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THE USE OF PROBIOTICS AS CURRENT ADJUVANT THERAPY FOR SARS COV-2 INFECTION IN GASTROINTESTINAL DISEASE

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ИСПОЛЬЗОВАНИЕ ПРОБИОТИКОВ В КАЧЕСТВЕ СОВРЕМЕННОЙ АДЪЮВАНТНОЙ ТЕРАПИИ ИНФЕКЦИИ SARS-CoV-2 ПРИ ЗАБОЛЕВАНИЯХ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА

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Abstract

Introduction.

SARS-CoV-2 is a virus that causes COVID-19 which is currently a pandemic situation. The symptoms of COVID-19 can vary from asymptomatic to acute respiratory distress syndrome. Some patients may also have gastrointestinal manifestations such as diarrhea, vomiting, and abdominal pain. Recently, it is known that some COVID-19 patients also showed microbial dysbiosis with decreased Lactobacillus and Bifidobacterium. With the increasing number of reported cases and gastrointestinal symptoms in COVID-19 patients, we are trying to summarize the possibility of using probiotics as the current adjuvant therapy for gastrointestinal disease due to SARS-CoV-2 infection.

Methods: We did a comprehensive literature search on PubMed, Science Direct, Google Scholar and screened bibliographies of other articles. The search yielded 2836 articles and 55 of them met eligibility criteria for this systematic review.

Results and Discussion: Probiotics can affect the gastrointestinal through some mechanism including: 1) competitive exclusion of pathogens and production of antimicrobial substances 2) enzymatic activities and production of volatile fatty acid 3) cell adhesion and mucin production 4) enhancement of epithelial barrier 5) modulation of the immune system. In recent data, probiotics are used in some COVID-19 patients with gastrointestinal disease. It is also considered to help overcome cytokine storms by suppressing proinflammatory cytokines and enhance the patient's immunity by modulating the immune system.

Conclusion: Probiotics can be used as the current adjuvant therapy to eliminate gastrointestinal disease in SARS-CoV-2 infection and prevent further complications of COVID-19. However, further clinical research still needed to determine the effectiveness of probiotics in COVID-19 patients.

Keywords: Probiotic, COVID-19, SARS-CoV-2, dysbiosis, gut-lung axis, gastrointestinal.

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Резюме

Введение.

SARS-CoV-2 — это вирус, явившийся причиной развития пандемии COVID-19. Выраженность симптомов COVID-19 может варьировать от бессимптомного течения до развития острого респираторного дистресс-синдрома. У некоторых пациентов также могут отмечаться желудочно-кишечные проявления, такие как диарея, рвота и боли в животе. Недавно было показано, что у некоторых пациентов с COVID-19 также наблюдался микробный дисбактериоз со снижением количества Lactobacillus и Bifidobacterium. С ростом числа зарегистрированных случаев проявления желудочно-кишечных симптомов у пациентов с COVID-19 нами была сделана попутка обобщения возможности использования пробиотиков в качестве современной адъювантной терапии желудочно-кишечных заболеваний, вызванных инфекцией SARS-CoV-2.

Методы: был проведен комплексный поиск литературы в базах данных PubMed, Science Direct, Google Scholar по указанноц теме, включая анализ библиографических источников других статей. В результате, обнаружено 2836 статей, 55 из них соответствовали критериям приемлемости включения в настоящий систематический обзор.

Результаты и обсуждение: Пробиотики могут влиять на желудочно-кишечный тракт через ряд механизмов, включая: 1) конкурентное исключение патогенов и выработку антимикробных веществ; 2) ферментативную активность и выработку летучих жирных кислот; 3) адгезию клеток и выработку муцина; 4) усиление эпителиального барьера; 5) модуляцию иммунной системы. Согласно последним данным, пробиотики используются у некоторых пациентов с COVID-19 с желудочно-кишечными проявлениями. Также считается, что они помогают компенсировать эффекты цитокинового шторма, подавляя провоспалительные цитокины, и повышают иммунитет пациента.

Заключение: Пробиотики можно использовать в качестве современной адъювантной терапии для купирования желудочно-кишечных проявлений при инфекции SARS-CoV-2 и предотвращения дальнейших осложнений COVID-19. Однако для определения эффективности пробиотиков у пациентов с COVID-19 необходимо проведение дальнейших клинических исследований.

Ключевые слова: пробиотик, COVID-19, SARS-CoV-2, дисбактериоз, ось кишечник-легкие, желудочно-кишечный

1 Introduction

Coronavirus Disease 2019 (COVID-19) which is currently pandemic situation in 2021. SARS-CoV-2 was first reported to have appeared in late December 2019 in Wuhan, China under the name 2019 novel Coronavirus [1]. On February 11, 2020, the disease SARS-CoV-2 was named COVID-19 by the World Health Organization (WHO). More than 100,000 people worldwide have been infected and the death toll has reached more than 4,000 cases causing COVID-19 to be declared a pandemic by WHO on March 11, 2020 [2, 3]. Based on June 14, 2020, COVID-19 has infected 7,690,708 people and caused 427,630 deaths worldwide. In Indonesia alone, COVID-19 has infected 37,420 people and caused 2,091 deaths as of June 14, 2020 [4]. The latest data from WHO on March 9th 2025 shows that COVID-19 has infected 778 million people and caused 7,1 million of deaths worldwide.

Symptoms of COVID-19 can vary widely from asymptomatic to acute respiratory distress syndrome but are most commonly associated with the respiratory system with fever. The main clinical manifestations of COVID-19 are fever, fatigue, and dry cough. Mild cases may show a low-grade fever, mild fatigue, and no signs of pneumonia. Patients with severe symptoms may have difficulty breathing and/or hypoxemia that occurs after 1 week. Critically ill patients may develop acute respiratory distress syndrome, septic shock, metabolic acidosis, coagulation dysfunction, and multiple organ dysfunction syndromes [5].

In addition to respiratory symptoms, some patients also have gastrointestinal manifestations such as diarrhea, vomiting, and abdominal pain [6]. Several studies have identified SARS-CoV-2 RNA in anal/rectal swabs [7, 8] and fecal specimens [9, 10] from COVID-19 patients, although The patient's upper respiratory tract was cleared of infection with SARS-CoV-2 [7, 8]. Furthermore, the viral receptor Angiotensin-Converting Enzyme 2 (ACE 2), which is expressed in the lungs, was also found to be expressed on

gastrointestinal epithelial cells. This is believed to allow SARS-CoV-2 to infect and replicate in the gastrointestinal tract. This has important implications for disease management, transmission, and control of infection SARS-CoV-2 [11, 6].

Several theories explain how SARS-CoV-2 causes gastrointestinal symptoms. First, the interaction between SARS-CoV-2 and ACE 2 can cause diarrhea. Enterocytic cells that express ACE 2 become cells infected with SARS-CoV-2 causing malabsorption, imbalanced intestinal secretions, and activation of the enteric nervous system which ultimately causes diarrhea. Second, SARS-CoV-2 indirectly damages the digestive system through a chain of inflammatory responses. Third, another possible cause of diarrhea in COVID-19 patients is the side effect of the antibiotics [1].

Recently, it has been recognized that some COVID-19 patients also exhibit microbial dysbiosis with reduced Lactobacillus and Bifidobacterium [13]. In this situation, probiotics are a reasonable choice. Probiotics are defined as live microorganisms which, when administered in adequate amounts, confer health benefits in humans [14]. On the other hand, probiotics have been shown to provide treatment and prevention of viral infections [15] due to their proven immunomodulatory activity and ability to increase interferon. Production [16]. The relationship between respiratory distress and gut microbiota is explained through the Gut-Lung axis theory [17].

To date, no specific antiviral drug or vaccine has been found for SARS-CoV-2. With the increasing number of COVID-19 patients and reported gastrointestinal symptoms, and only symptomatic COVID-19 treatment [18, 19], the researchers attempted to summarize the current possibilities of using probiotics as adjuvant therapy for gastrointestinal diseases caused by SARS-CoV-2.

METHODS

We compiled this literature review using the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) guidelines and was written using the last 10 years of journals (2011 - 2021) collected using literature searches on PubMed, Google Scholar, and Science Direct.

The literature search was conducted using the keywords “probiotic”, “SARS-CoV-2”, “COVID-19”, “gut-lung axis”, “gastrointestinal”, and “dysbiosis” using Boolean logic. In addition, articles obtained from other related research references were also added. We conducted a systematic review of research articles discussing the use of probiotics in gastrointestinal disease of COVID-19 patients worldwide.

After checking for duplication of articles, we filtered titles and abstracts. The research design included in the inclusion criteria included systematic review, narrative review, case report, cross-sectional, cohort, and experimental. After that, we read the full text of the articles that we collected and selected articles that match the aspects needed for this research. Articles published other than in English and not discussing the effects of probiotics on the gastrointestinal tract, COVID-19, and the gastrointestinal tract, and probiotics on COVID-19 will be excluded. Then we do the data extraction independently.

RESULTS AND DISCUSSION

Based on search results in journal databases and added references, 2836 articles were obtained. Then duplication checks and screening of titles and abstracts were carried out so that 134 articles were obtained to be read in full text and to check eligibility. 79 articles did not meet the eligibility criteria, so we included a total of 55 articles in the systematic review (Figure 1). There were 3 systematic review studies, 34 narrative review studies, 4 case report studies, 3 case series studies, 5 cross-sectional studies, 2 cohort studies, and 4

experimental studies. Most of the research was conducted in China and America. The data obtained were then analyzed comprehensively.

Mechanism of probiotic in Gastrointestinal

The gut microbiota consists of gut microbes which in healthy people are dominated by 4 phyla namely Actinobacteria, Firmicutes, Proteobacteria, Bacteroidetes [20] and play an important role in host health through protective, trophic, metabolic, and immunological actions. When gut microbes receive nutrients from the host, gut microbes also retaliate by regulating various physiological functions of the host such as digestion of food, providing protective immunity against pathogens, controlling the proliferation and differentiation of epithelial cells, and modifying insulin resistance, and influencing their secretion [21, 22].

The host will secrete specific factors such as microRNA and nonspecific factors such as antimicrobial peptides, mucus, and immunoglobulin A (IgA) that promote the growth of certain types of bacteria and inhibit the growth of other bacteria to get a beneficial gut microbiota [22]. However, the gut microbiota can undergo significant changes. called change. as "gut dysbiosis" which can occur due to several factors such as genetics, diet, age, and antibiotics [22].

Intestinal dysbiosis is associated with several diseases such as *Inflammatory Bowel Disease* (IBD), Diabetes Mellitus, allergies, autoimmune diseases, cardiovascular diseases, and diarrhea [21, 23]. Therefore, modulation of the composition and diversity of gut microorganisms is considered a promising therapy for this disease. this. There are many ways to modulate gut microorganisms, one of which is by administering probiotics [22]. Probiotics are believed to be the latest strategy that can be applied to restore microbial diversity and changes in gut microbiota both temporarily and permanently [23].

Probiotics given to the *host* have several mechanisms, including:

1) Competitive exclusion of pathogens and production of antimicrobial substances

Competitive exclusion is a situation in which one bacterial species competes for receptors in the intestinal tract more vigorously than another species. The exceptions are the result of different mechanisms of probiotics to inhibit pathogen adhesion, including the production of antimicrobial substances and stimulation of *intestinal epithelial cells* (IEC). Mechanisms thought to explain the competitive exclusion of pathogens include a decrease in luminal pH, competition for nutrients, and the production of bacteriocins and bacteriocin-like substances in some pathogens such as *Salmonella typhi and E. coli* [24, 25].

Several probiotic metabolites have shown roles in modulating the diversity of signals and metabolic pathways in cells. Several components of probiotic metabolites such as organic acids, bacteriocins, hydrogen peroxide, amines, etc. have been reported to interact with several targets in metabolic pathways that regulate cell proliferation, cell differentiation, apoptosis, inflammation, angiogenesis, and metastasis [24].

Some Lactobacillus and Bifidobacterium can produce antimicrobial peptides (bacteriocins) that prevent the proliferation of certain pathogens. Bacteriocins are small cationic molecules consisting of 30-60 amino acids. These molecules act on the bacterial cytoplasmic membrane and the target membrane vesicles are energized to disrupt the *proton-motive force* (PMF). Some examples such as probiotics *L.plantarum* and *L.acidophilus* have been shown to stop the growth of Helicobacter, C. difficle, rotavirus, Shigella spp. resistant to drugs, and E. coli in some gastrointestinal conditions and has activity against several uropathogens [24].

2) Enzymatic activity and production of *Volatile Fatty Acid* (VFA)

The activity of probiotic enzymes in the intestinal lumen influences the biological effects of the probiotics themselves. The activity of the *B-glucuronide* enzyme from bacteria in the intestine will hydrolyze the absorbed metabolites glucuronidation to a toxic form that causes intestinal damage. However, the administration

of *Bifidobacterium longum* in the diet can make changes in the gut microbiota and reduce the activity of the *B-glucuronidase* enzyme which is associated with the inhibition of the formation of aberrant formations and is a pre-neoplastic marker in colon cancer [24].

Furthermore, in a study, it was stated that the administration of probiotics, prebiotics, or both (synbiotics) for the therapy of *Non-Alcoholic Fatty Liver Disease* (NAFLD) in adult patients showed a decrease in liver aminotransferase enzyme activity [24]. Meanwhile, probiotic administration would decrease liver enzyme activity. . also affects VFA, as seen from the study with *L. gasseri* CECT5714 and *L. coryniformis* CECT5711 showed a higher increase in fecal butyrate, propionic acid, and acetic acid after 2 weeks of giving these probiotics. Another study stated that short-term administration of synbiotics consisting of the probiotic *B. longum* and the prebiotic inulin showed an increase in the production of acetate, succinate, butyrate, and isobutyrate. Therefore, short-term administration of synbiotics is considered effective in increasing the metabolic activity of the colonic microbiota in the elderly [24].

In elderly patients on total enteral nutrition, osmotic diarrhea and antibiotic-associated diarrhea are common which is a significant problem for these patients due to changes in gut microbiota and *Short Chain Fatty Acid (*SCFA) composition. A study showed that the administration of probiotic *S. boulardii* could reduce the incidence of diarrhea in patients receiving total enteral nutrition. SCFA and other probiotic metabolites are also believed to play a role in immune system regulation [24].

SCFAs are important energy sources for enterocytes and are key signaling molecules for the maintenance of gut health. In addition, SCFAs can enter the systemic circulation and interact with cell receptors in peripheral tissues. SCFAs have an important role in the regulation of homeostasis and energy metabolism. A wealth of evidence, mainly from animal and in vitro studies, has suggested a role for SCFAs in the prevention and treatment

of obesity and obesity-related disorders in glucose metabolism and insulin resistance [24, 26].

SCFA can interact with the SCFA *G protein-coupled receptor* (GPR) 41 and GPR43, resulting in increased secretion of polypeptide YY and *glucagon-like peptide* 1 in the gut, which in turn can increase satiety [26, 27]. Furthermore, SCFA can reach tissues. adipose tissue and contributes to reduced fat accumulation by interacting with GPR43, which results in decreased lipolysis & inflammation, and increased adipogenesis & leptin release [24].

Acetate, propionate, and butyrate may also promote *peroxisome proliferator-mediated adipogenesis* (PPAR), which may be regulated by a GPR43-associated mechanism. In addition, it has been suggested that acetate, propionate, and butyrate can reduce the secretion of proinflammatory cytokines and chemokines, possibly by reducing local macrophage infiltration. Furthermore, SCFAs appear to activate AMP kinase in muscle, increase insulin sensitivity and fatty acid oxidation and reduce lipid accumulation [24,26].

3) Cell adhesion and mucin production

Microbes designated as probiotics must attach to the intestinal mucosa to be able to colonize and interact with their *host*. This interaction is required for the modulation of resistance to pathogens and their role in the immune system [24, 28, 29].

Intestinal epithelial cells secrete mucin to prevent the adhesion of pathogenic bacteria. Lactic acid bacteria exhibit several surface determinants involved in interactions with intestinal epithelial cells and mucus. *Lactobacillus* protein can induce mucosal adhesion mediated by surface adhesives. In addition, the MUB protein (*Mucus-Binding Protein*) in *Lactobacillus reuteri* plays an important mucosal adhesion. These proteins play a role in facilitating intestinal colonization through degradation of the cell's extracellular matrix or by facilitating close contact with the epithelium [25].

Probiotics such as *L. Plantarum* have been reported to induce MUC2 and MUC3 mucins and inhibit the adhesion of intestinal pathogenic bacteria such as *E. coli*. This indicates that the mucosal layer and glycocalyx are increased in the intestinal epithelium, as well as the adhesion of Lactobacillus spp. at microbial *binding sites* indicating protection against pathogen invasion in the gut. In addition, probiotics have also been reported to increase mucin synthesis on the cell surface and modulate mucin gene expression [25].

4) Increased epithelial *barrier*

The intestinal barrier is a defense mechanism used to maintain epithelial integrity and protect organisms from the environment. The intestinal barrier consists of a mucus layer, antimicrobial peptides, secretory IgA, and an epithelial *junctional* adhesion complex. When there is damage to the intestinal barrier, bacterial and food antigens can enter the submucosa and induce an inflammatory response, which in turn leads to intestinal disorders such as IBD [25].

The mechanism of probiotics in enhancing the epithelial *barrier* is explained through increased expression of genes involved in *tight junction* signaling. For example, Lactobacillus bacteria can modulate the regulation of several genes encoding attachment junction proteins such as E-cadherin and B-catenin in the T84 cell barrier model. Furthermore, Lactobacillus bacteria can also affect the phosphorylation of attachment junction proteins and affect the amount of *protein kinase C* (PKC) isoforms [25].

Recent data suggest that probiotics can initiate repair of gut barrier function after the damage has occurred. *Escherichia coli* Nissle 1917 (EcN1917) not only prevents the breakdown of the intestinal mucosal barrier by enteropathogenic E. coli. but also capable of restoring mucosal integrity in T84 and Caco-2 cells through increased expression and redistribution of the tight junction protein of zonular occlusion (ZO-2) and PKC which ultimately reconstructs the *tight junction* complex. Likewise for Lactobacillus casei DN-114001 and VSL3 (a combination of prebiotics and probiotics). In addition, probiotics can

also prevent epithelial damage caused by proinflammatory cytokines so that they can strengthen the mucosal *barrie*r [25].

5) Immune system modulation

The gut microbiota can modulate the immune system through the production of molecules that have immunomodulatory and anti-inflammatory functions. One of the main mechanisms of probiotics is the regulation of the host immune response. The immune system can be divided into *innate* and *adaptive* immune systems. The adaptive immune response depends on B and T lymphocytes binding to antigens. Meanwhile, the innate immune response will work by recognizing *pathogen-associated molecular patterns* (PAMPs) that are shared by the majority of pathogens [24].

The primary response to pathogens is generated by *pattern recognition receptors* (PRRs), which bind to PAMPs. One part of PRR is Toll Like Receptors (TLRs). TLRs are transmembrane proteins that are expressed on several immune and non-immune cells, such as B cells, *natural killer cells* (NK cells), dendritic cells (DC), macrophages, fibroblast cells, epithelial cells, and endothelial cells. It is known that probiotics interact the most with host IEC cells and can fight dendritic cells, while dendritic cells and IEC can interact and respond to microorganisms through PRR [24, 25].

In addition, in the regulation of immune balance, T cells are partially regulated by host and microbial interactions. The imbalance between helper T cells (Th) and regulatory T cells (Treg) will cause an impaired immune response. Probiotics help maintain intestinal homeostasis by modulating immune responses and promoting the development of Treg cells [25, 30].

Modulation of secretory IgA (sIgA) and cytokine production

sIgA is produced by intestinal B cells and is expressed on the basolateral surface of the intestinal epithelium as an antibody transporter. In several studies, it was reported that probiotics showed the ability to potentially stimulate the production of sIgA so that it can

improve *barrier* function. Probiotics also interact with gut cells and specific immune cells resulting in the production of certain cytokines [24, 31].

Several species of *Lactobacilli* and *Bifidobacterium* are classified as probiotics that have anti-inflammatory properties by increasing IL-10 and Th-1 cytokines. The combination of probiotics was reported to be able to induce T cell and B cell hyporesponsiveness and reduce Th1, Th2, and Th17 cytokines without inducing apoptosis. Probiotics also induce the production of CD4+FoxP3+ Tregs from the $CD4^+CD25^+$ population and increase the suppressor activity of $CD4^+CD25^+$ Tregs [24].

Interaction of probiotics with TLR signaling pathways and cell cascade

TLR is part of PRR which can recognize microbial components widely. Dimerization of the TLR and *Toll-Interleukin-1* (IL-1) *Receptor* (TIR) results in the recruitment of adaptive molecules such as the *myeloid differentiation primary response protein* (MyD88), the adapter protein containing the TIR domain, and the TIR *domain-containing the adapter-inducing interferon- β* (TIR). TRIF) to initiate signal activation. MyD88 recruitment activates the *Mitogen-Activated Protein Kinase* (MAPK) and *nuclear factor* (NF)-κB signaling pathways [24, 25].

Probiotics and commensal microorganisms in the gut can create a TLR-mediated state of tolerance in DCs. TLR9 signaling is an important part of the pathway to elicit anti-inflammatory effects on epithelial cell surfaces by probiotics. Then DC initiates responses such as Th0 differentiation into Tregs which have inhibitory effects on Th1, Th2, and Th17 inflammatory responses [25].

Thus, probiotics are believed to have the ability to suppress inflammation through decreased expression of TLRs, the secretion of metabolites that can prevent TNF- α from entering mononuclear blood cells, and inhibit NFκB signaling pathways into enterocytes. shift the balance from Th1 / Th2. The mechanism that occurs is an increase in Th1 response and a decrease in Th2 cytokine secretion which includes a decrease in IL-4, IL-5, and IL-

13. Likewise with a decrease in IgE concentration and an increase in the production of *C-reactive* protein and IgA [25, 32].

COVID-19 dan *Gut – Lung Axis*

COVID-19 is an illness caused by *severe acute respiratory syndrome-2* (SARS-CoV-2) [33]. Symptoms of COVID-19 vary from asymptomatic, mild, or with flu-like symptoms such as fever, dry cough, runny nose, and fatigue. Additional symptoms may also include shaking, sore throat, anosmia, headache, joint pain, nausea, and diarrhea. Respiratory failure due to pneumonia can lead to acute respiratory distress syndrome (ARDS), multiorgan failure, and even death [34].

Angiotensin-converting enzyme 2 (ACE2) was identified as a functional SARS-CoV receptor that is widely expressed in the lung, heart, ileum, kidney, gastrointestinal epithelium, and bladder [11, 6]. SARS-CoV-2 binds to DC cells and macrophages via the ACE-2 receptor, a non-integrin dendritic-3-grabbing cell-specific intercellular adhesion molecule (DC-SIGN) and DC-SIGN-associated protein (DC-SIGNR, L. -SIGN) [33]. DC cells and macrophages as antigen-presenting cells (APCs) go to the lymph nodes to present the virus to T cells. T cells serve as a medium for the immune response to the coronavirus [35]. $CD4^+$ T cells activate B cells to produce specific antibodies virus, whereas $CD8^+$ T cells will kill virus-infected cells [33].

COVID-19 patients with severe symptoms show a condition of lymphopenia, especially a decrease in T cells in the periphery [36, 37]. In addition, an increase in proinflammatory cytokines such as IL-6, IL-10, *granulocyte-colony stimulate factor* (G-CSF), *monocyte chemoattractant protein 1* (MCP-1), *macrophage inflammatory protein* (MIP)1α, and TNF-α. Studies have also shown that viruses that infect lung epithelial cells activate the production of IL-8 in addition to IL-6. IL-8 is known as a chemoattractant against neutrophils and T cells. Neutrophils play a role in innate immunity against viruses.

However, like a double-edged sword, neutrophil levels that are too high can cause lung damage. Meanwhile, T cells play a role in the adaptive immune response [33].

Cytokines have an important role in the immunopathology of viral infections. Cytokine storms are a major cause of ARDS and multiorgan failure [38]. Dysregulation and an exaggerated immune response can cause more death than viral titers. In BALB/c mice infected with SARS-CoV, rapid viral replication can lead to the production of /β IFN followed by accumulation of pathogenic inflammatory mononuclear macrophages. Mononuclear macrophages will cause an increase in proinflammatory cytokines (TN-Fα, IL-6, IL1-β, nitric oxide synthase) [39]. Moreover, high response to proinflammatory cytokines induces apoptosis in lung epithelial and endothelial cells. This apoptosis will cause damage to the microvascular and alveolar epithelium which can cause vascular leakage and alveolar edema resulting in body hypoxia to ARDS [33, 40].

The gut and lungs have the potential to communicate through complex pathways involving the microbiota of both organs. This communication occurs through the gut-lung axis (GLA) mechanism (Figure 2). Just like in the intestines, the dominant bacteria in the lungs are Firmicutes and Bacteroidetes [41].

Cell wall fragments, protein moieties, and bacterial metabolites (eg SCFA) can migrate across the intestinal barrier to reach the systemic circulation and trigger an immune response in the lungs via the mesenteric lymphatic system [41, 42]. Antigens that enter the gastrointestinal tract are captured by Peyer's patches. Antigen will be carried by DC and macrophages to the mesenteric lymph nodes. These antigens cause the activation of T cells and B cells which will be converted into plasma cells. The sensitized T and B cells are distributed to effector sites including *gut-associated lymphoid* tissue (GALT), respiratory tract, and mammary glands. Secretory IgA will be produced to prevent pathogens from attacking the mucosa [41, 43].

Another important mechanism that occurs is through gut segmented fillingamentous bacteria (SFBs), colonization of commensal bacteria in the ileum that is involved in modulating the development of the immune system. SFBs regulate the polarization of $CD4^+$ T cells into the Th17 pathway that is important in the response to fungal pulmonary infections and pulmonary autoimmune manifestations [41, 44, 45]. Innate lymphoid cells involved in tissue repair appear to be transported from the gut to the lungs in response to the IL-25 inflammatory signal. In addition, an increased lung response to influenza in mice is associated with increased intestinal TLR activation required for the NF-B-dependent pathway of innate immunity and inflammation [41].

The gut microbiota influences the gut and lung immune systems through local and long-distance interactions, involving CD8+, Th17, IL-25, IL-13, prostaglandin E2, and NF-κB-dependent T cells. The lung microbiota influences mucosal immunity and plays a role in immune tolerance through recruitment of neutrophils, TLR2-mediated production of proinflammatory cytokines, and Th17-stimulated release of antimicrobial peptides such as β-defensin 2 [41].

Studies in mice with confirmed sepsis and ARDS have shown an increase in gut bacteria especially *Bacteroides* in the lungs [46]. The role of Th17 cells from the gut is important in mucosal protection through recruitment of neutrophils and secretion of antibacterial factors from the bronchial epithelium. Intestinal immunization in mice with inactivated non-typeable Haemophilus influenzae (NTHi) has also been shown to increase Th17 cells in the mesenteric lymph nodes and respiratory tract [43].

Probiotics Relationship with COVID-19

Gastrointestinal infection SARS-CoV-2 has attracted attention since SARS-CoV-2 RNA was first detected in the feces of patients in the United States.1 Gastrointestinal involvement has been shown to occur in coronavirus infections in humans and animals.[1]

Previous studies have shown that 10.6 % of SARS patients and nearly 30% of MERS patients have diarrhea [47].

Reports related to the current pandemic also mention that it is not uncommon for gastrointestinal symptoms to occur in COVID-19 patients [48]. One study stated that there were complaints of nausea/vomiting (5.6%) and diarrhea (3.8%) in COVID-19 patients [49]. Another study with 204 samples of COVID-19 patients in Hubei, China stated that 99 patients (48.5%) complained of digestive symptoms as the main complaint, including 7 cases without respiratory symptoms [1]. COVID-19 patient without digestive symptoms was easier to detect. healing and release. from hospital compared to COVID-19 patients with digestive symptoms (60% vs. 34.3%). This can happen because viral replication in the digestive tract makes the disease more severe [48].

Several theories explain how SARS-CoV-2 causes gastrointestinal symptoms. First, the interaction between SARS-CoV-2 and ACE 2 can cause diarrhea. Recent bioinformatics analysis revealed that ACE 2 is not only highly expressed in *alveolar type II* (AT2) cells in the lung, but also gastric gland cells and duodenal intestinal epithelial cells [50, 51]. ACE 2 is highly expressed in the proximal and distal to enterocytes, so that they are directly exposed to food and pathogens. Enterocyte cells that express ACE 2 become cells infected with SARS-CoV-2, causing malabsorption, imbalanced intestinal secretions, and activating the enteric nervous system which eventually causes diarrhea [1]. Second, SARS-CoV-2 indirectly damages the digestive system. through the inflammatory response chain. Third, another possible cause of diarrhea in COVID-19 patients is the side effect of the antibiotics used [1, 12].

COVID-19 patients have also been reported to have significantly impaired fecal microbiota characterized by an increase in opportunistic pathogens and a decrease in positive comments on admission or during hospitalization. The number of opportunistic pathogens that cause bacteremia such as *Clostridium Hathaway, Actinomyces viscosus, and*

Bacteroides nordii increased in Covid-19 patients receiving antibiotic therapy. In addition, an upper respiratory tract pathogen, *Actinomyces viscosus,* was identified in the intestines of Covid-19 patients. This indicates the presence of extra-intestinal microbial transmission [52].

Clinical evidence says some probiotics can help prevent bacterial and viral infections including gastroenteritis, sepsis, and respiratory infections. Viruses are the causative agents in more than 90% of respiratory tract diseases. The administration of probiotics has been shown to provide significant benefits in patients with respiratory tract infections [53].

In COVID-19, probiotics are thought to help overcome the cytokine storm by suppressing proinflammatory cytokines and boosting the patient's immune system by modulating the immune system. However, clinical research on probiotics in COVID-19 is lacking. A case report of a 9-year-old boy infected with SARS-CoV-2 who came to the hospital complaining of diarrhea for 2 days, showed that the patient's symptoms disappeared after 2 days of oral probiotics. significantly in COVID-19 patients with severe symptoms compared to COVID-19 patients with mild symptoms [55]. Reports in America with the administration of various probiotics (*Lactobacillus, Acidophilus, Bifidobacterium, and Saccharomyces boulardii)* and case reports with 62 COVID-19 patients in Zhejiang, China also showed good results.

So far, these reports have shown good results with the administration of probiotics as adjuvants in COVID-19 patients. In previous studies, probiotics were also said to reduce the incidence of diarrhea caused by antibiotics, pneumonia caused by ventilators, and prevent *Acute Respiratory Distress Syndrome* (ARDS) and *respiratory tract infections* [56, 57, 58]. Probiotics are believed to be used as the latest adjuvant therapy in COVID-19 patients and as preventive therapy for COVID-19 complications [58]. (Figure 3)

CONCLUSION

Probiotics have many benefits by using various mechanisms that can ultimately restore microbial diversity and improve changes in gut microbiota. A balanced gut microbiota will prevent pathogens from entering and boost the human immune system. In COVID-19, patients may experience gastrointestinal symptoms and it has been reported that SARS-CoV-2 can replicate in the intestine and remain in the patient's stool longer than in the oropharynx. Research has also shown that there are changes in the gut microbiota in some COVID-19 patients.

Changes in the gut and lung microbiota to the cytokines involved in this can be explained through the gut-lung theory. It is also mentioned that COVID-19 patients who experience gastrointestinal symptoms are more difficult to recover than COVID-19 patients without gastrointestinal symptoms. Recent case reports regarding the use of probiotics in COVID-19 patients are starting to show a glimmer of hope, where additional therapies such as probiotics are expected to be a differentiator in treating COVID-19 patients with gastrointestinal symptoms. Probiotics are said to overcome the cytokine storm by suppressing proinflammatory cytokines and boosting the patient's immune system by modulating the immune system.

Thus, through this study, we conclude that probiotics can be used as a new adjuvant therapy to relieve gastrointestinal disease in COVID-19 patients and prevent further complications of COVID-19. However, further clinical research is needed to determine the effectiveness of using probiotics in COVID-19 patients.

РИСУНКИ

Figure 1. PRISMA *Flow Chart.*

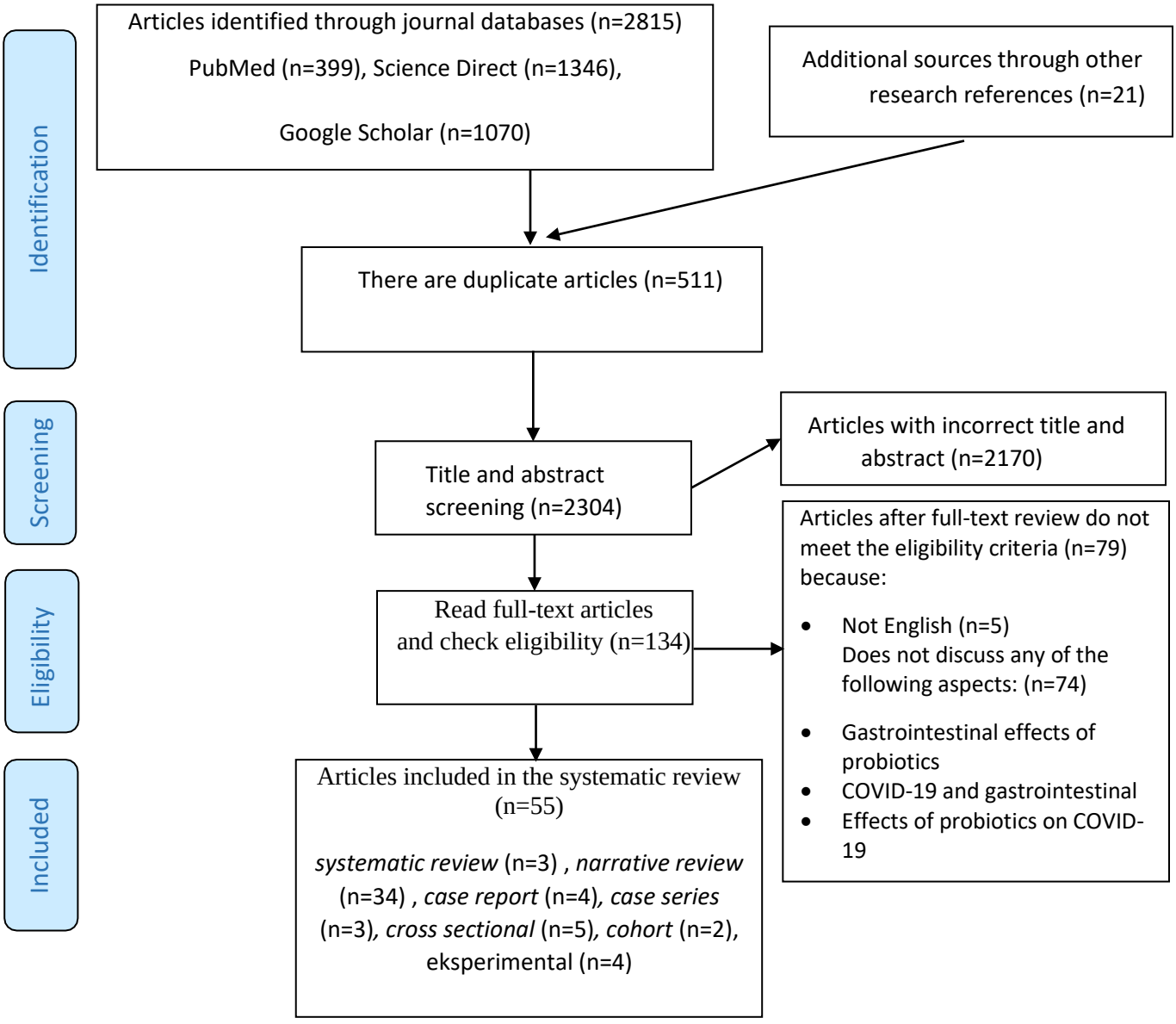
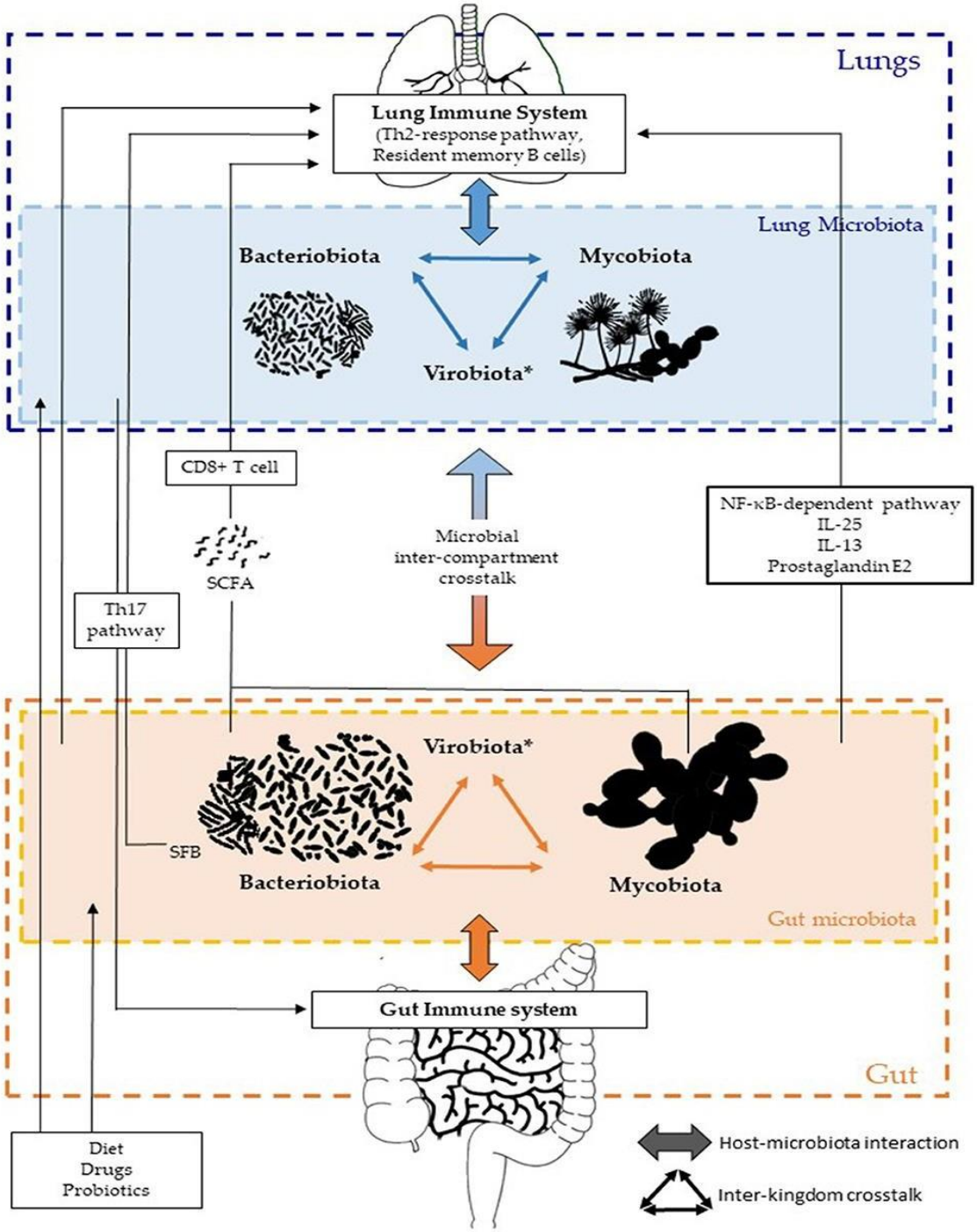

Identification
Screening
Eligibility
Included
Articles identified through journal databases (n=2815)
PubMed (n=399), Science Direct (n=1346),
Google Scholar (n=1070)
Additional sources through other research references (n=21)
There are duplicate articles (n=511)
Title and abstract screening (n=2304)
Articles with incorrect title and abstract (n=2170)
Read full-text articles and check eligibility (n=134)
Articles after full-text review do not meet the eligibility criteria (n=79) because:
Not English (n=5)
Does not discuss any of the following aspects: (n=74)
Gastrointestinal effects of probiotics
COVID-19 and gastrointestinal
Effects of probiotics on COVID-19
Articles included in the systematic review (n=55)
systematic review (n=3) , narrative review (n=34) , case report (n=4), case series (n=3), cross sectional (n=5), cohort (n=2), eksperimental (n=4)

Figure 2. *Gut-Lung Axis*. Th2, T helper 2; Th17, T helper 17; CD8+, *cluster*



differentiation 8+; SCFA, *short chain fatty acid*; NF-κB, *nuclear factor kappa* B; IL- 25, Interlekuin-25; IL-13, Interleukin-13; SFB, *segmented fillamentous bacteria.*[4]

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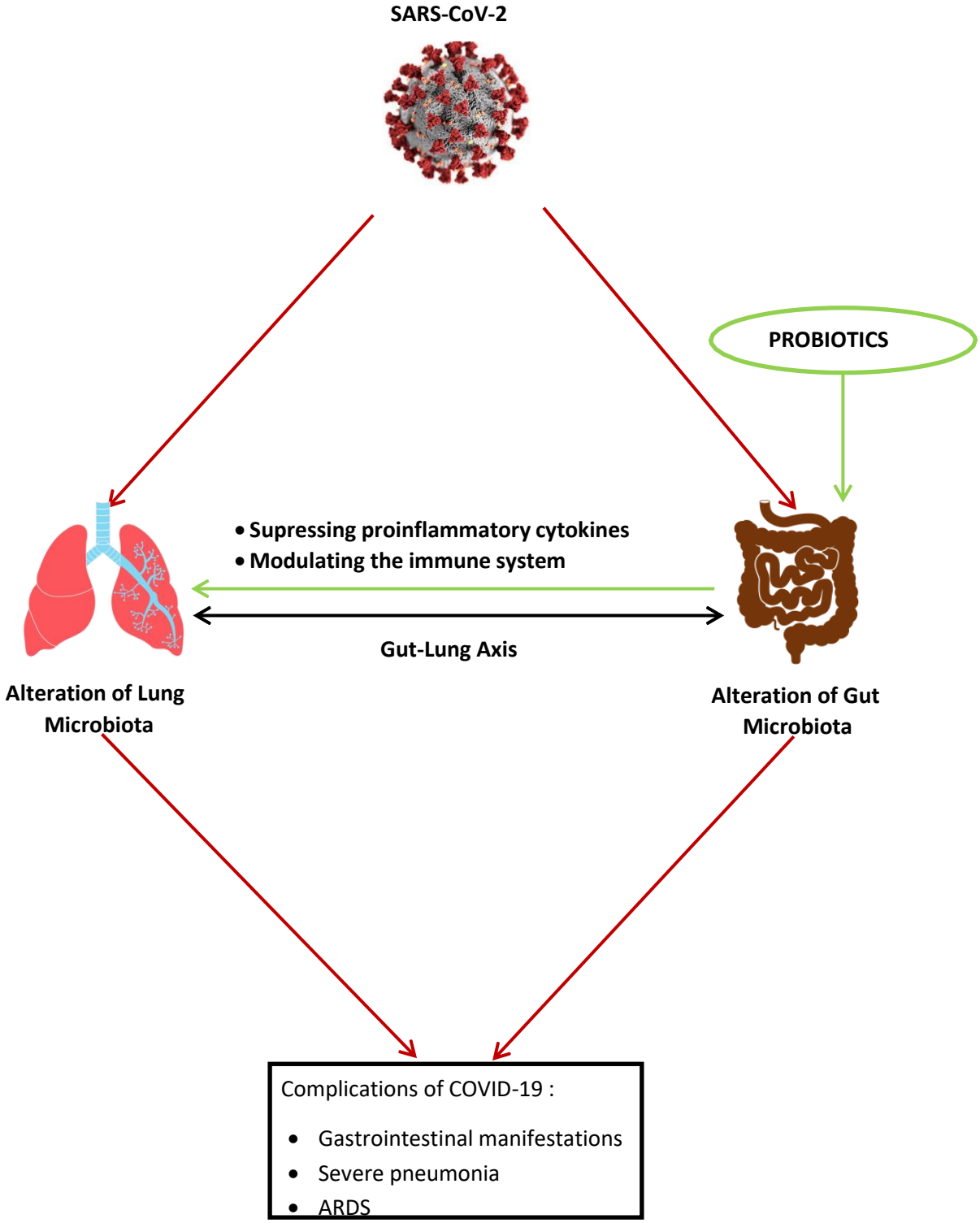
Figure 3. *The Mechanism of Probiotics in SARS-CoV-2 Infection.*



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ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

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Блок 3. Метаданные статьи

THE USE OF PROBIOTICS AS CURRENT ADJUVANT THERAPY FOR SARS COV-2 INFECTION IN GASTROINTESTINAL DISEASE

ИСПОЛЬЗОВАНИЕ ПРОБИОТИКОВ В КАЧЕСТВЕ СОВРЕМЕННОЙ АДЪЮВАНТНОЙ ТЕРАПИИ ИНФЕКЦИИ SARS-CoV-2 ПРИ ЗАБОЛЕВАНИЯХ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА

Сокращенное название статьи для верхнего колонтитула:

PROBIOTICS AS CURRENT ADJUVANT THERAPY FOR SARS COV-2 INFECTION IN GASTROINTESTINAL DISEASE

ПРОБИОТИКИ В КАЧЕСТВЕ СОВРЕМЕННОЙ АДЪЮВАНТНОЙ ТЕРАПИИ ИНФЕКЦИИ SARS-CoV-2 ПРИ ЗАБОЛЕВАНИЯХ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА

Keywords: Probiotic, COVID-19, SARS-CoV-2, dysbiosis, gut-lung axis, gastrointestinal.

Ключевые слова: пробиотик, COVID-19, SARS-CoV-2, дисбактериоз, ось кишечник-легкие, желудочно-кишечный

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