JMBFS

Journal of Microbiology, Biotechnology and Food Sciences

International peer-reviewed scientific online journal

Published by Faculty of Biotechnology and Food Sciences

IMPORTANCE OF PROBIOTICS IN THE PREVENTION AND TREATMENT OF COVID-19

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https://doi.org/10.55251/jmbfs.4594

ARTICLE INFO

Received 9. 3. 2021
Revised 27. 9. 2022
Accepted 20. 10. 2022
Published 1. 12. 2022

Review

OPEN ACCESS

ABSTRACT

The novel severe acute respiratory syndrome COVID-19 outbreak is brought on by the SARS-CoV-2 coronavirus. Taking into account the criticism that SARS-CoV-2 has received on a global scale, efficient preventive actions and treatment for COVID-19 would be an urgent need. New strategies were developed based on immune responses. The immunomodulating properties of a few bioactive substances, minerals, and micronutrients have led to recommendations. Probiotics' therapeutic uses in COVID-19 patients were looked into in this review. A decline in the amount of various probiotic species, including Bifidobacterium and Lactobacillus, was observed in some COVID-19 patients, which may be indicative of a compromised immune system. The use of probiotics has been predominantly explored for the inhibition and management handling of gastrointestinal disorders, but other potential properties of these microorganisms have been considered for nutritional effects, inflammatory diseases, *Helicobacter pylori* infections, allergic diseases, and anti-tumor properties. Some investigations have revealed that these probiotics stimulate and modify innate immune responses through multiple membrane molecules that transfer signaling massages with the epithelial cells of the gut. In addition to the gut microbiota, which has been widely studied, the physiopathology of numerous respiratory illnesses is known to depend on the lung microbiota. Through microaspiration and inhalation, which bacteria, molds, and viruses can create, the healthy lung acquired its unique microbiota. Probiotic strains might be used to influence these microbiotas, contributing novel views in the managing of respiratory diseases. Returning gut microbiota has been revealed to recover resistance to virus or pathogenic invades moreover at the respiratory mucosal stages.

Keywords: COVID-19, Probiotics, Microbiota, Coronavirus, Immunomodulation

INTRODUCTION

A novel coronavirus from the Coronaviridae family is the cause of the 2019 coronavirus disease (COVID-19). Two of the four coronavirus genera α- and β-CoV) can infect mammals **(Novel 2020)**. According to reports, the Middle East Respiratory Disease (MERS) outbreak was historically significant and had high mortality rates **(Vannabouathong, Devji et al. 2020)**. Currently, a new form of -CoV, specifically SARS-CoV-2 (called 2019 novel coronavirus), causes a global pandemic with a high mortality rate. There are no certain medications or vaccines to treat this serious communicable disease **(Li, Liu et al. 2020)**. Despite COVID-19 endangering public health, it is acknowledged as an international emergency **(Guo, Cao et al. 2020, He, Ren et al. 2020)**. Numerous reported pneumonia cases from Wuhan (China) are thought to be the first source of new coronavirus dissemination **(Andersen, Rambaut et al. 2020)**. However, many cases with no traveling history to Wuhan confirmed the human-to-human transmission of COVID-19 **(Chan, Yuan et al. 2020)**. The pathogenesis of SARS-CoV-2 was initiated after the entrance to human cells by genome replication. The ACE2 is proposed as a cell receptor of this virus that manages and regulates the cross-species, and the surface S-glycoproteins of coronavirus are responsible for attaching to ACE2 receptors on human cells **(Guo, Cao et al. 2020)**.

To date, the possible transmission route of SARS-CoV-2 included respiratory droplets, close contact, mucous membranes of eyes, mouth or nose, and aerosol also foods **(Zhu, Zhang et al. , Lu, Liu et al. 2020)**. Furthermore, many different clinical presentations were reported in patients from moderate to high, such as fever, dry cough, hard breathing, pneumonia, and respiratory infections **(Jamshaid, Zahid et al. 2020)**. Along with various treatments, strategies were assisted in this regard. Person-to-person transmission of the disease has been proven; although different countries have taken many control measures, it should be noted that travel to other areas should be avoided. Besides, many cases may be asymptomatic. Therefore, it is difficult to predict the time of epidemic peak and it will be more difficult to diagnose cases **(Peeri, Shrestha et al. 2020)**.

CURRENT TREATMENT STRATEGIES

Considering the global critic due to SARS-CoV-2, the implementation of efficient preventive actions and treatment for COVID-19 would be an urgent need **(Tang, Liu et al. 2020)**. Given the varied epidemiological features of SARS-CoV-2, the interruption of the spread chain by current prevention and control programs has not been accomplished. Generally, the primary proposed treatment has been included supportive treatments, anti-viral therapy, cellular therapy, immunotherapy, and Chinese medicine **(Li, Liu et al. 2020)**. The less evidence in therapeutic drugs for controlling the distribution and transmission of virus conducted the researchers to search about other potential ways to combat COVID-19. Also, ineffective anti-viral therapy approaches caused symptomatic and respiratory support to be the focal point of current treatment. Antiviral, antibiotic, anti-parasitic, and new small molecule anti-COVID-19 drugs-blocking cellular entry were among pathogen-targeting techniques that have been shown to be successful against SARS-CoV-2. The design based on host-targeting has been attempted as immunity modifiers such as monoclonal antibodies and interferon-α and corticosteroids that are recommended for COVID-19 treatment **(Jamshaid, Zahid et al. 2020)**. Recent symptomatic treatment approaches varied depending on the severity of the infection, ARDS and septic shock caused by COVID-19, antithrombotic medication, and plasma therapy **(Gandhi, Yokoe et al. 2020, Khan, Ali et al. 2020, Lu and Shi 2020)**.

New strategies were developed based on immune responses. Some bioactive compounds, minerals, micronutrients have been recommended due to their immunomodulation effects **(He, Ren et al. 2020)**. One of the most important treatments today is the use of various vaccines, including Live Attenuated Vaccines (LAVs) and Inactivated vaccines (IVs), Viral vectors, Nanotechnology approaches in vaccine, Nucleic acid-based vaccine (DNA and mRNA vaccines), Subunit vaccine and Peptide-based vaccines **(Umakanthan, Chattu et al. 2021)**. Probiotic use in promoting the COVID-19 state has received increased attention in this area **(Al-Tawfiq and Memish 2020)**. Many frameworks have documented the mechanism of probiotic intervention as COVID-19 treatment.

PROBIOTICS' IMPACT ON HEALTH AND DISEASE

According to WHO, FAO, and ISAPP, probiotics are live bacteria that improve the health of the host when given in excessive amounts **(Hill, Guarner et al. 2014)**. The use has been considered ever since long, previously known as food components **(Eslami, Yousefi et al. 2019)**. Probiotic use has mostly been investigated for the prevention and treatment of gastrointestinal ailments. Still, other potential properties of these microorganisms have been considered for nutritional effects, inflammatory diseases, *Helicobacter pylori* infections, allergic diseases, and anti-tumor properties **(Abdolshahi, Tabatabaiee Yazdi et al. 2016, Ghasemian, Eslami et al. 2018, Abdolshahi, Marvdashti et al. 2019, Eslami, Yousefi et al. 2019, Yousefi, Eslami et al. 2019)**. In cases of antibiotic-associated diarrhea, colitis, pouchitis, and irritable bowel syndrome, the effects of probiotics alone or in combination have been studied **(Verna and Lucak 2010)**. The most available probiotics are *Lactobacillus, Bifidobacteria*, and *Saccharomyces*, used in food and dairy products and supplements. Prebiotics selectively used by host microbes and beneficial to health **(Lebaka, Wee et al. 2018)**. Most prebiotics are carbohydrate-based and have also demonstrated a variety of health benefits, including the ability to limit the growth of pathogens and immune system modulation **(Sanders, Merenstein et al. 2019)**. Prebiotics are indigestible to absorption and digestion. Several molecules can perform as short-chain fatty acids (SCFA), peptidoglycans, and polysaccharides. The regulatory mechanism of the immune system is affected by prebiotics. Also, the effective functions of probiotics in treating several diseases caused by viruses are well documented **(Sanders, Merenstein et al. 2019)**.

PROBIOTIC EFFECTS ON IMMUNE RESPONSES

Mucus, the movement of the cilia, and secretory IgA in the respiratory tract secretion are the primary mechanisms by which the host achieves protection. Dendritic cells (DC) are persuaded by viral infection to initiate a series of immunological responses, which are followed by the activation of CD4+/CD8+ cells and an improvement in specific T and B cell intermediated immunity **(Madsen 2006)**. Microorganisms form a diverse and rich environment on the skin and mucosal surfaces. The correlation between gut microbiota and overall health has been confirmed. Gut microbiota is one of the greatest active sites of microorganisms playing a vital role in modifying the mucosal immune system **(Milani, Duranti et al. 2017)**. Diet can alter the gut microbiome, which uses nutrients from eating foods, discharges harmful or helpful metabolites, and regulating the immune system. The intestinal mucosal surface is a significant location of the entrance of pathogenic microorganisms into the human body, but in a healthy individual's epithelium and its microbiota offer an effective barrier against invading microorganisms **(Salek Farrokhi, Darabi et al. 2019)**. Different human diseases are linked to dysbiosis, a disruption of the gut microbiota's development and operation. Therefore, management of the gut microbiota has been nominated as a possible attitude for sustaining a healthy lifestyle and curing diseases. This approach can be it happens by stimulating favorable microbiota colonizing in the gastrointestinal tract (GIT) through the diet or probiotics administration. Probiotics were able to provide beneficial effects in reestablishing unbalanced microbiota and preserving gut immune homeostasis by improving immune system responses **(Hathaway-Schrader, Steinkamp et al. 2019)**. Some investigations have revealed that these probiotics stimulate and modify innate immune responses through multiple membrane molecules that transfer signaling massages with the epithelial cells of the gut. Immune system modulation has been demonstrated since an excessive immune response because of pathogenic infection can cause unwanted immunopathogenesis, leading to considerable damage to host tissues **(Taverniti 2013)**. Lungs and the stomach are anatomically distinct from one another. However, a gut-lung axis that might influence immune responses and the development of respiratory disorders has been supported by prospective anatomic correlation and multiple networks connecting their unique microbiota. By altering pro- and anti-inflammatory responses and sending out regulatory signals, the gut microbiota closely collaborates with the mucosal immune system **(Kayama, Okumura et al. 2020)**. Leukocyte activation and recruitment to the site of infection is encouraged by the high concentration of SCFAs (acetate, propionate, and butyrate) generated and released into the bloodstream by gut bacteria through binding to certain receptors. These prepared cells secrete certain antibodies that help the host defend itself by clearing intracellular pathogens and virus-infected cells from the body. For microbiota-induced myelopoiesis to occur, Toll-like receptors (TLR) or G-protein-coupled receptors (GPR41/43) signaling is essential. This also has an impact on immune cells that express MAMPs or SCFAs. The lung microbiota's resident antigens must also be encountered for the resident memory B cells to organize, especially in terms of immunity to viruses **(Zeng, Umar et al. 2019)**.

CLINICAL EVIDENCE OF PROBIOTIC IMMUNOMODULATION

Local and systemic immunological impacts are linked to interactions between different microbial components of the gut and lungs. These communications forcefully suggest that the GLA plays a key role in respiratory diseases. The gut microbiome clearly influences metabolic pathways, which is linked to altered cellular response. Communication between the immune system and the lung microbiota is comparably effective. For instance, inflammation in the lungs can change the makeup of the lung microbiota **(Budden, Gellatly et al. 2017)**. Therefore, produced metabolites by the gut microbiota modify gut immunity and affects the lung and brain among other organs. The mesenteric lymphatic system is a vital corridor among the lungs and gut, completed by microbiota and their particles or metabolites products that pass the gastrointestinal barrier, enter the bloodstream, and alter the lung's immunological response **(Parigi 2019)**. Due to a high-fiber diet, microbial dietary fiber metabolites act as signaling molecules for local antigen-presenting cells (APCs) in the lungs and through this way modulate inflammatory responses. Recently studies performed experimental models of asthma in SCFA receptor deficient Mice that revealed enhanced inflammatory responses. According to several research, the capacity for phagocytosis in the macrophages of germ-free mice is diminished and demonstrate a decreased cellular responsiveness concerning microbial antigens. However, amounts of monocytes and macrophages are enhanced. Still, they have a restricted aptitude to produce Chemokine C-X-C Motif Ligand 1 (CXCL1), and consequently caused tissue injury due to reduced neutrophil recruitment to the airways **(McCarville, Chen et al. 2020)**.

Segmented filamentous bacteria (SFBs), a commensal bacterium present in humans and most other animals' ileums, and involved in the altering of immune system responses, is one of the other important set of components that contribute to the long-reaching immunological function of the gut. SFBs caused naive CD4+ Tcell polarization toward Th17 cells involved in the immunological and inflammatory responses to lung infections **(Hansen, Hansen et al. 2014, Yousefi, Eslami et al. 2019)**. Recent research has highlighted the role of innate lymphoid cells, which migrate from the gut to the lungs in response to inflammatory cues, particularly IL-25, in tissue repair. The preparation of pulmonary releases of GM-CSF, IL-17, and other inflammatory cytokines by the lung and gut microbiota is essential for the development of bacterial illnesses such pneumonia and respiratory infections **(Najar Peerayeh, Rostami et al. 2016, Zhang, Li et al. 2020)**. The custom habit of comprehensive spectrum antibiotic treatments might result in destroying gut microbiota and worsens lung infection. Numerous studies have demonstrated the impact of the gut and lung microbiome on chronic respiratory illnesses. Reduced lung microbiota variety and some species are related to chronic respiratory disorders because of exacerbation conditions, enhanced gastrointestinal Permeability. However, Permeability of the gut may be exerting by hypoxemia or pro-inflammatory cytokine levels, and circulating gut microbiota products (such as trimethylamine-N-oxide) can be related to mortality in chronic respiratory diseases patients **(Candon, Perez-Arroyo et al. 2015)**.

PROBIOTICS: PREVENTION OF COVID-19

Besides the extensively investigated gut microbiota, microbiotas of other regions, lung microbiota is essential in various respiratory disorders' physiopathology. The lung microbiota has considerably smaller biomass in comparison to the gut microbiota. From birth all over the whole life period, a close association between the conformation the microbiome of the lungs and gut and the host's health condition can influence this gut–lung communication **(Faner, Sibila et al. 2017)**.

The oropharynx, upper respiratory tract, immigration, and host removal capacities of the microbes have an impact on the creation of the object (coughing and mucociliary clearance), immune system, local circumstances for microbial proliferation, like pH and amount oxygen concentration. The healthy individual's microbiota includes *Prevotella*, *Veillonella*, and *Streptococcus*, nevertheless the *Veillonella* and *Prevotella* while *Proteobacteria* can be found in the respiratory tract of intubated preterm newborns. The primary bacterial phyla in the lungs are identical to in the gut, mostly *Firmicutes* and *Bacteroidetes*, and in the next rank *Proteobacteria* and *Actinobacteria* **(Milani, Duranti et al. 2017)**.

The lung microbiota in acute respiratory distress syndrome (ARDS) resembles gut bacteria such Bacteroidetes and Enterobacteriaceae. Bacteria are able to travel through the colon wall and into the lungs due to a hyperpermeable gut. In addition to contributing to an inflammatory environment, gut microbiota dysbiosis has been linked to a number of lung diseases, including allergies, asthma, and cystic fibrosis, where it may be investigated by SARS-CoV-2 **(Amornphimoltham, Yuen et al. 2019)**. Probiotic strains might be used to influence these microbiotas, contributing novel views in the managing of respiratory diseases. Returning gut microbiota has been revealed to recover resistance to the virus or pathogenic invades, moreover, at the respiratory mucosal stages **(Hills, Pontefract et al. 2019)**.

A different significant effect applied via probiotics is to preserve the stability of junction among enterocytes; thus, admission to the entry of SARS-CoV2 is along with the risk of infection. Different clinical studies confirmed that probiotics like *L. rhamnosus GG* could assistance recovering gut and lung barrier integrity and homeostasis by enhancing Treg cells, Enhancing antiviral defense and lowering pro-inflammatory cytokines in respiratory infections as well as systemic infections. Immune responses becoming more active during the early stages of Covid-19 infection aids in eliminating the virus and preventing the sickness from getting worse **(Olaimat, Aolymat et al. 2020)**.

The potential influence of probiotic strains and their products was also assessed in an ex vivo model. *L. paracasei* and *L. plantarum* caused significant dose-related declines of several inflammatory mediators comprising IL-6, IL-8, and

prostaglandin **(Liu, Sheng et al. 2020)**. *L. plantarum* strains differed physiologically in that they produced acetic acid, oligosaccharides, exopolysaccharides, and tolerated gastrointestinal transit. They also synthesized conjugated linoleic acid (CLA) **(Darban, Malek et al. 2021)**.
Probiotics' anti-inflammatory benefits have been researched in recent studies. Weissella cibaria (JW15) inhibited lipopolysaccharide (LPS)-induced NO and PGE2 production by decreasing the expression of iNOS and cyclooxygenase-2 (COX-2). Additionally, it reduced the production of pro-inflammatory cytokines **(Ulisse, Gionchetti et al. 2001)**.

PROBIOTICS: CONTROL AND TREATMENT OF VIRAL INFECTIONS

Patients with a suppressed immune system come across dysbiosis conations in the gut microbiota, resulting in the digestive tract's harmful bacteria. The most severe and difficult-to-treat infections are those brought on by gut bacteria, and they frequently present a threat to life. Treatments with probiotics have been demonstrated to diminish upper or lower respiratory tract infections by improving immune response and combat viral infections **(Round and Mazmanian 2009)**.
Oral administration of various strains of *Lactobacillus* and *Bifidobacterium* have revealed suppression of infection indications alongside viral infections **(Round and Mazmanian 2009)**. Probiotics act as modulators of the intestinal flora and promote gut balance and play a role in interferon production as an anti-viral factor **(Sundararaman, Ray et al. 2020)**.
A few of the fundamental mechanisms behind probiotic effectiveness against viruses include host immune system modification, direct probiotic cell contact with the suggested viruses, and the creation of antiviral metabolites. There are many possibilities, ranging from altering the host microbiota to communicating with eukaryotic epithelial cells **(Ibrahem 2015)**.
Oral administration of Lactic acid bacteria and their products attend as anti-viral mediators. They are recognized as conferring health aids and also immunomodulatory, anti-tumor, competitive inhibition of pathogens (antibiofilm), and antioxidant properties **(Zhang, Yang et al. 2018)**.
As a probiotic defense against the pneumonia virus, *L. plantarum* or *L. reuteri* decreased granulocyte chemotaxis and release of numerous pro-inflammatory cytokines. and condensed virus recovery through TLR independent pathway. In the other clinical trial study, *L. plantarum* and *L. paracasei* in good subjects decreased the threat of obtaining common cold infections and pharyngeal indications **(Shinde 2019)**. Animal experiments verified probiotic's roles in reducing virus load titers and escalating Th cells in the lung and caused diminished virus replication. Probiotics are designated for their capability to suppress the virus by straight interacting with them and escaping viral particles' attack to mucosal cells and respiratory tract infections. By stimulating Th1 immune responses in mice, the probiotic strain prevented the generation of antigen-specific IgE. It had a protective effect against influenza A virus infection in vivo, which increased natural killer (NK) cell activity and IgA production in vitro **(Kho and Lal 2018)**.
In older people, probiotics like *L. casei* showed increased antibody responses to influenza virus inoculation and boosted the respiratory tract's innate immune response. Additionally, fight against various respiratory diseases in children and newborns, as well as the populations most at risk for respiratory infections **(Lehtoranta, Pitkäranta et al. 2014)**.

PROBIOTIC EFFECTS ON CORONAVIRUS INFECTIONS

There is increasing indication backing the benefit of probiotics as a preventive method to diminish, period and the need for drugs. A possible approach would be to modify the microbiome using probiotics, enabling inhibition or the treatment of respiratory illnesses like COVID-19. *L. plantarum* produces a variety of metabolites, such as: Gamma-aminobutyric acid (GABA), lactic acid, acetic acid, and plantaricin can all boost protection to viruses **(Dhar and Mohanty 2020, Novik and Savich 2020)**. Receptor recognition is the primary period of host cell infection by the virus and one of the most critical features of the host cell. The binding affinity among SARS-CoV and hACE2 can associate with viral transfection and infection. Computational demonstration and molecular dynamics study validate the anti-viral action of Plantaricin combinations. Several mechanistic methods include blocking the entrance of COVID-19 through binding with RNA-dependent RNA polymerase (RdRp), residual binding domain (RBD) to ACE2. In this work, the Plantaricin family of probiotic metabolites is used to target both spikes (S) glycoprotein by impairing RBD and ACE2. This computational method was used to restrict the entry of COVID-19 and prevent the effects of Plantaricin compounds by binding to RdRp, RBD, and ACE2. In this investigation, plantaricin metabolites were identified as a potential novel antiviral treatment option for COVID-19 **(Anwar, Altayb et al. 2020)**.

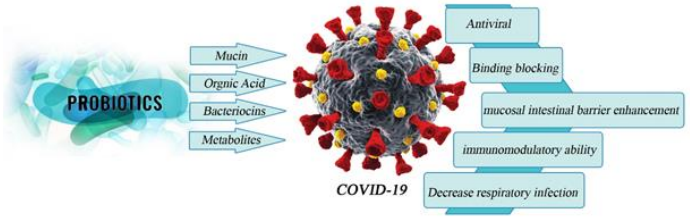

Fig 1 The probiotic effects on coronavirus infections

BACTERIOCINS AND GUT MICROBIOTA

The ability of metabolic products such lactic acid, H2O2, and bacteriocins delivered by LAB to reduce viral load has been studied. Bacteriocins can play a big part in host defense, according to another research. LAB probiotics have been found to create proteinaceous compounds synthesized by ribosomes that have bactericidal effect. These anti-microbial proteins have been shown to effectively combat potential pathogens by influencing the host microbiota and a variety of bodily functions. Maintaining gut homeostasis and biocontrolling harmful microorganisms are two potential uses for bacteriocins **(Garcia-Gutierrez, Mayer et al. 2019)**.
One of the primary anti-viral tools of probiotics, the inhibition of viral replication, has not yet been documented. Peptide CRL35 was produced by *Enterococcus faecium* by inhibiting the last phases of HSV-1/2 replication. *L. delbrueckii*, a very specific restriction on influenza virus H7N7 and H7N1 replication. This view's activity is probably more useful than in the inflammatory stages of the illness during the early stages of viral infection, when virus loads are relatively low. These factors support the idea that probiotics may be more beneficial as a preventative measure than the current standard of virus treatment.

THERAPEUTIC IMPLICATIONS

The current coronavirus disease outbreak (COVID-19) has sparked a flurry of research into ways to prevent, treat, and lower morbidity and fatality rates. Clinical tests showed the presence of cytokine storm symptoms and a significant amount of pro-inflammatory cytokines. IL-1, TNF, IFN, IL-2, IL-8, interferon-inducible protein 10 (IP-10), and macrophage inflammatory protein 1 (MIP-1) were among the chemokines present. Especially in severe patients may lead to more extended hospitalization and a rise in the mortality rate **(Mahooti, Miri et al. 2020)**. Therefore, addressing the urgent need to control the cytokine storm may be helpful in COVID-19 treatment. Several modalities such as anti-microbial peptides, bacteriophages, and probiotics can be considered. According to the studies, probiotics have immunomodulatory effects and could improve the intestinal epithelial barrier features. Additionally, they generate anti-microbial compounds, alter the ratio of pro- to anti-inflammatory cytokines, boost T cell and NK cell activity, and raise levels of systemic and mucosal-specific antibodies in the lungs **(Azad, Kalam et al. 2018, Sundararaman, Ray et al. 2020)** that may lead to viral clearance and prevention of acute respiratory distress syndrome (ARDS) **(Azad, Kalam et al. 2018)**. Probiotics have been shown to have antiviral action against common respiratory viruses **(Namba, Hatano et al. 2010, Luoto, Ruuskanen et al. 2014)**. When *L. plantarum* 06CC2 was taken orally, more IFN-, TNF-, IL-6, and IL-12 were produced in bronco-alveolar lavage fluid (BALF). Additionally, it has the capacity to control the quantity of neutrophils and macrophages infiltrating the BALF of infected mice **(Takeda, Takeshita et al. 2011)**.
On the other hand, probiotics and their bioactive peptides have an inhibitory impact on the ACE enzymes by blocking their active sites. Molecular dynamics studies demonstrated the anti-viral activity of Plantaricin compounds (metabolic products of *L. plantarum*) by blocking the entry by binding with RdRp, residual binding domain (RBD), and ACE2 **(Anwar, Altayb et al. 2020)**.
Several COVID-19 patients displayed lower levels of various probiotic species, including *Bifidobacterium* and *Lactobacillus* in their intestines, which may be related to weak immune system function. Re-normalization of the intestinal flora balance by consuming probiotics may lessen the likelihood of infection and the severity of illness **(AKTAŞ and Aslim 2020)**. According to recent research, the most important probiotics that might be associated to reducing the impact of the COVID-19 pandemic are included *B. longum*, *B. bifidum*, *B. breve L. plantarum*, *L. casei*, *L. gasseri*, *L. rhamnosus*, *Pediococcus pentosaceus*, and *Leuconostoc mesenteroides* ***(Baud, Agri et al. 2020, Khaled 2020)***. The therapeutic effects of probiotics against COVID-19 are not backed by any reliable research. Probiotics' immune-boosting and nutritional effects, as well as their antiviral abilities against a variety of respiratory viruses, point to probiotics as a supplemental treatment for COVID-19 disease that requires further clinical and laboratory research. Table 1 illustrated human studies that other probiotic strains assisted in the treatment of respiratory infections and effect of probiotics bacteria in respiratory infections shown in Table 2**.**

Table1 Use of probiotics to treat respiratory infections including Covid-19

Number of patient/ age	Type of disease	Probiotic strain	Product dose, Treatment Period	Treatment Outcome	Reference
70 /median age 59 years	COVID-19	*S. thermophilus* DSM 2345, *L. acidophilus* DSM 32241, *L. helveticus* DSM 32242, *L. paracasei* DSM 32243, *L. plantarum* DSM 32244, *L. brevis* DSM 27961, *B. lactis* DSM 32246, *B. lactis* DSM 32247	IG: received 2,400 billion bacteria each day along with hydroxychloroquine, antibiotics, and tocilizumab (Three equal doses) CG: received tocilizumab, antibiotics, and hydroxychloroquine, either separately or in combination.	-Fever, asthenia, headache, myalgia, and dyspnea all disappeared in the patients within seven days, and this trend became more pronounced starting on the second day of bacteriotherapy in IG. -Reduced likelihood of developing a respiratory failure requiring 8 times more resuscitation support in IG. - Every patient in IG recovered from the COVID19 sickness, and none required invasive mechanical ventilation or hospitalization to the intensive care unit.	(d'Ettorre, Ceccarelli et al. 2020)
2 male patients/ 76 and 73years (Case Report)	COVID-19	*S. cerevisiae*	Patients received oseltamivir and hydroxychloroquine, alone or in combination. Ultra-Levure (preparation of *S. cerevisiae* (*boulardii*)) at 250 to 500 mg/day.	-Disappearance of diarrhea in patients within 3 and 4 days. -Fungemia due to *Saccharomyces* in two COVID patients occurred. -Patients showed clinical improvement.	(Ventoulis, Sarmourli et al. 2020)
479 healthy adults / 18-67 years	Common cold episodes	*L.* gasseri PA 16/8, *B. longum* SP 07/3, *B. bifidum* MF 20/5 (Tribion harmonis™)	IG: 5×10^7 cfu/tablet during two winter/spring seasons, of the spray-dried probiotic bacteria along with vitamins and minerals (at least 3 months). CG: Tablet with vitamin minerals (1 tablet/day)	- Days with fever during an episode and the length of the common cold bouts were shorter in IG (almost 2 days). -A significantly higher enhancement of CD8+/CD4+ was observed in IG.	(de Vrese, Winkler et al. 2005)
272 healthy volunteers 18–65 years	Common cold episodes	*L. plantarum* HEAL 9 (DSM 15312) *L. paracasei* 8700:2 (DSM 13434)	IG: 1 g of lyophilized bacteria ($1\ 10^9$ cfu each day for 12 weeks) and 1 g of maltodextrin CG: 1.0 g maltodextrine	- In IG, there was a considerably lower likelihood of developing one or more episodes of the common cold, as well as a shorter duration of time experiencing symptoms and pharyngeal symptoms. - B lymphocyte proliferation was considerably reduced in IG compared to CG.	(Berggren, Ahrén et al. 2011)
222 healthy elderly participants / ≥70 years	Influenza vaccination	*L. casei* (Actimel® DN-114 001), *S. thermophiles*, *L. bulgaricus*	IG: Actimel® 100 g /bottle CG: a control dairy product that is not fermented 100 g per bottle 200 g each day from two bottles for 13 weeks.	-Following vaccination, there was a rise in the titers of influenza-specific antibodies, which were higher in IG than CG. - Five months following immunization, the intended to treat analysis revealed significant variations in seroconversion between the groups.	(Boge, Rémigy et al. 2009)
50 healthy adult human volunteers / 22-56 years	Influenza vaccination	*L. fermentum* CECT5716	IG: daily consumed a capsule containing 1×10^{10} cfu of *L. fermentum* in a matrix of the mix of methylcellulose for 28 days CG: Taken each day a 200 mg methylcellulose tablet.	- The IG had an increase in NK cells, whereas the CG did not (2 weeks after vaccination). - Following IG vaccination, there was a considerable rise in blood levels of total and specific anti-influenza IgM. - Five months after immunization, the incidence of an influenza-like illness was reduced in IG.	(Olivares, Díaz-Ropero et al. 2007)
235 critically ill adult patients who were expected to receive mechanical ventilation for ≥48 h / 18-80 years	VAP	*B. subtilis*, *E. faecalis*	IG: receive a capsule contained active *Bacillus subtilis* and *Enterococcus faecalis* at a concentration of 4.5×10^9/0.25 g and 0.5×10^9/0.25 g, respectively, three times per day by nasogastric feeding tube along with conventional prophylactic measures for a period of 14 days. CG: standard preventive strategies alone	-In the IG, the incidence of VAP was substantially lower than in the CG. - In the IG compared to the CG, the mean time to develop VAP was substantially longer. - In comparison to the CG, the IG had a smaller percentage of patients who had acquired stomach colonization of PPMOs. -Probiotic therapy had no positive impact on the frequency of clinically suspected VAP, consumption of antibiotics, time spent on mechanical ventilation, death, or length of hospital stay.	(Zeng, Wang et al. 2016)
100 adult critically ill patients undergoing mechanical ventilation for >48 hours / ≥18 years	VAP	*L.casei, L. acidophilus, L. rhamnosus, L. bulgaricus*, *B. breve, B. longum*, *S. thermophilus*	IG: got a probiotic mixture in the form of 2 capsules (1 capsule every 12 hours) every day for 14 days. 10^{10} microorganisms were found inside each capsule. CG: for 14 days, a placebo was given every day.	- VAP was less frequent in IG. - In the IG, the length of the ICU and hospital stays was also shorter.	(Mahmoodpoor, Hamishehkar et al. 2019)
1783 schoolchildren / 6–12 years	Influenza infection	*L. brevis* KB290 (KB290)	In one bottle (80 ml), there are 6 billion cfu and a combination of nutrients (0·6 g protein, <0·3 g fat, 7·6 g carbohydrate, <0·5 g fibre, 8 mg Na, 146 kJ) Group A received no therapy for the second eight-week period after receiving five days per week for that time. The drink was given to Group B during the second period but not the first.	-Reduced the risk of infection.	(Waki, Matsumoto et al. 2014)

961 women / 20–71 years	Influenza infection	*L.delbrueckii* ssp. *bulgaricus* OLL1073R-1 (OLL1073R-1)	IG: ingested daily for 16 weeks a 112 mL yogurt beverage that was cultured with OLL1073R-1. CG: During this time, he didn't eat any yogurt.	-There was no discernible difference in the flu's incidence rate. -Although the intervention had a considerable impact on serum IFN-production, it had no influence on -NK cell activity.	(Kinoshita, Maruyama et al. 2019)
152 volunteers	Experimental rhinovirus challenge (RV-A39)	*B. animalis* ssp. *lactis* Bl-04	IG: received a sachet every day for 28 days that included a minimum of 2 10^9 cfu of Bl-04 combined with 1 g of sucrose as a carrier. CG: daily received a sachet containing 1 g of sucrose for 28 days.	-The IG dramatically reduced the CXCL8 response to rhinovirus infection in nasal lavage. -Virus titre reduced in nasal lavage in IG.	(Turner, Woodfolk et al. 2017)

This table shows the probiotic strains used to treat viral diseases, including Covid-19. This table shows the dose used and the period of treatment along with the result obtained from the use of probiotics. **IG**: intervention group; **CG**: control group; **NK**: natural killer cell. **PPMOs**: potentially pathogenic microorganisms, **VAP**: ventilator-associated pneumonia

Table 2 Effect of probiotics bacteria in respiratory infections**.**

	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↑	↑	↑	↑	↑	↑
Property Probiotic Bacteria	Diarrhea	Fever	Headache	Myalgia	Dyspnea	Influenza-like illness	VAP	Gastric colonization of PPMOs	Duration of ICU	Risk of infection	CXCL8 response	CD8+ / CD4+	Influenza specific antibody	NK cells	Specific anti influenza IgA/IgM	Proliferation of B lymphocytes	IFN-γ
L. acidophilus	✓	✓	✓	✓	✓		✓		✓								
L. helveticus	✓	✓	✓	✓	✓												
L.casei							✓		✓				✓				
L. paracasei	✓	✓	✓	✓	✓											✓	
L. plantarum	✓	✓	✓	✓	✓											✓	
L. brevis	✓	✓	✓	✓	✓		✓		✓	✓							
***L.* gasseri**		✓										✓					
L. fermentum						✓								✓	✓		
L. rhamnosus							✓		✓								
L. bulgaricus							✓		✓				✓				✓
B. bifidum		✓										✓					
B. lactis	✓	✓	✓	✓	✓												
B. longum		✓					✓		✓			✓					
B. animalis											✓						
E. faecalis							✓	✓									
B. subtilis							✓	✓									
S. thermophilus	✓	✓	✓	✓	✓		✓						✓				
S. cerevisiae	✓	✓	✓	✓	✓												

This table shows the probiotic bacteria used in various respiratory infections and also shows the different effects that these bacteria have caused in these infections as increasing and decreasing.

↓: Decrease, ↑: Increase L: *lactobacillus***, B:** *Bifidobacterium***, E:** *Enterococcus***, *S. thermophilus*:** *Streptococcus thermophilus***, *B. subtilis:*** *Bacillus subtilis***, *S. cerevisiae*:** *saccharomyces cerevisiae***, NK**: natural killer cell. **PPMOs**: potentially pathogenic microorganisms.

THE POSSIBLE SIDE EFFECT OF PROBIOTIC

Since the COVID-19 global pandemic has an unexpected spread globally, it is hard to place a safe drug/product as fast as the virus is distributing. The possible potential of probiotics as non-pharmacological substances considering their advantages, availability, and posing negligible side effects have been successfully applied in the current phenomenon. However, some reported side effects that experienced in different clinical approaches should be taken into account. Mainly reported side effects were nausea, taste disturbance, and diarrhea **(Armuzzi, Cremonini et al. 2001, Çekin, Şahintürk et al. 2017, Batista, Da Silva et al. 2020)**. During follow-up, some studies observed a considerable decrease in adverse effects. Collectively, the administration of probiotics at the stage and dosage that have been tasted has been advised **(Infusino, Marazzato et al. 2020)**. The FDA also states that the probiotic is a generally recognizad as safe (GRAS) for humans organism **(Pourhossein and Moravejolahkami 2020)**. Therefore, it is estimated the low risk associated with probiotic administration. However, an overall control should be done regarding the strain and dose.

CONCLUSION

This research clarified the function of probiotics as a safe strategy for alleviating the SARS-COV-2 infection. Probiotics possessed notable effects on immune responses in the host and could promote the reaction toward infection. Besides, clinical studies indicated that probiotics in COVID-19 treatment could decrease the risk of other infections in patients with COVID-19.

Also, probiotics were capable of interrupting the synthesis of RNA and DNA in such viral infections. Since the control of cytokine storm may have benefits in COVID-19 treatment, probiotics and other modalities can be noticed regarding their immunomodulatory effects. In addition, probiotics have an inhibitory impact on the ACE enzymes and can block the active sites. It is proved that some strains of probiotic microorganisms produce anti-inflammatory interleukins and anti-body in versus the viruses. According to current knowledge, it is emerging needed to apply practical methods for preventing the COVID-19 infection. Considering how effective probiotics are at preventing viral infections, they can use as an alternative and adjuvant nutritional therapy for the treatment of new coronavirus. More clinical research is required for a comprehensive evaluation of the effects of determining strains of probiotics on COVID-19 infection.

Conflict of interest: In publishing this research, all authors have affirmed that they have no competing interests.

AUTHOR CONTRIBUTIONS

Conceptualization: all authors.
Writing-original draft: all authors.
Writing-review & editing: all authors.
Approval of final manuscript: all authors.

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