The Role of Minerals in COVID-19: An Umbrella Review

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ABSTRACT

Background: This umbrella review aims to synthesize the existing literature on the preventive and therapeutic benefits of minerals zinc, selenium, iron, copper, magnesium, phosphorus, and calcium in the context of COVID-19 prevention and management. The objective is to highlight the clinical applicability and identify avenues of future research.

Methods: A systematic search was conducted in PubMed and Google Scholar databases using predefined keywords for each mineral 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 and synthesis were performed, and reference overlap analysis was conducted (see Table S1 in the supplemental material).

Results: Narrative reviews highlighted the range of therapeutic properties of minerals including antimicrobial, antiviral, antioxidant, anti-inflammatory, and immune-modulating and the essential role they play in the prevention and treatment of many conditions, including acute respiratory conditions such as COVID-19. The systematic reviews highlighted that deficiency of key minerals such as zinc, selenium, iron, copper, magnesium, phosphorus, and calcium are associated with increased risk of infection and decreased rate of recovery. Iron supplementation may be beneficial as functional anemia is common in those with COVID-19. Zinc supplementation may shorten the duration of olfactory dysfunction.

Conclusion/Summary: Deficiency of minerals may increase the risk of infection and decrease the rate of recovery as it relates to COVID-19. Supplementation with and correction of zinc, iron and selenium deficiencies may improve clinical outcomes and immune responses in those with COVID-19.

Key Words Supplements, selenium, zinc, magnesium, iron, phosphorus, calcium, deficiency

INTRODUCTION

The prevention and treatment of the novel airborne virus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; see Appendix 1 for a list of terms and acronyms used in this article) and its resultant coronavirus disease 2019 (COVID-19), as well as the management of COVID syndrome or long COVID has become a critical research priority due to the lack of evidence-based treatment protocols.[1] Natural health products such as vitamins, minerals, and herbal supplements are commonly used, widely available self-prescribed products.[2,3] Improving overall health and maintaining health are frequently cited reasons for supplement use.[4] Nutritional gaps are commonly present in the general population and deficiencies in micronutrients may lead to serious health problems.[4] Nutritional counselling and guidance around supplementation are important services provided by healthcare practitioners, such as naturopathic doctors, in the prevention and treatment of non-communicable and communicable diseases.[2,5] Older people, immunocompromised people and those with underlying chronic conditions, all of whom are commonly associated with nutritional deficiencies, are at higher risk of developing critical forms of COVID-19, despite vaccination.[6,7] A shift in consumer behaviour reflected research findings that mineral supplementation may contribute to the prevention and treatment of COVID-19, with a switch from mineral supplementation for treatment of viral infections (curative) to preventive use based on their immune enhancing properties.[5,8,9] Forty-three percent of US consumers increased their intake of supplements with the intent of improving their immune function and wellness benefits during the COVID-19 pandemic. In China, 37.7% of survey participants reported the use of certain supplements to cope with COVID-19.[10]

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There are numerous studies focusing on the relationship between influenza-associated mortality, the incidence and duration of acute respiratory infections (ARIs) and baseline nutritional status.[11] Iron, zinc, magnesium, and selenium deficiencies are modifiable risk factors for poor immunogenicity and vaccine failure. Supplementation in institutionalized elderly patients resulted in higher antibody titres to the influenza vaccine.[11,12] Supplementation could address immunosenescence and baseline inflammation in the elderly, resulting in decreased infection rates and improved responses to COVID-19 vaccines.[11-13] Patient education by practitioners is important to drive behaviour patterns of supplementation as a large-scale preventive tool, especially in high-risk populations. Informed decisions by self-medicating consumers should be guided by evidence-based research. This will help them to avoid adverse effects from prolonged use of high-dose minerals, polypharmacy, and drug interactions. High-dose adjunctive micronutrient supplement use should be encouraged only in clinical settings where monitoring for toxic effects can take place.[10,14] Critically, inappropriate supplementation of ineffective minerals may delay the commencement of more effective treatment and allow COVID-19 progression.[14]

There is a need for research to provide an overview of the value of natural health products (NHPs) with regard to COVID-19. The objective of this study was to review the synthesis of literature on the use of minerals for the prevention and or treatment of COVID-19 and the management of COVID syndrome. Therefore, we conducted this comprehensive umbrella review to describe the published peer-reviewed literature and identify key areas to consider for research and clinical application.

METHODS

Design

Details of the ongoing living review preceding this study have been published in the Interim Report for the Live Review of Natural Health Products Researched with Respect to the COVID pandemic.[15] The live review provides a continually updated and evolving summary of the available evidence. Updated information on the live review can be accessed on the World Naturopathic Federation website[16]: https://worldnaturopathicfederation.org/live-review-of-natural-health-products-nhps-researched-with-respect-to-the-covid-pandemic/. This study follows on from the interim report on the Living Systematic Review and forms part of a larger umbrella review on NHPs. The umbrella review provides a synthesis of the research included in the Live Review. The focus of this study is on the use of minerals with respect to the COVID pandemic.

Search Strategy

Reviews included in this study were identified by the Live Review, which followed the Cochrane Guidelines for Living Systematic Reviews.[16,17] Monthly literature searches were conducted of the PubMed and Google Scholar databases between May 2022 and May 2023. The following search algorithm was used; "natur*," "herb*," "nutraceutical," "botanical," "medicinal plant," "Ayurvedic," "Chinese medicine," "herbal patent formula," "vitamin," "mineral," combined with "prevention," "prophylaxis," "deficiency," "treatment," "management," and "*COVID*," "Coronavirus," "SARS-CoV-2." Terms cited in the literature such as individual herb names, compounds, vitamins, and minerals were included in the search. Identified articles were categorized based on the type of review, namely systematic, narrative, meta-analysis, and other.

Inclusion and Exclusion Criteria

This study includes systematic and narrative reviews included in the Live Review. Narrative reviews were reviewed by two independent reviewers and appraised for methodological quality using the Scale for The Assessment of Narrative Review Articles (SANRA) guidelines.[18] Inclusion criteria for narrative reviews was if they had a scientific reasoning score of 1 and 2 and an overall total score of >5. Individuals providing data extraction were blind to the quality assessment criteria. Systematic reviews were reviewed by two independent reviewers and appraised for methodological quality using A Measurement Tool to Assess Systematic Reviews (AMSTAR) guidelines.[19] Systematic reviews were included if the answer was "Yes" or "Partially yes" to question 9 and "Yes" to question 13 of the AMSTAR checklist.[20] Individuals performing data extraction were blinded to the quality assessment criteria for inclusion or exclusion of studies.

Any discrepancies for the inclusion of criteria were verified by a separate reviewer. Data was extracted only for those studies that were statistically significant and only for outcomes relevant to NHPs or natural therapies. A reference overlap analysis was used for the systematic reviews ensuring results were not over amplified for any single study included. Extracted data was captured and collated in online spreadsheets.

Data Extraction

Data extraction for the narrative reviews was performed as follows: study number, study identification—American Medical Association (AMA) style, author(s), date, journal, country/world region, review objective, details of any search conducted, area of focus (prevention, treatment, post-COVID), single category/mixed category, doses, therapeutic considerations including properties (anti-inflammatory, antiviral, etc., available at https://www.ndhealthfacts.org/wiki/Action_of_Herbs), associations (relationship to other vitamins/minerals, pathways), therapeutic considerations, additional clinical notes. Automation tools were not used in this process.

Data extraction for systematic reviews was performed as follows: study number, study identification—AMA reference style, author(s), date, journal, area of focus (prevention, treatment, post-COVID), review objective, review type (narrative, systematic, or meta-analysis), search date, search databases, study designs included, country of included studies, publication date range, tools for assessment of risk of bias, methods of synthesis/analysis, interventions relevant to NHPs/natural therapies, outcomes measured, number of studies included in the review, number of participants, age of included participants, sex of participants (percentage that are female), results/findings, heterogeneity (only if a meta-analysis). Automation tools were not used during data extraction.

RESULTS

After the initial literature search and screening of the studies included in the Live Review was performed, 93 narrative reviews and 308 systematic reviews on NHPs were identified (Table 1). Of those, 12 narrative reviews and 32 systematic reviews pertained specifically to the use of minerals.

Narrative Reviews

Although narrative reviews are not usually included in umbrella reviews, they provide additional resources as well as an overview of the topic.[21] Of the 12 narrative reviews initially identified, eight (67%) remained for the final umbrella review after exclusion criteria were applied (Table 2). Based on the country of residence of the first author, two of the reviews were conducted from the USA,[22,23] while the others include one each from Australia,[24] Iran,[25] Italy,[26] Romania,[27] Serbia,[28] and Poland.[29] The minerals reviewed were copper,[25,27,28] iron,[28] magnesium,[25] selenium[23,25-29] and zinc.[22-28] Five of the narrative reviews focused on both prevention and treatment,[22,24-27] two on prevention,[23,29] and one on treatment.[28]

Systematic Reviews

Of the 32 systematic reviews initially identified, 14 (44%) remained for data extraction after the AMSTAR analysis. Of those, 12 (86%) were included in the umbrella review after all exclusion criteria were applied and duplicates removed (Table 3). Based on the country of origin of the first author, reviews were conducted from five World Health Organization (WHO) regions; the Eastern Mediterranean region (Iran[30]), the European region (Greece,[31] Italy[32], Netherlands,[33] Poland,[34] United Kingdom[35]), the Region of the Americas (two studies in the USA[36,37]), the South-East Asian region (Sri Lanka[38]), and the Western Pacific region (Australia,[39] China,[10] Singapore[40]). The mineral therapies reviewed were calcium,[31,40] iron,[33,35,40] magnesium,[31,40] phosphorus,[31] selenium[30-33,35,38,40] and zinc,[10,31-34,35-40] with zinc being the most frequently represented mineral in the research. Six mineral reviews focused on the use of minerals for the prevention[30,31,33,35,39,40] of

TABLE 1 Initial Findings of the Literature Search and Screening against Inclusion and Exclusion Criteria

	NR – Pre	NR – Post	% of NR included	SR – Pre	SR – Post	% of SR included
Vitamins	19	17	89.5%	92	59	64.1%
Minerals	12	8	66.7%	32	14	43.8%
Herbal	24	25	104.2%	99	51	51.5%
Nutrition	13	9	69.2%	1	5	500.0%
Other NHPs	16	15	93.8%	43	20	46.5%
Other Therapies	9	8	88.9%	41	15	36.6%
Total	93	82	88.2%	308	164	53.2%

NR – Pre=narrative reviews before screening against inclusion and exclusion criteria; NR – Post=narrative reviews after screening against inclusion and exclusion criteria; SR – Pre=systematic reviews before screening against inclusion and exclusion criteria; SR – Post=systematic reviews after screening against inclusion and exclusion criteria; NHP=natural health product.

TABLE 2 Main Characteristics of Included Narrative Reviews, Micronutrients and Area of Focus

Study No.	First Author, Year	Country	WHO Region	Mineral	Area of Focus
260	Notarbartolo et al., 2022[26]	Italy	EUR	Zinc Selenium	Prevention, Treatment
262	Pisoschi et al., 2022[27]	Romania	EUR	Copper Selenium Zinc	Prevention, Treatment
290	Prasad et al., 2022[22]	USA	AMR	Zinc	Prevention, Treatment
300	Ahvanooei et al., 2022[25]	Iran	EMR	Copper Magnesium Selenium Zinc	Prevention, Treatment
331	Paudel et al., 2022[24]	Australia	WPR	Zinc	Prevention, Treatment
343	Kieliszek et al., 2022[29]	Poland	EUR	Selenium	Prevention
344	Djordjevic et al., 2022[28]	Serbia	EUR	Copper Iron Selenium Zinc	Treatment
348	Bell et al., 2023[23]	USA	AMR	Selenium Zinc	Prevention

AFR=African region; AMR=region of the Americas; EMR=Eastern Mediterranean region; EUR=European region; SEAR=South-East Asian region; WHO=World Health Organization; WPR=Western Pacific region.

TABLE 3 Main Characteristics of Included Systematic Reviews, Micronutrients and Area of Focus

Study No.	First Author, Year	Country	WHO Region	Mineral	Area of Focus
502	Hunter et al., 2022[39]	Australia	WPR	Zinc	Prevention
511	James et al., 2021[35]	United Kingdom	EUR	Iron Selenium Zinc	Prevention
522	Wang et al., 2021[40]	Singapore	WPR	Calcium Iron Magnesium Selenium Zinc	Prevention
532	Vlieg-Boerstra et al., 2021[33]	Netherlands	EUR	Iron Selenium Zinc	Prevention
542	Pechlivanidou et al., 2022[31]	Greece	EUR	Calcium Magnesium Phosphorus Selenium Zinc	Prevention
556	Fakhrolmobasheri et al., 2021[30]	Iran	EMR	Selenium	Prevention
608	Jayawardena et al., 2020[38]	Sri Lanka	SEAR	Selenium Zinc	Treatment
609	Feng et al., 2021[10]	China	WPR	Zinc	Treatment
624	Balboni et al., 2022[32]	Italy	EUR	Selenium Zinc	Treatment
625	Abioye et al., 2021[36]	USA	AMR	Zinc	Treatment
706	Beran et al., 2022[37]	USA	AMR	Zinc	Treatment
756	Olczak-Pruc et al., 2022[34]	Poland	EUR	Zinc	Treatment

AFR=African region; AMR=region of the Americas; EMR=Eastern Mediterranean region; EUR=European region; SEAR=South-East Asian region; WHO=World Health Organization; WPR=Western Pacific region.

COVID-19 and five on treatment.[10,32,34,36-38] The included systematic reviews cited 72 primary publications in 106 unique instances across all reviews, representing a Corrected Cover Area (CCA) of 4.545% (CCA = 108-72 / (72x12)-72 = 0.04545), indicating a slight overlap (see Table S1 in the supplemental material).

Calcium

No narrative reviews discussed calcium, for either the prevention or treatment of COVID-19. Both systematic reviews that included calcium assessed the impact of micronutrient deficiencies on intensive care unit (ICU) admissions and risk of death.[31,40] One systematic review of 33 papers comprised of interventional (randomized controlled trials) and observational (cohort studies, cross-sectional studies, and case-controlled studies) studies, with relevant comparator groups and a total of 360,346 participants, assessed the impact of deficient micronutrients on the prevention of respiratory infection and on ICU admissions and risk of death. The paper concluded that calcium deficiency was not associated with clinical severity.[40] The second systematic review, which included 31 papers with 8,624 adult participants (mean age 61), found that calcium was a prognostic factor for COVID-19 patients. Normocalcemia and higher calcium blood levels were associated with higher survival rates. Low calcium blood levels were identified as a prognostic marker for the development of severe disease, significantly correlated with low chest computed tomography (CT) scores and higher numbers of ICU admissions.[31]

Copper

The three narrative reviews on copper highlighted the lower plasma levels found in COVID-19 cases[27] and its antimicrobial,[25,28] antiviral, antioxidant,[25,27,28] and immune-modulating[28] properties. The metabolic contribution of copper as an antioxidant enzyme[27] was also discussed. The proposed role of copper in the prevention and treatment of COVID-19 was indicated as an antioxidant defense.[25,27,28] No systematic reviews included results for copper.

Iron

One narrative review highlighted iron's antimicrobial and inflammatory modulating properties.[28] Djordjevic et al.[28] emphasized iron's metabolism as being important to COVID-19's pathogenesis due to its role as a prooxidant and its role in the induction of ferroptosis. Three systematic reviews reported on iron. James et al.[35] discussed the role of iron deficiency, anemia, and iron concentration in iron-dependent host cellular processes involved in viral replication, pulmonary response to hypoxic stress, and the role of iron in inflammation and immune impairment. One systematic review highlighted varied results of iron supplementation on the incidence of respiratory tract infection; two included studies showed an increased risk and five studies showed no significant effect.[33] Depending on what iron level biomarker was measured, both increased and decreased risk of mortality were reported.[40] Both Wang et al.[40] and Vlieg-Boerstra et al.[33] highlighted increased ferritin levels in patients with more severe cases of COVID-19 versus in those with milder cases.

Magnesium

One narrative review on magnesium discussed its role in shaping the innate and adaptive immune systems and its immune-modulating and anti-inflammatory properties; low magnesium levels activate inflammation, sensitize sentinel cells to harmful agents, and activate phagocytes.[25] One systematic review reported that COVID-19 survivors had significantly higher serum levels of magnesium and other nutrients at hospital admission than those who did not survive.[31] Another systematic review, which reviewed the effect of micronutrient supplementation or deficiency on novel coronavirus incidence and severity, did not find any significance to magnesium nutritional levels.[40]

Phosphorus

None of the narrative reviews reported on phosphorus. The one systematic review concluded that COVID-19 survival was associated with high blood levels of nutrients which included phosphorus.[31] Significantly low phosphorus blood levels were commonly detected in severe COVID-19 disease. Significantly more patients with low phosphorus were admitted to ICU versus patients with normal levels of phosphorus. Low phosphorus levels were significantly correlated with low chest CT scores.

Selenium

Six narrative reviews discussed significant findings for selenium in the prevention and treatment of COVID-19 and the positive implications of supplementation.[23,25-29] Selenium is an important immune modulator,[25-28] antioxidant[26-28] and antiviral.[27,28] Lower blood concentrations of selenium were reported in COVID-19–infected adults versus non-infected adults,[25,26,29] and higher mortality rates were noted in selenium-deficient patients.[23,27] Deficiency was reported to lead to increased risk of infection[27,28] and virulence of SARS-CoV-2.[27,28] Supplementation has been proposed to improve selenoprotein profile, alleviate viral-induced oxidative stress, organ decay, and cytokine storm, and hinder the mutation to virulent variants of SARS-CoV-2.[27,29]

Four systematic reviews reported significant findings for selenium.[30,31,38,40] Selenium's anti-inflammatory, immune-boosting, antiviral, and antithrombotic effects were reported.[30,38] Selenium deficiency was associated with worse clinical outcomes,[30] increased mortality risk,[30,31,40] and higher SARS-CoV-2 viral genome mutation rate,[30] and selenium levels in COVID-19 patients were lower than in healthy individuals.[30,31] Studies reviewed by Jayawardena et al.[38] showed mixed results for selenium and other multivitamin and mineral supplementation on the incidence and severity of ARIs in well-nourished, healthy adults.[38] Randomized controlled trials showed beneficial and detrimental effects of selenium supplementation in healthy adults with suboptimal selenium concentrations on the immune response to the influenza vaccine.[38] Beneficial effects included a dose-dependent increase in interleukin (IL)-8, IL-10, T-cell proliferation, and selenoprotein S (SEPS1) gene expression. Detrimental effects included lower granzyme B content of CD8 cells.[38] Long-term supplementation of selenium sulphide (100 ug) and zinc sulphate (20 mg) in institutionalized elderly participants reduced the incidence of respiratory tract infections and increased antibody titres in response to influenza vaccines.[38]

Zinc

One narrative review which included zinc did not report any evidence-based properties associated with COVID-19.[23] The six remaining narrative reviews that discussed zinc mentioned the following potential benefits and properties: antioxidant,[22,24,26,27] anti-inflammatory,[22,24-27] immunomodulatory,[22,24,26,27] and antiviral.[22,24-28]

Several narrative reviews highlighted zinc's role in modulating inflammatory cytokines,[24,26,27] its ability to interfere with viral entry into the host's cell,[24,26,27] its ability to decrease viral replication and coronavirus RNA polymerase,[24,26-28] and its effect on ACE-2 receptor activity.[26] Its ability to alleviate cytokine storms was discussed.[27] Zinc's ability to inhibit nuclear factor (NF)-κB signaling, its involvement in the recruitment, enhancement, and promotion of the activity of neutrophils, CD4+, and CD8+ T cells, and its triggering of IL-2 receptor expression were also discussed.[24,27] Deficiency was shown to enhance the production of proinflammatory cytokines (IL-1β, IL-6, and tumour necrosis factor [TNF]-α) and negatively affected the modulation of natural killer cells.[22,27] Deficiency was also shown to increase the incidence of acute respiratory infections and was linked to higher rates of complications, prolonged hospital stays, and increased mortality.[22,23,28]

Zinc supplementation was reported to reduce the incidence of infection in children and the elderly.[22,38] Zinc supplementation in adults, combined with nitazoxanide, ribavirin, and ivermectin, was shown to clear SARS-CoV-2 from the nasopharynx in a shorter time period than symptomatic treatment alone (phase I clinical trial).[26] It improved gustatory sensitivity (randomized clinical trial) and lowered the duration of anosmia/hyposmia (prospective clinical trial, 220 mg zinc sulfate equivalent to 50 mg elemental zinc twice daily) when compared with those who did not receive zinc supplementation or therapy.[26] Zinc treatment showed decreased rates of mortality (three retrospective cohort studies, one randomized controlled study), a lower incidence of ventilation usage and ICU stays (one retrospective cohort study), as well as decreased hospital stay durations (one retrospective cohort study) and symptom severity (one retrospective review study, one non-randomized controlled study).[22]

Of the 11 systematic reviews that included zinc, five investigated the impact of zinc nutritional status on the risk of infection and rate of recovery.[10,32,33,36,39] Zinc supplementation was investigated as a sublingual or intranasal spray, oral supplementation, and intravenous administration.[36]

Key findings include a reduction of symptom severity score,[39,40] lower COVID-19 in-hospital mortality,[31,34,35] and increased frequency of being discharged home when zinc was combined with azithromycin and hydroxychloroquine.[35] Zinc deficiency was associated with higher IL-6, a greater number of complications,[31] higher incidence,[40] and poorer outcomes.[31] One review found that sublingual zinc did not prevent clinical colds,[39] and another review found that zinc sulfate is likely to shorten the duration of olfactory dysfunction.[10] One systematic review found zinc supplementation may be beneficial in children under five by promoting an increase in interferon-gamma (IFN-γ) and IL-2.[38-40] Zinc, along with selenium and other nutraceuticals, vitamins, and probiotics, was shown to have an immune-enhancing effect important in preventing or treating viral infections.[10,38] There were mixed results as Beran et al.[37] and Balboni et al.[32] did not find any significant associations for zinc and the prevention and/or treatment of COVID-19.

DISCUSSION

As a part of the larger umbrella review on NHP research with respect to the COVID pandemic, this comprehensive review reports evidence on minerals such as calcium, iron, magnesium, phosphorus, selenium, and zinc. Our findings demonstrate that micronutrient status is an important modifiable risk factor in the prevention and/or treatment of COVID-19. Important factors highlighted include the detrimental effects of low serum levels of certain minerals on COVID-19 severity and disease outcomes as well as the possible benefits of supplementation.[30,31,38,40]

The association between nutrition and infection is well documented.[42] Minerals such as selenium and zinc, along with other nutraceuticals and probiotics, have shown immune-enhancing effects for either preventing or treating viral infections such a polio, HIV and hantavirus, and influenza-like illness,[30,35,38] and may contribute to the prevention and treatment of COVID-19.[5,8,30,35,38] Minerals' status has the potential to influence susceptibility to the risk of COVID-19 infection through its role in immune functioning, shaping the innate and adaptive immune systems.[30,35,38] Copper, iron, magnesium, selenium, and zinc's immune-modulating properties are well established.[22,24-28] These minerals play an integral role in sensitizing and activating sentinel cell tissue, such as resident macrophages or dendritic cells, and innate immune functions mediated by natural killer cells and neutrophils in response to viral threats.[25-43]

It is well established that micronutrient supplementation has the ability to lower the incidence of ARIs and lessen their duration and severity.[8] Based on our findings, supplementation is recommended for COVID-19 patients with mineral deficiencies.[30,31,38,40] Healthcare providers should recommend supplementation only in cases where low serum levels are suspected or have been confirmed. Infections such as COVID-19 may adversely influence mineral status, which should be a consideration when managing patients with no history of deficiency.[42] Almost 20% of the global population is affected by zinc deficiency.[36] This is a consideration when interpreting results from Beran et al.,[37] Fakhrolmobasheri et al.,[30] Jayawardena et al.,[38] Pechlivanidou et al.,[31] and Wang et al.,[40] as these reviews included studies carried out in regions where zinc deficiency is endemic. The same consideration should be applied to results obtained from studies conducted in regions where selenium and iron deficiencies exist. No benefit of supplementation in COVID-19 patients with non-deficiency was found, and therefore supplementation in this population is not recommended.[31] Patient education should include avoiding high doses of minerals, as they can be toxic.[44] For example, excess amounts of selenium at doses above 0.9 mg/day may lead to hair loss, fatigue, gastrointestinal disorders, peripheral neuropathies, and increasing risk for type 2 diabetes.[30-44] Magnesium doses in excess of 400 mg/day can cause diarrhea, and iron can cause constipation, nausea, and vomiting and reduce zinc uptake. Zinc toxicity can result in nausea and vomiting and immunosuppression, which would increase susceptibility to COVID-19 infection.[44]

This umbrella review has shown that minerals have antiviral properties (copper, selenium, zinc) and antimicrobial properties (copper, iron). Selenium was shown to hinder mutation of SARS-CoV-2 to more virulent variants.[27,28,30] These outcomes are in line with other research that indicates that nutritional status affects viral mutation and increased virulence as in the case of severe acute respiratory syndrome (SARS), acquired immune deficiency syndrome (AIDS),[45] swine-fever, dengue virus, influenza virus, and norovirus, among others.[46] Once viral mutations occur, patients with normal nutritional status become vulnerable to newly virulent viruses.[45] The public health implications are increased rates of the infection ($R_0 > 1$), higher patient loads and hospital admissions, as well as a threat to vaccine effectiveness, since mutations could give rise to vaccine-resistant strains over time.[47] Our understanding as healthcare practitioners of the underlying mechanisms and potential interventions for the SARS-CoV-2 virus are continuing to evolve. Novel therapies for the prevention and treatment of COVID-19 will continue to emerge. We recommend future studies include as-yet unstudied minerals for their potential use in the COVID pandemic.

High-risk populations associated with impaired immunity, such as the aged, immunocompromised, those with chronic disease, and those with nutritional deficiencies, are at a higher risk for COVID-19 infection and may have more severe disease outcomes.[6,7,48,49] This is supported by previous research showing positive outcomes for mineral supplementation in obese patients, resulting in improved immune functioning.[49] This umbrella review found that normal blood level ranges of calcium, magnesium, selenium, and zinc were associated with reduced disease severity and improved survival.[22,31] Ventilation use and ICU stays were also reduced,[22] as was number of days spent in hospital.[22,23,28] COVID-19–related hospitalizations place a tremendous burden on public healthcare systems,[50] and hospitalization can have negative psychological and socio-economic effects on patients.[51,52] Many patients are only partially insured or have no medical insurance which covers hospitalization or costs associated with COVID-19.[53] Hence interventions which reduce the severity of COVID-19 have a wider reaching societal impact than just preventing and or treating the illness itself.

The majority of viruses do not cause severe disease or severe inflammation in humans.[54] But we know that inflammation is a key feature of COVID-19.[55] Severe to critical illness in COVID-19 patients is linked to an excessive systemic inflammatory response that may result in lung damage, respiratory failure, the development of acute respiratory distress, and organ damage.[22] Long COVID symptoms are linked to inflammation, and more than half of patients affected by long COVID exhibit persistent inflammatory protein signatures (TNF, IL-6, IFN-γ).[56] This has an impact on the global burden of disease, as chronic inflammation and unchecked oxidation are etiological factors in the development of non-COVID-19–related diseases.[57] The use of minerals as an effective treatment approach to control COVID-19–induced inflammation and oxidation is supported by the findings of this umbrella review. There were significant findings to support zinc and selenium's anti-inflammatory and antioxidant properties, and further research is warranted to establish recommendations for standardized interventions for their use as stand-alone and/or adjuvant therapies in clinical settings. Zinc sulphate has also been found to improve sleep duration, efficiency, and latency. Approximately 74.8% of people with COVID-19 have sleep-related problems. It is thought that underlying inflammation is the cause of COVID-19–related sleep disturbances. Zinc could be useful in treating sleep disturbance related to acute COVID-19 infection as well as persistent sleep disturbances associated with long COVID cases or post-COVID syndrome.[58] Easily accessible mineral supplementation can be used as prevention therapy, especially in cases of deficiency, or as complementary self-treatment in mild cases of COVID-19.[11,12]

Addressing nutritional deficiencies could be a cost-effective, low-risk strategy in the prevention and management of infectious disease.[42,59,60] The primary preventive strategy for COVID-19 is the global vaccine program and its success relies on individuals' ability to mount an appropriate vaccine response.[59] In vulnerable populations who are prioritized to receive vaccines, such as the elderly or those with comorbidities, deficiency is common. Micronutrient deficiencies may affect vaccine responses. Selenium supplementation was shown to improve the vaccine response to a live, attenuated polio vaccine in healthy adults from the United Kingdom who were marginally selenium deficient. This was coupled with a lowered incidence of genetic mutation in recovered excreted polio viruses.[61] Anemia and iron deficiency were associated with reduced antibody responses to diphtheria, pneumococcal, and pertussis vaccinations, and a multi-nutrient supplementation containing iron improved the immune response to measles vaccinations in Kenyan infants when compared with the use of multi-nutrient iron-free powder.[59] Acute viral infection leads to functional iron deficiency and anemia of inflammation, and approximately 80% of hospitalized patients in Austria were functionally anemic at admission.[35] Calcium deficiency was associated with more severe COVID-19 disease progression.[31] Hence COVID-19 patients should be screened for deficiencies, which should be addressed to potentiate improved clinical outcomes. Prophylactic screening should be considered for at-risk populations. In 2020, the global dietary supplement market, which includes NHPs, had a market value of approximately US$220.3 billion. There is a need for high-quality research to produce clear, consolidated guidelines on the use of minerals as adjuvant therapy in clinical settings or over-the-counter treatments for the prevention and treatment of COVID-19 for widespread dissemination among healthcare practitioners and the general public.[10]

This study had limitations. No raw data was analyzed as this was beyond the scope of this review. Results were often based on highly heterogeneous effect sizes and therefore yielded conflicting outcomes.[38] There was a lack of information on therapeutic dosing, and when available, these differed vastly between studies.[31,38] Many of the narrative reviews referred to the same pool of studies, which is to be expected until the body of research expands over time. Many preclinical studies, animal-based models and *in vitro* studies were included.[38] It is difficult to infer recommendations for human use from such studies. Safety and efficiency in humans also remain inconclusive.[38] Mixed associations with outcomes could be attributed to the use of different biomarkers.[40] Confounding variables were not addressed by this review. Many of the study participants included in the reviews were elderly. Malnutrition and mineral deficiencies (zinc and selenium), which are common in the elderly,[62] and increasing age as an independent variable,[63] may result in impaired immune functioning, which is associated with increased morbidity and mortality in COVID-19. The prevalence of malnutrition and mineral deficiencies in people receiving long-term care or in hospitalized patients is well established.[60] Wang et al.[40] and Pechlivanidou et al.[31] identified and recruited participants from hospitals, clinics, and patient registries. The significant outcomes in these reviews were ICU admissions and the risk of death, both of which could have been confounded by pre-existing mineral deficiencies.

A strength of this study is that a team of reviewers conducted all of the tasks, reducing the risk of errors and inconsistencies. Another strength of this study is that a Corrected Cover Overlap was calculated for the systematic reviews, ensuring significant results were not overstated.[64] Almost all of the studies included in our review had a low risk of bias based on quality assessment. Evidence drawn from peer-reviewed publications employing study designs that include comparison to adequate control groups, such as randomized controlled trial designs, are increasingly called for by critics of complementary approaches to health care and from those who hope to enable evidence implementation.[65-68] It is our hope that this review of minerals in the context of NHP use for the prevention and treatment of COVID-19 will enable evidence implementation in clinical practice.

CONCLUSION

Reducing mineral deficiencies for the prevention of COVID-19 should be viewed as a public health priority. Supplementation of certain minerals, such as selenium, iron, and zinc, in those with clinical deficiencies could lead to improved COVID-19 outcomes. Further research should be undertaken on these minerals to ascertain efficacy, safety, and the optimum dose ranges for therapeutic effect with the least potential for side effects, ideally in randomized trials among COVID-19 patients.[36]

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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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SUPPLEMENTAL MATERIAL

Supplemental material linked to the online version of the paper at https://doi.org/10.54434/candj.164:

- Table S1

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APPENDIX 1: GLOSSARY OF TERMS

AIDS	acquired immune deficiency syndrome
AMA	American Medical Association
AMSTAR	a measurement tool to assess systematic reviews
ARI	acute respiratory infection
CCA	Corrected Cover Area
COVID	coronavirus disease
CT	computed tomography
ICU	intensive care unit
IL	interleukin
IFN-γ	interferon-gamma
NHP	natural health product
SANRA	scale for the assessment of narrative review articles
SARS-CoV-2	severe acute respiratory syndrome of the coronavirus-2
SEPS1	selenoprotein S
TNF	tumour necrosis factor
WHO	World Health Organization