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REVIEW

Alterations in microbiota of patients with COVID-19: implications for therapeutic interventions

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) recently caused a global pandemic, resulting in more than 702 million people being infected and over 6.9 million deaths. Patients with coronavirus disease (COVID-19) may suffer from diarrhea, sleep disorders, depression, and even cognitive impairment, which is associated with long COVID during recovery. However, there remains no consensus on effective treatment methods. Studies have found that patients with COVID-19 have alterations in microbiota and their metabolites, particularly in the gut, which may be involved in the regulation of immune responses. Consumption of probiotics may alleviate the discomfort caused by inflammation and oxidative stress. However, the pathophysiological process underlying the alleviation of COVID-19-related symptoms and complications by targeting the microbiota remains unclear. In the current study, we summarize the latest research and evidence on the COVID-19 pandemic, together with symptoms of SARS-CoV-2 and vaccine use, with a focus on the relationship between microbiota alterations and COVID-19-related symptoms and vaccine use. This work provides evidence that probiotic-based interventions may improve COVID-19 symptoms by regulating gut microbiota and systemic immunity. Probiotics may also be used as adjuvants to improve vaccine efficacy.

KEYWORDS
COVID-19, gut microbiota, immunity, probiotics, vaccine

Yong Qiu and Chunheng Mo contributed equally to this work.

1 | INTRODUCTION

During the coronavirus disease (COVID-19) pandemic, more than 702 million people were infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and over 6.9 million died, while new variants continue to emerge. Patients with COVID-19 may suffer from fever, sore throat, cough, diarrhea, sleep disorders, anxiety, depression, and cognitive impairment, which is associated with long COVID symptoms during recovery.[1–4] Despite some clinical trials of drugs to improve COVID-19 symptoms, there remains no consensus on effective treatment methods, and immunocompromised elderly people and children need special attention.[5–8]

Previous studies have suggested that patients with COVID-19 in the acute or recovery phase exhibit changes in the microbiota, especially the gut microbiota. The alterations in these microorganisms and their metabolites may be involved in the regulation of inflammation and the immune response to mediate virus progression and symptoms. However, the pathophysiological process underlying the alleviation of COVID-19-related symptoms and complications by targeting the microbiota remains unclear.[9–12] Here, we summarize the latest research and evidence on the COVID-19 pandemic, as well as the symptoms and vaccine use, with a focus on the relationship between microbiota alterations and COVID-19-related symptoms and vaccine use. We also examined the potential value of probiotics as adjuvants in vaccines and in alleviating COVID-19 symptoms. Thus, this study provides ideas for targeted and individualized intervention for treating COVID-19 and related complications.

In this review, we systematically explored the symptoms of COVID-19, the available vaccines, dynamic changes in microbiota, and microbiota-based implications for therapeutic interventions. We also summarize and discuss the underlying mechanisms, changes in microbiota during acute infection and recovery, gut microbiota dysbiosis and symptoms, vaccine-associated microbiota changes, probiotic-related treatment, and adjuvants that improve vaccine potency.

2 | PANDEMIC, SYMPTOMS, AND VACCINES OF THE COVID-19

2.1 | Prevalence and direction

Although the WHO declared the end of the pandemic, biologically relevant genome sequencing analyses of SARS-CoV-2 have indicated continued viral variability. The evolution of and change in virus lineages have underlying genetic mechanisms, with evolved strains showing stronger infectivity and immune escape ability. Studies on the affinity between the spike protein of different SARS-CoV-2 variants and the angiotensin-converting enzyme 2 (ACE2) receptor on the membrane of respiratory system cells have revealed that the virus is constantly mutating, resulting in immune escape. Viruses and host immunity may also be correlated, indicating a certain evolutionary direction.[13–16] It has been reported that approximately 10% of hospitalized patients are susceptible to COVID-19, which is associated with prolonged hospital stay and increased risk of postoperative complications, particularly in elderly patients with diabetes, chronic obstructive pulmonary disease, or other frail or immune abnormalities. The increase in COVID-19 cases will bring additional challenges and increase global medical burden. Furthermore, the potential harm and long-term impact of COVID-19 on children's health, psychology, and development deserves more attention, especially when adolescent mental health problems are prone to occur, as is becoming increasingly common. Therefore, it is necessary to explore new effective strategies for early intervention or prevention.[17–21]

2.2 | Symptoms and the long COVID

2.2.1 | Lingering symptoms during recovery

The symptoms of COVID-19 are heterogeneous, with those of acute infection including include dyspnea, diarrhea, sleep disorders, and olfactory abnormalities, which are often more serious in female patients. Additionally, the incidence of muscle pain and headache can reach 75% in the short term. Patients may also suffer from insomnia, anxiety, and persistent gastrointestinal symptoms. A previous study demonstrated that at 6 months after infection, the incidence of fatigue or muscle weakness was approximately 52%, while that of sleep disorders and anxiety or depression was more than 20%.[22–26] During the recovery period of COVID-19, patients may experience long COVID, characterized by chest pain, fatigue, and even cognitive impairment, with risk factors considered to include old age, frailty, and female sex.[27,28] Although some therapies have been used for prevention and treatment, signs and symptoms may occur in patients with COVID-19 and last for several months. A retrospective analysis suggested that neurological complications occur at a frequency of approximately 25%. Women infected with SARS-CoV-2 during pregnancy may have more severe long-term COVID-19 symptoms such as fatigue, myalgia, and olfactory disorders.[29,30] In addition, the discomfort, stress, and anxiety associated with COVID-19 may induce mental health problems. Indeed, subjects with persistent COVID-19

symptoms have been shown to have poorer mental health and health-related quality of life, with longer recovery for women with persistent symptoms. People infected with SARS-CoV-2 are at an increased risk of anxiety and depression, and those who have been previously affected by these disorders may experience worsening illness. A national cohort survey revealed that adolescents present with multiple symptoms, with approximately 30% still experiencing fatigue, headache, and mental health problems 3 months after infection. Consequently, people diagnosed with anxiety or depression before infection with SARS-CoV-2 had higher rates of severe illness than those without mental disorders.[31–34]

2.2.2 | COVID-19 causes cognitive impairment

A recent systematic review of 13,232 patients with COVID-19 revealed that approximately 22% developed cognitive impairment 12 weeks after COVID-19 diagnosis. Cognitive impairment may be more serious when combined with impaired lung function and severe inflammation.[35] Cognitive impairment is often accompanied by an abnormal psychological state, which affects the prognosis of patients and causes a chain reaction. A study involving 114 survivors of COVID-19-associated acute respiratory distress syndrome evaluated patients who were discharged from the intensive care unit and found that the rate of cognitive impairment at 3 months was 28%. These patients often have depression, anxiety, and stress disorders, all of which affect their quality of life.[36] COVID-19 may also induce brain structural changes. Indeed, Douaud et al.[37] analyzed the differences in magnetic resonance imaging before and after SARS-CoV-2 infection and found evidence of brain structural alterations, including a greater reduction in global brain size and gray matter thickness. Similarly, sequencing data analysis of brain samples from patients with COVID-19 and control individuals suggested inflammatory cell infiltration and broad cellular perturbations. The state of glial cells in COVID-19 may be similar to that observed in neurodegenerative diseases, in which the synaptic signals of neurons are affected and may be involved in cognitive impairment.[38] Elderly individuals are more prone to cognitive impairment due to aging and chronic comorbidities. Dementia and cognitive decline in the elderly may worsen mortality and convalescence complications after SARS-CoV-2 infection.[39] Patients with Alzheimer's disease (AD) and advanced age are more likely to contract and die from COVID-19.[40] A survey of nursing home residents with a median age of 80 years found that SARS-CoV-2 infection caused cognitive impairment, malnutrition, and depression in the elderly. This highlights the importance of rehabilitation to improve the long-term adverse effects of COVID-19, such as cognitive impairment, thus reducing the burden of medical care.[41]

2.2.3 | Potential contribution mechanisms mediating COVID-19-related symptoms

The inflammatory response and immune dysfunction may play an important role in long COVID-19. Inflammatory cells mediate chronic inflammation and tissue damage, leading to acute sequelae of COVID-19 symptoms, which may have an underlying epigenetic mechanism. Targeting key inflammatory factors, such as IL-6, may alleviate the persistent inflammatory burden caused by abnormal immune responses.[42,43] In addition, genome-wide association studies have suggested that mutations in enzyme genes encoding related functions are involved in the mechanism of olfactory dysfunction induced by SARS-CoV-2 variants, further suggesting epigenetic changes.[44] Moreover, metabolomics and proteomics studies of cerebrospinal fluid in neurological sequelae after acute SARS-CoV-2 infection have shown that sphingolipid metabolism disorder is associated with reduced inflammatory response, suggesting that metabolomic changes play a role in the repair process.[45]

Elderly individuals show alterations in the intestinal barrier composition of the intestinal flora, which is accompanied by decreased immune function. These findings are crucial for understanding the effects of COVID-19 on the brain in the acute phase and during long COVID. COVID-19 causes changes in the blood–brain barrier (BBB) and the infiltration of inflammatory cells into the brain.[46,47] Hypoxia may also aggravate cognitive impairment in patients with COVID-19. In a cross-sectional investigation, Dondaine et al.[48] divided 62 patients with COVID-19 into two groups according to their hypoxia status. The researchers further explored cognitive function, and they found that hypoxia may be linked to cognitive impairment.[48] Hypoxia may regulate cell metabolism and inflammation through HIF-1α activation. Therefore, targeted improvement of hypoxia may regulate multiple organ functional status and relieve potential complications associated with hypoxia.[49,50] Neuroinflammation, BBB disruption, and neuronal cell changes have been observed in the hippocampus of humans and hamsters with COVID-19. These findings may be related to neurogenesis, neuronal damage, and neurotransmitter abnormalities, which in turn contribute to cognitive impairment. Moreover, mice infected with SARS-CoV-2 showed persistent impairment of hippocampal neurogenesis, which is accompanied by loss of the myelin sheath.[51–53] SARS-CoV-2 spike proteins or protein fragments are released and enter the

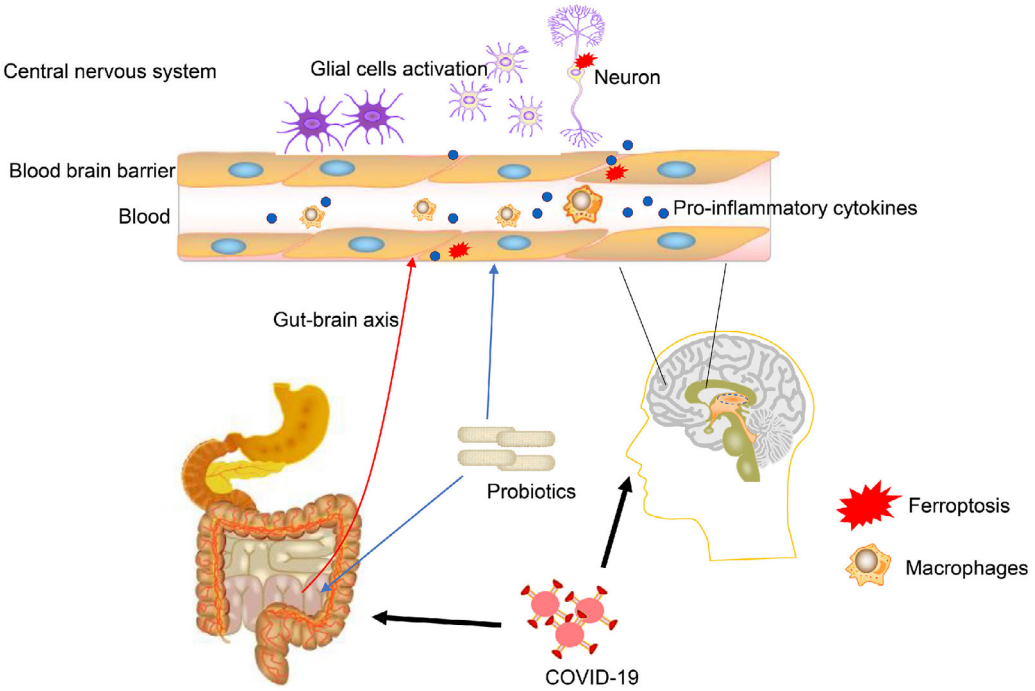

FIGURE 1 The process by which SARS-CoV-2 invades the brain, and the process by which probiotics regulate microbiota. The virus attacks the brain, causing intestinal dysfunction and neuroinflammation. Probiotic supplementation regulates the gut–brain axis and blood–brain barrier, thus alleviating symptoms by reducing glial cell activation and oxidative stress.

brain during infection; this is accompanied by glial activation and synaptic reduction, which may be associated with memory loss and cognitive impairment.[54] Overall, BBB damage, oxidative stress, neuroinflammation, hippocampal neuron dysfunction, hypoxia, and gut microbiota disorders may be involved in cognitive impairment in COVID-19.[55] A diagram of the virus attacking the brain, causing intestinal dysfunction and neuroinflammation is shown in Figure 1.

2.3 | Vaccines against SARS-CoV-2 and variants

Various vaccines have been used to prevent the COVID-19. Different vaccines stimulate the body's immune response in different ways and have achieved significant preventive effects. Wei et al. found that serial vaccination with recombinant protein vaccines on the basis of existing vaccine immunity can induce a stronger immune response and increase the titer of neutralizing antibodies (Figure 2).[56–62] However, the virus is constantly mutating, and there are still many COVID-19 patients. SARS-CoV-2 invades cranial nerves and brain regions, affect immune function, and disrupt BBB. Elderly individuals are prone to cognitive impairment due to a weaker immune system and the breakdown of BBB.[63] Vaccine significantly affected virus and pandemic trajectories. Previous infection with a SARS-CoV-2 variant provides some protection against symptomatic reinfection, and vaccines provide additional protection. The effectiveness of revaccination against confirmed SARS-CoV-2 infection decreases with time and increases with the third dose among adolescents, and strengthening vaccination could help reduce the burden on health care systems and adolescent morbidity. Access to an efficient health sector may influence vaccine decisions, and building a reasonably effective primary care system and ensuring a basic level of affordability for all should be at the head of pandemic preparedness strategies.[64–67] The vaccine may have additional protective effects in hippocampal neurogenesis. Indeed, it has been suggested that vaccine-induced enhancement of hippocampal neurogenesis may offer protection against age-related cognitive impairment and mental health conditions such as anxiety and depression in adults who have been vaccinated against SARS-CoV-2.[68,69] In addition, among adolescents, early vaccination in uninfected children who are exposed to the virus for the first time may enhance immunity against future variants, suggesting the long-term effectiveness of vaccines.[70]

Different types of vaccines are associated with differences in mortality and adverse cardiovascular events. Adverse events following COVID-19 mRNA vaccination include cardiovascular complications such as stroke,

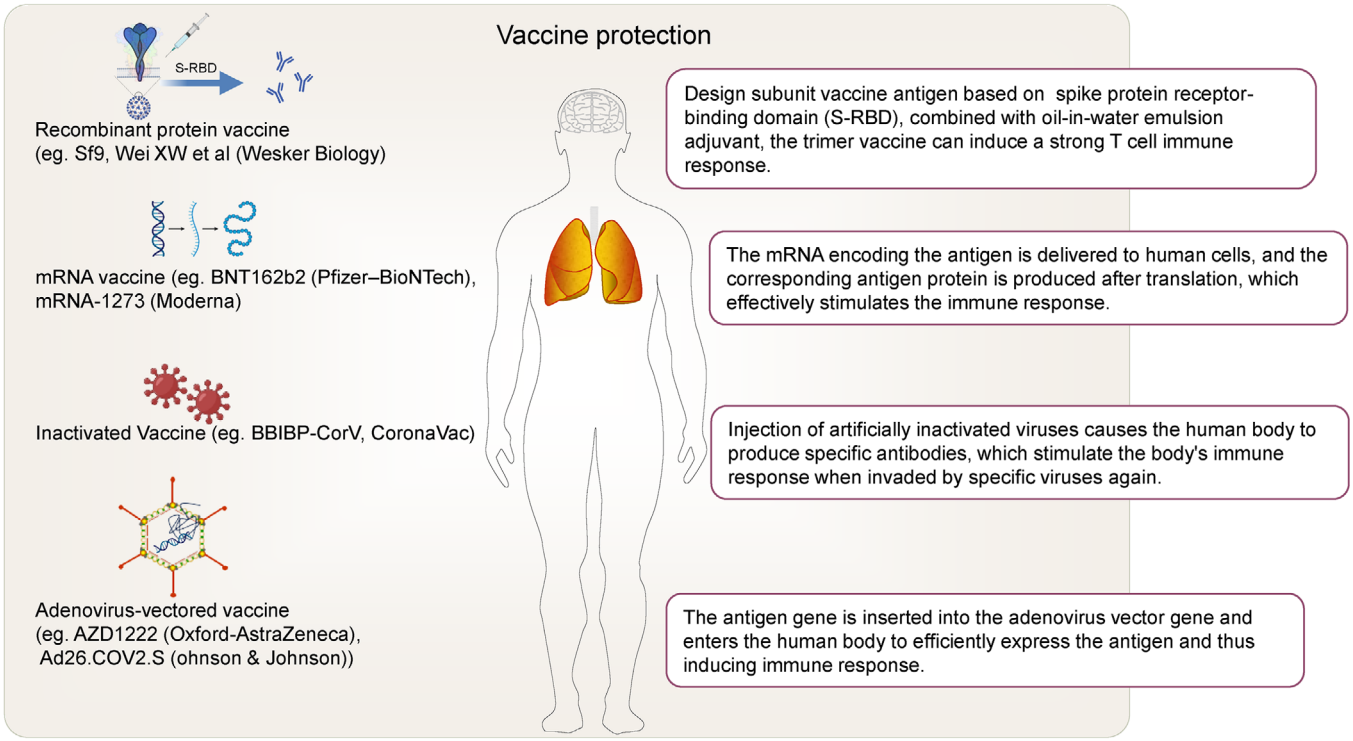

FIGURE 2 Different vaccines stimulate the body's immune response in different ways are shown. The four typical vaccines include recombinant protein vaccine, mRNA vaccine, inactivated vaccine, and adenovirus-vectored vaccine.

myocarditis, and thrombosis. A systematic review of confirmed cardiovascular complications after mRNA vaccines found that thrombosis, stroke, myocarditis, and pulmonary embolism were frequently reported with mRNA vaccines. The mean time from vaccination to first symptom onset was approximately 5 days.[71] In general, the vaccine has greatly improved the symptoms of COVID-19 patients, protected many susceptible people, and reduced the incidence of severe cases. Some potential vaccine-related side effects have also caused anxiety in some people. Further research and evidence are required to improve the efficacy of the vaccine while reducing complications or side effects.[72,73]

3 | DYNAMIC CHANGES OF MICROBIOTA IN COVID-19

Previous studies have shown that microbiomes play an important role in regulating host health and immunity. Microbiota alterations in COVID-19 provide new insights into the potential pathophysiological process of COVID-19-related symptoms and complications. Here we summarize gut microbiota dysbiosis and the changes in vaccine-associated microbiota and microbiota during acute infection and recovery.

3.1 | Changes in microbiota during acute infection with SARS-CoV-2 and recovery

3.1.1 | Alterations in gut microbiota

As an important immunomodulatory body, the microbiota dynamically changes following SARS-CoV-2 infection, which is related to the symptoms. Compared with healthy controls, patients with COVID-19 in the early stage of recovery exhibit decreased diversity and abundance of microbiota. Recovery does not immediately return the microbiota to normal levels, suggesting that patients with COVID-19 have a significant gut microbiota imbalance that may persist for an extended period of time. A study conducted at multiple time points during hospitalization suggested significant dynamic changes in the fecal microbiome, characterized by the consumption of some beneficial commensal bacteria and the deficiency of beneficial microorganisms. This intestinal ecological disorder persisted after virus clearance, while some symptoms disappeared. Furthermore, correlation analysis suggested that the abundance of harmful bacteria, such as *Enterobacteriaceae*, was correlated with the severity of symptoms. COVID-19 progression and severity are associated with changes in the gut microbiota following SARS-CoV-2 infection, which may be caused by changes in the

abundance of key bacterial groups that are associated with host immune dysregulation.[10,74–76] SARS-CoV-2 recognizes and invades cells through ACE2 and may affect immune and metabolic functions. The ACE2 receptor is highly expressed on intestinal cells, which are an important site for virus entry into the intestine. Following invasion, SARS-CoV-2 replicates in intestinal epithelial cells, causing gastrointestinal symptoms. The entry of SARS-CoV-2 into the bloodstream can further cause excessive activation of platelets and inflammatory cytokines, resulting in disturbance of the intestinal microenvironment and loss of the gut–blood barrier, aggravating the changes in intestinal flora. Numerous symptoms may accompany the severity of the disease.[77] The imbalance in gut microbiota may also be related to the imbalance in metabolite level, while the resulting inflammatory cytokine storm can cause overall immune disorders in the body. Viruses can easily invade the intestinal tract because of the high ACE2 expression in lung tissue and intestinal epithelial cells. The disruption of intestinal homeostasis during severe viral infection may be related to the progression and outcome of the disease, and the regulation of the gut–lung axis is critical to viral infection. The gut–lung axis involves ACE2, immune homeostasis, and dynamic regulation between the gut and lung. The human gut microbiota plays an important role in resisting viral infection. Changes in the abundance of gut microbiota or the concentration of its metabolites can cause immune disorders, and viruses can also regulate the homeostasis of the immune system.[78–80]

3.1.2 | Changes in the microbiota of the upper respiratory tract

According to previous studies, the gut microbiome interacts with the oropharynx. The microbial composition and function of the upper respiratory tract and gut are altered in patients with COVID-19, and these changes may correlate with disease severity. The changes in upper respiratory tract flora show specificity compared with the intestinal flora imbalance, and the changes in microbial flora abundance in the upper respiratory tract may also mediate drug resistance by regulating metabolism and immunity.[81] Gastrointestinal dysbiosis and related metabolic changes may also be associated with gastrointestinal symptoms. Indeed, patients with long COVID show differences in the abundance and function of oral and intestinal microbes and serum metabolites. Long-term follow-up and omics studies have found that patients with COVID-19 and long-term gastrointestinal symptoms have ectopic flora colonization from the gut to the mouth, which may be related to potentially harmful metabolites in the serum.[82] In addition, lipidemic correlation analysis of nasopharyngeal and gut microbiota in hospitalized patients during the pandemic period found that the microbiome had metabolic effects on the host immune response, suggesting that related metabolites regulate the inflammatory state and internal environmental disorders in patients with COVID-19. Nasopharyngeal microbiota may be associated with SARS-CoV-2 infection. Analysis of nasopharyngeal microbiota abundance in hospitalized patients with COVID-19 and healthy controls found that some gut microbiota and nasopharyngeal microbiota participate in the host immune response.[83–85]

3.1.3 | Changes in microbiota and immune microenvironment

SARS-CoV-2 infection is associated with intestinal inflammation, intestinal barrier disruption, and changes in lipid metabolism. A decrease in short-chain fatty acid (SCFA)-producing bacteria is associated with infection. Further analysis suggested a strong correlation between some intestinal flora and the severity of SARS-CoV-2 infection and inflammatory indicators.[86–88] Previous evidence has also shown that respiratory virus infection can cause an imbalance in gut microbiota, and diet, environmental factors, and genetic factors play an important role in the formation of the gut microbiota and immune response. In individuals with frailty and low immunity, such as the elderly, the diversity of intestinal flora is reduced, and the disorder of intestinal flora may be more significant.[89] The intestinal flora involved in the synthesis and metabolism of SCFAs may change significantly during SARS-CoV-2 infection. An analysis of the intestinal microbiome in patients with COVID-19 before and after the onset of symptoms revealed that compared with healthy controls, the function of intestinal flora in patients with severe COVID-19 was significantly changed, and the abundance and synthesis ability of SCFA-related bacteria were changed. A reduction in SCFA and L-isoleucine metabolites was also observed in patients with COVID-19 after remission. The concentrations of metabolites were significantly correlated with the blood inflammatory response, suggesting that related microorganisms mediate the host immune response, and related intestinal microbial pathways were identified.[90] When the intestinal flora is dysregulated and the microenvironment is abnormal, immune-related cytokines can further affect the immune and inflammatory responses in the lung through blood circulation. Recently, population-based Mendelian randomization studies have provided new evidence for the causal relationship between COVID-19 and changes in the gut microbiota. Multiple microbiotas were associated with SARS-CoV-2 infection and the disease severity, and hospitalization of patients with COVID-19 led to an increase in the abundance of *Bacteroidetes* ($p < 0.05$).[91] SARS-CoV-2

may also cause a high fever, although the physiological role of fever in the host's resistance to viral infection is unclear; however, the increase in body temperature may be accompanied by a change in the body's microbial flora, which may regulate the host's tolerance to the virus, thereby regulating the body's microenvironment in a form of feedback. High temperature exposure in mice can cause changes in the gut microbiota and microbiota-related metabolites, such as the increased production of bile acids in an intestinal microbiota-dependent manner. The amplification of signal cascades generated by deoxycholic acid produced by gut microbiota and its downstream receptor activation can inhibit viral replication and inflammatory cell infiltration and regulate human resistance to viral infection, suggesting that virus-induced hyperthermia increases host viral tolerance in the form of changes in intestinal microbial abundance.[92]

The gut microbiome is closely related to disease progression. The probiotic *Bifidobacterium* is reduced in patients with severe COVID-19. ACE2 may also play a complex regulatory role in SARS-CoV-2 infection and intestinal flora imbalance. Indeed, evidence suggests that intestinal flora can also regulate ACE2 expression and then regulate the gut–lung and gut–brain axis to mediate the dynamic interaction of the immune system. In elderly patients and those with severe COVID-19 with intestinal flora imbalance, inflammation is significantly dysregulated and may be involved in intestinal flora imbalance and microenvironment disorder. Patients with significant intestinal flora imbalance have a poor prognosis, which is accompanied by a decrease in the abundance of butyrate-producing flora, suggesting that changes in intestinal flora during hospitalization are related to the poor prognosis of patients with severe COVID-19.[93] Patients with COVID-19 with immune and metabolic abnormalities, such as diabetes, also exhibit some specific common flora changes. The relative abundance of *Shigella* and *Bacteroides* is higher in patients with COVID-19 with diabetes, suggesting that the imbalance in intestinal flora is increased and that dysregulated intestinal flora may also regulate metabolism and immunity.[94] As discussed above, COVID-19 changes the microbiota and the immune microenvironment in a closely related way.

3.2 | Gut microbiota dysbiosis and symptoms

3.2.1 | Dysbiosis is involved in the symptoms of COVID-19

Due to dysbiosis of the gut microbiota, metabolites have immunomodulatory effects on vaccine immunogenicity and also contribute to the occurrence and severity of COVID-19 symptoms via modulating the entry of SARS-CoV-2 into the body and the resulting inflammatory response.[95] The gut microbiota has also been linked to disease severity in COVID-19. The analysis of intestinal flora showed that the abundance of antibiotic-resistant *Enterobacteriaceae* in the gut of patients with COVID-19 increased after virus infection. Animal experiments have also found that COVID-19-related symptoms and sequelae, such as pneumonia and cognitive impairment, occur in fecal transplantation mice 1−4 months after SARS-CoV-2 infection, indicating that the gut microbiota may directly contribute to COVID-19-related symptoms. Fecal transplantation from patients with COVID-19 into germ-free mice causes lung inflammation and cognitive impairment, indicating that the long-term effects of the virus on intestinal flora directly mediate COVID-19-related symptoms and long COVID.[96,97] In addition, cohort studies on the association between gut microbiota and the severity of COVID-19 symptoms have found that some gut microbiota are significantly associated with disease severity. Moreover, the abundance of actinobacteria can predict poor prognosis after infection, suggesting the feasibility of prediction models based on gut microbiota.[98] Dysbiosis of gut microbiota is associated with increased susceptibility to the respiratory tract and immune microenvironment in the lung by regulating the gut–lung axis. Dysbiosis may also play an important role in central inflammation through the gut–brain axis to mediate central symptoms. Because the recovery of intestinal dysbiosis requires a certain period of time, the related symptoms mediated by intestinal dysbiosis may continue to affect patients with COVID-19.[99,100] Most patients with COVID-19 have mild symptoms and recover well, but some patients develop severe COVID-19. A strong immune system balanced by anti-inflammatory mechanisms is essential for recovery from SARS-CoV-2 infection. COVID-19 is often accompanied by gastrointestinal symptoms and intestinal flora dysbiosis, mainly manifested by an increase in opportunistic pathogens and a decrease in beneficial symbiotic bacteria. A previous study has highlighted the correlation between dysbiosis and clinical symptoms of COVID-19, and the gut microbiota is closely related to diarrhea and related gastrointestinal symptoms. Frail elderly people have higher disease severity and mortality, and the prognosis of COVID-19 is worse in patients with gastrointestinal symptoms, which may be related to a more significant intestinal flora disorder.[101,102] The composition of the gut microbiota can also be altered by dietary and antibiotic environmental factors. Indeed, a prospective cohort study found that the composition of the gut microbiota changed with the course of COVID-19 and was significantly correlated with cytokine levels, while the microbiota were significantly associated with poor prognosis. The gut microbiota may

also affect the body's immune response by regulating the cytokine response and metabolic process, thereby affecting the prognosis of COVID-19.[103] Although the mechanism by which the gut microbiota mediates COVID-19-related symptoms remains controversial, abnormal immune activation mediated by dysbiosis, microbiota-related specific metabolites, the gut–lung axis, and the gut–brain axis may be involved.

SARS-CoV-2 invades the respiratory tract and intestinal cells through the ACE2 receptor, leading to changes in intestinal flora and intestinal cell damage. Disorder of intestinal flora destroys the gut–blood barrier and triggers immune activation, which is associated with systemic symptoms.[77] Multiomics association analysis revealed a potential regulatory relationship between intestinal flora and metabolites such as branched-chain amino acids and the chemotactic response of inflammatory factors in patients with COVID-19, and the intestinal flora may regulate lung and brain functions through metabolites. The severity of COVID-19 is partly associated with host immune dysregulation, and Mendelian randomization studies have suggested that the gut microbiota is associated with susceptibility, hospitalization rate, and severity. Some patients with severe COVID-19 have more significant dysbiosis of gut microbiota due to ICU admission, with decreased abundance of beneficial bacteria such as butyric acid microbes, and increased levels of C-reactive protein. Therefore, changes in the gut microbiota during hospitalization may be associated with poor prognosis and increased 60-day mortality in patients with severe COVID-19.[104,105] The gastrointestinal tract may also be directly affected by the SARS-CoV-2 infection-mediated immune response and the release of inflammatory mediators, which can lead to the chemotaxis of viruses from the respiratory epithelium into the gastrointestinal tract. The impairment of intestinal barrier function is the key factor leading to the imbalance in flora and the translocation of inflammatory substances, which in turn induces a stronger systemic immune response and leads to COVID-19-related sequelae. Multiple components of the intestinal immune system are affected by inflammatory mediators, chemotaxis of immune cells, and secretion of immunoglobulins in COVID-19, leading to intestinal immune barrier dysfunction. The intestinal barrier can be maintained and self-repaired to a certain extent by intestinal flora and metabolites. However, excessive activation of the immune response and immune microenvironment can cause further epithelial damage.[106] A recent Mendelian randomization study on gut microbiota and COVID-19 susceptibility and severity further suggested a correlation between gut microbiota dysbiosis and COVID-19 symptoms, with some dysregulated flora, such as *Subdoligranulum* and *Lactobacillale* have been found to be associated with the severity of the disease ($p < 0.05$). These findings suggest that the gut microbiota may have a causal relationship with the severity of COVID-19, thus providing new evidence and ideas for the study of the pathogenesis of SARS-CoV-2 mediated by gut microbiota.[107,108]

3.2.2 | Potential causal relationship and pathophysiological processes between microbiota dysbiosis and COVID-19-related symptoms

Host immune disorders are closely related to intestinal microflora-regulated immune homeostasis and intestinal microenvironment disorders. Subsequently, related bacteria produce bioactive metabolites, inflammatory factor responses, and changes in the immune microenvironment, which may promote the progression of COVID-19. The bidirectional regulation between the gut microbiota and host immunity may play an important role in this process.[109] In addition, SARS-CoV-2 may cause the disorder of gut microbiota, thereby increasing susceptibility to COVID-19. The mechanisms by which the disturbance of gut microbiota increases susceptibility to COVID-19 and associated symptoms are poorly understood. However, the imbalance in intestinal microbiota caused by COVID-19 is known to affect the body's inflammatory and oxidative stress responses. Indeed, SCFAs are closely related to the inflammatory and oxidative state, which may be related to COVID-19-related complications. COVID-19 alters the composition of gut microbiota and decreases the abundance of probiotic-related bacteria. Metabolites produced by some bacteria can target the S protein of coronaviruses, thereby improving dysbiosis.[110,111] The reduced diversity of intestinal flora in patients with COVID can be accompanied by changes in circulating and intestinal SCFAs and an imbalance in circulating immune cell subsets. The proportions of $CD19^+$ B, $CD4^+$ T, $CD8^+$ T, and NK cells of patients with COVID-19 were significantly decreased, and the IL-6 and IL-10 levels were significantly increased, all of which were more prominent in critically ill patients. Further correlation analysis suggested that low SCFA levels in patients with COVID-19 may be an important cause of lymphopenia.[112] The influence of microbiota on the antiviral immune response includes the homing of dendritic cells and lymphocytes to the gut–lung axis. The composition of the gut microbiome influences ACE2 expression and inflammation.[113] Working memory, attention, processing, and analysis abilities are significantly affected in some patients with COVID-19 after infection, although the mechanisms underlying these chronic cognitive sequelae are currently unknown. SARS-CoV-2 can induce high levels of systemic cytokines,

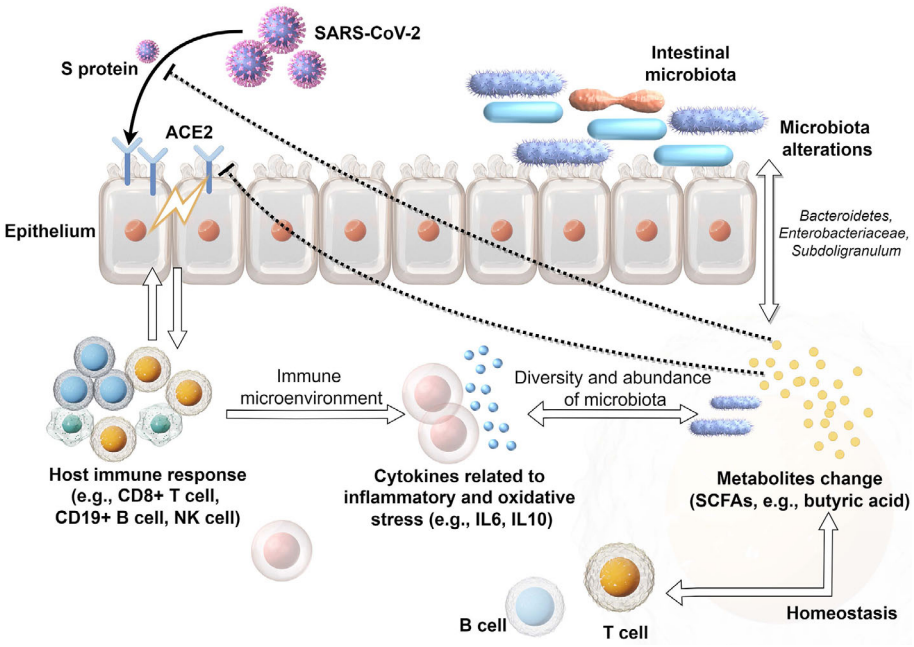

FIGURE 3 The potential causal relationship and processes between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and gut microbiota alterations. SARS-CoV-2 recognizes the angiotensin-converting enzyme 2 (ACE2) receptor in the intestinal epithelium through S protein and triggers abnormal immune responses, such as activation of CD8+ T cells. The immune microenvironment interacts with microbiota alterations, which is accompanied by changes in short-chain fatty acid (SCFA) metabolites. These metabolites may regulate the immune response, S protein activity, and ACE2 receptor expression.

induce damage to the cerebral vessels and intestinal wall, and destroy the neurovascular unit of the brain and BBB. Pathogenic microbiota produce harmful substances and inflammatory molecules in the gut, which then infiltrate into the brain, eventually causing neuroinflammation and cognitive impairment.[114] Gut–brain axis regulation is also reflected in some people with mental health disorders such as anxiety and depression, which are often accompanied by an abnormal abundance of gut microbiota, suggesting that intestinal flora disorder may also play a role in COVID-19-related anxiety and depression.[115,116] The potential causal relationship and processes between SARS-CoV-2 and gut microbiota alterations are shown in Figure 3.

A recent analysis using cortical sequencing data from patients with AD and COVID-19 found significant changes in astrocyte and neuronal cell populations, suggesting that synaptic dysfunction, neuronal damage, and neuroinflammation jointly contribute to cognitive impairment in COVID-19.[117] Meanwhile, another study detected abnormal expression of AD biomarkers in the cerebrospinal fluid and blood of patients with COVID-19, suggesting that brain microvascular damage plays a role in COVID-19-mediated cognitive impairment.[118] Indeed, systemic infections that accompany severe cases of COVID-19 trigger large increases in circulating chemokine and interleukin levels, which disrupt the BBB, leading to neuroinflammation and homeostasis imbalance.[119] Glial activation and neuroinflammation may play an important role in cognitive impairment caused by COVID-19. COVID-19 leads to the upregulation of genes responsible for promoting abnormal synaptic function and migration and synaptic phagocytosis in microglia, which may result in cognitive impairment.[120] Similarly, an analysis of brain pathology in elderly patients with cognitive impairment with COVID-19 found a marked enhancement of microglia in the hippocampus.[121] Another study involving brain tissue from 43 patients who died of COVID-19 at a median age of 76 years detected the virus protein in 21 brains. However, the available evidence is insufficient to show that COVID-19 directly causes central nervous system injury, indicating the complex mechanism of cognitive impairment caused by COVID-19.[122] Neuronal reactive autoantibodies are also known to be associated with COVID-19-related cognitive impairment. Alexopoulos et al.[123] analyzed antibodies and albumin in the cerebrospinal fluid and serum of patients with COVID-19 in a coma. The results suggested that cerebrospinal fluid SARS-CoV-2 antibodies may be related to BBB destruction, which in turn leads to inflammatory cell infiltration and neuroinflammation, the latter of which is closely related to cognitive deficits.[123] Similarly, the study by Franke et al.[124] included 11 patients with COVID-19 with unexplained neurological symptoms, and analyzed blood and cerebrospinal fluid samples to detect antineuronal and antiglial autoantibodies. Notably,

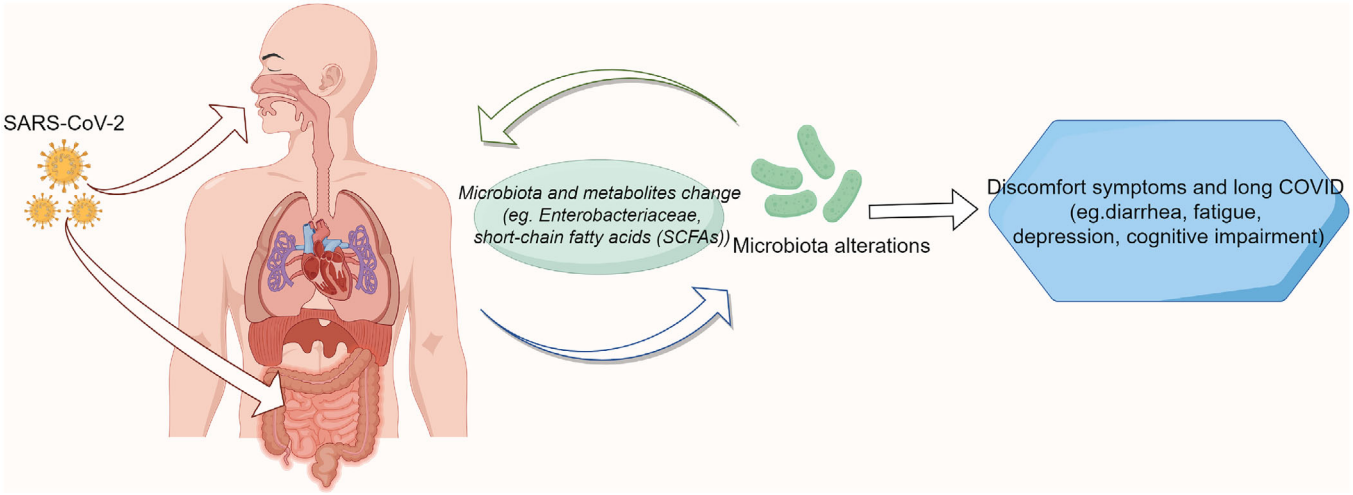

FIGURE 4 The changes in microbiota during SARS-CoV-2 acute infection and recovery. The abundance of gut microbiota (e.g. *Enterobacteriaceae*) and short-chain fatty acids (SCFAs) changes after infection, which may be associated with symptoms such as diarrhea, fatigue, depression, and cognitive impairment.

all participants showed antineuronal autoantibodies, which provided evidence for symptom interpretation and immunotherapy.[124] In one study, antineuronal autoantibodies were detected in the blood and cerebrospinal fluid of more than half of the patients with COVID-19 with cognitive impairment. However, further studies are needed to determine whether these antibodies play a direct role in cognitive impairment.[125] The changes in microbiota during acute infection and recovery and the potential association between microbiota dysbiosis and symptoms are shown in Figure 4.

3.3 | Vaccine-associated microbiota changes

SARS-CoV-2 has a significant impact on the gastrointestinal tract by invading intestinal epithelial cells, which in turn causes intestinal flora imbalance and a series of cascade reactions. The inactivated SARS-CoV-2 vaccine has also been shown to induce changes in intestinal microbiota, with a previous study demonstrating that vaccinated versus unvaccinated individuals had significantly different abundance ratios and biological functions of intestinal flora, as determined by sequencing and abundance analysis.[126–128] Vaccinated subjects showed a significant reduction in bacterial diversity, favoring an enterotype dominated by *Faecalibacterium* and gut microbiota enriched in *Faecalibacterium* and *Mollicutes*. Functional pathway enrichment analysis of microbiota abundance suggested that the transition of carbohydrate metabolism was positively correlated with vaccination, revealing that the abundance of bacteria related to neurodegenerative and cardiovascular diseases was significantly affected. These findings suggest that vaccination alters the composition of microbiota and its metabolites in the gut.[129] The gut microbiota is associated with the vaccine response, which provides a basis for further exploring the regulation of the gut microbiota to improve vaccine efficacy. Newborns can obtain immune protection against SARS-CoV-2 through antibodies generated by the vaccine in breast milk, and vaccines can induce changes in the composition of the human breast milk microbiome, which may affect the antibody level. The richness and composition of the human breast milk microbiome change dynamically during the entire vaccination process, and microbiota are associated with high IgA levels.[130] The gut microbiota may enhance or reduce the efficacy of vaccines through variations in metabolite composition. In addition to affecting gut microbiota abundance and composition, COVID-19 vaccines may reduce the gut microbiota biodiversity.[131] The efficacy of COVID-19 vaccines also differs across individuals, and the gut microbiota may have an impact on its immunogenicity and thus its effectiveness. It appears that different microbiome components either enhance or reduce the efficacy of COVID-19 vaccines, indicating a bidirectional relationship between the gut microbiome and the vaccine.[132] The human gut microbiota and its metabolites may be involved in vaccine response. Vaccination is accompanied by changes in the composition and functional pathways of the gut microbiota, and the gut microbiota and its functional spectrum are related to the vaccine response. The serum SCFA levels have been shown to exhibit clear differences between high- and low-response groups, while some SCFAs are positively correlated with antibody response. A dynamic change in the host immune system in

conjunction with changes in the gut microbiota contributes to the production of antibodies against SARS-CoV-2.[133,134]

Vaccines induce changes in the gut microbiota, the composition of which is associated with the immunogenicity and adverse events of SARS-CoV-2 vaccines, suggesting that the gut microbiota plays a key role in regulating the host immune response. *Prevotella copri* and *Megamonas* were found to be enriched in individuals with fewer adverse events following vaccination, suggesting that these bacterial groups play an anti-inflammatory role.[135] *Lactic acid bacteria* expressing foreign antigens have great potential as mucosal vaccines, while recombinant *Lactobacillus plantarum SK156* with the SARS-CoV-2 spike S1 epitope has been shown to induce humoral and cell-mediated immune responses in mice. Mucosal vaccines can significantly alter the intestinal flora and derived metabolites of mice by regulating their composition and function, and increasing the abundance of beneficial intestinal bacteria, such as *Muribaculaceae, Mucispirillum*, and *Ruminococcaceae*. In addition, functional analysis of the gut microbiota revealed increased metabolic pathways for amino acids, carbohydrates, and vitamins. The concentrations of SCFAs, especially butyric acid, were also changed by mucosal immunity, further suggesting that vaccination affected the composition and metabolite levels of gut microbiota. In turn, the gut microbiome and its metabolites may influence the immunogenicity of SARS-CoV-2 vaccines.[111,136] Although the mechanism of this vaccine-induced change in the microbiota and the bidirectional regulation of metabolites and inflammatory immune response caused by the changes in the microbiota has not been elucidated, exploring the relevant mechanisms provides new ideas for the optimization of vaccines and the selection of adjuvants. Vaccine-associated microbiota changes and the potential bidirectional regulation are shown in Figure 5.

4 | MICROBIOTA-BASED IMPLICATIONS FOR THERAPEUTIC INTERVENTIONS

The microbiota alterations in COVID-19 also have implications for probiotic-based interventions. Probiotics are groups of organisms that are beneficial to the human body, such as *bifidobacteria* and *lactobacilli*. Probiotics may regulate the composition of the gut microbiota and affect immune function.[137] We discuss the potential of probiotics to alleviate uncomfortable symptoms and cognitive impairment in COVID-19 and improve vaccine potency.

4.1 | Probiotic-related treatment of COVID-19

4.1.1 | Probiotics alleviate uncomfortable symptoms of COVID-19

Recent bibliometric analysis has revealed the immunomodulatory properties of probiotics in patients with COVID-19, highlighting their prospects for the adjuvant treatment of COVID-19. We summarize the recently published clinical trials of probiotics for the treatment of COVID-19 in Table 1.[138–144] Supplementing probiotics may reduce inflammatory markers and regulate immune function. Approximately 26% of patients have cognitive impairment after infection, and this damage may persist for months. Moreover, elderly individuals are more likely to be affected by COVID-19 because of frailty and comorbidities, and the impact is more severe.[145,146] A cross-sectional study involving 1539 hospitalized patients with COVID-19 and 466 healthy controls older than 60 years confirmed cognitive impairment 6 months after discharge, while the incidence of cognitive impairment was 12.45% at the 12-month follow-up.[147] Comprehensive analysis suggested that severe COVID-19 was associated with a higher risk of progressive cognitive decline (odds ratio: 19).[148] However, there are few reports on the efficacy of probiotics in relieving cognitive impairment associated with COVID-19.[149,150] Elderly patients with COVID-19 are often accompanied by intestinal dysfunction and microbiota changes. Probiotics may regulate the gut–brain axis, which can be used to improve intestinal damage or drug-related diarrhea caused by COVID-19 treatment.[151] Furthermore, it has been reported that probiotics promote mental flexibility, relieve stress, and significantly increase serum brain-derived neurotrophic factor (BDNF) levels in healthy elderly patients, suggesting that they may improve cognitive function in elderly patients. Probiotics regulate the function of intestinal flora and inflammation in the elderly, which suggests a beneficial effect of probiotics on cognitive impairment associated with COVID-19.[152]

The potential benefits of probiotics for the prevention and treatment of COVID-19 complications have attracted much attention. Elderly patients with COVID-19 are prone to fatigue and cognitive impairment during recovery. Rathi et al.[153] found that supplementation with probiotic complexes improves fatigue, attention, and memory. However, they did not focus on the improvement of cognition by probiotics. Mozota et al.[154] found that probiotic dairy products significantly affected inflammatory factors such as IL8 and IL19 and increased the Barthel index and nutritional status. In further research, Mozota et al.[155] evaluated the effect of *Ligilactobacillus salivarius* supplementation for

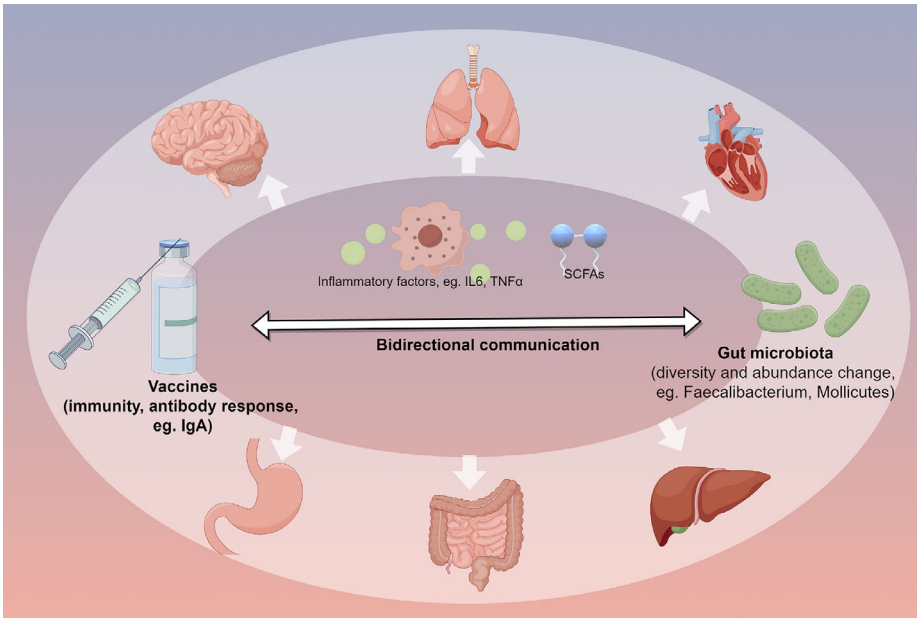

FIGURE 5 The changes in vaccine-associated gut microbiota diversity. Vaccines may influence the diversity and abundance of the gut microbiota through modulation of the immune response. In turn, microbiota regulate the immune response to vaccines, inflammatory responses, and organ homeostasis. IL6, interleukin 6; TNFα, tumor necrosis factor-α; SCFAs, short-chain fatty acids.

4 months on patients with COVID-19 over the age of 75 years. The results showed that the inflammatory factor and cognitive status changed significantly, but the cognitive score did not, suggesting a potential benefit of probiotics in immunity regulation.[155] Similarly, Vaezi et al.[138] included 78 patients with COVID-19 and randomly administered placebo or synbiotic capsules containing *Lactobacillus, Bifidobacterium*, and *Streptococcus* probiotics. After two daily interventions for 14 days, the level of interleukin 6 in the synbiotic supplementation group was significantly reduced.[138] In addition, Catinean et al.[156] suggested that patients receiving probiotic supplementation (five strains of bacillus; at least one month) may experience faster symptom resolution. Adjunctive therapy of *Limosilactobacillus reuteri* PBS072 and *Bifidobacterium breve* BB077 for 30 days improved the quality of sleep and mood, thus relieving stress.[157] The above evidence supports that probiotic supplements reduce potential complications and disease burden.

Probiotics and their metabolites may restore the normal composition of intestinal flora by regulating the intestinal environment and intestinal barrier. Probiotic supplementation can reduce the symptoms of COVID-19, such as diarrhea and dyspnea without obvious side effects.[158] Commensal gut bacteria protect the gut environment and defend against viruses by promoting beneficial immune interactions. Regulation of gut microbiota may have a systemic antiviral effect in SARS-CoV-2 infection, which is related to the repair of intestinal barrier and anti-inflammation. In addition, the use of probiotics can reduce the susceptibility of the population to respiratory virus infections such as COVID-19, while regulating the immune response to improve the potency of vaccines. Probiotics mainly regulate the microbiota and immune system by regulating the innate system response and the production of anti-inflammatory cytokines, thereby regulating the inflammatory and oxidative stress state of the body, and may regulate pneumonia and related symptoms.[159,160] A meta-analysis found that probiotics shortened the length of hospital stay, recovery time, and reduced the risk of death, suggesting the potential of probiotics as an adjuvant therapy to reduce the risk of death and symptoms in COVID-19.[161] Based on the gut–lung axis theory, there is a bidirectional interaction between gut microbiota and lung. Probiotics reduce serum C-reactive protein levels, shorten the length of hospital stay, and further improve respiratory symptoms through the gut–lung axis. In addition, probiotics can not only regulate the composition of intestinal flora and the concentration of related metabolites, but also affect the generation and function of Treg cells to further regulate immune function. Probiotics deserve more attention in regulating gut microbiota, maintaining intestinal homeostasis and serving as an antiviral mechanism.[162–164]

Studies of probiotic therapy as postexposure prophylaxis for COVID-19 also suggest a potential protective effect. One study included 182 participants with close exposure to COVID-19; it included a follow-up for analysis of symptoms and the fecal microbiome after 28 days of continuous probiotic supplementation. *Lacticaseibacillus rhamnosus GG* group had fewer disease symptoms than

TABLE 1 Clinical trials of probiotics in the treatment of COVID-19.

Study/country	Participants (control/intervention)	Intervention	Follow-up time	Side effect	Outcome	Conclusion
Vaezi et al. (2023)/Iran[138]	Adult COVID-19 patients (38/38)	Multistrain probiotics (e.g., *Lactobacillus, Bifidobacterium, Streptococcus*), 10^{18} CFU per day, twice daily for 2 weeks	14 days	None	COVID-19 clinical features, levels of proinflammatory IL-6, CRP, ESR, and so on	Synbiotic adjuvant therapy can be effective to modulate inflammatory responses against COVID-19.
Sandra et al. (2023)/Spain[139]	COVID-19 subjects who required more than 48 h of hospital admission (99/101)	Multistrain probiotic (e.g., *Lacticaseibacillus, Bifdobacterium*), 10^{9} CFU, three times a day for no more than 14 days	During the hospital stay	NA	Mortality, digestive symptoms, hospital stays	It was effective in treating diarrhea associated with COVID-19.
Richard et al. (2023)/Sweden and UK[140]	Healthy adults (78/81)	Probiotic product containing a minimum of 1×108 CFU of *Limosilactobacillus reuteri* DSM 17938 + 10 μg vitamin D3, twice daily for 6 months	6 months	Gastrointestinal complaints	Serum-specific antibody titers, symptom duration and severity after infection and so on.	Supplementation with specific probiotics might improve the long-term efficacy of mRNA-based COVID-19 vaccines via enhanced IgA response.
Pedro et al. (2022)/Mexico[141]	Adult symptomatic COVID-19 outpatients (150/150)	*Lactiplantibacillus plantarum*, plus strain *Pediococcus acidilactici*, totaling 2×10^{9} CFU, for 30 days	30 days	None	Nasopharyngeal viral load, duration of both digestive and nondigestive symptoms, fecal microbiota	Probiotic supplementation significantly increased specific IgM and IgG. It is thus hypothesized this probiotic primarily acts by interacting with the host's immune system rather than changing colonic microbiota composition.
Saviano et al. (2022)/Italy[142]	Patients with COVID-19 interstitial pneumonia (40/40)	*Bifidobacterium lactis LA 304*, *Lactobacillus salivarius LA 302*, and *Lactobacillus acidophilus LA 201*, probiotic mix twice a day for 10 days in addition to the standard COVID-19 therapy	10 days	None	FECAL inflammatory markers (fecal calprotectin and CRP), any reduction in the need for nasal cannula or Ventimask oxygen support, the length of hospital stay	Supplementation with a mix of probiotics for 10 days in patients with COVID-19 interstitial pneumonia significantly reduces inflammatory markers.

(Continues)

TABLE 1 (Continued)

Study/country	Participants (control/intervention)	Intervention	Follow-up time	Side effect	Outcome	Conclusion
De boeck et al. (2022)/Belgium[143]	Unvaccinated COVID-19 outpatients exhibiting mild-to-moderate symptoms (37/41)	Multispecies probiotic throat spray with *Lacticaseibacillus casei* AMBR2, *Lacticaseibacillus rhamnosus* GG, and *Lactiplantibacillus plantarum* WCFS1, for 14 days by spraying two puffs containing approximately 9.5×10^8 CFU of lactobacilli multiple times a day	1 week	NA	Symptom severity, time to improvement, viral loads, antibodies, and the respiratory microbiome	It may reduce nasopharyngeal viral loads and acute symptoms.
Francesco et al. (2022)/Italy and UK[144]	COVID-19 hospitalized patients (non-ICU and not already receiving mechanical ventilatory support) (25/25)	Oral probiotic S. *salivarius* K12 plus standard of care, up to 14 days	14 days	NA	Biochemical parameters, fever, oxygen saturation level, need and length of oxygen therapy, the rate of progression to ICU and death	The adjuvant use of S. *salivarius* K12, an oral probiotic endowed with a well-known capability to colonize the oral environment, improved the blood parameters and reduced the death rate.

COVID-19, coronavirus disease 2019; CFU, colony forming units; IL-6, interleukin-6; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ICU, intensive care unit.

placebo (26.4 vs. 42.9%), suggesting that probiotic prophylaxis is associated with a lower incidence of COVID-19 symptoms and changes in the gut microbiome.[165] Probiotics enhance the immunity of patients with SARS-COV-2, which in turn causes inflammation and increased cytokine secretion. Probiotics can also improve lung function in patients with SARS-COV-2 by regulating ACE2. Probiotic intake is associated with reduced levels of inflammatory markers, which can modulate inflammasomes to stimulate immune responses to block viral invasion and replication. Probiotics may also target SARS-CoV-2 by blocking viral invasion and replication and stimulating immune responses by modulating inflammasomes. In addition, some bacteria have relatively direct antiviral properties. For example, *lactic acid bacteria* can stimulate the host's innate antiviral immune defense system to produce antiviral peptides to prevent viral replication or invasion. Adherence of the SARS-CoV spike protein to the surface of *B. breve* may trigger the host immune response and trigger antibody production.[166–168] Probiotics also improved symptoms and viral clearance in outpatients with COVID-19, with supplementation reducing nasopharyngeal viral load, pulmonary infiltrates, and duration of unwell symptoms, as compared with placebo. Probiotic supplementation significantly increased COVID-19-specific IgM and IgG. However, probiotics did not significantly affect the composition and abundance of gut microbiota in some individuals, suggesting that probiotics can also directly communicate with the body's immune system to play an immunomodulatory role.[141] Given the ongoing effects of neuroinflammation caused by COVID-19 and its related anxiety, depression, and cognitive impairment, probiotic-mediated regulation of the gut–brain axis represents a novel idea for targeted intervention. Indeed, supplementation with probiotics *Lactiplantibacillus* can improve mood and sleep quality and protect cognitive function.[169]

4.1.2 | Probiotics may improve cognitive impairment in patients with COVID-19

The gut and brain are bidirectionally connected and regulate each other via the gut–brain axis. Using probiotics can regulate the immune response and inflammation to ameliorate BBB destruction, which plays a role in AD.[170] The frail elderly may have more severe symptoms after SARS-CoV-2 infection, which will aggravate any existing cognitive impairment. Probiotic supplementation has been shown to significantly change the levels of tryptophan metabolism-related metabolites in the elderly, among which indole-3-propionic acid (IPA) increased by 1.91 times and was positively correlated with serum BDNF levels. In vitro, IPA was found to increase BDNF levels in neurons and decrease TNF-α levels in microglia, which further suggests the role of microbial metabolites in regulating neuroinflammation and cognition.[171] Combined with machine learning algorithms and data model analysis, it was found that probiotic supplementation could regulate the anti-inflammatory effect through the enhancement of bifidobacterium and related metabolism, which promoted the recovery of patients and the improvement of discomfort symptoms, suggesting its potential for treating long COVID.[172] COVID-19 can invade the brain and cause damage to the BBB, activating microglia in the hippocampus and ultimately contributing to cognitive decline. However, a prospective observational cohort study focused on the correlation between long-term cognitive function in patients with severe COVID-19 and anti-inflammatory treatment found that the treatment did not significantly affect long-term cognitive function. The study included 96 patients who were followed up for 6 months after hospital discharge.[173] These findings may be due to the small sample size or short follow-up time, but may also be due to its complex pathophysiology. In this situation, whether probiotic adjuvant therapy may improve the regulation of neuroinflammation is a crucial consideration for future investigations. The potential cognitive benefits of probiotic adjuvant therapy are worth looking forward to.[174] A recent clinical cross-sectional study demonstrated a correlation between alterations in the gut microbiome composition of patients with AD and β-amyloid and tau pathological biomarkers, suggesting that changes in the gut microbiome may occur early in the disease process and have an association with cognitive impairment. Probiotics may mitigate COVID-19-induced cognitive impairments through the regulation of neuroinflammation, modulation of the gut microbiota, and gut homeostasis.[175,176] Overall, probiotics have important research potential and value in improving COVID-19-related cognitive impairment in the elderly, potentially via their complex regulation of various physiological processes (Figures 1 and 6).

4.2 | Adjuvant improve vaccines potency

Gut microbiota metabolites can enter the circulation and play an immunomodulatory role throughout the whole body. Moreover, these molecules are recognized by immune cells from the host, which can trigger or regulate different responses and affect the efficacy of vaccines. Recent studies have suggested that modulating the composition or abundance of gut microbiota may be a means to achieve a more effective protective immune response. Notably, there may be an association between better vaccine response and specific microbiota. The use of probiotics in combination with vaccines indicates that bacterial

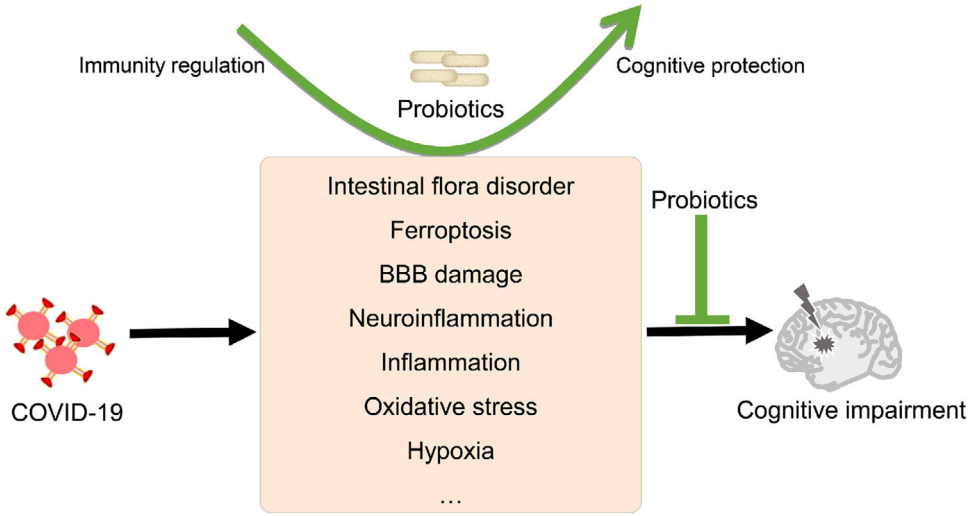

FIGURE 6 Potential mechanism of probiotics in the treatment of cognitive impairment caused by coronavirus disease 2019 (COVID-19). Cognitive impairment may be alleviated by probiotics through regulating microbiota imbalance, ferroptosis, the blood–brain barrier (BBB), neuroinflammation, oxidative stress, and hypoxia.

components can also be used as adjuvants to improve and optimize the response to respiratory virus vaccines.[177,178] Interindividual differences in efficacy may be partly due to robust immune responses induced by mRNA vaccines targeting the SARS-CoV-2 spike protein and changes in the composition and abundance of gut microbiota that affect vaccine immunogenicity. Indeed, the levels of anti-spike IgG measured before and 1 week after vaccination correlated with the diversity of gut microbiota, which normally correlates with vaccine immunogenicity. Functional pathway enrichment analysis suggested that SCFA metabolism and sulfur metabolism-related pathways may be involved, as well as being positively correlated with IgG levels. These results confirm that the gut microbiota composition influences the immunogenicity of SARS-CoV-2 mRNA vaccines.[179] The role of the gut microbiome in modulating the durability of immunity against COVID-19 vaccines remains unclear. Gut microbiota sequencing and blood analysis at baseline, 1 month, and 6 months after vaccination revealed that multiple inflammatory factors, chemokines, and antibodies were associated with gut microbiota and metabolites, and that the abundance of some microbiota was associated with higher antibody levels at 6 months, suggesting that microbiota adjuvants may prolong the durability of the immune response to the SARS-CoV-2 vaccine.[180]

The course of the immune response after vaccination in partially immunocompromised patients is helpful for studying vaccine response. In immunosuppressed patients with IBD, gut microbiota and metabolomics analysis demonstrated that the diversity of gut microbiota in sublevel responders was significantly lower, and that the abundance of some microbiota such as *Cholangiella* was associated with better serological response, suggesting that gut microbiota is involved in different serological responses after SARS-CoV-2 vaccination. Regulating the composition and abundance of the microbiota may affect the efficacy of the vaccine.[181] Aging leads to major changes in the composition and function of the gut microbiome, including decreased diversity. The immunogenicity of COVID-19 vaccines is affected by the composition of the gut microbiota, and the immune response to COVID-19 vaccines decreases with age. The microbiome may be an important determinant of vaccine immunity, but the mechanisms of abnormal cellular function that influence the aging process and vaccine response are incompletely understood. The imbalance in gut microbiota in the elderly is closely related to immune senescence and gut microbiota. The intervention of probiotics targeting gut microbiota may improve the problem of reduced immune response in frail individuals.[182,183] Furthermore, vaccine-induced immune responses may vary greatly among individuals, and vaccines are less immunogenic in populations at the highest risk of infectious diseases. The composition and function of the gut microbiota may serve as key factors regulating the immune response to vaccines. Gut microbiota disorder determines postvaccination immune efficacy, particularly susceptibility to SARS-CoV-2, and the severity of infection. Microbiota can comprehensively regulate the immune status of the body by regulating the levels of metabolites and inflammation, and can affect the functional activities of a variety of enzymes. Targeting the gut microbiota can affect the acquired immunity of secreted immunoglobulins and the microbiome to stimulate local gut immune responses. In addition, SARS-CoV-2 replication requires certain key enzymes, and regulation

of the abundance of bacterial flora and its metabolite concentrations by probiotics may affect related processes and improve vaccine efficacy.[184–186] The research and use of SARS-CoV-2 intranasal spray vaccine have attracted increasing attention. Considering the characteristics of upper respiratory tract flora changes after virus infection and its potential function in regulating the virus and immune microenvironment, further exploration of the role of flora and the mechanisms of immune regulation is imperative for developing and using related vaccines.[187]

4.3 | Diagnosis and others

Based on the correlation between SARS-CoV-2 infection and changes in the abundance of intestinal microbiota in patients at various stages of infection, COVID-19 has been found to cause a decrease in microbiota diversity, resulting in a reduction in butyrate-producing bacteria. These changes also indicate immune dysregulation and are associated with some discomfort symptoms and poor prognosis. These findings suggest that the detection and biomarker analysis of intestinal flora after SARS-CoV-2 infection can be used as a therapeutic or intervention target to promote the rapid recovery of patients.[188,189] In addition, the intestinal barrier composition of the intestinal flora of the elderly changes, which is accompanied by decreased immune function. Probiotics regulate the composition of intestinal flora, affect intestinal sugar metabolism and vitamin synthesis, and in turn improve the overall inflammatory state.[190] A retrospective analysis found that supplementation with probiotics for elderly individuals over the age of 65 years can regulate the levels of inflammatory factors such as IL-8 and Il-10, suggesting that probiotics may regulate inflammation and oxidative stress. Fermented lactic acid bacteria containing the glutamate decarboxylase gene may mediate the intestinal–brain axis through the neurotransmitter γ-aminobutyric acid to improve cognitive impairment in elderly patients.[191] In addition, surgery may cause intestinal flora disorders and BBB destruction, which are obviously related to postoperative delirium and postoperative cognitive impairment. Furthermore, supplementation with probiotics improved neuroinflammation and cognitive impairment in surgery.[192,193] Yang et al.[194] found that probiotic preparations improved memory impairment in aging mice. The mechanism may be related to the repair of intestinal barrier and BBB functions, as well as the regulation of interleukin and tumor necrosis factor-α, suggesting that probiotic therapy can target the intestinal–brain axis to improve cognition.[194] Furthermore, there is evidence that probiotics improve inflammation, oxidative stress, and flora polymorphism in patients with AD and repair the BBB to a certain extent, thus improving cognitive decline. Moreover, no significant side effects were observed in the treatment, suggesting that probiotics have wide application prospects in AD treatment.[195] A randomized controlled pilot trial comparing the effects of probiotics on cognitive function in patients with fibromyalgia also found that probiotics improve patients' decision-making ability to a certain extent, providing further evidence for probiotic supplementation in treating cognitive impairment.[196] The potential pathways of cognitive impairment include inflammation, oxidative stress, BBB destruction, and the intestinal–brain axis. Probiotics may regulate these processes to improve cognitive impairment in AD. It has been reported that anti-inflammatory bacteria (*Bifidobacterium, Faecalibacterium*) and inflammation-associated microbiota (*Streptococcus, Actinomyces*) change significantly during COVID-19. Probiotics such as *Limosilactobacillus fermentum* and *L. rhamnosus* may modulate intestinal dysbiosis and consequently relieve proinflammatory response.[75,197] Gut microbiota metabolites are closely related to host immune function. Therefore, probiotics may regulate the body's immune response by regulating flora balance and metabolism. Improvement of the inflammatory response caused by COVID-19 is conducive to recovery. Ferroptosis, a type of cell death caused by iron-dependent lipid peroxidation, has gradually attracted attention in the complications of COVID-19.[198] Supplementation with probiotics can also regulate the iron death process. It has been reported that glutathione peroxidase 4 (GPX4) inactivation, iron metabolism changes, and reactive oxygen species peroxidation upregulation are unique signs of COVID-19. COVID-19 may cause the iron-mediated death of multiorgan cells, leading to multiorgan damage. Ferroptosis plays an important role in COVID-19-related myocarditis and lung injury.[199,200] Ferroptosis characterized by lipid peroxidation and high glutathione consumption is likely to mediate COVID-19-related brain injury, suggesting that iron death intervention may be used as a novel treatment for brain injury. Targeted therapy directed by probiotics and their metabolites provide novel ideas for the treatment of these diseases with comorbid mechanisms, which is worthy of further exploration.[201–203]

5 | CONCLUSION AND PROSPECTS

Evidence suggests that COVID-19 may be accompanied by microbiota alterations, and dysbiosis of the gut microbiota contributes to COVID-19 symptoms and COVID-19 development through metabolites and immune responses. A probiotic-based intervention may improve COVID-19 symptoms by regulating the gut microbiota and systemic immunity. However, further evidence is required to

establish a causal relationship between changes in microbiota (e.g., *Bacteroidetes, Enterobacteriaceae*, and *Subdoligranulum*) and symptoms associated with COVID-19. In addition, probiotic supplements such as *Lactobacillus, Bifidobacterium*, and *Streptococcus* may regulate intestinal immunity and intestinal barrier function through specific molecular mechanisms.

Probiotics may also be used as adjuvants to improve vaccine efficacy and prepare for rapidly changing viruses and the next pandemic. Indeed, a significant reduction in bacterial diversity has been reported among vaccinated subjects. Microbiome components appear to either enhance or reduce the efficacy of COVID-19 vaccines, indicating a bidirectional relationship. The mechanism by which probiotics and SCFA metabolism affect IgG levels, and the specific dose and effect, are worthy of further investigation.

The role of probiotics in cognitive protection and immune regulation also offers insights into the treatment of aging, AD, and other diseases. Probiotics and their metabolites may be used to target microbiota and regulate ferroptosis and GPX4 to provide solutions to treat diseases with comorbid mechanisms. In addition, the pathophysiological processes of neuroinflammation and the gut–brain axis regulated by different probiotics and SCFAs require further study. Well-designed clinical trials are urgently needed to enhance content credibility.

AUTHOR CONTRIBUTIONS

Y. Q., G. C., and T. Z. conceived and designed this project. Y. Q., C. M., and G. C. wrote the manuscript. L. C., W. Y., G. C., and T. Z. checked and amended the manuscript. All authors contributed to the article, read, and approved the final manuscript.

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All authors declare no conflict of interest.

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Not applicable.

ETHICS STATEMENT

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