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The protective effect of probiotics on the treatment and improvement of respiratory disease caused by COVID-19 virus

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Abstract

The new viral pandemic of COVID-19 is caused by the new coronavirus (SARS-CoV-2), which has plunged the world into an economic and health crisis. The lack of specific treatment strategies is necessary to prevent the spread of infection caused by such a previously unknown viral agent. Evidence suggests that COVID-19 disease is associated with intestinal dysbiosis. Probiotics are living microbes that benefit human health by changing the composition of intestinal microbiota. The close relationship between the gastrointestinal tract and the respiratory tract indicates the influence of one on the function of the other. Emerging studies show the ability of probiotics to regulate immune responses in the respiratory tract. The efficacy of probiotics in several respiratory infections has been previously studied. Therefore, this study aimed to understand the available safety information provided by different species of probiotic bacteria in the process of improving the symptoms of respiratory infection caused by the COVID-19 virus.

Keywords: *COVID-19, immune response, probiotics, respiratory infections, treatment.*

Background

Acute respiratory infections (ARIs) including influenza, adenovirus, respiratory syncytial viral infections, enterovirus, and pneumonia are the leading causes of death in the world (1). Most of these infections are caused by DNA/RNA viruses, however, infections caused by RNA viruses are far more significant than infections caused by DNA viruses (2). Coronaviruses are a very important emerging family of RNA viruses that cause respiratory infections. Recently, the coronavirus pandemic disease (COVID-19) has caused acute respiratory syndrome (3). SARS-CoV-2 attaches to human cells through angiotensin-converting enzyme 2 (ACE2) receptors, one of the expression sites of these receptors is in the intestinal epithelium (4, 5). According to studies in COVID-19 patients, gastrointestinal symptoms such as diarrhea and vomiting in patients were significant, which, considering viral RNA and live viruses in the feces of these patients, indicates that the gastrointestinal tract is probably a site to replicate and activity of the virus (5-7). Evidence suggests that probiotics can partially correct the lung-intestinal axis by altering gastrointestinal symptoms and protecting the respiratory system (8). Probiotics, as defined by the Food and Agriculture Organization of the United Nations/World Health Organization, are living microbes that provide a health benefit to the host when used optimally. Over the past few decades, various studies have shown that some of the natural flora of the gastrointestinal tract, such as some species of probiotics, including several strains of *Lactobacillus*, in addition to producing nutrients, have positive effects on host health (9). Probiotics play a role in balancing the host's immune response, thereby stimulating the function of the mucosal barrier and modulating the immune system (10). In this review, we discuss the efficiency of probiotics and their protective effects on viral respiratory infection caused by the SARS-CoV-2 virus. Future research will potentially focus on treating various viral diseases using probiotics and prebiotics as rational supplements.

Coronaviruses

Coronaviruses are spherical and enveloped viruses that contain a positive single-stranded RNA genome. They have prominent spikes on their surface. Coronaviruses have 3 to 4 structural proteins including spike (S) which mediates cell binding and entry into the host cell, glycoprotein, integral membrane glycoprotein, and nucleocapsid phosphoprotein. Coronaviruses are a type of virus that infects various types of livestock, poultry, domestic and wild animals as well as humans. They belong to five groups of antigens that cause respiratory or intestinal infections (11). According to the new classification by the International Committee on Taxonomy of Viruses, coronaviruses are divided into three genera: alpha, beta, and gamma, which belong to the subfamily of coronavirinae, the family of coronaviridae, and superfamily of nidovirales. α-coronaviruses and β-coronaviruses infect mammals, while δ-and γ-coronaviruses infect birds (12). Although most coronavirus infections are colds in humans, the emergence of severe acute respiratory syndrome (SARS), the SARS-associated coronavirus (SARS-CoV), causes other important human diseases in addition to the beta-coronavirus. After identifying the SARS-associated human coronavirus (HCoV) as the new coronavirus, the causative agent of more severe human infections was identified as another alphacronavirus (NL63) capable of causing bronchiolitis in children and beta-coronavirus (HKU1) causing chronic respiratory disease in the elderly (13). SARS infectious disorder was first diagnosed in China in late 2002 and then spread around the world (14). The clinical manifestations of patients with SARS were three phases of the disease. The first stage of the disease was accompanied by fever, cough, sore throat, and myalgia, with shortness of breath often not appearing as a prominent feature until days 7 to 14 of the illness. In the second stage of the disease, hypoxia, and shortness of breath are accompanied by persistent fever and sometimes diarrhea, and by the third week, some patients develop acute respiratory distress syndrome. Deaths occurred in patients in the early 4th and late 108 days after the onset of the disease. The severity of the disease was associated with increasing age and the mortality rate was 50% in patients over 60 years (15-18). One of the coronaviruses, the Middle East Respiratory Syndrome (MERS-CoV) virus was first isolated in 2012 from a 60-year-old Saudi man who was diagnosed with Acute Respiratory Distress Syndrome (ARDS) and multiple organ failure, including kidney failure (19). In addition, MERS-CoV caused lower respiratory tract infections with symptoms of cough and fever (11). In both epidemics, the virus originated from bats and infected humans through other animal hosts, for example, *Paguma larvata* for SARS-CoV and camels for MERS-CoV were the primary hosts of the virus (20-22).

SARS-CoV-2 (COVID-19)

A novel coronavirus was identified in late 2019 in Wuhan, China, as the cause of a group of pneumonia cases. The disease spread with incredible speed, first leading to an epidemic throughout China and then becoming a global pandemic following an increase in the number of patients with the new coronavirus in other countries. In early 2020, the World Health Organization introduced the disease COVID-19, which stands for Coronavirus 2019 (23). Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a virus that causes COVID-19 (24). The higher transmission rate associated with the higher risk of mortality from COVID-19, usually due to acute respiratory distress syndrome (ARDS), is a unique feature of SARS-CoV-2 that distinguishes the disease from influenza (25). SARS-CoV-2 is a positive-sense single-stranded RNA virus (+ ssRNA, single-stranded RNA molecule) belonging to

the beta-coronavirus group, it is approximately 89% similar to SARS-like-CoVZXC21 and 82% similar to human SARS-CoV (26). The molecular structure of this virus is similar to other coronaviruses, and SARS-CoV-2 interacts with the host cell via ACE2 (angiotensin-converting enzyme 2), which is modulated by the S protein. In addition, SARS-CoV-2, like other coronaviruses, produces unstructured proteins and manipulates the host immune system and host cell physiology, which are virulence factors (4, 26). In COVID-19, what leads to different clinical symptoms in patients is due to the close interaction between the SARS-CoV-2 virus and the patient's immune system (27). While some people develop COVID-19 asymptomatic, others develop severe complications such as interstitial pneumonia and respiratory failure. To develop new therapies, it is important to understand the complexity of the immune system-virus interaction (27, 28). The novel coronavirus is transmitted through aerosols, such as airborne droplets scattered during the sneezing and coughing of symptomatic patients. The average incubation period is 6.4 days, which varies from 2.1 to 11.1 days (29).

Clinical features of SARS-CoV-2

Early in the onset of the pandemic, the most common symptoms, including fever, fatigue, and dry cough, were reported. Older patients were in the severe stage of the disease and were transferred to intensive care units (30). After further study in the European region, the patients' clinical manifestations were similar to previous reports, and fever was still the most common symptom, followed by cough, weakness, headache, sputum production, shortness of breath, sore throat, pleuritic pain, rhinobyon, rhinorrhoea, pharyngalgia and diarrhea (25, 31-33). Recently, in reports of studies on the clinical features of COVID-19, the most common symptoms, in addition to fever and cough, were CT scan (computer tomography) disorders. Further laboratory findings also showed lymphocytopenia, thrombocytopenia, and leukopenia. In addition, levels of alanine transaminase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), C-reactive protein (CRP), creatinine kinase (CK), erythrocyte sedimentation rate (ESR), white blood cell (WBC), D-dimer level, procalcitonin, urea, creatinine, and blood urea nitrogen (BUN) have been reported to be elevated in patients with COVID-19 (Fig.1) (34, 35). In addition, the new findings reported the main complications of COVID-19 were septic shock, coagulation disorders, respiratory distress syndrome, metabolic acidosis, and multiple organ failure (36).

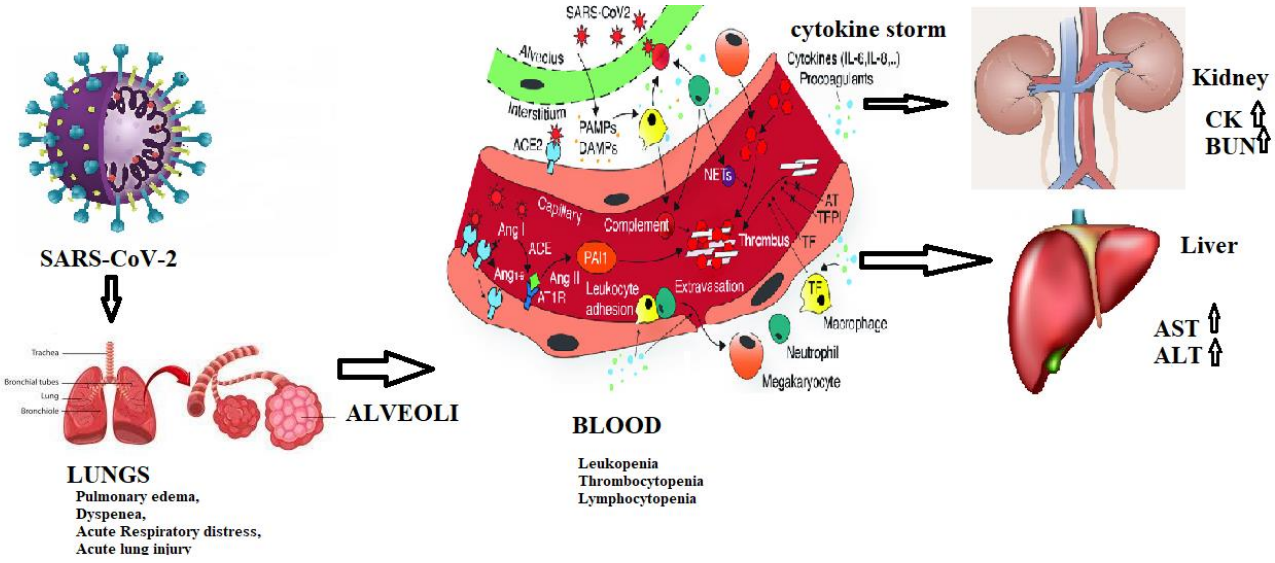


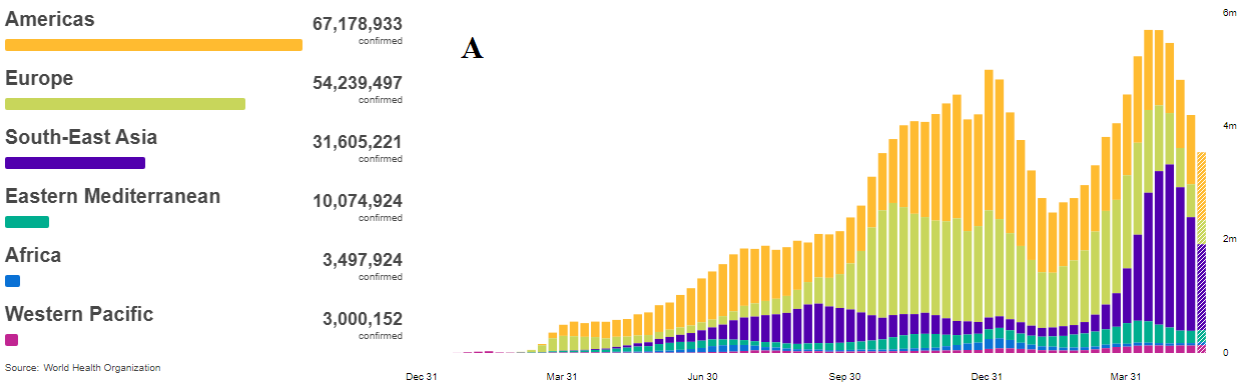
Fig.1 Pathogenesis and clinical features of COVID-19

Pathology of COVID-19 and human immunological responses

One of the leading causes of death for patients with COVID-19 was a severe immune response, and abnormal release of circulating cytokines, termed cytokine release syndrome (CRS) which are termed as cytokine storms include IL-6, IL-1, IL-2, IL-10, TNF-α, and IFN-γ. One of the clinical features reported in patients with COVID-19 is high levels of proinflammatory cytokines and chemokines such as MCP-1, IL-2, IL-7, TNF-α, G-CSF, MIP- 1A, MCP-3, IP-10, which is associated with disease severity. Also, elevated levels of anti-inflammatory cytokines such as IL-4 and IL-10 are manifested by the human immune system against COVID-19 infections. Excessive secretion of these cytokines damages the lungs and leads to the death of a patient with COVID-19 (37).

Epidemiology of SARS-CoV-2

At the end of 2019, more than 80,000 cases of COVID-19 were reported in China, according to the first Wuhan China report. A World Health Organization estimate showed that the epidemic in China peaked in early February 2020 (38). Initially, many COVID-19 cases were reported on other continents except Antarctica. These cases first occurred mostly in Chinese travelers and those who came in contact with them. The disease has since spread widely around the world, including to South Korea, Italy, Iran, Japan, and other American and European countries (24, 39). According to WHO reports at the end of May 2021, there were 169,597,415 confirmed cases of COVID-19, and the death rate from COVID-19 infection was reported to be 3,530,582. In addition, World Health Organization reports in late May 2021, based on the total incidence of COVID-19, showed that the United States of America, India, and Brazil had the highest incidence of 32,916,501, 27,894,800 and 16,391,930, respectively (Fig.2) (40).



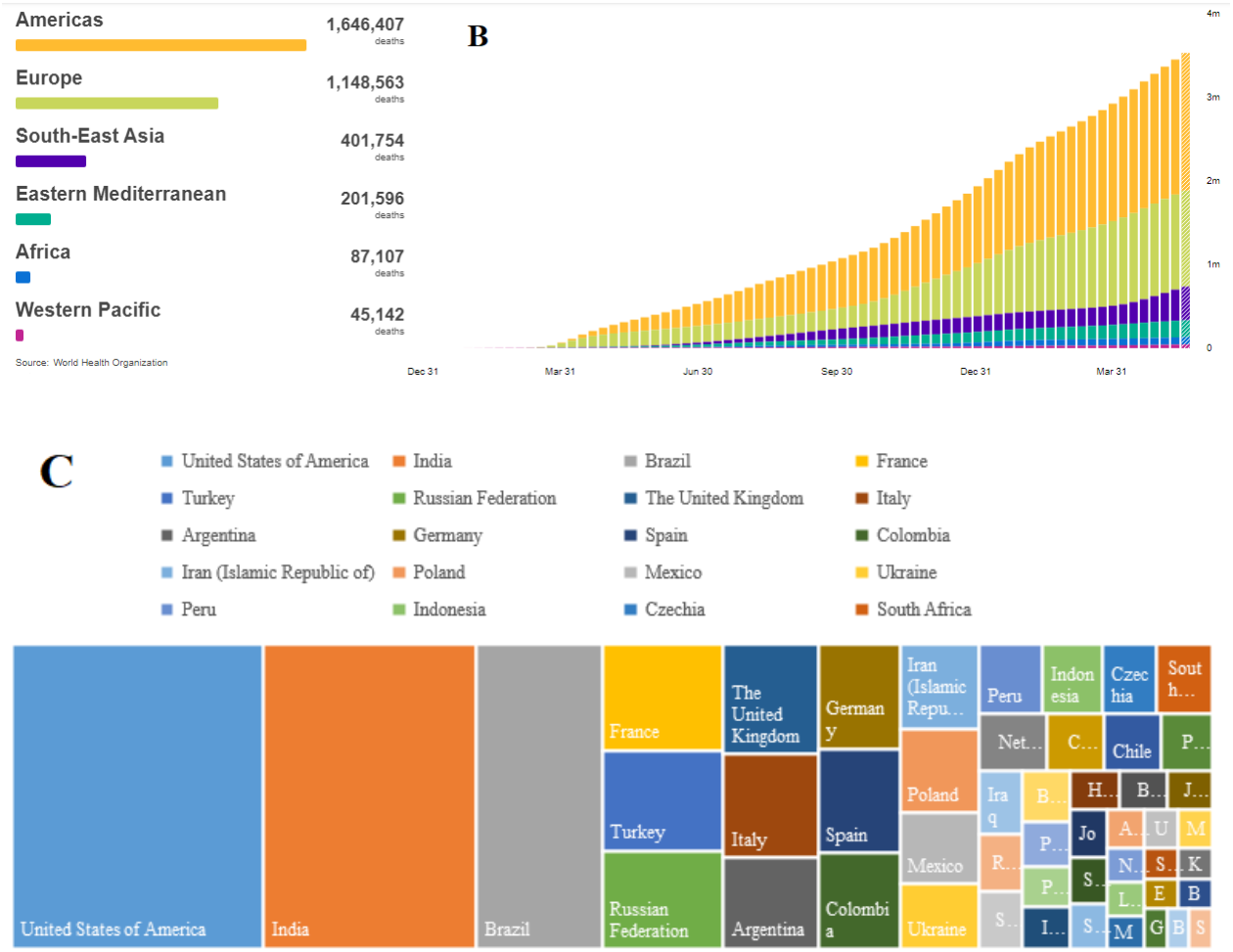


Fig.2 Globally confirmed cases of COVID-19 worldwide on 30 May 2021. A) Confirmed cases, B) Death cases, C) Confirmed cases by country.

SARS-CoV-2 infection and gastrointestinal tract

Although the link between the lungs and the gastrointestinal tract is not yet fully understood, it is evident that certain microbiota is present in the respiratory tract, but intestinal dysfunction/or secondary gut dysfunction occurs in patients with respiratory infections, indicating lung-gut crosstalk, and this phenomenon has also been observed in patients with COVID-19 (41). According to previous studies, the intestinal flora is closely related to respiratory virus infection and affects the development and progression of respiratory diseases through the gut-lung axis. Respiratory infections, such as the flu, affect the composition of the gut microbiota and, by disrupting the gut microflora, reduce the host's antiviral immune response, thus exacerbating the lung damage caused by these infections (42). According to several studies, enteritis and ventilator-associated pneumonia are modulated by the modulation of the intestinal microbiota, which can eliminate the side effects of antibiotics and can prevent the initial proliferation of the influenza virus in the lung epithelia. Targeting the gut microbiota is thought to be a new treatment option for COVID-19. Therefore, probiotics can be used to maintain the microbiological balance of the intestine and prevent secondary bacterial infection (41).

Chemical Drugs for treatment of COVID-19

At present, no specific drug has been introduced to treat COVID-19. As a result, supportive therapies were used such as anti-inflammatory drugs, oxygen therapy supplements, broad-spectrum antibiotics (to prevent coinciding bacterial infections), anticoagulants (to control thromboembolic complications), and antiviral drugs (43). Studies have shown that many antiviral drugs used to treat influenzas, such as oseltamivir, peramivir, zanamivir, ganciclovir, acyclovir, and ribavirin, were not effective in treating the symptoms of COVID-19 (44). However, among the RNA polymerase inhibitors, including favipiravir, which has extensive antiviral activity (45), along with chloroquine as a suppressor for the production and release of cytokines TNF-α and IL-6 (a drug used to treat malaria), was successful in treating several COVID-19 (46). In addition, Lopinavir and Ritonavir, which are used to treat HIV infection, reduced the COVID-19 viral load in patients (47). Tocilizumab (anti-IL-6 mAb), sarilumab (anti-IL-6R mAb), and anakinra (IL-1 receptor antagonist) were used to manage the cytokine storm in patients with

COVID-19 (48). Although physicians tried to use a combination of the above drugs to improve their effectiveness in the treatment of COVID-19, the side effects of these drugs and the uncertainty about the effectiveness of these drugs in all patients prevented to announcement of a consensus treatment using chemical drugs.

Probiotics

Probiotics are defined by the World Health Organization (WHO) and the United Nations Food and Agriculture Organization (FAO) as " live microorganisms that, when administered in adequate quantities as part of food, confer beneficial effects to the host through its intestinal microbiota " (49), probiotics find wide use in the respiratory, gastrointestinal, urogenital tracts, in allergic diseases, autoimmune cancers (50). Recent systematic reviews and meta-analyses have reported a positive, although the modest effect of probiotics in terms of prevention of respiratory tract infections (50), only one meta-analysis assessed the effectiveness of probiotics in the duration of respiratory conditions in children and adults was restricted to randomized clinical trials that used only probiotics of the genus *Lactobacillus* and *Bifidobacterium* (51). Scientists and the food and drug industries have been extensively studying the effects of probiotics on human health for many years. The findings of the studies showed that the prevention and treatment of acute and antibiotic-related diarrhea, inflammatory bowel disease, and irritable bowel syndrome (IBS) and the risk of sepsis and necrotizing enterocolitis by probiotics were effective. Other effects of probiotics were reported to kill *Helicobacter pylori*, reduce depression, prevent or treat atopic dermatitis, reduce cardiovascular risk factors associated with cardiometabolic syndrome, and reduce the incidence and severity of respiratory infections (52). Today, the microorganisms commonly used in the probiotic industry belong to *Lactobacillus* and *Bifidobacterium* genera, as well as *E. coli* Nissle 1917, *Streptococcus thermophilus*, and the yeast *Saccharomyces boulardii* (53). Some probiotic bacteria are listed in Table 1. Criteria for probiotic bacteria are bacterial strains that have the following characteristics: 1) ability to survive in the gastrointestinal tract and reproduce in the intestine, 2) usefulness through growth and activity in the human body, 3) non-pathogenic and non-toxic, 4) ability to protect against pathogenic microorganisms using several mechanisms and 5) lack of transferable antibiotic resistance (54).

Table.1 Microbes used as probiotics

Genus	Species
Lactobacillus	*acidophilus* *bulgaricus* *casei* *crispatus* *fermentum* *johnsonii* *gasseri* *paracasei* *lactis* *plantarum* *reuteri* *rhamnosus* *salivarius*
Bifidobacterium	*breve* *adolescentis* *animalis* *bifidum* *infantis* *longum* *lactis*
Propionibacterium	*freudenreichii*
Bacillus	*subtilis* *cereus*
Escherichia	*Coli* Nissle

Enterococcus	*faecium* *faecalis*
Streptococcus	*thermophilus*
Saccharomyces	*cerevisiae* *boulardii*

Action mechanism of probiotics

Probiotics are effective in human health through a variety of mechanisms such as protection against physiological stress, suppression of pathogens, induction of immune modulation, microbiome modification, and improvement of intestinal epithelial function (55, 56).

Effects of probiotics on epithelial cell inflammatory and immune system responses

Probiotics in the gastrointestinal tract (GIT), as the most microbiologically active ecosystem, play a key role in the function of the mucosal immune system, stimulating the immune system and creating a network of signals by the whole bacterium or its cell wall structure (57). Some of the effects of probiotics are mediated by the immune system, especially by balancing proinflammatory and anti-inflammatory cytokines (58). In addition, probiotics reduce the entrance of SARS-CoV-2 as well as the risk of COVID-19 by acting and maintaining the integrity of the junction between enterocytes (59). Probiotics also improve the innate immune response and can be used as immunobiotics to repair unbalanced microbiota and maintain intestinal immune homeostasis. Studies have shown that the innate immune system is stimulated by internal and external cellular molecules such as peptidoglycans, lipoteichoic acid phospho-polysaccharides, or DNA. Membrane molecules of probiotics can balance the innate immune system that communicates with intestinal epithelial cells, thereby improving the innate immune response (60). Restoration of intestinal microbiota improves resistance to viruses and pathogenic attacks on the surface of the respiratory mucosa (61). Previous studies have shown the effects of probiotics on the expression of genes related to the immune system, inflammatory activity, and the level of immune markers including modulation of intestinal epithelial cells NF-κB, mitogen-activated protein kinase (MAPK), IL-6, IL-8, IL-1β, and interferon γ (IFN-γ) were confirmed (62). It is noteworthy that in some studies, the effects of live and dead bacteria on gene expression were different, indicating the effect of cell surface and secreted active molecules on intestinal transcription (63). In addition, the immune effects of probiotics on the host include TNF-α secretion-dependent stimulation by lipoteichoic acid (LAT), modulation of proinflammatory cytokines, and T-helper 17 (TH17) cell response in the intestine and lung, and lung cell surface appendages and immune stimulation called SpaCBA, which binds to the intestinal mucosa and modulates TNF-α, IL-6, IL-10 and IL-12 (64, 65). The immunological benefits of probiotics may be due to the activation of local macrophages and the modulation of local and systemic IgA production to alter pro/anti-inflammatory cytokine profiles or a response modulation about food antigens (66, 67). In addition to the effects of probiotics in response to cytokines produced by inflammatory cells, probiotics also affect epithelial cell production. Some studies have shown that different types of probiotics such as *Bacteroides ovatus*, *E. coli* (SLF), and *L. rhamnosus* (LGG) produce a set of inflammatory cytokines, and LGG reduces the production of protein kinases C and IL-6. On the other hand, live and dead LGG inhibited NF-κB activation by inhibiting TNF-α-induced IL-8 production by Caco-2 cells (68, 69).

Production of antibodies by probiotics

Some studies have shown that taking *Bacillus coagulans* capsules increases CD3 + CD69 + and interferon-gamma (IFN-γ) cells (70). In addition, in another study, *Lactobacillus delbrueckii* increased influenza virus (IgA, IgG1) antibodies in the animal model (70). *Lactobacillus casei shirota*, as another potential probiotic, decreased plasma antibody titers in individuals with cytomegalovirus and Epstein-Barr virus by modulating the activity of natural killer cells (NK) (70). It was also shown that consumption of *Lactobacillus gasseri* and *Lactobacillus casei* enhanced the production of specific vaccine antibodies against influenza A/H1N1 and B viruses (70, 71). According to the evidence, the elements IgG, IgG1, and IgG3 in plasma in people taking the probiotic *Bifidobacterium animalis* ssp. *lactis* and *Lactobacillus paracasei* ssp. Increased (70). According to previous studies, more than 20 strains can improve anti-inflammatory interleukins and produce antibodies against viruses (72).

The effect of probiotics on respiratory infections

Probiotics have also been used to protect against respiratory infections. *Lactobacillus* (L.) *rhamnosus* GG, in addition to common protection against gastrointestinal infections, prevents respiratory infections (73). Several studies on the effectiveness of probiotics on respiratory viral infections were performed, which showed the beneficial effects of probiotics on the treatment of respiratory infections (74). Also, according to studies, the use of probiotics significantly decreases the incidence of ventilator-associated pneumonia (VAP) (75). Probiotics also play a role in reducing the duration of colds. Also, based on the available literature, specific strains of oral probiotics can be useful as a safe adjunctive therapy in children

with asthma. Although the first line of asthma treatment is still drug-based, certain strains of probiotics may prevent asthma exacerbations in children (76, 77). It seems that the protective effect of probiotics on respiratory infections is probably related to the increase in IgA concentration, the number of NK cells, and the activity of T and NK cells (78). Past studies have shown that probiotics can provide a safe means to reduce the risk of acute otitis media, the use of antibiotics, and the risk of recurrent respiratory infections in the first years of life (79). According to several systematic studies and meta-analyzes, probiotics reduce the severity, duration, and incidence of colds, respiratory infections, and flu-like symptoms in adults, the elderly, and children (50, 80). In some studies on the effects of various probiotics on respiratory infections, the best probiotic to affect the incidence of respiratory infections was *Lactobacillus casei rhamnosus* (LCA) (81). A meta-analysis published in 2013 showed that the use of *Lactobacillus rhamnosus* GG (LGG) compared with placebo reduced the incidence of acute otitis media and upper respiratory infections in children (82). Because the beneficial effects of probiotics on viral infections have been identified, certain probiotics reduce the duration and severity of acute rotavirus gastroenteritis (83).

Role of probiotic in COVID-19

Probiotics coexist with prebiotics to stimulate the growth and activity of probiotic microorganisms. Probiotics, as a possible treatment for COVID-19, manage cytokine storms and COVID-19-induced inflammation and reduce common infections, including ventilator-associated pneumonia. In addition, they express a potential link between the gut and the lung microbiota and respiratory health (84-87). Probiotic strains improve mucosal immunity and can help improve gut and lung barrier and homeostasis by increasing regulatory T cells, improving antiviral defenses, and reducing proinflammatory cytokines in respiratory infections such as COVID-19 (61).

ACE inhibitory effect of probiotics

SARS-CoV-2 is invaded by the host cell by binding to surface spike proteins to the angiotensin-converting enzyme (ACE2) receptor and is produced and amplified by the serine proteinase TMPRSS2 (88, 89). On the other hand, the mechanism of acute lung injury is also triggered by the activation of the renin-angiotensin system (RAS), in which ACE2 has a protective effect. Treating ACE inhibitors, ACE2 expression is increased by epithelial cells in the intestine, kidney, blood vessels, and lungs (90, 91). As a result, several probiotics, including LAB, have reportedly been able to produce ACE inhibitory peptides. Some sources have suggested prescribing foods and probiotics for prophylaxis for people suspected of Covid-19 (92). However, the potential role of probiotics in modulating ACE2 levels is suggested as a treatment option. In addition, by proving the non-catalytic role of ACE2 in the transport of amino acids in the gut, the therapeutic effect of ACE2 can be modified by its actions on the gastrointestinal tract or intestinal microbiome. Thus, it shows that there is a connection between the intestine and the lung (90, 93).

Role of probiotics on immunomodulatory against COVID-19

In COVID-19 infection, an increase in proinflammatory cytokines such as IL-1β, IL-6, IL-7, IL-17, IL-15, TNF-α, and IFN-γ causes inflammation of the airways (94), leading to a cytokine storm that eventually causes pulmonary fibrosis and damage to the respiratory organs (95). The inflammatory stimulus response is due to the activation of the Th1 cell response (96). In fact, disruption of the gut microbiota causes an imbalance of Th1/Th2 cells and leads to a storm of proinflammatory cytokines in the lungs, which are reduced by modulating the Th1/Th2 cells of the inflammatory response in the respiratory tract (97). Probiotic bacteria control the response of the lung immune system to viral infections by modulating the gut microbiota. Thus, probiotics reduce the excessive inflammatory response by acting on T cells to produce IFN-γ (98). In addition to stimulating the Th1/Th2 cell balance, probiotics activate the immune system in the airway mucosa (99). The response of inflammatory cytokines in the airway mucosal epithelium begins to regenerate the airways, leading to the narrowing of the airways, which causes respiratory problems and worsens the patient's condition (100). One of the therapeutic goals of probiotics is to prevent airway regeneration due to respiratory infection (101).

Conclusion

Because COVID-19, in addition to economic and health losses, has caused the death of many people worldwide, and because of the side effects and inefficiency of many antiviral drugs and antibiotics that are now used to treat and rescue patients with COVID-19, in this review, we aim to examine the effects of probiotics in the treatment of COVID-19. By targeting the gut-lung microbiota axis plays a very important role in the treatment and prevention of COVID-19 infection, we found that manipulation of microbial patterns using probiotics that are effective in modulation of the immune system, antibody production, modulation of pro-inflammatory cytokines and ACE inhibition, they can help reduce inflammation of lung cells and maintain intestinal microbial diversity. However, further efforts are needed to find new and more appropriate antiviral and anti-inflammatory therapies for these deadly infectious diseases.

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Consent for publication

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Ethical Statement

All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content. Also, the paper is not currently being considered for publication elsewhere.

Conflict of interest

The authors have no conflicts of interest to declare.

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