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Probiotic supplementation: A prospective approach in the treatment of COVID-19

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Abstract

Background: Despite strategies based on social distancing, the coronavirus disease 2019 (COVID-19) expands globally, and so far, many attempts have been made to achieve effective treatment for patients with COVID-19. This disease infects the lower respiratory tract and may lead to severe acute respiratory syndrome coronavirus (SARS-CoV). COVID-19 also can cause gastrointestinal infections. Therefore, COVID-19 patients with gastrointestinal symptoms are more likely to be complicated by SARS-CoV. In this disease, acquired immune responses are impaired, and uncontrolled inflammatory responses result in cytokine storms, leading to acute lung injury and thrombus formation. Probiotics are living microorganisms that contribute to the health of the host if administered in appropriate doses. **Aim:** This study aimed to provide evidence to show the importance of gut dysbiosis in viral disease, especially COVID-19. Therefore, we have focused on the impact of probiotics consumption on preventing severe symptoms of the disease. **Methods:** We have entirely searched SCOPUS, PubMed, and Google Scholar databases to collect evidence regarding the relationship between probiotics and viral infections to expand this relationship to the COVID-19. **Results:** It has been shown that probiotics directly counteract SARS-CoV in the gastrointestinal and respiratory tracts. Moreover, probiotics suppress severe immune responses and prevent cytokine storms to inhibit pathologic inflammatory conditions in the body via modulation of immune responses. **Conclusion:** According to available evidence based on their antiviral and respiratory activities, using probiotics might be an adjuvant therapy to reduce the burden and severity of this disease.

Keywords

Probiotics, coronavirus, coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus (SARS-CoV)

Introduction

In December 2019, cases of pneumonia and death were first reported in Wuhan, China. Shortly afterward, the number of cases increased dramatically and spread throughout China and the world. The causative agent of the disease has been confirmed as a new coronavirus (nCoV) and was officially named the coronavirus disease 2019 (COVID-19). Analysis of the viral genome shows that this coronavirus is close to the severe acute respiratory syndrome (SARS) in 2002 (Lu et al., 2020b). COVID-19 is presented with a variety of symptoms, from asymptomatic or mild to severe illness and death. Common symptoms of the COVID-19 include cough, fever, and shortness of breath. Other reported symptoms include weakness, respiratory distress, muscle aches, sore throat, and loss of taste and/or smell (Lovato et al., 2020).

Although SARS-coronavirus-2 (SARS-CoV-2) transmission is thought to occur primarily through respiratory droplets, the intestinal tract may also contribute to COVID-19 spreading. The genetic material of SARS-CoV-2 has been identified in patients' gastrointestinal tract and feces in sewage systems (Nishiura et al., 2020; Pan et al., 2020), indicating that SARS-CoV-2 can attack enterocytes. Extensive clinical studies in China showed that gastrointestinal symptoms are common in COVID-19 and are associated with its intensity (Huang et al., 2020; Lin et al., 2020). About half of the patients suffer from

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vomiting, diarrhea, and other gastrointestinal disorders; hence, physicians also associate gastrointestinal disorders with COVID-19 (Ding and Liang, 2020; Gu et al., 2020). In the elderly, COVID-19 infects the lower respiratory tract and may lead to fatal pneumonia (Lu et al., 2020a; Mahase, 2020; Nishiura et al., 2020). In the second week of infection, hypoxemia, difficulty in breathing, and acute respiratory distress syndrome (ARDS) also occur (Hui et al., 2020). In addition, secondary bacterial infections may lead to secondary bacterial pneumonia (Kannan et al., 2020).

The clinical diagnosis of COVID-19 is determined by clinical manifestations, molecular diagnosis of the viral genome by reverse transcriptase-polymerase chain reaction (RT-PCR), chest X-ray or computed tomography scan, and serological blood test. Elevated C-reactive protein (CRP) and inflammatory markers, increased cardiac markers, leukopenia, neutropenia, decreased albumin, thrombocytopenia, and abnormal kidney and liver function are the most common laboratory abnormalities in those with RT-PCR positive (Paranjpe et al., 2020; Zhu et al., 2020). Weak immune responses and the inability to fight against the virus increase the viral load, which leads to increased secretion of inflammatory cytokines into the bronchoalveolar lavage fluid and severe inflammatory/oxidative stress responses, resulting in severe lung damage. Antiviral therapies, antibiotics, corticosteroids, and anti-inflammatory drugs are commonly used in treatment protocols given to ARDS. Most anti-2019-nCoV therapeutic regimens are focused on immune modulators (such as corticosteroids and interferons (IFNs)), monoclonal antibodies, and inhibitors of viral polymerases (Gattinoni et al., 2020; Perales and Domingo, 2015). Despite social distancing and screening strategies, the prevalence of COVID-19 is rapidly increasing worldwide, and health care systems are on the verge of collapse. Although efforts are underway to find effective drug treatments, an effective vaccine for the disease may not be available soon. Therefore, additional preventive strategies are urgently needed (Baud et al., 2020)

Probiotics

Probiotics are live microorganisms that contribute to the host's health, provided that administered in appropriate doses. Many probiotic bacteria are members of the gut microbiota and are increasingly being included in foods to improve gut health and well-being. Recently, the immunogenic and immunomodulatory abilities of non-living probiotic products, such as bacterial exopolysaccharides and spores, have also been observed (Jung et al., 2017; Tonetti et al., 2020). Also, consuming foods rich in probiotics or their supplements has been shown to partially affect immune function by altering endogenous metabolic activities of microbiota (Galdeano et al., 2019). Probiotic bacteria are identified by genus, species, subspecies (if any), and a numerical design to specify an exact strain (Tsuda and Miyamoto, 2010). Some strains of probiotics have unique properties and special effects, such as antimicrobial activity, neurological effects, immunological or endocrine impacts, production of specific active ingredients, competitive elimination of pathogens, normalization of altered microbiota, short-chain fatty acids (SCFAs) production, and regulation of intestinal transport (Hill et al., 2014). Probiotics inhibit the overgrowth of pathogenic bacteria by secreting soluble agents or producing SCFAs, increase intestinal resistance to pathogens, improve epithelial barrier function, and prevent disease progression (Figure 1) (Hill et al., 2014).

Many randomized controlled trials and high-quality meta-analyses support probiotics' health effects (Guarner et al., 2012; Hill et al., 2014). Different types of probiotics have been reported to prevent many degenerative diseases, including obesity, diabetes, cancer, cardiovascular disease, liver disease, and inflammatory bowel disease (IBD). The imbalance of the intestinal microbiota composition leads to various diseases. Probiotics balance the intestinal microbiota composition by increasing the bacterial population, improving the function of the intestinal epithelial barrier, and increasing cytokine production. A variety of diets and nutrients positively affect the intestinal microbiota population (Kopeina et al., 2017; Liu et al., 2016; Morandi and Indraccolo, 2017; Ren et al., 2018; Yin et al., 2017). Different food components have differential effects on the intestinal microbiota. For example, consumption of whey and pea protein extracts increases intestinal microbiota such as *Bifidobacterium* and *Lactobacillus*, while whey has been shown to reduce the pathogenic bacteria, including *Bacteroides fragilis* and *Clostridium perfringens*. Also, it has been found that a low-fat diet has led to an increase in the *Bifidobacterium* in feces. In contrast, a high-saturated fat diet increases the relative proportion of Faecalibacterium prausnitzii. Despite digestible carbohydrates, indigestible carbohydrates such as fiber and resistant starch are fermented by intestinal microorganisms. Dietary fiber is a good source of carbohydrates for the microbiota to provide energy for them and consequently improves intestinal health (De Filippis et al., 2016; Dominika et al., 2011; Edwards et al., 2017; Farnworth et al., 2007; Kleessen et al., 1997).

A microbiota is a complex set of microorganisms that constantly colonize the mucosal surfaces of the human body. These microorganisms are considered important factors in health due to their important metabolites, the regulation of the immune system, and protection of the body against pathogens (Farnworth et al., 2007; Huttenhower et al., 2012; Methé et al., 2012). It should be noted that the human intestinal microbiota is composed of 10^{14} resident microorganisms (Gill et al., 2006). Alteration in the intestinal microbiota, called gut dysbiosis, is associated with various diseases and disorders such as IBD, type 2 diabetes, depression, and cardiovascular diseases (Khan et al., 2019; Sekirov et al., 2010; Zalar et al., 2018). Probiotics may also help treat and prevent acute diarrhea. Some probiotic strains, such as *Lactobacillus rhamnosus* GG and

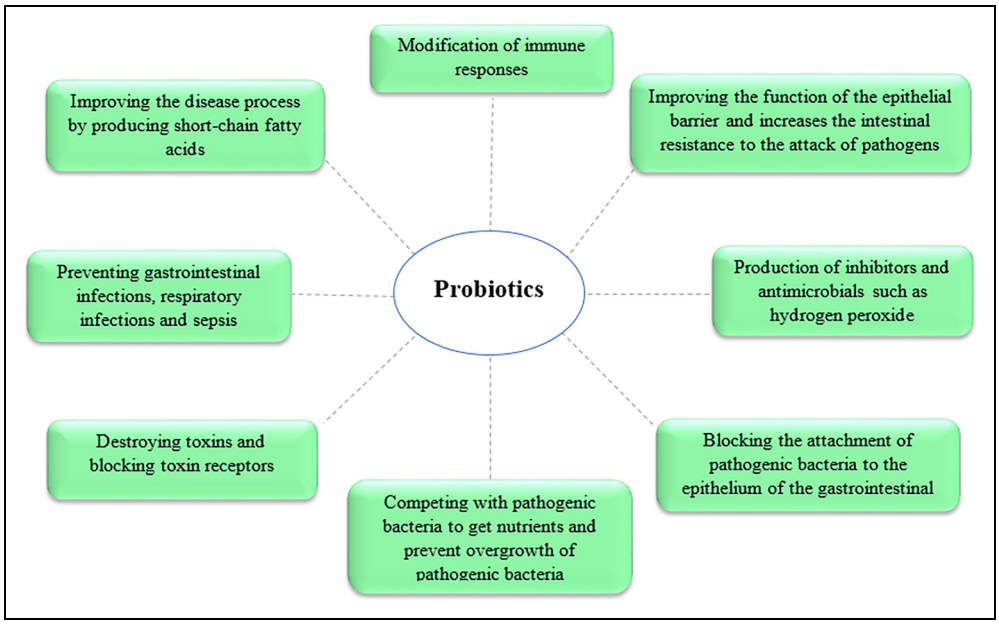

Figure 1. The role of probiotics in health and disease prevention.

Saccharomyces boulardii CNCM I-745, effectively reduce the duration and severity of acute infectious diarrhea in children (Figure 2) (Szajewska et al., 2007, 2014; Szajewska and Skórka, 2009). The effectiveness of intestinal microbiota in health and disease is becoming apparent more and more. There are studies on the therapeutic role of prebiotics and probiotics in gastrointestinal disorders, especially in the treatment of infectious gastroenteritis in children. These studies showed that probiotics prevented antibiotic-related diarrhea and reduced the side effects of antibiotic therapy for *Helicobacter pylori* (Figure 2) (Hempel et al., 2012; Malfertheiner et al., 2017; Szajewska et al., 2014).

IBD, such as Crohn's disease and ulcerative colitis, is a chronic inflammatory disease of the large intestine and small intestine that results from an unlimited immune response to germs in the intestines of susceptible individuals. Some fermented dairy products contain lactic acid bacteria (LAB) and *Bifidobacteria* as probiotics that modify the gut microbiota and may help in the treatment and prevention of IBD (Saez-Lara et al., 2015). A clinical study showed that the administration of probiotics reduced systemic pro-inflammatory biomarkers in colitis patients after 6 to 8 weeks of treatment (Plaza-Díaz et al., 2017). Also, some strains, including *L. rhamnosus*, *Bifidobacterium lactis*, and *Bifidobacterium longum* are able to modulate the expression of pro-inflammatory molecules and exert anti-inflammatory properties (Plaza-Diaz et al., 2014). Some probiotics prevent inflammation by increasing interleukin (IL)-10 and decreasing pro-inflammatory cytokines. They also reduce the secretion of pro-inflammatory cytokines such as IL-1β and IL-6 up to 70% and 80%, respectively (Sichetti et al., 2018). In a systematic study, probiotics decreased IL-6 and CRP and conversely increased levels of IL-10 in the serum of multiple sclerosis patients (Morshedi et al., 2019). Probiotics' potential in reducing the risk and severity of respiratory viral infections is supported by clinical and experimental studies of influenza, rhinovirus, and respiratory syncytial virus. Although none of these effects have been tested with SARS-CoV-2, some probiotic strains have shown antiviral activities against other coronaviruses (Figure 2) (Baud et al., 2020).

In a cross-sectional study, COVID-19 patients were classified into three groups regarding disease severity. The results showed that patients with critical conditions were slightly older than patients with severe and normal conditions. In addition, patients with critical conditions had more underlying diseases, and WBC, IL-6, D-dimer, PCT, LDH, and CRP in peripheral blood were significantly higher in this group compared with the other two groups. Simultaneously, the level of these markers was not significantly different between patients with severe and normal conditions. A number of patients were treated with antibiotics, especially critically ill patients, and a group of patients received probiotics. For critically ill patients, antibiotics dosage was high due to the need to prevent and control secondary infections (Tang et al., 2020).

Detection of changes in the intestinal microbiota composition might indicate disruption of the intestinal microflora in patients with COVID-19, especially in critically ill patients, to provide a clue to experimental antibiotic therapy. The results showed that dysbiosis in COVID-19 patients was correlated with disease severity and hematological parameters. The abundance of butyrate-producing bacteria, including *F. prausnitzii*, *Clostridium butyricum*, *Clostridium leptum*, and *Eubacterium rectale*, is significantly reduced in COVID-19, and this change in the bacterial population may distinguish critically ill patients from normal patients. In addition, the number of common

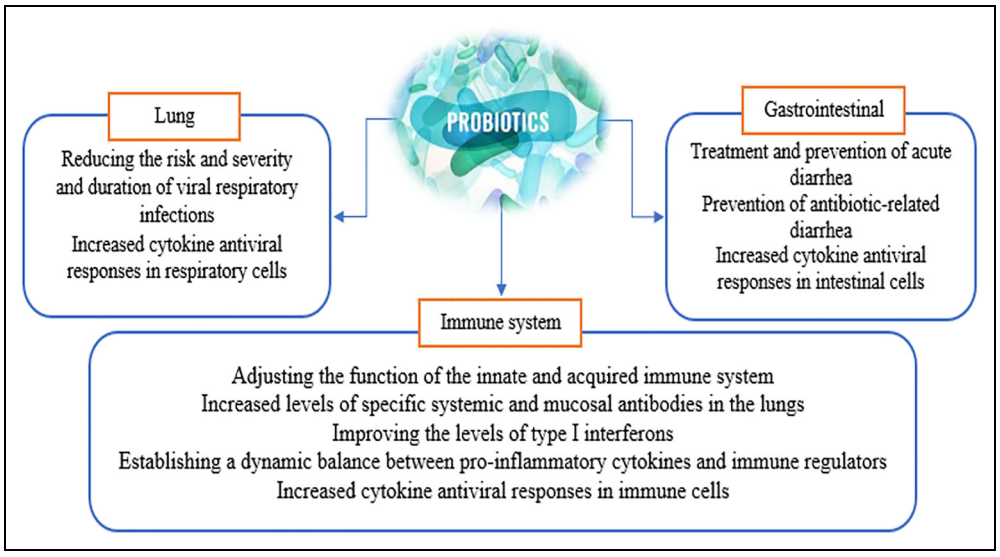

Figure 2. The role of probiotics in protecting against viral infections.

opportunistic pathogens, including *Enterococcus* (Ec) and *Enterobacteriaceae* (E) has increased, especially in critically ill patients with poor recovery. The results show that these bacteria can act as diagnostic biomarkers of COVID-19, and the Ec/E ratio can be used to predict death in critically ill patients (Tang et al., 2020). Although the precise mechanisms of probiotics and their metabolites have not been clearly established in respiratory infections, these infections have been shown to be affected by the probiotic strains, microbiota composition, and immunological status of an individual. Therefore, we review the current evidence of antiviral mechanisms and immunomodulatory of probiotics and the role of probiotics in the gastrointestinal tract and respiratory system with a focus on their immunomodulatory effects.

Direct possible counteraction of probiotics with SARS-CoV in the gastrointestinal tract and respiratory system

Clinical evidence suggests that some probiotics prevent bacterial and viral infections, including gastritis, sepsis, respiratory tract infections (RTIs), antibiotic-related diarrhea, and gastrointestinal infections (Baud et al., 2020). Mechanisms explaining the clinical efficacy of probiotics include competing with pathogens for nutrients, producing antimicrobials agents, strengthening the intestinal epithelial barrier, and modulating the host immune system (Figure 1) (Bermudez-Brito et al., 2012). Probiotics affect the innate and adaptive immune systems and reduce the severity of upper respiratory and gastrointestinal infections (Baud et al., 2020). Thus, probiotics are clinically effective in reducing the severity and duration of upper RTIs. These results have been concluded from a review of different strains of lactic acid-producing bacteria in improving symptoms or preventing various viral infections, such as reducing the titer of Ebola and cytomegalovirus, reducing the severity and duration of upper respiratory tract infection, or gastritis intestines (Kanauchi et al., 2018; Wang et al., 2016). A clinical trial study on 55 infants showed that rotavirus-related diarrhea was reduced by oral administration of *Bifidobacterium bifidum* and *Streptococcus thermophilus* (Saavedra et al., 1994). This effect has been confirmed in subsequent studies. This finding indicates interference in the virus entering the cells or inhibition of virus proliferation in the intestines. Although this mechanism may also effectively reduce coronavirus spread through the intestine, since probiotic strains are not injected into the respiratory tract, direct inhibition in the respiratory tract seems impossible (Enaud et al., 2020; Saavedra et al., 1994).

Probiotics restrain the spread of the virus to the submucosal compartment due to enhancing the mucosal intestinal barrier, which is one of the important preventive mechanisms of probiotics against the progression of viral infections. On the other hand, stimulation of mucus production is probably a strategy to increase probiotics adherence to the epithelium. Probiotics need to be colonized in the intestine to perform their beneficial effects (Toumi et al., 2013). In a mouse model of spontaneous ileitis, a multi-strain probiotic mixture has shown a preventive effect on intestinal inflammation by enhancing tumor necrosis factor-α (TNFα) secretion from epithelial cells and reducing cell permeability (Hussman, 2020; Zhou et al., 2020). This is a possible reason for using probiotics to prevent SARS-CoV-2 infection due to maintaining healthy gut-associated lymphoid tissue to actively prevent the virus from infecting intestinal cells (Dhar and Mohanty, 2020). SARS-CoV-2 causes gastrointestinal tract infection, inflammation of the mucosa, and sometimes diarrhea. In this condition, dysbiosis intensifies the immune response and mediates systemic inflammation. Evidence suggests

that oral administration of probiotics may play an important role in preventing systemic and intestinal effects of COVID-19 (Infusino et al., 2020). SARS-CoV-2 can attack human cells by binding its spike proteins to the angiotensin-converting enzyme 2 (ACE2) (Wu et al., 2020). This binding leads to dysbiosis of intestinal flora and gastrointestinal symptoms (Alhazzani et al., 2020; Guan et al., 2020; Li et al., 2020). The association between intestinal flora and ACE2 has been identified. ACE2 deficiency in the rat model impairs local tryptophan homeostasis and alters the intestinal microbiome and susceptibility to inflammation (Hashimoto et al., 2012). ACE2 can also regulate nutrient uptake by binding to amino acid carriers on intestinal epithelial cells (IECs), suggesting that SARS-CoV-2 may intervene with proteins in nutrients to uptake through ACE2 into the intestinal epithelium (Javed and Bröer, 2019; Singer et al., 2012; Vuille-dit-Bille et al., 2015). Studies have shown that ACE2 expression in the intestinal epithelium regulates the intestinal microbiome environment through intestinal amino acid homeostasis and that ACE2 receptors are significantly reduced when SARS-CoV-2 enters the cell. Decreased intestinal ACE2 can lead to changes in the microbiota which causes susceptibility to intestinal inflammation (Alhazzani et al., 2020; Curtis et al., 2020; Hao et al., 2015). Based on this evidence, bacterial therapy can be complementary for the prevention and restoration of intestinal mucosal layers by modulating intestinal microbiota and reducing inflammation. ACE2 is highly expressed in lung cells and the cytoplasm of gastrointestinal epithelial cells.

TMPRSS2 is also highly expressed in enterocytes as a protein responsible for priming the viral protein which is necessary for host cell entry (Bertram et al., 2012; Curtis et al., 2020). Viral nucleocapsid proteins have been observed in the cytoplasm of epithelial cells of the rectum, duodenum, and stomach (Xiao et al., 2020). Investigations suggest that SARS-CoV-2 is likely transmitted through the respiratory tract, but many findings suggest that the gut may play an important role in the pathogenetic development of the disease as well as a possible route of infection (Infusino et al., 2020). Due to the effect of probiotics on respiratory diseases, two randomized controlled trials showed that ventilator-associated pneumonia significantly had been decreased in critically ill ventilated patients receiving probiotics, such as *L. rhamnosus* GG, *Bacillus subtilis*, and *Enterococcus faecalis*, compared with placebo. Thereby, it can be assumed that COVID-19-associated pneumonia can be relieved in the same way (Morrow et al., 2010; Zeng et al., 2016). *Lactobacillus plantarum* has been shown to significantly reduce human H1N1 virus and avian influenza H7N9 virus in the lungs of mice and increase the median survival time of infected mice (Bae et al., 2018). Also, *L. plantarum* reduced virus-induced inflammation following acute infection by the pneumonia virus in mice, which induces inflammation in rodents and is related to the respiratory syncytial virus (Percopo et al., 2019). Interestingly, intravenous administration of lactobacilli protects against viral respiratory infections and directly enhances innate immune responses in the respiratory tract epithelium (Harata et al., 2010). Respiratory infections such as the flu are associated with an imbalance in the microbial population of the respiratory and gastrointestinal tracts. As reported in China, COVID-19 may be associated with gut dysbiosis of probiotics involved in intestinal homeostasis and causes inflammation and inadequate response to pathogens (Gao et al., 2020; Hanada et al., 2018; Sencio et al., 2020; Xu et al., 2020).

The epithelial surface of the mucosa covers the respiratory tract and is continually exposed to many microorganisms as well as it is considered the main entry point for respiratory viruses. The first step in the disease process is the attachment of the virus to the host cell, so it is beneficial for the host to interrupt this attachment. Probiotics bind directly to the virus and inhibit the binding of the virus to the host cell receptor. For example, it has been shown that certain strains of *Lactobacilli* can bind to and inactivate vesicular stomatitis virus (influenza-like virus) in vitro. Also, probiotics' adherence to the epithelial surface blocks viral adhesion through steric hindrance, and receptor sites are covered non-specifically (Botić et al., 2007; Lehtoranta, 2012). Probiotics regenerate the mucosa, and the intestinal mucosa attaches to viruses, preventing them from attaching to epithelial cells and preventing the virus from multiplying (Lehtoranta, 2012). Probiotics, through producing antimicrobials such as hydrogen peroxide, organic acids, bacteriocins, and biosurfactants, have direct antimicrobial activity against pathogens (Servin, 2004). There is evidence that the metabolic products of specific *Lactobacilli* and *Bifidobacteria* in epithelial cells and macrophages prevent vesicular stomatitis virus infection (Botić et al., 2007). Moreover, the antiviral activity of bacterial metabolites in yogurts prevents the replication of the influenza virus (Choi et al., 2009). In alveolar macrophages in vitro, it has been shown that probiotics induce low levels of nitric oxide (NO) synthesis, which is protective against viruses in respiratory cells. In fact, respiratory viruses infect cells with different mechanisms and receptors, and the antiviral effects of probiotics are in a strain-specific manner (Ivec et al., 2007; Pipenbaher et al., 2009; Yeo et al., 2014).

Immunomodulation by probiotic against COVID-19

In general, probiotics modulate the immune response through epithelial cells. They modulate and activate immune responses through stimulation or inhibition of macrophages and dendritic cells (DCs). Upon immune-stimulation, $CD8^+$ T lymphocytes differentiate into cytotoxic T lymphocytes, which annihilate virus-infected cells. $CD4^+$ T lymphocytes also differentiate into type 1 helper (TH1) and type 2 helper (TH2) cells. Phagocytes are activated by TH1 cells and are promoted to kill viruses. B cell proliferation is also increased by TH2 cells and migrate to secondary lymphoid organs in mucosa-associated lymphoid tissue

and become immunoglobulin-producing plasma cells, which can migrate to the site of infection. Also, secreted antibodies can neutralize the virus (Lehtoranta, 2012).

Evidence from influenza virus infection and three beta-coronavirus infections (Middle East respiratory syndrome, SARS, and COVID-19) emphasize some important immunopathological features of the disease, including uncontrolled acute inflammatory responses from $CD4^+$ and $CD8^+$ T cells, macrophages, neutrophils, DCs with a contribution of Toll-like receptors (TLRs), cytokines, chemokines, plus tissue regeneration processes and the secondary bacterial infection (Damjanovic et al., 2012; Perlman and Dandekar, 2005). Influenza virus infection causes strong immunological reactions to the virus, such as overproduction of cytokines and chemokines. Stimulation of cytotoxic mechanisms is essential for the destruction of virus-infected cells but might be harmful and lead to pulmonary immunopathology (Atto et al., 2019; Damjanovic et al., 2012; Eapen and Sohal, 2018). In addition, tissue damage from uncontrolled innate immune responses and excessive neutrophil infiltration due to influenza virus infection exacerbates disease and mortality (Damjanovic et al., 2012).

When SARS-CoV-2 enters, respiratory epithelial cells elicit an immune response by producing inflammatory cytokines with a weak IFN response. Pathogenic pro-inflammatory immune responses by TH1 cells and monocytes start with virus detection, which consequently leads to a cytokine storm following the infiltration of macrophages and neutrophils into lung tissue. SARS-CoV-2 can rapidly activate pathogenic TH1 cells to secrete pro-inflammatory cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-6. GM-CSF induces large amounts of IL-6, TNF-α, and other cytokines by activating inflammatory $CD14^+$ $CD16^+$ monocytes. Membrane-bound immune receptors (e.g. Fc receptors and TLRs) may contribute to an imbalanced inflammatory response. Also, a poor induction of IFN-γ may be an important booster for cytokine production. Cytokine storms in COVID-19 are characterized by overexpression of IL-6 and TNF-α. Acquired immune responses and uncontrolled innate inflammatory responses to SARS-CoV-2 may trigger cytokine storms (Hussman, 2020; Zhou et al., 2020). SARS-CoV-2 is thought to, directly and indirectly, infect intestinal epithelial and influence inflammation through releasing chemokines and pro-inflammatory cytokines. The elevated fecal calprotectin and serum IL-6 levels indicate that SARS-CoV-2 stimulates acute inflammatory responses in the intestine and is clinically represented by diarrhea (Ng and Tilg, 2020). Commensal bacteria play an important role in the formation of the host immune system and the development of immune responses in health and disease conditions (Chervonsky, 2009; Hooper and Gordon, 2001).

Further evidence has shown that the gastrointestinal microbiota is able to modulate neutrophil migration and function, as well as affect the differentiation of T cells into TH1, TH2, and TH17 or regulatory T cells (Tregs). Tregs may, in turn, induce tolerance in immune reactions against various bacteria in the lumen (Francino, 2014; Owaga et al., 2015). *Lactobacilli* and other probiotics have reportedly been able to help to regulate the immune system and protect the body against viral infections through increasing antiviral cytokine in respiratory and intestinal mucosa (Figure 2) (Biliavska et al., 2019; Chiba et al., 2013; Miettinen et al., 2000; Salva et al., 2011; Weiss et al., 2010). Oral administration of *L. brevis* in mice protects against influenza infection by amplifying IFN-γ, which has antiviral effects, as well as enhancing the production of neutralizing immunoglobulin A antibodies against the virus (Waki et al., 2014).

Commensal bacteria also regulate Treg cells, innate lymphocytes, and TH cells and greatly affect mucosal immunity. This immune-modulating activity can be used for therapeutic purposes in COVID-19. The ability of probiotics to induce immunomodulation is enhanced directly by interacting with immune cells or indirectly by supporting microbiota (Wieërs et al., 2020). Probiotics are also used to stimulate the immune system to generate a network of signals. They interact with IECs or immune cells associated with lamina propria through TLRs or other microbial pattern recognition receptors and stimulate the production of cytokines and chemokines. These molecules then communicate with other immune cells through signaling pathways and activate the mucosal immune system. Some probiotics have been shown to enhance the function of TH1 and Treg cells in the epithelial barrier by increasing the production of tight junction proteins and goblet and mucin cells (Smelt et al., 2013; de LeBlanc et al., 2008; Shinde et al., 2019, 2020). Probiotics enhance the release of IL-10 by activating regulatory T cells (Galdeano et al., 2019). Probiotics have also been shown to be effective in improving inflammatory conditions and regulating innate immunity using TLRs and associated signaling pathways (Galdeano et al., 2019). Probiotics contain immune stimulants such as lipoteichoic acid, peptidoglycan, muramyl dipeptide, and nucleic acid, which are considered TLR ligands (Kanauchi et al., 2018).

DCs constitute a significant subset of immune cells that link innate and acquired immune responses by identifying pathogenic and producing endogenous inflammatory signals. These cells are divided into plasmacytoid DCs (pDCs), myeloid DCs, and $CD8^+$ DCs. Meanwhile, pDCs are a rare and vital subset that acts as a "watchdog" for viral infections. To detect the presence of bacteria and viruses, pDCs use special TLRs. Activation of pDCs by TLRs results in the production of type I IFNs. The type I IFNs, including IFN-α and IFN-β, act as first-line defense components against viral infections by preventing virus replication. IFN-α plays a vital role in the antiviral immune response by inducing cytotoxic activity of natural killer (NK) cells, which helps the host defend against viral infections. Screening of different LAB for their ability to stimulate IFN-α production by pDCs showed that *L. Lactis* JCM

5805 was the most potent stimulant for IFN type I production (Asselin-Paturel et al., 2001; Fujii et al., 2017). The mechanism of antiviral effects of *L. lactis* JCM 5805 relies on the activation of pDCs. Direct activation of pDCs by *L. Lactis* JCM 5805 can be mentioned as the most logical mechanism for inhibiting viral infection. Another report says that certain probiotic bacteria can attach and inactivate rotaviruses. In addition to direct interaction with viruses, *L. Lactis* JCM 5805 likely compete for viral receptors at the target cell surface, produce antimicrobial and antiviral agents, and stimulate host immune systems (Haller et al., 2006; Jounai et al., 2012, 2015; Suzuki et al., 2016). A recent article evaluated the anti-inflammatory ability of *Weissella cibaria* (JW15) against lipopolysaccharide stimulation in RAW 264.7 cells. Heat-killed JW15 treatment reduced NO and prostaglandin E2 production by reducing the NO synthase and cyclooxygenase-2. In addition, treatment with heat-killed JW15 suppressed the expression of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α. The anti-inflammatory properties of heat-killed JW15 were associated with the mitogen-activated protein kinase signaling pathway, which modulates nuclear factor-κB (NF-κB) suppression. These results indicate that JW15 has anti-inflammatory potential and provides a molecular basis for the development of functional probiotic products (Yu et al., 2019). In addition, probiotic strains of *Lactobacillus paracasei* and *L. plantarum* significantly reduced the release of various inflammatory mediators, including IL-6, IL-8, and prostaglandin E2 (Schmitter et al., 2018). Mice receiving *L. paracasei* showed a lower prevalence of H3N2 influenza A infection, which was related to reduced infiltration of inflammatory cells into the lungs and faster elimination of the virus (Belkacem et al., 2017). *Bifidobacteria* have protective effects against influenza virus infection. After fatal infection with influenza A (H1N1), severe stimulation of humoral and cellular immunity along with lower levels of pro-inflammatory IL-6 production and increased survival were observed in mice receiving *B. bifidum* (Mahooti et al., 2019). Treatment of Caco2 cell line or DCs with multiple probiotics reduced the production of several inflammatory chemokines and cytokines such as interleukin-22, IL-8, and TNF-α and decreased apoptosis in IECs (Jounai et al., 2012).

On the other hand, the intestinal microbiota significantly regulates the innate and acquired immune system (Plaza-Díaz et al., 2017). Intestinal immune homeostasis is associated with fine-tuning pro-inflammatory responses balance such as Th17/Tregs ratio, which is ultimately controlled by commensal microorganisms (Round and Mazmanian, 2010). In response to pathogenic infections such as the coronavirus, the gut microbiome can be important in maintaining an optimal immune response to prevent a series of overreactive immune reactions that are ultimately harmful to the lungs and vital organs. In such cases, a balanced immune response is essential because an overreaction or a weak response can equally exacerbate clinical complications such as pneumonia and ARDS in a viral disease such as COVID-19 (Dhar and Mohanty, 2020). The intestinal microbiome plays a vital role in systemic and mucosal responses, especially in the lungs. Administration of some *Bifidobacteria* or *Lactobacilli* has a beneficial effect on the clearance of influenza virus from the respiratory tract (Abt et al., 2012; Ichinohe et al., 2011; Zelaya et al., 2016). Probiotic strains improve the levels of type I IFNs, increase the population and activity of antibody-secreting B cells, NK cells, T lymphocytes, as well as the levels of systemic and mucosal antibodies in the lungs (Figure 2) (de Vrese et al., 2005; Namba et al., 2010; Zelaya et al., 2016). There is also evidence that probiotic strains strike a dynamic balance between pro-inflammatory and anti-inflammatory cytokines that allow clearance of the virus and minimize the damage of immune responses to the lungs and may prevent ARDS, which is the main complication of COVID-19 (Figure 2) (Chong et al., 2019).

Metabolites secreted by intestinal microbiota, including SCFAs (e.g. butyrate, acetate, and propionate) and secondary bile acids secreted by symbiotic microorganisms (e.g. *Bacteroides*, *Lactobacillus*, and *Bifidobacteria*) bind to DCs and macrophages, thereby modulating their metabolism and function. In fact, the administration of probiotic strains such as *B. lactis* to healthy elderly volunteers resulted in a significant increase in the ratio of mononuclear leukocytes and NK cells' tumoricidal activity. It has been shown that the balanced composition of intestinal microbiota has a major effect on the effectiveness of lung immunity (Jia et al., 2018). Butyrate has been shown to enhance macrophage antimicrobial activity by altering glycolysis and inhibiting rapamycin (mechanistic target of rapamycin) activity. Sodium butyrate relieves acute lung damage in mice by suppressing the release of high-mobility group 1 box (HMGB1) and activating NF-κB (Li et al., 2018b). Activation of NF-κB increases the expression of inflammatory mediators in response to injury and inflammation. HMGB1 is a late pro-inflammatory mediator that participates in acute lung development. Experimental evidence also suggests that SCFA is involved in regulating the activity and differentiation of T cells following tissue inflammation (Kim et al., 2014). SCFAs speed up cellular metabolism and regulate gene expression to increase the differentiation of B cells into antibody-producing plasma cells. Therefore, SCFAs effectively improve innate and acquired immune responses through microbial fermentation (Kim et al., 2016). Immune barriers protect the lung mucosa against various microorganisms and environmental antigens and play an important role in systemic immunity and lung immune functions. For example, if the immune barrier of the intestinal mucosa becomes weak, invading microorganisms enter the lungs or bloodstream, leading to sepsis and ARDS (Dickson et al., 2016; Donaldson et al., 2016). SCFAs, including butyric acid, acetic acid, and propionic acid, are the most important metabolites of the intestinal flora. They are important in regulating systemic and

pulmonary immune and inflammatory responses (Gonçalves et al., 2018). The direct function of SCFAs is to lower intestinal pH and increase mucin production, which reduces the growth and adhesion of pathogenic microorganisms and improves epithelial integrity, as well as increasing systemic immunity (Jung et al., 2015). SCFAs exert biological effects primarily by inhibiting histone deacetylase (HDAC) and activating G protein-coupled receptors (GPCRs) (Li et al., 2018a).

SCFAs can also affect the number and function of Tregs, TH1, and TH17 cells by inhibiting HDAC, thus disrupting hyperactive inflammation and the immune response through the intestinal-pulmonary axis in the respiratory tract (Li et al., 2018a). Many studies have shown that GPCRs, especially GPR43, GPR41, and GPR109A, play an important role in regulating metabolism, inflammation, and immunity. SCFAs, especially butyrate, have a wide range of anti-inflammatory functions by activating GPR43 and arrestin-β2 and inhibiting the NF-κB pathway. SCFAs, by activating GPR41, can also regulate the circulation of $Ly6c^-$ monocytes and increase the function of $CD8^+$ T cells to protect against influenza infection. Butyrate has also been reported to induce the differentiation of IL-10-producing Tregs through GPR109A activation (Husted et al., 2017; Sun et al., 2017). Moreover, SCFAs can stimulate macrophage and DCs progenitor generation in the bone marrow. Phagocytic DCs, which compose the majority of cells that enter the lungs, enhance the function of the T cells and provide a protective mechanism against allergic inflammation and respiratory tract infection (Kopf et al., 2015). In addition to SCFA, *Lactobacillus* uses tryptophan as an energy source to produce ligands for the aryl hydrocarbon receptor. This receptor is required not only for the organogenesis of intestinal lymph follicles but also for maintaining the epithelial barriers and intraepithelial lymphocyte homeostasis (Gao et al., 2018).

Concluding remarks

Unfortunately, it is not yet possible to say whether people who have recovered from COVID-19 are resistant or prone to a secondary infection. Due to the high rate of mortality and economic damage to various communities to date, the cooperation of various academics, governments, institutions, and pharmaceutical companies is unavoidable to prevent further expansion of COVID-19 (Ahn et al., 2020). The pathophysiology of COVID-19 clearly demonstrates the susceptibility of SARS-CoV-2 to IFNs. Due to the antiviral and immunomodulatory activity of probiotics and their ability to stimulate IFN production, it is recommended that probiotics can be used as adjunctive therapy to prevent COVID-19. It is also recommended to add probiotics to the daily diet (such as yogurt, whey, etc.) to resist viral infections. Prescribed oral probiotic strains might reduce the incidence and severity of viral respiratory infections. When physicians use little-known anti-COVID-19 drugs, probiotic strains with antiviral and enhancing respiratory activity (rather than low-quality undocumented strains) can be prescribed to reduce the burden and severity of the disease (Chan et al., 2020; Pregliasco et al., 2008). Although oral probiotics are not currently a routine part of a specific protocol for the treatment of respiratory viral infections, many studies suggest their potential modulatory effect on the systemic immune system that can improve response to viruses and balance inflammatory response (Infusino et al., 2020). As shown by the available evidence, there is a potential strategy for the prevention and treatment of COVID-19 through improving the composition of the intestinal flora and its metabolites. Some specific intestinal microorganisms that can reduce intestinal ACE2 expression have also been identified as potential targets for protecting against SARS-CoV-2 (Zuo et al., 2020). These insights add new dimensions to the understanding of COVID-19 and can also be helpful in designing a more rational and personalized treatment plan for patients (He et al., 2020). A personalized diet may improve prophylaxis and can be used to accelerate the recovery of patients with COVID-19 and to alleviate their clinical complications (Abt et al., 2012). Although gut dysbiosis has been observed in the pathogenesis of some respiratory conditions, more targeted and newer therapeutic approaches are needed. Modification of the intestinal microbiota is expected to be a promising treatment for COVID-19 or its associated inflammatory complications. However, the use of probiotics as adjunctive therapy may need to be further studied (Li et al.). Although more detailed research is needed, probiotics are expected to be complementary for treating and preventing viral infections.

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Ethics approval

The study was approved by the Medical Ethics Committee of Kermanshah University of Medical Sciences, Kermanshah, Iran (ID: IR.KUMS.REC.1399.964).

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