



# Probiotics as Adjunctive Treatment for Patients Contracted COVID-19: Current Understanding and Future Needs

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## OPEN ACCESS

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equally to this work

### Specialty section:

This article was submitted to  
Nutrition and Microbes,  
a section of the journal  
Frontiers in Nutrition

**Received:** 19 February 2021

**Accepted:** 17 May 2021

**Published:** 10 June 2021

### Citation:

Peng J, Zhang M, Yao G, Kwok L-Y  
and Zhang W (2021) Probiotics as  
Adjunctive Treatment for Patients  
Contracted COVID-19: Current  
Understanding and Future Needs.  
*Front. Nutr.* 8:669808.  
doi: 10.3389/fnut.2021.669808

The coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which rages all over the world and seriously threatens human life and health. Currently, there is no optimal treatment for COVID-19, and emerging evidence found that COVID-19 infection results in gut microbiota dysbiosis. The intestinal microbial richness of patients of COVID-19 does not return to normal levels even six months after recovery, but probiotic adjunctive treatment has been found to restore gut homeostasis. An updated PubMed search returned four finished clinical trials that supported the use of probiotics as adjunctive treatment for COVID-19, while at least six clinical trials aiming to investigate beneficial effects of probiotic intake in managing COVID-19 are currently in progress worldwide. Here in we tentatively summarized the understanding of the actions and potential mechanisms of probiotics in the management of COVID-19. We also highlighted some future needs for probiotic researchers in the field. The success in using probiotics as adjunctive treatment for COVID-19 has expanded the scope of application of probiotics, meanwhile deepening our knowledge in the physiological function of probiotics in modulating the gut-lung axis.

**Keywords:** COVID-19, SARS-CoV-2, acute respiratory disease, pneumonia, probiotics, adjunctive treatment, gut-lung axis

## INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been raged across the globe since the end of 2019, seriously threatening human life and health (1, 2). Yet, the number of COVID-19 cases is still growing around the world. The severity of COVID-19 has brought and will certainly continue to bring tremendous financial and medical burdens to the society; thus, cost-effective health management strategies are urgently needed.

The symptoms of COVID-19 include fever, dyspnea, dry cough, upper and/or lower respiratory tract symptoms, myalgia, fatigue, diarrhea, or a combination of these 3–6 days after exposure (3–5). Other symptoms include headache, sore throat, rhinorrhea, and gastrointestinal disorders (4, 6). At the beginning of the outbreak, several drugs have been applied to manage the disease, including remdesivir and favipiravir. Among them, remdesivir was found to be the most promising drug that effectively cured the first COVID-19 patient in the United States (7). Currently, multiple effective

vaccines have been developed and are available to people worldwide. However, the decrease in gut microbiota richness and dysbiosis in patients with COVID-19 did not return to normal levels even six months after recovery, and the persistent gut dysbiosis was linked with the severity of disease and inflammatory reaction (8). Previous studies have shown that microbial diversity is a key determinant of microbial ecosystem stability (9, 10). A stable intestinal ecosystem enhances colonization resistance against opportunistic pathogens, while malnutrition hinders the recovery of intestinal health and lung function of patients with COVID-19 (11–13). Therefore, targeted auxiliary microecological therapy that helps restore healthy gut microbial communities is anticipated to accelerate full recovery from COVID-19 (8).

Probiotics are live microbes that, when administered in adequate amounts, confer health benefits on their hosts (14). To date, four clinical studies around the world have successfully applied probiotics as adjunctive treatment in managing COVID-19 (5, 15–17), while there are more than six undergoing clinical trials (18–20). The present review summarized the understanding of the actions and potential mechanisms of probiotics in the management of COVID-19, and highlighted some future needs for probiotic researchers in the field.

## PROBIOTICS AS ADJUNCTIVE TREATMENT FOR PATIENTS CONTRACTED COVID-19

In response to the outbreak of COVID-19, a Chinese infectious disease scientist proposed a treatment plan called “four-antibody, two-balance,” which was successfully implemented for treating SARS-CoV-2-associated acute respiratory distress syndrome (16). The four antibodies represented antiviral, antishock, antihypertension, and anti-infection therapy, while the “two-balance” referred to acid-base balance of water electrolysis and microecological balance (16). The microecological balance was considered to be of particular importance in the treatment, as microecological imbalance would lead to secondary infection of bacteria after recovering from the viral infection (16).

An updated PubMed search recovered four finished clinical studies from different countries that found positive effects of applying probiotics as adjunctive treatment in COVID-19. For example, Wu et al. found that taking a large dose of probiotics as adjuvant treatment significantly improved the symptoms of the disease, accompanied by the reduction in inflammation and recovery from gut microbiota abnormalities (17). A case study report found that some COVID-19 patients suffered from microbial dysbiosis characterized by decreased levels of intestinal *Lactobacillus* (*L.*) and *Bifidobacterium* (*B.*) (16). Xu et al. observed that most COVID-19 patients with relatively mild symptoms had received probiotics (5). Baud et al. summarized data from a large body of human studies and listed different probiotics that might have relevance to lowering burden brought by COVID-19, including *Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Lactobacillus gasseri*, *Bifidobacterium bifidum*, *Bifidobacterium*

*longum*, *Bifidobacterium breve*, *Leuconostoc mesenteroides*, and *Pediococcus pentosaceus* (15). Currently, there are at least six ongoing clinical trials aiming to investigate the beneficial effects of applying probiotics as adjunctive treatment in managing COVID-19 (18–20). It is noteworthy that a research scientist from Rutgers University designed a microbiota formula for early management of COVID-19 (20). This formula is a new prescription targeting to regulate the gut microbiota, aiming to prevent severe complications and hospitalization in high-risk patients of COVID-19 who suffer from underlying conditions like obesity or type-2 diabetes (20). The US Food and Drug Administration has approved the new formula for new drug clinical trial in a record time (20). Although this formula is different from ordinary probiotics-based products, the novel ecological approach focusing on managing the gut microbiota seems promising.

## THE UNDERSTANDING OF THE ACTIONS AND POTENTIAL MECHANISMS OF PROBIOTICS IN THE MANAGEMENT OF COVID-19

The study of human microflora and the function of probiotics can be traced back to the longevity theory proposed by Élie Metchnikoff, a famous Russian scientist who won the Nobel Prize in 1908. Over the last decades, the advent of high-throughput sequencing technologies has revealed much information of the mechanisms behind the health-promoting effects of probiotics in maintaining gut homeostasis. A number of random clinical trials (RCTs) were performed to evaluate the beneficial role of probiotics in adjunctive treatment of various gastrointestinal diseases, such as inflammatory bowel disease, irritable bowel syndrome, and antibiotic-associated diarrhea (21). Direct and indirect evidence of health outcome data generated from various clinical trials suggested that effective probiotic adjunctive treatments rely largely on modulating the gut and lungs, and the gut-lung axis.

### Restoration of a Healthy Gut Microbiota

Probiotics may enhance restoration of a stable gut microbiota in the colonic environment and prevent colonization by pathogenic organisms via a number of mechanisms (22, 23). For example, probiotics can bind to gut epithelial cells and result in competitive inhibition against gut wall adhesion of pathogenic microorganisms (22, 24). Once adhered to the gut epithelial cells, probiotics release substances that prevent the growth of pathogens and modulate intestinal permeability (22). In addition, probiotics can restore the intestinal health by attenuating inflammation and strengthening the epithelial barrier (25, 26). Firstly, probiotics can enhance the intestinal barrier function and prevent the invasion of pathogenic microorganisms by increasing the secretion of mucin (25, 27). Mucin is a highly glycosylated substance distributing in the cell membrane, and it is secreted into the intestinal cavity to form a mucus layer. The mucus layer is the first line of defense responsible for ensuring the integrity of the intestinal barrier, and pathogenic

microorganisms would not be able to reach the gut epithelial cells without breaking through the mucus layer. Secondly, probiotics may prevent the growth of pathogens directly by secreting antibacterial factors, such as antibacterial peptides, defensins, short-chain fatty acids, and bacteriocins (28, 29). Thirdly, probiotics may enhance the intestinal epithelium barrier function by increasing the expression of tight junction proteins (25).

Scarce clinical data are hitherto available; however, deprivation of important gut commensals, like *Lactobacillus* and *Bifidobacterium*, has been consistently reported in some patients of COVID-19 (16). These gut microbes are known to play a significant role in maintaining colonic homeostasis. Similarly, a six-month follow-up study found that the gut microbiota richness was compromised in COVID-19 patients compared with healthy individuals (8). Higher abundances of opportunistic pathogens, including *Collinsella aerofaciens*, *Collinsella tanakaei*, *Streptococcus infantis*, and *Morganella morganii*, accompanied by an elevated functional capacity for nucleotide de novo biosynthesis, amino acid biosynthesis and glycolysis, were observed in the fecal metagenomes of high SARS-CoV-2 infectivity patients, whilst the fecal metagenomes of low-to-none SARS-CoV-2 infectivity patients were characterized by abundant short-chain fatty acid producing-bacteria, such as *Parabacteroides merdae*, *Bacteroides stercoris*, *Alistipes onderdonkii*, and *Lachnospiraceae bacterium* (30). Thus, one important goal of the probiotic adjunctive treatment in managing COVID-19 would be to restore the gut microbiota diversity, composition, and metagenomic potential to comparable levels in healthy individuals.

## Modulation of Host Immunity

Probiotics are known to modulate the host immunity via regulating the innate and adapted cellular and humoral immunity (4, 31, 32). For example, a meta-analysis of clinical trials of *Lactobacillus acidophilus* and *L. plantarum* found that these species could improve host immunity by regulating the secretion of pro-inflammatory and anti-inflammatory cytokines (32, 33). Thus, it is possible that the probiotic administration employed similar mechanisms to exert immunomodulatory effects to patients contracted COVID-19.

Normally, the host immunoregulation is realized by dynamic interactions between immune effector cells (e.g., dendritic cells, macrophages, and lymphocytes) and cytokines (34). Omics tools have identified probiotics-originated immunomodulatory genes and compounds (35); particularly, genes relating to the quorum-sensing system, bacteriocin biosynthesis pathways, stress responses; and compounds such as vitamins and peptides have been found to regulate cytokine production (35). It is worth noting that the clinical outcomes of probiotics-directed immunoregulatory effects are often dependent on multiple factors in the treatment protocol, including the bacterial strain, dose of application, and treatment period (36). Since only limited clinical data are available, it is yet to investigate to what extent probiotics could help maintain gut immune homeostasis in COVID-19 patients.

## Modulation of the Gut-Lung Axis

Coronaviruses are divided into four genera:  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  (37). Six types of human coronaviruses were discovered before 2019, including two  $\alpha$ -coronaviruses, HCoV-229E and HCoV-NL63, and four  $\beta$ -coronaviruses, HCoV-HKU1, HCoV-OC43, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV). Four of them, HCoV-229E, HCoV-NL63, HCoV-HKU1, and HCoV-OC43, are usually causing mild upper respiratory tract infections (37), and they rarely invade the lower respiratory tract. In contrast, SARS-CoV and MERS-CoV are highly homologous with SARS-CoV-2, which can spread to the lungs and cause lower respiratory tract infections and severe respiratory syndrome in humans (38, 39). The causative agent of the COVID-19 pandemic, SARS-CoV-2, is a  $\beta$ -coronavirus. It is the seventh known coronavirus that can infect humans. COVID-19 is a lower respiratory tract infection that readily spreads downward and triggers deadly levels of lung inflammation (39). The gastrointestinal tract hosts trillions of resident microorganisms, and an unstable gut microbial community can trigger an onset and/or modulate the outcome of respiratory tract infections (24). Several recent meta-analyses of prebiotic and probiotic studies have reached the same conclusion that ingesting probiotics could effectively prevent respiratory infections and reduce the number of acute respiratory infections without side effects (40–42).

Recently, the gut-lung axis concept has been established, implicating bidirectional communications and mutual dependence between these two body compartments and that alterations of the gut microbial communities may have a profound effect on lung function and disease. Experimental evidence also supports that mucosal immunity is common to different body sites. Both dendritic cells present in the gut and macrophages located in the respiratory tract can collect and present antigens to lymphocytes in nearby lymphoid tissues. Locally activated cells would then further modulate host systemic immunity by circulating through the lymphatic system. Less evidence exists showing direct transfer of microorganisms between body sites, but the transmission of intestinal bacteria to the lungs by inhaling vomit or esophageal reflux has been reported (43). In that case, the transferred microbes would be recognized by immune cells after reaching the distant body compartment, and cytokines would be released in response. Thus, the immune and inflammatory state of the gastrointestinal tract could affect other parts of the body, including the lungs (31, 43). A clinical study concluded that co-administration of oral probiotic during treatment of COVID-19 had eight-fold lower risk of developing respiratory failure compared with the control subjects (41). The fact that the association of gut dysbiosis with an increased mortality in respiratory infections and severity in COVID-19-related symptoms as a result of regulatory dysfunction in inflammatory and/or anti-inflammatory mechanisms in the lungs and in the gut suggests a close connection and vital cross-talks between the two mucosal compartments (44). Further longitudinal studies are needed to clarify the role of the microbiota and gut-lung cross-talks in respiratory diseases, paving the way for future application of specific probiotic strains in managing COVID-19 (18, 45, 46).

## DISCUSSION

Changes in the gut microbiota and immunity have long been used as outcome parameters in RCTs for measuring the clinical efficacy of probiotic adjunctive treatment (47). However, the clinical outcomes described in RCTs for assessing the probiotic functions are still somewhat controversial, and the results obtained from RCTs should be cautiously interpreted because of some common limitations. For example, some RCTs were set up with a relatively small population size, hindering from obtaining a real picture of clinical efficacy and understanding of the mechanisms of the probiotic actions (22). Another plausible reason could be that the original claimed functions of the probiotics appeared to be affected by the manufacturing process (48).

Thus, in future, significantly more high-quality RCTs are necessary to achieve precise understanding of the clinical functions of probiotics as adjunctive treatments for various diseases, particularly in novel diseases like COVID-19. Proper analysis and cautious interpretation from large-scale RCTs that are soon finished will certainly help clarify the role and clinical effects of probiotics application in such cases. Moreover, stringent controls and standards should be followed in manufacturing probiotic products to ensure the product quality and genetic

stability of the cells. Last but not least, the success in using probiotics as adjunctive treatment for COVID-19 has expanded the scope of application of probiotics, which would further deepen our knowledge of the physiological function of probiotics in modulating the gut ecosystem and its interactions with the respiratory system.

## AUTHOR CONTRIBUTIONS

WZ conceived the article and wrote the first draft of the article. JP, MZ, and GY refined the structure of the article and updated the content of the article. L-YK modified the manuscript. All authors approved the final version of the manuscript.

## FUNDING

This research was supported by the National Natural Science Foundation of China (Grant No. 31922071).

## ACKNOWLEDGMENTS

We would like to thank the other postgraduate students in the laboratory for their assistance in retrieving the literature.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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