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Review Article

Micronutrients as immunomodulatory tools for COVID-19 management

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ABSTRACT

COVID-19 rapidly turned to a global pandemic posing lethal threats to overwhelming health care capabilities, despite its relatively low mortality rate. The clinical respiratory symptoms include dry cough, fever, anosmia, breathing difficulties, and subsequent respiratory failure. No known cure is available for COVID-19. Apart from the anti-viral strategy, the supports of immune effectors and modulation of immunosuppressive mechanisms is the rationale immunomodulation approach in COVID-19 management. Diet and nutrition are essential for healthy immunity. However, a group of micronutrients plays a dominant role in immunomodulation. The deficiency of most nutrients increases the individual susceptibility to virus infection with a tendency for severe clinical presentation. Despite a shred of evidence, the supplementation of a single nutrient is not promising in the general population. Individuals at high-risk for specific nutrient deficiencies likely benefit from supplementation. The individual dietary and nutritional status assessments are critical for determining the comprehensive actions in COVID-19.

1. Introduction

The coronavirus disease 2019 (COVID-19) is a respiratory disorder that is the consequence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1]. Since the first identified case in Wuhan, China, it took only three months for a global pandemic of the disease due to the highly contagious of this virus through droplets transmission [2–5].

The host responses to SARS-CoV-2 infection diverse; 78% of newly infected persons may remain asymptomatic, while 84.3%, 9.6%, and 6.1 % of clinical patients present with mild, moderate, and severe symptoms, respectively [6,7]. The viral responses of innate and adaptive immune machinery differ upon the host metabolic determinants, including age, sex, nutritional status, smoking habits, and co-existing medical conditions [6,8–12]. The findings of asymptomatic and mild clinical symptoms in younger individuals signify the role of host status in SARS-CoV-2 infection [9,13–15].

In contrast to the current anti-viral approach targeting the specific pathogen, an emerging strategy aims the host immunity activation to fight the virus [16,17]. With the expanding knowledge of cellular immunity mechanisms, the development of drugs, substances, or measures that modulate immune responses contributes to the management of many life-threatening infections [18–24]. Small clinical trials in the severe infection conditions explored the compassionate options to activate the early-responding immune effector cells through various immunoadjuvant agents, such as interleukin-7, anti-programmed death 1, interferon-γ, and granulocyte-macrophage colony-stimulating factor [16,25]. The clinical management of severe infections commonly includes the modulation of immunosuppressive mechanisms, i.e., the alleviation of T-cell exhaustion, myeloid-derived suppressor cells, or regulatory T cells [16,21,24,26,27].

The balance between the immune activation and the counter-regulatory immunosuppression is crucial upon the virus-host encountering responses [28,29]. This balance determines the variation of subsequent

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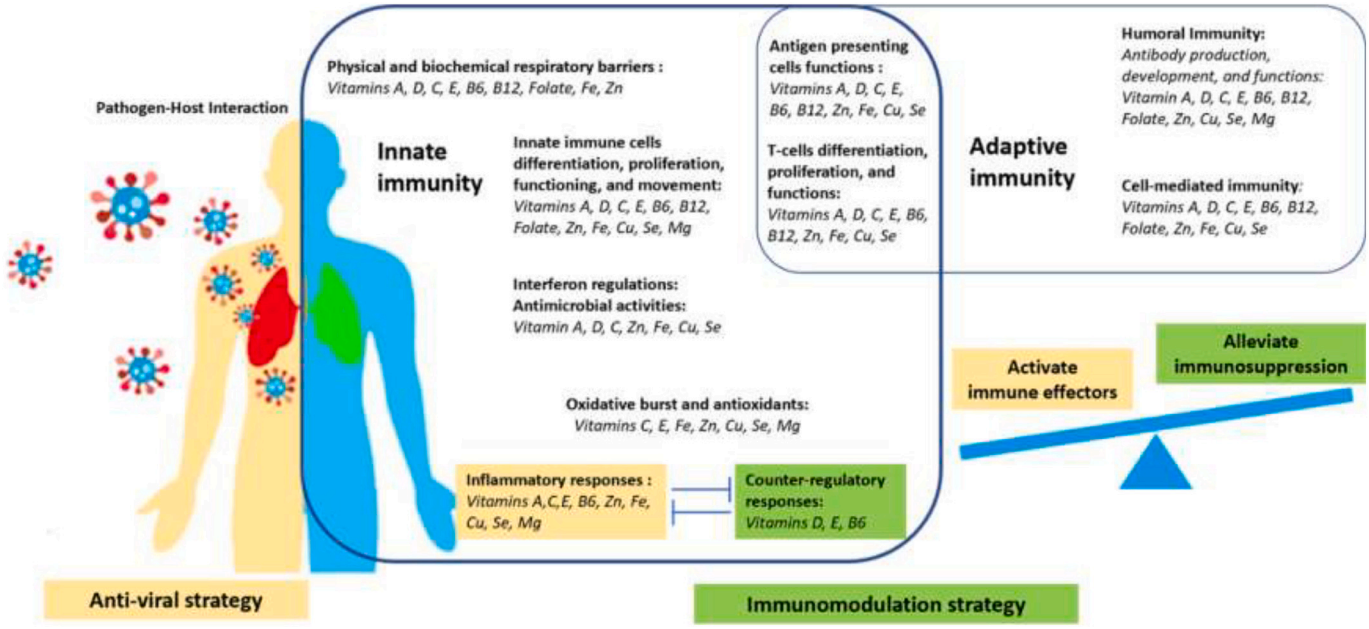

Fig. 1. The immunomodulation strategy and roles of a group of nutrients in different processes of virus-host immune responses.

clinical manifestations. Several micronutrients contribute to these immunomodulatory effects [16,30–34]. This article reviews some nutrients that can potentially modulate immunity to SARs-CoV-2 infection.

2. Nutrients and virus-host immunologic responses

Micronutrients involve in the continuum of host immune responses to the virus from the initial virus-host interaction, innate immune activation, to adaptive immune responses, as summarized in Fig. 1 [30,35]. The healthy immunity requires the synergistic contribution from multiple micronutrients, and single nutrient barely drives the whole immune machinery. However, the viral-host resistance relies on the support from a dominant group of nutrients, including vitamins A, C, D, E, B6, B12, folate, iron (Fe), zinc (Zn), copper (Zn), selenium (Se), and magnesium (Mg) [30,36–38].

The first-line defenses against the virus are the physical and biochemical barriers of the respiratory tract, which their normal epithelial differentiation and growth require vitamin A and Fe [36,37]. Vitamins A, C, D, and Zn regulate membrane fluidity, membrane integrity, gap-junction communication, and membrane repair [37,39–46]. Vitamin E mitigates the membrane lipid peroxidation from reactive oxygen species [37]. Vitamins A, D, C, and the trace elements Zn, Fe, Cu, and Se regulate the membrane-bounded antimicrobial peptide activities and mucosal-associated microbiota [30,47,48]. The mucosal migration and regulation of immune cell functions also synchronize with the integrated pathways of vitamins B6, B12, and folate [47,49].

Interferon (IFN) is a crucial anti-viral innate immune response than regulates and shapes the balance of Th1 and Th2 phenotypes in adaptive immunity [50]. IFN-λs are key antiviral cytokines at the epithelial barriers, and induce the inflammatory response and apoptotic cell death [50,51]. Apart from that, type I IFNs increase in responses to the viral activation of the toll-like receptor 7 and the mitochondrial antiviral-signaling [52,53]. Vitamins A, C, D, C, Zn, Fe, Cu, and Se regulate IFNs production [30,36,44,45,54–58].

Upon the intrusion of SARS-CoV-2 into the airway epithelial cells, innate immune cells respond through their movement, migration, differentiation, proliferation, and activation to counteract the viral replication. The cytokines and oxidative burst induce the pro-inflammatory milieu, while the virus delays and suppress type I IFNs responses [35]. Without the optimal counter-regulatory immune reactions, the activation of the Th1/Th17 phenotypes of adaptive immunity further exacerbates the hyperinflammatory conditions and the 'cytokine storms' [27,35,59]. However, healthy immunity eventually proceeds to the production of SARS-CoV-2 specific antibodies that neutralize the virus and resolve the infection [59,60].

Vitamins A, C, D, E, B6, B12, and folate, and the trace elements Zn, Fe, Cu, Se, as well as the mineral Mg comprise a group of nutrients that support the entire continuum of virus-host immune responses. Their contributions range from the regulation of number and function of innate immune cells such as neutrophils, natural killer cells, monocytes, and macrophages [36,37,45,54,61–73], the production of pro-, and anti-inflammatory cytokines, the responses to inflammation, the oxidative burst function, the reductive-oxidative hemodynamics [36,37,45,61–64,71,72,74–85], to the responses of adaptive immunity, including differentiation, proliferation, and functions of T-cells [32,36,37,45,54,71,77,84,86–95], the interactions with the presenting viral antigens [37,54,71,73,96], and the production and development of virus-specific antibodies [36,37,45,71,73,97,98].

Despite their synergistic contributions to virus-host responses, the deficiency state of specific nutrients increases an individual susceptibility to the severe clinical manifestation of SARS-CoV-2 infection. The following sections explore the consequences of some micronutrient deficiencies and the potential effects of their supplementations to COVID-19.

3. Vitamins

3.1. Vitamin D

Vitamin D is involved in a wide range of immunomodulatory activities, including the maintenance of immune barrier integrity [40–44,47,48], the production of antimicrobial peptides [99–102], the support of monocytes, macrophages, and dendritic cells functions [36,37,62–64], the modulation of oxidative burst potential [37,62–64], the promotion of anti-inflammatory cytokine production [62,74–76], the inhibition of IFN γ [54–58], nuclear factor κB [103], other pro-inflammatory cytokines [104,105], and the subsequent responses of adaptive immune cells [32,54,71,87–91].

The low level of vitamin D increases the risks, severity, morbidity,

Table 1
The immunomodulating properties, the risk for the deficiency states, and the impacts of supplementation of a group of nutrients.

Nutrients	Immunomodulating properties	Risks for deficiency states	Impacts of supplementation
Vitamin A	• maintaining the barrier integrity and normal differentiation of epithelial tissues [37,123] • mucosal immune responses and acts as an anti-inflammatory agent [39,47,124,125] • regulates the number and function of natural killer cells and supports the phagocytic and oxidative burst activities of macrophages [37,61] • the Th1/Th2 phenotypic differentiation and development [37,86] • downregulates IFN γ, interleukin 2, and tumor-necrosis factor α productions by Th1 cells, thus, maintains the normal antibody-mediated Th2 responses [36,37,45] • supports antibody production by B cells [37].	• increased susceptibility to virus-induced respiratory tract infections, measles, and diarrhea [37,107,126,127] • failed to mount the protective immunologic responses to the vaccine [128]	• improves antibody titer responses to vaccines [37] • Supplementation in vitamin A deficiency individuals reduced the incidence of Mycoplasma pneumoniae infection [129,130] • The supplementation of vitamin A to deficient children decreased their risk of all-cause mortality and morbidity from infectious diseases. Nevertheless, vitamin A supplementation showed no benefits for pneumonia [107,131,132].
Vitamin C	• epithelial barrier integrity [37,45] • innate immune cells activities, movement, functions, proliferation, and differentiation [36,37,45,54,61,65] • antimicrobial activities; increases serum complement proteins, and the production of IFN γ [36,45] • antioxidant, maintains the intracellular reductive-oxidative homeostasis [37,45,77] • roles in antibody production and supports of differentiation and proliferation of T-cells [36,45]	• increased the risk and severity of several respiratory infections, including pneumonia [37,45,107,110,117]	• shortens the symptoms of the common cold in children, reduces the incidence of pneumonia in the elderly [107,117–119] • combination of vitamin C and red ginseng reduced the influenza virus-induced lung inflammation and increased the survival rate in mice [120]. • high dose intravenous vitamin C shortens the recovery periods of severely ill patients with virus-induced acute respiratory distress syndrome [77,121,122]
Vitamin D	• immune barrier integrity [40–44,47,48] • production of antimicrobial peptides [99–102] • support innate cells functions [36,37,62–64] • modulation of oxidative burst [37,62–64] • promotion of anti-inflammatory cytokines • [62,74–76] • inhibition IFN γ [54–58], nuclear factor κB [103], other pro-inflammatory cytokines [104,105] • support adaptive immune cells [32,54,71,87–91]	• increases risks, severity, morbidity, and mortality of several respiratory conditions, such as rhinitis, asthma, tuberculosis, chronic pulmonary disorders, viral respiratory infections, and potentially including the COVID-19 [106–110] • deteriorates several pulmonary conditions [112–114]	• reduced risk of respiratory infections [115,116] • risk reduction benefit only in the vitamin D deficient individuals [61,107]
Vitamin E	• a potent lipid-soluble antioxidant that protects the cell membranes against the oxidative damage and supports the integrity of respiratory epithelial barriers [37,133,134] • enhances the natural killer cell cytotoxic activity and decreases prostaglandin E2 production by macrophages [36,37,54,61,66,78] • modulates the production of IFN-γ and interleukin 2 [36,132,135] • supports lymphocyte proliferation, T-cell-mediated functions, Th1 response optimization, and Th2 response suppression [36,37,61] • supports the active immune synapses between Th cells require vitamin E supports [54] • increases the proportion of antigen-experienced memory T-cells [96]	• impairs the functions of both humoral and cell-mediated adaptive immunity, thus facilitates viral infection with high virulent strains, severe subsequent pathologies, and abnormal immune responses [71,132,133,136]	• improves overall immune functions, reduced respiratory tract infection incidences, severity, lower virus load in lung tissues, and increased the antibody titers, particularly in the elderly [37,107,135,137]
Zinc	• modulates the functions of approximately 2,000 enzymes and 750 transcription factors involving in various biological and physiological processes, including immunity, growth, and development [46,138] • antiviral property; inhibits the RNA-dependent RNA polymerase enzyme [138,140,141] • maintains the integrity of immune barriers [46] • enhances the cytotoxic activity of natural killer cells and supports the cellular functions, growth, and differentiation of innate immune cells [37,54,61,67,68] • involves in complement protein activities and the IFN γ production [36,45] • modulation of the cytokine release and the Th17 and Th9 development [36,54,77,81–83,92,93] • influences on the antioxidant proteins [37,77] • supports the proliferation of cytotoxic T cells, the differentiation, development, and activation of T-cells, the cytokine production of Th1 cells, and the development of regulatory T cells [36,54,77,92–94]	• increases the risk and morbidity of inflammatory disorders, infections, and viral pneumonia, particularly in the children and elderly persons [37,93,107,110,127,143,144]	• Zinc supplementation in children reduced their susceptibilities, severity of symptoms, and the duration of common colds and viral pneumonia [77,107,138,145,146] • increased serum Zn levels and the number of T-cells in nursing home elderly [147]

(*continued on next page*)

Table 1 (*continued*)

Nutrients	Immunomodulating properties	Risks for deficiency states	Impacts of supplementation
	• involves in antibody production, mainly the immunoglobulin G [37,97,98].		
Selenium	• component of selenoproteins that are essential for the functions of the immune system and the reductive-oxidative homeostasis [61,148] • modulates the activities of virus-induced innate and adaptive immunity through the regulation of IFN α, IFN γ, and IFN β production • influences on the functions and differentiation of natural killer cells and T-cells, and the antibody production [36,45,71,84,95,149,150].	• increases the risk and virulence of virus-induced pulmonary infections, particularly in infants during their first six weeks of life [107,132,150,151]	• maintaining optimal Se status protects against several viral infections [148–150] • reduced the pathogenicity of influenza virus infection in association with diets that contain both low and high Se quantities [152] • enhances immune responses to the virus in deficit individuals [37,132]
Magnesium	• involves in nucleic acid metabolism, DNA replication, leukocyte activation, antigen-binding to macrophages, and apoptotic regulation [38,72,73] • influences both the cell-mediated and humoral adaptive immunity [73,153] • protect DNA from oxidative damages and reduce the superoxide anion production at high concentrations [72,85]	• increases the susceptibility to recurrent upper respiratory tract infections [73,153,154] • promotes chronic low-grade inflammation through the production of pro-inflammatory cytokines, acute-phase proteins, and free radicals [155]	• Normal Mg levels maintain healthy lung structure and functions, and lower Mg levels are associated with increased respiratory complications [156,157]

and mortality of several respiratory conditions, such as rhinitis, asthma, tuberculosis, chronic pulmonary disorders, viral respiratory infections, and possibly also the COVID-19 [106–110]. The potential role of vitamin D in the modulation of immune response to viral respiratory tract infection (ALRI) has been evidenced in a study involving a young patient with individual genetic polymorphisms of vitamin D receptors [111]. Vitamin D influences lung structures, size, volume, and functions. Vitamin D deficiency thus worsens several pulmonary conditions [112–114].

A recent meta-analysis reported the associations of individuals with adequate vitamin D levels or daily oral supplementation with vitamin D and the reduced risk of respiratory infections [115,116]. The previous studies also suggested this risk reduction benefit of the supplementation, but only in the vitamin D deficient individuals [61,107]. With this information, vitamin D supplementation is a potential preventive strategy of COVID-19 in the individual with an established deficient state or has a high risk of vitamin D deficiency.

3.2. Vitamin C

Vitamin C supports the epithelial barrier integrity through its contributions to the collagen synthesis, keratinocyte differentiation, fibroblast migration, and proliferation [37,45]. Innate immune cells require vitamin C to maintain their activities, movement, functions, proliferation, and differentiation [36,37,45,54,61,65]. Vitamin C promotes the antimicrobial activities, increases serum complement proteins, and stimulated the production of IFN-γ [36,45]. Vitamin C is a powerful antioxidant, thus, maintains the intracellular reductive-oxidative homeostasis during the active immune responses [37,45,77]. It also plays roles in antibody production from plasma cells together with the supports of differentiation and proliferation of T-cells, particularly the cytotoxic T-cells [36,45].

Vitamin C deficiency increased the risk and severity of several respiratory infections, including pneumonia [37,45,107,110,117]. Despite many conflicting and inconclusive pieces of evidence, the oral supplementation of vitamin C potentially shortens the symptoms of the common cold in children. It also reduces the incidence of pneumonia in the elderly [107,117–119]. The combination of vitamin C and red ginseng reduced the influenza virus-induced lung inflammation and increased the survival rate in mice [120]. The treatment with high dose intravenous vitamin C shortens the recovery periods of severely ill patients with virus-induced acute respiratory distress syndrome [77,121,122]. Concerning its affordability, availability, and safety, vitamin C is still a functional option to consider in the management of COVID-19.

3.3. Vitamin A

Vitamin A is an essential micronutrient for maintaining the barrier integrity and normal differentiation of epithelial tissues [37,123]. It supports the mucosal immune responses and acts as an anti-inflammatory agent [39,47,124,125]. Vitamin A regulates the number and function of natural killer cells and supports the phagocytic and oxidative burst activities of macrophages [37,61]. The Th1/Th2 phenotypic differentiation and development of T-cells require vitamin A [37,86]. It downregulates IFN-γ, interleukin 2, and tumor-necrosis factor α productions by Th1 cells, thus, maintains the normal antibody-mediated Th2 responses [36,37,45]. Vitamin A also supports antibody production by B cells [37].

Vitamin A deficiency is a common risk factor for the increased susceptibility to virus-induced respiratory tract infections, measles, and diarrhea [37,107,126,127]. Young cows with vitamin A deficiency failed to mount the protective immunologic responses to the BRSV-NP vaccine (amphiphilic polyanhydride nanoparticle-based vaccine encapsulating the fusion and attachment proteins from bovine respiratory syncytial virus), with the subsequent lung infections after challenging by the virus [128]. Vitamin A supplementation improves antibody titer responses to vaccines [37]. Supplementation of vitamin A to deficient individuals reduces the incidence of *Mycoplasma pneumoniae* infection, which is a common post-viral secondary bacterial infection in COVID-19 [129,130]. The supplementation in vitamin A deficit children, 6-month to 5-year of age, decreased their risk of all-cause mortality and morbidity from infectious diseases. Nevertheless, vitamin A supplementation showed no benefits for pneumonia [107,131,132]. Concerning the potential adverse effects of vitamin A, the supplementation is sensible in the COVID-19 management of undernourished individuals or those with the evidence of vitamin A deficiency [132].

3.4. Vitamin E

Vitamin E is a potent lipid-soluble antioxidant that protects cell membranes against oxidative damage and supports the integrity of respiratory epithelial barriers [37,133,134]. It enhances the natural killer cell cytotoxic activity and decreases prostaglandin E2 production by macrophages [36,37,54,61,66,78]. Vitamin E modulates the production of IFN-γ and interleukin 2 [36,132,135]. It supports lymphocyte proliferation, T-cell-mediated functions, Th1 response optimization, and Th2 response suppression [36,37,61]. The active immune synapses between Th cells require vitamin E supports [54]. Vitamin E also increases the proportion of antigen-experienced memory T-cells [96].

Vitamin E deficiency is rare in humans. The deficit state impairs the functions of both humoral and cell-mediated adaptive immunity, thus facilitates the viral infection with high virulent strains, severe subsequent pathologies, and abnormal immune responses [71,132,133,136]. Vitamin E supplementation improves overall immune functions, reduces respiratory tract infection incidences, severity, lowers virus load in lung tissues, and increases the antibody titers, particularly in the elderly [37,107,135,137]. Malnourished individuals should benefit from the inclusion of vitamin E supplementation in COVID-19 management.

4. Essential trace elements and magnesium

4.1. Zinc

Zinc is an essential trace element that modulates the functions of approximately 2,000 enzymes and 750 transcription factors involved in various biological and physiological processes, including immunity, growth, and development [46,138,139]. Zinc also possesses a variety of direct and indirect antiviral properties. For instance, the pyrrolidine dithiocarbamate - a Zn ionophore - inhibits the RNA-dependent RNA polymerase enzyme that promotes SARS-CoV-2 replication [138,140,141]. Zinc maintains the integrity of immune barriers through its cofactor function in metalloenzymes [46,142]. It enhances the cytotoxic activity of natural killer cells and supports the cellular functions, growth, and differentiation of innate immune cells [37,54,61,67,68]. Zinc involves in complement protein activities and the IFN-γ production [36,45]. It has anti-inflammatory properties by the modulation of the cytokine release and the Th17 and Th9 development [36,54,77,81–83,92,93]. Zinc also exerts anti-oxidant effects through its influences on antioxidant proteins [37,77]. It supports the proliferation of cytotoxic T cells, the differentiation, development, and activation of T-cells, the cytokine production of Th1 cells, and the development of regulatory T cells [36,54,77,92–94]. Zinc is involved in antibody production, mainly the immunoglobulin G antibody [37,97,98].

Zinc deficiency increases the risk and morbidity of inflammatory disorders, infections, and viral pneumonia, particularly in children and the elderly [37,93,107,110,127,143,144]. Supplementation of Zn in children reduced their susceptibilities, severity of symptoms, and the duration of common colds and viral pneumonia [77,107,138,145,146]. Zinc supplementation in nursing home elderly increased their serum Zn levels and their number of T-cells [147]. Despite the few shreds of confirming evidence, Zn supplementation can benefit in the management of COVID-19, particularly in high-risk individuals for Zn deficiency.

4.2. Selenium

Selenium is a trace component of selenoproteins that are essential for the functions of the immune system and the reductive-oxidative homeostasis [61,148]. It modulates the activities of virus-induced innate and adaptive immunity through the regulation of IFN-α, IFN-γ, and IFN-β production, the influences on the functions and differentiation of natural killer cells and T-cells, and the antibody production [36,45,71,84,95,149,150].

Selenium deficiency increases the risk and virulence of virus-induced pulmonary infections through the aberrant immune responses and excessive cytokines production, particularly in infants during their first six weeks of life [107,132,150,151]. At the same time, the maintaining of optimal Se status through an adequate diet protects against several viral infections [148–150]. Dietary selenium supplementation potentiates innate antiviral immune responses reducing, for instance, the pathogenicity of avian influenza virus infection [152]. Consequently, Se supplementation in deficit individuals distinctively enhances the immune responses to the virus [37,132]. Selenium supplementation is the rationale management of COVID-19 in susceptible hosts.

4.3. Magnesium

Magnesium is a crucial mineral for healthy physiologic functions, including bioenergetics, immune responses, and acid-base balance; it is involved in nucleic acid metabolism, DNA replication, leukocyte activation, antigen-binding to macrophages, and apoptotic regulation [38,72,73]. Magnesium influences both the cell-mediated and humoral adaptive immunity [73,153]. It can protect DNA from oxidative damages and reduce the superoxide anion production at high concentrations [72,85]. Magnesium deficiency increases the susceptibility to recurrent upper respiratory tract infections [73,153,154]. A deficiency of Mg promotes chronic low-grade inflammation through the production of pro-inflammatory cytokines, acute-phase proteins, and free radicals [155]. Normal Mg levels maintain healthy lung structure and functions, while its lower levels are often associated with increased respiratory complications [156,157]. To date, no available study explores the impact of Mg supplementation on the clinical virus-induced respiratory infection.

5. Other potential immunomodulators for the COVID-19 management

5.1. N-acetylcysteine

N-acetylcysteine (NAC) is a precursor of glutathione that is a thiol reducing agent with antioxidant and anti-inflammatory properties. NAC reduces the elasticity and viscosity of mucus and improves the clearance of pulmonary secretions. NAC reduces oxidative stress and inflammation in chronic obstructive pulmonary disease patients. With the exposure to the influenza virus, NAC inhibits the production of TNF-α in alveolar macrophages, the expression of intercellular adhesion molecule 1 in respiratory epithelial cells, and increases the heme oxygenase 1 level in cells [158–160]. The combination of NAC and glutathione reduced the antigen levels of human immunosuppressive virus 1 and their reverse transcriptase activities in a cell line study [161]. A murine model study reported the synergistic actions of NAC and Oseltamivir combination in survival rate improvement- up to 100%- from the lethal strain of influenza infection [162].

The clinical application of NAC in patients with community-acquired pneumonia reported the reduction of oxidative stress and inflammation, as shown by the improved levels of TNF-α and malondialdehyde [163]. The long-term administration of NAC in elderly persons reduced the severity and duration of influenza-like symptoms [164]. Concerning the safety profile of NAC, it can be a sensible option to include in COVID-19 management despite a few pieces of clinical evidence.

5.2. Polyphenolic compounds

Polyphenolic compounds are a major class of phytonutrients with several biological and pharmacological properties, including antioxidant, anti-inflammatory, antibacterial, and antiviral potentials [165]. The span of the antiviral property of polyphenols involves the viruses from the *Coronaviriade* family. Resveratrol inhibits the Middle East Respiratory Syndrome coronavirus *in vitro* [166]. Anti-viral face masks and the cleaning wipes have their fiber filter surface grafted with the polyphenol catechin [167,168].

A recent computerized virtual screening of molecular structures identified six polyphenol molecules, i.e., sanguiin, theaflavin gallate, theaflavin digallate, kaempferol, punicalagin, and protocatechuic acid, that potentially target the main protease of SARS-CoV- 2 [169]. Stilbene and flavonoid derivatives, such as herbacetin, isobavachalcone, quercetin 3-β-d-glucoside, and helichrysetin, inhibit 3C-like protease

[170,171]. Resveratrol inhibits the virus nucleocapsid protein synthesis, thus suppress viral replication [166]. Quercetin inhibits the helicase, an enzyme for viral replication [172]. Other polyphenols such as delphinidin and epigallocatechin gallate inhibit the entry attachment of the virus [173,174]. These polyphenols and flavonoids have potential effects on COVID-19 management. However, these pieces of evidence are all from *in vitro* studies; to date, there is no available *in vivo* study. It is then premature to conclude their clinical applications.

6. Concluding remarks

Due to the great impact on medical services and the massive demand for health care, COVID-19 rapidly turned into a global pandemic, posing a lethal threat to the population despite its low mortality rate. The clinical respiratory symptoms include dry cough, fever, anosmia, breathing difficulties, and subsequent respiratory failure. No known cure is available for COVID-19. Apart from the anti-viral strategy, the supports of immune effectors and modulation of immunosuppression is the rationale immunomodulation approach in COVID-19 management. Diet and nutrition are essential for healthy immunity, but a group of micronutrients somehow plays a dominant role in immunomodulation [175]. This paper reviews the mechanisms, the effects of their deficiency states, and the potential impacts of their supplementations in COVID-19, as summarized in Table 1. The deficiency states of most nutrients increase the individual susceptibility to virus infection with a tendency for severe clinical presentation. Despite a shred of evidence, the supplementation of a single nutrient is not promising in the general population. The high-risk individual of a specific micronutrient deficiency is likely to benefit from the supplementation. The individual dietary and nutritional status assessments are critical for determining the comprehensive actions in COVID-19.

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