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The Microbiota and Microbiome in COVID-19 in Adults and Children and Potential Therapeutic Interventions: A Review

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Abstract

The work presented is a comprehensive review of the role of the human microbiota in the context of the COVID-19 pandemic. A diverse microbial community heavily colonizes the human body called the microbiota, with the gut microbiota being the most diverse. The composition of the microbiota varies in different parts of the body and changes with age, diet, and other environmental factors. Emerging evidence suggests that the gut microbiota plays a critical role in modulating the host immune response and may influence the severity of COVID-19. Patients with COVID-19 have significant alterations in their gut and respiratory microbiota, characterized by a depletion of beneficial commensal bacteria and an enrichment of opportunistic pathogens. These changes in microbiota composition are associated with elevated inflammatory markers, a dysregulated immune response, and more severe disease outcomes. In addition, changes in the gut microbiota can affect lung and brain function, influencing the severity of COVID-19 cases and neurological symptoms, as well as long-term neurological complications associated with the disease. Due to the importance of the microbiota in COVID-19, several therapeutic approaches targeting the microbiota have been proposed to improve outcomes in this disease, including fecal microbiota transplantation, probiotic and prebiotic supplementation, postbiotic or microbiota-derived metabolite supplementation, dietary interventions, and lifestyle strategies. Overall, the review highlights the critical role of the human microbiota in the pathogenesis and progression of COVID-19 and the potential of microbiota-targeted interventions to improve patient outcomes.

Keywords: Microbiota, Gut microbiota, COVID-19, Dysbiosis, Immune system

Introduction

In the human microbiome, bacterial cells outnumber human tissue cells by a factor of 10, while bacterial genes outnumber human genes by a factor of 100 [1-4]. These microorganisms are found on all human body surfaces, including the digestive and respiratory systems [5-8]. However, the gut microbiota of different age groups shows significant differences; the gut microbiota of infants and young children is less diverse and more variable than that of adults. As children grow older, their microbiota becomes more stable and like that of adults. The human body provides access and a suitable environment for certain bacteria to colonize the body. The breakdown of indigestible carbohydrates and proteins, the digestion and absorption of food, the production of vitamins, and the induction, control, and function of host immunity are just a few of the many essential functions performed by the microbiota in and on the human body [9-13].

The microbiota influences human health and is associated with several diseases. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the 2019 global coronavirus disease pandemic (COVID-19), which has posed significant risks to public health and the global economy [14]. Patients with COVID-19 present with respiratory infection symptoms such as cough, shortness of breath, fever, malaise, and abnormal chest radiographs [15-20]. In addition, gastrointestinal symptoms such as diarrhea, nausea or vomiting, anorexia, and abdominal discomfort are present in a significant number of patients with COVID-19 [21-23]. Clinical studies have shown that respiratory and gastrointestinal microbiota balance is altered in hospitalized patients with COVID-19 [24-29]. Patients with SARS-CoV-2 may be more susceptible to secondary gastrointestinal and respiratory pathogenic infections. These are responsible for most of the morbidity and mortality associated with COVID-19. Consequently, the microbiota may be crucial in the spread of SARS-CoV-2 [30,31].

In this review, we have outlined the links between the microbiota and COVID-19 in terms of their clinical relevance and immunological mechanisms. In addition, we have reviewed several microbiota-focused approaches that could improve treatments against SARS-CoV-2 and rely on the immunological communication between the microbiota and COVID-19.

COVID-19

The *Coronaviridae* family includes many animal and human viruses, all with distinctive morphology. The etiologic agent of COVID-19 is SARS-CoV-2, a positive-sense single-stranded RNA betacoronavirus [32,33]. In addition to numerous non-structural proteins, it encodes membrane (M), nucleocapsid (N), spike (S), and envelope (E) structural proteins [34]. Protein S is essential for SARS-CoV-2 entry into host cells [35]. The viral S protein is a homotrimer consisting of the S1 and S2 subunits. The former mediates membrane fusion, while the latter binds to the host angiotensin-2 converting enzyme (ACE2) [36-38]. To activate viral protein S, cleave ACE2 receptors, and facilitate viral binding to the host cell membrane, the virus utilizes host cell surface proteases such as transmembrane serine protease 2 (TMPRSS2) [39-41]. SARS-CoV-2 can enter certain types of immune cells, such as macrophages, by phagocytosis or endocytosis, in addition to entry mediated by ACE2 and TMPRSS2 [42]. The gastrointestinal and respiratory tracts have high TMPRSS2 and ACE2 expression levels, respectively, and are the primary

targets for SARS-CoV-2 invasion, as the latter (respiratory tract) is connected to the external environment. In addition, significant microbial populations exist in both organ systems [43-49].

Epidemiology of COVID-19

The emergence of severe acute respiratory syndrome virus (SARS-CoV) in 2003 stimulated the study of this virus [50]. In late December 2019, SARS-CoV-2 was first identified in Wuhan, Hubei Province, China. A surveillance system was set up to look for unknown causes of pneumonia and detect the virus. On January 30, 2020, the World Health Organization declared COVID-19 a public health emergency of international concern [51]. According to the Centers for Disease Control and Prevention (CDC), "Viruses are constantly evolving as changes in the genetic code occur during genome replication," which can be caused by genetic mutations or viral recombination. Numerous variants have been identified during the pandemic. A variant of the SARS-CoV-2 virus must have one or more mutations to be distinguishable from other variants [52]. Researchers and public health organizations worldwide use the Pango lineage, also known as the Pango nomenclature, to monitor the transmission and spread of SARS-CoV-2, and the date it was recognized as a variant is shown in **Table 1** along with the registered variants of COVID-19 [53]. **Figure 1** shows the distribution of some of the most prevalent COVID-19 variants, considering only countries such as the United States, Mexico, Brazil, the European Union, Russia, and China. COVID-19 caused many changes in human organs, including intestinal or pulmonary microbiota changes.

Table 1 Classification of SARS-CoV-2 variants.

Lineage	Most common countries	Earliest date	Description
B	United States of America 40.0 %, United Kingdom 15.0 %, China 8.0 %, Mexico 5.0 %, Germany 3.0 %.	24/12/2019	One of the 2 original haplotypes of the pandemic (and first to be discovered).
B.1	United States of America 47.0 %, Turkey 11.0 %, United Kingdom 7.0 %, Canada 4.0 %, France 3.0 %.	01/01/2020	A large European lineage the origin of which roughly corresponds to the Northern Italian outbreak early in 2020.
B.1.1	United Kingdom 25.0 %, United States of America 15.0 %, Russia 6.0 %, Japan 6.0 %, Turkey 5.0 %.	19/01/2020	European lineage with 3 clear SNPs `28881GA`,`28882GA`,`28883GC`.
B.1.1.7 (Alpha)	United Kingdom 23.0 %, United States of America 20.0 %, Germany 9.0 %, Sweden 6.0 %, Denmark 6.0 %.	19/01/2020	UK lineage of concern, associated with the N501Y mutation. More information can be found at cov-lineages.org/global_report.html.

Lineage	Most common countries	Earliest date	Description
P.1 (Gamma)	Brazil 59.0 %, United States of America 26.0 %, Chile 3.0 %, Argentina 1.0 %, Spain 1.0 %.	07/04/2020	Alias of B.1.1.28.1, Brazilian lineage with a number of spike mutations with likely functional significance E484K, K417T, and N501Y. Described in https://virological.org/t/genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-manaus-preliminary-findings/586.
B.1.1.529 (Omicron)	United States of America 34.0 %, Germany 13.0 %, India 9.0 %, Turkey 5.0 %, Russia 5.0 %.	14/04/2020	South Africa and Botswana lineage.
BA.5.1.25	United States of America 56.0 %, Peru 8.0 %, Mexico 7.0 %, Canada 5.0 %, United Kingdom 4.0 %.	23/07/2020	Alias of B.1.1.529.5.1.25, mainly found in Mexico and Peru, defined by ORF7b:H42Y.
CK.1.3	United States of America 67.0 %, Mexico 11.0 %, Canada 10.0 %, United Kingdom 3.0 %, South Korea 2.0 %.	10/10/2022	Alias of B.1.1.529.5.2.24.1.3, Mexico, S:F157L, S:G181V
B.1.351 (Beta)	South Africa 20.0 %, Philippines 9.0 %, United States of America 9.0 %, Sweden 8.0 %, Germany 7.0 %.	18/02/2020	Lineage of concern detected in South Africa
B.1.427 (Epsilon)	United States of America 98.0 %, Mexico 1.0 %, Aruba 0.0 %, Canada 0.0 %, Argentina 0.0 %.	11/04/2020	USA lineage (CA).
B.1.617.2 (Delta)	India 22.0 %, Turkey 16.0 %, United States of America 14.0 %, Germany 7.0 %, United Kingdom 7.0 %.	27/03/2020	Predominantly India lineage with several spike mutations.
HP.1.1	United States of America 45.0 %, Mexico 37.0 %, Canada 11.0 %, Spain 2.0 %, United Kingdom 1.0 %.	29/04/2023	Alias of XBB.1.5.55.1.1, S:478R, Mexico, from sars-cov-2-variants/lineage-proposals, Submitted by Kenjiro Kosaki and Takako Shimura.
XBB.1.5.110	United States of America 64.0 %, Mexico 12.0 %, Canada 9.0 %, Ecuador 5.0 %, Sweden 3.0 %.	23/12/2022	ORF1aT4129I, Mexico.

Source: [53].

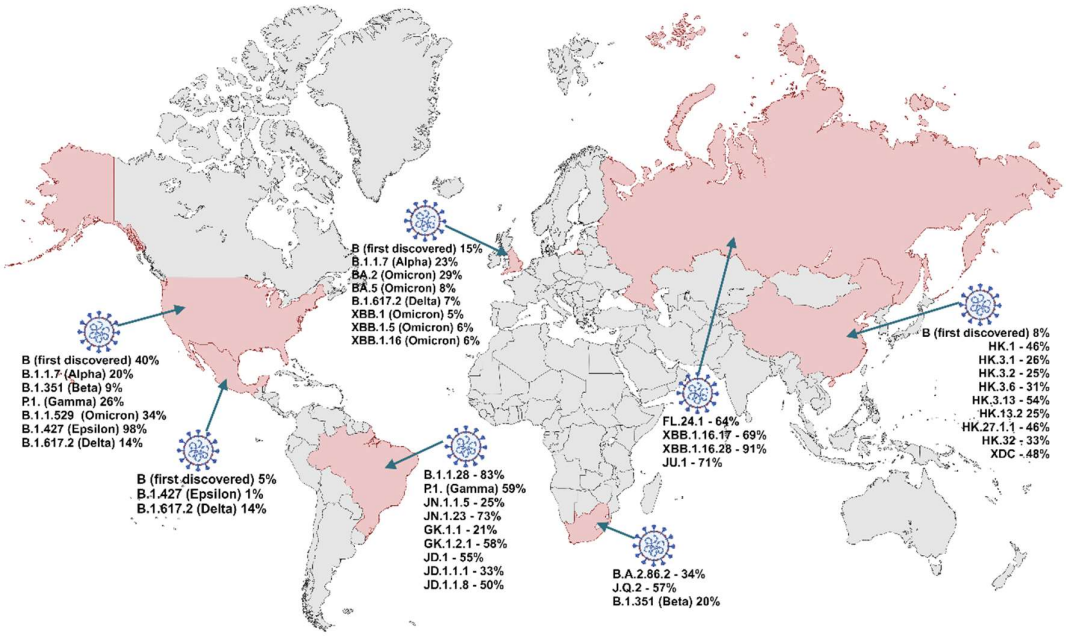

Figure 1 According to the Pango nomenclature, the map shows the distribution of the main COVID-19 variants in some countries [53]. This original image was created using BioRender: Scientific Imaging and Illustration Software (https://www.biorender.com/).

Microbiota

The gut microbiota is a complex population of commensal bacteria in the human gastrointestinal (GI) tract. The GI tract is estimated to contain more than 1014 species of bacteria, with a genetic content (microbiome) 100 times larger than the human genome [54-56]. In addition, the gut microbiota composition in children differs significantly from that of adults. Children have higher levels of Bifidobacterium and lower levels of Bacteroides and Firmicutes than adults. These differences may also be influenced by diet, environment, and host genetics [57]. Wandro S *et al*. followed the development of the gut microbiome in a single infant during the 1st 2.5 years of life. They found that the microbiome undergoes significant changes during early development. The study showed that the microbiome matures and becomes more complex over time, eventually resembling the adult microbiome [58].

Although the function of the human microbiota is not fully understood, it has been implicated in several diseases, including Parkinson's disease, type 2 diabetes, inflammatory bowel disease, and colorectal cancer [59]. Since 2012, the Human Microbiome Project (HMP) has provided a comprehensive analysis of the microbiota at different sites in the body, such as the gut, skin, oral cavity, nasal passages, and urogenital tract. The study found significant differences in microbial composition and diversity at these sites [60]. The gut microbiota is the most diverse and densely populated microbial community in the human body. It is

dominated by phyla *Firmicutes* and Bacteroidetes bacteria, with minor amounts of *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobes* [4]. According to Lee and Kim. *Firmicutes* and *Bacteroidetes* are more abundant in the gut than *Proteobacteria*, *Bacteroidetes*, and *Firmicutes* in the lungs (Lee and Kim. 2022). The skin microbiota varies significantly between different areas of the skin and is influenced by factors such as humidity, sebaceous gland activity, and environmental exposure. The most common skin bacteria include *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* species [61]. The oral cavity harbors a diverse microbiota, with distinct communities in different niches such as the tongue, teeth, gums, and saliva. The dominant genera are *Streptococcus*, *Actinomyces*, and *Veillonella* [62]. The nasal passages harbor a unique microbiota with common genera such as *Staphylococcus*, *Corynebacterium*, and *Moraxella*. The nasal microbiota composition may influence susceptibility to respiratory infections [63]. Finally, the urogenital tract microbiota differs between males and females. In females, the vaginal microbiota is dominated by *Lactobacillus* species, which play a crucial role in maintaining a low pH and protecting against infection. In males, the urogenital microbiota is less well characterized but includes species such as *Corynebacterium* and *Staphylococcus* [64]. These studies provide evidence for the distinct distribution of microbiota in different parts of the human body, highlighting unique microbial communities and their specific roles in health and disease; a representative composition of the microbiota of each body site is shown in more detail in **Figure 2**.

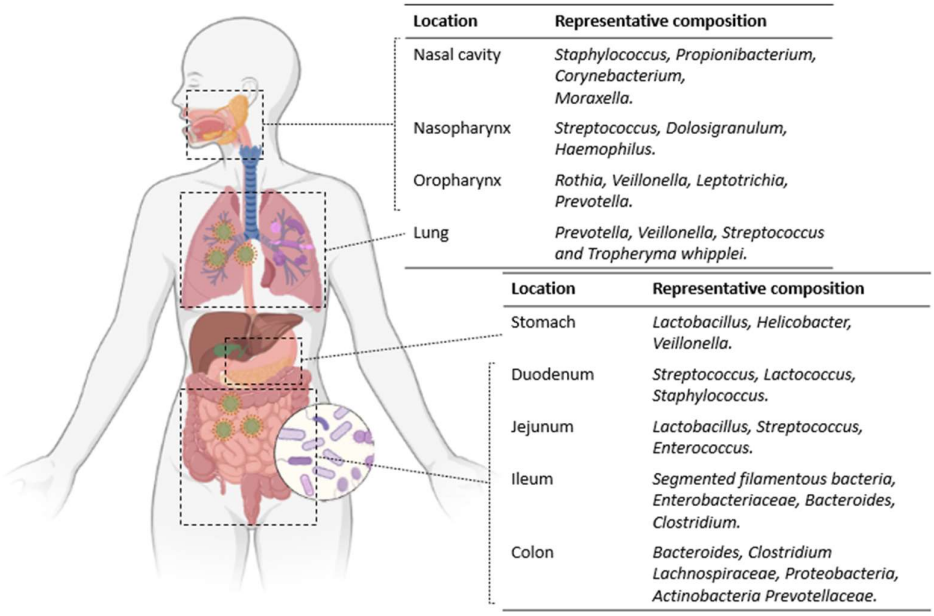

Figure 2 Microbiota composition in the human organism. This original image was created with BioRender: Scientific Image and Illustration Software (https://www.biorender.com).

Microbiota, immune system and COVID-19

From the perspective of the immune system, the GI tract is divided into 3 main compartments: The mucosa/intestinal-associated lymphoid tissue (MALT/GALT), the lamina propria (submucosa), and the

epithelial layer (mucosa). According to *in vitro* studies using intestinal organoids, SARS-CoV-2 infection of the GI epithelium induces an inflammatory and antiviral response [65]. Interferon (IFN) and tumor necrosis factor (TNF) are the 2 most studied cytokines when viral single-stranded RNA (sRNA) and its components are detected by Toll-like receptors (TLRs) [66]. In addition, the gut microbiota should not be neglected in COVID-19-induced gastrointestinal symptoms [67-69]. Indeed, COVID-19 causes dysbiosis in the gut microbiota, inflammation, and poorly controlled immune responses [70]. These inflammatory mediators act in concert to promote the recruitment of immune cells that initiate an inflammatory response, leading to tissue damage and gastrointestinal symptoms [71]. There is increasing evidence that the gut microbiota plays a critical role in the severity of COVID-19, and it has been documented that the gut microbiota changes after infection [59]. This complex microbial community is considered a significant environmental component that controls many host processes, particularly the immune system and metabolism, and is critical in determining health and disease status [72,73]. In addition, studies have demonstrated a relationship between the gut microbiota and the gut lung, 2 systems implicated in COVID-19.

Numerous studies have demonstrated the influence of gut microbiota on the lung, including one in which animals lacking gut microbiota had reduced pulmonary clearance of pathogens [74]. According to 1 study, intratracheal administration of lipopolysaccharide (LPS) can alter the lung microbiota, which alters the gut microbiota and increases bacterial load [75]. An extraordinary mechanism for developing the host immune system is observed in the human gut. The interaction and coordination of the gut's innate and adaptive immune systems, with a mutually beneficial link between the 2, results in intestinal homeostasis. The intestinal Peyer's patches, which contain dendritic cells, Langerhans cells, macrophages, and other cell types, control innate immunity through the intestinal microbiota [76]. These cells exhibit a degree of immunogenic tolerance to the gut microbiota, as evidenced by the "inflammatory anergy" development in macrophages [76,77].

The balance between pro-inflammatory responses, which are kept in check by Th17 cells, and regulatory T cells, which make up the anti-inflammatory response, determines immune homeostasis in the gut, which can also affect the lungs through the gut-lung axis [78]. In the gut, studies have shown that *Bacteroides fragilis* can induce the development of Th1 cells, and *Clostridia* can cause the development of regulatory T cells. Segmental filamentous bacteria can induce the development of Th17 cells [79-82]; similar to how the microbiome affects interferon signaling and increases chronic phase protein production during influenza virus infection, the metabolic activity of microbes in the gut influences cytokine production.

One theory is that the interaction of COVID-19 with the microbiome may influence cytokine production and possibly lead to an excess of proinflammatory cytokines [12]. Therefore, there is a possibility that COVID-19 interacts with the gut microbiota, which could lead to an increased level of immune cell activation [54]. In this sense, the gut microbiota plays an essential role in host immunity, and SARS-CoV-2 may interact with the gut microbiome and infect enterocytes to cause gastrointestinal symptoms.

COVID-19 has been shown to cause dysbiosis in the gut microbiota, inflammation, and poorly controlled immune responses [70]. However, other factors are known to be involved in disease progression, including host-specific factors such as genetics and environmental factors. For example, inflammatory mediators act in concert to promote the recruitment of immune cells that initiate an inflammatory response, leading to tissue damage and gastrointestinal symptoms [83]. This is important because host genetics has been shown to significantly influence gut microbiota composition. Lamichhane *et al*. identified specific genetic loci associated with the abundance of certain bacterial taxa, suggesting a heritable component in the microbiota composition [84]. In addition, genetic variants in the host may influence the interaction between the host and its microbiota; specific single nucleotide polymorphisms (SNPs) have been associated with differences in microbial composition and function [85]. On the other hand, genetic variants have been associated with severe COVID-19; particular genetic loci, including those related to immune response and inflammation, have been associated with an increased risk of severe disease [86]. Accordingly, genetic factors may influence the gut microbiota and affect the severity of COVID-19, with specific microbial signatures associated with host genetics associated with more severe disease outcomes [87]. In addition, certain HLA genotypes have been associated with specific microbial profiles that may also influence the host immune response [88].

The relationship between the host microbiota and COVID-19 has been considered very relevant for a better understanding the disease, and several studies have shown this. Zhang *et al*. found that patients with COVID-19 had significant changes in the composition of their gut microbiota compared to healthy controls. Specifically, there was a depletion of beneficial commensal bacteria and an enrichment of opportunistic pathogens [28]. Yeoh *et al*. [30] demonstrated that the gut microbiota composition in patients with COVID-19 was associated with disease severity. They found that certain microbial signatures were associated with elevated inflammatory markers and a dysregulated immune response. Several gut commensals with known immunomodulatory potential, such as *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and *Bifidobacteria*, were underrepresented. Furthermore, this altered composition showed a disease severity stratification consistent with elevated levels of inflammatory cytokines and blood markers such as C-reactive protein, lactate dehydrogenase, aspartate aminotransferase, and gamma-glutamyl transferase [30]. In the same direction, it has been reported that patients hospitalized for COVID-19 had dysbiosis of the intestinal microbiota, with a decrease in beneficial bacteria such as *Faecalibacterium prausnitzii* and an increase in opportunistic pathogens such as *Clostridium hathewayi* [28]. In addition, Yeoh *et al*. found that COVID-19 patients with severe disease had gut microbiota profiles associated with increased levels of proinflammatory cytokines, contributing to the cytokine storm observed in these patients [30]. These studies prove that specific microbial signatures are associated with elevated inflammatory markers and a dysregulated immune response in COVID-19, highlighting the importance of the gut microbiota in modulating the host immune response and disease outcome. These explanatory factors can be summarized in **Figure 3**.

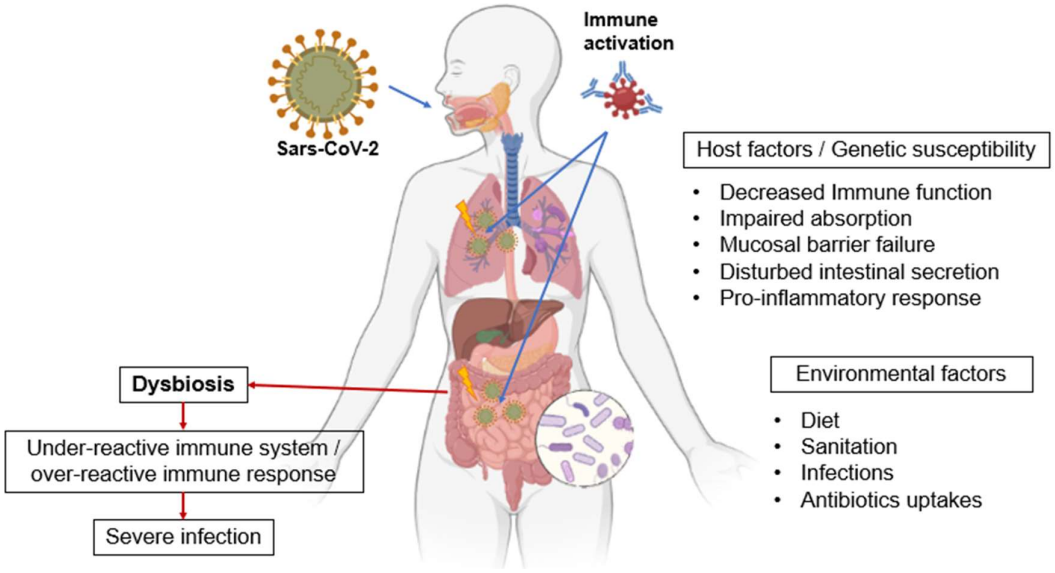

Figure 3 SARS-CoV-2 infection and factors involved in the host's pathogenesis and immune reaction. This original image was created with BioRender: Scientific Image and Illustration Software (https://www.biorender.com).

Dysbiosis of the intestinal microbiota and its effect on COVID-19

In addition to being strongly associated with the pathophysiology of many inflammatory disorders, dysbiosis, defined as changes in the gut microbiota that result in microbial imbalance, plays an essential role in various infections [54]. One of the most prevalent invasive pathogens that cause strong interactions between viruses and the commensal microbiota are viruses. Gut dysbiosis is associated with a wide range of multifactorial conditions, such as autoimmune, metabolic, inflammatory, neurodegenerative, and neoplastic diseases. Two strategies employed by innate and adaptive immunity to control colonization of the intestinal microbiota are the production of antimicrobial peptides and IgA antibodies [54]. There is a strong correlation between SARS-CoV-2 infection and the occurrence of dysbiosis of the intestinal microbiome, as demonstrated by the finding of severe diarrhea and the presence of SARS-CoV-2 virions in fecal samples in patients with COVID-19 [89].

Furthermore, alterations in the gut microbiome, characterized by increased opportunistic pathogenic bacteria and decreased beneficial commensal bacteria, are associated with SARS-CoV-2 in stool and the severity of COVID-19 symptoms [90]. Even after SARS-CoV-2 has been cleared and all signs of disease have disappeared, these modifications often continue. Alteration of the gut microbiota, which is undoubtedly capable of exposing healthy individuals to an abnormal inflammatory state, may also help explain the vulnerability and severity of COVID-19 [89].

It is becoming increasingly clear that the gut microbiota is an important immune system modulator, promoting local mucosal immunity. A recent study has highlighted the critical role of gut bacteria in determining lung inflammation [90]. The gut microbiota has significantly influenced susceptibility, severity, and recovery from COVID-19 in humans and animal models [91]. Interestingly, a bidirectional

relationship exists between gut microbiota and respiratory infections [90]. Pulmonary infections can spread to the bloodstream and other organs [91]. The microbiome, which is closely associated with respiratory viral infections, may influence the onset and course of disease through the gut-lung axis [90]. While the basal abundance of *Clostridium ramosum*, *Coprobacillus*, and *Clostridium hathewayi* was positively correlated with COVID-19 severity, the basal abundance of *Faecalibacterium prausnitzii* was negatively associated with disease severity [90]. SARS-CoV-2 infection triggers innate and adaptive immune responses, and exposure to a high SARS-CoV-2 viral load makes the disease more severe. This is explained by the inability of the adaptive immune system to effectively produce antibodies and cytotoxic CD8 cells against the virus in a short period. As a result, the innate immune response is less developed than the adaptive immune response. Thus, when the cytokine storm develops, a strong immune response is triggered, which impacts the severity and prognosis of the disease and may even lead to death [92].

COVID-19 patients had dramatic changes in the richness and diversity of their gut and bronchial microbiomes. The vast majority of scientific evidence suggests that COVID-19 patients shed viral RNA for more extended periods [93]. *Firmicutes* decrease in abundance after dysbiosis, while *Proteobacteria* and *Alistipes* increase. This behavior also occurs when exogenous pathogens such as SARS-CoV-2 enter the organism. Carbohydrate metabolism, glycolysis, and the creation of amino acids and nucleotides from scratch are processes in which the gut microbiota is involved. COVID-19 dysbiosis represents functional changes as a result of altered environmental microorganisms. *Morganella morganii*, *Collinsella tanakaei*, *Collinsella aerofaciens* and *Streptococcus infantis* are prominent in the stool microbiome of COVID-19 patients with mild symptoms and healthy individuals. Other bacteria that produce short-chain fatty acids that may help fight the SARS-CoV-2 virus include *Bacteroides stercoris*, *Lachnospiraceae*, *Parabacteroides merdae*, and *Alistipes* [94].

Following gastrointestinal symptoms, Blackett *et al*. [95] discovered variations in 5 non-specific microbial metabolic pathways. The tricarboxylic acid (TCA) cycle, which produces adenosine triphosphate (ATP), is directly related to 4 differentially expressed pathways. The 5th pathway is associated with the biosynthesis of thiazolethiamine (vitamin B1), an essential cofactor for the multienzyme pyruvate dehydrogenase complex that oxidizes glucose in the TCA cycle. All pathways showed the same directionality (lower activity in individuals with more GI symptoms), consistent with the close relationship of the TCA cycle to serotonin production [95]. A recent study by Liu *et al*. [96] on COVID-19 patients found 32 pathways that varied as a function of post-acute COVID-19 status (mainly fatigue). In summary, **Figure 3** illustrates the key role of the gut microbiota and its metabolites in modulating the host immune response during viral infections such as COVID-19. This could be summarized as follows: A) Viral infection: SARS-CoV-2 infection leads to alterations in the gut microbiota, resulting in dysbiosis, characterized by a decrease in beneficial commensal bacteria and an increase in opportunistic pathogens. B) Gut microbiota and metabolites: The gut microbiota produces several metabolites, including short-chain fatty acids (SCFA) and vitamins; these metabolites are critical in regulating the host immune response. C) Immune activation and resolution: Dysbiosis and associated changes in microbial metabolites can lead to an imbalance in the host immune response. This imbalance can lead to an excessive inflammatory response, known as a “cytokine storm,” associated with severe COVID-19 symptoms. Therefore, a healthy gut

microbiota and its metabolites may help maintain immune homeostasis and promote resolution of viral infection. D) Pathways and interactions: Gut microbiota and their metabolites can modulate host innate and adaptive immune responses through various mechanisms, such as interacting with pattern recognition receptors (PRRs) on immune cells, regulating inflammatory pathways, maintaining intestinal barrier function, and promoting antiviral immune responses. E) Potential outcomes: A balanced gut microbiota and its metabolites may contribute to a more effective immune response against viral infections, leading to better disease outcomes and faster recovery. Conversely, dysbiosis and imbalance of microbial metabolites may exacerbate the host immune response, leading to more severe disease progression and complications. In summary, **Figure 4** highlights the critical role of the gut microbiota and its metabolites in modulating the host immune response during viral infections such as COVID-19. Maintaining a healthy gut microbiome and optimizing the production of beneficial metabolites may be a promising approach to enhance the body's ability to fight viral infections and promote disease resolution.

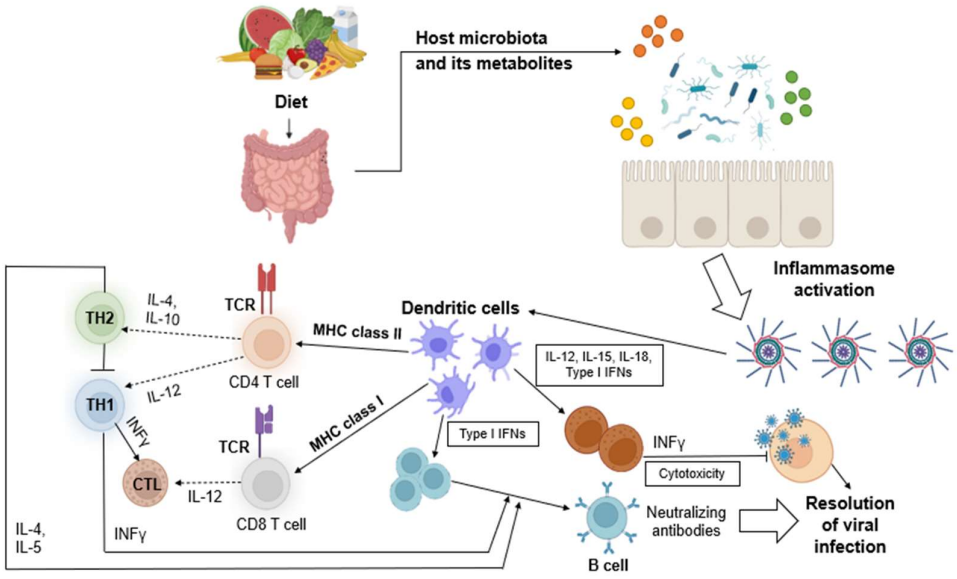

Figure 4 Implications of host microbiota and its metabolites for the immune activation and the resolution of viral infection. This original image was created with BioRender: Scientific Image and Illustration Software (https://www.biorender.com).

The gut-lung axis

The gut-lung axis describes how the function of the gut microbiota can affect that of distant organs such as the lungs. Interestingly, the gut microbiota influences the pattern of the lung microbiota (i.e., the microbial species that colonize the respiratory tract) and the nature of immunity to respiratory disease. The gut-lung connection is based on communication between immune cells, epithelial cells, and microorganisms that inhabit both systems. The gut-lung axis is essential for maintaining homeostasis and proper function of both systems, and its imbalance may contribute to disease development [97].

Respiratory infections alter the composition of the gut microbiota and its executive functions [72,97]; several factors, including the interaction of microbe-associated molecular patterns and pattern recognition receptors, the function of the intestinal barrier, the activity of resident immune cells in the lamina propria, and microbial metabolites, determine lung immunity under the control of the gut microbiota. For example, short-chain fatty acids, which are metabolites derived from the gut microbiota, influence lung immunity to respiratory viruses such as influenza by altering the differentiation of immune cell precursors from the bone marrow to the lung, thereby attenuating the major symptoms of respiratory viral infection such as inflammation and severe tissue damage; this mechanism may also be available to protect against SARS-CoV-2 virus due to the structural similarities shared by both respiratory viruses [72,98].

An altered composition of the intestinal and pulmonary microbiota has been observed in patients with COVID-19. Recent studies have shown that patients with COVID-19 have decreased diversity and abundance of beneficial bacteria in the gut, such as *Bifidobacterium and Faecalibacterium* [99,100]. Conversely, an increase in opportunistic pathogens such as *Candida*, *Enterococcus*, *Eggerthella*, and *Clostridium* has been found, the latter being closely correlated with the severity of COVID-19 by Zuo *et al*. [28,29,83,101]. In addition, variations in lung microbiota diversity have been found in patients with COVID-19 compared to healthy individuals [102].

This alteration in the gut-lung axis's microbiota can significantly impact disease severity and the patient's immune response. An imbalance in the gut microbiota can weaken the gut's barrier function, favoring permeability and allowing the translocation of pathogens and their products into the bloodstream [103-105]. This could trigger a systemic inflammatory response and exacerbate pulmonary inflammation in patients with COVID-19. In addition, changes in the pulmonary microbiota could affect the local immune response and the ability of the respiratory system to fight SARS-CoV-2 infection. Changes in the pulmonary microbiota have been associated with progressive respiratory disease because they can impair the immune response, increase viral infectivity, and promote the growth of opportunistic pathogenic bacteria [106,107].

The gut-brain axis

The gut-brain axis is a bidirectional communication system between the central nervous system and the gut that plays a critical role in regulating brain function and gut health [108,109]. Communication between the gut microbiota and the brain occurs through multiple pathways, including bacterial production of neurotransmitters and metabolites, immune system activation, and gut barrier function modulation [110-112]. Alteration of the microbiota in patients with COVID-19 may affect these pathways and consequently affect brain function and neurological symptoms [30].

COVID-19 has been associated with several neurological disorders, the most common being fatigue, anosmia, ageusia, depression, anxiety, memory impairment, attention deficit, and encephalitis [113-117]. In addition, it has been suggested that infected patients have an increased risk of developing neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, due to pathological processes associated with SARS-CoV-2 [118,119]. Although a deeper understanding of the pathophysiology of these neurological complications and the mechanisms involved is still needed, evidence

suggests that the gut microbiota is closely related to the progression of many neurological diseases in the context of a gut-brain axis [120-122].

Approaches to improve COVID-19 outcomes by modulating the microbiota

Patients with COVID-19 still have no cure, and only 1 drug has been approved to treat the disease: Remdesivir (Veklury). This antiviral drug can be administered intravenously to treat COVID-19 in adults and hospitalized children over 12 years of age. Remdesivir was initially developed to treat hepatitis C, and after researchers studied its efficacy in treating Ebola virus infection, it has now been expanded to treat COVID-19. Remdesivir inhibits SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), an enzyme critical for viral replication and viral RNA transcription in host cells [123]. Another antiviral drug, molnupiravir, targets the RdRp of the SARS-CoV-2 virus by preventing viral replication and RNA transfer; molnupiravir is administered orally, unlike remdesivir, which is administered by infusion [124]. According to recent phase II research, Molnupiravir is a good choice for COVID-19 patients with COVID-19 who received 800 mg of the drug twice daily for 5 days, clearing viral RNA faster than placebo controls [125]. The FDA has approved nirmatrelvir (Paxlovid) for the treatment of COVID-19. It is a viral protease inhibitor that inhibits the viral protease MPRO, a protein required for viral replication [126]. By inhibiting JAK1 and 2 signaling, the drug baricitinib treats rheumatoid arthritis by reducing inflammation; in addition, artificial intelligence systems predicted the ability of baricitinib to treat COVID-19. Studies have shown that baricitinib rapidly reduces IL-6 levels and SARS-CoV-2 viral load in patients with COVID-19 [127]. Studies have also shown that the combination of baricitinib and remdesivir helps patients with COVID-19 heal faster and experience fewer serious side effects overall [128].

Emerging data from intervention studies and animal models suggest that the microbiota may be a critical factor in developing protective antibody responses to vaccination [129-134]. For example, mice that received antibiotics and remained germ-free had reduced antibody responses to the seasonal influenza vaccine [135]. Therefore, microbiota-focused therapies are a viable strategy to maximize vaccine efficacy in addition to COVID-19 treatment, given that the microbiota is a key factor influencing immune responses to vaccination. However, the effects of the microbiota on immune responses to COVID-19 vaccination have only been investigated in a few studies, and more research is needed in this area [43].

In the context of COVID-19, it is essential to explore strategies that may improve the gut-lung and gut-brain axis function and consequently improve the prognosis of patients affected by the virus. Immunomodulation is highly dependent on the gut microbiome. Microbiota-based therapies such as fecal microbiota transplantation (FMT), probiotics, and prebiotics treat many human diseases, including diabetes, obesity, cancer, ulcerative colitis, Crohn's disease, and viral infections [136]. Probiotics and prebiotics can help restore microbiota composition, improve intestinal barrier function, and reduce systemic inflammation, which may benefit lung and brain function [78,137]. Recently, several studies have been conducted on COVID-19, and their consequences have been addressed by modifying the gut microbiota [137-143]. In FMT, feces or complex microbial communities purified from the fecal material of a healthy donor or produced from *in vitro* growth are implanted into a patient's digestive tract. FMT treats recurrent *Clostridioides difficile* infections, diabetes, and colitis [144-147]. Promising COVID-19 therapeutic

strategies that alter the gut microbiota include supplementation with microbiota-targeted substrates (prebiotics), such as specific dietary fibers, and/or direct transfer of one or more specific beneficial bacteria (probiotics) [137,148]. Therapy with prebiotics and/or probiotics is comparatively less hazardous and requires less preparation and administration than FMT. To restore and maintain the intestinal microbiota balance and prevent secondary infections, the National Health Commission of China has recommended the clinical administration of probiotics to patients with severe COVID-19. Numerous clinical trials have confirmed that probiotics and/or prebiotics are effective in shortening the duration and symptoms of COVID-19 [43].

Another strategy is to use short-chain fatty acids (SCFAs), such as butyrate, which have anti-inflammatory and immunomodulatory properties. Supplementation with SCFA may improve gut-lung and gut-brain axis function by reducing inflammation and improving intestinal barrier function, which may be particularly relevant in patients with COVID-19 [149,150].

In addition, several studies have raised the potential benefit of vitamin D supplementation in preventing and treating COVID-19. Increased susceptibility to several respiratory viral infections, particularly respiratory syncytial virus (RSV) infection and influenza, has been associated with vitamin D deficiency [151]. Through interactions with both cellular and viral components, vitamin D may modify the course of infection once it has begun. By regulating inflammatory responses, increasing ACE2 expression, decreasing the neutrophil-to-lymphocyte ratio, and inhibiting the complement system, vitamin D intake may have a significant impact on infection [152]. Therefore, determining the ideal timing and amount of vitamin D supplementation as a treatment strategy appears potentially beneficial [55].

Weight loss may also explain changes in the gut microbiome composition observed in respiratory infections. People who consume fewer calories have significantly more *Bacteroidetes* than *Firmicutes* in their bodies. Most research in human and mouse models has focused on probiotic treatments, mainly with *Lactobacillus spp.* [153].

Patients with moderate or asymptomatic COVID-19 infections and those in quarantine are advised to follow an anti-inflammatory and balanced diet rich in whole grains, legumes, vegetables, and fruits. In addition, plasma adiponectin levels are higher in fiber-rich diets, which is beneficial because of the anti-inflammatory effect mediated by the insulin-sensitizing activity of adipocytokines [142]. The adoption of dietary and lifestyle interventions may have beneficial effects on the microbiota and the function of these axes. Diets rich in fiber, antioxidants, and fatty acids have improved microbiota composition and reduced systemic inflammation [154]. **Figure 5** shows the effect of diet, probiotics, prebiotics, and preexisting conditions on COVID-19 on the microbiota in more detail [155]. Physical activity can also increase the diversity of the microbiota and promote the proliferation and development of beneficial species, thereby improving gut-lung and gut-brain axis function [156].

Finally, stress management and mental health promotion may also be essential strategies to improve the function of these axes in patients with COVID-19. Chronic stress can alter the composition of the microbiota and affect the function of the gut-brain axis, which may contribute to neuropsychiatric symptoms in patients with COVID-19 [157,158]. Therefore, stress-reduction techniques may benefit these patients' gut-brain axis function and mental health.

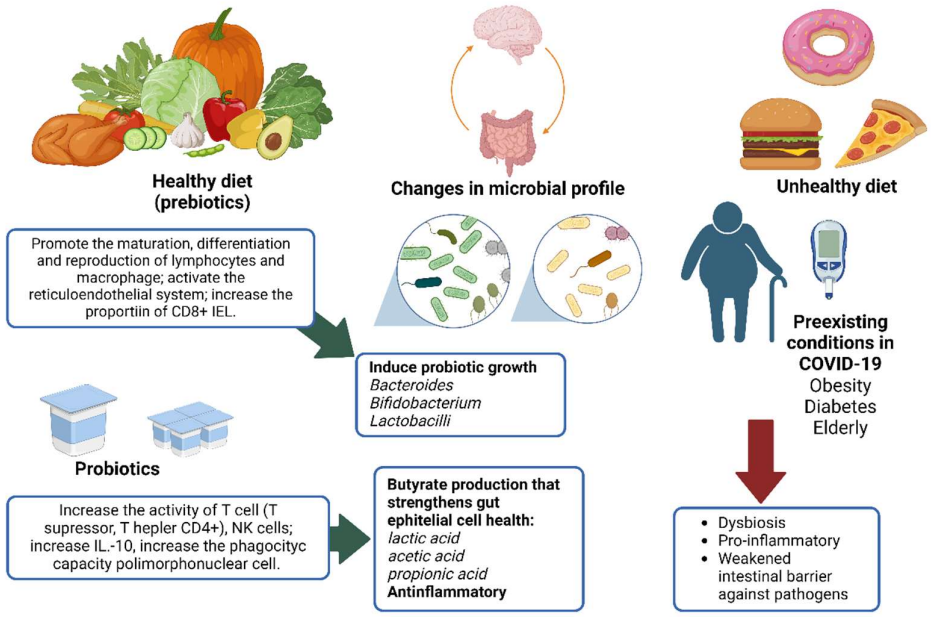

Figure 5 Changes in microbiota profile due to diet, probiotics, prebiotics, and pre-existing conditions in COVID-19. This original image was created using BioRender: Scientific Image and Illustration Software (https://www.biorender.com).

Conclusions

The severe acute respiratory syndrome virus outbreak in 2003 rekindled interest in the gut microbiota, which plays a vital role in host health and disease. The gut microbiota has been shown to change after infection and significantly impact susceptibility, severity, and recovery from COVID-19. In human and animal models, the gut microbiota has significantly impacted susceptibility, severity, and recovery from COVID-19. The diversity and richness of the gut and bronchial microbiomes of patients with COVID-19 have been observed to be altered, with lower diversity and abundance of good bacteria. The severity of COVID-19 was closely related to *Clostridium*, while an increase in opportunistic infections was observed. Patients with COVID-19 may have an altered microbiota that can affect communication pathways, brain function, and neurological symptoms. Emerging evidence suggests that the microbiome may be necessary for generating protective antibody responses to vaccination. Microbiota-targeted therapies are a promising option for maximizing vaccine efficacy. Prebiotics and probiotics can improve intestinal barrier function, restore microbiota composition, and reduce systemic inflammation. Diets rich in fiber, antioxidants, and fatty acids can also improve microbiota composition and reduce systemic inflammation. Thus, the current findings demonstrate the importance of microbiota regulation in improving COVID-19 disease outcomes and remission and potential target therapies to improve the immune response, especially in those most in need, such as the elderly or immunocompromised.

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