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REVIEW

Cross-talk between immune system and microbiota in COVID-19

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ABSTRACT

Introduction: Human gut microbiota plays a crucial role in providing protective responses against pathogens, particularly by regulating immune system homeostasis. There is a reciprocal interaction between the gut and lung microbiota, called the gut-lung axis (GLA). Any alteration in the gut microbiota or their metabolites can cause immune dysregulation, which can impair the antiviral activity of the immune system against respiratory viruses such as severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2.

Areas covered: This narrative review mainly outlines emerging data on the mechanisms underlying the interactions between the immune system and intestinal microbial dysbiosis, which is caused by an imbalance in the levels of essential metabolites. The authors will also discuss the role of probiotics in restoring the balance of the gut microbiota and modulation of cytokine storm.

Expert opinion: Microbiota-derived signals regulate the immune system and protect different tissues during severe viral respiratory infections. The GLA's equilibration could help manage the mortality and morbidity rates associated with SARS-CoV-2 infection.

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1. Introduction

Influenza and other respiratory virus infections are one of the leading causes of morbidity and mortality worldwide [1]. A competent immune system reduces mortality by protecting the host against viral infections and reducing susceptibility to secondary bacterial infections [2]. The World Health Organization (WHO) has stated that severe coronavirus disease 2019 (COVID-19) is a pandemic challenge [3]. COVID-19 is a lethal condition in patients with comorbidity, particularly those with immune system disorders. A healthy immune system can help people overcome clinical complications and return to work faster [4]. COVID-19 seems to cause a wide range of extrapulmonary difficulties affecting multiple organ systems. The pooled prevalence of all gastrointestinal (GI) problems was 17.6% in an early meta-analysis of 60 trials involving 4243 patients, most of whom were from China. The most prevalent presenting symptom was anorexia (26.8%), followed by diarrhea (12.5%), nausea/vomiting (10.2%), and abdominal pain (9.2%) [5]. Critically ill COVID-19 patients often develop GI complications during hospitalization, such as bowel ischemia, pancreatitis, GI bleeding, elevated transaminases, ogilvie syndrome, and severe ileus [6,7].

Gut microbiota is essential for the development of immune responses [8]. There are approximately 38 trillion microorganisms in our body, including bacteria, fungi, archaea, viruses, and other eukarya. Bacteria are more common among them, with at least 2,000 different species [9]. The gastrointestinal tract (GIT) is the main habitat of microbiota, since it provides the largest interface surface (250–400 m^2) of the body and is nutrient-rich. The GIT comprises over 2,000 bacteria species from 12 distinct phyla. The microbiome contains 3 million genes that are 150 to 500 times more than the number of genes in the human genome [10]. The gut microbiota can affect food digestion, production of energy and vitamins (B1, B5, B12, K, and folic acid), biliary acids deconjugation, and other vital biochemical aspects of our life [11,12]. On the other hand, microbiota has a remarkable impact on the activation and function of immune cells. Accordingly, a persistent microbial community imbalance in the gut is known as

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Article highlights

- Gut microbiota is essential for host immune system's induction, education, function, development of immune responses, and regulates the integrity of the mucosal barrier, provides bacterial metabolites, and regulates the immunoregulatory functions of intestinal epithelial cells by modulating the expression of antimicrobial factors.
- Dysbiosis is linked to dysimmunity, commonly described as a T-helper 2 (Th2)-overactive, and Treg-deficient state.
- Cross-talk between the healthy gut microbiota and lungs can significantly prevent respiratory tract infection in both influenza A virus and COVID-19 through reciprocal interaction, quorum-sensing molecules, and synthesis of antimicrobial agents.
- In COVID-19 patients, probiotic treatment could result in an eight-fold lower rate of respiratory failure.
- It seems that fecal microbiota transplantation could be used as a therapeutic and rehabilitative intervention in the COVID-19 patients.

dysbiosis [13], increasing the risk of infections and autoimmune diseases [14–19].

Many studies have recently shown a regulatory association between the gut microbiota and other organs, such as the gut–lung axis, gut–brain axis [20], gut–liver axis [21], gut-host hormonal axis [22], and gut–skin axis [23]. Noticeably, cross-talk between the healthy gut microbiota and lungs can significantly prevent respiratory tract infection in both influenza A virus and COVID-19 [24,25]. Based on these interactions, any alterations in the gut microbiota may directly affect the function of other organs. Furthermore, more than 50% of patients with inflammatory bowel disease (IBD) and 33% of patients with irritable bowel syndrome (IBS) are susceptible to respiratory complications as a result of dysbiosis without a history of acute or chronic respiratory disease [26,27].

The interaction of the gut microbiome and immune system [10] plays a protective role in preventing severe infection and controlling the viral load. The immune system is naïve in newborns and inefficient in older adults. Both groups are susceptible to viral infections and have a high mortality rate [28,29]. Recent molecular studies have also revealed differences in gut microbiota composition among infants, toddlers, adults, and the elderly [30]. It appears that an altered gut microbiota composition can make an infant more susceptible to infections and allergic disease [31]. Dysbiosis, or disruptions in the hemostasis of gut microbiota, may cause an uncontrolled and intense immune response to viral infections. Dysbiosis occurs when there is disparity in the number of normal bacteria and a rise in commensal, and/or opportunistic gut bacteria. Moreover, eubiosis is characterized by a species diversity dominated by members of only four bacterial phyla, including Firmicutes (e.g. *Lactobacillus and Clostridium*), Bacteroidetes (e.g. *Bacteroides*), Proteobacteria (e.g. *Escherichia*), and Actinobacteria (e.g. *Bifidobacterium*) [32,33]. Antibiotics, high-fat diet, stress, and air pollution have all been linked to dysbiosis, which has been shown to affect other body systems [17,34]. During COVID-19 infection, microbiota dysbiosis such as *Klebsiella oxytoca, Lactic Acid Bacteria*, and Tobacco mosaic virus were discovered [35]. In addition, a study found a link between the severity of COVID-19 infection and the prevalence of *Clostridium ramosum, Coprobacillus, Clostridium hathewayi, Faecalibacterium prausnitzii*, and *Alistipes onderdonkii* [36].

The present narrative review discusses the interaction between the healthy microbiome and the immune system during the initiation and progression of COVID-19. Finally, we overview the protective role of probiotics in the current COVID-19 pandemic.

2. Gut microbiota regulates the immune system

The number of microorganisms in the GI tract is reported to be more than 10^{14}. The total number of microbes encompasses about 10 times more than human cells [37]. Bacteria that inhabit the microbiota of the human gut are classified into phyla, classes, orders, families, genera, and species. *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria*, and *Verrucomicrobia* are the significant gut microbial phyla [38,39]. Recent research has discovered that species and strains of microorganisms can control the host defense against different pathogens. According to the rodent studies, *Bacteroides fragilis* strain No. 9343 protects against colitis, while strain 86–5443-2-2 induces colitis [17,40]. *Clostridial* cluster IV and XIVa have also been shown to cause colonic Treg cells [41].

On the other hand, the density of DNA and RNA viruses that comprise the intestinal virome is equal to that of bacterial cells. At the same time, they may exceed bacterial cells by a 20:1 ratio on gut mucosal surfaces and within mucus layers [42]. Through inducing immune system tolerance, the gut virome maintains and develops diversity in the human gut microbiota in a dynamic equilibrium with the host. The regulation of human metabolism, inflammation, and carcinogenesis are all influenced by gut virome. Recent evidence showed that *Bacteriophages* play a role in human liver metabolism and immune response modulation [43]. Developing an immunoregulatory network that protects against induction of mucosal IgE, which is linked to allergy susceptibility, is also dependent on intestinal microbial diversity during early-life colonization [44].

The gut microbiota, including bacteria, archaea, and eukarya, colonize within the GI tract and co-evolve with the host over thousands of years to develop an intricate and mutually beneficial interaction. The gut microbiota influences the host immune system's induction, education, and function [45,46]. On the other hand, the immune system has largely evolved to maintain the host's symbiotic relationship with these diverse and evolving microorganisms. This immune system-microbiota alliance interweaves the innate and adaptive arms of immunity in a dialog that selects, calibrates, and terminates responses. This interaction also enables the maintenance of regulatory pathways to maintain tolerance to innocuous antigens [45–48]. Gut microbiota may modulate systemic immunity by regulating innate and adaptive immune homeostasis by developing metabolites and antimicrobial peptides against various pathogens [10,49,50]. Several studies showed a cross-talk between the gut microbiota and antigen-presenting cells (APCs) and neutrophil regulation, besides forming CD4 + T cells both within and outside the intestine

[41,44,51–54]. A shift in the gut microbiota's composition can have either a pathological or beneficial effects, mediated by the gut microbiota's regulation of specific CD4 + T cell subtypes [55]. Dysbiosis is linked to dysimmunity, commonly described as T-helper 2 (Th2)-overactived and Treg-deficient state [19]. The gut microbiome's influence on the T cell compartment of the adaptive immune system is the best-understood mechanism by which the gut microbiota influences the systemic immunological response [46]. The GIT microbiota has been found to influence T cell development into Th1, Th2, and Th17 cells, as well as regulatory T cells [47]. It has been reported that *segmented filamentous bacteria* (SFBs) directly regulate the secretion of various antibacterial peptides leading to altered secretion of IL-17 by Th17 cells [56,57]. The number of Th17 cells in the lamina propria and the production of IgA in the intestinal mucosa were found to be reduced by SFBs [58,59].

In response to the microbiota signal, secretory IgA (sIgA), IL-12, IL-22, and IFN-α are secreted. sIgA regulates local immunity, viral infection colonization, and proliferation [60]. Short-chain fatty acids (SCFAs) are one of the common metabolites produced by the gut microbiota and rapidly absorbed by intestinal epithelial cells (IECs) [61]. SCFAs regulate immune cell bioactivity, such as glucose homeostasis, gene expression profile, anticancer activity, and inflammatory response. SCFAs can also serve as a source of energy for T cell differentiation (Th1, Th2, Th17, and T regulatory (Treg) cells). Interestingly, SCFAs can induce tolerance in dendritic cells (DCs) which contributes to the differentiation of naïve CD4 + T cells into Treg cells [62]. Common SCFAs include propionate (form *Bacteroidetes*), butyrate (form *Firmicutes*), and acetate (from most gut anaerobes) [60,63]. Butyrate enhances the differentiation of Treg cells and prevents the development of systemic inflammation [48]. The potential of microbiota-released signaling molecules to enter the circulation also enables resident bacteria in the gut to affect the immune system during immune cell formation in hematopoiesis, and hence alter infection response [64]. Moreover, the SCFA butyrate induces bone marrow monocyte differentiation from an inflammatory to a more tolerogenic phenotype [48]. A decrease in butyrate-producing bacteria and gut dysbiosis, in particular, resulted in reduced IL-22 production, which is necessary for gut and lung epithelial barrier integrity [65]. Acetate is the most abundant SCFA produced in high quantities by *Bifidobacteria*, and is found in the gut lumen and peripheral circulation [66]. Acetate modulates intestinal inflammation by activating G protein-coupled receptor 3 (GPR43) [67], thereby contributing to the maintenance of gut epithelial barrier function [68]. Acetate also has anti-inflammatory characteristics in neutrophils, decreasing NF-kB activation by suppressing the levels of pro-inflammatory mediators such as lipopolysaccharide-induced TNF-α [66].

The mucus in the intestines and lungs is considered the first defense line against pathogen colonization [69]. The luminal layer of the gut mucosa is a suitable site for the colonization of commensal bacteria. Furthermore, the gut microbiota regulates the integrity of the mucosal barrier, provides bacterial metabolites [37,70], and regulates the immunoregulatory functions of IECs by modulating the expression of antimicrobial factors [71,72]. As one of the critical bacterial metabolites, butyrate regulates transepithelial fluid transport, reduces mucosal inflammation and oxidative stress, improves the epithelial defense barrier, and controls visceral sensitivity and intestinal motility [73]. Moreover, butyrate provides a critical line of immunologic defense in the intestine *via* induction of DCs tolerance in the epithelium, which is associated with mucosal IgA production. Butyrate also suppresses mast cell degranulation in the intestinal mucosa and limits circulating inflammatory mediators' production [74]. So, the absence of the gut mucosa reduces the commensal bacteria adhesion and IECs integrity and result in direct contact with bacteria which eventually causes inflammation in the gut [75]. On the other hand, SCFAs induce the expression of pattern recognition receptors (PPRs) on DCs and macrophages, which regulate cytokine secretion and antibody synthesis (sIgA and IgM) [76].

The balanced production of antiviral cytokines is associated with specific GIT bacteria, including *Faecalibacterium, Oscillibacter, Pseudoflavonifractor, Anaerotruncus*, and *Bifidobacterium*. It has been reported that antibiotic administration in chickens resulted in higher susceptibility to the avian influenza virus (AIV) and reduced expression of IFN-α, IFN-β, and IL-22 levels [77]. The synthesis of microbial peptides in the gut is regulated by the key active components of innate immunity such as α-defensin (DEFA) and C-type lectins (REG3g and REG3b) [60]. Menendez *et al*. showed that germ-free mice had a significant decrease in the expression of DEFA [78]. Toll-like receptors (TLRs) and NOD-like receptors (NLRs) on DCs and macrophages help the immune system to distinguish between useful and pathogenic bacteria [79]. IECs also express these transmembrane receptors, which are involved in the recognition of different microbe-associated molecular patterns (MAMPs) *e.g*. peptidoglycan, capsular polysaccharides, lipopolysaccharides (LPS), and flagellin and bacterial DNA CpG motifs [80].

Gut-associated lymphoid tissue (GALT), composed of lamina propria, intraepithelial lymphocytes, mesenteric lymph nodes, Peyer patches, and isolated lymphoid follicles, helps defend against external factors that penetrate the luminal mechanical barrier [38]. Experimental evidence has established the role and function of gut microbiota in GALT regulation [81,82]. Accordingly, germ-free mice developed hypoplastic Peyer's patches/mesenteric lymph nodes in the small intestine, but no isolated lymphoid follicles (ILFs) [83]. The first colonization of gut microorganisms in full-term infants depends on GALT maturation and GI-Blood Barrier critical closure. These interactions result in the formation of symbiotic conditions, which are defined as a balance between immunity and infections [84].

During early life, critical host immune-microbiota interactions occur, which may have long-term effects on multiple immune arms that contribute to immune homeostasis and sensitivity to infectious and inflammatory diseases later. However, the mechanisms underlying these interactions are remaining unclear. In this regard, future studies are needed to determine the long-term effects of mild dysbiosis states

during the neonatal period on adult immunity and the risk of immune-mediated diseases [44].

3. Gut microbiota–lung axis

A healthy lung contains 10–100 bacteria per 1,000 cells [85]. *Bacteroidetes, Firmicutes*, and *Proteobacteria* are the most common phyla colonizing the healthy lung [86]. There is a constant cross-talk between the gut and lung mucosal compartments through the mesenteric lymphatic system and lung lymph nodes. Physical interaction, quorum-sensing molecules, and synthesis of antimicrobial agents could all be involved in these interactions, which could modulate the lung's immune response [87] .Changes in the microbial composition of the lung can influence the community of gut microbiota and *vice versa*. Due to possible barrier dysfunction, bacterial translocation from the gut to the lungs has been documented in sepsis and acute respiratory distress syndrome [88]. The gut and respiratory tract have been linked to control immunological responses, and dysbiosis in the gut microbiota leads to development of respiratory disease [89]. Mechanisms involved in microbiota-lung-gut-axis alteration in COVID-19 include direct lung damage, ACE2 expression, gut microbiota as lungs' defense against SARS-CoV-2, and immune response [90]. In 2012, researchers demonstrated that colonization of the influenza virus in the respiratory tract of mice causes intestinal dysbiosis by increasing *Enterobacteriaceae*, while reducing *Lactobacilli* and *Lactococci* [91]. In consistent with these findings, IBD and IBS patients with many lung disorders, including asthma, chronic obstructive pulmonary disease

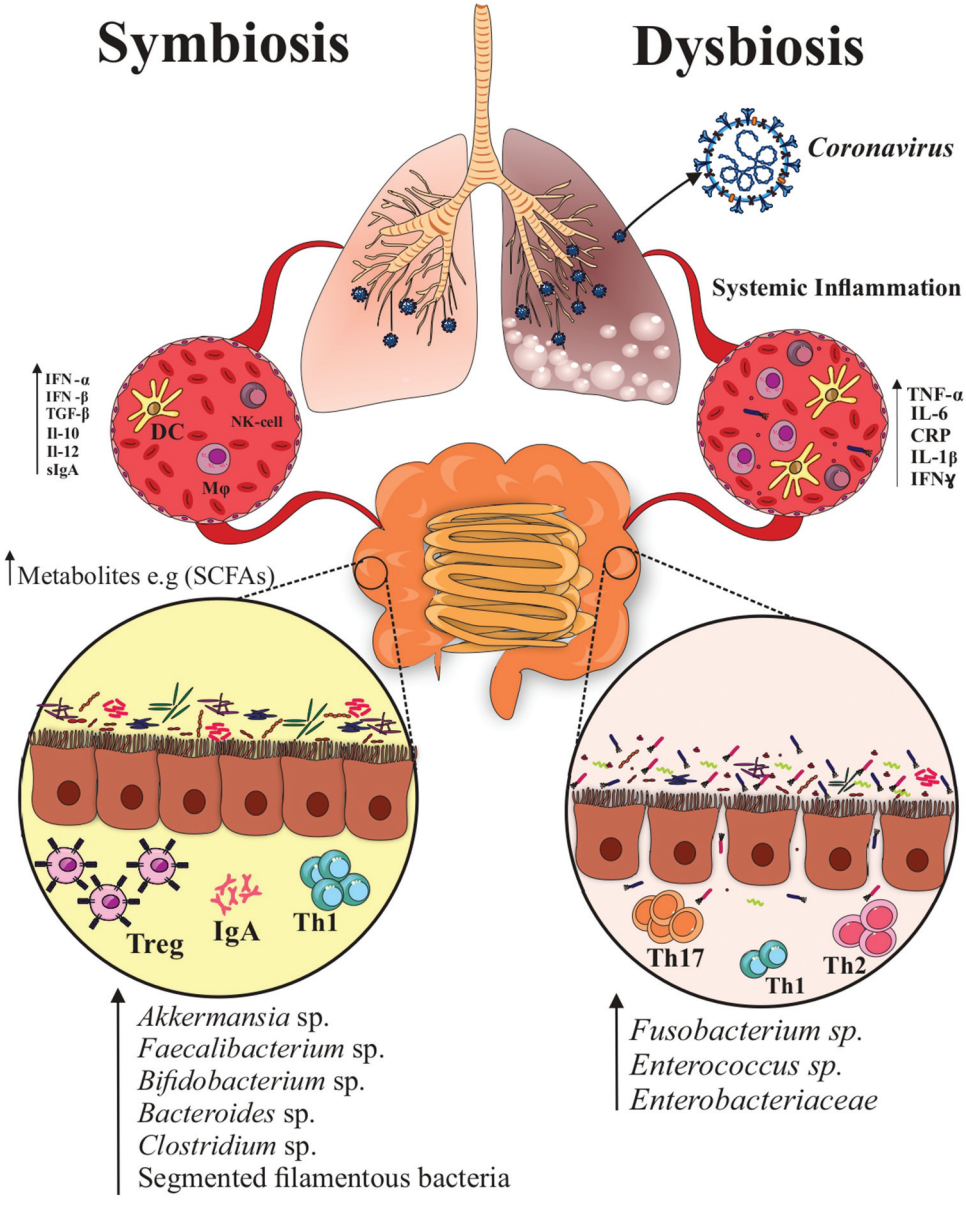

Figure 1. The gut-lung axis plays a critical role in the control of SARS-CoV-2 virulence. The gut microbiota regulates the innate and adaptive immunity by producing bacterial metabolites (SCFAs) and antimicrobial peptides against different pathogens. In addition, they regulate the integrity of the mucosal barrier and immune homeostasis. Dysbiosis can make negative impact on the balance and recruitment of immune cells in the lungs and increase inflammatory cytokines such as IL-6, TNF-α, and IL-1β, which could be the most important predisposing factor for sever COVID-19 infection.

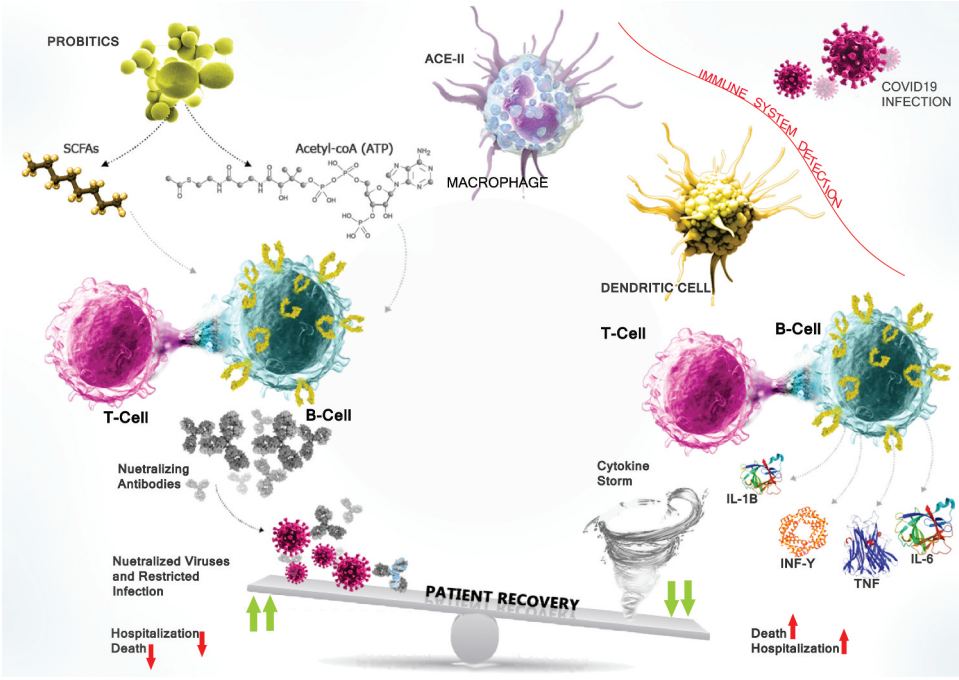

Figure 2. The interaction between the SARS-CoV-2 spike protein and ACE2 on the DCs and MQs contributes to the pathogenicity of COVID-19. Most critically ill patients in ICU, who are suffering from ARDS, have high levels of inflammatory cytokines owing to the complex immune dysregulation. Thus, the NAbs can potentially block the interaction between the SARS-CoV-2 spike protein and ACE2 on the cell membrane and thus prevent the entry of the virus and can control viral load. There are supporting evidence suggesting that probiotics affect pulmonary health through gut-lung cross-talk. MAMPs are the microbiota-derived products/metabolites, such as SCFAs that have increased cellular levels of acetyl-CoA, ATP, and lipid biogenesis to drive plasma B cell's differentiation and induce IgAs and NAbs secration against viral respiratory infections particularly SARS-CoV-2 and modulate immune reactions.

(COPD), influenza virus, and coronavirus, exhibited dysbiosis in their airway microbiota [92–94]. As illustrated in Figure 1, Figure 2 the commensal intestinal microbiota plays an essential role in regulating the immune response against respiratory virus infections such as influenza and coronavirus [8,95].

Moreover, alterations of the lung microbiota following infection can cause intestinal complications. Accordingly, *P. aeruginosa* pneumonia can reduce IECs proliferation and improve mucosal repair [96,97]. According to a meta-analysis, GI symptoms such as nausea, vomiting, diarrhea, and abdominal pain were seen in 17.6% of SARS-CoV-2 infected patients, and they were more common in severe cases [5]. These GI signs could be caused by SARS-CoV-2 directly infecting enterocytes through the GLA, or by immunoregulatory mechanisms [98]. On the other hand, dysbiosis in the gut microbiota negatively impacts on the balance and recruitment of immune cells in the lungs, which could be the most important predisposing factor in the development of respiratory tract infections [99]. In addition, this immune cell imbalance in the lungs reduces a load of certain beneficial bacteria (*Bifidobacteria, Akkermansia, Faecalibacterium, Lachnospira*, and *Veillonella*), which has been linked to an increased risk of asthma in neonates [100,101]. Table 1 summarizes the association between chronic respiratory diseases and changes in the microbial composition of the gut or respiratory tract.

Metabolites of gut bacteria can reach other organs *via* the bloodstream and regulate immune responses at distal mucosal sites such as the lungs. This control can be seen in the induction of antibody synthesis and anti-inflammatory responses [99,124]. Microbiota and viruses interact in both direct and indirect ways [125]. Microbiota-produced lipopolysaccharides (LPS) and peptidoglycans compete with viruses to bind to cell surface receptors, such as TLRs.COVID-19 infection symptoms are found to be more severe in the absence of LPS. TLR4 is one of the leading players of the immune system against COVID-19 infection. Indirectly, microbiota can regulate the secretion of IFN-α and antimicrobial peptides, which are essential in preventing virus-host cell fusion. Therefore, they can prevent viral colonization using the S protein [126–128]. According to the experimental studies in a mouse model, dysbiosis in the lung impacts the immune system, reducing the recruitment of APCs to the lungs and phagocytic activity. In addition, less intensive recruitment of immune cells results in an increase in viral load in the lungs [129,130] and a decrease in IFN-α and -β production which can negatively impact T cell priming [130]. It was shown that active resident memory B cells in the lungs also required encountering lung microbiota [131]. This interaction is reciprocal, and any changes in the gut microbiota directly affect the host's defense against acute respiratory pathogens as well as the risk of death [87].

4. Gut microbiota and immune system in COVID-19

Changes in the gut microbiota increase the risk of infectious, inflammatory, and endocrine diseases. Since there is no approved treatment or vaccine for many respiratory viral infections [132], a healthy immune system can play a key role in

Table 1. The association between respiratory chronic diseases and alterations of the intestinal and respiratory tract microbial composition.

	Alteration of gut bacteria			
Type of Disease/Infection	Decreased	Increased	Subject	Reference
Asthma (in children)	*Akkermansia muciniphila*, *Faecalibacterium prausnitzii Bifidobacteria*	*Clostridia*	Human	[102] [103]
Asthma (in adults)	*Bacteroidetes (specifically)*, *Prevotella spp.*	*Proteobacteria (Haemophilus, Moraxella, Neisseria spp.) Firmicutes (Lactobacillus spp.)*	Human	[85,104]
Chronic Obstructive Pulmonary Disease (COPD)		*Enterobacter cloacae, Citrobacter, Eggerthella, Pseudomonas, Anaerococcus, Proteus, Clostridium difficile, Salmonella*	Human	[105]
Cystic fibrosis (in children)	*Bacteroides vulgatus Bacteroides uniformis Firmicutes Faecalibacterium prausnitzii, Bifidobacterium adolescentis Bifidobacterium catenulatum, Eubacterium rectale*	*Streptococcus, Staphylococcus, Veillonella dispar, Clostridium difficile, Pseudomonas aeruginosa, Escherichia coli*	Human	[106]
Cystic fibrosis (in adults)	*Bacteroidetes, Faecalibacterium Prausnitzii*	*Firmicutes, Ruminococcus gnavus, Enterobacteriaceae, Clostridia species Proteobacteria phylum (Pseudomonas, Haemophilus, Burkholderia), Actinobacteria phylum*	Human	[107–111]
Lung cancer	*Bifidobacterium sp., Actinobacteria sp. Dialister, Enterobacter, Escherichia–Shigella, Fecalibacterium, and Kluyvera*	*Enterococcus sp. Veillonella, Bacteroides, Fusobacterium*	Human	[112,124]
Type of Disease/Infection	**Alteration of respiratory tract bacteria Decreased**	**Increased**	**Subject**	**Reference**
Coronaviruses and Adenoviruses infection		*M. catarrhalis*	Human	[113]
COPD and Rhinovirus infection		*Proteobacteria phylum*	Human	[130]
Rhinovirus infection		*H.parainfluenzae, Neisseria subflava, S. aureus*	Human	[114]
Rhinovirus infection (in children)		*S. pneumoniae*	Human	[115]
COPD and hRV infection		*H. influenza*	Human	[116]
hRV infection	*Haemophilus and Neisseria spp.*	*Propionibacterium S. pneumonia H. influenza*	Human	[113,117]
Enteroviruses		*S. pneumoniae*	Human	[113]
Influenza (in children)	*S. aureus*	*Prevotella, Streptobacillus, Porphyromonas, Granulicatella, Veillonella, Fusobacterium, Haemophilus.*	Human	[118]
Influenza A H1N1 infection		*Firmicutes (Staphylococcus and Streptococcus spp.), Proteobacteria (Pseudomonas amygdali, P. fluorescens, Pseudomonas sp. UK4, Acinetobacter baumanii and A. junii) Moraxella and Enterobacter spp.*	Human	[119]
Haemophilus influenza infection		*Neisseria*	Human	[120]
Influenza, Parainfluenza, Rhinovirus, Respiratory Syncytial Virus (RSV), Coronavirus, Adenovirus, Metapneumovirus		*Haemophilus and Moraxella*	Human	[120]
Pseudomonas aeruginosa infection		*Prevotella and Flavobacterium*	Human	[120]
H7N9 virus infection	*Faecalibacterium*		Human	[121]
Respiratory Syncytial Virus (RSV)		*H.influenzae*	Human	[113]
Tuberculosis infection		*Roseburia, Faecalibacterium, Phascolarctobacterium, Eubacterium*	Human	[122]
Recurrent tuberculosis	*Bacteroidetes, Prevotella and Lachnospira*	*Proteobacteria, Actinobacteria*	Human	[123]

reducing the severity of symptoms and mortality. SARS-CoV belongs to the subfamily of Orthocoronavirinae in the family of Coronaviridae. The enveloped and crown-like SARS-CoV virus is the second-largest genome size (27–32 kb) and single-strand positive-sense RNA (+ssRNA) of all RNA viruses (27–32 kb). Lv *et al*. reported an imbalance of fungal and bacterial flora in COVID-19 patients [133]. A study of the diverse array of fungal species, which refers to the diverse array of fungal species the gut mycobiota [134] showed that the most common symptom of fungal mycobiota dysbiosis in COVID-19-infected patients was the depletion of *Aspergillus* and *Penicillium*. Interestingly, the gut mycobiota profiles of COVID-19 patients with mild and severe symptoms were similar. In COVID-19 patients, the gut virome, especially in those with GI infections, can be very significant [135]. COVID-19 patients had significant differences in their fecal mycobiome at the time of hospitalization compared to controls, including *Candida albicans* enrichment and a highly heterogeneous mycobiome composition that lasted up to 12 days after nasopharyngeal clearance of SARS-CoV-2, according to a recent report [136]. Fecal metabolomic analysis in COVID-19 patients has revealed possible amino acid-related pathways that relate gut microbiota to inflammation [137]. In patients with COVID-19, Zuo *et al*. studied the temporal transcriptional activity of SARS-CoV-2 and its relationship with longitudinal fecal microbiota modifications. They showed that SARS-CoV-2 RNA was found in 46.7% of stool samples of patients without GI symptoms. In fecal samples with high SARS-CoV-2 active viral transcription and replication *in vitro* (infectivity), the numbers of particular opportunistic pathogens, such as *Collinsella*

aerofaciens and *Morganella morganii spp*. were higher than in fecal samples with low or no SARS-CoV-2 infectivity [138]. In a previous investigation, qRT-PCR revealed that 14 of the 15 patients with COVID-19 (93%) tested positive for SARS-CoV-2 in fecal samples. By contrast, stool viral RNA metagenomics revealed that seven (47%) of them were positive for SARS-CoV-2 [136]. Fecal viral RNA metagenomics only detected positive samples with an abundance of $>3.2 \times 10^4$ copies per mL inoculum, as determined by qRT-PCR [138]. In COVID-19 patients with moderate fever, Zhou *et al*. evaluated the correlation between gut microbiota dysbiosis and abnormal immunological responses. Patients with fever had a significant different gut microbiota composition than those who did not have a fever. Patients with fever had higher opportunistic infections, including *Enterococcus faecalis* and *Saccharomyces cerevisiae* [139]. In the cross-sectional study conducted by Gu *et al*., it was discovered that the microbiological profile of COVID-19 patients differed from that of patients with influenza A and healthy controls. They reported that COVID-19 patients had a lower microbial diversity, a higher concentration of opportunistic bacteria (Rothia, Streptococcus, Actinomyces, and Veillonella), and a lower proportion of beneficial microbes [140].COVID-19 severity is thought to be caused by a cytokine storm [36], which is linked to the gut bacterial population. Several immunomodulatory gut commensals, including *Faecalibacterium prausnitzii, Eubacterium rectale*, and *bifidobacteria* were reduced in COVID-19 patients [141]. Moreover, butyrate-producing bacteria including *Faecalibacterium prausnitzii*, *Clostridium butyricum, Clostridium leptum*, and *Eubacterium* were found to be in lower abundance [142]. Beneficial commensals including *Eubacterium ventriosum, Faecalibacterium prausnitzii, Lachnospiraceae taxa, Roseburia*, and *Bacteriodes spp. like B. dorei, B. massiliensis, B. ovatus*, and *B. thetaiotaomicron*, as well as *Bacteriodes spp. like B. dorei, B. massiliensis, B. ovatus* were diminished in COVID-19 cases, which correlated with the severity of the disease [143]. The previous studies have indicated that microbiota-derived SCFAs play an important role in promoting beneficial IL-18 and IL-22 secretion [144]. Moreover, Proteobacteria regulate the strong natural antiviral activity of IFN-α secretion [145]. The major phyla in the healthy gut and lungs are *Bacteroidetes* and *Firmicutes*. According to Yasui *et al*. feeding Lactobacillus casei to BALB/c mouse pups before inoculation with influenza virus decreases viral titers in the nasal lavage fluid and increases the activity of pulmonary natural killer (NK) cells. They demonstrated that the survival rate was nearly tripled under this type of regime [146]. Nasal administration of *Lactobacillus rhamnosus* also induced protection against respiratory syncytial virus infection in mice [147]. The SARS-CoV entry by TLRs (TLR3 or TLR7) results in airway inflammation [76]. Similarly, oral administration of immunobiotic *L. rhamnosus* in BALB/c mice was found to modulate antiviral immunity in the respiratory system. Activation of TLR3 and NK cells stimulate DCs to produce IL-12 as a critical factor in the development of effector CD4 Th1 and cytotoxic TCD8 lymphocyte responses [148,149].

Through the immediate response of the innate immune system to the coronavirus infection, macrophages and DCs regulate the virulence and disease outcomes. Furthermore, macrophages and DCs upregulate IFN-α production [76,150]. Some studies have shown that SARS-CoV inhibits the production of IFN-α and IFN-β [76]. Cinatl *et al*. showed that SARS-CoV could suppress the secretion of IFN-α, IFN-β, IL-18, and macrophage inhibitory factor (MIF), and downregulate the expression of antiviral genes (MIF). In addition, SARS-CoV could upregulate chemoattractant cytokines (CXC chemokines), IL-8, and oligoadenylate synthetase 2 (OAS2) in two intestinal cell lines, Caco2 and CL-14 [151]. In another study, it has been demonstrated that SARS-CoV infection downregulates the expression of IFN-α, IFN-β, as well as NFkβ, and also reduces the p56 level in Caco2 and 293 cell lines [152]. If the first line of immune response fails in eliminating the viral pathogens, the adaptive immune response is activated seven days following the SARS-CoV infection and this gap is a golden time for virus replication. The Angiotensin II converting enzyme (ACE2) is an essential receptor for infecting human cells by coronaviruses [153]. Fischer and colleagues have shown that gut microbiota and a healthy diet directly regulate the expression of ACE2 and the activation of the adaptive immune response following viral infection [154]. In this regard, the gut microbiota via its metabolite signals can regulate the immune response, reduce viral replication, and increase the survival rate during an epidemic and pandemic of viral infection [124].

5. Probiotics and a diet, modulation of severe complications in COVID-19

Although the evidence suggests that the gut contains a remarkable number of immune cells [155], the gut microbiome plays a crucial role in protecting the host against pathogens. Dysbiosis leads to break tolerance to harmless bacteria, inefficient immune response, and susceptibility to viral infections. Probiotics, known as beneficial live microorganisms, regulate dysbiosis and restore eubiosis [156]. Lactic acid bacteria (LAB) (*Lactobacillus* and *Bifidobacterium spp*) are the main probiotics species [157] that are well-known to the immune system and can regulate immune responses [158]. *Lactobacillus spp* acting *via* different pathways has antiviral features and could be considered a potent inducer of IFN-α and IFN-β production. Mullish *et al*. showed evidence for probiotics' possible effect in reducing viral upper respiratory tract infections (URTI) and maybe COVID-19, especially in overweight/obese adults. They discovered that probiotic supplementation could reduce URTI symptoms by 27%, with adults ≥ 45 years old and/or with a BMI ≥ 30 kg/m^2, obtaining the significant benefit of risk reduction [159]. In one early trial, probiotic supplementation to 28 hospitalized COVID-19 patients resulted in an eightfold decreased rate of respiratory failure compared to 42 patients receiving only medical treatment [160]. Probiotics treatment (*Bacillus subtilis, Enterococcus faecalis*, and *Lactobacillus rhamnosus GG*) was also found to lower ventilator dependency in COVID-19 patients who were severely ill compared to placebo. The mechanisms of probiotics' antiviral effects are still unclear [98]. Prebiotics are substrates that host certain microorganisms and are used to provide a health benefit such as fructans, galactomannan, oligosaccharides, arabinooligosaccharides, lactosucrose, acid

lactobionic, and polyunsaturated fatty acids [161]. Prebiotics can modulate the composition and function of the human microbiota, inducing immune system activation and pathogen inhibition in the GIT. To date, however, there is no evidence that prebiotics are associated with COVID-19 infections in any way [162].

Fecal microbiota *L. gasseri SBT2055* (LG2055) is resistant to bile acid and can be colonized in the human gut [163]. The most current data support the regulatory role of LG2055 in the IgA secretion, which inhibits the influenza A virus infection in mice [164–166]. Eguchi and colleagues showed the antiviral activity of L. *gasseri* SBT2055 in both *in vivo* and *in vitro* models. These bacteria reduced viral load in the lungs and suppressed pro-inflammatory cytokine production [167]. Recently, it has been demonstrated that the cell walls of *L. acidophilus* NCFM and live *Lactobacillus spp* enhanced the immune system's response to viral respiratory infection. Heat-killed *L. casei* [168], *L. pentosus* [169], *L. plantarum* [170], *L. reuteri* [170], and *L. rhamnosus* CRL1505 [171] participated in the regulation of the immune response in the respiratory tract and reduced lung damage after influenza and respiratory syncytial virus infections (RSV). The direct competition in binding to TLR3 between viral particles and local bacteria present in the lung resulted in decreased virus colonization in mice [172]. *Bifidobacterium*, the other group of LAB, regulates lung inflammation and infection. Supplementation with *B. breve* and *B. longum* (BL) improved the survival rate, restored lung injury, and eventually restored intestinal homeostasis [173–175]. Treatment with a *Bifidobacterium* probiotic can modulate pro-inflammatory cytokine levels and increase IL-10 and Foxp3$^+$ Treg expression in the lungs. Animal studies have demonstrated that oral administration of *B. longum* BB536 reduces the incidence of influenza and fever, and can also regulate proliferation of the influenza virus in the lungs [176].

In comparison with oral treatment, nasal administration of *L. rhamnosus* CRL1505 tends to be a more effective way to significantly activate the Th1 response and CD103$^+$c DCs [177]. Likewise, the nasal administration of *Lactobacillus* leads to faster colonization on the respiratory epithelium than oral way. The nasal administration is highly effective in suppressing the virus-induced inflammation and also diminishes the expression of inflammatory cytokines and chemokines (CXCL10, CXCL1, CCL2, TNF, IL-6) that damage lung tissue [170]. The effects of probiotics on the regulation of the immune system in infectious respiratory diseases have been summarized in Table 2.

Absorptive trapping and the development of lipopolysaccharides, which binds to and destabilizes the viral structure, are two mechanisms by which gut commensal bacteria (including those often found in probiotics) suppress viruses that enter the host *via* the upper respiratory tract [186]. The gut-lymph hypothesis, which describes gut bacteria within the draining chyle from the lower GIT entering the lymphatic system, is also one possible route by which probiotic bacteria may translocate from the gut to the lung [187]. Additional indirect pathways include modulating interferon responses in the lung stromal cells [188], promotion of APCs migration, and T cell antiviral responses mediated by TLRs [129].

Modifying nutrient availability *via* diet may be another effective microbiome-modulating strategy. A healthy diet is even more critical due to its effect on the microbial metabolome and richness of the microbiota diversity [189]. Therefore, alteration of the gut microbiota can increase the production of SCFAs *via* diet modification. Interestingly, adding indigestible carbohydrates increased butyrate production, which is linked to improved lung function. Also, fiber-rich diets can modulate innate immunity and reduce the GI signs and mortality rate from respiratory diseases [190,191]. Collectively, probiotics and

Table 2. The effects of probiotics on the immune system regulation in infectious respiratory diseases.

Probiotic	Efficacy	Subjects	Administration Rout	Reference
L. acidophilus	Induced secretion of IFN-α, IFN-β, and IL-12 from DCs via TLR2 and TLR-3	Mice	Oral	[146]
L. rhamnosus CRL1506	Production of IFN-α and IL-6	Mice	Oral	[51]
L. casei Shirota (*LcS*)	Activated Th1 immunity, phagocytic activity, NK cells activity, and production of mucosal IgA	Mice/Elderly people	Oral/ Intranasal	[178,179] [168]
L.delbrueckii ssp. bulgaricus OLL1073R-1	Increased NK cells activity	Elderly people	Oral	[180]
L. gasseri SBT2055 (LG2055)	Induced IFN-α & IFN-β production	Mice	Oral	[150]
Heat-killed *Lactobacillus plantarum* L-137	Increased phagocytic activity and NK cells activity, acquired immunity, proliferative response of T cells, and increased number of T cells	mice/ Healthy adults	Oral	[181,182]
Heat-killed *L. pentosus*	Modulation of Th1/Th2, enhanced NK cells activity, induced production of both IL-12 and IL-10	Mice	Oral	[169]
Heat-killed *L. plantarum*	Stimulation of IFN-β and IL-10 production	Mice	Intranasal	[170]
L. reuteri	Stimulation of IFN-α production	Mice	Nasal	[171]
L. rhamnosus CRL1505	Th1 response significantly activated CD103$^+$c DCs	Mice	Oral	[154]
L. Casei Shirota (LcS)	Activation of Th1 immunity	Mice	Intranasal	[168]
L. fermentum	Activation of macrophages	Mice	Intranasal	[113]
L. pentosus S-PT84	Enhanced splenic NK cells, modulating the Th1/Th2 balance	Mice	Intranasal	[183]
L. johnsonii	Reduction in the total number and proportion of activated CD11c+/CD11b+ CD11c+/CD8+ cells, reduced expression of airway Th2 cytokine	Mice	Intranasal	[184]
B. breve YIT4064	Enhanced IgG against IFV	Mice	Oral	[185]
B. longum BB536	Reduced the incidence of IFV and fever effect on host cellular immunity, enhanced production of Th1 cytokines, declined plasma IFN-Ɣ levels, enhanced NK cell activity and neutrophil bactericidal activity.	Mice	Oral	[171]
B. longum MM-2	Anti-viral effect, enhanced activity of NK cells in the lungs and spleen, Increased expression of IFN-α and Th1-related cytokines,	Mice/healthy adults	Oral	[171]

Mediterranean lifestyle are protective, increase survival rate, and protect lung tissue against the destructive effects of respiratory viruses (SARS-COV2, IFV, RSV, etc.) and could be considered an alternative therapy for improving immune response.

6. Fecal microbiota transplantation in COVID-19 patients

Fecal microbiota transplantation (FMT) is a novel treatment that has shown to be helpful in the treatment of recurrent Clostridioides difficile infections (rCDI). FMT has the potential to help with a variety of dysbiosis-related disorders. It refers to transferring a healthy person's distal gut microbia communities to another patient's intestinal tract. This treatment has been proven to restore a disrupted microbial diversity and related microbial functional networks, with a success rate of 90% for rCDI patients [192]. According to Bradley *et al*., decreased intestinal microbiota following antibiotic administration could cause a shift in the interferon signature triggered by commensals in the lung epithelium, promoting early influenza virus proliferation in the respiratory tract [188]. By monitoring COVID-19 patients, Liu *et al*. revealed persistent alteration in the fecal microbiome composition after recovery and discharge from hospital [193]. They reported that *Firmicutes, Bacteroidetes, Actinobacteria*, and *Proteobacteria* had relative abundances of 41.0%, 42.9%, 9.2%, and 4.0%, respectively, which differed from the general population. In healthy people, the dominant phyla are *Firmicutes* (60%) and *Bacteroidetes* (20%) [194]. Multiple research has shown that the FMT can promote immune function and consequently have an indirect protective effect against influenza virus infection [188]. Tiffany *et al*., used FMT on rhesus monkeys infected with chronic SIV who were receiving antiretroviral medication. After antibiotic therapy, microbiota shift was observed, whereas Th17 and Th22 frequencies in peripheral blood increased and CD4 T cell activation in the intestinal tract reduced following FMT [195]. Liu *et al*. investigated the effects of FMT on GI symptoms, gut dysbiosis, and immune status in 11 discharged COVID-19 patients. After FMT, the COVID-19's peripheral lymphocyte subset was altered. The gut microbiota was restored, and GI disorders were relieved, suggesting that FMT could be used as a therapeutic and rehabilitative intervention [193]. Further research is needed to understand whether FMT could be a viable technique for altering the gut microbiome to improve COVID-19's residual effect.

7. Conclusion

The link between human microbiota and COVID-19 is still unknown. This narrative review aimed to assess and summarize available evidence on the relationship between the microbiome and COVID-19 in patients in the pandemic era. The current study uncovered several major issues that call for more investigation on microbiota in COVID-19 patients. There is a crucial cross-talk between the gut microbiota and the lungs through the GLA. The protection of the gut microbiota hemostasis, especially in the absence of treatment for a viral respiratory infection, could be more practicable to regulate the immune system response and reduce the GI disorder after COVID-19 infection. Healthy gut microbiota might lead to asymptomatic or mild COVID-19 infection without any severe clinical complications. Probiotics have been shown to modulate the occurrence and severity of diseases, implying that they may be used to treat or prevent COVID-19. By preserving the human GI or lung, probiotics could help prevent COVID-19. More than ever, this pandemic has highlighted the importance of the gut microbial–host-immune axis and the impact of the fecal metabolome on inflammation control and regulation of the immune system. To investigate the possible preventive and therapeutic effects of probiotics against SARS-CoV-2 infection, *in vitro* and clinical studies are necessary.

8. Expert opinion

During hospitalization, gut microbiota composition may influence the immune response and change the severity and prognosis of COVID-19 [196]. Thus, a microbiome-oriented risk-assessment profile could be used to identify those at risk [197]. Additionally, since the human microbiome is adaptive and may be changed through dietary modifications [198], we believe that further research is urgently needed to assess the impact of microbiota and diet on COVID-19 [198]. However, the detection of enriched inflammatory-associated gut microorganisms in COVID-19 is controversial. The question is if they enriched or this was happened due to the reduction of the other microorganisms. It seems that longer follow-up is needed for COVID-19 patients, such as three months to 1 year after virus clearance. This will enable us to find a correlation of gut microbiota composition to long-term persisting symptoms. In addition, this can assess the possible alteration of the gut microbiota dysbiosis post-recovery. Also, it can help to determine whether enrichment or depletion of specific gut microorganisms can contribute to future health problems [141].

On the other hand, the described gut dysbiosis may just be a response to patients' health and defensive statuses rather than playing a central role in disease severity. Accordingly, it is not clear how much clinical practice during hospitalization can affect the gut microbiota composition in COVID-19 patients. Of note, it is anticipated that 50% to 75% of COVID-19 patients received antibiotics, while just about 7% of them displayed bacterial infections [199]. Moreover, according to Chinese studies, antibiotics were given to 58.71% of COVID-19 patients, while 2–36% suffering from diarrhea. Even though probiotics have only a little efficacy in treating antibiotic-induced diarrhea, the use of probiotics has been indicated to reduce susceptibility to recurrent infection [98]. Previously, it has been found that polypharmacy significantly impacts microbiota composition and that more alterations could be observed if the number of co-administered drugs increases [200].

In conclusion, the implication of sufficient, safe, and cost-benefit pre- and probiotics can support the microbiota. Their prescription can be used as an adjuvant therapy to modulate COVID-19 progression or as a preventive strategy for non-

infected individuals who are at risk during the COVID-19 pandemic.

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