Review Article

The prospects of employing probiotics in combating COVID-19

Moutoshi Chakraborty*, Saurab Kishore Munshi†‡

*Institute of Biotechnology and Genetic Engineering, Bangladesh Agricultural University, Gazipur, Bangladesh; †Department of Microbiology, Stamford University Bangladesh, Dhaka, Bangladesh

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

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-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,
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 those who deliver 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-γ, 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 multorgan 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.

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 I               | RNA-dependent RNA polymerase inhibitor                             | [42]       |
| Interferon beta              |                                          | NCT04350671           | Phase IV              | Anti-viral and immunomodulatory effects                            | [43]       |
| Canovoo + ritonavir           |                                          | NCT04291729           | Phase I               | Viral protease inhibitor                                           | [44]       |
| Azithromycin + hydroxychloroquine | Antimalarial                              | NCT04359316           | Phase I               | Secondary bacterial infection inhibitor                             | [38]       |
| Remdesivir                   | Antiviral                                | NCT04292899           | Phase III             | RNA-dependent RNA polymerase inhibitor                             | [38]       |
| Ribavirin                    | Antiviral                                | NCT04460443           | Phase I               | Viral RNA synthesis and mRNA capping inhibitor                     | [45]       |
| Oseltmivir                   |                                          | NCT04338698           | Phase I               | Viral protease inhibitor                                           | [46]       |
| ASC09F                       |                                          | NCT04261270           | Phase I               | JAK inhibitor                                                      | [47]       |
| Baricitinib                  |                                          | NCT04421027           | Phase I               | Viral protease inhibitor                                           | [46]       |
| Darunavir and cobicistat     |                                          | NCT04252274           | Phase I               | Viral protease inhibitor                                           | [46]       |
| Chloroquine or hydroxychloroquine | Antiparasitic                            | NCT04353336           | Phase I               | Disrupt viral S protein interaction with ACE2                     | [44,48]    |
| Nitazoxanide                 | Antiparasitic/ antiviral                  | NCT04463264           | Phase II              | Disrupt the host immune response to produce interferons           | [49]       |
| Lopinavir                    |                                          | NCT04455958           | Phase I               | Viral protease inhibitor                                           | [50-52]    |
| Ritonavir                    |                                          | NCT04455958           | Phase I               | Viral protease inhibitor                                           | [50-52]    |
| Interferon alpha             |                                          | NCT04379518           | Phase I               | Viral protease inhibitor                                           | [50-52]    |
| Camostat mesylate            |                                          | NCT04435015           | Phase I               | Viral protease inhibitor                                           | [50-52]    |
| Galidesivir                  |                                          | NCT03891420           | Phase I               | Viral protease inhibitor                                           | [50-52]    |

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 but 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 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                          | Reduces incidence and duration of RTIs | Helps to restore paracellular permeability of gut barrier | [128] |
| L. casei, L. plantarum, L. acidophilus, and L. delbrueckii subsp. bulgaricus, B. longum, B breve, and B. infantis | Kefir                           | Prevents gastrointestinal diseases | Enhances immune response by modulating gut microbiota | [126] |
| L. kimchii sp. nov. | Kimchi                          | Prevents gastrointestinal diseases | Enhances immune response and promote resistance against pathogen | [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-202193 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; Symbiotic 2000FORTE; Ergyphilus; combination B. longum, L. bulgaricus, S. thermophilus S. bouardii | Probiotic placebo               | Prevents ventilator-associated pneumonia and critical illness | Inhibits pathogen colonization and enhance immunity | [111] |
| L. plantarum | 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. thermophilus | 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...
| 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. johnsonii* | Probiotic milk | Reduce incidence and duration of RTIs | Enhances innate immune system by increasing phagocytosis, cytokine production, and NK cell activity | [109] |
| *C. butyricum* | Probiotic tablet | Reduces the risk of RTIs | Activates humoral as well as cellular immune responses | [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 | Influences inflammatory cytokine profile and modulates gut microflora | [145,146] |
| *L. rhamnosus* GG | Probiotic milk | Reduces incidence and duration of RTIs | Enhances humoral and cellular immunity | [147] |
| *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] |
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 Nutritional, 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* sp. 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] |

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.

REFERENCES

1. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. J Med Virol 2020;92:401-2.
2. World Health Organization. Director-General’s Remarks at the Media Briefing on 2019-nCoV on February 11, 2020. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020. [Last accessed on 2020 Jun 18].
3. Whiworth J. COVID-19: A fast evolving pandemic. Trans R Soc Trop Med Hyg 2020;114:241-8.
4. Zumbala S, Wong JF, Azhar EI, Hui DS, Yuen KY. Coronavirus-drug discovery and therapeutic options. Nat Rev Drug Discov 2016;15:327-47.
5. Su S, Wong G, Shi W, Liu J, Lai AC, Zhou J, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends Microbiol 2016;24:490-502.
6. Centers for Disease Control and Prevention. Frequently Asked Questions About SARS, 2005. Available from: https://www.cdc.gov/sars/about/faq.html. [Last accessed on 2020 Jun 18].
7. World Health Organization. Middle East Respiratory Syndrome Coronavirus (MERS-CoV), 2019. Available from: https://www.who.int/news-room/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov). [Last accessed on 2020 Jun 18].
8. Ahmed SF, Quadeer AA, McKay MR. Preliminary identification of potential vaccine targets for the COVID-19 coronavirus (SARS-CoV-2) based on SARS-CoV immunological studies. Viruses 2020;12:254.
9. Hemida MG, Ba Abdullah MM. The SARS-CoV-2 outbreak from a one health perspective. One Health 2020;10:100127.
10. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270-3.
11. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
12. Fontanet A, Autran B, Lina B, Kieny MP, Karim SSA, Sridhar D. SARS-CoV-2 variants and ending the COVID-19 pandemic. Lancet 2021;397:952-4.
13. Singh J, Rahman SA, Ehtesham NZ, Hira S, Hasnain SE. SARS-CoV-2 variants of concern are emerging in India. Nat Med 2021;27:1131-3.
14. Anderson RM, Heesterbeeck H, Klinkenberg D, Hollingsworth TD. How will country-based mitigation measures influence the course of the COVID-19 epidemic? Lancet 2020;395:931-4.
15. Dal Pozzo F, Thiery E. Antiviral chemotherapy in veterinary medicine: Current applications and perspectives. Rev Sci Tech 2014;33:791-801.
16. Villamagna AH, Gore SJ, Lewis JS, Doggett JS. The need for antiviral drugs for pandemic coronaviruses from a global health perspective. Front Med (Lausanne) 2020;7:596587.
17. Kim JH, Marks F, Clemens JD. Looking beyond COVID-19 vaccine phase 3 trials. Nat Med 2021;27:205-11.
18. World Health Organization. The Effects of Virus Variants on COVID-19 Vaccines, 2021. Available from: https://www.who.int/news-room/feature-stories/detail/the-effects-of-virus-variants-on-covid-19-vaccines. [Last accessed on 2021 Jun 30].
19. Hill C, Guerrier F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol 2014;11:506-14.
20. Kawahara T, Takahashi T, Oishi K, Tanaka H, Masuda M, Takahashi S, et al. Consecutive oral administration of *Bifidobacterium longum* MM-2 improves the defense system against influenza virus infection by enhancing natural killer cell activity in a murine model. Microbiol Immunol 2015;59:1-12.
21. Morrow LE, Gogineni LE, Gogineni MR. Preliminary identification of potential vaccine targets for the COVID-19 coronavirus (SARS-CoV-2) based on SARS-CoV immunological studies. Viruses 2020;12:254. [Last accessed on 2020 Jun 18].
22. Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-
infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut 2020;69:1002-9.

23. Lin L, Jiang X, Zhang Z, Huang S, Zhang Z, Fang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut 2020;69:997-1001.

24. López-Moreno A, Aguilera M. Probiotics dietary supplementation for modulating endocrine and fertility microbiota dysbiosis. Nutrients 2020;12:E757.

25. National Center for Complementary and Integrative Health. Probiotics: What You Need to Know. US Department of Health and Human Services; 2020. Available from: https://www.nccih.nih.gov/health/probiotics-what-you-need-to-know. [Last accessed on 2021 Feb 22].

26. Bogspati S, Poma AB, Kolanadleiv P. Novel 2019 coronavirus structure, mechanism of action, antiviral drug promises and rule out against its treatment. J Biomol Struct Dyn 2021;39:3409-18.

27. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271-80.e8.

28. Sims AC, Baric RS, Yount B, Burkett SE, Collins PL, Pickles RJ. Severe acute respiratory syndrome coronavirus infection of human ciliated airway epithelia: Role of ciliated cells in viral spread in the conducting airways of the lungs. J Clin Invest 2020;136:5885-90.

29. Gu J, Korteweg C. Pathology and pathogenesis of Severe Acute Respiratory Syndrome. Am J Pathol 2007;170:1136-47.

30. Qian Z, Travanty EA, Oko L, Edeen L, Berger J, Huang L, et al. Innate immune response of human alveolar type II cells infected with severe acute respiratory-syndrome coronavirus. Am J Respir Cell Mol Biol 2013;48:742-8.

31. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8:420-2.

32. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. Eur Respir J 2020;55:2000607.

33. Carlos WG, Cruz CS, Cao B, Pasnick S, Jamil S. Novel Wuhan (2019-NCoV) coronavirus. Am J Respir Crit Care Med 2020;201:7-8.

34. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA 2020;323:1239-42.

35. Fan C, Li K, Ding Y, Lu W, Wang J. ACE2 Expression in kidney and testis may cause kidney and testis damage after 2019-nCoV infection. Front Med 2020;7:563933.

36. He LH, Ren LF, Li JF, Wu YN, Li X, Zhang L. Intestinal Flora as a potential strategy to fight SARS-CoV-2 infection. Front Microbiol 2020;11:1388.

37. Gohil K, Samson R, Dastager S, Dharne Y. Probiotics dietary supplementation for modulating endocrine and fertility microbiota dysbiosis. Nutrients 2020;12:382:1199-207.

38. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, Evaluation and Treatment Coronavirus (COVID-19). USA: StatPearls Publishing, 2020.

39. Kumar V, Jung YS, Liang PH. Anti-SARS coronavirus agents: A patent review (2008-present). Expert Opin Ther Pat 2013;23:1337-48.

40. Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). Biosci Trends 2020;14:69-71.

41. Mifsud ED, Hayden FG, Hutt AC. Antivirals targeting the polyomavirus complex of influenza viruses. Antiviral Res 2019;169:104555.

42. Sallard E, Lessure FX, Yazdanpanah Y, Mentre F, Peier-Smadja N. Type 1 interferons as a potential treatment against COVID-19. Antiviral Res 2020;182:104791.

43. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30:267-91.

44. Arabi YM, Shahlooub S, Mandoorah Y, Al-Hameed F, Al-Omari A, Al Qasim E, et al. Ribavirin and interferon therapy for critically ill patients with Middle East respiratory syndrome: A multicenter observational study. Clin Infect Dis 2020;70:1837-44.

45. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov 2020;19:149-50.

46. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, et al. Baricitinib in potential treatment for 2019-nCoV acute respiratory syndrome. Lancet 2020;395:e30-e1.

47. Taccone FS, Gorham J, Vincent JL. Hydroxychloroquine in the management of critically ill patients with COVID-19: The need for an evidence base. Lancet Respir Med 2020;8:539-41.

48. Guo D. Old weapon for new enemy: Drug repurposing for treatment of newly emerging viral diseases. Virol Sin 2020;35:253-5.

49. Chan JF, Yao Y, Yeung ML, Deng W, Bao L, Jia L, et al. Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. J Infect Dis 2015;212:1904-13.

50. Kim DJ, Wu EJ, Kee SJ, Jung SJ, Jang HC. Combination therapy with lopinavir/ritonavir, ribavirin and interferon-α for Middle East respiratory syndrome. Antivir Ther 2016;21:455-9.

51. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 2020;11:222.

52. Warren TK, Wells J, Panchal RG, Stuthman KS, Garza NL, Van Tongeren SA, et al. Protection against tiovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430. Nature 2014;508:402-5.

53. Dhamla K, Sharan K, Tiwari R, Dadar M, Malik YS, Singh KP, et al. COVID-19, an emerging coronavirus infection: Advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics. Hum Vaccin Immunother 2020;16:1238-3.

54. Lao H, Tang QL, Shang YX, Liang SB, Yang M, Robinson N, et al. Can Chinese medicine be used for prevention of coronavirus disease 2019 (COVID-19)? A review of historical classics, research evidence and current prevention programs. Chin J Integr Med 2020;26:243-50.

55. Corcionivoschi N, Drinceanu D, Stef L, Luca I, Julean C. Probiotics identification and ways of action. Innov Rom Food Biotechnol 2010;6:1-15.

56. Hao Q, Dong BR, Wu T. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database Syst Rev 2015;2:CD006895.

57. Ng SC, Tilg H. COVID-19 and the gastrointestinal tract: More than meets the eye. Gut 2020;69:973-4.

58. Pan Y, Zhang D, Yang P, Poon LL, Wang Q. Viral load of SARSCoV-2 in clinical samples. Lancet Infect Dis 2020;20:411-2.

59. Wu F, Zhang J, Xiao A, Gu X, Liu JL, Armas F, et al. SARS-CoV-2 titers in wastewater are higher than expected from clinically confirmed cases. mSystems 2020;5:e00614-20.

60. Chan CKY, Tao J, Chan OS, Li HB, Pang H. Preventing respiratory tract infections by symbiotic interventions: A systematic review and meta-analysis of randomized controlled trials. Adv Nutr 2020;11:979-88.

61. Caballero-Franco C, Keller K, De Simone C, Chadee K. The VSL#3 probiotic formula induces mucin gene expression and secretion in colonic epithelial cells. Am J Physiol Gastrointest Liver Physiol 2007;292:G315-22.

62. Qin H, Zhang Z, Hang X, Jiang Y. L. plantarum prevents enteroinvasive Escherichia coli-induced tight junction proteins changes in intestinal epithelial cells. BMC Microbiol 2009;9:63.

63. Malondoanu Galdeano C, Cazorla SI, Lemme Dumit JM, Vélez E, Perdiguón G. Beneficial effects of probiotic consumption on the immune system. Ann Nutr Metab 2019;74:115-24.
bovine leukocyte interferon activity with potential to decrease the absorption of food-derived purines in the gut-lung axis in health and respiratory diseases: A probiotic influences of probiotics and the immune system. Biomed Res Int 2019;2019:6764919.

Reducing effect of Lactobacillus gasseri PA-3 on the absorption of food-derived purines in the human intestine. Nucleosides Nucleotides Nucleic Acids 2016;35:670-70.

Yamada N, Iwamoto C, Kano H, Yamaoka N, Fukuchi T, Keneko K, et al. Evaluation of purine utilization by Lactobacillus gasseri strains with potential to decrease the absorption of food-derived purines in the human intestine. J Med Microbiol 2020;69:25-31.

Yamanaka H, Taniguchi A, Tsuibo H, Kano H, et al. Reducing effect of Lactobacillus gasseri PA-3 on the absorption of food-derived purines. Milk Sci 2016;65:25-31.

Bozkurt HS, Quigley EM. Bifidobacteria and mucosal-associated invariant T (MAIT) cells: A new approach to colorectal cancer prevention? Gastrointest Disord 2019;1:266-72.

Chakraborty S, Benvenuto D, Bianchi M, Giovanetti M, Pascarella M, et al. Genomic and phenotypic evidence for Lactobacillus gasseri strains as potential alternative to antibiotics and future prophylactic potential in adults and children. Cochrane Database Syst Rev 2017;12:CD006095.

Guo Q, Goldenberg JZ, Humphrey C, El Dib R, Johnston BC. Probiotics for the prevention of gastrointestinal infections in shift workers in a randomized controlled study. J Dairy Sci 2019;102:4783-97.

Chong HX, Yusoff NA, Hor YY, Lew LC, Jafar MH, Choi SB, et al. Lactobacillus plantarum DR7 improved upper respiratory tract infections via enhancing immune and inflammatory parameters: A randomized, double-blind, placebo-controlled study. J Dairy Sci 2019;102:4783-97.

Zhang H, Yeh C, Jin Z, Ding L, Liu BY, Zhang L, et al. Prospective study of probiotic supplementation results in immune stimulation and improvement of upper respiratory infection rate. Synth Syst Biotechnol 2018;3:113-20.

Clau P, Kanmani P, Zelaya H, Tada A, Kober AKMH, Salva S, et al. Peptidoglycan from immunobiotic Lactobacillus rhamnosus improves resistance of infant mice to respiratory syncytial viral infection and secondary pneumococcal pneumonia. Front Immunol 2017;8:948.

Zhang CX, Wang HY, Chen T+. Interactions between intestinal microflora/probiotics and the immune system. Biomed Res Int 2019;2019:6764919.

Vinolo MA, Rodrigues HG, Nachbar RT, Curi R. Regulation of inflammation by short chain fatty acids. Nutrients 2011;3:858-76.

Bron PA, van Baaren P, Kleerebezem M. Emerging molecular insights into the interaction between probiotics and the host intestinal mucosa. Nat Rev Microbiol 2011;10:66-78.

Selle K, Klaenhammer TR. Genomic and phenotypic evidence for probiotic influences of Lactobacillus gasseri on human health. FEMS Microbiol Rev 2013;37:915-35.

Enaud R, Prevel R, Ciarlo E, Beaufils F, Weiers G, Guery B, et al. The gut-lung axis in health and respiratory diseases: A place for inter-organ and inter-domain crosstalks. Front Cell Infect Microbiol 2020;10:9.

Hanada S, Pirzadeh M, Carver KY, Deng JC. Respiratory viral infection-induced microbiome alterations and secondary bacterial pneumonia. Front Immunol 2018;9:2640.

Sencio V, Barthelemy A, Tavares LP, Machado MG, Souland D, Cuinat C, et al. Gut dybiosis during influenza contributes to pulmonary pneumococcal superinfection through altered short-chain fatty acid production. Cell Rep 2020;30:2934-47.e6.

Di Pierro F. A possible probiotic (S. salivarius K12) approach to improve oral and lung microbiota and raise defenses against SAR S-CoV-2. Minerva Med 2020;111:281-3.

Aub MC, Osborne LC, Monticelli LA, Doering TA, Alenghat T, Sonnenberg GF, et al. Commensal bacteria calibrate the activation threshold of innate antiviral immunity. Immunity 2012;37:158-70.

Zelaya H, Alvarez S, Kitzazawa H, Villena J. Respiratory antiviral immunity and immunobiotics: Beneficial effects on inflammation-coagulation interaction during influenza virus infection. Front Immunol 2020;11:633.

de Vrese M, Winkler P, Rautenberg P, Harder T, Noah C, Laue C, et al. Effect of Lactobacillus gasseri PA 16/8, Bifidobacterium longum SP 07/3, B. bifidum MF 20/5 on common cold episodes: A double blind, randomized, controlled trial. Clin Nutr 2005;24:481-91.

Namkhi K, Hatanaka M, Yasuhisa T, Takase M, Suzuki K. Effects of Bifidobacterium longum BB536 administration on influenza infection, influenza vaccine antibody titer, and cell-mediated immunity in the elderly. Biosci Biotechnol Biochem 2010;74:939-45.

Pregliasco F, Anchelini G, Fonte L, Giussani F, Schieppati S, Soletti L. A new chance of preventing winter diseases by the administration of symbiotic formulations. J Clin Gastroenterol 2008;42(Suppl 3 Pt 2):S224-33.

Guillemin F, Tondu F, Lacoin F, Schrezenmeir J. Consumption of a fermented dairy product containing the probiotic Lactobacillus casei DN-114001 reduces the duration of respiratory infections in the elderly in a randomised controlled trial. Br J Nutr 2010;103:58-68.

Guillemin F, Tanguy J, Flavigny A, de la Motte S, Schrezenmeir J. Effects of consumption of a fermented dairy product containing the probiotic Lactobacillus casei DN-114 001 on common respiratory and gastrointestinal infections in shift workers in a randomized controlled trial. J Am Coll Nutr 2010;29:455-68.

Lenoir-Wijckoop I, Gerlier L, Roy D, Reid G. The clinical and economic impact of probiotics consumption on respiratory tract infections: Projections for Canada. PLoS One 2016;11:e0166232.

Goldenberg JZ, Yap C, Lytvyn L, Lo CK, Beardsley J, Mertz D, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database Syst Rev 2017;12:CD006095.

Guo Q, Goldenberg JZ, Humphrey C, El Dib R, Johnston BC. Probiotics for the prevention of gastrointestinal infections in shift workers in a randomized controlled study. J Dairy Sci 2019;102:4783-97.

Lam L, Chi J, Patan A, Bajwa M, Kamaruddin M, Alapatt JN, et al. Consumption of a synbiotic formulation for the prevention of diarrhea in children on antibiotics? A double-blind, randomised, placebo-controlled study. BMJ Open 2015;5:e006474.
Prebiotic and probiotic supplementations prevent rhinovirus infections in preterm infants: A randomized, placebo-controlled trial. J Allergy Clin Immunol 2014;133:405-13.

102. Kumpu M, Lehtoranta L, Roivainen M, Rönkkö E, Ziegler T, Söderlund-Venermo M, et al. The use of the probiotic Lactobacillus rhamnosus GG and viral findings in the nasopharynx of children attending day care. J Med Virol 2013;85:1632-8.

103. Waki N, Matsumoto M, Fuku Y, Suganuma H. Effects of probiotic Lactobacillus brevis KB 290 on incidence of influenza infection among school children: An open-label pilot study. Lett Appl Microbiol 2014;59:565-71.

104. Panigrahi P, Parida S, Nanda NC, Satpathy R, Pradhan L, Chandel DS, et al. A randomized symbiotic trial to prevent sepsis among infants in rural India. Nature 2017;548:407-12.

105. Rautava S, Salminen S, Isolauri E. Specific probiotics in reducing the risk of acute infections in infancy – a randomised, double-blind, placebo-controlled study. Br J Nutr 2009;101:1722-6.

106. Olivares M, Díaz-Ropero MP, Sierra S, Lara-Villoslada F, Fonollá J, Navas M, et al. Oral intake of Lactobacillus fermentum CECT5716 enhances the effects of influenza vaccination. Nutrition 2007;23:254-60.

107. Turner RB, Woodfoul JA, Borish L, Steinke JW, Patrie JT, Muehling LM, et al. Effect of probiotic on innate inflammatory response and viral shedding in experimental rhinovirus infection-a randomised controlled trial. Benef Microbes 2017;8:207-15.

108. Pang IK, Iwasaki A. Control of antiviral immunity by pattern recognition and the microbiome. Immuno Rev 2012;245:209-26.

109. Wang B, Hylwka T, Smieja M, Surrente M, Bowdish DME, Leeb M. Probiotics to prevent respiratory infections in nursing homes: A pilot randomized controlled trial. J Am Geriatr Soc 2018;66:1346-52.

110. Kinoshita T, Maruyama K, Suyama K, Nishijima M, Akamatsu K, Jogamoto A, et al. The effects of OLL1073R-1 yogurt intake on influenza incidence and immunological markers among women healthcare workers: A randomized controlled trial. Food Nutc 2019;10:8129-36.

111. Bo L, Li J, Tao T, Bai Y, Ye X, Hotchkiss RS, et al. Probiotics for preventing ventilator-associated pneumonia. Cochrane Database Syst Rev 2014;10:CD009066.

112. Hu X, Zhang H, Lu H, Qian G, Lv L, Zhang C, et al. The effect of probiotic treatment on patients infected with the H1N1 influenza virus. PLoS One 2016;11:e0151976.

113. Liu YS, Liu Q, Jiang YL, Yang WT, Huang HB, Shi CW, et al. Surface-displayed porcine IFN-λ3 in Lactobacillus plantarum inhibits porcine enteric coronavirus infection of porcine intestinal epithelial cells. J Microbiol Biotechnol 2020;30:515-25.

114. Verma A, Xu K, Du T, Zhu P, Liang Z, Liao S, et al. Expression of human ACE2 in Lactobacillus and beneficial effects in diabetic retinopathy in mice. Mol Ther Methods Clin Dev 2019;14:161-70.

115. Gohil K, Samson R, Dustage S, Dharne M. Probiotics in the prophylaxis of COVID-19: Something is better than nothing. J Biotech 2021;11:1.

116. Baidara P, Chakraborty R, Holliday ZM, Mandal SM, Schrum AL. Oral probiotics in coronavirus disease 2019: Connecting the gut-lung axis to viral pathogenesis, inflammation, secondary infection and clinical trials. New Microbes New Infect 2021;40:100837.

117. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-CoV-2) outside of Wuhan, China: Retrospective case series. BMJ 2020;368:m6066.

118. Baud D, Dimopoulos Agri V, Gibson GR, Reid G, Giannoni E. Using probiotics to flatten the curve of coronavirus disease COVID-19 pandemic. Front Public Health 2020;8:186.

119. Wu C, Xu Q, Cao Z, Pan D, Zhu Y, Wang S, et al. The volatile and heterogenous gut microbiota shifts of COVID-19 patients over the course of a probiotics-assisted therapy. Res Square 2021;1:1-16.

120. International Scientific Association of Probiotics and Prebiotics Board of Directors. How some Probiotic Scientists are Working to Address COVID-19. 2020. Available from: https://iaspscience.org/how-some-probiotic-and-prebiotic-scientists-are-working-to-address-covid-19/.

121. d’Ettorre G, Ceccegalli R, Marazzato M, Campagna G, Pinacchio C, Alessandri F, et al. Challenges in the management of SARS-CoV2 infection: The role of oral bacteriotherapy as complementary therapeutic strategy to avoid the progression of COVID-19. Front Med (Lausanne) 2020;7:389.

122. U.S. National Library of Medicine (USNLM). Safety and Immunogenicity Study of an Inactivated SARS-CoV-2 Vaccine for Preventing against COVID-19. 2020. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04412538?term=vaccine&cond=COVID-19&draw=2. [Last accessed on 2021 Apr 05].

123. U.S. National Library of Medicine. Safety and Immunogenicity Study of Inactivated Vaccine for Prevention of SARS-CoV-2. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04383574?term=COVID-19&cond=vaccine&entry=CN&draw=2. [Last accessed on 2021 Apr 05].

124. Jacobs SE, Lamson DM, George KS, Walsh TJ. Human rhinoviruses. Clin Microbiol Rev 2013;26:135-62.

125. Moayyedi P, Ford AC, Talley NJ, Cremonini F, Foxx-Orenstein AE, Brandt LJ, et al. The efficacy of probiotics in the treat ment of irritable bowel syndrome: A systematic review. Gut 2010;59:325-32.

126. Ritchie ML, Romankan TN. A meta-analysis of probiotic efficacy for gastrointestinal diseases. PLoS One 2012;7:e34938.

127. Park KY, Jeong JK, Lee YE. Daily JW 3rd. Health benefits of kimchi (Korean fermented vegetables) as a probiotic food. J Med Food 2014;17:6-20.

128. Klarin B, Wullt M, Palmquist I, Molin G, Larsson A, Jeppsson B. Lactobacillus plantarum 299 v reduces colonisation of Clostridium difficile in critically ill patients treated with antibiotics. Acta Anaesthesiol Scand 2002;56:1096-102.

129. Shimizu K, Yamada T, Ogura H, Mohri T, Kiguchi T, Fujimi S, et al. Symbiotics modulate gut microbiota and reduce enteritis and ventilator-associated pneumonia in patients with sepsis: A randomized controlled trial. Crit Care 2018;22:239.

130. Kumpu M, Kekkonen RA, Korpela R, Tynkkynen S, Järvenpää T, Kautainen H, et al. Effect of live and inactivated Lactobacillus rhamnosus GG on experimentally induced rhinovirus colds: Randomised, double blind, placebo-controlled pilot trial. Benef Microbes 2015;6:631-9.

131. Spaiser SJ, Culepper T, Tieves C, Uhkonos M, Mai V, Percival SS, et al. Lactobacillus gasseri KS-13, Bifidobacterium bifidum G9-1, and Bifidobacterium longum MM-2 ingestion induces a less inflammatory cytokine profile and a potentially beneficial shift in gut microbiota in older adults: A randomized, double-blind, placebo-controlled, crossover study. J Am Coll Nutr 2015;34:459-69.

132. Manzanares W, Lemieux M, Langlois PL, Wischmeyer PE. Probiotic and symbiotic therapy in critical illness: A systematic review and meta-analysis. Crit Care 2016;19:262.

133. Bleicher G, Bliéhaut H, Mentec H, Moyse D. Saccharomyces boulardii prevents diarrhea in critically ill tube-fed patients. A multicenter, randomized, double-blind placebo-controlled trial. Intensive Care Med 1997;23:517-23.

134. Rayes N, Seehofer D, Hansen S, Boussein K, Müller AR, Serke S, et al. Early enteral supply of Lactobacillus and fiber versus selective bowel decontamination: A controlled trial in liver transplant recipients. Transplantation 2002;74:123-7.

135. Forestier C, Guelon D, Cluytens V, Gillart T, Sirot J, De Champs C. Oral probiotic and prevention of Pseudomonas aeruginosa infections: A randomized, double-blind, placebo-controlled pilot study in intensive care unit patients. Crit Care 2008;12:R69.

136. Szaewska H, Kolodziej M. Systematic review with meta-analysis: Saccharomyces boulardii in the prevention of antibiotic-associated diarrhea. Aliment Pharmacol Ther 2015;42:793-801.
137. Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrheae. Cochrane Database Syst Rev 2010;2010:CD003048.

138. Akatsu H, Iwabuchi N, Xiao JZ, Matsuyama Z, Kurihara R, Okuda K, et al. Clinical effects of probiotic Bifidobacterium longum BB536 on immune function and intestinal microbiota in elderly patients receiving enteral tube feeding. JPEN J Parenter Enteral Nutr 2013;37:631-40.

139. Berggren A, Lazou Ahrén I, Larsson N, Önning G. Randomised, double-blind and placebo-controlled study using new probiotic lactobacilli for strengthening the body immune defence against viral infections. Eur J Nutr 2011;50:203-10.

140. Smith TJ, Rigassio-Radler D, Denmark R, Haley T, Touger-Decker R. Effect of Lactobacillus rhamnosus LGG® and Bifidobacterium animalis ssp. lactis BB-12® on health-related quality of life in college students affected by upper respiratory infections. Br J Nutr 2011;50:203-10.

141. Tapiovaara L, Kumpu M, Mäkivuokko H, Waris M, Korpela R, Pitkäranta A, et al. Human rhinovirus in experimental infection after peroral Lactobacillus rhamnosus GG consumption, a pilot study. Int Forum Allergy Rhinol 2016;6:848-53.

142. Song JA, Kim HJ, Hong SK, Lee DH, Lee SW, Song CS, et al. Oral intake of Lactobacillus rhamnosus M21 enhances the survival rate of mice lethally infected with influenza virus. J Microbiol Immunol Infect 2016;49:16-23.

143. de Vrese M, Winkler P, Rautenberg P, Harder T, Noah C, Laue C, et al. Probiotic bacteria reduced duration and severity but not the incidence of common cold episodes in a double blind, randomized, controlled trial. Vaccine 2006;24:6670e4.

144. Falcão de Arruda IS, de Aguilar-Nascimento JE. Benefits of early enteral nutrition with glutamine and probiotics in brain injury patients. Clin Sci (Lond) 2004;106:287-92.

145. Guyonnet D, Chassany O, Ducrotte P, Picard C, Mouret M, Mercier CH, et al. Effect of a fermented milk containing Bifidobacterium animalis DN-173 010 on the health-related quality of life and symptoms in irritable bowel syndrome in adults in primary care: A multicentre, randomized, double-blind, controlled trial. Aliment Pharmacol Ther 2007;26:475-86.

146. Guyonnet D, Schlumberger A, Mhamdi L, Jakob S, Chassany O. Fermented milk containing Bifidobacterium lactis DN-173 010 improves gastrointestinal well-being and digestive symptoms in women reporting minor digestive symptoms: A randomised, double-blind, parallel, controlled study. Br J Nutr 2009;102:1654-62.

147. Hatakka K, Savilahti E, Pönnö K, Meurman JH, Poussa T, Näse L, et al. Effect of long term consumption of probiotic milk on infections in children attending day care centres: Double blind, randomised trial. BMJ 2001;322:1327.

148. Boge T, Rémigy M, Vaudaine S, Tanguy J, Bourdet-Sicard R, van der Werf S. A probiotic fermented dairy drink improves antibody response to influenza vaccination in the elderly in two randomised controlled trials. Vaccine 2009;27:5677-84.

149. Kotzampassi K, Giamarellos-Bourboulis EJ, Voudouris A, Kazamias P, Eleftheriadis E. Benefits of a synbiotic formula (Synbiotic 2000Forte) in critically Ill trauma patients: Early results of a randomized controlled trial. World J Surg 2006;30:1848-55.