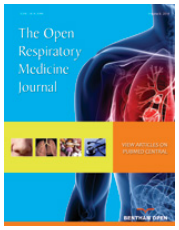

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REVIEW ARTICLE

Novel and Controversial Therapies in COVID-19

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Abstract:

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the coronavirus disease (COVID-19) pandemic, which has led scientists all over the world to push for the identification of novel therapies for COVID-19. The lack of a vaccine and specific treatment has led to a surge of novel therapies and their publicity in recent times. Under these unprecedented circumstances, a myriad of drugs used for other diseases is being evaluated and repositioned to treat COVID-19 (example- Remdesivir, Baricitinib). While multiple trials for potential drugs and vaccines are ongoing, and there are many unproven remedies with little or no supporting evidence. Presently, discussions are revolving around the use of multivitamins (Vitamin, C, D, A), minerals (selenium, zinc), probiotics, flavonoids, polyphenols, and herbal remedies (curcumin, artemisinin, herbal drinks). Our review delves further into the details of some of these controversial therapies for COVID-19.

Keywords: COVID-19, Novel therapy, Antioxidant, Controversial therapy, Review, Pneumonia.

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1. INTRODUCTION

In December 2019, an outbreak of pneumonia of unknown etiology was reported by the Wuhan Municipal Health Commission, in Wuhan, Hubei Province in China. Subsequently, novel coronavirus SARS CoV-2 was identified as the cause of the 2019 coronavirus disease (COVID-19) [1]. As the disease rapidly spread across borders and was proven difficult to contain, the World Health Organization (WHO) declared COVID-19 as a pandemic on March 11th, 2020. On June 22, 2020, there were more than 9 Million positive patients worldwide, with >469,000 global deaths [2].

Typically, COVID-19 presents as fever, dry cough, and fatigue. It may also show other mild symptoms such as nasal congestion, headache, conjunctivitis, sore throat, diarrhea, anosmia, or discoloration of fingers or toes. Approximately 80% of the patients recover without needing hospital treatment; however, the remaining 20% may require hospitalization, some even advance to critical illness. Patients with pre-existing conditions such as hypertension, underlying chronic heart and lung diseases, diabetes, and cancer are at a higher risk of experiencing COVID-19 related complications, which could lead to a poorer prognosis [3]. It is a fact that the various vitamins, trace elements, herbal remedies, and probiotics enhance immunity during times when there is no definitive preventive or therapeutic cure for viral infections like COVID-19, especially in the pediatric age groups considering the lockdown states [4 - 12]. Emergency Use Authorization (EUA) was issued on March 28th, 2020, by the Food and Drug Administration (FDA), which was later withdrawn based on the newer data. This sanction was for the use of oral formulations of hydroxychloroquine sulfate and chloroquine phosphate when recommended for the treatment of COVID-19 by a health care professional [13]. Likewise, the emergency use of antiviral drug Remdesivir for COVID-19 positive cases with the significant disease was warranted on May 1, 2020 [14]. In this time of uncertainty in several countries, non-evidence-based novel therapies are deployed to improve patient outcomes.

We aim to review these novels, yet controversial therapies that are being proposed and used in the treatment of COVID-19.

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2. DISCUSSION

2.1. Vitamin C

Vitamin C (VC), also known as ascorbic acid, is known for its antioxidant properties. This characteristic of VC appears to play an essential role in modulating elevated levels of oxidative stress like infections and cancers. Infections lead to an activation of our immune system, which releases various oxidizing agents grouped as Reactive Oxygen Species (ROS). Though these ROS are useful to deactivate the microorganisms, they prove to be detrimental to the host cells [15]. The duration of mechanical ventilation is reduced by 14% in a recent trial among 685 patients with the use of VC. Another multi-centric study confirmed the reduction in ventilation time by 25% with the dosage of 1-6g/day of VC in patients treated in critical care [16 - 18]. With a pandemic like COVID-19, additional safe, cost-effective, and immune-supportive strategies, such as VC, may be warranted to protect individuals and populations against developing a severe disease [19]. Thus, VC can be a potential prophylactic and therapeutic target for severe ARDS in COVID-19 patients [20]. Fowler *et al.* [21] and Wang *et al.* [22] suggested that VC has a therapeutic role in critically ill patients. Studies conducted by Hemilä *et al.* [23] and Messina *et al.* [24] point towards the promising nature of VC in effectively improving the morbidity and mortality of patients in regard to COVID-19. With the rise of epidemics like COVID-19, additional safe, cost-effective, and immune-supportive strategies, such as VC, may be warranted to protect individuals and populations against developing a severe disease [21 - 26]. Furthermore, previous evidences of VC to reduce the ICU stay and morbidity of patients in critical care with conditions like ARDS, sepsis, burns, trauma and respiratory failure, give an opportunity to investigate the role of VC in similar situations related to COVID-19 [27 - 35]. Though the studies differ in doses used in the treatment of critical patients with the coronavirus, VC definitely seems to improve the outcomes (Table **1**).

2.2. Vitamin D

The role of Vitamin D (VD) in providing immunity is unclear. The potential mechanisms include antiviral immunomodulation, induction of autophagy and apoptosis, and genetic or epigenetic regulation. Furthermore, the risk of viral infections can be reduced by VD. In addition, it has been observed in COVID-19 patients, that it works by enhancing the release of cytokines (pro-inflammatory) by the T helper type 2 cells, which will cause a diminution (anti-inflammatory) of the functioning of the T helper type 1 cells during various bacterial and viral crises [36, 37]. The high prevalence and outbreak of COVID during the winters raise the suspicion that there could be a relationship between VD deficiency and the infection leading to the high mortality rates in the elderly populations, who are known to produce lower amounts of VD, as compared to younger individuals when regularly exposed to sunlight [38]. Various studies have suggested that there exists a relationship between VD deficiency and COVID-19, thus suggesting it might act as an aid to decrease the fatal nature of the virus. Nair *et al.* and Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention interpret age as a risk factor for VD deficiency, which, if appropriately supplemented with VD, will improve COVID-19 outcomes. Similar studies report the association of low VD levels and positive blood cultures that might impact the severity of the condition [39 - 44]. More studies need to define VD deficiency and groups prone to the deficit in relation to the coronavirus in order to prevent and cure it (Table **2**).

2.3. Vitamin A

Vitamin A (VA) is a fat-soluble compound, which plays an essential role in many physiological functions like embryonic development, vision, immunity, cellular differentiation, and proliferation [45, 46]. WHO stated in an article that VA supplementation improved the outcome of respiratory infections in nutritionally challenged children [47]. It is a fact that VA improves the clinical results in patients affected by measles associated pneumonia. However, some studies show that low doses of VA are associated with a low risk of respiratory infection [48]. Though these results have not been consistent, VA still does not have an established role in epidemics like COVID-19. VA seems to have an effective role in improving the morbidity of COVID-19 cases by alleviating the functions of neutrophils, natural killer cells, monocytes or macrophages, T cells, and B cells [49]. Therefore, the role of VA in COVID-19 treatment remains inconclusive.

2.4. Selenium

The European Micronutrients recommendations network of excellence (EURRECCA) has stated that selenium plays a crucial role in five significant functions like cognition individuals aged >50 years, viral load and onset of Acute Respiratory Distress Syndrome (AIDS) in Human Immunodeficiency Virus (HIV) positive patients, immune functions, male fertility, and cancer (particularly for persons at risk of prostate cancer) [50]. Supplementing a moderate dose of selenium can strengthen cellular immunity, humoral immunity, and nonspecific immunity. Thus, its deficiency can impair immunity and is a potential form of protection for the prevention and therapies of infections of the respiratory system [51]. Selenium is known for its remarkable redox biology when it comes to neutralizing the release of the reactive oxygen species in the reaction to infections in the body. Numerous studies indicated the implication of its deficiencies with the evolution of various infections, cancers, neurodegenerative diseases, and cardiovascular diseases [50]. With the rise of infections like COVID-19, it is possible to say that selenium can have a protective and therapeutic role in improving morbidity rates. Selenium had improved effects after an influenza vaccine challenge [52].

A correlation between low selenium levels and an increased risk of COVID-19 related mortality has been found in China, leading to worse outcomes [53]. Thus, blinded randomized controlled trials are needed to explore the correlation between COVID-19 and selenium.

2.5. Zinc

Dietary zinc deficiency in developing countries is widespread and often exacerbated by acute and chronic

infections. It is a necessary component of numerous metalloproteins, including those critical for DNA replication and cell division, and is crucial for maintaining immunological integrity, predominantly cellular immunity and antioxidant activity. It is also associated with growth, impaired immunity, learning disabilities, and anorexia [54]. Studies show that children with Zinc deficiency are at an increased risk of respiratory tract infections. Many mechanisms have been implicated in the role of zinc deficiency in causing an increased susceptibility to Acute Respiratory Infections (ARI's). Zinc plays a vital barrier role in the cohesiveness of respiratory epithelial cells and controls the secretion of pro-inflammatory cytokines. Improved immunity has been confirmed with high dose Zinc supplementation for Torque Teno Virus (TTV) [55].

It is reported that Zinc supplementation could play a key role in preventing ARI in developing countries. It is supposed to lower the duration of respiratory tract infections, the number of episodes, the severity of bronchiolitis, and pneumonia [56]. But, this effect was minimal when other cases specific filters were applied [57]. Hence, the role of zinc in pandemics like COVID is unclear.

2.6. Probiotics/Microbiota

"Probiotics" are live microorganisms that are supposed to be beneficial to the health and well-being of an individual when ingested or applied to the body. The Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) have described probiotics as "live microorganisms which confer a health benefit on the host when administered in adequate amounts" [58]. The most commonly used probiotics are *Lactobacilli* and *Bifidobacteria* strains, and the yeast *Saccharomyces boulardii*. Some reports contemplate the use of probiotics in COVID-19. In a recent study, Trompette *et al.* stated that improving the diet quality in a susceptible COVID-19 individual could mitigate the risk of significant infection and complications [59]. Morrow *et al.* [60] conducted randomized controlled trials and reported that critically ill patients on mechanical ventilation if given probiotics (*i.e.*, live *Bacillus subtilis*, *Lactobacillus rhamnosus GG*, and *Enterococcus faecalis*) developed significantly less ventilator-associated pneumonia compared with the patients who were on placebo [60]. There is also an indication that probiotic strains maintain equilibrium between pro-inflammatory and immunoregulatory cytokines, which aid in viral clearance while reducing immune response-mediated lung damage, which might be of particular interest in preventing ARDS, a significant complication of COVID-19. An RCT with *Lactobacillus Plantarum* DR7 diminished plasma pro-inflammatory cytokines (IFN-π, TNF-α) in middle-aged adults (30 to 60 years of age) and boosted anti-inflammatory cytokines (IL-4, IL-10) in young adults (30 years of age), supplemented by reduction of plasma peroxidation and oxidative stress compared with placebo [61]. This finding might be helpful, as it shows to inhibit the cytokine storm occurring in COVID-19 patients. *Lactobacillus acidophilus* and *Bacillus clausii* in the animal study did not show any reduction in the expression of coronavirus receptors in the murine small intestine when compared with the control and the post-*Salmonella* infection models. Feng *et al.* conducted animal studies and found that coronaviruses receptors could increase in the presence of both invasive bacteria and their counterpart, probiotics (*Lactobacillus acidophilus and Bacillus clausii*) in the murine small intestine with control and post-salmonella infection models [62]. Due to a lack of substantial data, further clinical trials are warranted to understand the effect of probiotics in COVID-19.

2.7. PUFA and Omega-3

Polyunsaturated Fatty Acids (PUFA) are classified into two classes, the Omega-6 (N-6) family of PUFA (*e.g.*, linoleic acid, arachidonic acid) and the Omega-3 (N-3) family (*e.g.*, alpha-linolenic acid, Eicosapentaenoic Acid (EPA), Docosahexaenoic Acid (DHA). Such distinct groups of fatty acids have been extensively studied to understand their effects on cardiovascular and metabolic health, and cancer [63]. It is recognized that ω-3 PUFAs have anti-inflammatory properties and play an essential role in the body's inflammation resolution [64]. In several lung infections, the administration of PUFA can improve the patient's outcome in acute pneumonia. Sharma *et al.* reported in their study that the dietary supplementation of ω-3 PUFA supplementation exerts an overall beneficial effect against acute experimental pneumonia. This mechanism is operative through the up-regulation of nonspecific and specific host immune defenses [65]. Jones *et al.* concluded the susceptibility of poxvirus infection of mice was not affected by dietary fats utilization [66]. Dushianthan *et al.* [67] examined the effects of omega-3 fatty acids and antioxidants in adults with ARDS (a significant complication in COVID-19). The study showed an ambiguity in regards to the consumption of omega-3 and other antioxidants and their benefits towards the improvement of ICU length of stay and duration of ventilator days. They further concluded that the intervention of omega-3 usage produced a minuscule or no difference in all-cause mortality [67]. Considering the scarcity of data on hand, we have to rely on the results of ongoing trials to establish the role of ω-3 supplementation in ARDS and COVID-19.

Table 1. Summary of the evidence outlining the effects of Vitamin C use in COVID-19.

References	Name of the Study	Findings/ Conclusion
Fowler III *et al.* [21]	Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients with Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial	Administration of approximately 15g/day of IV VC for 4 days may reduce the mortality rates in sepsis-related ARDS patients.

(Table 1) contd.....

References	Name of the Study	Findings/ Conclusion
Carr *et al.* [25]	A new clinical trial to test high-dose vitamin C in patients with COVID-19	A new randomized control trial (RCT) tests the effects of IV VC in viral infections in 140 patients. The study will investigate the effects of IV VC with a dose of 24g/day for 7 days vs. placebo. It will assess the requirements for mechanical ventilation and vasopressor drugs, organ failure scores, ICU length of stay, and 28-day mortality.
Hemilä *et al.* [23]	Vitamin C and SARS coronavirus	Three RCTs reported that VC supplementation lowered the incidence of Pneumonia in VC supplemented group, showing that VC may affect the susceptibility of lower respiratory tract infections under specific conditions.
Wang *et al.* [22]	Effects of different ascorbic acid doses on the mortality of critically ill patients: a meta-analysis	IV Ascorbic acid at doses 3-5 g/day decreases the duration of vasopressor support and mechanical ventilation, thus reducing the overall mortality rates in ARDS patients.
Messina *et al.* [24]	Functional Role of Dietary Intervention to Improve the Outcome of COVID-19: A Hypothesis of work	Dietary supplementation with VC, Flavonoids, and polyphenols reduces inflammation and immune response, blocking nuclear NF- B translocation, hence has a potential effect in improving the response in COVID patients.
Cheng *et al.* [26]	Can early and high intravenous doses of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)	COVID-19 patients have high levels of inflammatory markers due to oxidative stress, leading to the activation of important pathways like Nrf 2 signaling. This could lead to modulation in the antioxidant response element (ARE) driven cytoprotective protein expression by various transcription factors. The use of high dose Intravenous VC can be a potential target to prevent and relieve oxidative stress in COVID-19 patients.
Shanghai Expert Panel *et al.* [27]	High Dose Vitamin C Infusions Being Used To Treat COVID-19	High-dose intravenous. 10g-20g intravenous dosage of VC was used for 8-10 hrs. for 50 moderate and 19 severe COVID-19 cases in China, which led to a successful treatment. Though critical cases needed higher doses, their oxygenation index improved, directing the situation towards cure and discharge.
Hemilä *et al.* [28]	Vitamin C Can Shorten the Length of Stay in the ICU: A Meta-Analysis	High-dose intravenous VC infusions (*e.g.*, 200 mg/kg body weight/day, divided into 4 doses) shorten the intensive care unit (ICU) stay by 7.8%, accompanied by a significant reduction in the mortality rate.
Berger *et al.* [29]	Vitamin C supplementation in the critically ill patient.	Patients under critical care like sepsis, burns, trauma, etc. have an improved clinical outcome when high dose VC (3g/day) is administered for several days.
Marik *et al.* [30, 31] Christin *et al.* [32]	1. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study 2. ARDS complicating pustular psoriasis: treatment with low-dose corticosteroids, vitamin C and thiamine 3. Vitamin C infusion for gastric acid aspiration-induced acute respiratory distress syndrome (ARDS)	Severe cases of ARDS show clinical benefit evidenced by improving symptoms and radiological signs with VC supplementation 24-48 hours post ECMO procedures.
Fowler III *et al.* [33] Spiegel *et al.* [34] Hager at al [35].	1. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the CITRIS-ALI randomized clinical trial 2. Myths in Emergency Medicine: Vitamin C Trial Lacks Answers for Sepsis 3. Vitamin C for Sepsis and Acute Respiratory Failure	Critical cases after organ failure have decreased mortality by 16.5%, respiratory assistance requirements by 2.5 days, ICU stays by 3.2 days, and hospital admission by 6.7 days after VC administration. However, inflammatory markers failed to improve significantly during the CITRIS-ALI trial.

Table 2. Summary of the evidence outlining the potential role of Vitamin D in COVID-19.

References	Name of the Study	Findings/Results
Wimalawansa, S.J. *et al.* [39]	The global epidemic of coronavirus--COVID-19: What we can do to minimize risks 5000 IU/d.	Individuals prone to COVID-19 need to have their VD levels more than 40-60ng/ml by supplementing 10,000IU/day for a few weeks followed by tapering to 5000IU/day.
Nair *et al.* [40]	Vitamin D: The “sunshine” vitamin	Supportive data for the effective role of VD in decreasing the risk of COVID-19 could be highlighted by increased case-fatality rates with chronic disease comorbidity and age, in which lower concentrations of 25(OH) D have been reported.

(Table 2) contd.....

References	Name of the Study	Findings/Results
Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention [41].	The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) in China	Since VD levels decrease with age, it may be important to assess the risk of VD as a factor owing to its high case fatality in older age groups.
Grant *et al.* [42]	Evidence that Vitamin D Supplementation Could Reduce the Risk of Influenza and COVID-19 Infections and Deaths	Treatment of Community Acquired Pneumonia (CAP) with VD did not significantly result in complete resolution but led to decreased concentration of IL-6, CRP in diabetic patients. VD contributes to the increased risk of ARDS development.
Moraes *et al.* [43] Lee *et al.* [44]	1. Vitamin D deficiency is independently associated with mortality among critically ill patients. 2. Vitamin D deficiency in critically ill patients.	There may be an etiological association between low VD levels, positive blood cultures, and mortality in critically ill patients admitted to ICU.

Table 3. Summary of the evidence for the use of Flavonoids and Polyphenols in COVID-19.

References	Type of Study	Results/ Conclusions
Deep *et al.* [69]	Bench/Lab study	They reported in conclusion that flavonoids: Hesperidine, Naringin, and Epigallocatechin Gallate (EGCG), were potent inhibitors of the nCoV-SP receptor-binding domain of S protein (RBD). At the same time, Quercetin showed affinity to human receptor human angiotensin-converting enzyme-2 (ACE-2) and found to be more efficient towards the viral spike glycoprotein. Quercetin effectively blocked the human ACE-2 receptor by binding to a substantial residue ASP38 and hindered the formation of the salt bridge with LYS353 and, ultimately, the well-recognized hotspot LYS353, which is well recognized by SARS-CoV-2.
Adem *et al.* [70]	Bench/ Lab Study	After Molecular docking, the study found that flavonoids like hesperidin and rutin may bind the main protease (Mpro) of COVID-19 better than Nelfinavir.
Bhatia *et al.* [71]	Bench/ Lab Study	They performed Virtual Screening by Molecular Docking approach, which established the top 6 docked polyphenols, which are primarily derivatives of Sanguiin, Theaflavin, Kaempferol, Punicalagin, and Protocatechuic acid. Sanguiin and Theaflavin were proposed to resolve breathing difficulties in patients with extreme COVID-19, as they already are established bronchodilators.
Ang *et al.* [72]	Systematic review	The team reviewed 12 pattern identifications, herbal compositions, and analyzed their herbal formulae, recommended by Chinese guidelines for the treatment of various pediatric COVID-19 stages. After thorough analysis, the herb Armeniacae semen was found to be most frequently used for the treatment of pediatric COVID-19 in the Chinese population. It reduced hyper-responsiveness in the airways and inhibited Th2 cells.

2.8. Polyphenols, Flavonoids, and Herbal Drinks

Polyphenols are natural plant compounds and are generally involved in the defense against ultraviolet radiation or pathogenic aggression. Over the last decade, the possible health benefits of dietary plant polyphenols as an antioxidant have been of great interest. The main classes of polyphenols are phenolic acids, flavonoids, lignans, and stilbenes. Out of these, one of the most prominent phenols is the class flavonoids. The benefit of continuing the use of polyphenols against cancer growth, cardiovascular disorders, diabetes, osteoporosis, and neurodegenerative diseases was implied in recent epidemiological studies. Their key role in being anti-inflammatory, anti-mutagenic, antioxidant, and anti-carcinogenic is diverse [68]. The summary of the use of flavonoids and polyphenols in COVID-19 is exhibited in Table **3**. Bhowmick *et al.* [69], and Adem *et al.* [70] reported the binding of flavonoids and polyphenols to the receptors of SARS-CoV-2, subsequently inhibiting it at a molecular level. They also proposed the affinity of flavonoids towards the ACE-2 receptor [69, 70]. Ang *et al.* [71] reported the use of *Armeniacae semen,* which was the most frequently used herbal supplement reducing the hyper-responsiveness on the airways for the treatment of pediatric COVID-19 in the Chinese population [71].

Bhatia *et al.* [72] suggested the use of "Black Tea," a theaflavin, in the routine diet as it is an inexpensive and easily accessible source of polyphenols. Polyphenols in black tea could potentially stop the replication and transmission of viruses and could be useful in the current health emergency state. The study suggested that patients quarantining at home with mild symptoms of COVID-19 can include these polyphenols in their diets. This dietary supplement could augment their physiological response against COVID-19. In-vitro testing should be conducted to assess the effectiveness of these polyphenols in the supportive treatment of COVID-19 [72].

2.9. Curcumin and Artemisinin

Curcumin is a chemical with potent anti-inflammatory and antioxidant properties, popularly found in turmeric. These novel compounds have been proposed as an adjunctive therapy on social media. Jena *et al.* depicted the role of curcumin and catechin in binding to the S-protein at the location where host cell binding is known to occur. Similarly, they documented the attachment of these molecules to ACE2 sites that served as a viral entry medium. The study concluded that curcumin has the potential to block the entry of viral protein by inhibiting the host cell receptor and virus binding [73].

On 14th April 2020, MGC pharmaceuticals announced the approval from the Human Research Ethics Committee ('Ethics Committee') of Nazareth Hospital EMMS in Israel to implement a Phase II placebo-controlled clinical trial to determine the safety and efficacy of a natural anti-infective formulation ('ArtemiC' or 'Product') in patients infected with

COVID-19 [74].

2.10. Colloidal Silver

Colloidal silver is composed of small silver particles in a liquid marketed as a dietary supplement claiming to have antiviral properties. There is, however, a shortage of evidence to support arguments related to its benefits. In reality, colloidal silver can be hazardous to one's health. Zachar *et al.* [75] concluded that successful Minimum Inhibitory Concentration (MIC) was achieved in both the bronchial tree and the alveoli after investigating its effect in specific locations of the respiratory system during viral and bacterial infections. They concluded that successful MIC was achieved in both the bronchial tree and the alveoli. This approach was proposed as a first-line treatment to suppress the progression of the SARS-COV-2 infection in the respiratory system [75]. Further studies are needed to support this hypothesis.

CONCLUSION

Nutrition and immunity go hand in hand and are known to have a direct relationship in reducing the risk and severity of any infection. Various macro and micronutrients have been implicated to affect morbidity and mortality positively when supplemented during the episodes of infection. Since the COVID-19 pandemic constitutes higher mortality due to respiratory failure, these nutrients may have a beneficial but not completely validated role as a prophylactic and therapeutic treatment. However, there is insufficient data to prove an association between COVID-19 and the benefits of nutrition. There is also a clear need to study the beneficial effects' applicability on the whole population or only on the groups that are nutritionally challenged. Robust nutritional surveys and blinded randomized clinical studies are needed to investigate the potential effects of such therapies on COVID-19.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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