D: serum levels	Incidence	13 (14,485)	Mean age: 70.3 years Male: 58.6%	Mean serum 25(OH)D levels were 17.7±6.9 ng/mL in COVID-19 negative patients, compared with positive patients 14.1±8.2 ng/mL (MD=3.93; 95% CI 2.84–5.02; $p < 0.001$)
Kiyumi et al. (2021) ⁵¹	Oman	Observational studies	NOS I^2 : 67%	Vit D: serum levels	Incidence, disease severity, mortality	43 (254,963)	Age range: >35 years Sex not reported	Higher prevalence of vitamin D deficiency and insufficiency in COVID-19 positive patients (59.0% and 40.1%, respectively) A significant association between 25(OH)D and symptom severity (OR=3.38, 95% CI 1.94–5.87, $p < .0001$) and mortality (OR=2.30, 95% CI 1.47–3.59, $p < .00001$)
Dramé et al. (2021) ⁵²	France	Observational studies	NOS I^2 : Not reported	Vit D: serum levels	Symptom severity, mortality, oxygen therapy, IMV	11 (1,008)	Age range: >60 years Female: 29.6%–77.3%	Those without vitamin D deficiency had better primary clinical outcomes (death rate, the severity of the disease, oxygen therapy requirement, ICU support). Serum vitamin D level was also higher in COVID-19–negative patients.

TABLE 2 (Part 2 of 6) Systematic Reviews Included in the Umbrella Review

Study	Country	Study Designs Included	Risk of Bias Tools and Heterogeneity	Vitamins Studied and Doses	Primary Outcomes	# of Studies (Total Participants)	Age and Sex of Participants	Findings
Crafa et al. (2021) ⁵³	Spain	Observational studies	PRISMA I^2 : 84–98%	Vit D: serum levels	Incidence, disease severity, mortality	30 (380,172)	Mean age: 35.2–83.4 years Male: 38.7%–100% (not reported = 2)	Serum levels of 25(OH)D were significantly lower in COVID-19-positive patients (MD -3.99 (-5.34, -2.64); $p < .00001$; $I^2 = 95\%$) Serum level of 25(OH)D was lower in patients with severe disease (MD -6.88 (-9.74, 4.03); $p < .00001$; $I^2 = 98\%$) and in those who died (MD -8.01 (-12.50, -3.51); $p = .0005$; $I^2 = 86\%$) Patients with Vitamin D deficiency had an increased risk of developing severe disease [OR=4.58 (2.24, 9.35); $p < .0001$; $I^2 = 84\%$].
Wang et al. (2021) ⁵⁴	Singapore	Observational studies	NHLBI, RoB 2 I^2 : 84.9%	Vit B: serum levels; Vit D: serum levels	Incidence, disease severity, mortality, ICU admission, progression to respiratory-related complications	33 Tot: 360346 Vit B: 50 Vit C: 0 Vit D: 557,048	Mean age: 32–87.7 years Male: 22.7%–71.4% (not reported = 2)	The absence of micronutrient deficiency reduced COVID-19 incidence (pooled OR=0.37, 95% CI 0.18–0.78).
Chiodini et al. (2021) ⁵⁵	Italy	Observational studies	NOS, Funnel plot, Egger's test I^2 : 0–89.6%	Vit D: serum levels	Mortality, hospital admission, LOS, ICU admission	17 (2,756)	Age range: >42 years Female: 28.6%–63% (not reported = 1)	Low level of 25(OH)D is associated with COVID-19 mortality (OR=2.47, 95% CI 1.50–4.05; $I^2 = 30.5\%$), higher rates of hospital admissions (OR=2.18, 95% CI 1.48–3.21; $I^2 = 0\%$) and longer hospital stays (0.52 days; 95% CI 0.25–0.80; $I^2 = 89.6\%$)
Dissanayake et al. (2021) ⁵⁶	Sri Lanka	Observational studies	NOS I^2 : 73–92%	Vit D: serum levels	Incidence, disease severity, mortality	76 (1,976,099)	Age range: >32 years Male: 23%–80.2% (not reported = 8)	Vitamin D deficiency increased the odds of developing COVID-19 (OR=1.46; 95% CI 1.28–1.65; $p < .0001$; $I^2 = 92\%$), severe disease (OR=1.90; 95% CI 1.52–2.38; $p < .0001$; $I^2 = 81\%$), and death (OR=2.07; 95% CI 1.28–3.35; $p = .003$; $I^2 = 73\%$) Lower 25(OH)D levels in COVID-19-positive patients (MD=-3.85 ng/mL; 95% CI -5.44 to -2.26; $p \leq .0001$), and in patients with severe COVID-19 symptoms (MD=-4.84 ng/mL; 95% CI -7.32 to -2.35; $p = .0001$) and in non-survivors (MD= -4.80 ng/mL; 95% CI -7.89 to -1.71; $p = .002$)
Ebrahimzadeh et al. (2021) ⁵⁷	Iran	Observational studies	NOS I^2 : 0–80.6%	Vit D: serum levels	In hospital mortality	13 (2,208)	Age range: 34–102 years Male: 44.4%–67%	There was a significant positive relationship between vitamin D deficiency and risk of COVID-19 in-hospital mortality (OR=2.11; 95% CI 1.03–4.32).
Tentolouris et al. (2022) ⁵⁸	Greece	Observational studies and RCTs	RoB 2 I^2 : Not reported	Vit D: 1000 IU up to 14 days to 400,000 IU orally one time	Mortality, ICU admission	10 (2,078)	Mean age: 53.1–88 years (not reported = 4) Sex not reported	There was a beneficial role of vitamin D supplementation on ICU admission (OR=0.326; 95% CI 0.149–0.712; $p = .005$).
Shah et al. (2022) ⁵⁹	India	Systematic reviews	AMSTAR, GRADE, Egger's test, Begg's test, Mazumdar's test, Funnel plot I^2 : Not reported	Vit D: 400 IU to 400,000 IU	Mortality, ICU admission, LOS, IMV	10 (548,458)	Not reported	Vitamin D supplementation reduced the risk of mortality (OR=0.48, 95% CI 0.346–0.664; $p < .001$); Reduced ICU admission (OR=0.35; 95% CI 0.28–0.44; $p < .001$); Reduced mechanical ventilation (OR=0.54; 95% CI 0.411–0.708; $p < .001$)

TABLE 2 (Part 3 of 6) Systematic Reviews Included in the Umbrella Review

Study	Country	Study Designs Included	Risk of Bias Tools and Heterogeneity	Vitamins Studied and Doses	Primary Outcomes	# of Studies (Total Participants)	Age and Sex of Participants	Findings
Bignardi et al. (2022) ⁶⁰	Italy	Observational studies and RCTs	NOS, RoB 2 I ² : 0%	Not reported (mixed serum levels and supplementation)	Mortality, hospitalization, ICU admission, IMV	17 (3,108)	Age range: 35–88 years Sex not reported	Low 25(OH)D levels associated with mortality (RR=1.42, 95% CI 1.14–1.71, I ² =0.0%), need for ICU admission (RR=1.76, 95% CI 1.03–2.49, I ² =0.0%), and need for ventilation (RR=3.58, 95% CI 1.45–5.70, I ² =0.0%).
Pechlivanidou et al. (2022) ⁶¹	Greece	Observational studies and interventions	Risk of bias tools not reported I ² : Not reported	Wide range of studies with mixed serum levels and supplementation	Mortality, survival	31 Vit B: 1 Vit C: 2 Vit D: 13 Vit E: 1 Tot: 8,624 Vit B: 310 Vit C: 212 Vit D: 2,334 Vit E: 110	Mean age: 52–70 years Female: 20%–59%	Supports the therapeutic use of vitamin D, insufficient data on other micronutrients to draw conclusions.
Dadras et al. (2022) ⁶²	Thailand	Observational studies and RCTs	NOS I ² : Not reported	Vit D: serum levels	Disease severity, disease duration, mortality	35 (unclear how many on vitamin D) Total population not reported	Age range: 60–93 years Sex not reported	Deficiency in 25(OH)D predicted a poorer prognosis and mortality in the elderly and is associated with more severe lung involvement and longer disease duration.
Migliorini et al. (2022) ⁶³	Germany	Observational studies and RCTs	NOS, Jadad I ² : Not reported	Not reported	Incidence, disease severity, disease progression	23 Tot: 3,443 Vit C: 1,488 Vit D: 3,443	Mean age: 45–74 years Male: 50%–52%	Supports the use of Vitamin C or Vitamin D supplementation.
Mishra et al. (2022) ⁶⁴	India	Observational studies	PRISMA, NIH, NHLBI, Funnel plot, Egger's test I ² : 94.2%	Vit D: serum levels	Comorbidities with COVID-19 infection	16 (386,631)	Age range: 2–82 years Female: 53.16%	Lower serum 25(OH)D levels in COVID-19-positive patients (MD=-1.70; 95% CI -2.74 to -0.66; p=.001) with a 95% prediction interval of -5.85 to 2.45.
Mazaheri-Tehrani et al. (2022) ⁶⁵	Iran	Observational studies	Egger's test I ² : 93.07%	Vit D: serum levels	Incidence, disease severity	7 (1,799)	Mean age: 27–32 years Female: 100% (pregnant)	No significant difference in serum vitamin D levels between COVID-19 cases and healthy controls (WMD=-2.55, 95% CI -6.85 to -1.74). Serum vitamin D levels are significantly lower in severe cases (WMD=-2.71, 95% CI -4.18 to -1.24). Vitamin D deficiency prevalent amongst most participants.
Sloan et al. (2022) ⁶⁶	Brazil	Observational studies, interventions and RCTs	RoB 2 I ² : Not reported	Vit D: 2000 IU/day–200,000 IU one time	Not reported	10 (Not stated)	Age range: 18–71 years Sex not reported	Recommend serum vitamin D levels greater than 30 ng/mL, preferably 40–60 ng/mL. Large bolus doses seemed to have little significant effect.

TABLE 2 (Part 4 of 6) Systematic Reviews Included in the Umbrella Review

Study	Country	Study Designs Included	Risk of Bias Tools and Heterogeneity	Vitamins Studied and Doses	Primary Outcomes	# of Studies (Total Participants)	Age and Sex of Participants	Findings
Petrelli et al. (2023) ⁶⁷	Italy	Observational studies, interventions and RCTs	Egger's test I ² : 77% for severity, 50% for mortality	Vit D: 357 IU/day–60,000 IU/day (others specified)	Incidence, ICU admission, mortality	27 (1,276,7045)	Not reported	Low levels of D3 were significantly associated with severity (OR=1.97, 95% CI 1.55–2.51, <i>p</i> <.01; I ² =77%, <i>p</i> <.01) and mortality (OR=1.83, 95% CI 1.55–2.16, <i>p</i> <.01; I ² =50%, <i>p</i> <.01) risk due to COVID-19. Low levels of vitamin D3 were associated with a significant risk of COVID-19 (OR=1.72, 95% CI 1.51–1.97, <i>p</i> <.01; I ² =76%, <i>p</i> <.01). After diagnosis of COVID-19, vitamin D supplementation was associated with significantly reduced infection severity (e.g., ICU admission) (OR=0.38, 95% CI 0.28–0.5, <i>p</i> <.01; I ² =0%, <i>p</i> =.71).
Feng et al. (2021) ⁶⁸	China	RCTs	RoB 2 I ² : Not reported	Vit D: 200,000 IU/day dissolved in 10 mL peanut oil solution	LOS	12 Vit D: 1 Tot: 1,952 Vit D: 237	Mean age: 56.2 years Sex not reported	Insufficient data
Ao et al. (2022) ⁶⁹	China	Observational studies and RCTs	Jadad, NOS I ² : 26% for severity, 0% for mortality	Vit C: 2–24 g IV for 3–7 days	Mortality, disease severity	7 (807)	Age range: 36–78 years Male: 33%–66.7%	No statistically significant results found
Kwak et al. (2021) ⁷⁰	Korea	Observational studies and RCTs	Funnel plot, Egger's test I ² : 20.9% for mortality, 94.6% for length of hospital stay	Vit C: 1–12 g/day or 50–100 mg/kg/day; from every 6 hrs up to 10 days	Hospital mortality, LOS	8 (1,021)	Not reported	No statistically significant results found
Stroehlein et al. (2021) ⁷¹	Germany	RCTs	RoB 2 I ² : Not reported	Vit D: 0.532 mg orally up to 7 days, to 200,000 IU one time	All-cause mortality, IVM, LOS, serum vitamin D status, ICU admission, adverse events (any grade).	3 (356)	Age range: 42–64 years Male: 6%–69%	Low certainty of evidence
Varikasuvu et al. (2022) ⁷²	India	RCTs	RoB 2, Funnel plot, Begg's test, Egger's test I ² : >50%	Vit D: 1,000 IU–80,000 daily up to 2 weeks; or 200,000 IU orally one time	ICU admission, mortality, RT-PCR positivity	6 (551)	Age range: 18–56 years Male: 44%–59%	Vitamin D reduced the rates of RT-PCR positivity (RR=0.46, 95% CI 0.24–0.89, Z=2.31, <i>p</i> =.02, I ² =0%). Vitamin D is associated with fewer rates of ICU admission, mortality events, and RT-PCR positivity (relative risk, RR=0.60, 95% CI 0.40–0.92, Z=2.33, <i>p</i> =.02, I ² =48%).
Argano et al. (2022) ⁷³	Italy	Systematic reviews and meta-analyses	AMSTAR I ² : Not reported	Wide range of studies with mixed serum levels and supplementation	Inflammatory process in patients affected by DM	6 (1,594)	Not reported	Supports the therapeutic administration of supplemental vitamin D in diabetic patients to reduce COVID-19 respiratory complications.
Rawat et al. (2021) ⁷⁴	India	RCTs	RoB 2 I ² : 0% for mortality, 0% for duration, 92% for LOS, 0% for IMV	Vit C: 50 mg/kg/day up to 24 g/day	Mortality, ICU LOS, hospital LOS, IMV incidence.	6 (572)	Age range: 36–79 years Sex not reported	No statistically significant results found in the meta-analysis

TABLE 2 (Part 5 of 6) Systematic Reviews Included in the Umbrella Review

Study	Country	Study Designs Included	Risk of Bias Tools and Heterogeneity	Vitamins Studied and Doses	Primary Outcomes	# of Studies (Total Participants)	Age and Sex of Participants	Findings
Gavrielatou et al. (2022) ⁵	Greece	Observational studies and RCTs	RoB 2 I^2 : 74%	Vit C: high-dose IV	Vasopressor-free days, continuous renal replacement therapy-free days, ventilator-free days, ICU-free days, ICU-mortality	11 (1,807)	Age range: 41–81 years Female: 24.8%	No statistically significant results found in the meta-analysis.
da Rocha et al. (2021) ⁶	Brazil	RCTs and interventions	RoB 2 I^2 : Not reported	Vit D: 0.532 mg to 200,000 IU	Duration of IMV, mortality rate, adverse events	3 (385)	Age range: 40–71 years Sex not reported	Supports the therapeutic use of supplementary vitamin D to mitigate respiratory complications associated with COVID-19 or to preemptively mitigate the severity of COVID-19 in the event of infection.
Bania et al. (2022) ⁷	Greece	Observational studies, interventions and RCTs	RoB 2 I^2 : Not reported	1000 IU/day to 50,000 IU/wk to 120,000 IU/mo to 200,000 one time	LOS, IMV/intubation, ICU admission, mortality	11 (1,070)	Age range: 27–89 years Sex not reported	Supports the therapeutic use of supplementary vitamin D to mitigate respiratory complications associated with COVID-19 or to preemptively mitigate the severity of COVID-19 in the event of infection.
Hariyanto et al. (2022) ⁸	Indonesia	Observational studies, interventions and RCTs	Funnel plot I^2 : <25%– >50%	Vit D: 25,000 IU/month up to 200,000 IU/day for 2 days	ICU admission, IMV, mortality	11 (2,265)	Age range: 31–97 years Sex not reported	Vitamin D supplementation reduced ICU admission (OR=0.27, 95% CI 0.09–0.76, p = .010, I^2 = 70%, random-effect modelling); Reduced the need for mechanical ventilation (OR=0.34, 95% CI 0.16–0.72, p = .005, I^2 = 61%, random-effect modelling); Reduced mortality from COVID-19 (OR=0.37, 95% CI 0.21–0.66, p < .001, I^2 = 50%, random-effect modelling).
Hosseini et al. (2022) ⁹	Canada	Observational studies, interventions and RCTs	RoB 2 I^2 : >50%	Vit D: <1000 IU/day–10,000 IU/day	Incidence, hospital admission, ICU admission, mortality	23 (5,870,189)	Age range: 15–100 years Sex not reported	Vitamin D supplementation was significantly associated with a reduced risk of ICU admission (RR=0.35, 95% CI 0.20–0.62) and mortality (RR=0.46, 95% CI 0.30–0.70).
Beran et al. (2022) ⁸⁰	USA	Observational studies and RCTs	Jadad, NOS, Egger's test, Funnel plot I^2 : Not reported	Vit C: 1 g–8 g oral or 50 mg–24 g IV up to 18 days Vit D: wide range of dosages and durations	Mortality, intubation rate, LOS	26 (5,633)	Age range: 29–79 years Sex not reported	No sig effects with vitamin C; Vitamin D adequacy reduced intubation rate (RR=0.55, 95% CI 0.32–0.97, p = .04, I^2 = 48%) and LOS (MD= -1.26; 95% CI -2.27 to -0.25; p = .01, I^2 = 0%).
Alhathri et al. (2022) ⁸¹	Saudi Arabia	Observational studies, interventions and RCTs	Forest plot, Funnel plot I^2 for Vit C 0%–96%; Vit D: serum levels only	Vit C: 24–168 g for 5–7 days; Vit D: serum levels only	Incidence, duration	27 (11,711)	Not reported	Serum levels of vitamin D are low in COVID-19–positive patients (p < .001). No significant variations found for vitamin C supplementation.
D'Ecclesiis et al. (2022) ⁸²	Italy	Observational studies and interventions	NOS, RoB2, Egger's test, Begg's test, Funnel plot I^2 : <50%	Vit D: 1000 IU daily to 400,000 IU one time (mixed studies with serum and supplementation)	Symptom severity, ICU admission, IMV/intubation, LOS, mortality	38 (205,565)	Mean age: 35.6–90 years Male: 32%–92%	Vitamin D supplementation was associated with a reduced risk of disease severity (SRR=0.38, 95% CI 0.20–0.72, 6 studies) and mortality (SRR=0.35, 95% CI 0.17–0.70, 8 studies), particularly in older individuals and at higher latitudes.

TABLE 2 (Part 6 of 6) Systematic Reviews Included in the Umbrella Review

Study	Country	Study Designs Included	Risk of Bias Tools and Heterogeneity	Vitamins Studied and Doses	Primary Outcomes	# of Studies (Total Participants)	Age and Sex of Participants	Findings
Oiczak-Pruc et al. (2022) ⁸³	Poland	Interventions	RoB 2, ROBINS-I I ² : Not reported	Vit C: ≤ 1 g/day– > 10 g/day	Mortality, LOS, ICU admission	19 (1,817)	Age range: ≥ 18 years Sex not reported	Vitamin C supplementation reduced the risk of in-hospital mortality (OR=0.59; 95% CI 0.37–0.95; <i>p</i> =.03). The ICU length of stay was longer in patients treated with vitamin C vs. standard therapy, 11.1 (7.3) vs. 8.3 (4.7) days (MD=1.91; 95% CI 0.89–2.93; <i>p</i> <.001).
Kümmel et al. (2022) ⁸⁴	Germany	RCTs	Funnel plot, Begg's test, Egger's test I ² : 0% for mortality, 66% for ICU admission, 24% for length of hospitalization	Vit D: 0.5 µg–5,000 µg	Mortality, ICU admission, LOS	8 (657)	Mean age: 39.7 years Female: 100%	Trend for reduced mortality (OR=0.74, 95% CI 0.32–1.71, <i>p</i> =.48), with even stronger effects, when vitamin D was administered repeatedly (OR=0.33, 95% CI 0.1–1.14).
Huang et al. (2022) ⁸⁵	Korea	Observational studies and RCTs	RoB 2, NOS, Funnel plots, Egger's test I ² : >50%	Vit C: 500 mg orally–24 g IV	Mortality, ICU duration, LOS, IMV	19 (949)	Age range: ≥60 years Sex not reported	Vitamin C supplementation reduced the risk of mortality (RR=0.81, 95% CI 0.62–1.07; <i>I</i> ² =58%; <i>Q</i> =40.95; <i>p</i> <.01); no significant differences in LOS, ventilation, ICU duration
Kow et al. (2023) ⁸⁶	Malaysia	RCTs	RoB 2 I ² : Not reported	Vit C: 200 mg–8 g orally daily or 6 g–28 g IV daily	Mortality	11 (939)	Mean age: 42–67 years (all ≥ 18 years) Sex not reported	Vitamin C supplementation reduced the risk of all-cause mortality (pooled OR=0.53; 95% CI 0.30–0.92), especially in patients with severe COVID-19 (pooled OR=0.47; 95% CI 0.26–0.84).
Vollbracht et al. (2021) ⁸⁷	Germany	Observational studies, interventions, RCTs, pre-clinical	NA I ² : Not reported but heterogeneity mentioned	Vit C: > 1 g IV daily	Symptom severity, oxygen status	9 (720)	Not reported	Supports the therapeutic use of high dose vitamin C to improve oxygen status and mitigate the severity of COVID-19.
Hawke et al. (2022) ⁸⁸	Canada	RCTs and interventions	RoB 2 I ² : Not reported	Vit B3: 2000 mg daily for 22 weeks	Insufficient data	42 Vit B: 1 Tot: 5,814 Vit B3: 200	Age range: <18–65+ Sex not reported	

AMSTAR=a measurement tool to assess systematic reviews; CI=confidence interval; DM=diabetes mellitus; GRADE=grading of recommendations, assessment, development and evaluations; ICU=intensive care unit; IMV=invasive mechanical ventilation; IV=intravenous; JBI=Joanna Briggs Institute critical appraisal tool; LOS=length of stay; MD=mean deviation; NHLBI=National Heart, Lung and Blood Institute quality assessment tool; NIH=National Institutes of Health; NOS=Newcastle-Ottawa scale; OR=odds ratio; PRISMA=preferred reporting items for systematic reviews and meta-analyses; RCT=randomized controlled trial; RoB 2=Cochrane risk of bias tool; ROBINS-I=risk of bias in non-randomized studies – of interventions; RR=relative risk; RT-PCR=reverse transcription-polymerase chain reaction test; SMD=standardized mean difference; SRR=standardized rate ratio; WMD=weighted mean difference.

effects,^{33,35,36,39,41,42} and three covered its immunomodulatory benefits.^{33,35,36,42}

The systematic reviews of vitamin C generally found positive associations between its therapeutic supplementation and reduced COVID-19 severity. Eleven of the 13 systematic reviews included a meta-analysis, but only three of them found significant results. In Huang et al. (2022),⁸⁵ vitamin C supplementation reduced the risk of mortality (relative risk [RR] = 0.81, $p < 0.01$). In Olczak-Pruc et al. (2022),⁸³ vitamin C supplementation reduced the risk of in-hospital mortality (odds ratio [OR] = 0.59, $p = 0.03$) but the researchers also found that the length of stay in the intensive care unit (ICU) was greater in patients treated with vitamin C compared with standard therapy alone, with an average of 11.1 days compared with 8.3 days (mean deviation [MD] = 1.91, $p < 0.001$). In Kow et al. (2023),⁸⁶ vitamin C supplementation reduced the risk of all-cause mortality (pooled OR = 0.53; 95% confidence interval [CI] 0.30–0.92), especially in patients with severe COVID-19 (pooled OR = 0.47; 95% CI 0.26–0.84).

The doses of vitamin C administered in the included studies ranged substantially and covered both oral and intravenous (IV) applications within the same systematic reviews. With regard to oral doses, these ranged from 200 mg to 8 g daily, while doses for IV application ranged from 6 g to 28 g daily. None of the reviews examined the dose–effect relationship. As for the duration, IV therapy was administered between 1 and 10 days, but oral therapy had prolonged durations.

Vitamin C, therefore, demonstrates potential benefits in the prevention and treatment of COVID-19, but the strength of evidence remains uncertain. Given the wide variability in vitamin C dosing and administration observed across these studies, many non-significant findings among the systematic reviews may be due to methodological issues in the research.

Vitamin D

Vitamin D had the greatest number of narrative reviews ($n=12$), 11 of which provided an extensive evaluation of its mechanisms, its properties, and its applicability related to COVID-19. Three studies discussed vitamin D as an antioxidant,^{32,35,40} eight as an anti-inflammatory,^{33–36,38,40,41,44} nine as an immunomodulator,^{32–39,44} and two as an antiviral.^{35,37} In most cases, the reviews focused on the importance of addressing deficiency as measured by serum status of 25-hydroxy vitamin D or 25(OH)D.

None of the systematic reviews discussed any severe adverse effects or therapeutic concerns with regard to vitamin D. In fact, the general consensus is that there is a clinical value in measuring serum 25(OH)D levels because deficiency and inadequacy are associated with increased COVID-19 incidence, severity of symptoms, length of stay in hospital, ventilation requirements, and mortality.

For the 28 studies that conducted a meta-analysis, findings were consistently supportive of maintaining adequate levels of 25(OH)D and/or the therapeutic use of vitamin D supplementation. For example, 11 reviews found statistically significant associations between low levels of 25(OH)D and the incidence of getting a COVID-19 infection,^{45,47,49–51,53,55,56,64,67,81} and eight with disease

severity.^{46,48,51,53,55,56,65,67} Inadequate levels of 25(OH)D were also reported to have a significant association with COVID-19–related mortality in nine of the systematic reviews.^{46,48,51,53,55–57,60,67}

With regard to vitamin D supplementation, five reviews found significant associations with a reduced risk of ICU admission,^{58,59,72,78,79} and five found it reduced the risk of mortality.^{59,72,78,82,84}

As for vitamin D dosing, the wide range from 357 IU/day to 400,000 IU as a single bolus complicates the effectiveness of data analysis. Though some studies described loading doses compared with maintenance doses, three studies highlighted that repeated administration of smaller doses would provide better effects than single large bolus doses.^{60,66,84}

In summary, the most fitting take-home message would be to ensure the patient reaches adequate serum levels, preferably 100–150 nmol/L (40–60 ng/mL),⁶⁶ with appropriate vitamin D supplementation and dosing for the patient to reach desired serum levels.

Vitamin E

Of the narrative reviews, only one outlined the antioxidant, anti-inflammatory, and immunomodulatory components of vitamin E in relation to COVID-19 specifically.³³ The authors discussed vitamin E's ability to reduce the production of nitrogen oxide and downregulate inflammation (prostaglandin E2 and cyclooxygenase), while modulating the Th1/Th2 balance and protein kinase C.

In the absence of systematic reviews specifically investigating the impact of vitamin E on COVID-19, definitive conclusions cannot be reached.

Overlap Analysis

Calculating the Corrected Covered Area at 2.31%, we found there was only a slight overlap across all systematic reviews. We further examined 15 reviews containing more than 10 articles cited more than once across all included reviews, particularly for the topics on vitamin D. Nonetheless, the impact any occurrence of overlap would have on our review findings was slight.

DISCUSSION

The synthesis of narrative and systematic reviews in this umbrella study presents a comprehensive overview of the potential roles of vitamins A, B group, C, D, and E in the context of COVID-19 management. The inclusion of narrative reviews alongside systematic reviews enhances the breadth of understanding, providing a holistic exploration of vitamins for COVID-19 prevention and management. Although only a subset of the initially included narrative and systematic reviews was retained for final analysis, these reviews collectively shed light on potential benefits and mechanisms associated with various vitamins.

Vitamin A emerges as a theoretical candidate for immunomodulation, anti-inflammatory action, and antimicrobial effects. The absence of systematic reviews specifically focusing on vitamin A highlights the need for more comprehensive investigations. Similarly, the activity of the vitamin B group in cell function regulation, energy metabolism, and immune response modulation

(particularly vitamins B6, B9, and B12) warrant attention. Unfortunately, the limited number of systematic reviews on the vitamin B group as a treatment option for COVID-19 leave these water-soluble vitamins as theoretical aids that require further research. Finally, discussion of vitamin E within narrative reviews underscores its potential antioxidant and anti-inflammatory effects. However, the absence of systematic reviews limits our ability to draw definitive conclusions regarding its impact on COVID-19 outcomes and thus emphasizes the need for dedicated research in this area.

In contrast, the systematic reviews available for vitamins C and D offer clearer insights into their effects, but the strength of evidence is far greater for vitamin D. Narrative reviews consistently discussed vitamin C's antioxidant, anti-inflammatory, and immunomodulatory properties, but the evidence remains rather theoretical. As to vitamin D's significance in addressing deficiency-related COVID-19 risks, it is confirmed to be an important antioxidant, anti-inflammatory, immunomodulator, and an antiviral agent. The mechanisms of action discussed for vitamin D are then effectively put into practice in multiple trials.

The systematic reviews on vitamin C reveal a notable pattern: while all of them discussed positive associations between vitamin C supplementation and reduced COVID-19 severity, only a few presented statistically significant results. A closer examination may elucidate why 70% of studies found no statistically significant results. First, these systematic reviews and meta-analyses all had a small number of studies on vitamin C included (ranging from two to 11 studies) with an insufficient population size to obtain statistical power for significant findings. The systematic reviews with a greater number of studies also had the greatest heterogeneity (I^2 from 74% to 96%), reducing the confidence in the pooled estimate or effect size. Further discrepancies could be attributed to variations in study populations, methodologies, and outcome measures among the included studies in the systematic reviews. One of the main reasons for this high level of heterogeneity is that the doses of vitamin C administered in the included studies ranged substantially, with both oral and IV applications within the same systematic reviews complicating the interpretation of outcomes. On the one hand, the lowest dose included in a study (200 mg daily taken orally), was based on the maximum absorption efficiency^{89,90} and was suggested by some authors as an optimal dose for primary prevention of disease.⁹¹ On the other hand, studies had up to 8 g taken orally in daily divided doses, presenting a drastic difference in oral treatment regimens. Similarly, 6 g to 28 g of IV administration in the studies included presents such a wide range of dosing approaches that a dose-response relationship warrants further study. Such an analysis would have been especially valuable considering that IV vitamin C bypasses intestinal absorption for higher plasma concentrations to be achieved but renal excretion can restore vitamin C to baseline within hours.⁹² These pharmacokinetics must be considered for clinically relevant interpretation of the research findings.

There is also the concern that baseline measures of plasma vitamin C concentration were not considered in these studies. Because of the intricate way in which the body will absorb, distribute,

metabolize, and eliminate vitamins to regulate plasma levels, the outcomes of vitamin C supplementation can vary significantly based on an individual's vitamin C status. This divergence is particularly notable between those who have sufficient vitamin C levels (plasma concentrations near saturation) and those with sub-optimal (plasma concentrations <50 $\mu\text{mol/L}$), marginally deficient (plasma concentrations <23 $\mu\text{mol/L}$), or severely deficient (plasma concentrations <11 $\mu\text{mol/L}$) levels.⁹³ Future research on vitamin C should ensure that interventions or statistical analyses consider serum levels. Similarly, clinical application should be carried out with due consideration of the individual's baseline vitamin C status. In summary, the research on vitamin C suggests it has potential benefits in the prevention and treatment of COVID-19, but the heterogeneity of included studies invites careful consideration of the precise dosing and administration protocol for patients.

With respect to vitamin D, this essential nutrient emerges as a central theme within the body of systematic reviews, underscoring its role in both the prevention and treatment of COVID-19. Systematic reviews consistently highlight the significance of maintaining adequate vitamin D levels in addressing the multifaceted challenges posed by the pandemic. The recurring findings across these reviews provide compelling evidence that optimizing vitamin D status could substantially mitigate the risks associated with COVID-19, spanning from disease incidence to severity and mortality.

Nevertheless, the diverse outcomes observed in the systematic reviews suggest a complex interplay of factors, including variations in dosing and formulations, study populations, methodologies, and geographical contexts. The intricate pharmacokinetics of vitamin D contribute to the nuanced interpretation of outcomes, as its metabolism is influenced by factors such as age and body mass,⁹⁴ as well as skin pigmentation, latitude, sun exposure, and dietary intake.⁹⁵⁻⁹⁷ This diversity of factors inevitably results in a wide range of dosing strategies aimed at achieving individualized 25(OH)D sufficiency. Consequently, the observed mixed outcomes in systematic reviews are reflective of this personalized approach, with dosage variations aligning well with the distinct requirements of diverse patient profiles.

The challenge lies in striking a balance between establishing an effective dosing regimen that attains the desired therapeutic effects while minimizing potential adverse outcomes. The reviewed systematic studies clearly lean towards vitamin D being an effective vitamin for COVID-19 prevention and treatment. Nonetheless, the optimal dosing protocol remains an area of ongoing investigation, meriting further research and refinement. Despite this complexity, repeated dosing seems to yield superior outcomes compared with a single large bolus dose.

Clinical Relevance and Implications

The synthesis of narrative and systematic reviews has implications for practitioners, policymakers, and researchers. Clinicians should consider the varying levels of evidence and the specific contexts in which these vitamins are being administered.

Vitamin D's significance in addressing deficiency-related risks presents a strong rationale for incorporating 25(OH)D assessment

into clinical practice, considering vitamin D deficiency is strongly associated with worse COVID-19 outcomes. Supplementation strategies in clinical practice must emphasize personalized dosing to reach the ideal serum levels of 100–150 nmol/L (40–60 ng/mL). The fundamental role of vitamin D in immune modulation signifies its potential to become a vital adjunct in the fight against the pandemic in hospitalized and outpatient settings. Optimal administration strategies to achieve and maintain optimal vitamin D levels require further fine-tuning with future research endeavours.

The evidence for vitamin C is weaker than it is for vitamin D. Concerns over the heterogeneity of included studies point to the strong need for further research on oral and IV treatments in separate research studies. Nonetheless, study results are leaning towards controlled dosing regimens to enhance immunity and mitigate the impact of COVID-19 in hospitalized or ICU settings. Therefore, in clinical practice, vitamin C may be carefully considered as a possible adjunct for COVID-19 treatment.

The lack of comprehensive systematic exploration of the group of B vitamins and the speculative nature of findings for vitamins A and E necessitate caution in their clinical application for COVID-19 management. Furthermore, added caution is required for special populations. Though several studies focused specifically on the elderly, and one on pregnant women, discretion should also be used in the application of any vitamin therapy to children or other subpopulations (e.g., immunocompromised, other comorbidities) because of a lack of research on these specific groups.

Strengths

Though it is not typical to include narrative reviews in an umbrella review, the inclusion of high-quality narrative reviews, according to SANRA guidelines, provides a complement to systematic reviews in their provision of clinically relevant treatment options. The collected systematic reviews also underwent a rigorous quality assessment, aligning with AMSTAR scoring tools. Using such quality assessments ensured robustness and minimized potential biases. By scrutinizing overlapping references and outcomes across systematic reviews, a cohesive framework emerged, enabling the identification of overarching patterns and discrepancies among the various systematic reviews. This umbrella review allowed for a holistic understanding of the synthesized evidence, empowering the extraction of meaningful insights that helped formulate comprehensive conclusions in the context of the potential role vitamins can play in COVID-19 prevention and management.

Limitations

At the beginning of the COVID-19 pandemic, researchers found a very limited number of relevant studies to include in their systematic reviews and were therefore hindered in drawing effective conclusions or running meta-analyses. In comparison, researchers who waited for more data to be published had stronger evidence to present. Many studies relied on the treatment of upper respiratory tract infections (URTIs) to hypothesize on the mechanisms of action of vitamins on COVID-19. Unfortunately, such URTI treatment often fails to acknowledge the unique cytokine

storm that COVID-19 triggers, which is why studies that did not specifically address COVID-19 were excluded. Furthermore, according to the reference overlap table, several systematic reviews used the same studies. This suggests a potential for limited diversity and breadth of evidence, which could impact the robustness and comprehensiveness of the conclusions drawn from those reviews. We also cannot ignore great variations in heterogeneity and publication bias among the systematic reviews in this umbrella review. Moreover, occasional disparities in data interpretation among extraction volunteers introduce a methodological limitation.

Of important note, some studies claimed significant results based on *p* values, despite the 95% confidence interval crossing the 1,^{83,85} ultimately contradicting themselves and reducing the level of trust readers can have in their data interpretation. Studies that did not account for variations in the dose (or ignored vitamin dosing as a factor) were less likely to find clinically relevant results. Future studies need to consider separating serum levels of a nutrient from its therapeutic supplementation in their methodological criteria. Similarly, studies should analyze results from oral and IV administrations separately, considering their dose and delivery affect the pharmacokinetics and pharmacodynamics of vitamin therapy. Closer attention to the dose–response relationship, along with cross-correlations to the stage of disease (prevention, early stage, mild vs severe cases, and post-COVID), also warrant further investigation. Since low doses may be ineffective and high doses have a higher likelihood of adverse effects, future research needs to control for dosing variability and report accordingly.

CONCLUSION

Several noteworthy findings emerge from this comprehensive examination of the potential roles vitamins play in COVID-19 prevention, treatment, and management. While narrative reviews suggest promising attributes of vitamins A, B, C, D, and E in combating COVID-19, the absence of systematic reviews on certain vitamins hinders conclusive insights. Vitamin B exhibits theoretical benefits in cell regulation and immunity, yet its role lacks comprehensive systematic investigation. Vitamins A and E showcase intriguing properties but require further systematic exploration specifically related to COVID-19. Small sample sizes and high heterogeneity among the included studies on vitamin C devalue the aggregated results. Nonetheless, there were sufficient systematic reviews on vitamin C to suggest possible associations between its adjunct supplementation and a reduced risk of COVID-19 severity, despite varying dosages and forms of administration complicating the interpretation relevant to clinical application. Conversely, results on vitamin D were much more conclusive. Vitamin D warrants substantial attention, as its deficiency correlates with heightened COVID-19 risks. The systematic reviews confirm serum adequacy leads to reduced risks of COVID-19 infection, severity, and mortality. Personalization of vitamin D dosing is suggested to reach ideal serum levels. Overall, this analysis underscores the need for meticulous research to establish more robust conclusions.

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CONFLICTS OF INTEREST DISCLOSURE

We have read and understood the *CAND Journal's* policy on conflicts of interest and declare that we have none.

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APPENDIX 1: GLOSSARY OF TERMS

25(OH)D	25 hydroxy vitamin D
AMSTAR	Assessment of Multiple Systematic Reviews
CI	confidence interval
COVID-19	coronavirus-19 (aka SARS-CoV-2, novel coronavirus)
CRP	C-reactive protein
EF	Endothelial function
FBF	forearm blood flow
FMD	flow mediated dilation
FoxP3	Forkhead box P3
GRADE	grading of recommendations, assessment, development and evaluations
ICU	intensive care unit
IL-6	interleukin-6
IV	intravenous
JBI	JBI critical appraisal checklist
LOS	length of stay
NHLBI	the national heart, lung and blood institute quality assessment tool
NIH	National Institutes of Health (NIH) quality assessment tools
NOS	Newcastle-Ottawa scale
OR	odds ratio
PRISMA	preferred reporting items for systematic reviews and meta-analyses
RoB 2	Cochrane risk of bias tool
ROBINS-I	risk of bias in non-randomized studies – of interventions
RR	relative risk
SARS-CoV-2	severe acute respiratory syndrome of the coronavirus 2
TNF- α	tumor necrosis factor- α
URTI	upper respiratory tract infections
WHO	World Health Organisation