Title: Potential Effects Immunomodulators on Probiotics in COVID-19 Preventing Infection in the Future. A Narrative Review

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1. Role of the pathogenesis COVID-19
2. Potential effect from probiotics as immunomodulators
3. Effect of immunomodulators from probiotics for the prevention of COVID-19

ABSTRACT.

After the outbreak in December 2019, Coronavirus Disease (COVID-19) has become a global health problem because of its rapid spread throughout the world. To date, there are no effective therapies to treat or prevent COVID-19 infection. Probiotic bacteria are widely used to prevent gastrointestinal infections by modulating intestinal microbiota. Therefore, this literature review focuses on the potential possessed by probiotic bacteria for the prevention of future COVID-19 infections. Information was extracted from PubMed and Google Scholar using the keywords: "COVID-19", "immunomodulator", "inflammation", and "probiotic" and synthesize in a narrative review. The results showed that probiotic bacteria have immunomodulatory activity that can increase immunity against pathogens by regulating the immune system through modulation of intestinal microbiota and interactions with the lymphatic system in the digestive tract. The ability of the immune system regulation by probiotic bacteria has the effect of increasing the body's defense mechanisms against pathogens that infect the respiratory tract. However, further evidence is still needed regarding the effect of probiotic immunomodulators in combating future COVID-19 infections.

Key Words: COVID-19 virus infection, Immune system, Inflammation, Probiotics, Review Literature as Topic.

Introduction

Since its appearance in December 2019 in Wuhan, China, Coronavirus Disease (COVID-19) has become a worldwide pandemic by infecting more than 43,000 people in 28 countries as February 11, 2020 and becoming a health problem in many countries. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19 and can be transmitted through patient droplets or direct contact with COVID-19 patients.[1] The SARS-CoV-2 virus is a type of virus of the genus β-coronavirus that is enveloped in a non-segmented positive-sense RNA virus. The SARS-CoV-2 virus has the same genus as SARS-CoV and the middle east respiratory syndrome coronavirus (MERS-CoV) which can cause deadly respiratory infections.[2]

Symptoms of COVID-19 patients include symptoms similar to influenza infections such as fever, coughing, muscle aches and dyspnea. Treatment for COVID-19 patients is still limited to giving symptomatic therapy to patients. Providing care to patients is done to prevent complications that arise. The most common complications arise are acute respiratory distress syndrome (ARDS), anemia, acute heart injury and secondary infection. Some of the treatments that are often used include the use of invasive mechanical ventilation, systemic corticosteroids and antiviral therapy. However, some of the uses of the treatment are still unclear as to their effectiveness and there are no effective drugs for treating COVID-19.[3]

Treatment through immune system modulation attracts much attention because it initiates the body's response to fight viral infections. The use of many immunomodulating agents was developed to initiate the body's immune system against infection and reduce the risk of damage to the host due to the activity of the immune response from proinflammatory cytokines. With research on vaccines to prevent COVID-19 still in development stages, the use of immunomodulators in modulating the immune system is useful for pathology due to viral infections.[4]

Recent studies have shown the immunomodulatory effects of probiotic bacteria. Probiotics are defined as being "living microorganisms which, when consumed in sufficient quantities, provide health benefits to the host." Probiotics are widely used in the fermented food processing industry such as cheese, yoghurt or as supplements. Probiotic activity in influencing the immune system by regulation of T cells, type 3 innate lymphoid cells and helper 17 T cells through metabolites produced by probiotics or through interactions with the intestinal mucosal immune system.[5]

The purpose of this review literature is to discuss the immunomodulatory effects and the potential of probiotics to prevent COVID-19 infection.

METHODS

Literature Search Strategy

A comprehensive electronic literature search was carried out using search tools from Medline (PubMed) and Google Scholar to identify relevant publications regarding COVID-19, immunomodulators, and probiotics. Database parameters performed using keywords include "COVID-19", "immunomodulator", "inflammation", and "probiotic". The literature used is full-text written in English and published in the last 10 years. The

literature used consists of keywords that include "COVID-19", "immunomodulator", "inflammation", and "probiotic".

Eligibility Criteria

Excluded articles did not have a full-text publication or were not written in English. Inclusion criteria parameters include full-text in English, published less than 10 years ago, articles have the keywords "COVID-19", "immunomodulator", "inflammation", and "probiotic", articles studying COVID-19, probiotics, probiotic activity as an immunomodulator, and probiotic immunomodulatory activity in the respiratory tract.

RESULTS AND DISCUSSION

Pathogenesis of COVID-19

The SARS-CoV-2 virus, the cause of COVID-19, has the same genome as the SARS virus that targets angiotensin-converting enzyme 2 (ACE2) cells as receptor cells in host targeting. The virus has an incubation period of 2-14 days during which the virus is transmitted. Targeting of the virus is contained in the lung organs which causes symptoms that are similar to pneumonia with characteristic changes in lung opacity through CT imaging. Other symptoms of COVID-19 that are similar to pneumonia include fever, cough, shortness of breath and sore throat.[6] Some symptoms found in COVID-19 patients with gastrointestinal symptoms such as diarrhea, nausea and vomiting due to ACE2 receptors are also found in intestinal epithelial cells. The finding of SARS-CoV-2 nucleic acid in a patient's stool reveals a potential route for viral infection through feces.[7]

COVID-19 also impacts the body's immune system during the period of the disease. During the COVID-19 infection stage, an increase in neutrophil-lymphocyte-ratio (NLR) and T lymphopenia is found especially in the decrease of CD4 + T cells in patients with COVID-19. NLR, which is a systemic infection biomarker, was also found as part of a proinflammatory cytokine storm (TNF-α, IL-1, IL-6) and chemokine (IL-8) which correlated with the severity of COVID-19 patients. The cytopathic effect of proinflammatory cytokine activity results in excessive inflammation which is at risk of causing death.[8]

The emergence of cytokine storms caused as a response to immunity to the virus results in the disruption of immune homeostasis and self-tolerance through interference with regulator T cells that play a role in the control of specific autoimmunity and tissue.[8] Uncontrolled cytokine storm activity in the immune system's reaction to a viral infection affects the process of remodeling the airway tissue which risks increasing the severity of the patient causing a risk of death.[9,10]

Potential Health Effects of Probiotics

Probiotics are a type of bacteria that can provide health benefits for the host. Some of the characteristics possessed by probiotic bacteria include the ability to survive in the gastrointestinal tract and multiply in the intestine, have benefits for the host through growth in the host body, are non-pathogenic or toxic, protect from pathogens (i.e., bacteria, virus or fungi), and less resistant to antibiotic transfer. Probiotic bacteria that have different strains, even though genus and species have similarities, can provide different benefits to the health of the host.[11]

Probiotic bacteria from the genus Lactobacillus and Bifidobacterium are widely used, they are known as probiotic lactic acid bacteria (LAB). Probiotics work by binding to the intestinal mucosa and producing antimicrobial compounds, increasing the defense function of the intestinal barrier, and modulating immunity against intestinal pathogen infections. Probiotics have an important role to play in fighting intestinal infections, diarrhea, antibiotic-related diarrhea, prevention of colorectal cancer, and treatment agents for gastroenteritis infections caused by various pathogens such as *Escherichia coli*, *Bacillus, Salmonella, Shigella*, *Vibrio cholera, Klebsiella* and *Pseudomonas*.[12]

Lactobacillus and Bifidobacterium bacteria which are probiotic bacteria that are widely used have the structure of lipoteichoic acid (LTA), surface layer associated proteins (SLAPs) and mucin binding proteins (Mubs) that bind to glycocalyx in the intestinal epithelial layer. Glycocalyx contains glycolipids and glycoproteins that interact with the structure layers of LTA, SLAPs and Mubs from probiotic bacteria. The composition between the structure of probiotic bacteria and intestinal mucosa has hydrophobic and adhesion properties that can synthesize the extracellular matrix components of fibronectin, collagen, and laminin.[13,14]

Through the mechanism of adhesion on the surface of the intestinal epithelium, probiotic bacteria exerts an increased effect on the integrity of the intestinal barrier and results in maintenance of immune tolerance, decreases the translocation of pathogenic bacteria across the intestinal mucosa, and prevents phenotypic changes due to diseases such as gastrointestinal infections, irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD).[15] The immune tolerance response from the interaction between the intestinal mucosa and the probiotic bacteria induces a balance in the microflora in the intestinal environment.[16]

In probiotic bacteria, there is the ability of antitoxin to produce a serine protease and phosphatase so that it degrades toxins from *E. coli* and *C. difficile* as well as the ability to intervene pathogens in the gastrointestinal tract by destroying tight junction between pathogenic bacteria with epithelium and viruses with enterocytes. Probiotic bacteria also can interact with other microbiota in the intestinal environment and can rehabilitate intestinal microbiota balance in diarrheal infection conditions.[17]

Besides being widely used because the activity of probiotic bacteria prevents disturbances in the digestive tract, the ability of fermentation in probiotic bacteria has an effect on the body's metabolism by managing the diet of food consumed. Microbiota dysbiosis correlates with the onset of blood pressure and lipid intake from food that enters the body's circulation. Disorders caused by intestinal microbiota dysbiosis correlate with the onset of hypertension, obesity, and metabolic syndrome. With the interaction activity between intestinal microbiota, probiotic bacteria have potential as antihypertensive, cholesterol-lowering and anti-cholesterol levels in metabolic syndrome.[18,19]

Probiotic Immunomodulatory Activity

Probiotic bacteria have immunobiotic functions, namely probiotic bacteria which are prepared to balance the immune system through the synthesis of both anti-inflammatory cytokines such as interleukin-10 (IL-10) and proinflammatory cytokines such as interleukin-6 (IL-6), and balance the immune response of Th1 / Th2

through antigen presenting cell (APC) of patch peyers.[20,21] The ability to initiate immune system modulation from probiotics can minimize epithelial injury resulting from the inflammatory response. [22]

The immunobiotic ability of Lactobacillus and Bifidobacterium bacteria through the production of lactic acid can modulate the immune response in the intestinal mucosa by interacting with Toll-like Receptor 2 (TLR2).[21] Probiotic interactions in the intestinal environment induce a Th1 immune response that results in the production of interferon cytokines (IFN) -β and activate the bactericidal activity of macrophages.[23] The host of intestinal probiotic interactions will trigger lymphatic maturation, epithelial repair through endotoxin signaling and promote intestinal microbial mucosal tolerance.[24]

The ability of probiotic bacteria that can modulate the body's immune system through activation of natural killer cells, dendritic cells, intraepithelial lymphocyte cells and macrophages that have an important role in the innate immune system. Probiotic bacteria work by binding to aryl hydrocarbon receptors and activating macrophages and dendritic cells so that there will be a stimulus to release TNF-α proinflammatory cytokines from epithelial cells and enhance the immune system in the fight against pathogenic invasion. Research conducted by Villena et al (2014) shows the defense mechanism of intestinal cells through the administration of probiotic bacteria through immunoregulators with the production of proinflammatory cytokines such as IL-6 and TNF-α in response to pathogens and the production of anti-inflammatory cytokines IL-10.[21]

Besides their immunomodulator role in the innate immune system, probiotics also have anti-inflammatory potential through bioactive peptide compounds. The compounds produced from these probiotic bacteria can restore intestinal permeabilities. Also, the probiotic activity suppresses the activity of Th2 cells to produce IgE, interleukin-4 (IL-4) and IL-13 preventing asthma and allergic reactions.[25,26] Also, anti-inflammatory activity in the lungs plays a role in decreasing lung inflammation such as decreasing levels of proinflammatory cytokines and C-reactive protein (CRP).[27]

Probiotic bacteria produce metabolites in the form of short-chain fatty acids (SCFA) consisting of acetate, propionate, and butyrate which are widely present in the colon epithelium; parts of the butyrate are used as energy by the colonocytes while the rest of the other SCFA is absorbed into the portal circulation through the intestine.[28] The SCFA metabolite binds specifically to the G-protein-coupled receptor 43 / free fatty acid receptor 2 (GPR43 / FFAR2), GPR41 / FFAR3 and GPR109A, interactions on these receptors result in the development of macrophages and increase the differentiation of dendritic cell precursors that can migrate to the lungs lung and change the regulator T cells with Th2 cells.[29]

Interaction between the intestinal relationship with the lungs is mediated by the lymphatic system through the TLR4 dependency mechanism and produces IgA associated with gut-associated lymphoid tissue (GALT). These probiotic bacteria will induce regulatory T cells and initiate cell T helper 17 (Th17) production and Th1 immune memory response. Circulation of the lymphatic system from the intestinal axis - the lungs move Th17 cells from the intestinal mucosa to the bronchial epithelial mucosa in the lymph nodes in the airways. The effect, besides suppressing the activity of pathogens that attack the respiratory system, the activity of probiotic

interactions in the intestine with the airways prevents damage to the airway tissue by controlling the defense of the host immune system in the lungs.[30]

Immunomodulatory Effect from Probiotic Against Covid-19

COVID-19 infection that attacks the lung tissue activates inflammation in the airways. The results from the serum sampling of COVID-19 patients has showed an increase in the number of proinflammatory cytokines such as IL-1B, IL-6, IL-15, IL-15, IL-17 IFN-γ and TNF-α which led to the emergence of cytokine storms and correlated with the severity of the disease.[31] The emergence of cytokine storms results in pulmonary fibrosis and damage to respiratory organs.[32] The inflammatory stimulus-response is due to the activation of the Th1 cell response.[33]

The potential effect of probiotics in influencing the activity of cytokine storms due to COVID-19 infection can be through interactions in the gut microbiota with the immune system. Disruption to the intestinal microbiota environment results in an imbalance of Th1 / Th2 cells, which results in the production of proinflammatory cytokine storms in the lungs. Through modulation of intestinal microbiota, there is a shift in the balance between Th1 / Th2 cells which reduces the inflammatory response in the respiratory tract and reduces the severity of the disease.[34]

The activity of modulating intestinal microbiota through the administration of probiotic bacteria has an impact on controlling the lung's immune system response to viral infections. Probiotic bacteria can reduce the excessive inflammatory response in the face of viral infections by influencing T cells to produce IFN-γ.[35] The activity of probiotic bacteria in regulating the immune system is carried out through interactions with regulatory T cells in Peyer's patches on the intestinal surface thereby preventing excessive cytokine storm activity in fighting viral infections.[36]

In addition to stimulating the regulation of Th1 / Th2 cell balance, the activity of probiotic bacteria can initiate a defense system in the airway mucosa.[37] As a result of the response of proinflammatory cytokines in the airway mucosal epithelium, airway remodeling activity arises which is initiated by matrix metalloprotease-9 (MMP-9) causing narrowing of the airways. Airway remodeling arising from pro-inflammatory cytokines increases persistent breathing difficulties and worsens the patient's condition.[38] Prevention of airway remodeling due to viral infection makes therapeutic targets for probiotic bacteria to prevent worsening the condition of patients in COVID-19.[39,40]

Conclusion

With the development of therapies and vaccines for the prevention of COVID-19 infection which are still long to be given to humans, the immunomodulatory effects of probiotic bacteria have the potential for the prevention of COVID-19 infections. The ability of probiotic bacteria to regulate the immune system through modulation of the gut microbiota can increase immunity in fighting COVID-19 infection and reduce the risk of secondary bacterial infection due to prolonged antibiotic exposure in several experimental COVID-19 treatment. The findings from previous studies still need further research on a broader subject to ensure the

1 safety of therapy, so that the immunomodulatory potential of the probiotic bacteria can be maximized in the
2 fight against COVID-19 infection in the future.
3

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