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REVIEW

The emerging role of probiotics as a mitigation strategy against coronavirus disease 2019 (COVID-19)

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Abstract

COVID-19 is an acute respiratory infection accompanied by pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has affected millions of people globally. To date, there are no highly efficient therapies for this infection. Probiotic bacteria can interact with the gut microbiome to strengthen the immune system, enhance immune responses, and induce appropriate immune signaling pathways. Several probiotics have been confirmed to reduce the duration of bacterial or viral infections. Immune fitness may be one of the approaches by which protection against viral infections can be reinforced. In general, prevention is more efficient than therapy in fighting viral infections. Thus, probiotics have emerged as suitable candidates for controlling these infections. During the COVID-19 pandemic, any approach with the capacity to induce mucosal and systemic reactions could potentially be useful. Here, we summarize findings regarding the effectiveness of various probiotics for preventing virus-induced respiratory infectious diseases, especially those that could be employed for COVID-19 patients. However, the benefits of probiotics are strain-specific, and it is necessary to identify the bacterial strains that are scientifically established to be beneficial.

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Introduction

Respiratory infections (RIs) cause high morbidity and mortality globally. The viruses most frequently responsible for these infections include influenza viruses (IVs), coronaviruses, respiratory syncytial virus (RSV), parainfluenza viruses (PIVs), adenoviruses, and rhinoviruses (RVs) [14, 142]. The severity of viral respiratory infections varies widely, and severe disorders mostly occur in children and older adults [184]. Fatalities are often observed following a viral infection, which can be exacerbated by underlying conditions or coinfection of the paranasal sinuses, middle ear, or lungs [184]. Most importantly, an outbreak of SARS-CoV-2, which causes the disease COVID-19, was initially reported in China in December 2019 and quickly spread worldwide [124, 126, 127, 170]. By December 16, 2020, the virus had caused 71,581,532 confirmed cases and 1,618,374 deaths worldwide [137]. Currently, there are no highly effective drugs for treatment of COVID-19 [57, 124, 125, 128]. Consequently, it is crucial to discover alternative and safe approaches to reduce the risk of this infection.

Currently, some probiotics have been reported to prevent and alleviate bacterial and viral infections (VIs) [84]. Most of our findings regarding the reinforcement of immune reactions by probiotics have been from *in vivo* investigations. For instance, intranasal inoculation of mice with *Lactobacillus reuteri* and *Lactobacillus plantarum* has shown protective effects against lethal viral pneumonia [84]. The expected outcome of probiotic treatment in human investigations includes alleviation of diarrhea in infants and reduction of the severity of milk allergy in children and irritable bowel syndrome [44]. Probiotics likely affect mucosae by adjusting the microbiota, hindering the growth of pathogens, and increasing local and systemic immune reactions [68].

Regarding the advantages of probiotics in viral diseases, particular probiotic strains have been found to be efficient in reducing the duration and severity of gastroenteritis caused by rotaviruses [56]. More importantly, there is increasing evidence that probiotics are beneficial in the control of viral respiratory infections [97, 178]. Recent immunological studies have provided a better understanding of the role of innate immune responses and subsequent adaptive immune responses in the recognition and eradication of viral infections. For instance, it has been found that the production of type 1 interferons (IFNs) mainly mediates the control of viral infection, immune pathology, and the management of inflammatory cytokines via Toll-like receptors and retinoic-acid-inducible gene I [129, 158, 180]. Several studies have elucidated the immunostimulatory effects of probiotic bacteria and have described their capability to prevent VIs [3, 13, 100]. Accordingly, probiotic administration may be effective in reducing and/or blocking SARS-CoV-2 infection, which has caused an enormous health and economic burden. This review describes current preventive and curative trial studies based on the use of probiotics against viral respiratory tract infections. We then outline the possible application of probiotic bacteria as a prophylactic approach against COVID-19.

Viral respiratory infections

The respiratory tract (upper or lower) is affected by many VIs [34, 169]. These infections are clinically categorized based on the type of infection (e.g., bronchiolitis, common cold, pneumonia), and not based on the type of causative agent (influenza) [34, 169]. Although particular viral pathogens generally cause characteristic clinical outcomes (e.g., respiratory syncytial virus causes bronchiolitis, while rhinoviruses cause the common cold), each pathogen can cause viral respiratory syndromes [8, 146]. The severity of viral respiratory disorders varies widely, and severe disorders are more likely to occur in children and older adults [31, 175, 186]. In most cases, respiratory viral infections are limited to the upper parts of the respiratory tract, where they induce relatively mild symptoms such as runny nose and sneezing [145]. Nevertheless, in susceptible individuals such as the elderly and newborns, infection can affect the lower respiratory airways, leading to wheezing, bronchiolitis, shortness of breath, and pneumonia [31, 175, 186]. Common respiratory viral pathogens include RSV, metapneumovirus, PIVs, bocaviruses, adenoviruses, IVs, RVs, and coronaviruses [14, 85].

Recent developments in virology have led to the development of standardized diagnostic techniques and the discovery of novel respiratory viruses such as influenza virus A (IVA), influenza virus B (IVB) and novel human coronaviruses (HCoVs) with the ability to cause a pandemic [214]. In contrast to the regular seasonal outbreaks of influenza, pandemics occur irregularly. For example, the so-called Spanish influenza pandemic in 1918 was the worst in recorded history and was responsible for about 50–100 million deaths [161, 179]. The influenza pandemic in 2009 was caused by IVA (H1N1) and is believed to have caused 100,000 to 400,000 deaths [35]. Coronaviruses are a large family of viruses with a broad range of hosts (humans and animals). Sometimes, an animal coronavirus can shift its host specificity, allowing it to infect humans [41, 199]. Several well-known human coronaviruses, including 229E, NL63, OC43, and KHU1, have emerged recently and induce mild-to-moderate RIs such as the common cold [212]. However, SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) can

cause critical RIs, and in 2003, the SARS-CoV-1 outbreak infected 8098 people, causing 774 deaths, while from 2012 to 2019, MERS infected 2494 people, causing 858 deaths [141]. SARS-CoV-2, which was first discovered in China, has caused an ongoing worldwide pandemic and, by October 1, 2020, this virus was responsible for 33,842,281 confirmed cases and 1,010,634 deaths worldwide [137].

Immune reactions and pathogenesis of COVID-19

It has been found that in severe cases of SARS-CoV-2 disease, the number of naive T helper (Th) lymphocytes increases while the number of memory Th lymphocytes and $CD28^+$ T lymphocytes decreases [150, 190]. The balance between memory T lymphocytes and naïve T lymphocytes is essential for proper host immune reactions [160]. Additionally, decreased numbers of natural killer (NK) cells and B lymphocytes have been observed in SARS-CoV-2 infection [107, 185]. Another important finding is the documented association between inflammatory signs, such as IL-6 production, erythrocyte sedimentation, and C-reactive protein induction [193]. Although the proportion of $CD4^+/CD8^+$ T lymphocytes in COVID-19 patients is usually the same as in uninfected subjects, an elevation of this ratio and a decreased proportion of $CD8^+$ T lymphocytes and B lymphocytes have been suggested as predictors of poor outcome in follow-up [190, 193].

After the virus enters a cell, viral antigens are given to antigen-presenting cells (APCs), and this step is crucial in antiviral immunity [104]. The histocompatibility complex (MHC or human leukocyte antigen [HLA]) presents the viral antigen (antigenic peptide) to specific cytotoxic T lymphocytes (CTLs) [104]. Therefore, understanding SARS-CoV-2 antigen presentation will help researchers better understand COVID-19 pathogenesis [104]. So far, our information about SARS-CoV-2 is incomplete, and most of our current knowledge is from earlier investigations on SARS-CoV-1 and MERS-CoV. MHC I, rather than MHC II, is the source of SARS-CoV-1 antigen presentation to CTLs [104, 108]. Previous research has shown a correlation of HLA polymorphisms such as HLA-B*4601, HLA-B*0703, HLA-DR B1*1202, and HLA-Cw*0801, with susceptibility to SARS-CoV-1 infection. In contrast, some alleles, such as HLA-DR0301, HLA-Cw1502, and HLA-A*0201, have been linked to protection against SARS-CoV-1 disease [104]. MHC II is correlated with host susceptibility to MERS-CoV disease (such as HLA-DRB1*11:01 and HLA-DQB1*02:0) [66]. It has also been shown that a mannose-binding lectin polymorphism is correlated with an increased risk of SARS-CoV-1 infection [183]. These investigations provide significant insights into for COVID-19 pathogenesis.

Antigen presentation initiates the induction of adaptive immunity (humoral and cellular responses via virus-specific B and T cells) [104]. As in other acute VIs, typical IgM and IgG responses are generated against SARS-CoV-1 [104]. The specific IgM produced against SARS-CoV-1 disappears at the end of week 12. In contrast, the IgG antibody can persist for a longer period, suggesting its potential protective role. The S and N proteins of SARS-CoV-1 are primary targets for the production of specific IgGs [40, 101, 104]. Compared to humoral responses, more studies have been conducted on cellular immunity against coronaviruses. Recent analysis of the peripheral blood of SARS-CoV-2-infected subjects has demonstrated reduced numbers of $CD4^+$ and $CD8^+$ T cells. Similarly, a significant reduction in $CD4^+$ and $CD8^+$ T cells is correlated with the acute phase of SARS-CoV-1 infection [104]. Even in the absence of antigens, $CD4^+$ and $CD8^+$ memory T cells can persist for four years in some SARS patients, with T cell propagation, DTH reactions, and IFN-γ generation [49]. A specific memory T cell response to the SARS-CoV-1 S peptide could still be observed in 14 out of 23 recovered patients, even six years after infection [177]. Regarding MERS-CoV, specific $CD8^+$ T cell responses are responsible for clearing this virus in mice [215]. These findings might provide a basis for developing appropriate therapeutic approaches for treating SARS-CoV-2 infections.

Potential mechanisms of action of probiotics in prevention of respiratory viral infections

Probiotics are live microorganisms that confer a health benefit on the host [50]. They commonly affect the innate and adaptive immune responses and can reduce the severity of disease in various disorders, including respiratory tract infections [73, 98, 140]. Recently, some probiotics were found to exert their immunomodulatory effect through their components, such as peptidoglycan, lipoteichoic acid, nucleic acid, which stimulates Toll-like receptors, and muramyl dipeptide, which stimulates Nod-like receptors [147]. Immune modulation occurs through regulatory T cells, type 3 innate lymphoid cells, and Th17 cells by recognizing the probiotic strain or its components and its effect on mucosal immunity [58, 84, 143]. The mechanism of action of probiotics in VIs is not entirely appreciated. However, it has been suggested that bacterial probiotics might bind to viruses, thus hindering viral binding to the host receptor [84]. Overall, the following mechanisms have been proposed for the effects of probiotics on viral respiratory infections (Fig. 1):

- Direct effect by a trapping strategy
- Activation of the immune reactions by interleukins, NK cells, Th1, and IgA production

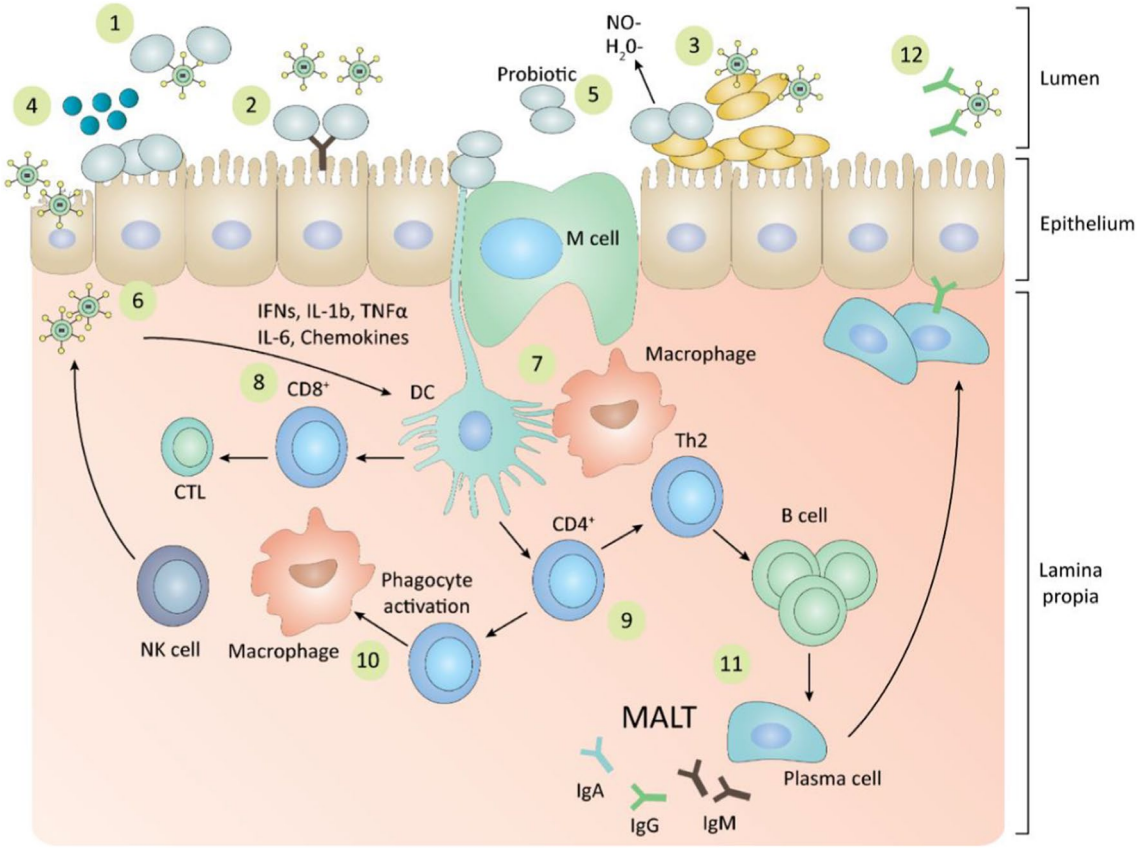

Fig. 1 The antiviral effects of probiotics during respiratory viral infections. MALT, mucosa-associated lymphoid tissue; NK cell, natural killer cell; CTL, cytotoxic T lymphocyte; Th1, T helper 1; Th2, T helper 2; DC, dendritic cell; M cell, microfold cell; IgM, immunoglobulin M; IgG, immunoglobulin G; IgA, immunoglobulin A; IFNs, interferons; IL-1b, interleukin 1 beta; TNF-a, tumour necrosis gactor alpha; IL-6, interleukin 6; NO, nitric oxide

- Induction of mucosal protection (gut mucins may attach to viruses and restrain viral replication)
- Production of antiviral components such as bacteriocins and hydrogen peroxide (H_2O_2)
- Induction of low-level nitric oxide (NO) generation by host cells and dehydrogenase formation
- Immunomodulation of immune cells (such as macrophages and dendritic cells [DCs])
- Induction of the differentiation of $CD8^+$ T cells into CTLs, which kill infected cells
- Differentiation of $CD4^+$ T cells into Th1 and Th2 cells (and induction of B cells by Th2-cells) [84, 178].

Clinical outcomes of using probiotics as a prophylactic approach for viral respiratory infections

Lactobacillus and *Bifidobacterium* are two main genera that are commonly used as probiotics [52]. The beneficial effects of probiotics on viral infections have been reported [97, 178]. A list of probiotic bacteria administered in viral respiratory infections is shown in Table 1. In this section, we describe some of the promising research findings (Table 2).

Luoto and colleagues studied early modifications of immune responses and gut microbiota following *Lactobacillus rhamnosus* GG administration to reduce the risk of viral respiratory infections in preterm newborns during their first year of life [113]. They found a significant reduction in the frequency of VRIs, in particular rhinovirus infections, when administering specific probiotic metabolites such as galactooligosaccharides and polydextrose. They also observed immunomodulatory effects that conferred clinical benefits exceeding those due to interference with viral growth [113]. The rationale for the administration of probiotics for the prevention of VRIs is based on their capacity to diminish colonization of respiratory epithelia by pathogens and control mucosal resistance via activation of inflammasomes and systemic immune reactions [55, 79]. It has been demonstrated that early treatment with dietary *L. rhamnosus* GG in preterm newborns can have long-lasting effects and decrease the risk of VRIs. In separate studies, Kumpu and colleagues

Table 1 Clinical outcome of using probiotic bacterial strains for viral respiratory infections.

Bacterial strain	Viral respiratory infection	Outcome	Reference
Lactobacillus GG (LGG)	Respiratory tract infections	The study assessed the performance of LGG in the restriction of respiratory tract diseases in children attending daycare centers. Their results indicated that LGG treatment could be advised as a valid means of reducing the risk of upper respiratory tract diseases in children attending daycare centers.	[75]
Lactobacillus paracasei N1115	Upper respiratory tract infections (URTI)	The investigation was to evaluate whether yogurt enriched with a probiotic strain could benefit middle-aged and older adults suffering from severe URTIs in a randomized, blank-controlled, parallel-group trial. The study results recommended that yogurt with chosen probiotic strains such as N1115 may diminish the risk of severe upper tract diseases in the elderly. The augmentation of T-cell-mediated immune protection might be one of the critical underlying mechanisms by which probiotics help to alleviate infections.	[149]
Haemophilus influenzae, Streptococcus, Corynebacterium, Moraxella, *Staphylococcus aureus*	Respiratory syncytial virus (RSV)	The study assessed whether specific nasopharyngeal microbiota are correlated with distinct host transcriptomic profiles and infection severity in children infected with RSV. The study results showed that the interplay between RSV and nasopharyngeal microbiota might temper host immune responses, possibly altering the clinical severity of the disease.	[36]
Lactobacillus rhamnosus GG	Respiratory tract infections	The study hypothesized that early prebiotic or probiotic supplementation could decrease the risk of virus-associated RTIs throughout the first year of life in a cohort study on preterm infants. The results demonstrated that altering gut microbiota with specific prebiotics and probiotics might represent a novel and cost-effective approach to decreasing the risk of rhinovirus infections.	[113]
Lactobacillus rhamnosus GG	Respiratory illness	This study showed that long-term daily use of milk containing *Lactobacillus rhamnosus* GG decreased the rate of respiratory illnesses in children attending daycare centers (those who finished the treatment course, and not the whole population).	[90]

Table 1 (continued)

Bacterial strain	Viral respiratory infection	Outcome	Reference
Lactobacillus rhamnosus GG	Respiratory tract infection	In this randomized, double-blinded, placebo-controlled 28-week intervention, nasopharyngeal swab specimens were obtained from children suffering from respiratory infections who were given normal milk (N = 97) or the same milk enriched with the probiotic *Lactobacillus rhamnosus* GG (N = 97). This study showed that children taking *Lactobacillus rhamnosus GG* had a shorter time with respiratory manifestations than children in the control group. However, probiotic treatment did not decrease the amount of viral shedding or the severity of respiratory signs.	[93]
Lactobacillus casei rhamnosus	Respiratory tract infection	This study examined the treatment and prevention performance of three commercial probiotic products on pediatric infectious diseases in a double-blind, randomized, controlled trial. This investigation showed that *L. casei* could alleviate bacterial, viral, and respiratory infections.	[106]
Bifidobacterium lactis subs *plactis* Bl-04 *Lactobacillus acidophilus* NCFM *Bifidobacterium animalis* subsp. *Lactis* Bi-07	Respiratory tract infection	This study aimed to examine the effect of supplementation with probiotics on respiratory and gastrointestinal disorders in healthy working men and women. This study indicated that the Bl-04 probiotic taken as a nutritional supplement was beneficial for decreasing the risk of URTI in healthy, physically active adults.	[201]
Lactobacillus gasseri PA 16/8, *Bifidobacterium longum* SP 07/3, *B. bifidum* MF 20/5	Common cold	This study evaluated the effects of using *L. gasseri* PA 16/8, *B. longum* SP 07/3, and *B. bifidum* MF 20/5 (5×10^7) cfu/tablet) for at least three months on the severity of manifestations and the frequency and duration of the common cold. This study showed that the intake of probiotic bacteria for at least three months significantly decreased the duration by approximately two days and diminished the severity of manifestations.	[38]
Lactobacillus fermentum (CECT5716)	Influenza	The co-adjuvant capacity of the oral administration of the breast-milk-isolated strain *Lactobacillus fermentum* (CECT5716) with an anti-influenza vaccine was evaluated. This study demonstrated that oral treatment with *L. fermentum* CECT5716 potentiates the immunologic responses to the anti-influenza vaccine and may enhance protection by boosting the T-helper type 1 response and eliciting the virus-neutralizing antibodies.	[135]

Table 1 (continued)

Bacterial strain	Viral respiratory infection	Outcome	Reference
Lactobacillus casei DN-114 001	Respiratory tract infection	The study investigated the ability of a dairy product containing the probiotic strain *Lactobacillus casei* DN-114 001 to protect independently-living elderly individuals against widespread infectious diseases. The results showed that the consumption of the probiotic was correlated with a reduced duration of routine infectious disorders, particularly URTIs such as rhinopharyngitis, compared with a control group.	[63]
Lactobacillus bulgaricus OLL1073R-1	Respiratory tract infection	This study evaluated whether the consumption of yogurt fermented with *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 had a protective effect against the common cold. The results showed that the consumption of yoghurt fermented with *L. bulgaricus* OLL1073R-1 increased natural killer cell activity and reduced the risk of catching a common cold in the elderly.	[119]
Porphyromonas spp., *Granulicatella* spp., *Fusobacterium* spp., *Lachnospiraceae* spp., *Haemophilus* spp.	Influenza	This study evaluated whether precise bacterial community structures in the nasopharynx of children during hospitalization are correlated with various clinical consequences of influenza. The results showed that the expanded bacterial diversity in the nasopharynx of children was considerably correlated with influenza severity. Patients with severe influenza showed a reduced relative frequency of *S. aureus* and increased abundance of *Prevotella*, *Streptobacillus*, *Porphyromonas*, *Granulicatella*, *Veillonella*, *Fusobacterium*, and *Haemophilus* in their nasopharynx. This suggests the potential application of microbial signatures as prognostic biomarkers of influenza outcome.	[96]

surveyed the ability of *L. rhamnosus* GG to decrease the incidence and/or signs of viral infection in children [92]. They found that the duration of respiratory symptoms was notably shorter lower in children who received *L. rhamnosus* GG than in those who did not. However, in their study, *L. rhamnosus* GG treatment did not significantly decrease the incidence or symptoms of VRIs in the nasopharynx. This could be due to the comparably low dose of diurnal *L. rhamnosus* GG (10^8 CFU) administered in this trial compared with others [92].

Kumpu and colleagues identified several types of respiratory viruses in the nasopharynx of infants visiting daycare centers [92]. Hojsak and colleagues also investigated the ability of *Lactobacillus* GG to restrict gastrointestinal and respiratory tract infections (RTIs) in infants who visited daycare centers [75] and that the daily consumption of probiotics significantly decreased the incidence of upper RTIs.

In another study by Kumpu and colleagues, the effect of long-term daily consumption of milk containing *L. rhamnosus* GG was investigated on children with VRIs [91]. According to their results, a statistically significant reduction in respiratory manifestations was observed in the *L. rhamnosus* GG group compared to children in the placebo group. Lin and colleagues compared the efficacy of commercial probiotics on the incidence of VRIs in infants [110]. An exciting result of their work was that probiotic supplementation reduced the number of clinical visits, notably among those who had frequently been referred to physicians [110]. It concomitantly increased the number of infants who did not visit a physician during the interference phase, and the use of *L. rhamnosus* decreased VIs by 18% in the interference

Table 2 Candidate probiotics in various clinical COVID-19 evaluations

Title	Country	Description	References
Study to Evaluate the Effect of a Probiotic in COVID-19 (NCT04390477)	Spain	In this recent perspective case-control pilot investigation, the potential influence of a probiotic mix on symptoms, duration of hospitalization and the rate of patients with negative PCR after infection with SARS-CoV-2 was evaluated. In this study, the investigators demonstrated a positive effect of probiotics on the gut microbiome and less severe clinical symptoms of the disease. The daily oral capsule containing probiotic strains with maltodextrin as an excipient that was administered for 30 days.	[30]
Evaluation of the Probiotic *Lactobacillus coryniformis* K8 on COVID-19 Prevention in Healthcare Workers (NCT04366180)	Spain	This study aims to assess the effects of *Lactobacillus coryniformis* K8 on the frequency and severity of COVID-19 in health workers exposed to the virus. This is a preventive study. The probiotic group will receive one capsule with *Lactobacillus* K8 per day (3×10^9 cfu/day) for two months.	[27]
Evaluation of the effect of taking Newgen beta-gluten probiotic composite powder to nutrition intervention of patients with novel coronavirus pneumonia (COVID-19) (ChiCTR2000030897)	China	This study intends to use beta-gluten probiotic composite powder as nutrition interference in subjects with COVID-19 to investigate the practical clinical pathway, which is of great importance for the prevention and therapy of SARS-CoV-2. This study plans to collect 20 random subjects. The study cases will randomly be allocated to the nutrition interference group and the control group.	[78]
A clinical study for probiotics in the regulation of intestinal function and microflora structure of novel coronavirus pneumonia (COVID-19) (ChiCTR2000029999)	China	Aims of this study included: (1) investigating intestinal impairment in the course of new coronavirus pneumonia, and blood or imaging indicators of clinical intestinal impairment; (2) using metagenomics and macro virus genomics to investigate the dynamic variations of intestinal flora abundance and structure and metabolomics before and after intervention with microecological agents as well as their impact on the clinical outcome. (3) The use of specific strains and metabolites to promote probiotics and nutritional products for novel influenza.	[167]

Table 2 (continued)

Title	Country	Description	References
A prospective, multicenter, open-label, randomized, parallel-controlled trial for probiotics to evaluate efficacy and safety in patients infected with 2019 novel coronavirus pneumonia (COVID-19) (CHICTR2000029974)	China	Inclusion criteria included: 1. The patient or his/her legal guardian consented to participate in the investigation and signed the informed consent. 2. Those diagnosed with mild or moderate novel coronavirus pneumonia (NCP) or those with severe NCP could take medicines orally or via a stomach tube. NCP cases were identified based on the following pathogenic evidence: 2-1) The presence of novel coronavirus in respiratory samples or blood specimens was confirmed by real-time RT-PCR. 2-2) The genetic sequence of the virus discovered in respiratory or blood specimens was highly similar to that of the known coronavirus. 3. Patients were adults aged ≥ 18 years. 4. The subjects could interact well with researchers and complete the study according to the protocol. Exclusion criteria: 1. The inability to consume medications or take medicine via a stomach tube; critical severe NCP 2. Severe hypo-immunity due to, but not restricted to, one of the following: 2-1) HIV/AIDS, the status was still variable in the manner of mediation, and the last measured level of $CD4^+$ T lymphocytes was less than 200. 2-2) Organ transplantation and systematic immune therapy. 2-3) Long-term systematic management with corticosteroids described as a daily intake of over 40 mg of prednisone or equivalent in the 14 days before the first medication. 3. Allergy to test medicines. 4. Poor conversation skills, comprehension, ability to follow the protocol to finish the study. 5. Severe illnesses such as malignancy or mental illness, or inability to participate in the study according to investigators' judgment.	[148]
Washed Microbiota Transplantation for Patients With 2019-nCoV Infection (NCT04251767)	China	Gut dysbiosis co-exists in cases with SARS-CoV-2 pneumonia. Some of these patients would improve secondary bacterial infections and antibiotic-associated diarrhea (AAD). The current study on employing washed microbiota transplantation (WMT) as saving therapy in critically ill patients with AAD demonstrated the critical clinical advantages and safety of WMT. This clinical trial aims to evaluate the outcome of WMT coupled with standard treatment for patients with SARS-CoV-2 pneumonia, particularly for those with dysbiosis-related conditions.	[25]
Efficacy of *L. plantarum* and *P. acidilactici* in Adults With SARS-CoV-2 and COVID19 (NCT04517422)	Spain	Clinical research focuses on evaluating the influence of a combination of *L. plantarum* and *P. acidilactici* as a coadjuvant in adults positive for SARS-CoV-2 with mild clinical COVID-19 symptoms. The primary purpose is to evaluate how this combination of probiotics decreases the risk of development of moderate or severe COVID and risk of death. Additionally, this RCT is beginning to examine the benefits of the combination of these strains to modulate fecal microbiome and investigate how this correlates with clinical improvement.	[26]

Table 2 (continued)

Title	Country	Description	References
Symbiotic Therapy of Gastrointestinal Symptoms During Covid-19 Infection (Syn-Cov) (NCT04420676)	Austria	Researchers hypothesize that the consumption of Omni-Biotic® 10 AAD can diminish the duration of diarrhea in COVID-19 patients. Researchers further hypothesize that Omni-Biotic® 10 AAD can decrease stool frequency, improve stool consistency, improve other gastrointestinal symptoms of COVID-19, lessen disease duration and severity, reduce intestinal inflammation and improve dysbiosis. The investigators aim to perform a randomized, double-blind, placebo-controlled study using telemedicine in patients with COVID-19.	[28]
Oxygen-Ozone as Adjuvant Treatment in Early Control of COVID-19 Progression and Modulation of the Gut Microbial Flora (PROBIOZOVID) (NCT04366089)	Italy	Italy was the first European country influenced by a severe outbreak of the SARS-CoV-2 epidemic, with high morbidity and mortality correlated with the disease. In light of its pandemic spread and the minimal therapeutic options, COVID-19 is deemed an unusual global health challenge. Hence, the evaluation of new resources, designed in the first instance for other pathologies but potentially active against COVID-19, represents a preference in clinical investigations. This is an interventional, non-pharmacological, open, randomized, prospective, non-profit study on the adjuvant use of oxygen-ozone therapy plus probiotic supplementation in the early control of disease progression in patients with COVID-19. Contextually, all cases are treated with the current standard of care based on the interim guidelines of the Italian Society of Infectious and Tropical Diseases. The main purpose of the study is to evaluate the effectiveness of an ozone therapy-based intervention (accompanied by supplementation with probiotics) in containing the progression of COVID-19 and in preventing the need for hospitalization in intensive care units.	[30]
Efficacy of Intranasal Probiotic Treatment to Reduce Severity of Symptoms in COVID19 Infection (NCT04458519)	Canada	The current study is a randomized, single-blinded trial. In this study, patients with a diagnosis of COVID-19 infection within the past 96 hours and not needing hospitalization will be recruited into a trial of BID nasal irrigation for 14 days, followed by a 14 day observation period. Spraying will be performed with either Probiorinse probiotic nasal irrigation solution or NeilMed Sinus rinse. In this study, patients will be able to recognize their treatments, but study staff will be blinded.	[29]

group [110]. Probiotics, depending on the strain and species, can be potent modulators of the immune system [116, 117]. Lin and colleagues showed the effect of *Lactobacillus* spp. on antigen-specific IgG and cytokine reactions [110]. Specific *Lactobacillus* strains can induce myeloid DCs to activate T cells and induce the production of Th1 cytokines. They can therefore be considered potential biotherapeutic agents [130]. West and colleagues studied the effects of using a single strain, *Bifidobacterium lactis* subsp. *lactis* Bl-04, as a probiotic or a combination of *Lactobacillus acidophilus* NCFM and *Bifidobacterium animalis* subsp. *lactis* Bi-07 on pulmonary and gastrointestinal diseases in healthy subjects [202]. They found that daily *B. lactis* Bl-04 supplementation led to a 27% decline in RTI incidence compared to a placebo. In seasonal infections similar to the common cold, a delay in disease incidence indicated an affirmative clinical advantage from supplementation.

Vrese and colleagues examined whether the consumption of probiotic bacteria for at least three months in winter/spring could affect the severity of signs, the frequency, and the duration of the common cold, as well as immune reactions in normal adults [39]. They showed that probiotic bacteria significantly decreased the average duration of infection and lessened the severity of symptoms [39]. These results were comparable to those of neuraminidase inhibitors (NIs), which, when used during the first 48 h of IV infection, decreased the severity of signs and decreased the infection duration by one day [39]. In contrast to NIs, probiotics can be administered as a part of the diurnal regimen and do not impose further costs. The reduced severity and duration of cold symptoms may be due to immunostimulatory effects, and in response to specific probiotic strains, distinct cell lines, such as peripheral blood mononuclear cells, monocytes, DCs, and intestinal cells from human mucosa have been shown to secrete pro- or anti-inflammatory cytokines and co-stimulatory molecules [15, 24, 71]. According to a study by Vrese and colleagues, CTLs, along with $CD8^+$ T cells (suppressor cells), increased significantly throughout the initial 14 days of supplementation in a probiotic-treated group that was compared to control subjects [39].

Although vaccination against IVs is known to prevent severe illnesses, particularly in communities at risk, in some cases, vaccine efficacy is low, suggesting the need to develop new adjuvant components [122]. Some *Lactobacillus* strains (e.g., *Lactobacillus fermentum* CECT5716) have been suggested as suitable coadjuvants for increasing antibody production after IV vaccination [37]. During IV infection, innate immunity forms an early barrier against the virus via executive cells, molecules, and agents involved in the restriction of viral spread [105, 176]. In this regard, Olivares and colleagues showed that oral administration of *L. fermentum* CECT5716 led to an increase in NK cells 14 days after vaccination [134]. Although IgA and IgG provide the crucial protective humoral immunity induced by IV infection, these authors observed an enhancement of the specific anti-IV IgA response in subjects receiving probiotics, but no such effect on IgG or IgM levels was observed [134].

Guillemard and colleagues investigated the beneficial effect of *Lactobacillus casei* DN-114 001 for protection of older adults against common RIs [64]. In their study, fermented products were shown to decrease the duration of common RIs. More importantly, significant reductions were observed for all RIs, in particular, rhinopharyngitis. In an unblinded trial, elderly individuals immunized against influenza and pneumococcus demonstrated a lower frequency of disease, particularly viral respiratory infections, after administration of a nutritional complement consisting of *L. paracasei* and additional nutrients such as vitamins [19]. The reduced duration of RIs could be correlated with a lowered risk of medical complications, because infections with human rhinoviruses, the most prevalent cause of RIs, were found to be correlated with a high incidence of prolonged disease and a lower rate of pulmonary disorders in older individuals [70, 188]. For instance, Guillemard and colleagues found that consumption of fermented dairy products containing *L. casei* DN-114 001 was linked to a significant reduction in the duration of common rhinopharyngitis, providing evidence that probiotics may have beneficial effects on RIs in the elderly [64].

Makino and colleagues assessed whether the consumption of yogurt fermented with *Lactobacillus bulgaricus* OLL1073R-1 improves immunity against RTIs such as the common cold and IV infections [119]. Their results showed that *L. bulgaricus* OLL1073R-1 significantly diminished the risk of common cold among the elderly. It was previously reported that 1073R-1 yogurt and its polysaccharides intensify NK cell activity in mice [118]. NK cells are involved in antiviral defense, and low NK cell activity has been linked to the development of common cold, pneumonia, acute bronchitis, and death in older adults [62, 133]. Hence, the effect of 1073R-1 yogurt is mainly associated with the immunostimulatory effect of polysaccharides formed by *L. bulgaricus* OLL1073R-1.

Potential role of commensal microbiota in protecting the respiratory tract against infectious agents

A notable difference in lung microbiota composition has been observed between SARS-CoV-2 pneumonia patients and healthy subjects, suggesting the occurrence of dysbiosis in the lung microbiota of COVID-19 patients [46]. *Streptococcus salivarius* is a prevailing commensal bacterium in the healthy oral and upper respiratory tract [46]. There have been several reports on interference by this bacterium with

the growth of potential pathogens [46]. Along with other oral commensals, *S. salivarius* is commonly found in the lung and is associated with maintenance of good health [46]. The lung microbiota of COVID-19 patients is significantly modified and enriched in potentially pathogenic bacteria [46]. Strain K12 is the best-studied strain of *S. salivarius* [46]. Establishment of an upper respiratory tract (URT) infection with strain K12 can significantly decrease the occurrence of many viral URT infections, both in children and in older adults, possibly owing to its ability to induce IFN-γ release and activate NK cells without triggering destructive inflammatory responses [16]. Although its efficacy against COVID-19 has never been investigated explicitly, its clinical potential as well as its safety profile, which can last >20 years following probiotic application, might encourage medical doctors to reconsider prescribing it as a supplement to help control viral respiratory infections and associated pneumonia by enhancing host immune functions.

Probiotic bacteria can inhibit colonization and establishment of infection by viral and bacterial pathogens [22]. For example, proteases generated by *Staphylococcus epidermidis* can degrade the biofilm structure of *Staphylococcus aureus* [82, 123, 152, 187]. In this regard, nasal administration of a bacterium that belongs to the healthy human microbiota benefits the patient by re-establishing a microbial balance and reducing the level of various pathogens in the airways [89].

IFN-λ is a significant immune regulator in various VIs in the epithelial layer (mucosa), and stimulation of IFN-λ production results in a quick response of immune cells to human respiratory viruses [53, 86]. IFN-λ is thought to be involved in the initial defense against viral attackers in the host respiratory system and plays a crucial role in local antiviral innate immunity [53, 86]. Nevertheless, our current knowledge about the modulators that contribute to the production of IFN-λ, particularly in natural RVIs, is limited. The human mucosal surface is exposed to elements of the external environment and is thus sensitive to colonization and invasion by numerous pathogens [47]. Mucosal immunity appears to have evolved to accommodate the interaction between the host and the mucosal microbiome, with protection mediated by the microbiome against infections from outside microbial pathogens [74]. Various inhaled microbial pathogens encounter immune cells soon after their first contact with respiratory mucosa, and the microbial community in the nasal passage affects the primary immune reactions directly [87]. Understanding the microbiome of human nasal mucosa could provide substantial knowledge about the susceptibility of the respiratory tract to viral infections and components involved in immune reactions, such as IFNs. In a study on the regulation of the homeostasis of the human immune system by its microbiome, Kim and colleagues evaluated the microbial composition of healthy nasal mucosa [87]. They subsequently evaluated whether nasal commensal microbes are involved in signaling as part of the defense mechanism against IVA [87]. They identified *S. epidermidis* as the most frequent microbial population. They found that *S. epidermidis* cells collected from nasal mucosa of healthy subjects accelerated the elimination of IVA from the nasal epithelium via immune responses mediated by IFN-λ [87]. In addition, nasal *S. epidermidis* cells from humans prevented IVA infection in mice by promoting innate immune reactions mediated by IFN-λ in the nasal mucosa [87]. There have been reports of a crucial mechanistic association between susceptibility to various VIs and innate nasal immunity mediated by the microbiome.

Compositional and structural variations in the host respiratory microbiota arising from various environmental factors have been predicted, and the host respiratory microbiome has been found to be important for immune protection [10, 151]. Therefore, an understanding of the composition of the respiratory mucosal microbiome and the substantial adverse effects of medications on these microbial communities is needed to develop novel methods for treating and preventing RIs. Nasal mucosa cells are crucial players in immunological resistance to infections of the respiratory system. They are responsible for the filtration of various respiratory microbial pathogens from normal inhalation to pressurized airflow. Various RVs confront host immunity primarily in the lower and upper respiratory epithelia [67, 81]. Protection against various viral infections can be attributed to the innate immune mechanisms of the human nasal epithelium for counteracting invasions by respiratory viruses [87]. Therefore, researchers must focus on the involvement of nasal microbiota, particularly *S. epidermidis* strains, in mucosal innate immune defense strategies against viruses. In the respiratory tract, innate immunity contributes to antiviral immunity through secretion of IFNs [139, 144]. The activity of type 1 IFNs in the stimulation of antiviral innate and adaptive immune reactions has been studied extensively [136, 198]. IFN-λ is an important factor in antiviral reactions against influenza viruses and rhinoviruses in human lungs [87]. It is also the prevailing IFN stimulated by IVA and is involved in the primary defense barrier against VIs in nasal epithelial cells [87]. Studies have focused on studying the host immune moderators involved in the production of IFN-λ cytokines in the nasal mucosal layer, suggesting that the nasal microbiota may control IFN-λ production [87]. Kim and colleagues demonstrated that *S. epidermidis* has potent antiviral activity in the nasal epithelium and that all antiviral reactions induced by this organism are mediated by IFN-λ, and not IFN-γ, IFN-β, or IFN-α [87].

Recent data have shown that commensal *S. epidermidis* can be sensed by Toll-like receptor 2 in the host nasal epithelium. However, IFN-λ stimulated by *S. epidermidis* via signal transduction (ST) is associated with transcription factors (TFs). IFN regulatory factor 3 (IRF3) and IFN

regulatory factor 7 (IRF7) are TFs that are associated with IFN-λ and IFN production by direct ST via the phosphorylation of IRF7 and IRF3 [32, 217]. While IRF3 is usually thought to be required for triggering of IFN transcription, a deficiency in IRF3 has been shown to have little effect on the expression of IFN [32]. In contrast, the absence of IRF7 significantly reduces IFN production in the host airway epithelium [32]. Kim and colleagues showed that *S. epidermidis* cells as nasal commensals can increase the phosphorylation of IRF7 relative to IRF3 and eventually stimulate immune responses related to IFN-λ in the host nasal epithelium [87]. However, they did not determine the molecular mechanism that prompted phosphorylation of IRF7 by *S. epidermidis*. It can be speculated that free molecules from *S. epidermidis* interact with IRF7 and prompt strong IFN-related antiviral immune reactions in the airways. Comparative genomic studies can explain how innate immunity reactions are stimulated to react with symbiotic commensals. These findings provide further information about how the nasal commensals enhance IFN-dependent innate immunity against IVA infections to protect the respiratory tract. These findings indicate that, as the prevailing nasal commensal in humans, *S. epidermidis* improves protection against IVA infection in nasal epithelium via IRF-7-dependent production of IFN-λ and prevents IVA lung infection via the suppression of IVA replication in nasal mucosa. Therefore, intranasal inoculation with *S. epidermidis* might be an effective way of preventing viral respiratory infections through the stimulation of IFN-λ-related innate immune reactions.

Most importantly, in a promising approach, researchers from Stanford University have started a clinical trial to investigate whether IFN-λ-treatment can help COVID-19 patients and decrease transmission of virus, since IFN- λ appears to help control viral respiratory diseases such as influenza and SARS [121].

Dysbiosis of gut microbiota in COVID-19 patients

Dysbiosis, which is defined as a persistent imbalance of the microbiota, has been associated with several intestinal and extraintestinal diseases [11]. Studies have indicated an association between the pharyngeal microbiota and SARS-CoV-2 infection [18]. According to these studies, the composition of the pharyngeal microbiota change with age, with older individuals having a less diverse microbial community [5]. This might contribute to the higher susceptibility of the aged to COVID-19, but more investigations are needed to confirm this. Dysbiosis can lead to an inflammatory milieu that can be exploited by SARS-CoV-2 [5]. It has been found that cytokines are elevated following COVID-9, possibly leading to a "cytokine storm," which can be more harmful than the virus itself [5, 209]. Recent studies have recognized bacterial markers associated with sensitivity to SARS-CoV-2 infection [59]. Based on the data from COVID-19 subjects, a blood proteomic risk score (PRS) was designed to predict the progression and severity of SARS-CoV-2 disease [59]. It was found that *Ruminococcus gnavus* had a positive correlation with inflammation, while *Clostridia* spp. showed a negative correlation [59]. A strong association was also demonstrated between the severity of SARS-CoV-2 infection in the elderly and the bacteria mentioned above as well as the PRS. This study investigated a subgroup of 301 healthy individuals over three years [59]. Interestingly, microbiome modifications were indicated by the PRS, implying that dysbiosis stimulated protein modifications [59].

The SARS-CoV-2 S glycoprotein binds to human ACE2 [205], an enzyme that is expressed in esophageal and intestinal epithelia as well as lung tissue, and this could contribute to dysbiosis in the normal flora and gastrointestinal symptoms following SARS-CoV-2 infection [61, 76, 102]. Moreover, SARS-CoV-2 and its genetic material have been identified in the faeces of patients with diarrhea [95, 216, 218] indicating the presence of SARS-CoV-2 in the human gastrointestinal tract and its possible transmission by the fecal-oral route.

The potential effects of probiotics on coronavirus infections and COVID-19

Many studies are being undertaken to investigate the effects of probiotics on several coronavirus strains, as they are safe and capable of modulating immune reactions [83, 131]. In addition, a clinical study has described an imbalance in intestinal microbiota and significantly reduced levels of probiotics such as *Lactobacillus* and *Bifidobacterium* in COVID-19 cases, possibly facilitating secondary bacterial infections [206]. A recent study has demonstrated that porcine epidemic diarrhea virus (PEDV) can be inhibited using cell-free supernatants or live lactic acid bacteria [171]. In that study, using CPE reduction assays and qualitative immunofluorescence, it was shown that probiotics could be useful in eliminating PEDV in a strain-specific manner [171]. In a different study, *Lactobacillus casei* was employed as a vehicle for the DC-targeting peptide (DC-pep) along with the PEDV core neutralizing epitope (COE) antigen [196]. It was shown that a genetically modified *Lactobacillus casei* oral vaccine could induce the production of IgG (systemic) and SIgA antibody (mucosal) in a murine model [196]. Several other studies have employed various probiotics to present PEDV genes or antigens of interest [111, 114, 196, 197]. Liu et al. [111] showed that an altered *Lactobacillus plantarum*

strain had antiviral activity against coronavirus infections in a porcine intestinal epithelial cell line.

The sequencing of microbiota in COVID-19 patients has shown a significant decrease in bifidobacteria and lactobacilli as the prevailing symbiotic bacteria and an increase in the number of opportunistic bacteria such as *Corynebacterium* or *Ruthenibacterium* [51]. The immune system in the lung can be affected by intestinal dysbiosis, which therefore might aggravate respiratory distresses caused by COVID-19 [23]. In this regard, oral bacteriotherapy might be useful. Some strains of the genera *Lactobacilli* and *Bifidobacterium* have a protective function against IV, RVs, RSV, adenovirus, and pneumovirus [20, 115]. As no definitive treatments or guidelines have been established for COVID-19, d'Ettorre et al. [33] investigated the efficacy of oral bacteriotherapy as an additional curative option to prevent the progress of COVID-19. Their bacterial formulation included *Streptococcus thermophilus* 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 [33]. They investigated two groups: 1) patients treated with hydroxychloroquine, tocilizumab, and antimicrobials alone or in combination and 2) patients treated with oral bacteriotherapy plus a conventional medication regimen [33]. Their results showed that patients who also received bacteriotherapy had a higher survival rate and a lower need for intensive resuscitation [33]. The predicted risk of developing respiratory collapse due to COVID-19 infection was lower in patients who received oral bacteriotherapy [33]. When other manifestations of COVID-19 were considered, including asthenia, pyrexia, cough, dyspnea, diarrhea, and myalgia, a notable improvement was already seen as early as 24–48 h after the start of the bacteriotherapy [33]. The authors hypothesized that in COVID-19 patients, bacterial compounds with the "proper" immunological and biochemical profiles could promote host immunity. The antioxidant pathway nuclear factor erythroid 2p45-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) were elevated in response to the bacterial formulation [21]. These molecules can modulate oxidative stress, thereby exerting antiviral functions [33]. Antiviral activity of Nrf2 and HO-1 has been observed against human immunodeficiency virus (HIV), IV, RSV, Ebola virus, and dengue virus [45, 48, 69, 72, 182]. Interestingly, the beneficial characteristics of HO-1 include activity against respiratory viruses.

COVID-19 is a severe pulmonary disease, with manifestations including fever, cough, breathing difficulty, fatigue, muscle pain, diarrhea, sore throat, and abdominal disorders [137, 170]. While most patients experience mild symptoms, some experience viral pneumonia and multiple organ failure [211]. Until now, COVID-19 prevention has been based on maintaining good hygiene by washing hands and avoiding contact with infected individuals [138], but reinforcing the immune system might also be helpful (Fig. 2) [173]. In the human body, trillions of beneficial bacteria live in homeostasis to help their host to digest food, produce precursors for neurotransmitters, and enhance the immune response against pathogens [12]. It has been found that microbiota dysbiosis is associated with several disorders [42]. Probiotic bacteria can interact with microbiota to reinforce the immune system and prompt immune reactions [203, 208]. Some probiotics have been found to prevent bacterial and viral infections or decrease their duration. *Lactobacillus reuteri* DSM 17938 has been shown to be protective against RI signs and gastrointestinal disorders such as diarrhea in children [2, 65, 200]. It has also been found that probiotics can be useful in enhancing vaccine immunogenicity, increasing the rate of seroconversion and seroprotection in adults immunized with flu vaccines [99]. Additionally, probiotics, together with vitamins, can enhance the immune system. For example, vitamin D can modulate immune reactions [7].

Although its pathophysiological mechanism has not been entirely elucidated, COVID-19 is known to affect the lungs and airways [210]. However, since immunological mechanisms play an important role in the course of the disease, a novel therapeutic approach involving probiotic bacterial strains might be promising because of their involvement in immune modulation [120, 204, 210]. In this regard, interleukin-17 is a pro-inflammatory cytokine with a crucial role in the adaptive immune system, and it is also a potent inducer of endoplasmic reticulum stress autophagy through inositol-requiring enzyme 1 [17, 88]. By blocking this interleukin, autophagy mediated by endoplasmic reticulum stress and inflammation can be prevented [60, 88]. Interestingly, *Bifidobacterium* strains have an inhibitory effect on interleukin-17 [17]. Consequently, administration of high doses of *Bifidobacterium* strains such as *B. animalis* subsp. *lacti* BB-12 as well as lipopolysaccharides from this strain [164, 174] could be used as a therapeutic and preventive approach in COVID-19 patients, particularly in those with gastrointestinal symptoms.

A biotechnology company (Biosearch Life) found that *Lactobacillus coryniformis* CECT5711 K8 can decrease virus transmission during respiratory infections in older adults. Accordingly, they assessed the efficacy of K8 in diminishing the frequency or severity of SARS-CoV-2 in a clinical trial [80]. In a study by Xu et al. [207], some COVID-19 patients develop intestinal microbial dysbiosis with lowered levels of probiotics such as *Bifidobacterium* and *Lactobacillus*. Therefore, gastrointestinal health should be assessed in all COVID-19 patients. The application of probiotics and nutritional support has been shown to maintain intestinal microbiota equilibrium and decrease the hazard of secondary bacterial infections [207]. Recent work by

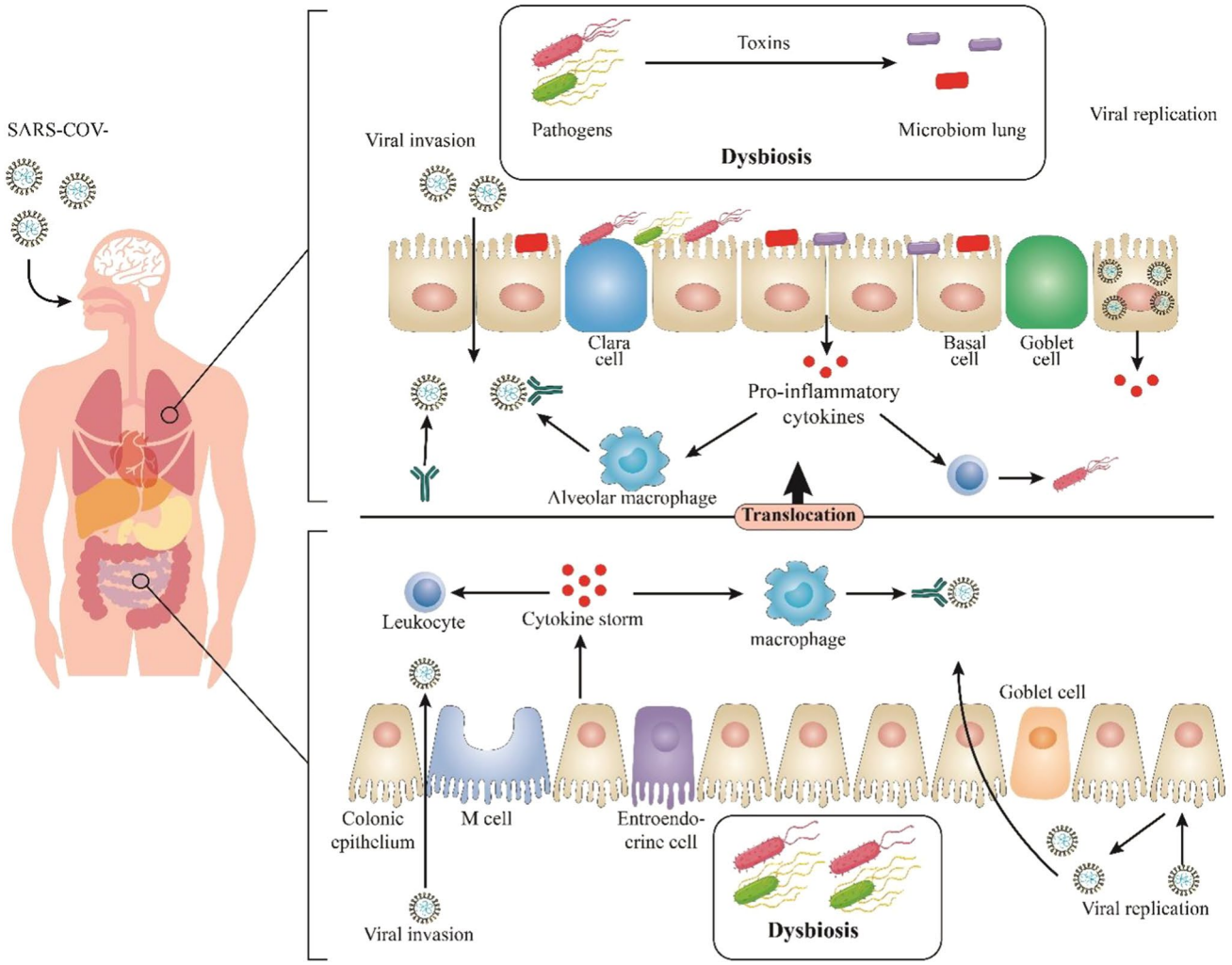

Fig. 2 The antiviral effects of probiotics during SARS-CoV-2 infection

Yoon et al. showed that *Lactobacillus gasseri* could decrease the spread of SARS-CoV-2 by inhibiting purine as the viral energy source, as this source is required for mutation of the virus; hence, it can be expected that probiotic bacteria can be considered as potent supplements to suppress the spread of COVID-19 by inhibiting purine activity [157]. However, the reinforcement of immune reactions by safe strategies, such as maintaining a normal gut microbial heterogeneity and preventing colonic dysbiosis in the aged, children, and the general community, is probably beneficial for recovery from COVID-19. A balanced diet with probiotics and vitamin supplementation can help to reinforce the immune system against SARS-CoV-2.

Several metabolites derived from *Lactobacillus plantarum*, including plantaricin, lactic acid, acetic acid, and gamma-aminobutyric acid, can boost the immune response against viral pathogens [4]. In order to initiate infection, the virus must recognize its receptor. Lie et al. [103] suggested that the binding affinity of SARS-CoV-2 for hACE2 is linked to the rate of viral transmission and the severity of disease. SARS-CoV-2 enters host cells through S glycoprotein homotrimers on the viral surface [181, 191]. The S glycoprotein binds human ACE2 receptors with high affinity [189]. Anwar et al. [6] targeted both the S glycoprotein and ACE2 using a plantaricin metabolite and showed that plantaricin, via binding to the receptor binding domain (RBD), prevents the entry of SARS-CoV-2. They also targeted the viral RNA-dependent RNA polymerase (RdRp), which is required for viral replication. Anwar et al. [6] chose four metabolites produced by *Lactobacillus plantarum* (metabolites derived from plantaricin, including plantaricin BN, plantaricin JLA-9, plantaricin W, and plantaricin D) to design antiviral drugs that, based on computer simulations, showed the potential to be employed as probiotics to delay, prevent, and eliminate SARS-CoV-2 in individuals by hindrance or inactivation of RdRp, prevention of the emergence of newly budded virus

progeny, inhibition of the RBD fragment of the S protein, or interference with other proteins such as the ACE2 receptor. They used computational analysis to predict the antiviral activity of plantaricin compounds through several different mechanisms. Metabolic products of *Lactobacillus plantarum* inhibit viral entry by interacting with RdRp, RBD, and ACE2 [1, 6]. Blocking the S protein, a major structural protein with a pivotal function in the life cycle of SARS-CoV-2, could be one of the most promising strategies [6]. This was confirmed by a molecular model that established the durability of the networks of plantaricin w and SARS-CoV-2 (RdRp, RBD, and ACE2 receptor) [6]. Computational and molecular models can accurately identify drugs that can be repurposed without requiring clinical trials. Moreover, it would be challenging to discover a medication that has a more favorable protection profile or a lower cost than macrolides. The use of plantaricin metabolites under proper medical supervision should be considered as a temporary measure until a definite antiviral drug is discovered for COVID-19.

A promising probiotic-based oral candidate vaccine against SARS-CoV-2

Several vaccines have been developed against SARS-CoV-2, and others are undergoing clinical trials [54, 192, 213]. Injected vaccines are costly and require expert administration, whereas, oral vaccines are more affordable, simple to store, easy to administer, and bio-friendly [94, 162, 166]. It has also been shown that oral vaccines can induce the robust production of specific IgG and IgA as well asTh1 and Th17 responses, thereby inhibiting viral replication in the respiratory tract and intestinal mucosa [109, 132, 195]. Thus, an efficient oral vaccine for SARS-CoV-2 would be of great benefit.

Lactic acid bacteria are potentially suitable bacterial vectors for oral DNA and protein delivery. They are frequently present in the human intestine and are beneficial in several gastro-intestinal and inflammatory diseases [43, 77, 159, 163, 168, 172]. *L. plantarum* is generally known as a probiotic that can be employed in food, vaccines, and medication [9, 112, 153–156, 165]. Therefore, Wang et al. [194] developed an *L. plantarum* expression system for SARS-CoV-2 S protein production. By optimizing the codon usage of the S gene, the S protein was efficiently presented on the bacterial surface, leading to the generation of many misfolded peptide chains. This protein showed strong reactivity with an anti-HA-tagged rabbit polyclonal antibody and SARS-Cov-2-S-protein-specific monoclonal antibodies [194]. The stability of the immunogenic protein is crucial for oral vaccines. Therefore, they examined the stability of the S protein presented on the bacterial surface and found that it was resistant to heat and low pH. The expression level of this protein was elevated following exposure to 0.2% bile salt, implying that the recombinant form of *L. plantarum* Lp18:S could be applied as an oral vaccine for COVID-19 [194].

Conclusion

SARS-CoV-2 is a newly emerging pathogen, and researchers are still in the early stage of understanding how this virus acts and the mechanisms by which it induces an immune response. Although the advantages of drugs and vaccines for the treatment and prevention of VIs have been demonstrated, their efficiency can be limited by changes that occur in viral populations, making it challenging to apply an entirely practical approach to prevent viral infections. However, the administration of probiotics can be beneficial in preventing VRIs, including COVID-19, and probiotic therapy may be considered as an alternative for the amelioration and/or prevention of COVID-19 disease. Overall, the application of probiotic bacteria against COVID-19 appears to be promising, both in terms of vaccination and treatment.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

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