Tzu Chi Medical Journal 2022; 34 (2): 148-159

Review Article

The prospects of employing probiotics in combating COVID-19

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Abstract

Unanticipated pathogenic risk and emerging transmittable diseases can result from interspecies exchanges of viruses among animals and humans. The emergence of the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causing coronavirus disease-19 (COVID-19) pandemic has recently exemplified this mechanism. Cough, fever, fatigue, headache, sputum production, hemoptysis, dyspnea, diarrhea, and gastrointestinal disorders are the characteristic features of the disease. The most prevalent and serious manifestation of the infection tends to be pneumonia. The new strains of SARS-CoV-2 with more infectivity have been emerging at regular intervals. There is currently no World Health Organization-approved particular drug for COVID-19. Besides, developing novel antivirals would take much time. Thus, repurposing the application of natural products can provide alternatives and can facilitate medication against COVID-19 as well as can slow down the aggressive progression of the disease before the arrival of approved drugs. Probiotics have long been known for their positive effects on the gut microbiome and impact on immune responses. Particularly, their involvement against viral diseases, especially those of the upper and lower respiratory tract, is of current interest for their prospective application against COVID-19. In this review, we comprehensively address the mode of action of probiotics and their possible intervention against coronavirus diseases correlating with their efficacy against viral diseases. In this regard, we explored recently published relevant research and review articles in MEDLINE/PubMed related to COVID-19 and the effects of probiotics on viral infections.

Keywords: *Coronavirus disease 19, Gut microbiome, Probiotics, Respiratory infections, Severe acute respiratory syndrome coronavirus-2*

Submission : 17-Apr-2021
Revision : 31-May-2021
Acceptance : 26-Jul-2021
Web Publication : 05-Oct-2021

Introduction

During the 2nd week of December 2019, several pneumonia cases of unknown sources registered at a small regional fish and wild animal marketplace in Wuhan, Hubei Province in China [1]. The Chinese Center for Disease Control and Prevention reported this disease as a novel coronavirus infection on January 7, 2020, and on February 11, 2020, the World Health Organization (WHO) declared a new name for the epidemic as 2019-new coronavirus disease (2019-nCoV) which currently referred as coronavirus disease-19 (COVID-19) [2]. In addition, the causative agent of COVID-19 was named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). On March 11, 2020, when the number of infected countries was 114, with over 118,000 cases and more than 4000 deaths, the WHO announced COVID-19 as a global pandemic [2,3]. The occurrence of COVID-19 is not the 1st epidemic or pandemic by a coronavirus. The epidemic of SARS-CoV and Middle East respiratory syndrome (MERS)-CoV proved the potential of coronavirus to overcome the interspecies boundary and affect human beings in the 21st century [4,5]. SARS-CoV killed 774 individuals in 2003, whereas MERS-CoV killed 858 individuals from 2012 to 2019 [6,7]. SARS-CoV-2 is a single-stranded positive-sense RNA virus of about 30 kilobase genome and appears as a typical crown-like structure under the electron microscope owing to the existence of glycoprotein spikes on its surface [8-10]. CoVs mostly show a wide range of clinical signs and symptoms in humans, including respiratory, enteric, nervous, and systemic manifestations [9,11].

The emergence of new variants of SARS-CoV-2 (especially, lineages B.1.617 and B.1.618 in India, B.1.1.28.1 in Brazil,

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Access this article online
Quick Response Code:
Website: www.tcmjmed.com
DOI: 10.4103/tcmj.tcmj_104_21

How to cite this article: Chakraborty M, Munshi SK. The prospects of employing probiotics in combating COVID-19. Tzu Chi Med J 2022;34(2):148-59.

B.1.1.7 in UK and B.1.351 in South Africa) with more transmissibility and severity in recent times heightened the risk of COVID-19 by many folds and initiates a second or third wave of infection in many countries [12,13]. Many countries are trying hard to implement effective prevention and control measures [14]. The design and formulation of successful antiviral agents are largely obstructed as the viruses are obligate intracellular parasites and multiplying inside the host cells [15]. No specific COVID-19 therapeutic is currently available since the production of novel antiviral medications takes a significant amount of time and resources to formulate and validate drugs [14,16]. A few potential vaccines got approval and have started to be implemented in many countries but their efficiency for long-term protection and potential to combat the emerging variants is in doubt [17,18]. The application of natural substances such as probiotics may provide solutions in this situation and can facilitate treatment against COVID-19.

Probiotics are live microorganisms that offer a health advantage to the host when delivered in adequate amounts [19]. *Lactobacillus rhamnosus*, *Lactobacillus reuteri*, and certain strains of *Lacticaseibacillus casei*, *Bifidobacteria* spp., *Bacillus coagulans*, *Escherichia coli* strain Nissle 1917, *Enterococcus faecium* SF68, and the yeast *Saccharomyces boulardii* are the common probiotic microbes [20]. They can strengthen the host immunity by boosting the concentration of useful microbiota, enhancing the functionality of the gastrointestinal barrier, modifying the gut microbiota, competing for epithelial adherence, and immunomodulation, thus reducing gastrointestinal diseases and also respiratory tract infections (RTIs) [21]. Several clinical findings suggest that gastrointestinal signs are prevalent in COVID-19 and are linked to the severity of the disease [22,23]. Probiotics are safe and are usually supplied as a part of fermented foods such as yogurt and other dairy food products [24]. They can also be delivered symbiotically with prebiotics that can promote the growth or activity of probiotic microbes [25]. The pathway of how the host species and immune system functionally interact with probiotics is complex and not yet fully explained. This review will focus on the overview of COVID-19 pathogenicity and the difficulties associated with generating and implementing rational remedial options against COVID-19. This is an attempt to justify the probability of employing probiotics as means to reduce the severity of COVID-19 caused by SARS-CoV-2 through analyzing the mode of action of probiotics against viral diseases.

Overview of coronavirus disease-19

Mechanism of action

COVID-19 is an infectious viral disease that can spread by inhalation or absorption of viral droplets as a consequence of coughing and sneezing, and touching the contaminated surface [26]. SARS-CoV-2 contains four structural proteins, such as nucleocapsid, spike, membrane, and envelop protein, and other nonstructural proteins [26]. The inhaled virus particles in the nasal cavity bind to the epithelial cell receptor angiotensin-converting enzyme-2 (ACE2) through its spike protein to gain intracellular access and begin to replicate [27]. The virus continues to proliferate and concurrently passes through the airways across the respiratory tract, and clinical signs begin to emerge [28]. The virus is confined to the upper respiratory airways in about 80% of affected individuals who only show mild illness. However, the virus travels down to the lower respiratory tract in about 20% of people and induces severe illness. The viruses enter the lungs' alveoli and infect type II alveolar cells, and multiply there [29,30]. Viral particles act as a pulmonary toxin after inducing apoptosis of alveolar type II cells, while they further invade type II cells in neighboring alveoli [31]. Wide areas of the lung will subsequently lose most of their type II cells resulting in alveolar damage, called lung fibrosis. Other immune cells (neutrophils, macrophages, T cells, dendritic cells [DCs], etc.) are then activated from the blood, and a robust innate and enhanced immune system is triggered to reverse the damages caused in certain patients. This event may lead to a cytokine storm [32]. Unregulated production of cytokines (interleukin-2 [IL-2], IL-6, IL-17, granulocyte macrophage colony stimulating factor, INF-g, etc.) is known as cytokine storm which aggravates the systemic inflammatory reaction and fibrosis of the lungs that could potentially contribute to acute respiratory distress syndrome (ARDS) [31].

Clinical manifestation

COVID-19's clinical presentations range from asymptomatic types to clinical complications marked by multiorgan and systemic signs of respiratory failure [11]. Cough, fever, and weakness are the most frequent symptoms, alongside patients may also experience headache, hemoptysis, sputum production, dyspnea, diarrhea, and gastrointestinal disturbances [33,34]. Recent research has shown that lung membranes, kidney cells, and cells in testes' seminiferous ducts have relatively higher ACE2 expression [34]. As a result, COVID-19 can bind directly to some of these ACE2 carrying cells and damage patients' kidneys and testicular tissues [35]. Researchers found several signs and symptoms in the gastrointestinal system during COVID-19, including loss of smell or taste, loss of appetite, vomiting, diarrhea, and other gastrointestinal tract disorders. Compared to persons without gastrointestinal tract complications, the physical condition of persons having gastrointestinal complications during COVID-19 infection is worse. In the gastrointestinal tract, COVID-19 kills the gut bacteria that trigger these manifestations [36,37]. Individuals with moderate symptoms have been reported to improve after 1 week, while serious cases of progressive respiratory dysfunction leading to alveolar damage by the virus have been reported to result in serious complications, even death [38].

Current therapeutic efforts against coronavirus disease-19

Unfortunately, no drug against COVID-19 has yet officially been approved. The primary health management approach focuses on reducing clinical complications and supporting treatment, including sufficient oxygen and mechanical ventilation when needed [39]. Pressure has been rising to seek a selective drug to combat the virus effectively. The main goal of this effort has been to repurpose existing

drugs included with virus-binding molecules, molecules or inhibitors targeting particular enzymes engaged in viral transcription and replication, small molecule inhibitors targeting important proteases or other viral proteins, RNA synthesis, Janus kinases, and inhibit viral S protein interacting with ACE2 [40,41]. Numbers of anti-CoV agents are available, largely preclinical chemicals that yet to be assessed as anti-COVID-19 drugs. Few of these drugs have already been included in COVID-19 phase III and IV trials, such as favipiravir, remdesivir, oseltamivir, ribavirin, ASC09F, lopinavir, ritonavir, hydroxychloroquine, darunavir, and cobicistat [Table 1]. To date, there is a lack of supportive data on the safety and effectiveness of the drugs currently used for the treatment of other CoV diseases [54,55]. However, researchers may need long-term research work to generate, manufacture, standardize, evaluate, and trade novel medicines for this emerging virus.

Probiotic: A hope against the current pandemic

Since Elie Metchnikoff first discovered probiotic microorganisms, numerous studies have been conducted on the impacts of probiotics on the immune system of the host [56]. Probiotics are characterized by the WHO and FAO as "living microbes that impart a health gain on a host when delivered in adequate amounts" [56]. The health benefits of *Lactobacillus* spp. and *Bifidobacterium* spp. on the host have been proven [20]. With advanced and intensive scientific efforts, novel strains and genera of probiotics are constantly evolving. Probiotics have been shown to shorten the duration of respiratory illnesses and reduce vulnerability to pathogens [57]. Hence, the use of probiotics could plausibly aid in the prevention of respiratory complications in the cases of COVID-19. Although SARS-CoV-2 transmission is assumed to occur primarily through respiratory droplets, the intestine can also take part in COVID-19 pathogenesis [22,23,58-60]. To understand their role against gastrointestinal manifestations of COVID-19, there is a need to evaluate the nutritional and gastrointestinal activity of probiotics [31,61]. The probiotic mechanisms against viral infections and their potential application against COVID-19 complications are discussed below.

Mode of action of probiotics against viral infections with a special emphasis on coronavirus disease-19

Mechanisms that may justify the therapeutic effectiveness of probiotics involve adhesion and coaggregation abilities, competition for nutrient sources and binding sites, the release of antimicrobial compounds, strengthening of intestinal barrier activity through modulation of tight junctions and mucin secretion, and immunomodulation through interaction with microbe-associated molecular pattern (MAMP) receptors [62-66]. Studies have shown that probiotics may help reduce the occurrence of diarrhea and rotavirus shedding [67,68] suggesting their interaction with viral entrance and suppression of viral replication in the gut. Probiotics have the potential to suppress purine in foods and drinks. Purines are crucial for the synthesis of viral RNA. Lowering in purine supply can decelerate the replication of viruses and prevent viral infectious diseases [69-71]. Decreasing purine accessibility may therefore be an essential mechanism of probiotics against viral illnesses. This mechanism may contribute to the reduction of COVID-19 spread through the intestines and thereby might prevent SARS-CoV-2 associated diarrhea.

Probiotics may also resist coronavirus replication by reducing endoplasmic reticulum stress-associated autophagy, particularly inositol requiring enzyme-1 mechanisms, over its own anti-IL-17 impact [72]. Evidently, a cytokine storm tends to be the key pathogenic event that triggers viral infection-induced pneumonia [73]. Probiotics take part in

Table 1: The updated list of drugs under clinical trials for the treatment of coronavirus disease-19 patients

Drugs	Active against diseases	Clinical trial number	Clinical phase status	Mechanism of action	References
Favipiravir	Antiviral	NCT04359615	Phase IV	RNA-dependent RNA polymerase inhibitor	[42]
Interferon beta		NCT04350671		Anti-viral and immunomodulatory effects	[43]
Ganovo + ritonavir		NCT04291729		Viral protease inhibitor	[44]
Azithromycin + hydroxychloroquine	Antimalarial	NCT04359316		Secondary bacterial infection inhibitor	[38]
Remdesivir	Antiviral	NCT04292899	Phase III	RNA-dependent RNA polymerase inhibitor	[38]
Ribavirin		NCT04460443		Viral RNA synthesis and mRNA capping inhibitor	[45]
Oseltamivir		NCT04338698		Viral protease inhibitor	[46]
ASC09F		NCT04261270			[46]
Baricitinib		NCT04421027		JAK inhibitor	[47]
Darunavir and cobicistat		NCT04252274		Viral protease inhibitor	[46]
Chloroquine or hydroxychloroquine	Antiparasitic	NCT04353336		Disrupt viral S protein interaction with ACE2	[44,48]
Nitazoxanide	Antiparasitic/ antiviral	NCT04463264	Phase II	Induces the host innate immune response to produce interferons	[49]
Lopinavir	Antiviral	NCT04455958		Viral protease inhibitor	[50-52]
Ritonavir		NCT04455958			
Interferon alpha		NCT04379518		Induces the body's innate anti-viral response	[43]
Camostat mesylate		NCT04435015	Phase I	Serine protease inhibitor	[27]
Galidesivir		NCT03891420		Viral RNA polymerase function inhibitor	[53]

JAK: Janus kinases, ACE2: Angiotensin-converting enzyme-2, mRNA: Messenger RNA

plasma pro-inflammatory cytokine (tumor necrosis factor alpha and/or IFN-γ) suppression and anti-inflammatory cytokine (IL-4 and/or IL-10) enhancement, along with decreasing oxidative stress rates and plasma peroxidation [74], which reduces the incidence, duration, and signs of RTIs [75]. In view of the cytokine storm, which appears to happen in many COVID-19 patients, this immune-modulation probably has some impact [37,73].

Bacterial secondary pneumonia is a major complication during any pandemic and epidemic by respiratory viral diseases that can increase mortality and morbidity. Bacterial association and colonization, destruction of epithelial barriers, and modification of the respiratory tract's innate immune system are promoted by viral infections [64]. An experiment showed that metabolites such as peptidoglycan from microbiome metabolism enhanced the innate respiratory antiviral immune response and reduced bacterial proliferation in the lung and respiratory inflammatory injury [76]. Vitamins synthesized by the intestinal microbiota may critically involve in the regulation of the immune system [77]. Moreover, probiotic strains were reported to increase the concentration of butyrate (a colonocyte fuel) by raising the integrity of tight junctions [78].

A cascade of the immune response is induced against microorganisms regulated by the interaction of pattern recognition receptors of epithelial cells, DCs, and macrophages with MAMPs [79]. Hence, probiotics, by binding their MAMPs (lipoteichoic acids, peptidoglycan, S-layer proteins, and nucleic acids) with PPRs (toll-like receptors, NOD-like receptors, C-type lectin receptors) expressed in the host intestinal mucosa, can modulate the immune system [79,80]. Interestingly, differential immunomodulatory capacities of probiotic strains lie on the differences in MAMP profiles [79]. Probiotics can thereby help align inflammatory responses to pathogens with the normal homeostasis of the intestine and their function. The entire immune system could be benefited from the restoration of homeostasis in the gut microbiome by probiotics which consequently favor the gut immune response to act against respiratory infections [79]. This circumstance may also have some impact on COVID-19 infection.

In addition to stimulating the gut barrier and metabolic functions, probiotics can colonize and elicit immunomodulatory effects [66]. Lungs have their own microbiota and an intestinal link. A host microbiota and immune interactions may affect the path of respiratory diseases [81]. Imbalance in the microbial communities of the respiratory and gastrointestinal tracts may result in RTIs such as influenza [82,83]. This dysbiosis may also lead to secondary bacterial infections by altering subsequent immune responses. COVID-19 might have an association with intestinal dysbiosis which can be resolved possibly through the restoration of gut homeostasis by employing probiotic strains [31,84].

It has also been shown that probiotic bacterial strains control mucin expression, strengthen the mucosal layer and indirectly help the gut's immune system [62]. Also, the intestinal microbiome has a vital impact on systemic immune responses [85,86]. Probiotic strains can accelerate the number and activity of antigen-presenting cells, NK cells, and T cells, as well as increase the levels of type 1 interferon and specific antibodies (systemic and mucosal) in the lungs [86-88]. Probiotic strains can also able to change the complex balance between proinflammatory and immunoregulatory cytokines, which allow for viral clearance as well as reduce immune-response damage to the lungs. This could be of particular concern if the COVID-19 complication of ARDS is to be avoided.

Evidence of applying probiotics in various disease complications and the prospects against coronavirus disease-19

Probiotics can not only prevent GTI and antibiotic-related diarrhea infections may also prevent infections elsewhere, such as sepsis and RTI infections [89-95]. A randomized, double-blind, placebo-controlled clinical trial on 70 children getting yogurt with probiotics *L. rhamnosus* GG, *Bifidobacterium lactis,* and *L. acidophilus* reported a boosting of gastrointestinal well-being and resolved digestive symptoms and a decline in gastrointestinal disorders [96]. Some reports evident that antibiotic-associated diarrhea has been prevented by *Lactobacillus* and *Bifidobacterium* [97-100].

Viruses are responsible for over 90% of upper RTIs [57]. Several studies have reported the positive effect of probiotics on the prevention of upper RTIs. In a meta-analysis of 12 randomized control trials (RCTs), 3,720 adults and children who were provided with probiotics showed a 2-fold lower risk of developing upper RTI and the severity of the disease has been reduced small-scale but substantial [57]. A study with 479 adults reported *Lactobacillus gasseri* PA 16/8, *Bifidobacterium longum* SP 07/3, and *Bifidobacterium bifidum* MF 20/5 along with vitamins and minerals to reduce the length of common cold symptoms including the duration with fever [87]. Several studies documented the impact of probiotics on the prevention of viral upper RTIs infections as well. An RCT, including 94 preterm infants, showed that the incidence of clinically defined virus-associated RTI was reduced by 2–3 folds by the prebiotic mixture of Galacto-oligosaccharides and polydextrose (1:1), or probiotic *L. rhamnosus* GG, given between 3 and 60 days after their birth [101]. It was evident by a report that live *L. rhamnosis* GG may be more efficient than the inactivated form of the same strain to minimize rhinovirus infection [102]. An open-label study on 1783 school children reported a decreased incidence of RTI influenza following ingestion of *Lactobacillus brevis* [103]. Reduction in the sepsis and lower RTI were elucidated in an RCT including >4000 infants in India treated with a strain of *Lactobacillus plantarum* in combination with prebiotics [104].

The pieces of evidence suggest that this pandemic is affecting adults more than children. An RCT found promising results against viral diseases in 27 elderly individuals receiving *Bifidobacterium longum* [88]. Furthermore, lactic acid bacteria, which are prominent sources of probiotics, are found to be a part of the upper respiratory tract microbiota in healthy people and some strains have the reputation of preventing recurrent otitis media [105]. Probiotics have been shown to have some impacts on common colds and

upper respiratory infections in adults [106]. Several studies reported that the innate inflammatory response against the rhinovirus has an association with their pathogenesis for the common cold [107]. Hence, several attempts have been made to modulate the immune response optimally for combating viral infections by employing probiotics [108]. In this respect, an investigation was carried out to determine the impact of *Bifidobacterium animalis* ssp. *Lactis* Bl-04 on human rhinovirus in healthy adults [107]. They reported the reduction in CXCL8 response in the nasal lavage which resulted in a decline in the rhinovirus replication. They claimed a modest modulation of innate immune host responses as a decrease in virus shedding in the nasal secretions was found.

Another study by Wang *et al*. [109] assessed the impact of administering *L. rhamnosus* GG in elderly patients of 65 and more ages admitted in the nursing home. According to their findings, the elderly individuals were found to become less vulnerable to influenza and other respiratory viral infections when administered with probiotics compared to placebo receiving individuals. A study on the other hand found no effect on the rate of influenza infection following ingestion of yogurt fermented with probiotic *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 though an acceleration in IFN-α level in the probiotic treated group was observed by the immunological analysis [110]. A meta-analysis with nearly 2,000 patients found that probiotics could minimize ventilator-associated pneumonia and critical disease incidences [111]. Hu *et al*. [112] found H7N9 influenza A virus infection to be responsible for lowering the intestinal microbial diversity as well as microbiome in patients. They reported a gradual increase in the microbial diversity and innate immunity by continuous administration of probiotics after withdrawal of antibiotic treatment.

Such clinical shreds of evidence let us consider highlighting the use of probiotics to slow down the progression of the coronavirus pandemic. Some current investigations also supported this assumption. Liu *et al*. [113], for example, demonstrated that their modified *Lactobacillus plantarum* acts in the intestinal porcine epithelial cell line as a potent anti-coronaviral agent. Verma *et al*. [114] evident the production of ACE-2 (well known as a receptor for SARS-CoV-2 binding) in *Lactobacillus paracasei*. If this ACE-2 can successfully bind the spike protein of SARS-CoV-2, their entry into the host cell will be prevented and thereby, the risk of infections will be lowered [115]. Furthermore, a clinical survey recorded gut microbiome imbalances including a decrease in probiotic levels such as *Lactobacillus* and *Bifidobacterium* among some patients with COVID-19, which may lead to secondary infection in response to bacterial translocation [31]. The evidence suggests the role of oral probiotics against the intestinal and systemic effects of COVID-19 [116]. Xu *et al*. [117] in their study found most of the COVID-19 patients who received probiotics encountered relatively mild symptoms. Baud *et al*. [118] found a profound correlation between the application of different probiotics such as *Lactobacillus casei, Lactobacillus plantarum, L. rhamnosus, Lactobacillus gasseri, Bifidobacterium bifidum, Bifidobacterium longum, Bifidobacterium breve, Leuconostoc mesenteroides*, and *Pediococcus pentosaceus* and the lowering of complications due to COVID-19 in a large human study population. Wu *et al*. [119] observed a remarkable reduction in COVID-19 symptoms along with the lowering of inflammation and restoration of gut microbiota after taking a large dose of probiotics. Current research in Belgium evident the efficacy of different lactobacilli in reducing the viral activity in the nasopharynx and oropharynx through mediating enhancement in the epithelial barrier and anti-inflammatory effects alongside minimizing the risk of secondary bacterial infections in COVID-19 [120]. d'Ettorre *et al*. [121] examined the potential of oral bacteriotherapy formulated with *Streptococcus thermophiles* DSM 32345, *L. acidophilus* DSM 32241, *Lactobacillus helveticus* DSM 32242, *Lactobacillus paracasei* DSM 32243, *Lactobacillus Plantarum* DSM 32244, *Lactobacillus brevis* DSM 27961, *Bifidobacterium lactis* DSM 32246, *Bifidobacterium lactis* DSM 32247 against the progression of COVID-19 complications. Patients who received bacteriotherapy showed a higher survival rate and were with a lower risk of developing respiratory collapse along with notable improvement in other manifestations of COVID-19 in 24–48 h of administration possibly through promoting host immunity. Although several randomized controlled studies have shown that probiotic administration in COVID-19 patients can thwart ventilator-associated pneumonia, the impact on mortality reduction remains unknown [122,123]. However, the study of probiotic therapies could be appropriate during a pandemic. A list of different probiotics which may have a prospect against COVID-19 is given in Table 2 along with their sources, effects, and possible mechanisms.

Conclusion

By modulating host immune responses, upholding gut homeostasis, and releasing interferon, the probiotics have the potential to control the cytokine storm caused by SARS-CoV-2 [30,31]. The promising effect has been shown by Lactobacilli and *Bifidobacteria*, against SARS-CoV-2 induced gut dysbiosis. The approach involving modulation of intestinal microbiota can be considered as one of the therapeutic options against COVID-19 and its comorbidities. However, in combating COVID-19, the prospect of using probiotics remains uncertain and a lot remains to be learned. In particular, specific beneficial strains have to be distinguished since each strain exerts a certain effect. Governments are funding several drug development and testing research. They also need to finance probiotic studies. Owing to excel the dissemination of probiotic strains and native beneficial microbes, the use of established prebiotics (e.g. fructans or galactans) should also be recommended. As soon the probiotic research enters the next step, the mode of action of each probiotic and its effective clinical use are required to be determined. If the forthcoming clinical trials rely on characterizing the effect of introducing probiotics on the baseline individual microflora and their genetic pattern of responses, the potency of probiotic application in human disease prevention and treatment can thereby be revealed. This adds to future demand for custom medicinal products. Furthermore, current translational and

Table 2: List of potential probiotics with their sources, effects against various diseases, and possible mechanisms that could have prospects against coronavirus disease-19

Probiotics	Sources or administered forms	Effects	Possible Mechanisms	References
L. rhamnosus GG, *B. lactis* and *L. acidophilus*	Yogurt	Prevents gastrointestinal diseases, and resolved gastrointestinal well-being and digestive symptoms	Modulates the immune system or the composition of gut microbiota and their bi-products	[96]
L. delbrueckii, *L. bulgaricus* and *S. salivarius* thermophilus	Yogurt	Prevents antibiotic-associated diarrhea	Modulates the gastrointestinal flora composition and immune response	[98]
L. bulgaricus OLL1073R-1 and S. thermophiles	Yogurt	Reduces incidence of RTIs	Increases IFN-γ production in serum	[124]
Lactobacillus sp., and *Bifidobacterium* sp.	Yogurt	Prevents irritable bowel syndrome	Exerts anti-inflammatory activities	[125]
L. casei, *L. plantarum*, *L. acidophilus*, and *L. delbrueckii* subsp. *bulgaricus*, *B. longum*, *B.breve*, and *B. infantis*	Kefir	Prevents gastrointestinal diseases	Enhances immune responses by enhancing epithelial barrier functions	[126]
L. kimchii sp. nov.	Kimchi	Prevents gastrointestinal diseases	Modulates the immune system by increasing NK cells and macrophages activities	[127]
L. plantarum 299v	Fermented oatmeal gruel	Reduces incidence and duration of RTIs	Helps to restore paracellular permeability of gut barrier	[128]
B. breve Yakult, and *L.casei* Shirota	Fermented drinks	Reduces the duration of ventilator-associated pneumonia	Enhances immune response by modulating gut microbiota	[129]
L. brevis KB290	Fermented drinks	Reduces incidence and duration of RTIs	Enhances immune response and promote resistance against pathogen	[103]
L. rhamnosus GG	Probiotic juice	Reduces the duration of RTIs	Immunomodulatory interactions with intestinal epithelial cells	[130]
L. plantarum DR7	Placebo products Selangor, Malaysia	Reduces the risk of RTIs	Enhances immune response by increasing plasma anti-inflammatory cytokine, and suppressing pro-inflammatory cytokine	[74]
L. gasseri KS-13, *B. bifidum* G9-1, and *B. longum* MM-2	Probiotic placebo	Enhances CD4+lymphocytes circulation and digestive health	Produces a less inflammatory cytokine profile by changing the microbial communities in the gastrointestinal tract	[131]
L. plantarum ATCC-202195 with fructooligosaccharide	Probiotic placebo	Prevents sepsis and reduces mortality rate	Inhibits pathogen adherence and translocation	[104]
L. plantarum	Probiotic placebo	Prevents ventilator-associated pneumonia and critical illness	Inhibits pathogen adherence, modulates local and systemic immune response, and improves gut barrier function	[132]
L. casei rhamnosus; *L. plantarum*; Synbiotic 2000FORTE; Ergyphilus; combination *B. longum*, *L. bulgaricus*, S. thermophilus	Probiotic placebo	Prevents ventilator-associated pneumonia and critical illness	Inhibits pathogen colonization and enhance immunity	[111]
S. boulardii	Probiotic placebo	Reduces the duration of diarrhea	Stimulates intestinal secretion of immunoglobulins and brush border membrane enzymes of intestinal cells	[133]
B. longum, *L. bulgaricus*, *S. thermophiles*	Probiotic placebo	Prevents ventilator-associated pneumonia	Enhances innate immunity by modulating gut microflora	[35]
L. plantarum 299	Probiotic placebo	Reduces bowel symptoms and duration of stay in the intensive care unit	Enhances immune response by influencing cytokine release and immunoglobulin production	[134]
L. casei rhamnosus	Probiotic placebo	Reduces incidences of RTIs and ventilator-associated pneumonia	Inhibits pathogenic growth by adhering to intestinal cells and transiently colonizing the intestinal tract	[135]

Contd...

Table 2: Contd...

Probiotics	Sources or administered forms	Effects	Possible Mechanisms	References
L. rhamnosus GG	Probiotic placebo	Prevents antibiotic-associated diarrhea	Enhances probiotic adherence to intestinal epithelial cells by producing soluble proteins	[99]
S. boulardii	Probiotic placebo	Prevents antibiotic-associated diarrhea	Imparts anti-inflammatory activity by modulating MAP kinase signaling pathways	[136]
Lactobacillus sp., and *S. boulardii*	Probiotic placebo	Reduces the risk of antibiotic-associated diarrhea	Restoration of gut microbiome, inhibition of epithelial and mucosal adherence of pathogens, lowering pH	[97,100]
L. rhamnosus GG and *S. boulardii*	Probiotic placebo	Reduces the duration of acute infectious diarrhea	Enhances immune response by influencing gut mucosal barrier integrity	[137]
B. longum	Probiotic sachet	Enhances innate immunity and microbiota diversity	Enhances immune response by increasing NK cells activity	[138]
L. plantarum HEAL 9 and *L. paracasei* 8700:2	Probiotic sachet	Reduces symptoms of RTIs	Enhances innate immune system by increasing immune cell counts	[139]
B. animalis	Probiotic sachet	Reduce the severity of RTIs	Enhance innate immunity by interacting with gut microbiome	[107]
L. rhamnosus LGG and *B. animalis* ssp. *lactis* BB-12	Probiotic sachet	Reduce the severity of RTIs	Prevents replication of virus and modulates immune function	[140]
L. rhamnosus GG	Probiotic capsule	Reduce incidence of RTIs	Enhances innate immunity	[141]
L. rhamnosus GG	Probiotic capsule	Reduces the risk of RTIs	Increases IFN-γ production	[110]
L. rhamnosus GG	Probiotic capsule	Reduces the risk of RTIs	Enhances innate immune system by increasing phagocytosis, cytokine production, and NK cell activity	[109]
L. rhamnosus M21	Probiotic capsule	Reduces the risk of RTIs	Activates humoral as well as cellular immune responses	[142]
C. butyricum	Probiotic tablet	Reduces the risk of RTIs	Enhances innate immunity and microbiota diversity	[112]
L. gasseri PA 16/8, *B. longum* SP 07/3, and *B. bifidum* MF 20/5	Probiotic milk	Reduces the severity and duration of RTIs	Increases innate immunity by increasing immune cell counts	[143]
L. rhamnosus GG	Probiotic milk	Reduce incidence and duration of RTIs	Activates mucosal innate immune responses	[102]
L. johnsonii	Fermented milk	Reduces the infections, duration of stay in the intensive care unit and under mechanical ventilation	Improves intestinal barrier and hinders pathogen adhesion	[144]
B. animalis DN-173 010, *B. lactis* DN-173 010	Activia, Danone, USA	Prevents gastrointestinal diseases, and improved gastrointestinal well-being and digestive symptoms	Influences inflammatory cytokine profile and modulates gut microflora	[145,146]
L. rhamnosus GG	Gefilus milk, Riihimäki, Finland	Reduces gastrointestinal and respiratory infections	Enhances humoral and cellular immunity	[147]
L. casei DN-114 001	DanActive/Actimel fermented drink, Danone, USA	Reduces incidence and duration of RTIs	Enhances immune response by increasing leukocytes, neutrophils, and NK cell counts and producing cytokines in serum	[90,91]
L. casei DN-114001	Actimel fermented drink, Danone, USA	Reduces the risk of RTIs	Enhances immune response by increasing immune cell counts	[148]
L. gasseri PA 16/8, *B. longum* SP 07/3, and *B. bifidum* MF 20/5	Tribion harmonis, Merck	Reduces duration and severity of flu-like illness	Influences immune cells to release pro- and anti-inflammatory cytokines and expresses costimulatory molecules	[87]
L. rhamnosus GG	Culturelle, Cromwell, USA	Reduces the risk of viral RTIs and improves digestive health	Enhances gut barrier integrity	[101]

Contd...

Table 2: Contd...

Probiotics	Sources or administered forms	Effects	Possible Mechanisms	References
B. longum BB536	Morinaga milk, Tokyo, Japan	Reduces the risk of RTIs	Enhances innate immunity by increasing neutrophils and NK cells activities	[88]
L. rhamnosus GG and *B. lactis* Bb-12	Enfamil; Mead Johnson Nutritionals, Evansville, IN, USA	Reduces the risk of recurrent otitis media and respiratory infections	Enhances mucosa-associated immune system by immunomodulation and reducing pathogen colonization	[105]
P. pentosaceus 5-33:3, *L. mesenteroides* 32-77:1, *L. paracasei* ssp. *paracasei* 19, *L. plantarum* 2,362 plus inulin, oat bran, pectin, and resistant starch	Medipharm, Sweden	Reduces the rate of SIRS, infections, sepsis, duration of stay in the intensive care unit, under mechanical ventilation, and mortality	Enhances innate immunity by modulating gut microflora and improving immunological gut barrier function	[149]

L. rhamnosus: *Lactobacillus rhamnosus*, *B. lactis*: *Bifidobacterium lactis*, *L. acidophilus*: *Lactobacillus acidophilus*, *L. delbrueckii*: *Lactobacillus delbrueckii*, *S. salivarius*: *Streptococcus salivarius*, *S. thermophiles*: *Streptococcus thermophiles*, *L. casei*: *Lacticaseibacillus casei*, *L. plantarum*: *Lactiplantibacillus plantarum*, *B. longum*: *Bifidobacterium longum*, *B. breve*: *Bifidobacterium breve*, *B. infantis*: *Bifidobacterium infantis*, *L. kimchii*: *Lactobacillus kimchii*, *L. brevis*: *Lactobacillus brevis*, *L. gasseri*: *Lactobacillus gasseri*, *B. bifidum*: *Bifidobacterium Bifidum*, *L. bulgaricus*: *Lactobacillus bulgaricus*, *S. boulardii*: *Saccharomyces boulardii*, *L. paracasei*: *Lacticaseibacillus paracasei*, *B. animalis*: *Bifidobacterium animalis*, *C. butyricum*: *Clostridium butyricum*, *L. johnsonii*: *Lactobacillus johnsonii*, *L. mesenteroides*: *Leuconostoc mesenteroides*, *P. pentosaceus*: *Pediococcus pentosaceus*, SIRS: Systemic inflammatory response syndrome, RTIs: Respiratory tract infections, IFN-γ: Interferon gamma, MAP: Mitogen-activated protein, NK: Natural killer

clinical research could include the evaluation of probiotics as biomarkers for therapeutic purposes. This confirms that probiotic-derived immune stimulation may potentially encourage long-standing resistance to virus infections and human diseases.

Acknowledgment

The authors would like to thank all the researchers whose articles are cited in this manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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