THE ROLE OF MINERAL AND SYNBIOTIC TO ENHANCE IMMUNITY DURING COVID-19 PANDEMIC : A LITERATURE REVIEW

Stefania Widya Setyaningtyas[1,2], Dominikus Raditya Atmaka[1,2*], Qonita Rachmah[1,2], Nila Reswari Haryana[3], Mahmud Aditya Rifqi[1,2,4], Rian Diana[1,2], Alif Nurria Nastiti[1], Asri Meidyah Agustin[1]

[1]Nutrition Department, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia
[2]Center for Health and Nutrition Education, Counseling and Empowerment, Universitas Airlangga, Surabaya, Indonesia
[3]Nutrition Program, Faculty of Public Health, Universitas Negeri Medan, Medan, Indonesia
[4]Graduate School of Health Sciences, Hokkaido University, Japan
*E-mail: dominikus.raditya@fkm.unair.ac.id

ABSTRACT

COVID-19 has become a pandemic in the last 3 years worldwide and cases cause high mortality and morbidity. To reduce COVID-19 infection, we need to keep our immune system healthy. Several nutrients have been shown to have specific abilities to increase the power of the immune system, but their use in the treatment of COVID-19 is still being debated. This review aims to determine the role of minerals and synbiotics in increasing immunity during the COVID-19 pandemic. Specific minerals such as zinc, selenium, iron and copper have promising potential to treat COVID-19 by reducing clinical impact, markers of inflammation, and improving immunological biomarkers. In addition to increasing mineral intake, maintaining a healthy immune system can also be done by improving the health of the gut microbiota. One of the therapies that is considered to have a positive impact on handling COVID-19 is using synbiotics (a combination of prebiotics and probiotics). However, the safety and efficacy of mineral and synbiotic supplementation in COVID-19 patients as adjunctive therapy still requires further research. Minerals and synbiotics can help boost the immune system and reduce symptoms during a COVID-19 infection.

Keywords: COVID-19; immunity; mineral; synbiotic; SARS-CoV-2

INTRODUCTION

Coronavirus Disease-19 (COVID-19) is an acute infectious respiratory disease transmitted through droplets and caused by an RNA virus called SARS-CoV-2. World Health Organization has announced that COVID-19 are globally pandemic after its outbreak in all countries. Indonesia itself has gone through third wave of COVID-19 cases with more than 6 million positive cases and 157 thousand death cases on 26 May 2022. COVID-19 specifically gives symptoms like fever, headache, difficulty of breathing, dyspnea, dry cough, vomit, diarrhea, and for several cases leave invasive lesion in the lungs (C. Huang et al., 2020; Shi et al., 2020). Severity of the COVID-19 cases are very diverse and depends on the occurrence of several comorbidities like cardiovascular disease, hypertension, metabolic syndrome, lung diseases, and diabetes mellitus type 2. The mortality also higher in older people and has at least one comorbidities (Mungroo et al., 2020; Zheng et al., 2020).

As it rapid transmission and evolution, until now there are no specific drugs that have been found to cure or prevent COVID-19 infection. So that it is important for people to always make sure their immune system in its best condition so that can fight COVID-19 without further symptom. Human immunity is a complex system that need several nutrients in order to make immune cells work optimally and can combat pathogenic agents (Shetty, 2010; Wood, 2006). One of which mineral that plays major role in providing better immune system, namely zinc, iron, selenium, and cooper. Several studies has showed information about the correlation between mineral and immune system both innate and adaptive (Gombart et al., 2020; Wintergerst et al., 2007). Deficiencies of several mineral known can affect immune cell function and make people more susceptible to infections (Calder et al., 2020; Gombart et al., 2020). So that it is important to make sure adequate intake of mineral during COVID-19 pandemic.

In order to gain an optimal immune system against COVID-19, it is necessary to also maintain

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gut health. It is important because the SARS-CoV 2 can enter bloodstream through Angiotensin Converting Enzyme (ACE2) receptor which mostly can be found in digestive tract (Li et al., 2003; Zou et al., 2020). This also answer why many cases of COVID-19 has developed digestive symptom during infection period. Several studies has shown that the usage of synbiotic (combination of prebiotic and probiotic) can act as prevention to infections related to gut by helping balance intestinal microecology, improve the microbiota dysbiosis, and prevent secondary infections caused by bacterial translocation (Xu et al., 2020). But, the connection between synbiotic and COVID-19 still unclear and need further studies.

Reviewing the needs to explore the connection between mineral and synbiotic intake, it is necessary to make a review to investigate these correlation. In this review, we assessed the role of mineral and synbiotic in supporting the immune system and its correlation to COVID-19.

THE ROLE OF MINERAL IN THE IMMUNE SYSTEM

1. Zinc

Zinc takes significant part within the immune system. The free form of zinc has an immediate antiviral effect (Alpert, 2017). The daily requirement for zinc is 8-11 mg/day, with an upper limit of 40 mg/day. Zinc intake as many as 30-50 mg/day during infection is recommended to control RNA virus, such as influenza and coronavirus (Institute of Medicine, 2001; McCarty & DiNicolantonio, 2020). If zinc deficiency occurs, then there will be an increase in the risks of viral infection, thymic atrophy, lymphopenia, and decreased lymphocyte responses. Zinc can be found in lean red meat, whole grain cereals, nuts and legumes (Hidayati et al., 2019).

Zinc can inhibit enzymatic activities, SARS-CoV RNA polymerase replication, and inhibit ACE2 activities. Zn^{2+} also reduces the permeability of cell membranes without damaging nor penetrating the cells. Zinc provides protective effects in the prevention and COVID-19 therapy, where zinc increases the capillary epithelial barriers and inhibit the transcapillary protein plasma movement. Therefore, zinc reduces local oedemic incidents, inflammation, exudation, and mucus secretion, preventing lung injury due to the use of a ventilator, modulating the antiviral immunity, and being a regulator of the tight junction of ZO-1 and Claudin-1 proteins to increase its barrier functions so that the virus can be prevented (Hunter et al., 2020; Skalny et al., 2020).

Zinc is vital for cell growth and differentiation of both innate and humoral immune cells, and also modulate cytokine release and trigger T cell $CD8^{+}$ proliferation (Wintergerst et al., 2007). Zinc is also vital for the intracellular binding of tyrosine kinase at T cell receptors, which is required for the development and activation of T lymphocytes (Wintergerst et al., 2006). Furthermore, zinc is a cofactor for 750 transcriptional factors for protein synthesis related to the immune and a cofactor for 200 enzymes involved in the formation of antioxidants, such as superoxide dismutase (SOD) and SMAD anti-inflammatory protein, by stabilizing the tertiary structure and being an essential component on the catalytic site of enzymes (Andreini et al., 2011; Gammoh & Rink, 2017). Zinc is needed in the production of the metallothionine antioxidant complex that is responsible for the lungs' elasticity. Moreover, it has been noticed that zinc plays a role in doubled-reducing the mortality rate due to pneumonia in people with adequate zinc intake (Barnett et al., 2010).

Zinc supplementation causes transient zinc chelation by N,N,N',N'-tetrakis(2-pyridinylmethyl)-1,2-ethanediamine (TPEN) to induct the antiviral inside cells through the activation of NF-κB that triggers the interferon signaling. Zinc also roles as an anti-inflammatory agent, which triggers the development of Treg, Th17, and Th9 cells and helps the production of IgG antibody (Bonaventura et al., 2015; Gombart et al., 2020; Subramanian Vignesh & Deepe Jr, 2016). Zinc is a part of some antiviral compounds, namely zinc N-ethyl-N-phenyldithiocarbamate (EPDTC). Zn^{2+} ion also triggers viricidal activities by damaging the receptors on the surface of the viral cell through ions-centered tetrahedral geometric coordination that functions as an inhibitor against 3C and 3C-like proteases

(Lee et al., 2009). Zinc is also able to decrease the expressions of IL-6 plasma, IFN-α, IL-1b, and TNF-α genes. On the other hand, zinc can increase the IFN-α mediated by JAK1/STAT1 through signaling and increase antivirus enzyme, for instance, latent ribonuclease (RNase L) and protein kinase RNA (PKR), which results in RNA degradation and RNA translation inhibition (Günzel & Yu, 2013).

In vitro study revealed that zinc could reduce the ability of RNA replication by inhibiting RNA polymerase as in coronavirus (Martindale et al., 2020). The antiviral zinc-finger protein complex (ZAP) controls the process of virus entry, DNA/RNA replication, and the spread of viral infections (Wang et al., 2010). ZAP ACCHC3 can bind to RNA and facilitate intracellular RNA detection by activating retinoic acid-inducible gene-I (RIG-1)-like receptors (RLRs) and MDA5. The process then causes the kinases such as TBK1 and IkK phosphorylases the interferon regulatory transcription factor 3 (IRF3) and IkB-alpha (inhibitor of NK-kB) that increases the type-1 interferon. IFN-α triggers the signal to escalate the antiviral protein (RNase L and PKR) that degrades and restrains the process of RNA translation. Zinc inhibit the NK-kB activities using A20 (ZAP) protein expression that decreases TNF receptor regulation and initiates TLR-NK-kB tracks. Zinc also acts as a cyclic nucleotide phosphodiesterase (PDE). When PDE is inhibited, it will increase cyclic nucleotide guanosin monophosphate (cGMP) which activates PKA (protein kinase A) and inhibits NK-kB.

2. Iron

Iron is one of the essential nutrients for the body with various functions, including energy metabolism, growth and development, and the immune system (Sundari & Nuryanto, 2016). Iron can be found in numerous food sources, for instance, red meat, liver (beef and chicken), beans, red rice, and dark green leafy vegetables (spinach, kale, and others) (Calder, 2020). Iron is needed by the ribonucleotide reductase enzymes to synthesize the DNA, which functions to form lymphocyte-T cells. Iron deficiency can impaired the myeloperoxidase enzyme functions in the immune system (Sundari & Nuryanto, 2016).

Care needs to be taken in providing iron supplementation in people suffering from infectious diseases. Studies in tropical areas affirmed that iron administration to children with a dose above a certain threshold could escalate the risk of malaria and other infections, including pneumonia. Therefore, the intervention of iron in malaria-endemic areas is not recommended due to several reasons. First, excess iron may lead to the disruption of the immune functions. Second, excess iron can worsen the inflammation. Third, microorganisms need iron to support the growth of the pathogen (Cherayil, 2010; Drakesmith & Prentice, 2012; Ganz, 2018; Ganz & Nemeth, 2015; Nairz et al., 2017, 2018; Oppenheimer, 2001; Weiss, 2002).

Based on those reasons, hence, some methods have been developed to restrain iron-binding or used by pathogens. A study revealed that the provision of iron as much as 50 mg for four days in a week to school-aged children with iron deficiency increased the risk in respiratory tract infections. On the other hand, the addition of omega-3 PUFA as much as 500 mg for four days a week can decrease the adverse effects of iron supplementation (Malan et al., 2015). A meta-analysis study in Chinese children disclosed that those who undergo recurrent respiratory tract infections tend to be lack of iron on their hair (Mao et al., 2014). Thus, it can be implied that the administration of iron must be precise, whether the doses, the patient's condition, or the way of administering.

3. Selenium

Selenium was discovered by John Jakob Berzelius, a Swedish scientist, in 1817. According to Avery J.C. and Hoffman PR, selenium in the human immune system can be studied from the perspectives of immunobiology, leucocyte function increase, and the immune response towards pathogens and anti-cancers (Avery & Hoffmann, 2018). In general, seafood and internal organs are rich sources of selenium. In addition, meat, whole grains, dairy products, and eggs are also good sources of selenium (Kusmana, 2017).

Selenium deficiency can generate immune-incompetence, which will enlarge the risks of viral infections. Epidemiological study in China revealed the positive correlations between the

population selenium levels and COVID-19 recovery rates in 17 cities (Zhang et al., 2020); the higher the selenium level in the body, the faster the recovery of COVID-19 patients. Selenium is one of the micronutrients with essential roles in the immune system, particularly in suppressing the occurrence of oxidative stress. COVID-19 includes in viral infections related to the increase in oxidative stress by enhancing enzyme-producing ROS. Selenium, in the form of sodium selenite reduces the ROS production and the apoptosis of infected cells (Kretz-Remy & Arrigo, 2001).

RNA virus could be a trigger of NF-κB (Nuclear Factor kappa B) activation. The activation of NF-κB in cells infected with the nucleocapsid protein from the SARS-CoV can cause the severity of inflammation in lung lesions in SARS patients (Liao et al., 2005). Selenium has a role as the NF-κB inhibitor among mice exposed to the SARS-CoV, which relates to the survival/immunity (DeDiego et al., 2014).

Besides the functions that have been elucidated, selenium also enhance the activity of the glutathione peroxidase (GSH-Px) (Ghneim, 2017)Selenium in the glutathione peroxidase acts as the catalysator in breaking down the peroxides to be a non-toxic/non-reactive bond. Together with vitamin E, selenium can protect endothelial cells/ cell membranes that become the target of SAR-CoV-2 infection (Brigelius-Flohé et al., 2003). The integrity of cell membranes is fundamental, given the cytokine production is determined by the receptor in the cell membrane; hence, selenium is influential in increasing cellular immunity. Selenium is also an antioxidant that boosting the immune system. Selenium deficiency has a significant impact on the activity of selenoprotein antioxidant (specifically Gpx 1 expression) and on reducing the mRNA signal related to the inflammatory pathways. Thus, reducing the body's resistance against the viruses (Z. Huang et al., 2012).

4. Copper

Copper acts as the cofactor in the cellular metabolic reactions and copper-dependent enzymes catalyst reactions that involve molecular oxygen species. Several copper enzymes play a role in the body's antioxidant defenses (Shetty, 2010). Copper is a micronutrient needed by pathogens and the host during the viral infection. Copper support Th cells, B cells, neutrophil, NK cells, and macrophage that influences the innate and adaptive immune responses (Raha et al., 2020). Copper also supports macrophage functions (copper accumulates in the phagolysosomes of macrophages to fight infectious agents), neutrophil, monocytes, and also increases the activity of NK cells. Furthermore, copper plays a role in the differentiation and proliferation of T cells, as a component of intrinsic antimicrobial which has anti-inflamatory action, antioxidant, and oxidative burst (Gombart et al., 2020). It is believed that copper has a role in the inflammatory responses given copper is a part of Cu/Zn SOD enzymes, which are the keys in the defense against ROS in maintaining the balance of intracellular antioxidant along with selenium and zinc (Gombart et al., 2020; Wintergerst et al., 2007).

The data regarding copper deficiency in humans is very limited due to lack of efficiency usages, homeostasis, and the appropriate parameters to determine the status of copper. The sufficient amount of copper intake enhanced the Th1 responses, decrease T cell proliferation, and increase B cell circulations. A high dose of copper intake (7 mg per day) for healthy adult males in an extended period can reduce the percentage of neutrophilic circulation, IL-2 serum receptor, and antibody titers against influenza virus strain Beijing. On the contrary, the same dose for the same subjects can increase the average immune responses (IL-6). Moreover, there is a pro-oxidant effect that makes this high dose of intake protect red blood cells against peroxidation induced in vitro (Wintergerst et al., 2007).

Copper can kill certain contagious viruses, such as bronchitis virus, poliovirus, HIV type 1, both enveloped and nonenveloped viruses, and single or double-stranded DNA and RNA viruses. Thus, the addition of copper intake can encourage both the innate and adaptive immune systems (Raha et al., 2020). However, until recently, the registered trials to disclose the impact of copper supplementation on COVID-19 patients is not yet published.

THE ROLE OF SYNBIOTIC IN THE IMMUNE SYSTEM

The use of synbiotic (combination of prebiotic and probiotic) in preventing the risks of infections began to be noticed. The Zhejiang Hospital of China recommended the provision of synbiotic in COVID-19 patients to help balance intestinal microecology, improve the microbiota dysbiosis, and prevent secondary infections caused by bacterial translocation (Xu et al., 2020).

1. Probiotics

Some studies have revealed the effects of probiotics (Bifidobacterium and Lactobacillus) provisions in reducing respiratory infections (de Araujo et al., 2015; Ichinohe et al., 2011). Probiotics can escalate the interferon and the number and activities of antigen, NK cells, T cells, as well as specific antibody both systemic and mucosal (Namba et al., 2010; Zelaya et al., 2016). Probiotics are proven influential in regulating pro-inflammatory and immunoregulatory cytokines that control the clearance virus and prevents lung damages caused by the immune responses. *Lactobacillus plantarum DR7* is affirmed to be able to suppress the proinflammatory plasma cytokines (IFN-gamma and TNF-alpha), increasing the anti-inflammatory cytokines (IL-4, IL-10), and decreasing the plasma peroxides and the oxidative stress (Chong et al., 2019). It is important in COVID-19 patients which experiencing the cytokine storm. Probiotics can also enhance the tight junction integrity and production of the short chain fatty acid (SCFA) Butyrate, and provide nutrition for colonocytes thus, reduce the SARS-CoV-2 invasion (Baud et al., 2020). Studies also found that probiotics could upsurge the amount of leucocyte, neutrophil, IL-2. TNF-beta, decrease the cytokine expressions (TNF-alpha, IL-1beta, IL-6, IL-8, IL-5, IL13), and IgA saliva level can produce bacteriocin and reuterin, promote phagocytosis, and can maintain Th1 and Th2 homeostasis (Fooks & Gibson, 2002; Guillemard et al., 2010).

Lactobacillus plantarum, as one type of probiotics has been shown to have antiviral activities against coronavirus in the intestinal epithelial cells. *L.plantarum* can also provide IFN-λ3 to suppress the enteric coronavirus infection and can be used as an alternative antiviral therapy (Liu et al., 2020). Several meta-analyses showed the presence of probiotic effects (*Lactobacillus rhamnosus GG, Bacillus subtilis,* and *Enterococcus faecalis*) in decreasing the incidence and the viral infection duration of the critically ill patients with respiratory tract infections (Hao et al., 2015; King et al., 2014). Xu et al., in their study, concluded that many COVID-19 patients in China experience dysbiosis of intestinal microbiota, which is marked by the decrease in Lactobacillus and Bifidobacterium because the use of antibiotics and COVID-19 causes diarrhea (Xu et al., 2020).

Probiotics, such as *Lactobacillus plantarum, Lactobacillus casei, Bifidobacterium animalis, Bacillus coagulans, Streptococcus salivarius*, and *Enterococcus faecium* have proinflammatory interleukin inhibitor effects. On the other hand, *Lactobacillus gasseri, Lactobacillus rhamnosus,* and *Bifidobacterium longum* are acknowledged for their ability to increase the antibody. *Bifidobacterium animalis* can prevent the coronavirus replication by lowering the inositol-requiring enzyme 1 (IRE1) pathway, thereby reducing interleukin 17 (Bozkurt et al., 2019). *Lactococcus lactis* JCM5805 activates plasmacytoid dendritic cells (pDC), where the pDC acts as the cells that produce IFN1 (Siegal et al., 1999; Trinchieri & Santoli, 1978) and mucosal T cells (Tezuka et al., 2011). Moreover, pDC can directly prevent viral spread and replication (Theofilopoulos et al., 2004), and activate the NK cells (Tezuka et al., 2011). Additionally, some probiotics, for instance, *Enterococcus faecium* HDRsEf1, can reduce the mRNA TLR4, TLR5, TLR7, and TLR8 (Tian et al., 2016).

Probiotics in Indonesian foods can be found from sayur asin, tempoyak, mandai, tape, growol tempe, kecap, bakasang, dadih, and many more. Mostly these foods are rich in lactic acid bacteria that good to our health (Nuraida, 2015).

2. Prebiotics

Prebiotics, which are undigested carbohydrates such as inulin, polydextrose, oligosaccharides, fiber, and resistant starch, are used by intestinal microbes for fermentation. Prebiotics are also acknowledged to increase the immunity and the diversity of the gut microbiota, as well as aiding digestion (Bouhnik et al., 2007). As an example,

prebiotics obtained from wheat is proven to reduce the proinflammatory cytokine IL-6 and to boost the anti-inflammatory cytokine IL-10 (Keim & Martin, 2014; West et al., 2017). Prebiotics such as wheat bran, fructooligosaccharides (FOS), and galactosaccharides (GOS) can increase the butyrate levels that reduce inflammation and improve the respiratory fibrosis (Anand & Mande, 2018). SCFA from prebiotic metabolism strengthens the gastrointestinal association with lymphoid tissue (FALT) (Schley & Field, 2002). Hence, administering prebiotics and probiotics to COVID-19 patients can help to improve the intestinal dysbiosis conditions, thereby accelerating the healing process. Prebiotics can help fight respiratory infections as proven by Trompette et al. in their research, where the subject mice fed with prebiotic dietary fiber experienced an increase in macrophage and a reduction in the production of chemokine CXCL1, which causes neutrophil increases in the lungs, as well as adding the $CD8^+$ cell functions (Trompette et al., 2018).

An RCT involving 94 premature babies revealed that the intervention of mixed prebiotic galactooligosaccharide and polydextrose (1:1) or probiotic *Lactobacillus rhamnosus GG* reduces the incidence of respiratory tract infections by 2-30 times compared to placebo (Guillemard et al., 2010). Additionally, the administrations of synbiotic *Pediococcus pentosaceus* 5-33:3, *Leuconostoc mesenteroides* 32-77:1, *L. paracasei ssp. paracasei* 19, *L. plantarum* 2,362 in conjunction with inulin, oat bran, pectin, and resistant starch in critically ill patients with a ventilator are proven to decrease the rates of infections, sepsis, SIRS, length of treatment, the period of using a ventilator, and mortality (Kotzampassi et al., 2006).

In Indonesia, prebiotic are mostly can be found in tuber crops, like gembili, yam, dahlia rooth, potato, sweet potato, and cassava. Prebiotic also can be found in chicory, artichoke, and garlic (Zubaidah & Akhadiana, 2013).

CONCLUSION

Enhancing immune system during COVID-19 pandemic is necessary. The use of zinc during COVID-19 infection can give better result of treatment. Minerals with anti-inflammatory and antioxidant properties can help to reduce inflammatory response during COVID-19 infection. The usage of synbiotic also can help enhance immune system by balancing intestinal microecology and microbiota balance so it can help preventing the infection of COVID-19. However, the safety and efficacy of nutritional supplementation, including minerals and synbiotic as adjunctive therapy for COVID-19 patient needs further studies.

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