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REVIEW ARTICLE

Nutrients in prevention, treatment, and management of viral infections; special focus on Coronavirus

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ABSTRACT

Background: The coronavirus disease 2019 (COVID-19) is a pandemic caused by coronavirus with mild to severe respiratory symptoms. This paper aimed to investigate the effect of nutrients on the immune system and their possible roles in the prevention, treatment, and management of COVID-19 in adults.
Methods: This Systematic review was designed based on the guideline of the Preferred Reporting for Systematic Reviews (PRISMA). The articles that focussed on nutrition, immune system, viral infection, and coronaviruses were collected by searching databases for both published papers and accepted manuscripts from 1990 to 2020. Irrelevant papers and articles without English abstract were excluded from the review process.
Results: Some nutrients are actively involved in the proper functioning and strengthening of the human immune system against viral infections including dietary protein, omega-3 fatty acids, vitamin A, vitamin D, vitamin E, vitamin B_1, vitamin B_6, vitamin B_{12}, vitamin C, iron, zinc, and selenium. Few studies were done on the effect of dietary components on prevention of COVID-19, but supplementation with these nutrients may be effective in improving the health status of patients with viral infections.
Conclusion: Following a balanced diet and supplementation with proper nutrients may play a vital role in prevention, treatment, and management of COVID-19. However, further clinical trials are needed to confirm these findings and presenting the strong recommendations against this pandemic.

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Introduction

The coronavirus disease 2019 (COVID-19) is a pandemic caused by coronavirus with mild to severe respiratory symptoms in both men and women with different ages (Cheng and Shan 2020). Coronaviruses are a large family of viruses that are common in humans and many different species of animals including camels, cattle, cats, and bats (Brian and Baric 2005). The symptoms usually start between 2 and 14 days after a person gets infected and mainly includes fever, cough, and shortness of breath (Lake 2020). The molecular mechanisms involved in COVID-19 are not yet clear, but probably include inter- and intramolecular interactions that facilitate viral replication (de Wilde *et al*. 2018). Currently, there are no approved vaccines or pharmaceutical therapies available for treatment of COVID-19. Social distancing, self-quarantine, and maintain a healthy immune system are among the best ways to prevent the spread of the infection (Derwand and Scholz 2020, Jayawardena *et al*. 2020)

The human immune system is a complex and efficient defense system consisting of an integrated set of cells, chemical mediators, and a series of defensive "modular" factors to modulate immune response and protect the body from external insults (Scully *et al*. 2017). One of the most important factors that influence the human immune system is nutrition (Lopez Plaza and Bermejo Lopez 2017). Individuals with nutrient deficiencies have weakened immune system and they are more susceptible to viral infections such as COVID-19, and also for exacerbations of the condition after the disease (Lopez Plaza and Bermejo Lopez 2017).

Supplementation with some nutrients may support the body's natural defense system by enhancing the immunity, epithelial barriers, cellular immunity, and antibody production (Wintergerst *et al*. 2007). A balanced diet, especially in terms of adequate immune boosting components such as protein, vitamins, and minerals enhances the resistance against infections (Cotter *et al*. 2019). Therefore, providing a good nutritional status and correction of the deficiency of

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immune-related nutrients may be essential for prevention and treatment of viral infections (Pae *et al*. 2012). This review aimed to investigate the latest findings on identifying the effective nutrients on the immune system against viral infections and to present the potentially effective nutrients in the prevention, treatment, and management of COVID-19.

Methods

Study framework

In this systematic review, all articles that focussed on nutrition, the immune system, viral infection, and coronaviruses were collected by searching databases including PubMed, Scopus, Google Scholar, ISI, Embase (Elsevier), and Researchgate for both the accepted manuscripts in peer-reviewed journals and the published papers in the indexed journals from 1990 to 2020.

Study question

The formula question was based on the PICO style as follows: What is the effect of nutrients and dietary supplements on boosting the immune system on preventing and treating COVID-19 compared to other people who do not get enough nutrients? P: People with or without infection; I: Eating a healthy diet or supplement; C: People who don't get a healthy diet or supplement; O: Not getting coronavirus or treating people with coronavirus. The study protocol was approved by ethics committee of Guilan University of Medical Sciences, Rasht, Iran (code IR.GUMS.REC.1399.003).

Search strategy

The current research was performed using the terms of medical subject headings (MeSH) and combinations of the keywords according to the following search strategy: "corona or coronavirus or COVID or COVID-19 or viral or virus or Middle East Respiratory Syndrome or MERS" AND "nutrient or vitamin or mineral or macronutrient or micronutrient or protein or fat or carbohydrate or retinol or calcitriol or tocopherol or phyllo Quinone or thiamine or pyridoxine or ascorbic acid or cobalamin or folic acid or pantothenic acid or biotin or calcium or phosphorus or magnesium or sulphur or iron or iodine or copper or zinc or selenium".

Inclusion and exclusion criteria

All articles collected in the electronic search process as well as the references used in these articles were reviewed ($n = 670$). Duplicated articles were removed ($n = 430$), and then titles and abstracts of all imported studies were screened by two researchers according to the specific selection criteria. Inclusion criteria were: randomised clinical trials (RCTs), case-control, in-vivo studies, and meta-analyses on RCTs which focussed on the role of nutrients on immune system and viral infections. Irrelevant papers and articles without English abstract were excluded from the review process. Finally, 51 articles including 14 meta-analyses were included in review process (17–68) (Figure 1).

Data extraction

Full texts of the studies were independently reviewed by two researchers. Data were extracted from included studies

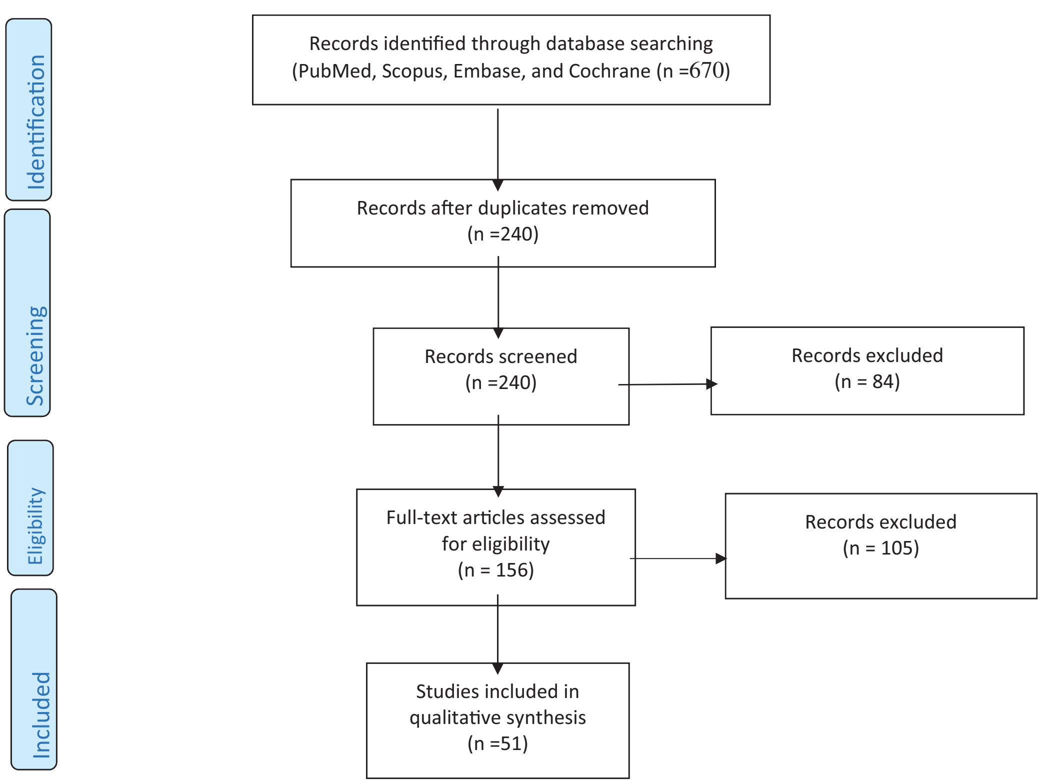

Figure 1. The flow diagram according to the PRISMA guidelines.

for evidence synthesis including author/date, type of study, sample size, intervention, control, primary outcome, results, and *p* values. Then, the accuracy and quality of the included data were checked by a third investigator.

Results

Some nutrients were reported to be actively involved in the proper functioning and strengthening of the immune system, including dietary protein, omega-3 fatty acids, vitamin A, vitamin D, vitamin E, vitamin B_1, vitamin B_6, vitamin B_{12}, vitamin C, iron, zinc, and selenium. Supplementation with some of these dietary components was also reported to be effective in improving the health status of patients with viral infections. Strong evidences including meta-analyses on RCTs are presented in Table 1. The roles of these immune-boosting nutrients are discussed below.

Dietary protein

Dietary protein is considered a vital component in the support and strength the immune system and in the prevention and treatment of viral infections (Kurpad 2006). Amino acids have some critical roles in immune responses including (1) the proliferation and activation of T lymphocytes, B lymphocytes, natural killer cells, and macrophages; (2) regulation of intracellular redox status and gene expression; and (3) the production of antibodies, cytokines and other cytotoxic substances (Li *et al*. 2007). Protein recommendation is estimated 0.8 gr/kg/day in healthy adults, and 1 gr/kg/day in patients with risk of viral infection in order to strengthen the immune system against infections (Kurpad 2006, Wilson *et al*. 2019).

Moreover, some amino acids have key roles in the function of the immune system against viruses. For example, arginine improves the immune system by enhancing T-cells activity. Åkerstrom et al. identified that Nitric oxide (NO), which is produced by arginine, may inhibit the SARS-CoV replication cycle (Akerstrom *et al*. 2005). NO was also reported to has an important role in regulating airway function and in treating airway inflammation and lung diseases (The 2020, Zhu *et al*. 2020). Supportive results were reported in healthy subjects who had significantly increased lymphocyte counts after an oral dose of 30 grams of arginine for 3 days (Visek 1986). However, there are some evidences that additional arginine is not safe in severe septic conditions, especially in patients with shock. This effect of arginine could be due to NO over production, which might have detrimental effects on cardiovascular stability. No direct study has been conducted in the case of Covid-19, but it seems that a dose of $\sim$2% of energy (about 10 gr in a standard 2000 kcal diet) is optimal, safe, and effective when given before a severe infection (Shils and Shike 2006, Alexander and Supp 2014, Mahan and Raymond 2017).

Omega-3 fatty acids

Omega-3 (ω-3) fatty acids can boost the immune system through different mechanisms such as improving B cell activity, decreasing cytokines, decrease inflammatory eicosanoids, and increasing phagocytosis (Chen *et al*. 2010, Zhao and Wang 2018, Gutiérrez *et al*. 2019, Kunisawa *et al*. 2019). Moreover, Kelch like ECH associated protein 1 (KEAP1) is a docosahexaenoic acid (DHA)-dependent protein and provides a cell protection mechanism against oxidative insults when endogenous stress defense mechanisms are imbalanced (Mildenberger *et al*. 2017). The result of a study on healthy subjects indicated that an eicosapentaenoic acid (EPA) intake of 2.7 g/day significantly decreased PGE2 production (Miles and Calder 2012).

The role of omega-3 in improving the health status of patients with infection and respiratory complications has been frequently reported. A meta-analysis identified that omega-3 fatty acids have some effects in improving the situation of the patients with sepsis (Chen *et al*. 2018). Several studies found that omega-3 fatty acids can improve the ratio of CD4–CD8 in patients with severe sepsis which is an indicator for improving patient's immune function and may reduce the mortality rate of these patients (Gao *et al*. 2016, Chang *et al*. 2017, Chen *et al*. 2018).

Three studies investigating a formula containing EPA, DHA, and gamma-Linolenic acid (GLA) in critically ill patients with severe sepsis, acute respiratory distress syndrome (ARDS), and Acute Lung Injury (ALI) reported that this formula could decrease duration of mechanical ventilation and improve oxygenation (Gadek *et al*. 1999, Pontes-Arruda *et al*. 2006, Singer *et al*. 2006). Another meta-analysis on omega-3 found that ω-3 fatty acids in enteral nutrition formulas may be associated with improved rate of the partial pressure of oxygen to fraction of inspired oxygen (PaO2-to-FiO2 ratio), improved ICU length of stay (LOS), and decreased duration of mechanical ventilation in critically ill patients with ARDS. The infection rate, Gas exchange, and liver function were also improved (Langlois *et al*. 2019). No studies are available on the effect of omega-3 on COVID-19. However, the ω-3 PUFA-derived lipid mediator could markedly attenuate influenza virus replication via the RNA export machinery (Messina *et al*. 2020).

Vitamin A

Vitamin A (also called "anti-infection" vitamin) acts as an anti-inflammatory factor involved in improving immune system function and mucosal integrity which protects the body against infections (Stephensen 2001).

Semba et al. reported that vitamin A could decrease the mortality and morbidity rates in infectious diseases such as measles, diarrheal disease, measles-related pneumonia, human immunodeficiency virus (HIV) infection, and malaria (Semba 1999). Children with acute measles infection who received high-dose vitamin A supplementation (60 mg RE on admission and the following day) had higher IgG responses to measles virus and higher circulating lymphocyte counts (Coutsoudis *et al*. 1992). Vitamin A was suggested as an option to the treatment of coronavirus and prevention of the lung infection (Zhang and Liu 2020). Several mechanisms are reported for the anti-infection effects of vitamin A.

Table 1. characteristics of meta-analyses on the effect of nutrients on viral infections.

Study	Design	Sample size	Intervention	Control	Primary outcome	Results	*p* value
Heys et al. (1999)	A meta-analysis of RCTs	Eleven prospective, randomised controlled trials evaluating 1009 patients	L-arginine + n-3 EFAs + RNA supplementation	standard diet	The effect of nutritional support on infectious complications.	Nutritional support supplemented with key nutrients to patients with critical illnesses could reduce infection and reduced the hospital stay.	NS
Chen *et al*. (2018)	A meta-analysis of RCTs	Twenty five studies involving 2417 participants.	Omega 3 fatty acid supplementation.	Standard diet	The effect of omega-3 fatty acids on reducing the mortality of sepsis and sepsis-induced acute respiratory distress syndrome (ARDS) in adults	Omega-3 fatty acid supplementation reduced the mortality rate of sepsis and sepsis-induced ARDS.	.02
Zhao and Wang (2018)	A meta-analysis of RCTs	Sixteen RCTs involving 1008 patients (506 in the omega-3 group, 502 in the control group)	Omega 3 fatty acid supplementation.	Standard diet	The immune efficacy of ω-3 polyunsaturated fatty acid-supplemented parenteral nutrition in patients with gastrointestinal malignancy.	Early intervention with Omega-3 fatty acid emulsion improved the postoperative indicators of immune function, reduced inflammatory reactions, and improved the postoperative status.	.001
Chen et al. (2010)	A meta-analysis of RCTs	13 RCTs involving 892 patients	fish oil-enriched parenteral nutrition	Standard diet	The safety and efficacy of a fish oil-enriched parenteral nutrition regimen in patients undergoing major abdominal surgery	Fish oil-supplemented parenteral nutrition was safe, improved clinical outcomes, as well as leukotriene synthesis.	<.001
Langlois et al. (2019)	A meta-analysis of RCTs	Twelve RCTs ($n = 1280$ patients)	Administration of ω-3 PUFA	Standard diet	The clinical benefits of ω-3 PUFA administration on gas exchange and clinical outcomes in Acute respiratory distress syndrome (ARDS) patients.	In critically ill patients with ARDS, ω-3 PUFAs in enteral immune modulatory diets was associated with an improvement in early and late PaO_2-to-FiO_2 ratio, and improved ICU length of stay and mechanical ventilation duration.	.003
Martineau et al. (2017)	A meta-analysis of RCTs	25 RCTs (a total of 11,321 participants)	Administation vitamin D supplemention.	——	The overall effect of vitamin D supplementation on the risk of acute respiratory infections (ARIs).	Vitamin D supplementation was safe, and it protected against ARIs.	$p < .001$
Hu et al. (2019)	A meta-analysis of RCTs	A total of 7 studies involving 814 chronic hepatitis B patients and 696 healthy controls	Vitamin D level in patients with hepatitis B.	Standard diet	To determine whether vitamin D levels were correlated with hepatitis B virus loads	vitamin D level was lower in chronic hepatitis B (CHB) patients than that of healthy controls and was inversely correlated with hepatitis B virus) HBV viral loads	$p < .001$
Saboori et al. (2015)	A meta-analysis of randomised controlled trials	12 articles involving 246 participants in the intervention groups and 249 participants in control groups	Vitamin E supplementation.	Standard diet	To assess the effect of vitamin E supplementation on CRP levels.	Vitamin E supplementation reduced CRP level	.001
Jafarnejad et al. (2018)	A meta analysis of RCTs	12 studies were included with 446 participants in supplementation groups and 447 in control groups	Administation vitamin C supplementation	Standard diet	The effects of vitamin C supplementation on serum CRP levels	vitamin C supplementation reduced the circulating CRP level	.02
Wang et al. (2019)	A meta-analysis of RCTs	12 RCTs	Intravenous administation vitamin C supplementation to critically ill patients	Placebo	The effects of ascorbic acid high dose (3–10 g) on the mortality of critically ill adults	Intravenous ascorbic acid reduced the duration of vasopressor support, mechanical ventilation, and overall mortality rates	.015

(*continued*)

Table 1. Continued.

Study	Design	Sample size	Intervention	Control	Primary outcome	Results	*p* value
Landucci et al. (2014)	A meta-analysis of RCTs	9 RCTs including 921 patients	intravenous selenium supplementation	placebo	Effect of selenium supplementation on outcome in critically ill patients.	Selenium supplementation was associated with a reduction in 28-day mortality	.04
Li et al. (2019)	A meta-analysis of RCTs	Thirteen RCTs with a total population of 1922 patients with sepsis	Administration selenium supplementation for patient with sepsis	placebo	The clinical outcomes of selenium therapy in patients with sepsis	selenium had benefit effects for sepsis patients and reduced duration of vasopressor therapy, staying time in intensive care unit and hospital, and ventilator-associated pneumonia	.009

Vitamin A contributes to the phagocytic and oxidative activities of macrophages. Vitamin A helps regulate the number and function of NK cells. Vitamin A also helps to regulate the production of IL-2 and the pro-inflammatory TNF-α, which activates the microbial action of macrophages. Vitamin A is also involved in development and differentiation of Th1 and Th2 cells (Gombart *et al*. 2020).

Vitamin D

Vitamin D has antimicrobial and anti-oxidative effects and helps to the immune system against lung infection and airway inflammation (Hansdottir and Monick 2011). Recent studies reported that vitamin D may prevent respiratory infections, especially viral infections (Laplana *et al*. 2018, Teymoori-Rad *et al*. 2019). A meta-analysis on vitamin D found that vitamin D supplementation has protective effects against acute respiratory infections (ARIs) (Martineau *et al*. 2017). Another meta-analysis indicated that vitamin D level was lower in chronic hepatitis B (CHB) patients than that of healthy controls and its level was inversely correlated with hepatitis B virus (HBV) loads (Hu *et al*. 2019). Vitamin D enhances innate cellular immunity partly through the induction of antimicrobial peptides, including human cathelicidin, LL-37, and defensins. These host-derived peptides kill the invading pathogens by perturbing their cell membranes and can neutralise the biological activities of endotoxins.

Vitamin D reduces the expression of pro-inflammatory cytokines such as tumour necrosis factor and interferon-gamma (INF), and increases the expression of anti-inflammatory cytokines. Furthermore, 1,25(OH)2D3 promotes the induction of the T regulatory cells, thereby inhibiting inflammatory processes (Agier *et al*. 2015). Vitamin D also promotes differentiation of monocytes to macrophages, increases their killing capacity; modulates the production of inflammatory cytokines; and supports antigen presentation. Furthermore, vitamin D metabolites regulate production of specific antimicrobial proteins that directly kill pathogens, and thus are likely to help reduce infection in the lungs (Calder *et al*. 2020).

A few studies were done on the association of vitamin D and coronaviruses. The combined supplementation of vitamin D with melatonin could offer a synergistic alternative for the prevention and treatment of pulmonary infection by COVID −19. Nonnecke et al. reported that lower levels of vitamin D in calves caused the increased risk of infection with bovine coronavirus (Nonnecke *et al*. 2014). A recent study reported that the goal should be to raise 25(OH) D serum concentrations above 40–60 ng/mL (100–150 nmol/L) for the treatment of people who become infected with COVID-19. It is recommended that people at risk of influenza and/or COVID-19 consider taking 10,000 IU/d of vitamin D3 for a few weeks to rapidly raise 25(OH) D concentrations, followed by 5000 IU/d [43].

Vitamin E

Vitamin E boosts the immune system and fights disease-causing pathogens such as bacteria and viruses through its

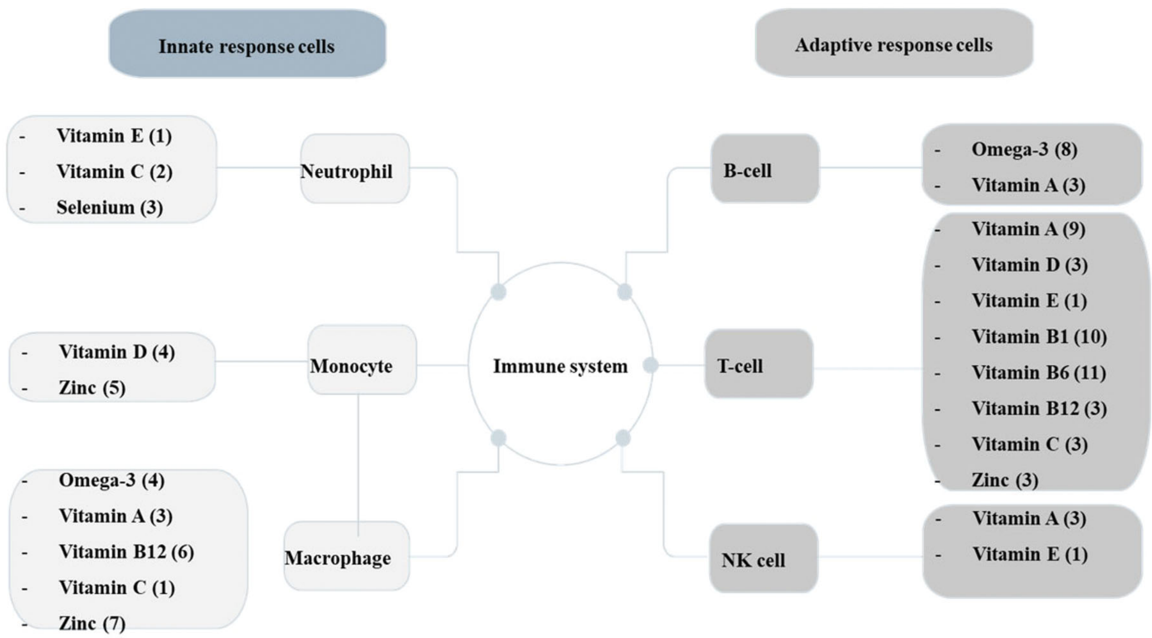

Figure 2. Immune system supporting nutrients.

strong anti-oxidative activity and maintaining the integrity of T-cell membranes (Lewis *et al.* 2019, Calder *et al.* 2020). No direct study has been conducted in the case of association of vitamin E and Covid-19. However, recent studies indicated that vitamin E reduced the duration of infection with the influenza virus (Galabov *et al.* 2015). Meydani et al. reported that vitamin E–treated group (received 200 IU daily) had fewer days with common cold per person-year (Meydani *et al.* 2004).

Suggested mechanisms involved in the effects of vitamin E are: 1) the reduction of PGE2 production by the inhibition of COX2 activity mediated through decreasing NO production, 2) the improvement of effective immune synapse formation in naive T cells and the initiation of T cell activation signals, and 3) the modulation of Th1/Th2 balance. Higher NK cells activity and lower IL-12 production and migration were induced by vitamin E, but the underlying mechanisms need to be further elucidated (Lee and Han 2018).

Vitamin B_1 (thiamine)

Vitamin B_1 has some anti-inflammatory effects through influences on pro-apoptotic proteins, mitochondrial membrane integrity, cytochrome C release, P38 mitogen-activated protein kinase (p38-MAPK) activity, and the oxidative stress-induced NF-kappaB pathway. Deficiency of vitamin B_1 may cause inflammation, T cell infiltration, overexpression of pro-inflammatory cytokines such as IL-1, TNF, and IL-6, and increasing the level of arachidonic acid-derived eicosanoids (Spinas *et al.* 2015). Donnino et al. reported that administration 200 mg thiamine in 50 ml of dextrose 5%, twice daily for 7 days, decreased the mortality rate in adult patients with septic shock and elevated lactate (Donnino *et al.* 2016).

Vitamin B_6 (pyridoxine)

Pyridoxine has a key role in the production of T cells and interleukins (Qian *et al.* 2017). Vitamin B6 has a role in lymphocyte maturation (Gombart *et al.* 2020) and vitamin B6 deficiency has been associated with a dramatic depletion of thoracic duct lymphocytes and a reduction in lymphocyte proliferation (Qian *et al.* 2017). Future studies are required to evaluate the possible effects of pyridoxine on coronavirus and COVID-19(Gombart *et al.* 2020).

Vitamin B_{12} (cobalamin)

Cobalamin plays a vital role in the immune system through helping in the production of white blood cells. Vitamin B12 may act as an immunomodulatory factor and enhance the number of cytotoxic T cells against viral infections (Tamura *et al.* 1999, Gombart *et al.* 2020). Vitamin B12 may also be used as a therapeutic agent in sepsis and systemic inflammatory response syndrome (SIRS). Vitamin B12 may help to maintain the normal function of macrophages. It also has some anti-inflammatory effects such as regulating Nuclear factor-κB (NF-κB), a key activator of the pro-inflammatory pathways. It also has a proven role in bacteriostasis and phagocytosis (Romain *et al.* 2016).

Vitamin C (ascorbic acid)

Ascorbic acid improves the chemotaxis of phagocytes and helps to kill bacteria and viruses by modulation of the accumulation of phagocytic cells such as neutrophils (Carr and Maggini 2017). Vitamin C affects several aspects of immunity, including supporting epithelial barrier function, growth and function of both innate and adaptive immune cells, white blood cell migration to sites of infection, phagocytosis and microbial killing, and antibody production (Calder *et al.*

2020). Hemilä reported that vitamin C might affect the immune system through improving the function of phagocytes, the transformation of T lymphocytes, and the production of interferon (Hemila and Douglas 1999). There is also some evidence that vitamin C may improve the health status of patients with pneumonia (Hemila and Douglas 1999).

Vitamin C may protect against infection caused by coronavirus (Zhang and Liu 2020). Atherton et al. reported that vitamin C improved immune functions of chick embryo tracheal organ cultures against coronavirus infection (Atherton *et al*. 1978). When sepsis happens, the immune cells such as the cytokine is activated, and neutrophils accumulate in the lungs, destroying alveolar capillaries. Vitamin C may help to prevent the excess activation and accumulation of neutrophils, and decrease alveolar epithelial water channel damage. A controlled, randomised trial found that 200 mg/day of vitamin C improved respiratory symptoms and lowered the mortality rate in severely ill elderly patients [34]. However, a meta-analysis reported that vitamin C administration is associated with no significant effect on survival, length of ICU or hospital stay (Putzu *et al*. 2019). Further studies are needed to investigate the association of vitamin C with COVID-19.

Iron

Iron is a vital mineral for both health and infection. Iron is essential for differentiation and growth of epithelial tissue and some iron-containing proteins, such as the haem scavenger HPX, are a central component of the immune system (Nunez *et al*. 2018). Moreover, iron is required for the production of reactive oxygen species (ROS) by neutrophils to kill pathogens (Gombart *et al*. 2020). De Silva et al. reported that 60 mg/daily elemental Fe reduced respiratory infection in children (de Silva *et al*. 2003).

Zinc

Zinc is essential for the development, differentiation, and activation of T lymphocytes (Gombart *et al*. 2020). Zinc deficiency weakens the immune system by reducing macrophages and monocytes and increasing oxidative stress (Maywald *et al*. 2017, Sanna *et al*. 2018). The various functions of macrophages include phagocytosis and the secretion of immune-mediating factors can be impaired by zinc imbalance. Despite extensive research, the molecular mechanisms by which zinc regulates the function of macrophages remain poorly understood (Gao *et al*. 2018). Increased intracellular Zn^{2+} concentrations are known to efficiently impair the replication of several RNA viruses. Velthuis et al. reported that coronavirus replication can be inhibited by increased Zn^{2+} levels. The concentration of 2 μM Zn^{2+} inhibited the replication of SARS-coronavirus (SARS-CoV) in cell culture (te Velthuis *et al*. 2010).

Selenium

Adequate intake of selenium improves immunity and reduces inflammation, mainly through boosting the synthesis of glutamine peroxidase, which protects neutrophils from oxidative stress (Avery and Hoffmann 2018, Gombart *et al*. 2020). Selenium deficiency and suppressed selenoprotein expression have been associated with higher levels of inflammatory cytokines in various tissues including the gastrointestinal tract, the uterus, mammary gland, and other tissues. Dietary selenium deficiency that causes oxidative stress in the host can alter the viral genome, so that a normally benign or mildly pathogenic virus can become highly virulent in the deficient host under oxidative stress (Zhang and Liu 2020). Lei et al. reported that selenium supplementation might improve the immune function and the response to viral infections such as lethal influenza infection (Yu *et al*. 2011).

On the other hand, a mouse model of allergic asthma showed that selenium deficiency reduced airway inflammation while adequate selenium intake induced higher levels of inflammation. In addition, increasing the selenium intake through diet raised expression levels of stress-related selenoproteins as well as genes involved in inflammation and interferon γ (IFNγ) responses (Avery and Hoffmann 2018).

Discussion

This review indicated that some nutrients including dietary protein, omega-3 fatty acids, vitamin A, vitamin D, vitamin E, vitamin B_1, vitamin B_6, vitamin B_{12}, vitamin C, iron, zinc, and selenium have important effects on the immune system (Figure 2). These nutrients increase the body's ability to coping with viral infections. High doses of vitamins and minerals do not yet have a proven protective effect in prevention of infectious diseases in healthy people. However, supplementation according to the Recommended Dietary Allowance (RDA) is recommended for most of healthy people who do not have sufficient intake of nutrient rich sources. On the other hand, some studies demonstrated that supplementation with these nutrients can significantly improve the health-related outcomes in patients with COVID-19.

There are very few studies that have examined the exact effect of nutrients on the coronaviruses. Erol et al. indicated that intravenous high-dose vitamin C could be an effective choice of treatment in the early stages of COVID-19 (Erol 2020). Vitamin C reinforces the maintenance of the alveolar epithelial barrier and transcriptionally upregulates the protein channels (aquaporin-5, ENaC, and $Na+/K+$ ATPase) regulating the alveolar fluid clearance. High dose intravenous vitamin C (HDIVC) has been implicated in reducing plasma cell-free DNA which is the facilitator of systemic inflammation in sepsis-induced multi-organ failure. Interestingly, syndecan-1 in the plasma which is associated with increased mortality in severe sepsis and ARDS patients can be reduced significantly by HDIVC (Kakodkar *et al*. 2020). Gant et al. in a review study reported that vitamin D supplementation can reduce the risk of influenza and COVID-19 infections [38].

The exact molecular mechanism of the effect of the nutrients on corona virus infection are not clear. Kesrtom et al. found that NO inhibited the synthesis of viral protein and RNA (Akerstrom *et al*. 2005). Moreover, COVID-19 is significantly associated with extreme rise in pro-inflammatory cytokines such as IL6 and and C-reactive protein (CRP) (Chen *et al*. 2020). Vitamin D may help in treatment of COVID 19 infection through decrease viral replication rates and reduce the concentrations of inflammatory cytokines [38]. Te Velthuis et al. found that the combination of zinc and pyrithione can efficiently impair the replication of SARS-coronavirus (SARS-CoV) (Yu *et al*. 2011). It is Suggested that chloroquine (CQ) is effective in the control of COVID 19 infection and this drug has an immune-modulating activity (Wang *et al*. 2020). Chloroquine is a zinc ionophore increasing Zn^{2+} flux into the cell. Intracellular Zn^{2+} concentration may mediate the CQ and its metabolite hydroxychloroquine (HCQ) antiviral effects against SARS-coV-2 (Xue *et al*. 2014). Future longitudinal studies are needed to investigate the association of dietary components with COVID-19 and to identify the underlying mechanisms.

Conclusion

This study comprehensively investigated the role of macro- and micro nutrients in supporting the immune system and in the prevention and treatment of infections. Moreover, findings of recent papers on the association of nutrients and coronaviruses were presented. Some nutrients have key roles in the function of the immune system against viral infections. Following an immune-boosting diet is important in order to the prevention of viral infections such as COVID-19. Supplementation with proper dietary components may also improve the health-related outcome of patients with COVID-19. However, there are some limitations including lack of clinical trial studies on the effects of the nutrients on COVID-19 and insufficient data on the effects of supplementation in healthy subjects for the prevention of COVID-19. Further studies are needed to confirm these findings and presenting the strong recommendations for patients with viral infections.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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