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Human microbiome in post-acute COVID-19 syndrome (PACS)

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ABSTRACT

The global COVID-19 pandemic, which began in 2019, is still ongoing. SARS-CoV-2, also known as the severe acute respiratory syndrome coronavirus 2, is the causative agent. Diarrhea, nausea, and vomiting are common GI symptoms observed in a significant number of COVID-19 patients. Additionally, the respiratory and GI tracts express high level of transmembrane protease serine 2 (TMPRSS2) and angiotensin-converting enzyme-2 (ACE2), making them primary sites for human microbiota and targets for SARS-CoV-2 infection. A growing body of research indicates that individuals with COVID-19 and post-acute COVID-19 syndrome (PACS) exhibit considerable alterations in their microbiome. In various human disorders, including diabetes, obesity, cancer, ulcerative colitis, Crohn's disease, and several viral infections, the microbiota play a significant immunomodulatory role.

In this review, we investigate the potential therapeutic implications of the interactions between host microbiota and COVID-19. Microbiota-derived metabolites and components serve as primary mediators of microbiota-host interactions, influencing host immunity. We discuss the various mechanisms through which these metabolites or components produced by the microbiota impact the host's immune response to SARS-CoV-2 infection. Additionally, we address confounding factors in microbiome studies. Finally, we examine and discuss about a range of potential microbiota-based prophylactic measures and treatments for COVID-19 and PACS, as well as their effects on clinical outcomes and disease severity.

1. Introduction

A group of symptoms known as post-acute COVID-19 syndrome (PACS) manifests two months or more after the initial SARS-CoV-2 infection. PACS is classified as chronic COVID-19 (also referred to as "Long COVID" or "Long Haul COVID") when symptoms persist beyond twelve weeks, while post-acute COVID-19 is defined as symptoms lasting more than three weeks after the onset of the first symptoms. In other words, "long COVID" refers to a multisystem condition affecting individuals who have either recovered from a relatively mild acute COVID-19 illness but continue to experience ongoing symptoms, or who have endured the typical symptoms for a significantly longer duration than expected (Montani et al., 2022). COVID-19 survivors have reported a wide array of persistent, erratic, perplexing, and multisystem symptom complexes, including fatigue, dyspnea, dry cough, chest pain, musculoskeletal aches, joint pain, headaches, myalgias, prolonged loss of taste or smell, appetite loss, GI issues, diarrhea, sleep disturbances, cognitive impairments—such as forgetfulness and memory issues, often referred to as "brain fog mental health disturbances." All of these symptoms adversely affect quality of life and can impede the recovery process. At times, symptoms may even resolve only to reappear later. These aftereffects resemble the collection of clinical signs and symptoms previously identified as chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) (Pintos et al., 2022). Not only can hospitalized and critically ill COVID-19 survivors experience a wide range of persistent lasting symptoms, but non-hospitalized individuals who are asymptomatic or mildly ill have also been documented to experience similar issues. It is anticipated that there will be a significant influx of patients suffering from persistent and severe PACS, as well as other subacute and long-term health consequences, due to the unprecedented scale of the pandemic and the large number of people infected globally. Consequently, it is essential to more thoroughly predict and manage this underappreciated silent wave of PACS and the "unexpected" medium- to long-term multiorgan health repercussions in COVID-19 survivors. A

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long-term healthcare strategy and a COVID-19 survivor registry are vital tools for researching the long-term health issues that affect the quality of life of these individuals (Shelley, 2020). Premature atrial contractions have a complex etiology, with multiple mechanisms potentially contributing to various clinical presentations. The development of PACS may be influenced by immunological dysregulation, chronic inflammatory responses, autoimmune mimicry, pathogen reactivation, and alterations in the host microbiome (Batiha et al., 2022). Prolonged inflammation plays a major role in its pathophysiology and can also lead to other symptoms, such as neurological issues and cognitive impairment. A growing body of research indicates that individuals with COVID-19 and PACS exhibit significant changes in their microbiome. In many human disorders, including diabetes, obesity, cancer, ulcerative colitis, Crohn's disease, and several viral infections, the microbiota play a crucial immunomodulatory role. The human microbiota is characterized by a diverse microbial population that can coexist symbiotically in various anatomical locations within the human body (Rastogi et al., 2022). Infected individuals with SARS-CoV-2 primarily experience disturbances in the homeostasis of respiratory and GI microbiota (Xu et al., 2021, Hernández-Terán et al., 2021, Mizutani et al., 2022). The COVID-19 pandemic has highlighted the disruption of the microbiome in post-acute sequelae of COVID-19 (PASC), making it an urgent medical concern that warrants further investigation. We are still in the early stages of understanding PACs.

Thus, the purpose of this review was to evaluate the immunological processes and clinical significance of the associations between the microbiome and COVID-19. We also evaluated a number of studies that focus on the microbiota and are based on the immunological interactions between the COVID-19 virus and the microbiota, which may improve anti-SARS-CoV-2 therapies. The abbreviations used in this paper are shown in Table 1.

1.1. Relationship between Microbiota and COVID-19

Several investigations have demonstrated that the microbiota can influence the host through various mechanisms and contribute to the spread of SARS-CoV-2. An essential regulatory protein of the renin-angiotensin system, angiotensin converting enzyme 2 (ACE2), along with the microbiota, can first converts angiotensin II into angiotensin ang (Montani et al., 2022, Pintos et al., 2022, Shelley, 2020, Batiha et al., 2022, Rastogi et al., 2022, Xu et al., 2021, Hernández-Terán et al., 2021, Koester et al., 2021). To maintain systemic metabolic homeostasis, ACE2, Ang (Montani et al., 2022, Pintos et al., 2022, Shelley, 2020, Batiha et al., 2022, Rastogi et al., 2022, Xu et al., 2021, Hernández-Terán et al., 2021), and its receptor Mas form an anti-inflammatory and antioxidant axis (Rajilić-Stojanović and de Vos, 2014). Following the COVID-19 pandemic, researchers discovered that ACE2 facilitates the entry of SARS-CoV-2 into the human body (Lee et al., 2022, Macpherson and McCoy, 2013). To cleave and activate the SARS-CoV-2 spike protein (S protein) and bind it to its receptor ACE2, SARS-CoV-2 relies on transmembrane serine protease 2 (TMPRSS2) and furin (Louis and Flint, 2017). The salivary glands, oral mucosal epithelial cells, and ileocolonic epithelial cells are significant sources of ACE2 and TMPRSS2 (Durack and Lynch, 2019).

Independent of the renin-angiotensin system (RAS), ACE2 stabilizes the expression of the amino acid transporter B0AT1, regulates the

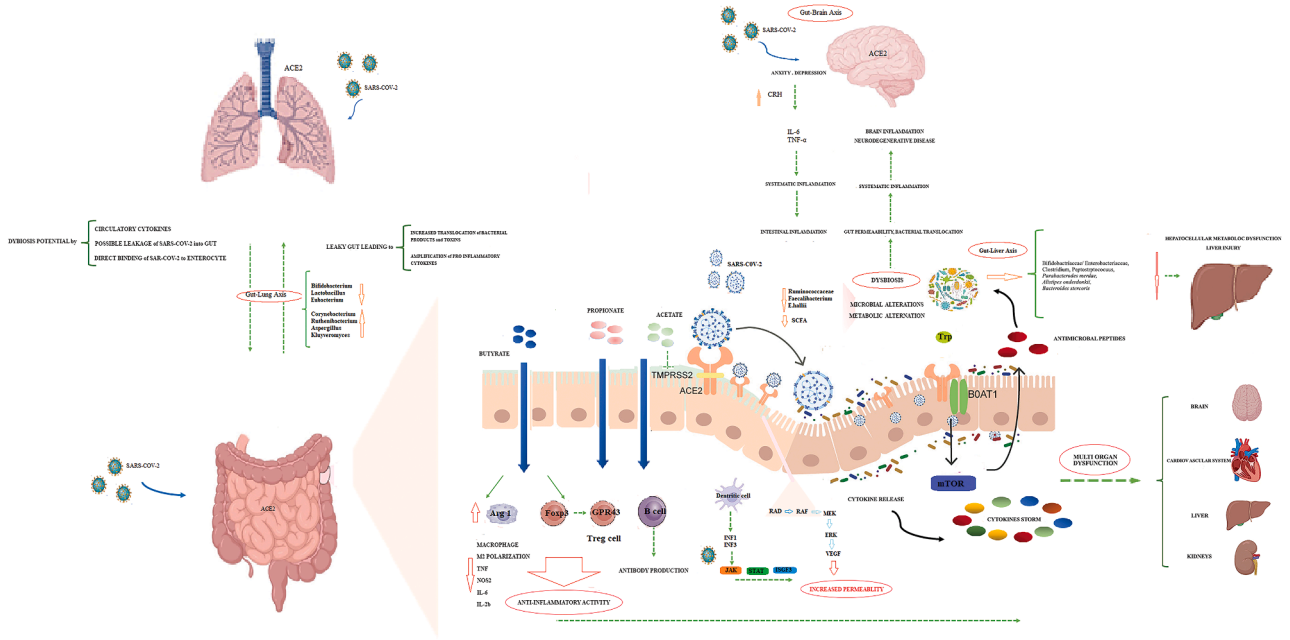

Fig. 1. Schematic diagram of the relationships among SARS-CoV-2, ACE2, host immunity, and microorganisms. (1) SCFAs -acetate, propionate, and butyrate- are produced by the gut microbiota and can reduce inflammation brought on by SARS-CoV-2 infection. By downregulating *Nos2, Il6*, and *Il12b*, decreasing the generation of tumor necrosis factor (TNF), and upregulating arginase 1 (ARG1), butyrate encourages M2-like macrophage polarization and anti-inflammatory action. Butyrate inhibits histone deacetylases and promotes the development of naive T cells into Treg cells by upregulating transcription at the *Foxp3* promoter and related enhancer sites. Propionate increases Treg cell proliferation by activating GPR43 on the cells. Acetate has anti-inflammatory properties because it stimulates B cells to produce anti-SARS-CoV-2 antibodies. Conversely, SCFAs have the ability to downregulate antiviral pathways and *TMPRSS2* gene expression, which prevents viruses from entering the body. (2) TMPRSS2 activates SARS-CoV-2, which then attaches to ACE2 to enter the gut, where it might rupture the gut barrier and lead to dysbiosis of the microbiota. (3) The JAK-STAT pathway of type I and type III interferon responses is suppressed by SARS-CoV-2 infection, and the *ISGF3*-encoded protein that inhibits viral infection will be lessened. Moreover, an infection with SARS-CoV-2 decreases ACE2 expression, impairs its capacity to control the RAS system, and overactivates the immune system. A cytokine storm can be triggered by dysregulated gut microorganisms and their metabolites, which can also increase cytokine production. (4) In intestinal epithelial cells, the SARS-CoV-2 S protein stimulates the Ras-Raf-MEK-ERK-VEGF pathway and stimulates the synthesis of VEGF, vascular endothelial growth factor, which causes inflammation and vascular permeability. (5) Through mTOR-mediated antimicrobial peptide synthesis, ACE2 controls the expression of the amino acid transporter B0AT1, which influences the makeup of the microbiota. An increase in pro-inflammatory cytokines floods the circulatory system with the entrance of the bacterial products and toxins from the GI tract.

expression of antimicrobial peptides (AMPs), controls the uptake of neutral amino acids, and influences the composition of the microbiota (Adak and Khan, 2019). Additionally, ACE2 alters the microbial composition by promoting AMP production through the mTOR (Suez et al., 2022). Cellular expression of ACE2 is negatively regulated by SARS-CoV-2 infection, which inhibits its enzymatic activity (Sonnenburg et al., 2016). This inhibition leads to intestinal barrier disruption, dysbiosis of the microbiota, and exacerbation of systemic inflammation (Berg et al., 2020). Conversely, the expression of ACE2 in the intestines can also be modulated by the gut microbiota (Koester et al., 2021).

Bacteroides thetaiotaomicron (*B. thetaiotaomicron*) and *Bacteroides dorei* (*B. dorei*) are among the *Bacteroidetes* whose fecal SARS-CoV-2 burden is significantly inversely associated. In the meantime, these bacteria may suppress the expression of ACE2 in the stomach. Conversely, *Firmicutes* can upregulate ACE2 expression and exhibit a positive correlation with COVID-19 severity (König et al., 2022). This raises the counterintuitive possibility that individuals with severe COVID-19 and high viral loads may have elevated ACE2 levels. Research indicates that the respiratory epithelium of COVID-19 patients exhibited three times higher levels of ACE2 expression compared to the control group (Martín et al., 2023). This conflicting outcome may be attributed to ACE2′s dual function (VanElzakker et al., 2019). On one hand, ACE2 facilitates the virus's entry into cells by acting as a receptor for SARS CoV-2. On the other hand, ACE2 protects the organism from harm in various pathological conditions by functioning as an amino acid transport regulator and a negative regulator of the renin-angiotensin system (VanElzakker et al., 2019). For instance, ACE2 plays a crucial role in protecting mice from sepsis and severe acute lung injury caused by acid inhalation (Lamers et al., 2020). Therefore, further investigation into the intricate connection between ACE2 and microbes remains essential.

Another important area of interest is the relationship between microbial metabolites and COVID-19. Several studies have shown that metabolites of microbiota, including SCFAs, aromatic compounds, amino acids, bile acids, vitamins, and lipids, can influence the host and play a role in the progression of disease (Meringer and Mehandru, 2022). There is extensive research on the links between microbial metabolites and a various illnesses. For instance, one study reported that mice with elevated SCFAs in their blood showed reduced susceptibility to allergic lung inflammation (Beyerstedt et al., 2021). When the bile acid metabolic pathway of GI commensal bacteria was knocked out in mice, the percentage of colonic RORγ^{+} regulatory T cells decreased and the colon's susceptibility to colitis rose (Cheema and Pluznick, 2019). Through its micro-ecosystem and the intricate, varied metabolites of its microbiota, the microbiota hinders SARS-CoV-2 infections. According to a study, the rise in bacterial products in plasma from COVID-19 patients was linked to an increase in inflammatory mediators, including TNFSF14 and oncostatin M (Hashimoto et al., 2012). Numerous investigations have now clearly demonstrated that COVID-19 patients have lower levels of short-chain fatty acid-producing bacteria (Villapol, 2020). In order to investigate the connection between the pathophysiology and severity of COVID-19 and gut microbiota metabolomics (Han et al., 2020), we discovered that urea synthesis was elevated in patients with COVID-19 due to poor synthesis of SCFAs and L-isoleucine in their gut flora, which is also linked to increased disease severity and inflammatory markers, including CRP and CXCL-10. The complex effects of SCFAs include immunological modulation and anti-inflammatory properties (Chen et al., 2022), as well as effects on metabolism (Giannos and Prokopidis, 2022). For instance, it reduces inflammation by controlling immune cell activity, such as Treg and macrophage (Mφ) function (Guo et al., 2023). Several types of bacteria create short-chain fatty acids, or SCFAs. These consist of propionate (10–20 %; produced by *Bacteroidetes* and a few *Firmicutes*), butyrate (10–40 %; produced by a few *Clostridia*), and acetate (50–70 %), which are produced by numerous bacterial taxa (Xiong et al., 2023). Many studies have been conducted on butyrate. Remarkably, a recent comprehensive review of the literature found that butyrate suppresses the expression of the ACE2 and TMPRSS2 genes, increases the amount of ADAM17, a metallopeptidase involved in ACE2 shedding, and increases several important antiviral pathways, including TLR (Grasselli et al., 2021). Three byproducts of the bacteria Tryptamine, the 5-hydroxytryptamine receptor agonist, pyrazine 2,5-bis (3-indolylmethyl) pyrazine, and N6-(D2-isopentenyl) adenosine all have anti-SARS-CoV-2 activity and resemble clinical antiviral medications in their structures and actions (Nori et al., 2021). High doses of 25-hydroxyvitamin D significantly decreased ICU admissions of hospitalized COVID-19 patients (see Fig. 1)(de Almeida et al., 2022).

1.2. Gut microbiota dysbiosis

Up to 10^{14} resident microorganisms, including bacteria, viruses, fungi, and other eukaryotes, are present in the human gut microbiota, with bacteria being the most prevalent type. *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Verrucomicrobia*, and *Fusobacteria* are the phyla that are most prevalent in the gut (Rajilić-Stojanović and de Vos, 2014). *Bacteroidia* (*Bacteroidetes*) and *Clostridia* (*Firmicutes*) classes of bacteria, in particular, have been shown to grow in the duodenum and colon, while facultative anaerobic Bacilli (*Firmicutes*) and *Enterobacterales* (*Proteobacteria*) taxa have decreased (Lee et al., 2022, Macpherson and McCoy, 2013). The creation of vitamins and SCFAs, energy extraction from diets, and immunomodulation through the control of TH17 and Treg balance are just a few of the many roles that the gut microbiota plays (Louis and Flint, 2017, Durack and Lynch, 2019, Adak and Khan, 2019). Prebiotics, such as microbiota-accessible carbohydrates (MAC), probiotics, and postbiotics, such as their byproducts (SCFAs), are in a complex equilibrium (Suez et al., 2022, Sonnenburg et al., 2016), involving several networks that influence processes in both health and disease by acting as axes (i.e., the gut-lung, gut-liver, and gut-brain axes) between the gut microbiota and other body sites. A shift in the quantity and/or variety of microorganisms within the microbiota is commonly linked to an imbalance of the vital homeostasis between the *Firmicutes, Bacteroidetes, Actinobacteria*, and *Proteobacteria* phyla. This condition is known as dysbiosis (Berg et al., 2020). Increased bacterial translocation, a disturbed intestinal barrier, neuroinflammation, and neuroimmune dysfunction are all thought to result from intestinal dysbiosis-induced immunometabolic changes (e.g., decreased production of antimicrobial peptides, SCFAs, altered tryptophan/kynurenine pathway) (König et al., 2022, Martín et al., 2023, VanElzakker et al., 2019). While the respiratory tract is the primary target of COVID-19, there are other lines of evidence suggesting significant involvement of the GI tract as well (Lamers et al., 2020, Meringer and Mehandru, 2022). Enteric ACE2 integrity and function may be significantly reduced by SARS-CoV-2 infection of enterocytes, which is mediated by ACE2, TMPRSS2, and TMPRSS4. When ACE2 expression is reduced, angiotensin (Ang) II and other renin-angiotensin system components are upregulated (Beyerstedt et al., 2021). Surprisingly, sex-specific changes in gut microbial composition and metabolomics can be brought about by elevated Ang II levels (Cheema and Pluznick, 2019). Furthermore, a decrease in mTOR-mediated AMP synthesis, independent of RAS, may result in gut dysbiosis as a consequence of the SARS-CoV-2 infection-induced loss of ACE2 function (Hashimoto et al., 2012). Since severe GI distress is frequently experienced during the acute phase of COVID-19, there is compelling evidence that the ensuing gut microbiota dysbiosis may endure for an extended period of time (Villapol, 2020). Importantly, symptoms like diarrhea are frequently experienced by individuals with milder infections who may not need to be hospitalized (Han et al., 2020). In fact, six months after infection, microbiome analyses in PACS patients showed reduced diversity, indicating that COVID-19-induced dysbiosis can endure permanently and sustain inflammation (Chen et al., 2022, Giannos and Prokopidis, 2022). Strong evidence linking gut dysbiosis to PACS has been accumulating from observational and interventional studies, in part because of its well-established links to CFS, a disorder that has many of the same

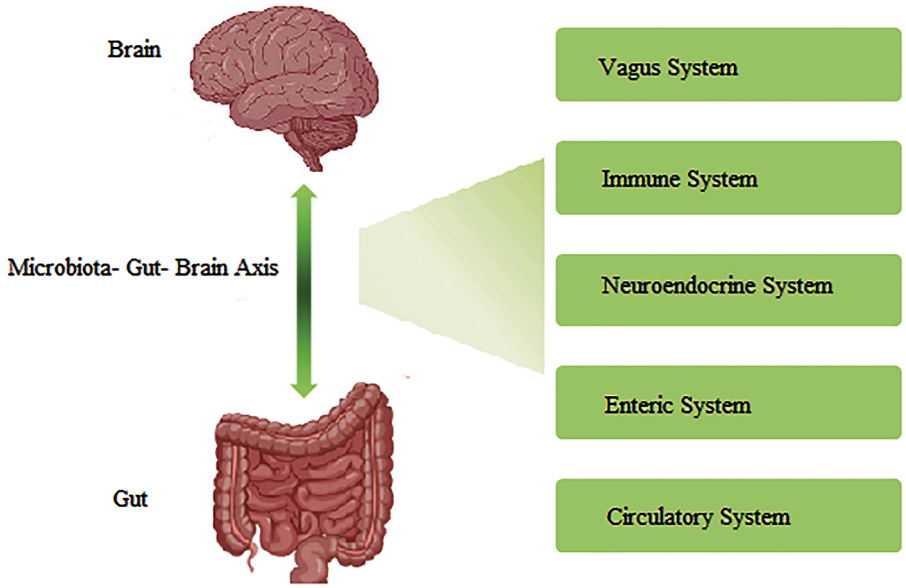

Fig. 2. Bidirectional communication of microbial gut-brain axis. The vagus nerve system, immune system, circulatory system, neuroendocrine system, and enteric nervous system are the main ways of bidirectional communication.

symptoms as PACS (Guo et al., 2023, Xiong et al., 2023). Deficiencies in beneficial gut microbial strains and elevated pathogen concentrations have been shown to in both severe and moderate COVID-19 patients across both acute and chronic disease stages. Hospitalized COVID-19 patients have been shown to have blooms of pathogenic and opportunistic bacteria, including antibiotic-resistant ones, which increase their risk of developing multidrug-resistant infections and raise the mortality rate from septic shock to as high as 57 % (Grasselli et al., 2021, Nori et al., 2021). Those with long COVID-19 experienced gut dysbiosis that persisted for at least 14 months, with higher levels of *Ruminococcus gnavus* (*R. gnavus*) and *Bacteroides vulgatus* and lower levels of *Faecalibacterium prausnitzii* (*F. prausnitzii*); low levels of butyrate-producing bacteria are strongly correlated with long COVID at six months. Persistent respiratory and neurological problems have been linked to particular gut bacteria. Furthermore, stool samples from COVID-19 patients contain SARS-CoV-2 RNA. According to one study, this RNA persists in the feces of 3.8 % of participants seven months after diagnosis and 12.7 % of participants four months after diagnosis. The majority of individuals with inflammatory bowel disease and persistent COVID symptoms seven months after infection had persistent antigens in their gut mucosa. Patients with long COVID show higher amounts of fungal translocation from the gut and/or lung epithelium in their plasma than either SARS-CoV-2-negative controls or patients without long COVID, which may induce cytokine production. The commensal probiotic bacterium *Bifidobacterium longum* was used as a partial treatment for mice that had decreased lung defenses and lost cognitive functioning when gut microbes from individuals with prolonged COVID-19 were transferred to healthy mice (de Almeida et al., 2022).

The scientists also looked into the possibility that PACS development could be influenced by the gut flora profile upon admission. Stool sample analyses performed upon hospital admission showed clear differences in bacterial clusters between PACS-positive and PACS-negative patients (Liu et al., 2022). Patients lacking PACS-COVID-19 showed gut bacterial compositions enriched for 19 bacteria, typified by *Bifidobacterium, Blautia*, and *Bacteroidetes*, in contrast to PACS patients. Compared to healthy controls, patients with PACS showed noticeably lower diversity and richness of gut microbes. Six months later, 13 different types of bacteria, including *Blautia wexlerae* and *Bifidobacterium longum*, were negatively correlated with PACS. Therefore, these species might have a protective role while recovering from an infection with SARS-CoV-2. On the other hand, PACS showed a positive correlation with *Actinomyces* sp. S6 Spd3, *Actinomyces johnsonii*, and *Atopobium parvulum*. Additionally, the investigators noted that a number of PACS symptoms were linked to specific bacterial species, including *R. gnavus, Clostridium innocuum*, and *Erysipelatoclostridium ramosum*, which remained present from admission through six-month follow-up (Liu et al., 2022). Combined, these results imply that the gut microbiota composition at admission may indicate that patient's vulnerability to long-term COVID-19 complications.

1.2.1. *Gut–brain axis*

The gut-brain axis (GBA), which refers to the bidirectional relationship between the brain and the gut, involves multiple channels, such as hormones, neurotransmitters, bacterial metabolites, and neuroanatomical communications (Manosso et al., 2021). Such communication is mainly carried out by the vagus nerve, and the GI tract produces these molecules (hormones and neurotransmitters). Neurotransmitters and hormones may interact with vagus nerve receptors during communication, sending information from the nerves to the brain (see Fig. 2) (Manosso et al., 2021, Alexander et al., 2021). Numerous hormones have direct effects on the central nervous system (CNS) after passing through the blood-brain barrier (BBB). The BBB is also impacted by neuroendocrine pathways that function through the hypothalamic-pituitary-adrenal (HPA) axis and are linked to stress. The adrenal cortex's secretion of glucocorticoids like cortisol is linked to the stress-HPA axis. The gut microbiota is impacted by cortisol, which is linked to increased intestinal permeability and GI motility (Manosso et al., 2021, Yeoh et al., 2021, Matsuoka and Kanai, 2015). Additionally, inflammation and poor metabolite production derived from bacteria, particularly SCFA production, may result from the stress-HPA axis (see Fig. 1) (Yeoh et al., 2021).

The gut bacteriome, virome, and mycobiome, which further regulate brain activity, are known to be impacted by a variety of diseases, including Coronaviruses, HIV, Zika virus, Enteroviruses, Rotaviruses, Influenza virus, among others, which can disrupt the GBA. Numerous PASC and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) investigations have revealed changes in GBS-associated critical modulators, including cytokines, cholecystokinin, lipopolysaccharide (LPS), 5-hydroxytryptamine, and SCFAs, which are driven by the microbiome's modification (Vakili et al., 2022). Additionally, weariness seems to be associated with neuroinflammation, a primary clinical manifestation of post-acute infection syndrome (PAIS), as one of the

possible outcomes (Omdal, 2020). The hypothalamic torpor nucleus was linked to exhaustion in a rat study, indicating that activation of GBA in the brain may activate the relevant fatigue region (Hrvatin et al., 2020). In both PASC and ME/CFS, the pathogen can either directly produce inflammation in the brain or initially use the gut microbiota to cause systemic inflammation. This inflammation subsequently leads to heightened inflammatory responses, immune dysregulation, and neurological symptoms (Tate et al., 2022). Numerous gut bacterial species that were changed throughout the PAIS, including *B. thetaiotaomicron, Eubacterium rectale*, and *F. prausnitzii*, were known to have immunomodulatory properties. For example, there was an inverse correlation between the intensity of symptoms in ME/CFS and *F. prausnitzii* (Guo et al., 2023).

According to the gut-brain axis model, dysbiosis would likely need to coexist with increased gut permeability as a result of an impaired intestinal barrier, allowing neurotoxic and neuroinflammatory chemicals such as peptidoglycan (PGN) and LPS to infiltrate the body systemically. The presence of LPS causes both brain microglial activation and systemic inflammation (Brown, 2019). Endotoxin has previously been detected at high concentrations in COVID-19 hospitalized patients; however, it is unknown if this endotoxin is present during the post-acute phase of the disease and if it plays a role in the neurocognitive symptoms associated with PACS (Prasad et al., 2022, Teixeira et al., 2021). Significantly, it has been shown that rats can experience direct LPS infiltration into the brain, where it binds to endothelial cell receptors at blood–brain interfaces, worsening the endothelial damage caused by the virus and cytokines mentioned above (Vargas-Caraveo et al., 2017). The fact that LPS has been demonstrated to impact the blood–brain barrier (BBB) in the thalamus, frontal cortex, cerebellum, and pons-medulla while maintaining the integrity of the BBB in other brain areas is particularly noteworthy. In the context of PACS, thalamic and frontal deficits are particularly relevant because these regions are critical to higher-order cognitive processes (Vakhtin et al., 2014, Jung and Haier, 2007). Thus, systemic LPS may have a triple effect in COVID-19′s post-acute pathology by inducing pro-inflammatory cytokines and Mφs activation, interacting directly with the cerebrovascular endothelium while the virus is active, and increasing the exposure of certain brain regions to neurotoxins through the compromised BBB.

It has also been demonstrated that PGN concentrations in blood plasma represent intestinal permeability brought on by ischemia, hemorrhagic shock, and ethanol-induced damage (Shimizu et al., 2002). Importantly, idiopathic inflammatory and autoimmune diseases like multiple sclerosis have been linked to the presence of gut-derived PGN in brain dendritic cells (DCs) and Mφs (Visser et al., 2005). Furthermore, PGN's neurotoxicity was shown in rats by inducing the production of microglial and astrocytic nitric oxide, which mediates neuronal cell death (Buskila et al., 2005). In addition to its role in innate immunity, PGN has been linked to the pathophysiology of neurodevelopment disorders like autism spectrum disorder. This connection may be related to the neurotoxic properties of PGN and its potential effects on cognition (Arentsen et al., 2017, Gonzalez-Santana and Heijtz, 2020). Interestingly, PGN concentrations in blood plasma have also been demonstrated to be higher in hospitalized COVID-19 patients than LPS concentrations (Prasad et al., 2022). Accordingly, in the PACS context, PGN concentration may have a role in both neurotoxicity and chronic neuroinflammation along the gut-brain axis. By attaching to angiotensin-converting enzyme 2 (ACE2) receptors and inducing the production of high levels of systemic cytokines, SARS-CoV-2 damages the intestinal wall and cerebral blood vessels, weakening the intestinal barrier and possibly increasing their permeability to toxic substances. This compromises the brain's neurovascular unit. These compounds are thought to be produced by pathogenic microbiota arising from intestinal post-COVID-19 dysbiosis, considering the significant impact COVID-19 has on the GI tract. Therefore, COVID-19 may set up a situation where neurotoxic and neuroinflammatory compounds readily increase within the gut lumen and come into contact with a compromised neurovascular unit, allowing them to enter the brain and ultimately result in cognitive deficiencies (Plummer et al., 2023). The gut-brain disease mechanism has been well documented in several disorders, including depression (Valles-Colomer et al., 2019), anxiety (Kim and Shin, 2018), neurodegenerative conditions (Ryman et al., 2023), and other chronic multi-symptom illnesses (Keating et al., 2019) such as Gulf War syndrome. Inflammation throughout the body brought on by increased intestinal permeability has been linked to disorders such as irritable bowel syndrome (Moser et al., 2018), and because COVID-19 is known to cause cytokine storms that can be lethal, these pathways are extremely relevant to the virus (Cron et al., 2021).

1.2.2. Gut-lung axis

Because the lungs are continuously exposed to a wide range of external stimuli, they are at the forefront of immunity. The pulmonary immune system is mostly shaped by the microbiome, and a healthy lung contains a wide variety of bacteria. Microbes release substances that support respiratory functions, increase innate and adaptive immunity (both systemic and site-specific in the lungs), and stop pathogens from invading the lungs (Khatiwada and Subedi, 2020). Differentiated ecological niches from the *Bacteroidetes, Firmicutes*, and *Proteobacteria* phyla as well as the *Prevotella, Streptococcus, Veillonella, Fusobacterium*, and *Haemophilus* genera characterize the lung microbiota of healthy individuals (Mathieu et al., 2018). A healthy microbiome prevents dangerous germs from growing and entering the lungs. Growth inhibitors may be secreted while nutrient access restrictions may be one of the factors causing this growth restriction (Khatiwada and Subedi, 2020).

Studies reveal a significant interaction between changes in the gut and lung microbiota, with observable consequences for the degree of symptoms and the course of infection (Li and Fan, 2020, Budden et al., 2017). Pro-inflammatory cytokines like IL-6 and IL-10 are essential for coordinating immune responses, drawing immune cells, and escalating the continuing inflammation in the context of COVID-19 lung infection (Soroosh et al., 2013). In the meantime, DCs stimulate the gut's immune system by mobilizing B and T cells to increase TNFα, IFN-γ, and IL-6 (Duffy et al., 2013). Moreover, elevated TNF-α levels in the gut of COVID-19 patients have been associated with certain bacteria, such as *Veillonella parvula*, which exacerbates inflammation (Maddah et al., 2023). Acute lung injury and symptoms like asthma are caused by inflammation because it causes oxidative production, attracts leukocytes to pulmonary tissue, and stimulates the synthesis of adhesion molecules like ICAM-1 and VCAM-1 (Khailova et al., 2017). At the same time, caspase-3 pathways cause endothelial cells to undergo apoptosis, which lowers the number of Treg cells and anti-inflammatory cytokines (van der Veeken et al., 2016). Research indicates that the mucosal immune system, which is mostly made up of bronchial-associated lymphoid tissue (BALT) and gut-associated lymphoid tissue (GALT), is shared between the lungs and the gut. In response to respiratory infections, GALT, specifically has been shown to contribute more significantly by facilitating the transfer of factors and immune cells from GALT to BALT (Zhou et al., 2021). Moreover, the mesenteric lymphatic system connects the lung and the stomach to the systemic circulation, creating a connection between the GI tract's first immunization and the lung's targeted action (Santacroce et al., 2021). As a result of altered gut microbiome composition, increased gut and lung permeability, decreased E-cadherin levels, increased circulation of pro-inflammatory cytokines, and endothelial cell apoptosis, there is ultimately an exaggerated inflammatory response.

Research has demonstrated a rise in *Actinobacteria* within the gut microbiota of COVID-19 infected people, correlating this finding with increased gp130/sIL-6Rß levels linked to systemic inflammatory diseases (Mizutani et al., 2022, Wang et al., 2023). sIL-6Rß acts as a trans signal for IL-6, and its level correlates with the severity of COVID-19 (Chen et al., 2021). Furthermore, the abundance of the class Clostridia, which was reduced in COVID-19 patients, showed an inverse

correlation with levels of interferon (IFN)-g and IL-28A/IFN-λ2 (Mizutani et al., 2022). Furthermore, researchers have found that COVID-19 patients had greater concentrations of pathogenic *Enterobacteriaceae*, which are known to create endotoxins that limit epithelial cell protein production and exacerbate lung injury (Li and Fan, 2020, Ten Have et al., 2019). Additionally, depletion of butyrate-producing bacteria, mainly *Faecalibacterium*, belongs to the class Clostridia, after infection has been observed in COVID-19 patients, makings it difficult to control lung inflammation (Mizutani et al., 2022). Butyrate, an essential SCFA, has been shown to have important effects in various lung diseases such as allergic asthma (AA), chronic obstructive pulmonary disease (COPD), and lung fibrosis (LF) (Corrêa et al., 2022). Butyrate acts mainly as an energy source for colonocytes and impacts mucosal homeostasis by affecting the epithelial barrier and the associated immune system (Corrêa et al., 2022).

Patients with COVID-19 may have pathogenic bacteria in their guts, such as those from the *Rothia* and *Streptococcus* genera, which could affect lung health through the gut-lung axis (Gu et al., 2020). These microorganisms contribute to the development of secondary bacterial lung infections, with *Rothia* primarily advancing the pathophysiology of pneumonia (Ramanan et al., 2014). The intestines of COVID-19 patients have higher levels of genera such as *Bacteroides, Parabacteroides, Enterocloster*, and *Flavonifractor*, which cause protein fermentation to produce putrefactive metabolites (Groves et al., 2018, Mancabelli et al., 2022). Ammonia and amine accumulation are signs of putrefactive dysbiosis, due to this metabolic activity. Polyamine buildup in the pulmonary epithelium can result in hemorrhage and lung edema (Hoet and Nemery, 2000). Lastly, putrefactive dysbiosis may ultimately lead to excessive systemic inflammation, exacerbating the severity of dysbiosis. This is because it is characterized by reduced carbohydrate metabolism through pathways like glyoxylate, sucrose, galactose, and decarboxylate, and increases in catabolism of amino acids like tryptophan, phenylalanine, lysine, and tyrosine (Devi et al., 2022).

Critical immune cells such as $CD4^+$ T cells, $CD8^+$ T cells, and $CD16^+ 56^+$ NK cells can be diminished by elevated levels of pathogenic bacteria (e.g., *Corynebacterium* and *Ruthenibacterium*) and fungi (e.g., *Aspergillus* and *Kluyveromyces*) in combination with decreased levels of beneficial probiotics (e.g., *Bifidobacterium, Lactobacillus*, and *Eubacterium*) (see Fig. 1) (Rinninella et al., 2019). This immunodeficiency due to gut dysbiosis greatly increases the rate of virus replication in the lungs, which may impede the virus's ability to be cleared. In one investigation, severe COVID-19 patients had hypoxia due to immunodepletion caused by gut dysbiosis (Yu et al., 2019). An imbalance of microbes in the lungs could be a major factor in the development of COVID-19. Hemolysin BL and non-hemolytic toxins, which are released when pathogenic bacteria like *Bacillus cereus* multiply, can lead to severe GI symptoms like nausea, vomiting, and diarrhea (Han et al., 2024). Furthermore, in immunocompromised individuals, *Candida glabrata*, a fungal pathogen detected in the respiratory tracts of intubated COVID-19 patients, can cause potentially fatal mucosal infections. It can also spread to the GI tract and cause invasive candidiasis, which can cause morbidity and mortality (Merenstein et al., 2022, Charlet et al., 2018). This emphasizes how crucial it is to comprehend and address the intricate relationship that exists between COVID-19 systemic illness symptoms and pulmonary microbiological abnormalities.

Dysbiosis of the oral microbiome was noted in ME/CFS patients with PASC; this was typified by a rise in the number of *Leptotrichia, Prevotella*, and *Fusobacterium* spp. (Haran et al., 2021). Compared to patients without PASC or healthy controls, patients with long COVID-19 had higher amounts of fungal translocation from the gut and lung epithelium, which triggered cytokine production (Giron et al., 2022). In COVID-19 patients, this fungal-related coinfection has been associated with higher mortality rates; the case fatality rate for secondary fungal infections is roughly 54.6 % (Borman et al., 2022). Previous studies have also revealed evidence of active fungal and viral infections in ME/CFS patients experiencing persistent and unexplained symptoms (König et al., 2021).

Persistent symptoms following recovery from COVID-19 may be caused by imbalances in the gut microbiota, and these changes in the microbiota persist for at least 30 days following virus clearance (Yeoh et al., 2021).

An observational study using 16S ribosomal RNA sequencing of fecal samples and elevated plasma LBP levels revealed a correlation between dysbiosis and respiratory dysfunction following discharge in 85 COVID-19 patients. After three months post-hospital discharge, respiratory dysfunction assessed by the lungs' capacity to diffuse carbon monoxide (DLCO) was associated with reduced abundance of several members of the *Ruminococcaceae* family (*Ruminococcus, Subdoligranulum*), and *Lachnospiraceae* family (FCS020 group, *Eubacterium ventriosum* group, *Fusicatenibacter, Lachnospiraceae* ND3007 group), as well as increased abundance of the genera *Flavonifractor* and *Veillonella* (possibly linked to fibrosis). These findings suggest that gut-lung crosstalk may play a role in chronic lung failure and persistent COVID-19 symptoms (Zhang et al., 2023).

In a similar vein, a pilot study assessing the intestinal microbiota of 15 COVID-19 hospitalized patients revealed notable changes in the microbiome after hospitalization, including a decrease in helpful microbes and an increase in opportunistic microorganisms. The intestinal dysbiosis persisted even after SARS-CoV-2 vanished and respiratory symptoms improved. There was a positive correlation between COVID-19 severity and the relative abundances of *Coprobacillus, Clostridium ramosum*, and *Clostridium hathewayi* at baseline. Furthermore, there was an inverse relationship between the severity of COVID-19 and the number of *F. prausnitzii*, which promotes an anti-inflammatory milieu (Zuo et al., 2020). *B. dorei, B. massiliensis, B. ovatus*, and *B. thetaiotaomicron*, which downregulated ACE2 expression in the mouse gut, were found in relative abundance during the hospital stay (Groves et al., 2018) and were negatively correlated to the amount of virus in COVID-19 patients' feces (Zuo et al., 2020).

1.2.3. Gut-lung-brain axis

The pulmonary system, the CNS, and the GI system interact intricately to influence a number of physiological and pathological processes, collectively known as the "gut-lung-brain" axis (Xie et al., 2024, Haldar et al., 2023). According to recent research, bidirectional communication along this axis is critical for the onset and progression of brain illnesses (Vakili et al., 2022, Bajinka et al., 2022, Li et al., 2023). Notably, emerging research suggests that this gut-brain communication transcends conventional domains and involves the respiratory system as an essential mediator (Li et al., 2023). These complex relationships show how the gut and lung have a significant impact on brain health by exchanging signals, immunological factors, and microbial metabolites (Park and Im, 2022, Ahmed et al., 2022).

The microbiota-gut-brain axis has been linked to the lungs in recent studies, and this axis has also been implicated during COVID-19 (Johnson et al., 2021, Manosso et al., 2021). The disruption of anti-inflammatory pathways and normal respiratory and GI functioning arises from inflammation and neurodegeneration in the brain stem caused by COVID-19, which affects cranial nerve signaling and involves the lungs. Furthermore, during intestinal microbial dysbiosis in COVID-19 patients, changes in the gut microbiota have been demonstrated to reduce levels of beneficial bacteria (*Bifidobacterium* and *Lactobacillus*) (Xu et al., 2020). Inadequate clinical outcomes for the condition may be largely attributed to the translocation of microorganisms and subsequent tissue damage. During a COVID-19 infection, the gut-brain-lung axis can also provide insights about potential avenues for therapeutic development (Johnson et al., 2021).

1.2.4. Gut-liver axis

Abnormalities in liver chemistry (LCA) function as autonomous markers of severe COVID-19, particularly in patients with chronic liver disease (Chen and Vitetta, 2021). Moreover, among COVID-19 patients,

the increasing severity of LCA is a strong predictor of early in-hospital mortality (Satapathy et al., 2021).

There are several different mechanisms underlying this liver injury. The minimal expression of ACE2 receptors in hepatocytes suggests that direct viral injury to liver cells is uncommon (Hamming et al., 2004). The virus is less likely to directly damage liver cells due to the liver's low expression of ACE2 receptors. Therefore, the cause of liver damage in COVID-19 patients is challenging to pinpoint. The interaction between the gut microbiota and the liver can be influenced by a variety of factors, including the environment, genetics, and diet.

The gut-liver axis represents the reciprocal relationships between liver physiology and gut microbiota. Although the makeup of the gut microbiota can be impacted by chronic liver disease, dysbiosis can lead to inflammation of the liver through the biliary tract, portal vein, and systemic circulation (Tripathi et al., 2018). Chronic liver disease has been linked to gut dysbiosis because it decreases anti-inflammatory mechanisms and increases inflammation (Tripathi et al., 2018, Chen et al., 2021). LCA, a measure of the degree of pathogenic alterations in the liver, has been linked to inflammation, especially the cytokine storm in COVID-19 (Phipps et al., 2020).

The gut microbiome of COVID-19 patients with chronic liver disease may be severely disrupted. SARS-CoV-2 intestinal infections, which are frequent in COVID-19 patients, can exacerbate pre-existing gut dysbiosis in patients with chronic liver disease (Chen et al., 2021). Due to increased intestinal permeability brought on by endotoxins and bacteria translocation, gut dysbiosis can cause inflammation in the intestines and liver. Kupffer cells, Mφs, and DCs can be stimulated by endotoxins and bacteria that reach the liver to release large amounts of pro-inflammatory cytokines. Recent research has shown that pro-inflammatory T and B cell subtypes in the liver are also a result of gut dysbiosis (Tripathi et al., 2018, Barrow et al., 2021). Furthermore, metabolites from commensal bacteria such as butyrate, indole, and bile acid derivatives, which have anti-inflammatory properties, are produced less frequently when the gut is dysbiotic (Chen et al., 2021).

Post-COVID patients also exhibit significantly decreased bile acid and bile salt transporters, which may disrupt gut flora (Leng et al., 2020, Pinol-Jimenez et al., 2022).

Liver cirrhosis is also a significant risk factor for severe COVID-19, indicated by a lower *Bifidobacteriaceae/Enterobacteriaceae* (B/E) ratio (Ullah et al., 2022). After recovering from COVID-19, a study also found that immunomodulatory bacteria, like *Bifidobacterium* and *F. prausnitzii*, remained at decreased levels for up to 30 days (Yeoh et al., 2021). The severity of the illness and the compromised immune response were linked to these reduced microorganism counts (see Fig. 1) (Yeoh et al., 2021).

2. Confounding factors in microbiome studies

Because of the high sensitivity of DNA sequencing tools and the relative unknown underlying microbial populations inside a sample, microbiome research is especially prone to high levels of biases. There are many stages in a normal microbiome investigation where biases are introduced (Jagessar et al., 2019). These biases can often distort observations of the true microbial composition in a sample (Kenyon et al., 2019). While sometimes such biases can be subtle, they often result in significant consequences for biological conclusions.

According to preliminary evidence, gut and airway dysbiosis may be involved in COVID-19 and long-term COVID neurological sequelae. In fact, future preventive and therapeutic approaches may be significantly impacted by the generation and interpretation of such data. Study design, location, material source, microbial technology, sample size, and patient characteristics—such as age, body mass index (BMI), gender, sexual behavior, COVID-19 severity, comorbidities, recent use of antibiotics/probiotics, diet, and lifestyle—may all influence final observations. Ancona G's mini-review study, which aimed to critically critique the papers, revealed that the most common study design was cross-sectional (Tang et al., 2021). Only 20 % of the studies focused on long-term COVID-19, and fewer than half (45 %) used a longitudinal or prospective design. A crucial component was the study's geographic focus: of the 22 studies, 19 (86 %) were situated in Asia (18 in China, 1 in South Korea), and 3 (19 %) in Europe; no other locations were included. Although nutrition and lifestyle significantly impact microbial core composition, these factors were not examined (Zhang et al., 2023, Konturek et al., 2016, Quraishi et al., 2020). Nineteen out of 22 studies (86 %) used a fecal sample as the material source, whereas three studies (14 %) relied on anal swab analysis. The majority of studies (12/22) analyzed microbiota using next-generation sequencing (NGS) technology, specifically ribosomal-S16-DNA hypervariable region sequencing (V4 or V3–V4 areas preferred); seven of the 22 studies employed shotgun metagenomic sequencing, while one used multi-omics techniques (Mak et al., 2020), one nanopore technology (Barrow et al., 2021), and another used quantitative PCR (Giannoni et al., 2020). Studies on patient characteristics included both males and females; however, sexual behavior was not examined, despite the fact that it has been shown to have an impact on the microbiome core in a number of disease models (Lynn et al., 2022, Qian et al., 2021). Out of 22 studies, only seven contained BMI data, and when control groups were included, they were frequently matched for BMI. Fifty percent of the research participants were 50 years of age or younger. Several authors stated that small sample size was a limitation, with more than two-thirds of studies enrolling fewer than 40 individuals (13/21, 62 %). Most research reported the COVID-19 severity index, and there was significant variation across studies. There was a lack of information on concurrent medications and comorbidities; diabetes and hypertension were the most often reported conditions. For individuals recruited after the vaccine rollout, little information was typically provided regarding their COVID-19 vaccination status; just one study examined the alterations in the microbiota of two patient groups who received different vaccinations (de Jong et al., 2020). In a number of trials, probiotics and/or antibiotics were given to patients during hospitalization; however, the majority of published studies did not provide thorough analysis of this data..

3. Microbiota's potential for COVID-19 and PACS prevention, diagnosis and treatment

The human microbiota contributes to the development, control, and triggering of immunological responses, all of which are vital to the preservation of host health. Given that COVID-19 presents previously unheard-of difficulties for international healthcare systems, there is an urgent need for novel approaches to the diagnosis, management, and treatment of the illness (Filip et al., 2022). Thus, human microbiota has emerged as a viable means for future prognostic, prevention, therapeutic, and diagnostic uses, especially in relation to COVID-19 and its long-term aftereffects, PACS (Farsi et al., 2022, Zhang et al., 2021).

The respiratory tract and gut microbiota of COVID-19 patients showed dysbiosis, demonstrating the strong correlation between the microbiota and the host immunological response to the virus (De and Dutta, 2022). As previously mentioned, these changes in the arrangement of microbes have been associated to the intensity of COVID-19 and post-COVID-19 symptoms, and they have been suggested as possible indicators of diagnosis and prognosis. These biomarkers might be essential for determining who is more likely to experience severe illness progression or consequences (Papadopoulou et al., 2022).

Finding the microbiological biomarkers associated with the severity of COVID-19 could be useful in creating individualized treatment plans. A thorough understanding of the microbial population structure and functional activity could be achieved through intestinal (Zhang et al., 2021, Neag et al., 2022, Mazzarelli et al., 2022) and airway (Alsayed et al., 2023, Zhu et al., 2022, Ren et al., 2021, Durán-Manuel et al., 2022) microbiota profiling techniques, including metagenomic sequencing and metatranscriptomic profiling. This would also aid in the creation of microbial biomarkers to detect COVID-19 severity and PACS

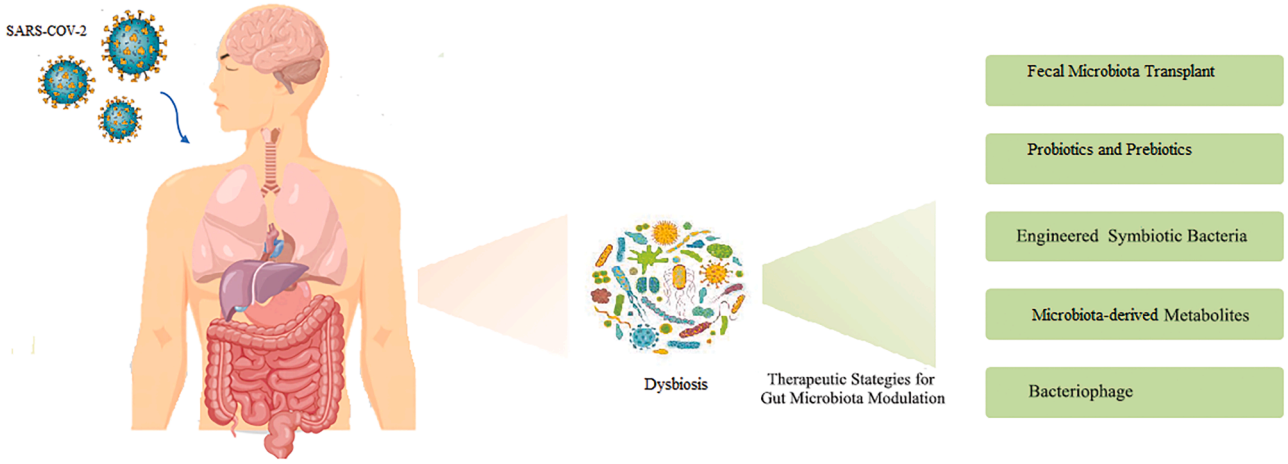

Fig. 3. Therapeutic strategies for gut microbiota modulation.

(Ojala et al., 2023, Athanasopoulou et al., 2023).

Additionally, fecal microbiota profiles for COVID-19 can be utilized as noninvasive diagnostic markers (Mańkowska-Wierzbicka et al., 2023). Patients with PACS may also benefit from microbiota-based diagnostics, as certain bacterial taxa have been shown to correlate with symptoms severity. Techniques based on microbiota may offer non-invasive means of managing and diagnosing PACS (Conti et al., 2023, Fernández-Lázaro et al., 2021, Scarpellini and Tack, 2023). Furthermore, probiotics, prebiotics, bacteriophages therapy, microbiome-derived metabolites, and fecal microbiota transplantation (FMT) have all been investigated as potential therapeutic approaches for COVID-19 or PACS, and they have demonstrated encouraging therapeutic outcomes (Wang et al., 2022). In individuals with COVID-19 and PACS, these strategies may help reduce inflammation, improve immunological dysregulation, and lower the risk of subsequent infections (see Fig. 3) (Xavier-Santos et al., 2022, Kazemian et al., 2021).

3.1. *Fecal microbiota transplant*

In a FMT, a patient's digestive tract is implanted with feces or complex microbial communities obtained from *in vitro* cultivation or purified fecal material from a healthy donor. FMT has shown promise in treating recurrent *Clostridium difficile* infection (Van Nood et al., 2013, De Groot et al., 2021), colitis, diabetes, metabolic diseases (Jayasinghe et al., 2016), hepatic encephalopathy (Bajaj et al., 2017), and Good's syndrome (Jagessar et al., 2019).

Fecal transplantation has also been proposed as a treatment for ME/CFS. Preliminary evidence suggests that the microbiome may play a significant role in the illness, particularly in relation to its neurological symptoms (Kenyon et al., 2019). To determine if FMT is beneficial in treating ME/CFS, two controlled studies in double-blind randomized trials are now in progress (NCT04158427 and NCT03691987). As of right now, no trial has been completed to assess the clinical effectiveness of FMT treatment in neuropsychiatric diseases following COVID-19 (NCT05556733).

FMT may be useful in patients with prolonged COVID due to gut microbial dysbiosis, the impact of the gut-lung axis, and correlations between gut microbiota and long COVID. A recent attempt was made to confirm the effectiveness of FMT as an immunomodulatory risk reducer in COVID-19 disease progression linked to intensifying cytokine storms and inflammation through a registered clinical experiment (ClinicalTrials.gov Identifier No. NCT04824222). In this study, standard pharmaceutical treatments were given to the control group, while FMT was administered orally to the experimental group in the form of 30- to 50-dose-in, double-cover, enteric-release, gastro-resistant, frozen 60 g capsules (Tang et al., 2021). One of the primary outcome measures is the frequency of adverse events in the safety pilot group up to day 30 following administration. Another outcome metric is the percentage of patients in the study and control groups who required intensive care unit (ICU) hospitalization, invasive ventilation, ventilators, high flow nasal cannula oxygen therapy (HFNOT), continuous positive airway pressure (CPAP), or both. These measures correspond to grades 5–7 disease exacerbation on the COVID-19 performance status scale.

The clinical trial NCT04251767, which examined the impact of microbiota transplantation on reducing the severity of acute COVID-19 in a randomized-controlled trial, was discontinued to comply with current regulatory regulations (Zhang et al., 2023). However, because of the unknown effects of SARS-CoV-2 on the safety and effectiveness of FMT, the continuing COVID-19 pandemic has linked the treatment of CDI and other disorders to FMT 90,91. Numerous investigations have demonstrated the post-FMT decrease in IL-6 and other inflammatory cytokines (Konturek et al., 2016). Moreover, microbiota study in FMT-treated IBD patients reveals a shift toward bacterial species that promote the growth of regulatory T cells and the production of the anti-inflammatory cytokine IL-10 (Quraishi et al., 2020). These findings support the use of FMT as a therapy or adjuvant to calm cytokine storms in COVID-19 patients with severe instances.

3.2. *Probiotics and prebiotics*

Promising treatment and prevention approaches for COVID-19 that alter gut microbiota include supplementing with microbiota-targeted substrates (prebiotics), such as specific dietary fibers, and/or directly administering one or more beneficial bacteria (probiotics) (Mak et al., 2020, Giannoni et al., 2020). Compared to FMT, probiotic and/or prebiotic therapy is generally safer and simpler to prepare and administer.

Despite the emergence of new strains of SARS-CoV-2, mass vaccination remains the most effective method of prevention and control (Lynn et al., 2022). Research indicates that the gut microbiota of individuals can influence the host's immunological balance, thereby affecting the effectiveness and immunogenicity of the vaccine (Qian et al., 2021, de Jong et al., 2020). Probiotics have been shown to enhance vaccine immunogenicity and increase the seroprotection to seroconversion ratio in individuals vaccinated against Influenza (Lei et al., 2017). Thus, increasing probiotics may improve vaccine efficacy and immunological responses in vulnerable groups. Patients with COVID-19 benefit from the presence of *lactobacillus* in their intestines, which helps maintain GI homeostasis and reduce inflammatory responses (Sun et al., 2018, Wang et al., 2020). To express the SARSCoV-2 S protein, Wang et al. used *Lactobacillus plantarum* (*L. plantarum*). Their findings showed that the protein could be expressed on the bacterium's surface and exhibited high antigenicity, effectively inducing the

production of specific monoclonal and polyclonal antibodies against the SARS-Cov-2-S protein. Therefore, an optimal oral vaccine for SARS-CoV-2 infection is developed by recombining *L. plantarum* with the gene encoding the SARS-CoV-2 S protein (Wang et al., 2020). Furthermore, probiotics reduce the pro-inflammatory to anti-inflammatory cytokine ratio, which is particularly beneficial in preventing cytokine storms in COVID-19 patients (Aziz et al., 2020, Li et al., 2021). In summary, the preventive use of probiotics formulations may help boost antiviral protective responses and inhibit excessive inflammatory responses due to the probiotics' role in modulating innate immunity (Tomkinson et al., 2023).

By supporting immunological homeostasis and modulating inflammatory responses, the appropriate administration of probiotics and prebiotics can protect the intestinal barrier, decrease intestinal permeability, and thus alleviate intestinal symptoms in COVID-19 patients (Trompette et al., 2018, Hu et al., 2021). Recent studies have demonstrated that probiotics can boost T cell activity and quantity, thereby directly enhancing the immunological response and immune functioning (Dhar and Mohanty, 2020). Probiotics also strengthen gut barrier functions and diversify the microbiome (Badgeley et al., 2021). For decades, VSL#3, a blend of eight probiotics, has been used safely and effectively worldwide. It has been shown that by enhancing gut microecology, VSL#3 reduces enteritis and strengthens the intestinal mucosal barrier (Tankou et al., 2018). By reducing fungal colonization, increasing *Lactobacillus* and *Bifidobacterium* population, and improving microbiota diversity, VSL#3 may lessen the severity of COVID-19-induced GI symptoms. A comprehensive meta-analysis evaluating the therapeutic efficacy of probiotics in preventing treatment-related diarrhea found that combining capsules with different strains of *Bifidobacterium* and *Lactobacillus* was beneficial in reducing the incidence of acute diarrhea (Chitapanarux et al., 2010). Additionally, d'Ettorre et al. reported that patients treated with probiotics experienced fewer GI symptoms than those receiving a placebo after a seven-day administration of a combination of *Streptococcus thermophilus* DSM 32345, *Lactobacillus acidophilus* DSM 32241, *Lactobacillus helveticus* DSM 32242, *Lacticaseibacillus paracasei* DSM 32243, L. *plantarum* DSM 32244, *Lactobacillus evi, Lactobacillus brevis* DSM 27961, *Bifidobacterium lactis* (*B. lactis*) DSM 3246, and *B. lactis* DSM 32247 (d'Ettorre et al., 2020).

Raising dietary fiber intake can alter gut microbiota composition, which may alleviate GI and non-GI symptoms, such as anxiety and palpitations in individuals with PASC (Barrea et al., 2022).

In COVID-19 patients, a balanced diet supports gut microbiota equilibrium. Numerous studies have reported associations between dietary habits and inflammatory responses in COVID-19-positive patients (Majidi et al., 2022). A diet rich in fruits, nuts, olive oil, vegetables, and whole grains correlates with an increase in probiotics and a reduction in inflammatory conditions among COVID-19 patients (Majidi et al., 2021).

Additionally, adequate consumption of specific dietary fibers (Zhao et al., 2018), supports the growth of beneficial bacteria in the intestine, potentially lowering the risk of contracting SARS-CoV-2 (Merino et al., 2021). SCAFs, such as butyric acid, are produced by gut microbiota fermentation of fermentable dietary fibers like inulin. These SCAFs reduce excessive inflammatory responses caused by leukocytes in the lungs and improve the immunoregulatory function of $CD8^{+}$ T cell (Antunes et al., 2019). In a study where acetate, butyrate, or propionate was administered as drinking water to mice infected with respiratory syncytial virus (RSV), acetate was found to bind to G-protein coupled receptor 43 (GPR43), resulting in an antiviral effect. This suggests that preventive and therapeutic measures to increase probiotics may enhance antiviral capacity and reduce long-term GI complications in COVID-19 patients.

3.3. Engineered symbiotic bacteria

Developments in synthetic biology and gene editing are making it easier and more practical to create microorganisms that are tailored to treat COVID-19. Today, we can genetically modify symbiotic bacteria to perform specific tasks, generate the necessary metabolites, and locate themselves in the host at the right places. To treat colitis, a strain of *Lactococcus lactis* was modified to express and secrete the anti-inflammatory cytokine IL-10 (Steidler et al., 2000, Adeloye et al., 2021). By forcing this strain to produce IL-10 and require exogenous thymidine for survival, the strain's biosafety was guaranteed (Braat et al., 2006). SARS-CoV-2-induced cytokine storms and COVID-19 severity and fatality are closely correlated. Therefore, a promising COVID-19 treatment could result from the creation and use of similarly modified strains that create anti-inflammatory chemicals in the lungs and decrease pro-inflammatory storms. However, more clinical research is needed to confirm the security and effectiveness of this technique.

3.4. Microbiota-derived metabolites

Direct supplementation of metabolites produced by the beneficial microbiota, such as SCFAs, presents a promising strategy for treating COVID-19.

Research indicates that specific beneficial bacteria, including *Lactobacillus reuteri* and *Bifidobacterium pseudolongum* are found in significantly lower concentrations in mice infected with *Klebsiella pneumoniae* (*K. pneumoniae*). Fluctuations in the quantity and diversity of intestinal microbes are closely correlated with fluctuations in host metabolite concentrations, as demonstrated by a Spearman correlation analysis. The digestive tracts and blood of the infected group had lower concentrations of acetate, propionate, and butyrate than those of the control group. Oral supplementation with the aforementioned SCFAs can lower susceptibility to *K. pneumoniae* infection, as evidenced by a reduction in lung bacterial burden and an increase in survival (Wu et al., 2020).

Sencio et al. reported that a sublethal influenza infection momentarily changed the composition and fermentation activities of the mice's gut microbiome, which showed up as a drop in SCFA levels. In the meantime, less production of the primary SCFA acetate is the cause of the decreased alveolar Mφ bactericidal activity (Sencio et al., 2020). The H7N9 infection will also change the composition of the gut bacteria in mice, mainly by promoting the growth of *Ruminococcus, Akkermansia*, and *Ruminococcaceae*_UCG_010 and inhibiting the growth of *Lachnocosterium* and *Rikenellaceae*. Also, there was a positive correlation between the abundance of *Akkermansia muciniphila* and H7N9 infection (Hu et al., 2021).

3.5. Bacteriophage

Antibiotics were routinely administered to patients due to the potential for COVID-19 to cause bacterial co-infection. However, antibiotic treatment can disrupt the natural symbiotic microbiota by removing bacterial pathogens and overuse can lead to increased bacterial resistance and dysbiosis of the microbiota. While several studies have shown that antibiotic use is not directly associated with the development of PACS or ME/CFS (König et al., 2022, Bai et al., 2022), one study found that administering an oral bacteriophage cocktail targeting various bacterial types significantly improved the oxygen saturation and respiratory rates of PASC patients and reduced inflammatory markers (Zurabov et al., 2022).

Moreover, metformin is often recommended for diabetes in order to regulate blood sugar levels, partly by altering the gut microbiota. According to a recent study, compared to controls, metformin therapy was associated with a 42 % reduction in COVID-19 sequelae (Bramante et al., 2022). The health benefits of metformin, particularly its effects on the gut microbiota, may be linked to an increase in *Escherichia coli* abundance, a decrease in *Intestinibacter bartlettii* abundance, and increased

SCFA production in humans (Mueller et al., 2021). It has been suggested that metformin may phosphorylate ACE2 via AMP-activated protein kinase, causing a conformational shift that could prevent SARS-CoV-2 from binding to the receptor. *In vitro*, metformin has been shown to stimulate ACE2 and TMPRSS2 mRNA expression in human hepatocytes (Malhotra et al., 2020). Finally, the local microbiota influences the level of ACE2 activity. The efficacy of metformin may offer insight into additional possible treatments for PASC and COVID-19-related intestinal conditions.

4. Discussion

The global COVID-19 pandemic has posed a significant challenge to health systems across the globe, necessitating the full mobilization of health resources. Chronic SARS-CoV-2 infection-related issues have surfaced as a result of subsequent COVID-19 waves, and are referred to as "post-acute COVID-19 syndrome" or "long COVID-19." Patients with post-acute COVID-19 syndrome experience multifactorial dyspnea and multiple organ involvement, typically with overlapping symptoms, which has a significant negative impact on their quality of life. Notably, some of these persistent symptoms may be part of a multisystem condition such as CFS, while others are not directly linked to the original severity of COVID-19. In light of the global SARS-CoV-2 pandemic and the need for interdisciplinary care to address these long-term consequences, post-acute COVID-19 syndrome is expected to pose a significant challenge to healthcare practitioners in the coming years.

There is increasing evidence that severe disruption of the microbiota during COVID-19 is linked to disease severity, mortality, and PACS, despite PACS being a diverse clinical diagnosis with an unknown etiology. These findings imply that the gut microbiota and the pathophysiological pathways triggered by acute COVID-19 and PACS may be dynamically related. The displacement of commensal microorganisms by opportunistic pathogens is associated with harmful consequences and a worsening of the disease in affected individuals.

Furthermore, these findings highlight the need for future research to focus on the composition of the gut microbiota to prevent dysbiosis and provide potential preventative and therapeutic strategies against COVID-19 and PACS.

Additionally, various studies examining the persistence of gut dysbiosis in COVID-19 patients and/or participants with long COVID suggest that SARS-CoV-2 infection causes persistent gut dysbiosis in COVID-19 patients who develop long COVID. Six months after the initial infection, the gut microbiota of COVID-19 patients who did not develop prolong COVID had recovered. To define the dynamics of this recovery and understand why these dynamics differ in individuals who develop long-term COVID, new research analyzing the gut microbiota of recovering COVID-19 patients at various timepoints will be required.

Although, the upper respiratory tract microbiota in long-term COVID-19 patients has been well investigated, little is known about the gut microbiota in this population. This includes the oral, nasal, oropharyngeal, and primarily the nasopharyngeal microbiotas. Furthermore, such dysbiosis of the upper respiratory tract frequently persists well after COVID-19 and SARS-CoV-2 symptoms have resolved. Notably, the oral microbiota of patients with long COVID-19 was found to have relevant bacterial abundance changes potentially contributing to persistent inflammation. These findings support the theory that the upper respiratory tract microbiota may be a key player in the pathophysiology of long COVID-19. These findings suggest that more research is necessary to characterize the respiratory microbiota of long COVID patients and determine whether it plays a role in this condition's pathophysiology (Álvarez-Santacruz et al., 2024).

Moreover, dysbiosis of the gut microbiota may be involved in various conditions affecting the liver, heart, brain, and lungs (Hou et al., 2022). The relationship between the microbiota and the brain through the gut-brain axis, which is thought to be a bidirectional system, is another important area of study. At the gut level, the blood–brain barrier is involved in producing cytokines and microbiota-derived metabolites, including SCFAs, tryptophan, and linoleic acid metabolites; conversely, the brain regulates gut activity through the neuroendocrine and parasympathetic systems (i.e., regulation of intestinal permeability via the vagus nerve) (Gomaa, 2020).

Therefore, some of the neurological and respiratory symptoms linked to the gut-brain and gut-lung axes may be caused by persistent alterations of the gut microbiota following the initial infection.

It is interesting to note that various SARS-CoV-2 genotypes have been shown to modify the gut microbiome of mice in different ways (Upadhyay et al., 2023). However, a recent meta-analysis and systematic review revealed that several persistent COVID-19 symptoms differ depending on the SARS-CoV-2 variant that caused the infection (Du et al., 2022). This could be viewed as additional evidence that the microbiota may play a role in the initiation and/or severity of long-term COVID-19 and that future research should consider the SARS-CoV-2 variant that caused the initial infection. Furthermore, more investigation is required to determine whether dysbiosis could lead to the production of bacterial toxins, which could impair mitochondrial function and exacerbate the fatigue experienced by long-term COVID patients (Popkov et al., 2019).

However, causality has not yet been proven by existing studies. Numerous processes may be involved, given the diverse constellations of symptoms and severity seen in PACS patients. Well-designed longitudinal studies involving both animals and humans that account for factors such as vaccination status, physical activity levels, antibiotic use, and other potential confounding factors are essential to systematically investigate the relationship between the microbiome and the development of PACS to shed light on this issue and advance the field. Although the area is challenging, there are many prospects for advancement, and the current understanding of the microbiome offers a unique opportunity to apply microbiome-related technologies in PACS prevention, diagnosis, and treatment.

Although many clinical trials assessing the effectiveness of microbiota-modulation treatments, including dietary intervention, prebiotics, probiotics, and FMT, are still in the early development phases, the available data appears highly encouraging.

Remarkably, fecal samples from COVID-19 patients have been shown to induce symptoms similar to the disease in germ-free mice, including lung inflammation, poorer outcomes during pulmonary infections, and impaired cognitive function (Mendes de Almeida et al., 2023). This strongly suggests that the gut microbiota may be a viable therapeutic target and may directly contribute to long-term COVID sequelae. In this regard, there have already been some promising findings. One such example is SIM01, an oral, microencapsulated formulation that provides a total of 20 billion colony-forming units per daily dose and combines three lyophilized species of the *Bifidobacterium* genus with three prebiotics known to promote the growth of these bacteria. The oral microbiome formula has the potential to mitigate the negative health effects of COVID-19 in patients with type 2 diabetes and the elderly. It can accelerate the formation of antibodies against SARS-CoV-2, reduce pro-inflammatory immune markers, decrease nasopharyngeal viral load, and improve gut dysbiosis in COVID-19 hospitalized patients (Wong et al., 2023, Zhang et al., 2022). The next natural step would be to provide SIM01 to long-term COVID patients; it would be valuable to analyze the effects.

5. Conclusion

This review sheds light on the connection between COVID-19 and the microbiota. SARS-CoV-2 infection can occur in the respiratory system, intestinal tract, and oral cavity, where microorganisms experience notable alterations. Microbiota are powerful immunomodulatory factors in human health and disease. Micro-ecosystem abnormalities cause cytokine storms, immunological barrier destruction, and immune response suppression, which broadly affect tissues and organs

Table 1
Abbreviation used.

Abbreviation	Meaning
COVID-19	Coronavirus Disease 2019
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
PACS	Post-Acute COVID-19 Syndrome
ACE-2	Angiotensin-Converting Enzyme-2
MIP	Macrophage Inflammatory Protein
MCP	Monocyte Chemoattractant Protein
TNF-α	Tumor Necrosis Factor-Alpha
IFN-γ	Interferon-Gamma
FMT	Fecal Microbiota Transplantation
VEGF	Vascular Endothelial Growth Factor
MALT	Mucosa-Associated Lymphoid Tissue
BALT	Bronchus-Associated Lymphoid Tissue
GALT	Gut-Associated Lymphoid Tissue
LPS	Lipopolysaccharide
SCFAs	Short-Chain Fatty Acids
Hemolysin BL	Hemolysin L2/Bacillus-Like
GI	Gastrointestinal
B0AT1	Broad-Spectrum Amino Acid Transporter 1
mTOR	Mammalian Target Of Rapamycin
CRP	C-Reactive Protein
BBB	Blood-Brain Barrier
CNS	Central Nervous System
AT2R	Angiotensin II Receptor Type 2
TGF-β	Transforming Growth Factor
LCA	Liver Chemistry Abnormalities
Dysbiosis	Dysregulation of the Gut Microbiota
PAMP	Pathogen Associated Molecular Pattern
ICAM-1	Intercellular Adhesion Molecule-1
VCAM-1	Vascular Cell Adhesion Molecule-1
gp130	Glycoprotein 130
sILsingle bond6Rb	Soluble Interleukin-6 Receptor Beta
IFN-I2	Interferon Iota-2
CD16 + 56+ NK cells	Cluster Of Differentiation 16-Positive 56-Positive Natural Killer Cell
Hemolysin BL	Hemolysin L2/Bacillus-Like
ME/CFS	Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
RAS	Renin Angiotensin System
AMP	Antimicrobial Peptides
TLR	Toll-like receptor
VEGF	Vascular Endothelial Growth Factor
ARG1	Arginase 1
MAC	Microbiota Accessible Carbohydrates
Ang	Angiotensin
HPA	Hypothalamic-Pituitary-Adrenal
PAIS	Post-Acute Infection Syndrome
PGN	Peptidoglycan
NGS	Next-Generation Sequencing
BMI	Body Mass Index
ICU	Intensive Care Unit
HFNOT	High Flow Nasal Cannula Oxygen Therapy
CPAP	Continuous Positive Airway Pressure
IBD patients	Continuous Positive Airway Pressure
RSV	Respiratory Syncytial Virus
GPR43	G Protein Coupled Receptor 43
CXCL-10	C-X-C Motif Chemokine 10

throughout the body. Additionally, microbiota metabolites can influence immunity through a variety of mechanisms. For instance, SCFAs might prevent viral infection by downregulating the expression of the ACE2 and TMRSS2 genes. Additionally, the receptor for viral entry into the host, ACE2, may interact with the microbiota. There is growing evidence that the substantial disruption of these microbiota during COVID-19 is associated with disease severity and mortality and PACS.

There have been reports of the microbiota's potential as a diagnostic marker for numerous various illnesses. We provide an overview of its potential as a COVID-19 diagnostic marker and suggest a potential non-invasive testing approach. Long-term consequences on the body result from gut dysbiosis, which lasts long after the infection is eradicated. Thus, the goal of clinical care should be to both eradicate the virus and replenish the aberrant gut flora. Numerous clinical trials are evaluating the efficacy of adjuvant therapy with probiotics as well as other microbiota-based treatments. However, the outcomes of these clinical trials have not yet been published. Microbiota and microecological therapy are anticipated to grow in importance as COVID-19 intervention strategies in the future and could be helpful in containing and preventing the pandemic.

Authors' contributions

AF and HS wrote the manuscript. AAIM and RK revised the manuscript. All authors read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that there is no conflict of interests.

Data availability

No data was used for the research described in the article.

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