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The effects of probiotics in strengthening immunity against the COVID-19 infection

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ABSTRACT

A severe form of COVID-19 infection causes increasing in inflammatory cytokines, namely cytokine storm. Therefore, immunity of patients with COVID-19 should be strengthened in order against this infection. This paper aimed to evaluate the possible effects of probiotics in strengthening immunity patients with COVID-19. It is a narrative literature review papers based on PubMed, Science Direct, and Google Scholar databases. The keywords were COVID-19 pandemic, immunity, probiotics. Inclusion criteria were review and research paper. Exclusion criteria were not peer-reviewed journals and unavailable full text. Probiotics are beneficial live microbes, and they are well known for their immune and nutritional properties. The potential roles of probiotics to increase the immune system against the COVID-19 infection need to be studied in further clinical research. Most of the research related to the roles of lactic acid bacteria (LAB) are found in fermented food as probiotics. Many LAB are found in Indonesian fermented foods. Lactic acid bacteria roles are essential in the production of fermented foods. They also give some health benefits such as improving antioxidant activity, increasing antimicrobial agents production, and as probiotics.

ABSTRAK

Bentuk infeksi COVID-19 yang parah menyebabkan peningkatan sitokin inflamasi yang disebut badai sitokin. Oleh karena itu, kekebalan pasien COVID-19 harus diperkuat untuk melawan infeksi tersebut. Tujuan dari makalah ini adalah untuk mengkaji kemungkinan efek probiotik dalam memperkuat kekebalan pasien COVID-19. Ini adalah tinjauan pustaka naratif berdasarkan database di PubMed, Science Direct, dan Google Cendekia. Kata kuncinya adalah pandemi COVID-19, imunitas, probiotik. Kriteria inklusi adalah tinjauan pustaka dan paper penelitian. Kriteria eksklusi bukan jurnal *peer-review* dan naskah lengkap yang tidak tersedia. Probiotik adalah mikroba hidup yang bermanfaat dan dikenal luas karena sifat kekebalan dan nutrisinya. Peran potensial probiotik untuk meningkatkan sistem kekebalan tubuh terhadap infeksi COVID-19 perlu dipelajari dalam penelitian klinis lebih lanjut. Sebagian besar penelitian mengaitkan peran bakteri asam laktat (BAL) dalam makanan fermentasi sebagai probiotik. Bakteri asam laktat banyak ditemukan pada makanan fermentasi Indonesia. Bakteri asam laktat mengungkapkan beberapa efek penting seperti meningkatkan aktivitas antioksidan, meningkatkan produksi agen antimikroba, dan sebagai probiotik. Peran BAL sangat penting dalam produksi makanan fermentasi, termasuk makanan Indonesia. Oleh karena itu, ada kemungkinan peran probiotik dalam memperkuat kekebalan terhadap infeksi COVID-19.

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INTRODUCTION

The nutritional and immune roles of probiotics and prebiotics are well studied. However, their potentials to increase immunity against COVID-19 infections need further clinical and laboratory trials.[1] Probiotic usually belong to the genera of Lactobacillus and Bifidobacterium.[2] The panel of the International Scientific Association for Probiotics and Prebiotics (ISAPP) updated the definition of prebiotic. It is a substrate that is selectively used by host microorganisms for health benefits.[3] The Food and Agriculture Organization of the United Nations (FAO) defines probiotics as live microorganisms which when administered in adequate amounts confer a health benefit on the host.[4] Postbiotic is preparation of inanimate microorganisms and/or their components that confers a health benefit on the host. Effective postbiotics contain inactivated microbial cells or their components, with or without metabolites.[5]Coronavirus disease 2019 (COVID-19) is a newly emerged respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has spread all over the world and caused pandemic.[6] The COVID-19 infection which led to various clinical presentations from asymptomatic until severe infection. Most patients experience mild to moderate symptoms, however, approximately 15% of patients get severe pneumonia. Meanwhile, 5% of them suffer from acute respiratory distress syndrome (ARDS), multiple organ failure, or septic shock.[7]

The treatments are symptomatic treatment and oxygen mechanical ventilation was given for patients who suffer from respiratory failure.[8]

Several antiviral drugs are also administered. Besides the research about vaccine development and the target of the blockade of viral entry, treatments for the immunopathology of the infection are the major focus.[7]

SARS-CoV-2 infection can affect innate and adaptive immune responses. Uncontrolled inflammation of innate responses and impaired adaptive immune can damage the tissues. The effects can be local and systemic. Patients with severe COVID-19 have lymphopenia. There are reduced numbers of CD4+ T cells, CD8+ T cells, natural killer (NK) cells, and B cells. The number of monocytes, eosinophils, and basophils is also decreased. An increase in neutrophil count reveals higher disease severity. It also has a poor clinical outcome. NK cells and CD8+ T cells are upregulated in COVID-19 infection. In patients who have recovered from the COVID-19 infection, the numbers of CD4+ T cells, CD8+ T cells, NK cells, and B cells are back to normal. Therefore, SARS-CoV-2-specific antibodies will be found. Convalescent plasma containing neutralizing antibodies is used to treat severe diseases. The preliminary results reveal better symptoms for severely infected COVID-19 patients who developed ARDS (acute respiratory distress syndrome).[7]

SARS-CoV-2 infection is related to gut microbiota changes. The quality of diet might alter the intestinal microbiota. Thus, this mechanism can affect the immune-host reaction. Therefore, the nutritional aspect should be a concern when taking care of the COVID-19 infected patients. Administration of probiotics showed positive effects on oxidative stress. The transport function is also affected, especially in the angiotensin-converting enzyme 2 (ACE2) receptor. ACE2 as the receptor for the SARS coronavirus is critical for the expression of neutral amino acid transporters in the gut.[9]

Most of the research related to the roles of lactic acid bacteria (LAB) is found in fermented food as probiotics. Many LAB are found in Indonesian fermented food.[10] The fermented food is categorized into the lactic, alcoholic, mold, and high salt fermentation. Fruit and vegetables undergo lactic fermentation. Cassava has alcoholic and lactic fermentation.

Soybean can be modified by high salt and mold fermentation. Traditional Indonesian fermented foods contain LAB, including Lactobacillus, Enterococcus, Weisella, Pediococcus, and Leuconostoc.[11] Those LAB can be used as starter cultures. Their functional and physiological properties are important to be considered as probiotics. Indigenous LAB strains are essential in improving the quality and safety of fermented foods. The LAB reveal some essential effects such as improving antioxidant activity, increasing the production of antimicrobial agents, and as probiotics.[12]

Terasi is one of the most famous fermented food in Indonesia. It is fermented shrimp.[13] Based on the research, the fermented ship contains bacteriocin from the gram-positive bacteria, and *Virgibacillus salexigens* isolated from shrimp paste.[14] Bacteriocin is important in the preservation process. Bacteriocin can also inhibit the pathogen bacteria such as *Escherichia coli, Vibrio parahaemiliticus*, and *Staphylococcus aureus*.[15]

Lactic acid bacteria roles are essential in the production of fermented foods, including Indonesian food.[1] Lactic acid bacteria is often associated with probiotics and gut microbiota. Probiotics and the indigenous gut microbiota are critical in supporting intestinal health. Therefore, LAB, probiotics, and gut microbiota have been scientifically correlated with each other. Lactic acid bacteria are essential. For example, they can produce the enzyme (linamarase) to hydrolyze the cyanogenic compound of cassava.[16] In another case, *Lactobacillus plantarum* (IFK-10) and *Pediococcus pentosaceus* (IFK-11), act as GABA-producing bacteria. They can be used as a starter culture to MSG into GABA during 24 h of cultivation.[17]

Several LAB has been recognized as probiotics that reveal significant health benefits. Yogurt is the most popular fermented food, and some LAB from Indonesian fermented food reveal probiotics properties. They are beneficial for the gut microbiota and intestinal health. Probiotics are live microorganisms that give health benefits to the host. Speciation of bacteria strains identity should be established too. Strain identity is essential to link a strain to a specific health effect. This will enable proper surveillance and epidemiological studies. A combination of phenotypic and genetic tests should be used. The nomenclature of the bacteria must be precise and scientific-based on the current nomenclature.[1] Based on taxonomy revision of LAB, four probiotics candidate strains, i.e., Mut7, Mut-13, T-3, Dad-13 are *Lactiplantibacillus plantarum* subsp. Plantarum, while SNP-2 is *Lacticaseibacillus paracasei* subsp. Paracasei.[18]

Immunomodulation includes the natural and also treatment options to modify the immune response of the host. Immunomodulators can be categorized as immunostimulants and immunosuppressants. Immunostimulants can stimulate the immune system, meanwhile, immunosuppressants suppress the immune system.[1] SARS-CoV-2 RNA is also detected in the gastrointestinal tract and feces. Coronaviruses can invade enterocytes. Therefore, enterocytes are also reservoirs for the virus. The clinical studies in China revealed that gastrointestinal symptoms are commonly found in patients that were infected by the COVID-19.[19] Probiotics have roles in maintaining the equilibrium state of gut microbiota and the immune cells in the gut.[12] Therefore, probiotics might have essential roles in fighting against the COVID-19 infection.[20] In the gastrointestinal tract, peptidoglycan in gram-positive and lipopolysaccharide in gram-negative revealed significant roles in improving the immune system.[1]

Gut microbiota has a critical role in fighting against the lung disorders such as asthma, pneumonia, bronchitis, and viral infection. The viral infection disturbs the equilibrium state of the gut microbiota.[21] The most essential probiotics to increase

the immunity against the COVID-19 infection, namely *L. casei, L. gasseri, L. rhamnosus, L. plantarum, P. pentosaceus, B. longum, B. bifidum, B. breve,* and *L. mesenteroides*.[19] Recent research in China revealed that COVID-19 infection causes an imbalance of intestinal natural microbiota. It was based on the reduced counts of Bifidobacterium spp. and Lactobacillus spp. in the intestine of the patients infected by COVID-19.[22] There is microbial dysbiosis in patients with COVID-19 infection. Their test results showed decreased Lactobacillus and Bifidobacterium.[23] In a retrospective study from China (Zhejiang province), it was revealed that most of the patients who had mild symptoms, had consumed probiotics and the other usual treatments such as interferon-alpha inhalation, ritonavir, lopinavir, and arbidol.[22]

The COVID-19 could induce poor oxygenation and dysbiosis of gut microorganisms. There is a significant reduction of probiotics (Bifidobacterium spp., Eubacterium spp., and Lactobacillus spp.). The number of pathogens, namely Corynebacterium spp., Actinobacteria spp., and Ruthenibacterium spp. was also increased. The COVID-19 infection might cause problems in the intestinal system. The research reveals that the genus of Lactobacillus and bifidobacterium could neutralize gastrointestinal dysbiosis.[12]

Alleviating the cytokine storm in the COVID-19 patients

The cytokine storm is found in patients with severe COVID-19 infection. It is caused by the production of a huge amount of proinflammatory cytokines.[8] This cytokine storm causes damage to the gastrointestinal tract, lung, cardiovascular system, brain, kidney, liver, eyes, and microcirculation.[1]

Research has shown that probiotics could regulate immune cells and epithelial cells in the intestinum. Probiotics reveal functional roles in maintaining equilibrium between the necessary and unnecessary immune responses (innate and adaptive). It is the greatest immunomodulatory tool for people.[1] There are approximately160 species of bacteria in the gut microbiome. More than 70% of the immune cells reside in the gastrointestinal tract. Therefore, there is an essential association between the intestinal microflora and the immune system. Inflammation can disrupt the gut microbiota and elevate the levels of ACE2.[24]

Several biological interactions in the immune response by the probiotics are direct interaction with epithelial cells, dendritic cells, epithelial cells, lymphocytes, gene expression, and also signaling pathways. A biological role of probiotics is regulating the immune response. However, further clinical research is needed.[19,23] Improving human immunity could be done by giving probiotic supplementations.[21]

The immune benefits of probiotics are done by stimulating the IgA secretion, improving the biological functions of macrophages and phagocytosis, and also adjusting the regulatory cells. There is scientific proof about the importance of probiotics and nutrition elements in increasing the immune system. These might be the essential roles of management of the COVID-19 infection.[1]

Therefore, this paper aimed to investigate the roles of probiotics in increasing immunity against COVID-19 infection.

METHODS

This was a narrative literature review. Literature was taken from PubMed, Science Direct, and Google Scholar search engines. Inclusion criteria were full text, review, and research. Exclusion criteria were only abstract and more than ten years of publication date. The screening was done by the title, abstract, and full text. Finally, there were 29 journals.

The study selection began with the removal of duplicate records. The irrelevant studies were excluded by screening the titles and abstracts. If

the free full text is available in English or Indonesian, then the reading and selection would be continued. Otherwise, it would be removed. Full-text screening steps were reading the abstract and conclusion and examining the type of the text. Case reports and pre-print articles were excluded.

RESULTS AND DISCUSSION

Probiotics are well known for their immune and nutritional properties. The potential roles to increase the immune system against the COVID-19 infection need to be studied in further clinical research. Coronavirus disease (COVID-19) is contagious that caused many problems, including health and economic problems which the cases are still increasing. The immune benefits of probiotics and prebiotics are good. However, their potential roles in fighting against the COVID-19 infection need further investigation.[1]

SARS-Cov-2 is the β-coronavirus genus. It has more than 79% homology with the coronavirus for severe acute respiratory syndrome (SARS-CoV). Approximately 50% homology is found with the coronavirus that is responsible for the Middle East respiratory syndrome (MERS-CoV).[25] Policies from the government in the world such as safety measures, isolation, and social distancing are not sufficient to control the transmission of COVID-19 infection. Those steps need to be accompanied by prompt medical management of COVID-19 infection. More prophylactic approaches are also necessary to prevent the infection of the COVID-19.[26]A variety of symptoms are identified in the COVID-19 infection. The symptoms are flu-like systems, severe respiratory infection, pneumonia, and failure of body organs. Air droplets are the main source of transmission. The gastrointestinal tract might also be involved in the pathogenesis of COVID-19 infection because RNA of SARS-CoV-2 was found in the patients' gut and feces. SARS-CoV-2 can infect the intestinal cells. This condition is found in a carrier for COVID-19. The clinical data showed that gut infection is common in coronavirus. It causes the severity of diseases.[26]Probiotics are vital microorganisms that reveal several beneficial effects in the host. Medical data showed that particular strains of probiotics are useful in the prevention of viral and bacterial infections.[26] Probiotics supplementation may alleviate the clinical presentation and morbidity. Probiotics may inhibit cytokine storms. Probiotics boost innate immunity. The adaptive immunity exaggeration is evaded. Probiotics suppress the inflammatory cytokine response. Probiotics may reduce the severity of ARDS. Probiotic secreting lactic acid lowers the level of intestinal pH. Probiotics can increase the absorption of vitamin D. The levels of vitamin D can be improved. Probiotics enhance the expression of vitamin D receptor (VDR) protein. The transcriptional activity increases. Besides, probiotics also enhance the expression of defensins. Supplementation of probiotics for COVID-19 patients might alleviate the infection. The COVID-19 curve might flatten. However, there are no randomized clinical trials to demonstrate conclusive evidence. Many clinical trials are done to study the importance of probiotics administration in the prevention and treatment of COVID-19 infection in the world recently.[27]

Evidence that supports that probiotics can fight against COVID-19 infection

Probiotics can alleviate drug-associated diarrhea, they are useful in fighting against gastrointestinal tract infections, they are essential in controlling respiratory tract infections and sepsis, and they are well known for their effects on decreasing necrotizing enterocolitis, nosocomial sepsis, and mortality risk in newborns. A randomized controlled trial in India studied more than 5,000 infants with lactobacillus plantarum strain associated

with prebiotics. The results revealed a declining level of sepsis and lower respiratory tract infections.[26]Multiple studies of 13 randomized controlled trials revealed that kids who were given probiotics have a decreasing risk of lower and upper respiratory tract infections. Administration of *L. gasseri, B. longum*, and *B. bifidum* showed fever reduction. Another randomized controlled trial of 93 newborns was given galacto-oligosaccharides and polydextrose prebiotic combination. The newborns showed better symptoms than the placebo group.[26]

Many probiotics are selected from LAB in the upper respiratory tract of healthy persons. Those probiotic strains can prevent persistent otitis media. Therefore, probiotics have a contribution in slowing down the coronavirus infection. Besides viral infection, probiotics can also reduce bacterial infections in adults. Multiple experimental data of a randomized controlled trial showed that 2,000 infected patients of ventilator-related pneumonia gained better recovery.[26]

However, there were also contradictory results in various trials. *Bifidobacterium animalis* and *L. rhamnosus* did not decrease the virus number in the nasopharynx, although they are beneficial in the intestinal tract.[26]

The mechanism of probiotics in preventing COVID-19 infection

Studies revealed that probiotics improve the epithelial barrier of the intestines, enhance the immune system, and produce antipathogen elements. The administration of *B. bifidum* and *S. thermophilus* showed a decline in diarrheal incidents. It also reduced rotavirus shedding. Probiotics interrupt the entry of the virus into the cell and inhibit viral replication in the host intestine. Therefore, probiotics could reduce the coronavirus invasion through the gastrointestinal tract through that mechanism.[26]

Dysbacteriosis change the functions of the immune system. This condition will end in secondary bacterial infection. Studies showed that the COVID-19 infection is accompanied by intestinal dysbacteriosis. It causes severe infection. The restoration of gut homeostasis might be done by probiotic strains. Therefore, when probiotic strains are orally administered, they may stimulate gut-lung association. The microbiota of the gut can enhance the immune system, including the lung. Administration of Bifidobacteria and Lactobacilli strains revealed a positive effect on the clearance of the influenza virus during respiratory infection.[26]

Certain strains of probiotic enhanced interferon type I levels. Other mechanisms are elevating the number and function of antigen-presenting cells, T cells, and natural killer cells. The level of certain antibodies is increased at the mucosa and systemic. Probiotics can also maintain stability among immunoregulatory and pro-inflammatory cytokines. This mechanism is critical in the acute respiratory distress syndrome, as a major threat of COVID-19 infection. Suppression of plasma pro-inflammatory cytokines (IFN-γ and TNF-α) was revealed with the use of Lactobacillus DR7. There was also improvement in anti-inflammatory cytokines, namely IL-4 and IL-10, decreasing oxidative stress levels and peroxidation of plasma cells. Therefore, probiotics act as immunomodulatory for the immune system.[26]

The important aspects of further research are the strains of probiotics and the right dose to reduce the invasion of SARS-CoV-2. This is the mechanism of the antiviral activity of the probiotics. The safety aspect of probiotics is well known, even in the most susceptible patients. however, bacteremia and fungemia might develop in immunocompromised persons. Therefore, there should be dosage adjustment for every patient.[27]

A single-center, the quadruple-blinded randomized clinical trial

revealed that among non-hospitalized patients with mild to moderate COVID-19 infection, probiotic administration with the strains of *P. acidilactici* KAP021, and *L. plantarum* KABP022, KABP023, and KABP033 increased the remission on day 30. The result was statistically significant. Meanwhile, the effect on hospitalization, mortality, and duration of ICU stay was not assessed because of lack of occurrences. There were significant effects on symptom duration, lung abnormalities, viral load, and SARS-CoV2-specific IgM and IgG. The probiotics were well tolerated.[28]

The benefit of probiotics as prophylactic and complementary therapy for patients with respiratory tract infection is a promising strategy to reduce the severity of the diseases. Besides, there are also reductions in symptoms and the duration of the disease. Quality of life and remission are improved. However, the specific type of probiotic, duration of treatment, and optimal dose need to be studied in further clinical trials.[29]

TABLE 1. Probiotic usage and recommendation based on the authors of the selected journals

Author	Article type	Summary of Recommended probiotics/LAB
Khaled[1]	Review	Bifidobacterium, Lactobacillus, and Saccharomyces are the most common probiotics.
Rahayu *et al.*[2]	Review	*L. plantarum* Dad-13
Gibson *et al.*[3]	Review (ISAAP consensus)	Lactobacillus and Bidifobacterium. Live microorganisms which when administered in adequate amounts confer a health benefit on the host (consensus of ISAAP)
Hill *et al.*[4]	Review	*L. rhamnosus* GG could enhance the epithelial barrier function
Salminen *et al.*[5]	Review	-
Xu *et al.*[6]	Review	-
Cao *et al.*[7]	Review	-
Huang *et al.*[8]	Review	-
Jabczyk *et al.*[9]	Review	Bifidobacterium and Lactobacillus increase in the number of helper T cells in the lung parenchyma (*L. plantarum, L. reuteri, L. rhamnosus, B. infantis*)
Karyantina *et al.*[10]	Research	Pediococcus (LAB) in the jambal roti
Nuraida *et al.*[11] (2014)	Review	Lactobacillus, Pediococcus, Enterococcus, Weisella and Leuconostoc
Sundararaman *et al.*[12]	Review	*L. plantarum, L. casei, L. rhamnosus, B. infantis, L. lactis*
Prihanto & Muyasyaroh[13]	Research	Terasi contains bacteriocin and high amino acid
Kobayashi *et al.*[14]	Research	Fermented shrimps contain bacteriocin from the gram-positive bacteria, *V. salexigens.*
Romadhon *et al.*[15]	Research	Bacteriosin can also inhibit the pathogen bacteria such as *E. coli, Vibrio parahaemiliticus,* and *S. aureus*
Elegado *et al.*[16]	Research	LAB produce enzyme (linamarase) to hydrolyze the cyanogenic compound of cassava.
Yogeswara *et al.*[17]	Research	*L. plantarum* (IFK-10) and *P. pentosaceus* (IFK-11), act as GABA-producing bacteria. They can be used as starter culture to MSG into GABA during 24 h of cultivation
Zheng *et al.*[18]	Review	*L. plantarum* and *L. paracasei*

TABLE 1. cont.

Author	Article Type	Summary of Recommended probiotics/LAB
Baud *et al.*[19]	Review	*L. casei, L. gasseri, L. rhamnosus, L. plantarum*, Bifidobacterium, Pediococcus
Rishi *et al.*[20]	Review	-
Dhar *et al.*[21]	Review	-
Xu *et al.*[22]	Review	*L. rhamnosus* GG, live *B. subtilis*, and *E. faecalis.*
Mak *et al.*[23]	Review	Interventional faecal microbiota transfer
Burchill *et al.*[24]	Review	-
Gao *et al.*[25]	Review	*L. casei, L. gasseri, B. longum, B. bifidum, L. rhamnosus, L. plantarum, B. breve, P. pentosaceus,* and *L. mesenteroides*
Zafar *et al.*[26]	Review	*B. lactis,*
Kurian *et al.*[27]	Review	*L. reuteri,*
Gutierrez *et al.*[28]	Research	*L. plantarum* KABP022, KABP023 and KAPB033, plus strain *P. acidilactici* KABP
Barbandi *et al.*[29]	Systematic review	*L. rhamnosus, L. brevis, L. acidophilus, L. plantarum*

CONCLUSION

Many LAB are found in Indonesian fermented foods. The LAB have essential roles in the production of fermented foods. They also give some health benefits such as improving antioxidant activity, increasing antimicrobial agents production, and as probiotics. Therefore, there are possible roles of probiotics in strengthening immunity against the COVID-19 infection. The immune benefits of probiotics and prebiotics are good. However, their potential roles in fighting against the COVID-19 infection need further investigation.

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