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*Review*

# The Role of the Gut-Lung Axis in COVID-19 Infections and Its Modulation to Improve Clinical Outcomes

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**Abstract**

The main entry point of SARS-CoV-2 is the respiratory tract and as such immune defence in this site determines if the virus will spill-over to the systemic circulation and circulate and infect other major organs. The first line of mucosal immune defence is composed of mucins, an epithelial barrier, and immune cells in the nasal cavity. The lung immune defence is carried out by numerous alveoli. The lung microbiota is a key factor in determining the efficacy of lung mucosal immunity protection. The intestinal microbiota has been demonstrated to affect the severity of COVID-19. Gut dysbiosis is involved in hyperinflammation and multiple organ failure through communications with multiple organs. The gut lung axis could be the earliest axis affected in COVID-19. Through the gut-lung axis, gut dysbiosis can affect the pathogenesis of the lung in COVID-19. In this review, we summarise the effects that gut dysbiosis can progress on the lung, and the lung microbiota. The possible mechanisms and approaches for modulation are discussed.

**Keywords:** gut-lung axis; microbiota; dysbiosis; COVID-19; mucosal immunity

## 1. Introduction

The main entry site for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the respiratory tract [1]. The inhaled virus binds to ACE2-expressing cells in the nasal cavity and enter the cells [2]. The virus replicates in these cells, which causes cell damage and death. The shedding of virus particles in the cell debris are then inhaled into the lung. In the lung, the virus can enter the systemic circulation with ease due to high mucosal permeability [3,4]. It has also been demonstrated that the oral cavity is also an important site for the replication of the SARS-CoV-2 virus [5]. In additional animal experiments the SARS-CoV-2 virus has been demonstrated to also be transmittable through ocular conjunctival inoculation [6].

The outcomes of SARS-CoV-2 infections depend on the interactions between the virus and host immunity. High titre concentrations of the virus can increase the proficiency of the virus to break through the defensive mechanisms. It has been reported that plasma that coronavirus disease 2019 (COVID-19) viral load in hospitalized patients, correlated with the severity of the disease, mortality rate, decreased number of lymphocytes and increased inflammatory markers CRP and IL-6 [7]. SARS-CoV-2 infections can dedifferentiate multiciliate cells and damage mucociliary clearance of the virus [8]. In severe COVID-19, the lung becomes highly inflammatory, which can progress morbidity and mortality via acute respiratory distress syndrome, respiratory failure and multiple organ failure [1,9]. Therefore, improving the first line defence in the lung can block the SARS-CoV-2 infections and decrease the entry of the virus into the system circulation, reducing the severity of COVID-19.

Clinical evidence supports the posit that COVID-19 viral entry can also occur in the gastrointestinal tract, as noted recently with a report that showed that SARS-CoV-2 can cause COVID-19 via gut infection [10], this representing the gut as a viral target organ. Moreover, it has been reported that SARS-CoV-2 receptor, ACE2 occurs in intestinal enterocytes [11]. Recently the intestinal microbiota composition was reflective of disease severity and dysfunctional immune responses in patients infected with COVID-19 [12]. This study suggested the presence of a dysbiotic intestinal microbiome that persists following viral peak resolution, and depletion of immunomodulatory intestinal microbiota with adverse levels in microbiota abundance and diversity [12]. The study also suggested strengthening the intestinal microbiome with beneficial microbes (e.g., probiotics) as a therapeutic solution to mitigate the severity of the infectious disease.

In this narrative review we summarise how the gut-lung axis affects the lung defence to COVID-19 virus infections through immune modulation, particularly the interactions of the gut and lung microbiota (Fig. 1). We further posit that the gut-lung axis is of critical importance in immune defence of the lungs.

## 2. The Lung Microbiota in Health and Disease and Lung Mucosal Immunity

The healthy lung was long thought to be a sterile organ, however advances in molecular sequencing technolo-

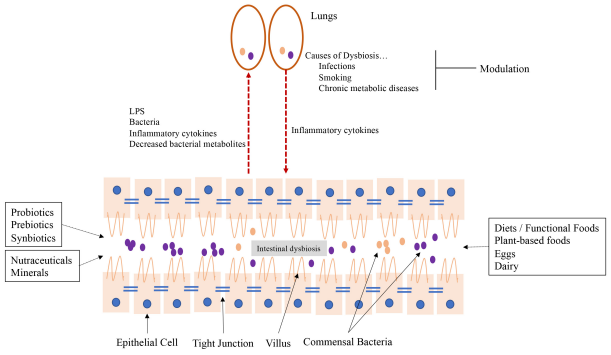


**Fig. 1. Interactions between the gut microbiota and the lung microbiota.** Intestinal dysbiosis can lead to gut inflammation and increased gut permeability, allowing translocations of LPS, bacteria, inflammatory cytokines into the circulation and the lung. Meanwhile, the production of anti-inflammatory gut commensal bacterial metabolites is decreased. Lung microbiota dysbiosis that could be caused by infections, smoking and chronic diseases can affect gut microbiota through inflammatory cytokines. Gut dysbiosis can be improved by probiotics, prebiotics, nutraceuticals, minerals, and diets directed at high plant-based food consumption, eggs and dairy.

gies have detected bacteria at low levels [13,14]. The lung microbiota is a dynamic system that is now well recognised, i.e., the lung is not sterile but colonized with commensal microbes [15]. The role of the lung microbiota could be compared to that of the gut microbiota, although the numbers of microbes are less than that demonstrated and profiled in the intestines. The lung microbiota presents with a biomass that is considerably less when compared to that of the ascending colon displaying considerable diversity [16,17]. The origin of the microbiota of the lung is from the oral cavity, inhalation from air and, also the digestive tract. Furthermore, the composition of the lung microbiome is primarily dependent on the microbial colonization that originates from the oropharynx and upper respiratory tract sites through (i) salivary micro-inhalations; (ii) on host elimination abilities especially through coughing and mucociliary clearance; (iii) on the interactions with the host's immune system; (iv) and on the local conditions that allow for microbial proliferation, such as so happens with pH and or the concentration of oxygen [18].

At the phylum level, the bacteria in the lungs show similarity in composition to that of in the intestines [13,16]. The predominant bacterial phyla belong to the *Firmicutes* and *Bacteroides* phyla and to lesser extent to the *Proteobacteria,* and *Actinobacteria* phyla [13]. Whereas at the genus level, the most abundant bacteria are from the *Pseudomonas*, *Streptococcus*, *Prevotella*, *Fusobacteria*, *Porphyromonas* and *Veillonella* genera [19]. A study reported that *Streptococcus* accounted for 27.1% of the total bacterial reads, with *Prevotella* accounting for 11.6% and *Veillonella* with 7.1% [20].

Moreover, in healthy individuals clinical research report the presence of fungi that may have been environmentally acquired, such as those from the Ascomycota (*Aspergillus, Cladosporium, Eremothecium*, and *Vanderwaltozyma*) and Microsporidia (*Systenostrema*) phyla [21]. In those patients that present with increasingly severe pulmonary and immunologic deficits, reports show that these patients have increased representation of medically relevant fungal organisms that include *Candida*, *Cryptococcus*, and *Aspergillus* [22]. Furthermore, this study also showed that when analysing covariation of fungal and bacterial taxa, oropharyngeal communities abundance in *Candida* were reported also abundant in *mitis* group *Streptococci*, a community pattern that was concluded to be associated with pathogenic polymicrobial biofilms [22].

Dysbiosis describes an aberrant altered deviation of a healthy microbiome network in an anatomical site. Numerous respiratory illnesses have been linked to altered microbial patterns that differ from those observed in healthy populations [23]. Moreover, in many respiratory diseases, the reports associate the lung disease with lung dysbiosis [24,25]. For example, infection with *rhinovirus* can lead to asthma [26,27]. In asthma, the diversity of the microbiota is decreased; the pathogenic bacterium *Staphylococcus* is increased while beneficial bacteria are decreased in abundance. The dysbiosis of the lung microbiota further weakens the immune system to provide appropriate responses, thereby accelerating lung infective diseases [26,27].

In chronic obstructive pulmonary disease (COPD) reports show a difference in those subject and specimen types that describe dysbiosis during both periods of stable COPD and the acute phase exacerbations of the respiratory disease [28]. For example, during the stable phase of the respiratory disease, the relative abundance of *Pseudomonas* was increased and that of *Prevotella* decreased in bronchial wash when comparing the lung microbiomes between healthy smokers and non-smokers [28]. Further, in a large-scale meta-analysis of sputum collected data sets, there was reported significant enrichment of *Haemophilus*, *Streptococcus*, *Moraxella*, and *Lactobacillus* bacterial genera. Concomitantly there was depletion of several genera, relative to the healthy controls [29]. A cross-sectional study of 72 COPD patients, with increased relative abundance in the sputum of those patients with *Pseudomonas* and decreased *Treponema* [30], the changes correlated with airflow limitation. In a prospective study of 101 patients with COPD greater disease severity was associated with increased *Haemophilus* and decreased *Prevotella* and *Veillonella* genera [31]. Additional studies of COPD that investigated microbial profiles have reported associations with bronchodilator responsiveness and peak expiratory flow rate were associated with disparate lung microbiota compositions [32]. What drove the dysbiosis of these adverse lung microbiome associations were increases in abundance

of the *Streptococcus*, *Prevotella*, *Veillonella*, *Staphylococcus*, and *Pseudomonas* genera [32]. Diversity was reported lower in stable COPD compared with healthy smokers and non-smokers [28,33] and is further decreased during acute exacerbations of the disease [34]. Moreover, a lower diversity of the lung microbiome from lower respiratory tract specimens also has been reported associated with decreased lung function and exacerbation frequency in those patients with stable COPD [35].

The mucosal surfaces of the lungs and the upper respiratory tract including the nasopharynx-associated lymphoid tissue (i.e., tonsils, adenoids, nasopharynx) serve as entry sites for infective agents and as such are inductive sites for the mucosal immune system [36,37]. Mucosal immunity comprises the largest component of the immune system that has evolved to protect the host from infectious threats at mucosal surfaces with the provision of immune cells and the production of immunoglobulins [38]. Secretory immunoglobulin A (SIgA) is elaborated in high quantities exceeding all other immunoglobulin subtypes combined (e.g., IgG) [38]. Epithelial cell monolayers form a barrier on mucosal surfaces and line different organs, separating the underlying organs from their surroundings, through the formation of tight junctions between the cells. The tight junctions give rise to an enclosure structure that provides a physical barrier to prevent cross-over of pathobionts/infective agents to the hosts. It also exerts anti-pathobiont activities through the secretion of AMPs and SIgA antibodies. Hence SIgA is the first line of defence resistance to infective agents, i.e., bacterial or viral, by inhibiting the adhesion of the infective insults to the epithelial cells. In addition, IgA can neutralize extra- and intracellular pathobiont toxins as it can bind a wide range of antigens due to their low affinity. IgA antibodies can bind to lipopolysaccharides (LPS), DNAs, flagellin, capsular polysaccharides and viral components [3,39]; and can eliminate pathogens or antigens via an IgA-mediated excretory pathway that binding to IgA progresses poly-immunoglobulin receptor mediated transport of immune complexes [40]. Epithelial cells infected viruses secrete a broad range of interferons and as such can have direct immune effects and confer resistance to uninfected cells [41]. Hence type I IFNs by activating innate immune responses contain viral infections. Impairment of type I IFN production has been associated with the severity of COVID-19 [42,43]. Type I interferons (IFN-alpha and IFN beta) bind to their receptors to induce anti-viral gene expression, which result in the impairment of viral entry, replication, transcription, and translation. It also increases the degradation of viral nucleic acids and proteins [44].

Mucosal immune responses play key roles in host defence from invasive insults by microbes and viruses, with structures that include mucus production, the epithelial barrier, and immune cell activation. Mucus is the first line of immune defence, representing a layer of dense, gel-like material containing mucins, AMPs to carry out the mucociliary clearance [45–47]. The major component is mucin (MUC), which is a glycoprotein. The out layer of the mucus is composed of MUC5AC and MUC5B, whereas the inner layer contains MUC1, MUC4 and MUC16 tethered to the cell membranes. The various anti-microbial peptides contained in the outer layer mucus can exert anti-pathogenic microbial effects such as defensins and lactoferrin. Defensins (alpha and beta) have both direct and indirect effects on viral infections [48,49]. Lactoferrin is a glycoprotein secreted by mucosal epithelial cells and neutrophils. It has a very strong immunomodulatory effect through binding to negatively charged molecules such as immune cell receptors toll-like receptors, cytokines, chemokines; DNA and RNA molecules and LPS [50–53]. Lactoferrin can also inhibit iron sensitive pathogens through the chelation of iron. Lactoferrin has been advanced to protect the eye from SARS-CoV-2 infections [54] and proposed for the treatments of COVID-19 and other eye diseases [55,56]. SIgA antibodies secreted by immune cells and transported to the mucus can exert anti-microbial effects through binding to various molecules.

Macrophages and dendritic cells comprise important participants in shaping mucosal immunity [57]. Alveolar macrophages, the main immune cells in the lung, play key roles in defending from pathobiont invasion. They are unique macrophages different from the macrophages in other sites [58]. Alveolar macrophages phagocytose inhaled pathogens and produce inflammatory cytokines to eliminate pathogens. They not only communicate with epithelial cells but also regulatory T cells to maintain effective and balanced immune responses. Over activation of lung residential macrophages is associated with acute respiratory distress syndrome (ARDS) [59]. Except secretion of AMPs, ECs also produce anti-inflammatory membrane proteins such as CD200 to regulate alveolar macrophages [60]. These cells secret IgA antibodies.

The lung microbiota has the capacity to promote defence from pathobiont invasion through the surrogate activity of the immune system and the mucosal epithelial barrier effects [19]. The lung microbiota can prime the development of the mucosal immune system and maintenance in the lungs. There are a range of immune cells in the fluid portion of the alveoli including macrophages, dendritic cells, lymphocytes, and neutrophils, where the lung resident macrophages are the predominant immune cell responders. These cells interact with the lung microbiota to maintain lung homeostasis. Dysbiosis of the lung microbiota can reduce the resistance of the lung to virulent factors, resulting in the progression of the disease status.

## 3. Gut-Lung Axis in COVID-19

As reported, diseases in the respiratory system can result in gut dysbiosis. SARS-CoV-2 infections could cause lung dysbiosis, leading to decreased defence mechanisms [61]. SARS-CoV-2 virus infections may be contained by

appropriate immune responses, resulting in mild or moderate symptoms. However, it could cause severe disease if the viral loads are high, and the immune system is unable to respond with an appropriate response. Hyperinflammation in the lung can cause ARDS, leading to decreased oxygen supply and lung failure. In addition, weaken defence in the lung, leading to increased susceptibility to secondary bacterial infections, which accelerate the hyperinflammation formation and increase mortality rate. A narrative review reported that approximately 16% of hospitalized COVID-19 patients have secondary bacterial infections and 6.3% have fungal infections [62]. Among secondary bacterial infections, approximately 50% are infected by Gram-negative bacteria. The most common bacteria were *Pseudomonas aeruginosa*, *Klebsiella species*, *Staphylococcus aureus*, *Escherichia coli.* and *Stenotrophomonas maltophilia* [63]. The most common fungal species is *Aspergillus fumigatus*. A study investigated 19 COVID-19 patients in ICU, all had secondary infections, 17 with *Acinetobacter baumannii*, resisting to all evaluated antibiotics and 2 with *staphylococcus aureus* with one resisting to methicillin [64]. All patients with antibiotic resistance died, only one discharged. This indicates that secondary infections with antibiotic resistance are fatal. LPS from Gram-negative bacteria can bind to TLR4 to activate NF-kB to promote inflammation. Gram-positive bacteria could produce exotoxins to accelerate the progression of the disease [63].

Gut dysbiosis can affect the lung physiology and diseases of the lung whilst lung disorders can also cause gut dysbiosis, forming a bidirectional gut-lung axis [17]. IBD that causes gut dysbiosis is associated with obstructive pulmonary diseases (COPD) [65,66]. Gut dysbiosis increased gut permeability could deliver toxic bacterial metabolites to the lung via the systemic circulation, participating in the pathogenesis of COPD. Use of antibiotics that promote and cause intestinal dysbiosis was associated with an increased incidence of asthma in children [67]. Decreased abundance of *Bifidobacteria*, *Akkermansia* and *Faecalibacterium* increases the risk of asthma in children. In a clinical trial with 20 asthma patients, it was demonstrated that treatment with a regimen including ciprofloxacin, 500 mg every 12 hrs; vancomycin 500 mg every 8 hrs and metronidazole 500 mg every 8 hrs for 7 days and challenge with a house dust mite and LPS led to gut dysbiosis and increased asthma responses [68].

A recent systemic review provided an overview of the effects of respiratory tract infections on the gut microbiota. The infections by SARS-CoV-2, influenza, tuberculosis, community-acquired pneumonia and recurrent RTI caused a decrease in gut microbiome diversity (Shannon index) of 1.45 and a lower abundance of taxa [69]. Overall, there was a depletion of *Lachnospiraceae*, *Ruminococcaceae* and *Ruminococcus*, and enrichment of *Enterococcus*. Wang *et al*. [70] reported that influenza infection caused gut dysbiosis with increased *Enterobacteriaceae* and decreased *Lactobacillus* and *Lactococcus*. The mechanism was identified not to be the due to direct viral infections but mediated by IFN-gamma produced by lung $CCR9^{+}CD4^{+}$ T cells that were recruited to the small intestine, stimulating IL-15 and IL-17A. Groves *et al*. [71] showed that infections of respiratory syncytial virus (RSV) and influenza in a mouse model resulted in gut dysbiosis with increased Bacteroidetes and decreased Firmicutes. Increased levels of fecal lipocalin-2 indicated there was low-grade gut inflammation.

The bi-directional interactions of gut-lung axis could be critical in COVID-19 severity. It has been well studied that gut dysbiosis plays critical roles in the severity of COVID-19 and the susceptibility [1,12,72,73]. Gut dysbiosis could mediate many risk factors that cause severe COVID-19 such as advanced age, underlying diseases, and use of antibiotics. All these risk factors progress gut dysbiosis, which can increase systemic inflammation to facilitate the formation of hyperinflammation. Yeoh reported that the gut microbiota compositions were associated with the severity of the disease [12]. In COVID-19 patients, reported *Faecalibacterium prausnitzii*, *Eubacterium rectale* and *Bifidobacteria* reductions and inversely correlated with blood levels of proinflammatory cytokines, CRP and liver function tests such as lactate dehydrogenase, aspartate aminotransferase and gamma-glutamyl transferase. Gu studied the alterations of the gut microbiota in COVID-19 patients, showing increased opportunistic bacteria such as *Streptococcus*, *Rothia*, *Veillonella*, and *Actinomyces* and low abundance of beneficial bacteria [74]. Gut dysbiosis increased the severity of COVID-19 was also indicated by increased hospitalization time [75]. Newsome showed that the gut microbiota in the recovered COVID-19 patients was different to those patients with active infections [76]. Hence what was reported was that patients with active infections were found to have a significantly different gut microbiota than recovered patients. The most enriched genus reported from infected patients was *Campylobacter*, with *Agathobacter* and *Faecalibacterium* being enriched in the recovered patients [76]. No difference in microbial community structure between recovered patients and uninfected controls was observed, nor a difference in alpha diversity between the three groups. Overall, the gut microbiota is skewed towards dysbiosis in COVID-19 patients and with adjunctive treatments becomes less so (i.e., eubiosis) as patients recover from the infection [77]. Dysbiosis of the gut microbiota is associated with infection severity with decreased abundance of beneficial bacteria including short-chain fatty acid (SCFA)-producing bacteria and increased pathogenic bacteria [78–80]. SCFA could be further studied to provide the mechanistic insight as to the role that gut dysbiosis has in the gut-lung axis in COVID-19.

Sencio *et al*. [72] reported that gut dysbiosis following SARS-CoV-2 infections correlated with disease severity in hamsters. In the hamster model, SARS-CoV-2 in-

fections caused lung pathogenesis similar to that observed in humans [72]. The results also demonstrated that mild intestinal inflammation could be associated with adverse gut barrier changes, liver inflammation and fat metabolism. The gut dysbiosis was characterised by increased deleterious bacteria like *Enterobacteriaceae* and *Desulfovibrionaceae* and decreased beneficial bacteria *Ruminococcaceae* and *Lachnospiraceae* families that include SCFA-producing bacteria. Blood levels of SCFAs were found reduced transiently but supplementation of SCFAs did not change the course of the disease. Sokol *et al*. [81], also characterised the dynamic changes of the microbiota in non-human primates. The peak of the changes were 10–13 days post infections and the gut dysbiosis remained unrecovered after 26 days. The main changes found, were increased pathogenic bacteria and decreased beneficial bacteria, leading to decreased SCFAs, bile acids and tryptophan metabolites. Results that are consistent with data reported from studies with humans.

The main infectious site for the SARS-CoV-2 virus is the respiratory system. SARS-CoV-2 virus infects ACE2 expressing cells and replicate in these cells in the nasal cavity. Replicated viruses then infect the lung, causing lung inflammation and lung microbiota dysbiosis [82]. This can impact the gut microbiota that progresses gut dysbiosis [69]. In addition, SARS-CoV-2 can also directly infect the gastrointestinal tract, which is also causal for gut dysbiosis. Gut dysbiosis could also originate from the oral cavity. Ren *et al*. [83], showed that oral butyrate-producing bacteria were reduced while LPS-producing bacteria were increased.

Gut dysbiosis is not only causal for intestinal inflammation but also with the susceptibility to the translocation of inflammatory cytokines, immune cells, LPS and bacteria across the intestinal epithelial barrier into the mucosa and then into the systemic circulation and other end organs. This can adversely add to the already existing inflammatory response caused by SARS-CoV-2 infections. Importantly, blood vessel endothelial cells contain very high levels of ACE2 and as such can be easily damaged, leading to coagulation abnormalities. Blood clotting sequalae in end organs can be fatal. An additional mechanism of gut dysbiosis causal inflammation is the decreased production of commensal bacterial anti-inflammatory metabolites (e.g., butyrate) [84].

It has been reported that influenza infections can cause reduced SCFA such as acetate in the lungs [85]. Reduced acetate levels decrease the bactericidal effect of alveolar macrophages, leading to possible secondary pneumococcal infections. Pharmacological activation of FFAR2 reduced bacterial superinfection. Antiviral effect of acetate has also been demonstrated and reported [86].

As previously summarised in other sections of this report, the gut microbiota and the lung microbiota give rise to bidirectional interactions. The gut microbiota can provide metabolites such as butyrate, bile acids that can through gut effects promote lung microbiota growth as well as maintain immune homeostasis to prevent hyperinflammation. Gut dysbiosis causes gut inflammation and disruption of the intestinal epithelial barrier (i.e., leaky gut), resulting in decreased commensal bacterial metabolites delivered to the lung and increased transportation of inflammatory cytokines, LPS and bacteria translocated into the circulation and then to the lung. These effects can lead to lung inflammation and gut dysbiosis. It has been considered that viral infections in the respiratory system can cause both lung and gut dysbiosis [87]. The interactions of the gut microbiota and the lung microbiota become disrupted.

## 4. Approaches to Improve the Gut-Lung Axis

As the gut-lung axis plays a key role in the severity of COVID-19 [88], particularly host-virus interactions in the early stages of the infection, improving the gut-lung axis could be significant in reducing COVID-19 severity and mortality rate. This could be achieved by modulating both the gut and lung microbiota. Interestingly, the make-up of the intestinal microbiota may significantly influence COVID-19 severity and immune responses [12]. The intestines not only harbour the largest bacterial biomass but also is the site of the largest immunological organ, where the microbiome is known to influence immune responses in addition to influencing an array of physiological functions of the host [89]. Hence it is key to improve intestinal microbial diversity and abundance where the bacterial cohort serve to aid in digestion, improve absorption and production of essential nutrients, regulating immune responses as well as metabolic and nervous activity [90].

### *4.1 Modulation of the Gut Microbiota*

It is important to note that the requisite for a balanced nutritional intake is imperative during the progression of and recovery from any illness in order to improve health outcomes [91]. Hence, recent reports on the public health crisis that is the COVID-19 pandemic has indicated that there may be long term effects of malnutrition that predisposes patients to severe COVID-19 in an age dependent manner [92,93]. The gut microbiota has been extensively studied and many approaches have been reported to modulate the intestinal microbiome [94]. The use of probiotics, prebiotics and synbiotics as well as dietary practices can effectively improve the gut-lung axis for the prevention and treatment of lung diseases [95].

#### 4.1.1 Probiotics

Probiotics are living organisms, which can alter the gut microbiota compositions to bring health benefits. Probiotics have been used in many clinical trials for improving COVID-19 outcomes. Currently, commonly used probiotic bacteria in COVID-19 are from the *Bifidobacterium* and *Lactobacillus* genera. However, next generation of pro-

biotics which include butyrate-producing bacteria could be included in probiotic formulations as the important role of butyrate in COVID-19 [1,96].

Numerous studies including *in vitro* cell cultures and clinical trials (Table 1, Ref. [97–110]) have reported the effectiveness of probiotics in COVID-19 infections. In cell culture and animal studies, the supernatant or fermented product from probiotic formulations down-regulated ACE2 expression, inhibited viral replication and decreased pro-inflammatory cytokine production [97–99]. Several clinical trials demonstrated that various probiotics increased immune responses against COVID-19 [100–103]. Other clinical trials have reported that probiotics decreased inflammatory markers and reduced symptoms [104–108] such as fatigue and diarrhea. In addition, the probiotic *S. salivarius* K12 reduced infection rate and SLAB51 increased blood levels of $pO_2$, $O_2Hb$ and $SaO_2$ by reducing oxygen consumption in the intestines [109,110]. Indeed, the effect of probiotics on the improvement of COVID-19 symptomatology has been correlated with decreased viral load and increased immune responses.

A clinical trial reported that the administration of a probiotic composed of three strains of *Lactobacillus plantarum* KABP022, KABP023 and KAPB033 and *Pediococcus acidilactici* KABP021 strain in a 1:1 formula, totalling $2 \times 10^9$ colony-forming units for 30 days reduced COVID-19 patient symptoms, improving outcomes [102,111]. Complete remission was 51.3% (78 out of 147) in probiotic group compared to 28.1% (41 out of 146) in placebo group. The probiotic reduced nasopharyngeal viral load and lung infiltrates with increased levels of specific IgM and IgG against SARS-CoV-2 virus. However, the clinical trial did not characterize the alteration of gut microbiota and commensal bacterial metabolites, which could provide the mechanisms for the dramatic effect of the probiotic. With more outcomes of clinical trials of probiotics in COVID-19, an optimal probiotic formulation for COVID-19 treatment could be available. In addition, an ongoing clinical study is also investigating the efficacy of *L. Plantarum* and *P. acidilactici* in adults diagnosed with SARS-CoV-2 and COVID-19 [111].

Overall, cell cultures and clinical trials (Table 1) have demonstrated that probiotics can be effective in reducing infectivity of the SARS-CoV-2 virus and can improve COVID-19 outcomes in various clinical scenarios. With additional clinical trials with probiotic formulations in COVID-19 an optimal probiotic formulation for COVID-19 treatment could become available. Furthermore, characterizing the shifts in the gut microbiota and commensal bacterial metabolites that ensue with COVID-19 infections of the gut could provide mechanistic insight as to the beneficial effects that probiotics may significantly have on abrogating COVID-19 infections and symptoms, and hence facilitating improvement in the overall health of the community.

#### 4.1.2 Prebiotics

Prebiotics provide substances for probiotics to produce beneficial bacterial metabolites. Commonly used prebiotics are GOS, FOS and inulin [1]. Through fermentation, they are converted to SCFAs, which has been demonstrated to regulate immune responses and exert anti-microbial effects. These prebiotics have been shown to increase beneficial bacteria from the genera *Bifidobacterium* and *Lactobacillus*. Recently it has been reported that GOS, FOS and inulin also increase butyrate-producing bacteria.

Recently, other prebiotics have also been well studied such as human milk oligosaccharides (HMOs), which have been identified as beneficial gut prebiotics [112–114]. HMO contains around 200 types of oligosaccharides. Some of the HMOs can be degraded, whereas intact HMOs can be fermented. HMOs that have not been degraded can adhere with pathogens to prevent infections. In addition, HMOs also act against biofilm formulation to weaken the invasion capacity of pathogens [115]. Recently, HMOs have been proposed to be applied in COVID-19 [116]. As HMOs are rare in the market-place, bovine milk oligosaccharides (BMOs) have been studied for their prebiotic beneficial effects [117].

Polysaccharides from marine products such as algae and seaweed could improve the abundance and diversity of the gut microbiota [118]. Fucoidan from brown seaweed increased the abundance of *Lactobacillus*, *Akkermansia*, SCFA-producing *Blautia* and *Alloprevotella* [119–122]. Marine products could be used for improving the gut-lung axis in COVID-19.

#### 4.1.3 Synbiotics

Synbiotics are functional foods composed of both probiotics and prebiotics, which can increase fermentation processes in the gut [123]. A recent clinical trial reported that a formula (SIM01) composed of *Bifidobacterium* strains, GOS, xylooligosaccharide and resistant dextrin was effective in reducing the severity of COVID-19 [100]. Patients that administered SIM01 developed greater levels of IgG antibodies than controls (88% vs 66.3%) and less patients failed to develop IgG antibodies (1% vs 26.7%). SIM01 reduced inflammatory markers including IL-6, MCP-1, M-CSF, TNF-alpha and IL-1RA. Moreover, it reduced nasopharyngeal SAR-CoV-2 viral loads. Metagenomic analysis showed pathogenic bacteria were decreased while commensal bacteria were enriched. Optimally, probiotics should be included in all formulations of synbiotics.

#### 4.1.4 Nutraceuticals and Minerals

Nutraceuticals and minerals are necessary for maintaining a healthy gut microbiota and nutraceutical and mineral deficits have been associated with severe COVID-19 infections [42]. Therefore, supplementation with nutraceuticals and minerals keeping blood levels in healthy ranges would facilitate and result with better communication

**Table 1. Published Studies on the Effects of Probiotics to Attenuate COVID-19 Symptoms.**

| Study Type \| References | Composition* | Outcome |
|---|---|---|
| Cell Culture Lab Studies | | |
| Rather (2021) [97] | *L. plantarum* Probio-88 | Cell-free supernatant inhibited replication of SARS-CoV-2 through plantaricin E and F |
| Paparo (2021) [98] | Cow milk fermented by *L. paracasei* CBAL74 (FM-CBAL74) | Incubation of enterocytes with FM-CBAL74 resulted in<br>↓ expression of ACE2<br>↓ numbers of infected cells with<br>↓ regulation IL6 \| VEGF$\beta$ \|<br>IL-15 \| IL-1$\beta$ |
| Lab Animal Studies | | |
| Pham (2021) [99] | *2% mycelium powder fermented by L. rhamnosus* EH8 at $10^7$ cfu/mL fed to ICR mice for 2-weeks | Fermentation products<br>↓ PDE4B-mediated IL-6 production by SARS-CoV-2 membrane glycoprotein in mice<br>↑ Butyrate |
| Clinical Trials | | |
| Zhang (2022) [100] | *B.* strains \| galactooligosaccharides \| xylooligosaccharide, and resistant dextrin (SIM01) $100 \times 10^9$ cfu/day for 5-weeks | ↑ IgG antibody responses<br>↓ inflammatory responses |
| Kageyama (2022) [101] | *L. plantarum* or *B. longum* $1 \times 10^{11}$ cfu b.i.d for 7 days | *Lactobacillus*<br>↑ TNF-a \| ↑ IL-1beta \| ↑ IL-18<br>↓ IL-6 |
| Gutierrez-Castrellon (2022) [102] | 1:1 to probiotic formula *L. plantarum* KABP022 \| KABP023 \| and KAPB033 + *P. acidilactici* KABP021 $2 \times 10^9$ cfu or placebo/day for 4-weeks | ↑ specific IgM and IgG against SARS-CoV2 compared to placebo |
| Fernandez-Ferreiro (2022) [103] | *Loigolactobacillus coryniformis* K8 CECT 5711 $3 \times 10^9$ cfu/day for 12-weeks | Vaccinated elderly with mRNA vaccine<br>↑ IgA levels after COVID-19 infections |
| Mozota (2021) [104] | *L. salivarius* MP101 $10^9$ cfu/day for 16-weeks | ↑ Barthel index \| ↑ MNA score<br>↓ levels BAFF/TNFSF13B APRIL/TNFSF13 \| IL8 \| IL31 osteopontin \| sTNF-R1 \| sTNF-R2<br>↑ chitinase 3-like 1 \| IL19 \| IL35 \| pentraxin 3 |
| Santinelli (2022) [105] | SLAB51 containing:<br>*S. thermophilus* DSM 32245<br>*B. lactis* DSM32246<br>*B. lactis* DSM 32247<br>*L. acidophilus* DSM 32241<br>*L. helveticus* DSM 32242<br>*L. paracasei* DSM 32243<br>*L. plantarum* DSM 32244<br>*L. brevis* DSM 27961<br>$24 \times 10^{11}$ cfu per day during hospitalization over19-38 days; median 23 days) | ↓ CF |

**Table 1. Continued.**

| Study Type \| References | Composition* | Outcome |
|---|---|---|
| Ivashkin (2021) [106] | *L. rhamnosus* PDV 1705<br>*B. bifidum* PDV 0903<br>*B. longum* subsp. *infantis* PDV 1911<br>*B. longum* subsp. *longum* PDV 2301<br>$10^9$cfu t.i.d./day for 2-weeks | ↓ diarrhea but not mortality and severity markers |
| Mullish (2021) [107] | *L. acidophilus* CUL60 (NCIMB 30157)<br>*L. acidophilus* CUL21 (NCIMB 30156)<br>*L. plantarum* CUL66 (NCIMB 30280)<br>*B. bifidum* CUL20 (NCIMB 30153)<br>*B. animalis* subsp. *lactis* CUL34 (NCIMB 30172) | ↓ upper respiratory tract symptoms |
| Tang (2021) [108] | *Lactobacillus rhamnosus* GG 2 capsules $10 \times 10^9$ cfu for 4-weeks | the probiotic within 7 days of exposure to SARS-CoV-2<br>↓ incidence of symptoms |
| Pierro (2021) [109] | *S. salivarius* K12 daily for 12-weeks | Partially protected infection of SARS-CoV-2 in children |
| Ceccarelli (2021) [110] | SLAB51 containing<br>*S. thermophilus* DSM 32245<br>*B.lactis* DSM32246<br>*B.lactis* DSM 32247<br>*L. acidophilus* DSM 32241<br>*L. helveticus* DSM 32242<br>*L. paracasei* DSM 32243<br>*L. plantarum* DSM 32244<br>*B. brevis* DSM 27961<br>$24 \times 10^{11}$ cfu/day during hospitalization | ↓ $O_2$ consumption in the intestines<br>↑ blood levels of $pO_2$ \| $O_2Hb$ \| $SaO_2$ in COVID-19 patients requiring non-invasive oxygen therapy and presenting a CT lung involvement $\geq$50% |

*CF, chronic fatigue; *L.*, *Lactobacillus*; *B.*, *Bifidobacterium*; *S.*, *Streptococcus*; *P.*, *Pediococuus*; cfu, colony forming units; b.i.d., twice per day; t.i.d., three times per day.

between the gut and lung. A recent report showed that minerals and nutritional supplements reduced COVID-19 severity [124]. In the clinical trial, the intervention group of patients were administered along with a hospital diet, medical treatment and nutraceuticals / minerals (vitamins, minerals, fibre, omega-3, amino acids, B-complex vitamins, and probiotics (*Saccharomyces boulardii*). The primary outcome showed that mechanical ventilation decreased by 10% by day 15 and survival rate increased by 38% compared to the control group.

As described in the introduction section of this report, lactoferrin secreted by the lungs, eyes and the gastrointestinal tract is of great importance for defence against SARS-CoV-2 infections. Clinically intuitively, lactoferrin could be supplemented to COVID-19 patients. Indeed, an *in vitro* cell culture study reported that lactoferrin demonstrated the strongest effect against SARS-CoV-2 infections, among 1400 compounds tested [125]. Lactoferrin can also have anti-inflammatory effects and reduce gut permeability. Several other studies also have demonstrated that lactoferrin reduced LPS-induced inflammation via suppression of TLR4/MyD88/NF-kB pathway [126–128]. *In vitro* studies have also demonstrated that bovine lactoferrin can increase the integrity of the epithelial intestinal barrier [129].

#### 4.1.5 Diet/Functional Foods

Diet quality has been associated with an increased risk of morbidity and mortality from severe COVID-19 infections and a diet characterized by healthy plant-based foods can reduce the risk of COVID-19 infection severity [130].

##### 4.1.5.1 Plant-Based Diets

It has been shown that a population in Okinawa, Japan with healthy plant-based foods has 9% lower risk of COVID-19 infection and 41% lower risk of severe COVID-19 [130,131]. Another study from five European countries and the USA also showed that people with a plan-based diets or pescatarian diets had a 73% lower risk of moderate and severe COVID-19 [132] and were advanced as protective against severe COVID-19. A formulation containing 60% amaranth, 25% oats and 15% banana peel powder has been analysed and selected as a functional food for COVID-19 [133]. Oat beta-glucans facilitate the fermented functional beverages [134]. It may warrant clinical trials in COVID-19. These plant-based diets been well associated with improvement of gut microbiota [135–137]. Therefore, the beneficial effects of these diets could be mediated by gut microbiota, which warrant further studies.

##### 4.1.5.2 Eggs

A review has proposed to use dairy products and eggs in COVID-19 prevention and treatment [138]. By weight, eggs composed of egg white (63%), eggshell (9.5%) and yolk (27.5%) [138]. In a whole egg, protein, fat, carbohydrates, and ash represent about 12.6% protein, 9.5% fat and small amount of carbohydrates (0.7%) and trace of minerals/vitamins (1.1%) [139]. Ovomucin accounts for 2–4% of egg white proteins. The major egg white's proteins are ovalbumin, ovotransferrin and ovomucoid, and minor proteins are ovomacroglobulin (ovostatin), cystatin, lysozyme, avidin, ovoinhibitor and ovomucin. Lipids exclusively exist in the yolk in the form of lipoproteins. Eggs are full of complete nutrients sufficient for the growth of hens and thus provide a good range of nutrients including essential amino acids, which are beneficial for COVID-19 prevention and treatment. Importantly, eggs and their components have been reported to improve gut microbiota. A recent study reported that egg consumption improved gut microbiota [140]. Fermented egg-milk beverage also increased beneficial bacteria from *Lachnospiraceae* and *Lactobacillus* [141]. Ovomucin has been reported to improve gut microbiota through inhibiting pathogenic bacteria [142]. Ovotransferrin has also anti-microbial and anti-inflammatory effects [143–146].

##### 4.1.5.3 Milk

Milk is known to modulate gut microbiota and exert anti-viral effect [147]. Milk contains 13% solid materials, which is accounted for by 5% lactose, 0.3% fats, 4% proteins, 0.1% vitamins and trace of minerals [138,148]. The proteins in the milk fall in three categories including caseins (78%), whey (18%) and milk fat globule membrane proteins (4%). Casein (alpha-, beta-, gamma-, and kappa-casein) can increase mucin secretion to increase mucosal immunity, improving gut microbiota and decreasing inflammation [149]. Whey proteins include alpha-lactalbumin, immunoglobulins and serum albumin as well as minor fractions lactoferrin, glycomacropeptide, lactoperoxidase and lysozyme [150]. Whey proteins have bifidogenic effect [151] and direct effect on SARS-CoV-2 viral infections by interfering the binding of the virus to the host cells [150]. Further, a bovine lactoferrin/whey protein Ig-rich fraction clinical study for the common cold, reported a significantly decreased incidence of colds and the cumulative number of cold-related symptoms over placebo [152]. In a meta-analysis of randomized clinical trials, it was reported that lactoferrin a key immunomodulatory protein exhibits antibacterial and antiviral properties [153]. The study concluded that lactoferrin showed significant promise in reducing the risk of respiratory tract infections and potential use as an adjuvant in COVID-19 infections [153]. Milk and its many components are known to improve gut microbiota [154]. Therefore, the beneficial effects of milk on COVID-19 could be associated with gut microbiota improvement and as such warrant further verification.

##### 4.1.5.4 Fermented Milk Products

Fermented milk products such as yogurt, kefir and cheese have been regarded to be possibly beneficial adjunctive foods in COVID-19 via the inclusion of probiotics

[155]. Yogurt, in which natural probiotics are found, is fermented from milk by two strains of probiotics *Lactobacillus delbrueckii* subsp *bulgaricus* and *Streptoccocus thermophilus* [156]. Additional probiotics could be added to the standard yogurt formulation such as *Lactobacillus casei*, *Bifidobacterial spp.* and *Lactobacillus acidophilus* [156]. A study with 200 COVID-19 patients reported that after a year of consumption of yogurt it was reported to be negatively associated to the severity of COVID-19 [157]. An additional study investigating diet reported that consumption of yogurt was associated with decreased incidence of COVID-19 infections [158]. A novel formulation formulated with *Bifidobacterium animalis ssp. lactis*, *Lactobacillus acidophilus* and 0.03% propolis and 2.5% cinnamon for use in COVID-19 showed significant suppressive effects [159]. Moreover, Kefir has been reported to have anti-viral effects through immune modulation and has been proposed for COVID-19 [160].

### *4.2 Modulation of the Lung Microbiota*

Even though that the lung microbiota presents a significantly lower biomass than that in the intestines [16], the lung microbiota is a critical participant in the pathogenesis of COVID-19. Hence maintenance and improvement of the lung microbiota assumes a greater importance. Currently, there are no approaches to improve the microbiota of the lungs. However, measures could be adopted that could prevent damage to the lung microbiota. Smoking is known to damage the microbiota of the lungs and hence cessation of smoking will be beneficial for the prevention and treatment of COVID-19 [161]. Also, it has been reported that inhaled corticosteroids cause lung dysbiosis in COPD [162]. Proper treatments of chronic lung diseases should also facilitate the promotion of homeostasis of the lung microbiota. Studies have reported that whey protein lysozyme aerosol treatment reduces pathobiont infections, inflammation, and lung tissue injury [163–165]. Therefore, possible improvements in the lung microbiota warrant further studies.

### *4.3 Physical Activity and the Intestinal Microbiota*

Research continues to report the overall health benefits of interventions that attribute physical activity with enhanced health outcomes [166] albeit some of the reported data is contentious. Several studies have been conducted that report finding at least an association between physical activity and or physical exercise and the probability of modulating the gut microbiome [167]. Although dietary aspects of physical activity research present with study confounders, the synthesis of the findings suggests that the intestinal microbiome diversity was associated with aerobic exercise [167]. Further, that the abundance of the *Prevotella* genus would appear to be associated with training duration [167]. The recent systematic review also reported that there were no significant changes in intestinal microbiome richness and diversity reported when exercising according to the minimum dose recommended by the World Health Organizations. Rather that intense and prolonged physical exercise can induce a higher abundance of pro-inflammatory bacteria and that physical activity does not lead to significant intestinal microbiome $\alpha/\beta$-diversity in elderly populations (i.e., those 60+ years of age) [167].

Notwithstanding though high levels of physical activity and exercise has equated to improved microbial diversity and with enhanced diversity and abundance of beneficial microbial species in the intestines [166,168]. Studies have reported that research evidence that advocates outdoor physical activity presents an overall effective coping and preventative strategy on the impact of COVID-19 [169]. A report of 48,440 adult patients also showed that patients diagnosed with COVID-19 that were consistently inactive had a greater risk of hospitalisation (OR 2.26; 95% CI 1.81 to 2.83), admission to the ICU (OR 1.73; 95% CI 1.18 to 2.55) and death (OR 2.49; 95% CI 1.33 to 4.67) due to COVID-19 than those patients who were consistently meeting physical activity guidelines [170]. Further, among the infected adults who consistently met physical activity guidelines showed a strong association with reduced risk for severe COVID-19 outcomes [170].

## 4. Conclusions

The gut-lung axis has a bi-directional flow of effects and cross-talk, and play critical roles in many lung diseases [171]. The gut microbiota has been often demonstrated to be highly important in COVID-19 susceptibility, severity, and recovery in clinical settings and from animal models. The gut-lung axis could represent the role of gut dysbiosis in COVID-19. The lung is the initial infectious site of SARS-CoV-2. The virus spreads to the systemic circulation and other organs if the infections in the lung cannot be contained. Therefore, early modulation of the gut microbiota then assumes important significance. Various approaches could be adopted to improve the gut microbiota. However, no definitive formulations are currently available, notwithstanding numerous modes for modulating the intestinal microbiome have been advanced that can effectively improve gut bacterial abundance and diversity for health. What has been posited and is important to note is that diet insecurity has been recently cited as associated with compromised diet quality, especially among low-income adults, and as such may be a risk for COVID-19 infections [172], and possibly for long term COVID-19.

Combination of several approaches that modulate the gut microbiota could provide greater health benefits to the lung-gut axis. For example, combinations of whey and eggs with inulin have been shown to increase the capability to improve the gut microbiota in obese rats [173]. A randomized trial reported that whey protein with GOS improved sleep quality and stress through modulation of the gut microbiota [174]. Lastly the effects of lifestyle effects relevant to prudent nutritional practices and the adoption of

some form of exercise regimes provide practical solutions to improve the intestinal microbiome-host functionality and in turn also improve the lung-gut axis.

## Author Contributions

JC and LV drafted the initial manuscript; JC and LV edited and approved the final version of the manuscript.

## Ethics Approval and Consent to Participate

Not applicable.


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## Conflict of Interest

The authors declare no conflict of interest.

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