Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Narrative Review

Micronutrients for potential therapeutic use against COVID-19; a review

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SUMMARY

Background: SARS CoV-2 has caused a pandemic that has challenged both clinicians and researchers in finding an effective treatment option. Currently there only exists a two series vaccine that has a high efficacy in preventing infection. There is no standard effective treatment against SARS CoV-2 however several nutraceuticals such as melatonin, zinc, selenium, vitamin C and vitamin D are being proposed as prevention and treatment options.

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (Sars-CoV-2) is a novel virus which originated in Wuhan, China in December 2019. Sars-CoV-2 causes coronavirus disease (COVID-19) and has caused a pandemic which estimates 106,871,361 cases and 2,332,163 deaths thus far [1]. With a pandemic of this magnitude and new strains being found which are more infectious and lethal, there is a strong need for treatment and more over prevention of infection [2].

Although a vaccine does hold promise with prevention of new cases of COVID-19, there is currently no agreed upon treatment for patients with COVID-19 except for supportive care [3,4]. The COVID-19 vaccine has provided a respite decreasing the infectious rate of COVID-19, as the Pfizer/BioNTech vaccine was reported to be 95% effective after two doses, and 52% effective after the first dose alone. The Moderna vaccine was reported to be 94.1% effective after two doses [3,4]. Although there are more developed and available for the public, this high percent of effectiveness is used to demonstrate the promise a vaccine has.

Regarding treatment for an active infection, Remdesivir is an anti-viral agent which early on showed benefit in hospitalized patients however, recently, the use of remdesivir was shown not to improve patient outcomes in hospitalized patients [4]. Bamlanivimab and REGEN-COV are monoclonal antibodies which have a reduction in viral load neutralization and does show promise, however its use is limited to patients in an outpatient setting, who do not require oxygen and have several risk factors [5]. Given the current state of treatment options, other modalities of treatment such as nutraceuticals have been investigated as potential therapies for preventing or treating COVID19. The aim of this review is to discuss specific micronutrients such as melatonin, zinc, selenium, vitamin C and vitamin D and their evidence behind their efficacy in treating or preventing COVID-19. Micronutrients as a potential therapy for COVID-19 has gained attention recently due to their anti-inflammatory properties, cost effectiveness, availability to the public and relative safety.

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2. Discussion

SARS-CoV-2 is a non-segmented, enveloped, positive-sense RNA virus which targets the nasal and bronchial epithelium of host cells [6]. SARS-CoV-2 enters these cells via a spike protein by attaching onto angiotensin-converting enzyme 2 [ACE2] receptors whereby it replicates, forming new viral structures which are released from the host cell to continue this process [7,8]. Since nasal epithelial and bronchial cells have a high expression of ACE2 receptors, SARS-CoV-2 targets these cells and begins the replication cycle here. In most cases, there is a local immune response via interferon-beta [IFN-β] and C-X-C motif chemokine ligand 10 [CXCL-1O] which results in upper respiratory tract infection and produces symptoms such as cough, fever and rhinorrhea [8]. This local immune response usually resolves the infection, however in severe instances, the infection progresses, and the virus infects type II alveolar cells. Infection of these cells propagates and destroys these cells which results in diffuse alveolar damage [9]. During this phase, multiple interleukins and cytokines such as IL-1, IL-2, IL-6,IL-8,IL-10, IFN-β, CCL3, IP-10 and TNF-α are released and induces a "cytokine storm" [10]. The "cytokine storm" attracts neutrophils, CD4 helper and CD8 cytotoxic cells which fight the infection but in doing so produce a constant inflammatory state. The inflammatory response promotes apoptosis and necrosis of the surrounding tissue which then induces further inflammation. This then damages both type I and II alveolar cells and as a result increases permeability of blood vessels and subsequently causes acute respiratory distress syndrome (ARDS) [9,10].

Given the pathophysiology of COVID19, selecting micronutrients that inhibit any of these pathways would be beneficial for therapy in treating or preventing a COVID-19 infection [Table 1]. Specific micronutrients that have received much attention are melatonin, zinc, selenium, vitamin C and vitamin D in the prevention or as a therapy against a COVID-19 infection [Table 2].

2.1. Melatonin

Melatonin is produced by the pineal gland and released at nighttime to regulate the sleep—wake cycle and blood pressure [11]. Melatonin also has a role in the immune system as it has anti-inflammatory properties and immune modulation properties [11]. Regarding its anti-inflammatory properties, melatonin has been shown to down regulate pro-inflammatory cytokines such as IL-2,6,12,TNF-α, IFN-γ and NF-kβ[12,13]. These pro-inflammatory cytokines, especially NF-kβ are all increasing in acute lung injury and in ARDS which occur during an infection with COVID-19 [13]. As an immunomodulator, melatonin increases proliferation of both T and B lymphocytes [14]. A meta-analysis of 22 trials, of varying melatonin doses, showed that melatonin reduced TNF-α and IL-6 levels [15]. Although the doses did vary, the utility of it as a treatment for COVID-19 cannot be extrapolated based on this as an effective dose was not established. Regarding its safety, melatonin is a safe supplement, even in doses of 1 g a day [13]. As a preventative treatment for COVID19, a recent observational study of 26,779 individuals was done by Zhou et al. which showed a 28% reduced likelihood of a positive SARS-CoV-2 laboratory test in all combined populations when adjusting for age, sex, race and other comorbidities [16]. Although it is encouraging as a preventative measure for COVID19, there were several limitations to the study as cited by the authors. One of which was that their data set did not include individuals that were asymptomatic or have minimal symptoms and therefore melatonin use in this group could not be evaluated [16]. Based on these findings, further studies must be done to evaluate the efficacy of melatonin as a preventative treatment, however initial results are encouraging.

Table 1
Summary of mechanism of action of each micronutrient.

Micronutrient	Proposed Mechanism of Action
Melatonin	Down regulates pro-inflammatory cytokines such as IL-2,6,12,TNF-α, IFN-γ and NF-kβ
Zinc	1) Reduces the production of inflammatory cytokines 2) Stimulate CD8+ T cells 3) Inhibits RNA dependent RNA polymerase
Selenium	1) Decreases IL-1β and IL-6 production 2) Decreases platelet formation and potential thrombus formation
Vitamin C	Protects cells against oxidative damage by scavenging reactive oxygen species
Vitamin D	1) Response from innate and adaptive immune system 2) Formation of gap junctions

2.2. Zinc

Zinc is a trace element that is required for the functioning of enzymes, transcription factors, cellular signaling and most pertinent to this topic; immune functioning [17]. Zinc has a role in immune function by acting as an anti-inflammatory agent as well as a signaling molecule in the immune system. As an anti-inflammatory, zinc reduces the production of IL-6 as well as IL-1β which are proinflammatory cytokines [18]. Zinc affects the immune system as an important signaling molecule in the production of IL-2, IFN-Y and IL-12, which stimulate CD8+ T cells [19]. In contrast, patients with zinc deficiency characteristically have a poor immune system response due to a lack of activation of both T helper cells and CD8 T cells as well as a blunted production of IFN-α, due to the absence of zinc [20]. Zinc does have anti-viral properties as in vitro studies have shown that zinc does play a role in inhibiting RNA-dependent RNA polymerase in influenza, RSV and in SARS-coronavirus [21,22]. This study was limited to zinc being coupled with ionophores and it was done in vitro so one cannot extrapolate if it is applicable to SARS CoV-2. The use of zinc as a therapy for COVID-19 is an ongoing area of research and currently there exist only trials for its use against COVID19 [23]. What has been found however, is that patients with COVID-19 had poorer outcomes; as measured by longer hospital stays and an increased mortality, if they had hypozincemia [24,25] and as shown by Jothimani et al., the odds ratio of developing a complication from COVID19 was 5.54 in zinc deficient patients [25]. As a preventative treatment, zinc does increase mucociliary clearance by increasing ciliary beat frequency in respiratory epithelium [26,27]. This could prevent infection as viruses such as SARS-CoV-2 damage ciliary epithelium and can potentiate viral entry and secondary bacterial infections [26]. Zinc is also responsible for preserving tissue barriers, especially in lung parenchyma which prevents viral entry [26]. Although both properties hypothetically show the potential zinc has as an adjunct for prevention, doses of zinc at which these occur have not been established. What is also interesting is that the intake of too much zinc; 300 mg/day for 6 weeks has been shown to impair neutrophil and lymphocyte function [28]. By taking in too much zinc, this can blunt a local immune response and make one more susceptible to infections.

2.3. Selenium

Selenium is a trace mineral which is required for the formation of selenoproteins and selenite, which are used for anti-inflammatories, antioxidants, prevents thrombosis and defense against viral infections [29,30]. The mechanism in which selenium exerts its effect as an antiviral is that it inhibits the enzyme protein

Table 2
Summary of efficacy of treatment and prevention of COVID-19.

Micronutrient	Efficacy of treatment and prevention against COVID-19
Melatonin	**Treatment**: Uncertain at this time however does reduce inflammation **Prevention**: Uncertain however one study should a 28% reduced likelihood of a positive SARS-CoV-2 test [16]
Zinc	**Treatment:** Uncertain efficacy however patients with lower zinc levels have an increased mortality **Prevention**: No efficacy reported so far
Selenium	**Treatment:** Increased recovery rate from COVID-19 infection **Prevention:** No efficacy reported so far
Vitamin C	**Treatment:** No improvement in SOFA, ventilation free days or inflammatory markers however decreased mortality **Prevention:** No efficacy reported so far
Vitamin D	**Treatment**: Potential to reduce cytokine storm formation **Prevention**: No efficacy reported so far

disulfide isomerase; which is responsible for a viral glycoprotein attachment and therefore preventing the virus from entering its host cell [30]. Selenium also decreases IL-1β and IL-6 which pro-inflammatory cytokines [31]. Selenium; specifically selenite decreases platelet formation and potential thrombus formation by decreasing thromboxane A2 and inhibiting vasoconstriction [32]. Knowing this, one can speculate if selenium would have any benefit in COVID-19 patients as COVID-19 increases venous thromboembolism formation [8]. In a study done by Zhang et al., there was a positive correlation found between concentration of selenium in hair and COVID-19 recovery rates; those with higher amounts of selenium had faster recovery times when infected with COVID-19 [33]. Moreover, it was also reported that Enshi, a city of Hubei, China, which had the highest selenium concentration, had the fastest the recovery rate of COVID-19, which was triple that of the rest of the cities sampled [33]. A similar study done in Germany by Moghaddam et al. also showed low blood levels in selenium was associated with a higher mortality in COVID19 patients [34]. These studies only showed correlation and not causation so further investigation would be needed. Selenium does play an important role in the immune system however no data is available on its use as an adjunct for treatment or prevention of COVID-19.

2.4. Vitamin C (Ascorbic acid)

Vitamin C, or ascorbic acid, is a water-soluble essential vitamin that may only be obtained through consumption of nutrient-rich foods [35]. Vitamin C protects cells against oxidative damage by scavenging reactive oxygen species (ROS) and is an essential cofactor for enzymes required in the production of cortisol, vasopressin, and catecholamines [36]. Vitamin C is present in high intracellular concentrations in leukocytes but is rapidly depleted during infection causing a shift in the ratio of antioxidant defenses to oxidant generation. This increase in oxidant generation causes proinflammatory cytokine release and initiation of the inflammatory cascade [35]. Decreased levels of vitamin C have been reported in patients with chronic conditions including diabetes, chronic obstructive pulmonary disease (COPD), and hypertension, all of which are predictors of mortality in COVID-19 infection [37]. Low levels of vitamin C is also widely prevalent among critically ill patients, patients with acute respiratory infections, and patients with acute respiratory distress syndrome [35,36]. Supplementation with high-dose intravenous vitamin C has been demonstrated to be safe and feasible while significantly reducing vasopressor support, limiting organ injury, decreasing the duration of mechanical ventilation, and decreasing ICU stay [36].

In severe cases of COVID-19, a rapid increase in cytokines causes neutrophil sequestration in lung tissues. This “cytokine storm” causes damage to the alveolar capillaries and is the underlying mechanism in acute respiratory distress syndrome (ARDS) [36]. The proinflammatory cytokines, TNF-alpha and IL-1β rapidly increase during acute infection with SARS-CoV-2 and promote increased secretion of IL-6 and IL-8 thereby facilitating the ongoing pro-inflammatory state in COVID-19 infection. Vitamin C is known to counteract the increase in TNF-α and increases the anti-inflammatory cytokine IL-10 that provides a negative feedback on IL-6 [35].

The CITRIS-ALI trial demonstrated that intravenous vitamin C supplementation of 50 mg/kg every 6 h for 96 h did not significantly alter QSOFA scores or levels of inflammatory markers compared to placebo in patients with sepsis and ARDS, but it did significantly improve 28-day all-cause mortality [38]. A recently published, multicenter, double-blinded, randomized controlled clinical trial demonstrated that 12 g of vitamin C infused intravenously two times per day for seven days to patients with severe COVID-19 infection admitted to the ICU did not significantly improve invasive mechanical ventilation-free days, QSOFA scores, or inflammatory markers at 28 days. Consistent with the CITRIS-ALI trial, this study did demonstrate significant improvement in the ICU mortality in the high-dose vitamin C group [36]. These two trials suggest that supplementation with high-dose intravenous vitamin C may provide some benefit in severely ill, vitamin C-deficient patients [35]. However, adverse events in the setting of high-dose vitamin C supplementation in the absence of deficiency justifies caution against advising this as a preventive strategy. Most concerning is the association of high doses of vitamin C with formation of kidney stones, especially among patients with high oxalate levels at baseline [39].

2.5. Vitamin D

Vitamin D is a fat-soluble nutrient that acts as a steroid hormone precursor. Ultraviolet B (UVB) radiation exposure of the epidermis transforms 7-dehydrocholesterol to cholecalciferol, the circulating precursor of vitamin D [35]. Vitamin D is also present in foods and supplements as ergocalciferol and cholecalciferol, both of which undergo further metabolism in the liver, and then in the kidneys to the active form 1,25-hydroxyvitamin D [35,39]. Risk factors for Vitamin D deficiency include age, smoking, obesity, hypertension, and diabetes [40]. Epidemiological observations of influenza A epidemics have implicated vitamin D as the driver of the “seasonal stimulus” hypothesis, suggesting that peak influenza cases in the winter months coincides with reduced sun exposure leading to reduced synthesis and serum levels of vitamin D affecting immune function [39].

Both innate and adaptive immune responses are dependent upon vitamin D. Cell physical barriers are improved through vitamin D-enhanced production of tight, gap, and adherens junctions [40]. The expression of antimicrobial peptides cathelicidin and defensins maintains tight and gap junctions between tracheobronchial epithelial cells, and in their absence or dysfunction, the risks of infection and pulmonary edema are increased [35].

Vitamin D may decrease or prevent cytokine storm in patients with COVID-19 through immunomodulatory effects on production of pro-inflammatory cytokines [40]. Pro-inflammatory cytokines are produced by T helper type 1 cells, and vitamin D reduces this cell response by increasing T helper type 2 cell response that produce anti-inflammatory cytokines [35].

Low vitamin D levels have been consistently associated with acute respiratory infections in observational studies, and the risk of ARDS may also be increased in this setting [39]. Vitamin D deficiency has been consistently demonstrated in COVID-19 patients and is associated with poorer outcomes [41]. Supplementation of Vitamin D has been suggested to reduce mortality in COVID-19, but trial evidence has been inconsistent to date [39]. While large-scale randomized controlled trials are still needed to support specific recommendations, expert opinion supports avoidance of vitamin D deficiency, and supplementation in accordance with government guidelines in the setting of deficiency and COVID-19 infection [42].

3. Conclusion

COVID-19 has posed a great challenge to health care officials and clinicians worldwide. Currently, the vaccine against SARS CoV-2 offers the protection against infection against this virus. Although preliminary data is encouraging regarding the use of nutraceuticals, further research is needed in the efficacy of these agents.

Contributions

Dr. Richard Giovane: Conceptualization, data curation and writing original manuscript.

Dr. Stephanie Kinsley: Data curation and writing original manuscript.

Dr. Emily Keeton: Review and editing manuscript.

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Declaration of competing interest

The Authors did not report any potential conflicts of interest.

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