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Review Article

Advances in the Interaction between Intestinal Microbiota and COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) is a global epidemic disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Many digestive symptoms have been reported in patients infected with this virus, however, the relationship between the intestinal microbiota and SARS-CoV-2 remains unknown. This review aims to elucidate the interaction between intestinal microbiota and SARS-CoV-2, and review the mechanism of interaction between these two items as well as the effects of probiotics. This review further discusses various studies on gastrointestinal symptoms and changes in intestinal microbiota in COVID-19 patients. To further understand the mechanism, we focused on the role of angiotensin converting enzyme 2 and transmembrane protease serine 2 in this viral infection. There is a correlation between many diseases and dysbiosis of intestinal microbiota. SARS-CoV-2 can lead to dysbiosis of intestinal microbiota through a variety of mechanisms, with a decrease in the abundance and diversity of probiotics and an increase in that of pathogenic bacteria. Dysbiosis of intestinal microbiota results in the translocation of intestinal flora, aggravation of systemic inflammation, and lung injury. Modulating the intestinal microbiota ameliorates digestive symptoms and pathology in infectious respiratory diseases. Intestinal microbiota and SARS-CoV-2 interact through a variety of mechanisms; SARS-CoV-2 can cause dysbiosis of the intestinal microbiota, while dysbiosis of intestinal microbiota, in turn, aggravates COVID-19.

Introduction

There is a large number of microbial communities, approximately 500 to 2,000 species, present in the gastrointestinal tract. The intestinal microbiota performs many essential functions that help the host to maintain health.[1] Studies indicate that host homeostasis and disease development are maintained by the immune system. Intestinal microbiota may contribute to the progression of coronavirus disease 2019 (COVID-19) due to the gut-lung interaction with the immune system.[2] Dysbiosis of intestinal microbiota results in changes in the composition of intestinal flora, gut permeability, and bacterial translocation. These processes eventually lead to multiple organ failure and may also result in the translocation of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from the lung into the intestinal tract.[3]

COVID-19 is a global epidemic that spreads acute respiratory infection caused by SARS-CoV-2. SARS-CoV-2 is a single-stranded RNA-enveloped virus belonging to the β-coronavirus genus. Full-genome analysis showed that SARS-CoV-2 shares 79.6% sequence identity with SARS-CoV and belongs to the same genus of coronaviruses.[4] The main transmission modes are respiratory droplets and close contact with an infected patient.[5] The clinical features of COVID-19 include high rates of transmission, destruction of multiple organs, and more serious symptoms in the elderly.[6–8] Additionally, multiple other clinical manifestations may also be observed, such as fever, dyspnea to pneumonia, acute respiratory distress syndrome, multiple organ failure, all of which may lead to death.[9] Digestive disorders appear to precede or follow respiratory symptoms[7] as previous studies have reported the incidence of gastrointestinal symptoms in 2% to 50% of COVID-19 cases.[10–13] The digestive system is not only a part of disease expression, but is also a potential driver of disease severity and viral transmission.[9] This review highlights the relationship between intestinal micro-

Keywords: Intestinal microbiota; SARS-CoV-2; COVID-19; Angiotensin converting enzyme 2; Transmembrane serine protease 2.

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin converting enzyme 2; TMPRSS2, transmembrane protease serine 2; RNA, ribonucleic acid; Ang II, angiotensin II; mTOR, mechanistic target of rapamycin; FMT, fecal microbiota transplantation.

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biota dysbiosis and SARS-CoV-2 infection.

Structure and function of the human intestinal microbiota

The intestinal microbiota is established from infant birth status and is relatively stable and resilient in adults with temporal patterns.[14,15] The intestinal microbiota of different individuals is relatively stable,[16] however, the diversity of intestinal flora decreases with biological age.[17] Most of the flora in the human intestinal tract is located in the colon, while the amount of bacteria in the jejunum, ileum, and duodenum decreases in turn. The intestinal flora of humans consists of approximately 100 trillion resident microorganisms, including bacteria, viruses, fungi, and chlamydiae.[18] The healthy state is characterized by between 500 and 2,000 microbial species, which comprise the four most common bacteria phyla of *Firmicutes*, *Bacteroidetes, Actinobacteria*, and *Proteobacteria*.[19]

The intestinal microbiota provides many beneficial functions in modulating intestinal barrier function, supporting the host immune system, inhibiting tumors, promoting vitamin synthesis, aiding digestion and absorption, and enhancing primary alveolar macrophage function.[20,21] Intestinal bacteria as well as products and metabolites of intestinal bacteria, play beneficial roles in the intestinal mucosal barrier by enhancing tight junctions and decreasing the permeability of the epithelium.[20] Differentiation and maturation of intestinal T helper 17 cells and secretion of IgA can be induced by intestinal flora, which are important components of intestinal mucosal immunity and participate in the regulation of human autoimmune diseases.[22,23] The intestinal microbiota directly or indirectly, through enzymes, makes an important contribution to the metabolism of dietary carbohydrates, proteins, bile acids, and vitamins.[24]

Intestinal microbiota dysbiosis and disease

Multiple factors can lead to changes in the intestinal microbiota, such as exercise, diet, obesity, drug utilization, host genetics, and disease.[15,25] Exercise can enhance the number of beneficial microbial species and improve the development of commensal intestinal bacteria.[26] A high-fat diet-induced intestinal microbiota dysbiosis increases intestinal permeability and causes an inflammatory response, whereas methionine-restricted diets can increase the abundance of *Bifidobacterium, Lactobacillus*, and *Bacteroides*.[27] Overuse of antibiotics can also lead to intestinal microbiota dysbiosis and superinfection, which in turn can aggravate the primary disease.[28,29]

There is a correlation between intestinal microbiota imbalance and many diseases. Microbial dysbiosis contributes to the development of liver cirrhosis, increases carcinoma susceptibility, and aggravates inflammatory bowel disease.[30] The number of *Enterobacteriaceae, Enterococcus,* and *Saccharomyces* was significantly greater in liver cirrhosis patients, but the number of *Lactobacillus, Bacteroides,* and *Clostridium* was significantly decreased.[30] *Fusobacterium* were also enriched in colorectal carcinomas, while *Bacteroidetes* and *Firmicutes* were significantly reduced in tumors.[31] The characteristics of intestinal microbiota can be used to predict biological age and the prognosis of diseases, to treat diseases, and to develop new drugs.[17] Intestinal microbiota plays an important role in the regulation of lung inflammation. The generation of metabolites of intestinal microbiota, such as short chain fatty acids, can suppress respiratory inflammation by activating G protein-coupled receptors.[32] Type 2 diabetes has a significantly lower abundance of verrucomicrobiae, which may be a potential biomarker thereof.[33] Based on a population view, the microbial synthesis potential of the dopamine metabolite 3,4-dihydroxyphenylacetic acid correlates positively with the mental quality of life, and microbial γ-aminobutyric acid production may play a role in the evolution of depression.[34] Nevertheless, the mechanism of interaction between microbiota and the host, especially at the molecular and biochemical levels, needs further study. These studies suggest that maintaining a normal intestinal microecology is one of the most important treatment strategies to maintain the dynamic balance of the immune system and reduce the occurrence of diseases.

The alterations of intestinal microbiota in COVID-19 patients

Dysbiosis of the intestinal microbiota can lead to a variety of gastrointestinal symptoms, leading to multi-organ dysfunction, the symptoms of which include diarrhea (4.8–50.0%), nausea, and vomiting (3.9%).[11,35,36] COVID-19 patients with gastrointestinal symptoms are also more likely to have higher rates of fever, fatigue, and shortness of breath, compared with patients without gastrointestinal symptoms.[37] However, a study of 138 COVID-19 patients found that diarrhea was present in 10.1% of patients, but there was no significant correlation between the occurrence of diarrhea and the need for intensive care.[38] Due to the limited data at present, medical staff should pay attention to COVID-19 patients who are complicated with gastrointestinal symptoms and who may be in a more severe condition. Whether gastrointestinal symptoms are a factor of poor prognosis remains to be studied further.

Dysbiosis of intestinal microbiota in COVID-19 exhibits a decrease in the abundance and diversity of probiotics and an increase in those of opportunistic pathogen bacteria. The probiotic bacteria, such as *Bifidobacterium* and *Lactobacillus*, decreased, and was dominated by pathogenic bacteria such as *Streptococcus, Rothia, Veillonella, Erysipelatoclostridium,* and *Actinomyces*.[9,39] *Bifdobacterium*and *Lactobacillus* can enhance the secretion of IgA and maintain mucus-secreting goblet cells, which in turn benefit the defensive effect of mucosal barriers.[20,24] Lu *et al.* found that *Streptococcus and Rothia* were likely to increase the risk of secondary bacterial lung infections in H7N9 patients.[40] Dysbiosis of the intestinal microbiota causes deficiencies in nutrient absorption in the gut and immune regulation, as well as lung injury.[41,42]

In some COVID-19 patients who have needed to be administered antibiotics, the drugs generally affect the intestinal microbiota. Zuo *et al.*[43] found that COVID-19 patients receiving empirical antibiotics or antibiotic-naïve therapy were characterized by the enrichment of opportunistic pathogens and the depletion of beneficial commensals. COVID-19 patients without antibiotic therapy had an enriched population of opportunistic pathogens, including *Clostridium hathewayi, Actinomycesviscosus,* and *Bacteroidesnordii*. These opportunistic pathogens are known to cause bacteremia.[44] While receiving antibiotics, patients demonstrated a further depletion of probiotics such as *F. prausnitzii, Lachnospiraceae* bacterium 5_1_63FAA, *Eubacteriumrectale, Ruminococcusobeum,* and *Doreaformicigenerans*, which are symbionts beneficial to host immunity.[43] This suggests that the use of antibiotics should be considered carefully as it may exacerbate intestinal flora disorders.

This dysbiosis of intestinal microbiota in patients with COVID-19 can persist in a subset up to 12 days after nasopharyngeal clearance of SARS-CoV-2.[45] Although SARS-CoV-2 infection may be cured in the respiratory tract, loss of probiotics and gastrointestinal tract SARS-CoV-2 persisted in some COVID-19 pa-

tients.[43,46] On the other hand, COVID-19 patients were enriched with fungal pathogens such as candida and aspergillus.[45] Candida albicans caused by intestinal colonization aggravates inflammation in the gastrointestinal tract.[47] Therefore, attention should be paid to the monitoring of intestinal microecological disorders in COVID-19 patients with gastrointestinal symptoms. Since these studies involved a small number of cases, more studies need to be conducted in the future, especially regarding the study of intestinal fungi.

Interaction and mechanism between COVID-19 and intestinal microbiota

There is evidence to suggest the presence of crucial cross-talk between the gastrointestinal microbiota and the lungs (gut-lung axis). The gut-lung axis mainly refers to the gastrointestinal microbiota, which can strengthen lung resistance, eliminate pathogenic bacteria and reduce or slow down the occurrence and development of respiratory diseases through the regulation of the immune response signal pathway. At the same time, disorders of the respiratory tract also impact the gastrointestinal tract through immune regulation.[48] The main reason for this extrapulmonary phenomenon may be that the virus damages the intestinal mucosa and changes the intestinal flora, while dysbiosis of intestinal microbiota aggravates the severity of COVID-19.[2] The RNA of SARS-CoV-2 can be detected in and be isolated from stool, and can be accompanied by intestinal microbiota disorders.[49] However, Wolfel *et al.*[50] reported that SARS-CoV-2 was isolated from samples derived from the throat or lung in COVID-19 patients, but not from stool samples despite high concentrations of virus RNA. This results suggests that whether the fecal-oral transmission route is utilized by SARS-COV-2 still needs more research.

Effects of SARS-CoV-2 on intestinal microbiota

COVID-19 can cause systemic inflammation syndrome, acute respiratory distress syndrome, shock, and antimicrobial use, all of which directly or indirectly cause dysbiosis of intestinal microbiota. Among these options, the combination of SARS-CoV-2 and angiotensin converting enzyme 2 (ACE2) plays a unique role in intestinal microecology. SARS-CoV-2 infects host cells by binding to the receptor of ACE2 and transmembrane serine protease 2 (TMPRSS2).[51] ACE2 and TMPRSS2 are not only co-expressed in lung AT1 and AT2 cells but are also highly expressed in enterocytes from the ileum and colon.[51,52] SARS-CoV-2 has four structural proteins, which are necessary for particle formation and include spike, membrane, envelope, and nucleocapsid proteins.[53] The first step of viral infection is entry into host cells. The spike protein on the viral envelope can bind to the specific cellular receptor ACE2 on the membrane of host cells. Spike protein can then be cleaved into S1 and S2 subunits. S1 is the receptor binding domain that contributes to the SARS-CoV-2 attachment to the surface of the human cell, and thus promotes the S2-mediated fusion process of SARS-CoV-2 with host cell membrane.[54] TMPRSS2 of host cell protease cleaves the spike protein, promoting the virus to release fusion peptides for membrane fusion.[55]

ACE2 is essential for neutral amino acid transporters in the gastrointestinal tract. Amino acid malnutrition can result in intestinal inflammation by ACE2, which plays an important role in innate immunity, amino acid homeostasis, and maintenance of intestinal microbiota.[56,57] ACE2 is necessary for intestinal B(0) AT1 expression, which is involved in the absorption of amino acids. When ACE2 is decreased or knocked out, tryptophan cannot be effectively absorbed and the mTOR pathway activity in the small intestine is reduced. This results in decreased expression of antimicrobial peptides in intestinal Paneth cells, which can lead to changes in the composition of intestinal flora and increase the risk of bacterial translocation and endotoxemia.[56,58–60]

ACE2 is a negative regulator of the renin-angiotensin system (RAS) and converts angiotensin II (Ang II) to vasoprotective heptapeptide (Ang-(1-7)).[61] Ang-(1-7) binds with the receptor Mas to construct the ACE2-Ang-(1-7)-Mas axis, which exerts beneficial effects by improving endothelial function, anti-oxidative stress, and inhibits the inflammatory response and alleviates intestinal inflammation.[62–64] In addition, Yang *et al.* reported that colonized gut microbiota decrease in colonic ACE2 expression through the presence or absence of the microbiota rats. This suggests that the variability of gut microbial composition is one of factors for the susceptibility of COVID-19.[57]

TMPRSS2 is a protease that belongs to the type II transmembrane serine protease family. The cells expressing TMPRSS2 play a role in infecting and propagating SARS-CoV-2.[65] TMPRSS2 knockout mice can reduce the primary sites of infection and increase virus spread within the respiratory tract and immunopathological injury after infection by SARS-CoV.[66] This suggests that TMPRSS2 plays a critical role in coronavirus infection and will be one of the selected targets for drug therapy in the future.

Moreover, influenza pulmonary infection can change the intestinal microecology through type I interferons (IFNs). High levels of type I IFNs increase interlukin-17 production and Th17 cell activation, which promotes the production of pro-inflammatory cytokines and chemokines and destroys intestinal epithelial cells.[67]

The binding of SARS-CoV-2 to the ACE2 receptor results in ACE2 downregulation. TMPRSS2 enhances the spread of this virus, hindering the absorption of intestinal nutrients, aggravating intestinal inflammation, reducing the function of intestinal mucosal barrier, and causing intestinal flora translocation and abnormal composition. However, the exact mechanism by which SARS-CoV-2 interacts with intestinal microbiota is still unclear.

Effects of intestinal microbiota dysbiosison COVID-19

Normal intestinal microbiota play an important role in the regulation of lung immunity and host defense.[21] Dysbiosis of the intestinal microbiota leads to deficient energy harvesting and immune protection, is correlated to diarrhea and systemic invasion by microbial pathogens, and increases the burden of lung infection patients.[68] Dysbiosis of the intestinal microbiota therefore induces the translocation of intestinal flora, the aggravation of systemic inflammation and lung injury.

Respiratory influenza virus infection induces intestinal injury by microbiota-mediated Th17 cell-dependent inflammation,[69] which increases the risk of bacterial translocation. Dickson *et al.* found that the lung microbiome is enriched with intestinal bacteria in a murine model of sepsis and in humans with established acute respiratory distress syndrome. Overall, the gut-lung translocation and disorder of the lung microbiome are associated with indices of systemic and alveolar inflammation, respectively.[70] In contrast, the cytokine storm is caused by the massive release of cytokines and chemokines, leading to widespread and uncontrolled disorders of the host immune defense in COVID-19 patients.[9,71,72]

Dysbiosis of intestinal microbiota can result in the enhancement of pulmonary influenza virus amplification, leading to the aggravation of airway inflammation and the progression of sepsis.[69,70,73,74]

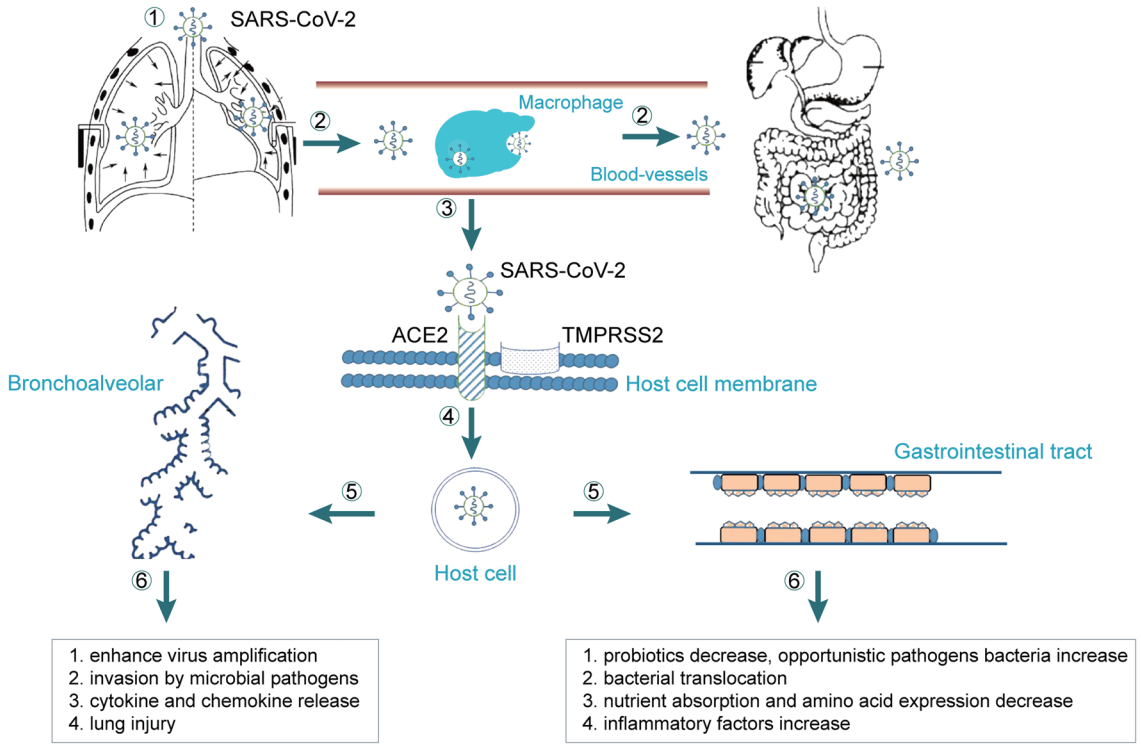

Fig. 1. A model for the process by which SARS-CoV-2 enters host cells in the lung and gastrointestinal tract. The spike glycoprotein of SARS-CoV-2 binds to the angiotensin converting enzyme 2 (ACE2) on host cells, allowing the virus enter. Transmembrane protease serine 2 (TMPRSS2) also participates in this process by cleaving the spike glycoprotein, promoting the virus to release fusion peptides for membrane fusion.

Through the BALB/c pulmonary influenza virus infection mouse model with dysbiosis of intestinal microbiota, Pang *et al.*[74] found that the lung viral load significantly increased and suggested that intestinal dysbacteriosis might affect antiviral immunity in the lung.[74] For intestinal dysbacteriosis COVID-19 patients, whether there is similar performance, and whether the virulence and infectivity of the virus change still need further research (Fig. 1).

Effects of probiotics on COVID-19

Probiotics are living microorganisms that, when used at a reasonable dosage, are beneficial to the health of the host. Probiotics can improve intestinal flora disorders, reduce secondary infections, and improve immunity.[75–78] About 12.3% of COVID-19 patients need invasive ventilation.[7] Probiotics have been reported to reduce enteritis, the duration of intensive care unit stays, and ventilator-associated pneumonia in patients with sepsis.[75,79] Modulating the intestinal microbiota has been reported to have ameliorated the symptoms and pathology in a sepsis mouse model.[80] Studies have further found that probiotics can reduce the incidence of respiratory diseases in the elderly and children.[81,82] d'Ettorre *et al.* found that from 28 COVID-19 patients the risk of developing respiratory failure was eight-fold lower in patients receiving oral bacteriotherapy, and the prevalence of patients transferred to the intensive care unit and mortality was lower.[83] Previous studies have found that probiotics can produce exopolysaccharides, increase leukocyte and natural killer cell counts, decrease inflammatory cytokine expression, and influence both innate and adaptive immune responses.[82] However, the potential mechanisms of probiotics on COVID-19 are not yet well defined.

Fecal microbiota transplantation (FMT) is one of the treatment strategies to restore the dynamic balance of intestinal microbiota. Considering that SARS-CoV-2 may be potentially transmitted through a fecal-oral route, the use of FMT should be conducted with caution during the epidemic of COVID-19.[84] To preserve intestinal balance and reduce the risk of secondary bacterial infections, the use of probiotics is recommended for the treatment of patients with severe COVID-19 in China.[9] Clinical trials testing probiotic treatments for COVID-19 are being undertaken, however, until reliable data is available against this approach, probiotic use should be recommended (Table 1).

Future direction

COVID-19 is a global epidemic that can cause multiple organ failure within the digestive system. It is necessary to confirm the mechanism and interaction between intestinal microbiota and COVID-19. SARS-CoV-2 infects host cells by binding to the receptor of ACE2, which is co-expressed in the lung and intestinal tract. Further studies are needed to identify other binding receptors by which this virus infects host cells. Dysbiosis of intestinal microbiota may occur in COVID-19 patients, but further studies on the gastrointestinal injury of these patients are needed. Noninvasive tests such as calprotectin, computerized tomography enterograph, magnetic resonance enterograph, may be used to assess the gastrointestinal injury. Moreover, the intestinal microbiota participates in helping the host to maintain homeostasis through a gut-lung interaction. Clinical attention should focus on the efficacy and mecha-

Table 1. The latest literature sources on COVID-19 and intestinal microbiota

No	Author	Year	Objects	Sample size	Conclusions
1	Zuo *et al.*[43]	2020	COVID-19 patients	15	Fecal microbiota alterations were associated with fecal levels of SARS-CoV-2 and COVID-19 severity, with persistent alterations during hospitalization.
2	Zuo *et al.*[45]	2020	COVID-19 patients	30	COVID-19 patients have enrichment of fungal pathogens from the genera Candida and Aspergillus. Up to 12 days after nasopharyngeal clearance of SARS-CoV-2, prolonged dysbiosis persisted in COVID-19 patients.
3	Zuo *et al.*[49]	2020	COVID-19 patients	15	Gut microbiota of patients with active SARS-CoV-2 gastrointestinal infection was characterised by enrichment of opportunistic pathogens, loss of salutary bacteria and increased functional capacity for nucleotide and amino acid biosynthesis and carbohydrate metabolism.
4	Zhou *et al.*[10]	2020	COVID-19 patients	254	The gastrointestinal symptom group appeared to have a similar rate of complications, treatment, and clinical prognosis as the non–gastrointestinal symptom group in COVID-19 patients
5	Yang *et al.*[57]	2020	rat		Gut microbiota colonized decrease in colonic ACE2 expression
6	Xing *et al.*[46]	2020	COVID-19 patients	3	SARS-CoV-2 may exist in children's gastrointestinal tract for a longer time than the respiratory system.
7	Wolfel *et al.*[50]	2020	COVID-19 patients	9	Pharyngeal virus shedding was very high during the first week of symptoms, with a peak RNA copies per throat swab on day 4. Infectious virus was readily isolated from samples derived from the throat or lung, but not from stool samples.
8	Wei *et al.*[13]	2020	COVID-19 patients	84	A higher proportion of COVID-19 patients with diarrhea have virus RNA in the stool. Elimination of SARS-CoV-2 from stool takes longer than that from the nose and throat.
9	Pan *et al.*[36]	2020	COVID-19 patients	204	COVID-19 patients with digestive symptoms have a longer time from onset to admission, evidence of longer coagulation, and higher liver enzyme levels.
10	Matsuyama *et al.*[65]	2020	VeroE6/ TMPRSS2 cells	/	TMPRSS2 may also play an important role in SARS-CoV-2 cell entry and is likely to be a key protease for SARS-CoV-2 replication.
11	Gu *et al.*[39]	2020	COVID-19 patients	30	COVID-19 patients had significantly reduced bacterial diversity, a significantly higher relative abundance of opportunistic pathogens, such as Streptococcus, Rothia, Veillonella and Actinomyces, and a lower relative abundance of beneficial symbionts
12	d'Ettorre *et al.*[83]	2020	COVID-19 patients	70	Using the specific bacterial formulation ameliorated the impact on the clinical conditions of COVID-19 patients

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin converting enzyme 2; TMPRSS2, transmembrane protease serine 2.

nism of probiotic therapy in COVID-19 patients.

Conclusion

A variety of mechanisms are involved in the interaction between the intestinal microbiota and COVID-19. SARS-CoV-2 can cause dysbiosis of intestinal microbiota and intestinal damage, with dysbiosis of intestinal microbiota aggravating a systemic inflammatory response and lung injury. Modulating the intestinal microbiota improves digestive symptoms and the pathology of respiratory infectious diseases. Probiotics may have therapeutic value for COVID-19. Nevertheless, more studies on the interaction between intestinal flora and COVID-19 are needed in the future.

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Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

Study design (ZJH, LYC); manuscript writing (ZJH, YXL). The authors read and approved the final manuscript.

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