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Review Article

Microbiology Section

Gut-Lung Axis-A Compass to Navigate Microbiome Landscape in COVID-19

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ABSTRACT

The waves of the Coronavirus Disease 2019 (COVID-19) pandemic have disrupted healthcare systems globally, with a staggering number of confirmed cases reaching 593 million and a death toll of six million. While the primary target organ of COVID-19 is the lungs, the novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) also shows a preference for the intestinal epithelium, which expresses Angiotensin Converting Enzyme 2 (ACE2), a receptor necessary for viral entry into host cells. The composition and abundance of beneficial gut microbiota play a critical role in protecting against severe disease and complications, whereas dysbiosis contribute to systemic inflammation and immune imbalances during SARS-CoV-2 infection. Recent insights into the microbiome have emphasised the importance of the gut-lung axis and the microenvironments of the gut and lungs in the context of COVID-19. These findings offer opportunities for the development of new diagnostic and therapeutic strategies. In this review, the significance of the gut-lung axis, as well as the intestinal and pulmonary microbiota, in COVID-19, were explored with a particular focus on their potential applications.

Keywords: Coronavirus disease 2019, Microbiota, Probiotics, Severe acute respiratory syndrome coronavirus-2

INTRODUCTION

Over the past three years, the world is experiencing the adverse impacts of a novel coronavirus pandemic. On 31 December, 2019, a cluster of viral pneumonia cases were reported from Wuhan, China. Subsequently, on 24th January 2020, 41 cases of SARS-CoV-2, like pneumonia of unknown aetiology were reported from Wuhan [1]. The causative agent was identified as a novel beta-coronavirus. It was named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV) and the infectious syndrome was officially named as Coronavirus Disease 2019 (COVID-19) by the World Health Organisation (WHO) [2,3]. The pandemic spread of SARS-CoV-2 has posed a major public health challenge with 593 million confirmed cases and a death toll of six million globally [4].

Although COVID-19 is primarily a respiratory infection, its pathogenesis includes diverse metabolic and immunological mechanisms contributing to multi-system dysfunction involving lungs, cardiovascular system, kidneys and Gastrointestinal Tract (GIT) [5]. While abdominal symptoms are common in cases of COVID-19, the implications of gut microbiota in SARS-CoV-2 infection is yet to be characterised. In the light of current research, it is evident that commensal microbial flora, especially intestinal microbiota plays an essential role in maintaining the homeostasis in various organs [6]. Gut microbiota not only prevents mucosal colonisation by pathogens, but also regulates immune response and permeation of microbes, microbial products and metabolites into systemic circulation [7]. Microbial products such as Short Chain Fatty Acids (SCFA) and Desaminotyrosine (DAT) are reported to have immunomodulatory action [8]. Through these molecules, intestinal microbiota exerts its communication and regulatory influence on other organ systems. This bidirectional interaction of intestinal and respiratory microbial flora constitutes gut-lung axis. In this article, we aim to review the role of gut-lung axis and intestinal and pulmonary microbiota in COVID-19 and focus on its implications and potential therapies based of currently published research evidences.

Microbiome and its Significance

Commensal microbes found on the skin and mucosal surfaces of humans have co-adapted over millions of years [9]. However, their role in health and disease has largely gone unnoticed. The term "microbiome" encompasses the diverse community of microorganisms residing inside and on the human body. The human microbiome consists of approximately 100 trillion prokaryotic (bacterial) and eukaryotic (protozoa and fungi) cells, outnumbering the host's cells [10]. Traditionally, infectious disease research has focused on specific pathogens rather than taking a holistic approach. However, current research provides compelling evidence of the critical role played by the human microbiome in nutrient and drug metabolism, immune response regulation, maintenance of mucosal integrity, and protection against pathogen colonisation [6]. While beneficial microbes promote homeostasis, attrition of the beneficial microbiota is linked to an increase in the risk of infection, malignancy and diverse metabolic and immune disorders [7].

Gut Microbiome

Human digestive system provides a vast mucosal surface harbouring largest population of microbiota. This colonising species establish a symbiotic association with the host achieving health and homeostasis [6]. In normal conditions, the microbiota supports the host by preventing invasion by foreign pathogens and by regulating digestion, metabolism, and immunomodulation, in return it receives nutrition and ecological niche from the host [11]. This state of equilibrium is named as eubiosis. In contrast, dysbiosis refers to a state of imbalance in host-microbiome relationship due to disruption of beneficial microbiota [12]. Dysbiosis promotes colonisation by harmful species leading to infection as well as metabolic and immune disorders such as asthma, arthritis, metabolic syndromes such as obesity and insulin resistance, diabetes, cirrhosis, Non-Alcoholic Fatty Liver Disease (NAFLD) neurodegenerative disorders [13].

Gut microbiota is currently being studied by 16S rRNA gene sequencing and metabolomics [14]. Gut microbiome is mainly comprised of members of Firmicutes and Bacteroidetes phyla [15]. Although the composition and density of microbiota varies throughout the GIT, it has been identified that *Bacteroides, Prevotella, Porphyromonas, Clostridium, Eubacterium, Enterococcus, Streptococcus, Peptostreptococcus, Ruminococcus, Enterobacterium, Lactobacillus, Fusobacteria, Fecalibacterium, Lachnospira, Butyrivibrio*

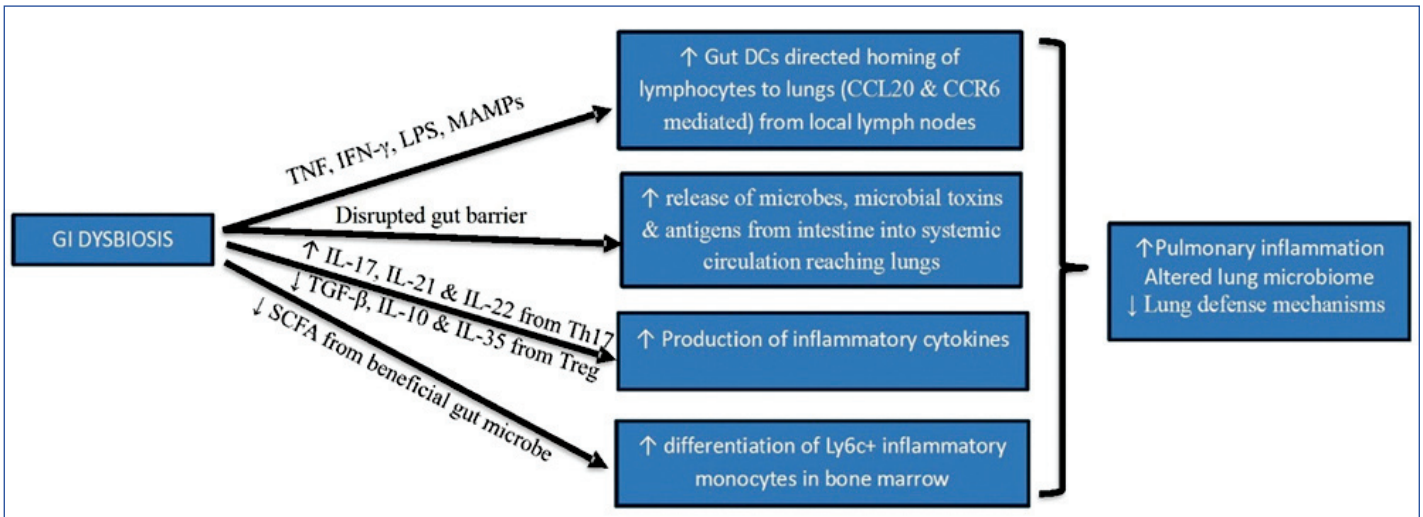
and Roseburia are the predominant bacterial genera in human colon and caecum [6]. Diverse range of microbe-derived metabolites are implicated in the bidirectional communication between gut and distant organs like lungs, heart, liver, kidneys and brain, establishing gut-organ axis [8].

Gut-lung Axis

Gut-lung microbiome axis has profound implications on pulmonary function in health and disease. The mechanisms of gut-lung interactions are illustrated in [Table/Fig-1]. Studies have reported influence of gut microbiome on homing of immune cells to lungs [8,16]. Both respiratory and intestinal tract are constantly exposed to microbes and antigens from external environment. Owing to the large proportion of immune cells present in Gut-Associated Lymphoid Tissue (GALT), gut microbiota affect both innate and adaptive immune response in all organs [16]. Dendritic Cells (DC) in GALT after sampling microbial antigen from intestinal microenvironment travel to local lymph nodes where they activate naive lymphocytes and direct them to migrate to specific tissues which express specific chemotactic chemokines [17]. CCL20 chemokine and its receptor CCR6 are implicated in homing of lymphocytes to lungs [18]. This trafficking of lymphocytes to lungs is enhanced in the state of dysbiosis through increased production of inflammatory cytokines and microbial components {bacterial lipopolysaccharide and Microbe-Associated Molecular Patterns (MAMPs)} [19].

Ly6C$^-$ patrolling monocyte subtypes and supress inflammation and tissue damage. In contrast, dysbiosis promotes differentiation of Ly6C$^+$ monocytes in bone marrow aggravating inflammation [24].

The protective gut barrier has immense influence on microbiome and immune response in lungs. Gut barrier is composed of resident microbiota, mucus layer containing secretory Immunoglobulin A (IgA) and anti-microbial peptides, immune cells of lamina propria and intestinal epithelial cells connected through tight junctions [25]. This complex interface (gut barrier) regulates the tripartite interaction of external environment, resident microbiota and host immune system. Intestinal conditions, such as inflammatory bowel disease, food allergy, alcohol, high fat diet, as well as extraintestinal disorders, such as diabetes, obesity and Non Steroidal Anti-inflammatory Drugs (NSAIDs) are known to impair gut barrier [25]. Dysbiosis induces pro-inflammatory state through activation of innate and acquired immune system and may impair functions of this barrier. In an animal experiment, dysbiosis was linked to gut barrier dysfunction, resulting from disengagement of a tight junction protein [26]. While barrier function of gut and immune system determine the composition of gut microbiome, disruption of the gut barrier leads to hyperpermeability (leaky gut) causing sustained release of microbes, microbial products, toxins and antigens from intestine into systemic circulation and remote organs like lungs [25]. Lung defence mechanisms, such as neutrophil recruitment, phagocytic



[Table/Fig-1]: Mechanisms of pulmonary pathology in GI dysbiosis [16,45].

Furthermore, it is observed that gut microbiota conserves the balance between pro-and anti-inflammatory immune response by modulating the differentiation of T-helper type 17 cells and regulatory T cells (Treg) in gut and other organs [19]. T-helper type 17 cells produce Interleukin 17 (IL-17) and IL-22 which enhance neutrophil recruitment resulting in pro-inflammatory response [20]. In contrast, Treg produce inhibitory cytokines, such as, Transforming Growth Factor beta (TGF-β), IL-10, and IL-35 and supress immune response and associated inflammation. Certain bacterial species may have direct association in T cell differentiation. *Bacteroides fragilis* was found to correct T-helper type 1/T-helper type 2 imbalances [21]. Segmented Filamentous Bacteria (SFB) were shown to promote differentiation of T-helper type 17 cells in mice [22].

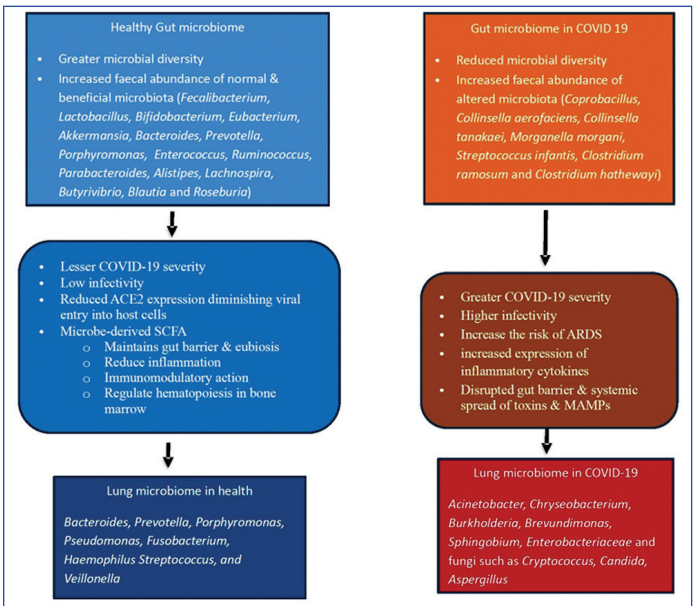
Interestingly, gut microbe-derived SCFA apparently can also regulate the differentiation of bone marrow stem cells and govern immune response in lungs [23]. Bone marrow myeloid precursor cells generate Macrophages Dendritic cell Precursors (MDP) which in turn give rise to Common Dendritic cell Precursor (CDP) and two subtypes of monocytes, namely Lymphocyte Antigen 6C$^+$(Ly6C$^+$) and Lymphocyte Antigen 6C$^-$(Ly6C$^-$). Differentiation of MDP to inflammatory or anti-inflammatory immune cells is determined by SCFA. In state of eubiosis, SCFA diffuses in bone marrow, increases action of alveolar macrophages, production of antibacterial factors by respiratory epithelium, and composition of lung microbiota depends on gut microbiome and inflammatory mediators such as IL-8, IL-6, C-Reactive Protein (CRP) may have an important role [16].

Gut Microbiome in COVID-19

Involvement of GI system in COVID-19 has continuously been a controversial aspect. GI symptoms such as loss of appetite, nausea, vomiting, diarrhoea, and abdominal pain are not uncommon in patients with SARS-CoV-2 infection. Diarrhoea occurs in 2-20% of the COVID-19 cases [27-29]. In some patients, diarrhoea may even precede respiratory manifestations or can be the sole presenting symptom of COVID-19 [30]. In a study conducted by Chen Y et al., patients with lower richness of gut microbiota after recovery from COVID-19 also had elevated CRP and increased disease severity [31].

Gut and lung microbiome and their consequent interactions in COVID-19 differ substantially from that of healthy individuals [Table/Fig-2] [32-41]. Recent studies have demonstrated a clear difference in gut microbiome in COVID-19 patients in comparison to control in terms of decreased richness and diversity of microbiota as well as a shift in relative abundance of specific taxa. Most studies revealed that intestinal dysbiosis persisted for a prolonged period

after recovery from SARS-CoV-2 infection and it may take about six months to restore gut eubiosis [31-33]. Faecal abundance of beneficial and symbiotic species has been identified more frequently in normal controls and COVID-19 patients with low infectivity, lesser severity and convalescence [32-34], whereas, predominance of opportunistic and pathogenic microbes have been found to have association with higher infectivity, increased inflammation and severe disease. In an observational study on faecal metagenome analysis by shotgun sequencing, authors noticed greater infectivity in patients with dominance of *Collinsella aerofaciens, Collinsella tanakaei, Morganella morgani* and *Streptococcus infantis*, whereas *Parabacteroides merdae, Bacteroides stercoris, Alistipes onderdonkii* and *Lachnospiraceae*, etc SCFA producing microbiota were associated with lower infectivity [34]. De Maio F et al., monitored the change in faecal microbiota in COVID-19 patients at 48 hours and after six months of recovery in comparison to control group [32]. They reported that COVID-19 patients during acute illness had relative abundance of *Bacteroidetes* and reduced microbiota diversity which improved after six months of recovery with the regrowth of symbionts such as *Ruminococcaceae*, *Blautia* and *Lachnospiraceae* [32]. Nashed L et al., evaluated faecal microbiome of 0 to 24-month-old children. They observed diminished faecal abundance of beneficial flora, such as, *Bifidobacterium bifidum* and *Akkermansia muciniphila* in SARS-CoV-2 positive children [35]. In a pilot study, Zuo T et al., found that severity of COVID-19 was greater in patients with high faecal abundance of *Coprobacillus, Clostridium ramosum,* and *Clostridium hathewayi*, whereas high faecal abundance of *Faecalibacterium prausnitzii* and *Bacteroides* species such as *B. dorei, B. thetaiotaomicron, B. massiliensis,* and *B. ovatus* correlated well with lesser severity and lower faecal viral load [33]. The same group also detected in higher proportion of opportunistic fungi such as *Candida albicans, C. auris* and *Aspergillus* in faecal samples of COVID-19 patients in comparison to controls [36].



[Table/Fig-2]: Intestinal and pulmonary microbiome in healthy and COVID-19 positive individuals.

Lung Microbiome in COVID-19

It has long been believed that unlike the Upper Respiratory Tract (URT), bronchopulmonary tree is devoid of microbial flora [37]. The poor yield of culture based identification had been a major issue contributing to the paucity of information on lung microbiota [37]. However, sequence-based advanced identification assays have confirmed presence of diverse taxa of microbes interacting in pulmonary ecological niche in recent years [37]. On account of the nutrient-constrained environment of the lungs, the microbiome of lung is less dense with low biomass in comparison to its intestinal counterpart [37]. Microbes gain access to bronchopulmonary tree through inhalation or microaspiration from the orodigestive tract [13]. Several studies have reported dynamic nature of lung microbiome, where the microbial species may vary person to person and also shows spatial variation in different regions of the respiratory tract of an individual [38,39]. Despite these variations, *Bacteroidetes, Proteobacteria*, and *Firmicutes* are the main microbiota in healthy subjects [13]. Bacterial genera such as *Pseudomonas, Prevotella, Porphyromonas, Fusobacterium, Haemophilus, Streptococcus,* and *Veillonella* have been detected as the core components of bacterial microbiome of the lung [40].

Unlike gut microbiome, the perturbation of lung microbiome has not been thoroughly explored in COVID-19. This may be related to the technical challenges like low biomass of lung microbiota and risk of contamination with upper respiratory flora during bronchoscopy [37]. Nevertheless, there is evidence of dysbiosis of lung in SARS-CoV-2 infection. Fan J et al., studied the microbial profile of pulmonary tissue from 20 fatal cases of COVID-19 [41]. Among the bacterial microbiota, *Acinetobacter* was most abundant, followed by *Chryseobacterium, Burkholderia, Brevundimonas, Sphingobium* and *Enterobacteriaceae*. The lung mycobiome in these patients was comprised of several fungal genera. Among these fungi, *Cryptococcus* was most predominant, followed by *Candida, Aspergillus, Alternaria, Cladosporium, Issatchenkia, Wallemia, Dipodascus, Mortierella, Naganishia,* and *Diutina* [41]. In another study, Maes M et al., compared the occurrence of Ventilator Associated Pneumonia (VAP) and composition of lung microbiome in 81 COVID-19 positive and 144 non COVID-19 patients on invasive ventilation [42]. It was noted that invasive aspergillosis was more frequent among COVID-19 patients, although the pathogens causing VAP and the lung microbiome were comparable in both the groups. While some authors have reported preponderance of oral and nasopharyngeal flora, others revealed abundance of gut-associated bacteria (*Enterobacteriaceae*) in the lungs was associated with COVID-19 morbidity and mortality [41,43].

COVID-19 Pathogenesis and Gut-lung Axis

Although lungs have been considered as the primary target organ in COVID-19, it is now recognised as a multisystem disorder [5]. The entry of SARS-CoV-2 in host cells is mediated by S protein, which binds to its receptor, ACE2 on host cells [5]. In addition to type 2 alveolar cells of lungs, intestinal cells, heart, kidneys, and endothelial cells also exhibit high levels of expression of ACE2, which is believed to be the molecular basis of extrapulmonary manifestations of COVID-19 such as diarrhoea, abdominal pain, myocardial ischaemia, Acute Kidney Injury (AKI) and thromboembolism [5,8]. After clathrin-mediated endocytosis into the host cells, SARS-CoV-2 replicates and gives rise to new viral progeny. In early phase of infection, viral load gradually increases with viral replication. With the activation of innate and acquired immunity, the viral load gradually declines in immunocompetent host. The systemic manifestations and grave complications of SARS-CoV-2 are essentially attributed to dysregulated immune response and consequent systemic inflammation rather than direct Cytopathic Effect (CPE) of the virus [5]. Pattern Recognition Receptors (PRR) are proteins associated with innate immunity. Various PRRs, such as Toll-like Receptors (TLRs), Nucleotide Oligomerisation Domain (NOD)-like receptors and Intracellular Retinoic Acid-Inducible Gene-I-Like Receptors (RLR) are expressed on monocytes, macrophages, DCs, fibroblasts, and epithelial cells [16]. PRRs bind to microbial products as well as products released from damaged or decaying host cells known as MAMPs and Damage-Associated Molecular Patterns (DAMPs), respectively [44,45]. PRR binding to MAMPs and DAMPs triggers leucocyte recruitment and activation of inflammasome pathway, leading to release of proinflammatory cytokines such as IL-6, Tumour Necrosis Factor (TNF), IL-1 and IL-10 (cytokine storm) and coagulation cascade [46]. Activation of Antigen-Presenting

Cells (APCs) by these cytokines, promotes exaggerated cellular and humoural acquired immune response against SARS-CoV-2 which also contributes to systemic inflammation and multiple organ dysfunction [5].

On account of recent studies, it is evident that gut-lung axis has an important role in COVID-19 pathogenesis. While intestinal dysbiosis promotes migration of microbes and immune cells to lungs, the abundance of gut-associated bacteria, such as *Lachnospiraceae* and *Enterobacteriaceae* in lung microbiota have been described to increase the risk of Acute Respiratory Distress Syndrome (ARDS) [47]. Furthermore, GI dysbiosis is frequently associated with increased expression of inflammatory cytokines such as Interferon gamma (IFN-γ), IL-6, Chemokine (C-C motif) Ligand 2 (CCL2), and decreased Tregs in the lung and GIT [48]. In dysbiosis, MAMPs may disseminate to extraintestinal tissues where they bind to PRRs on cells of innate immune system and stimulate secretion of proinflammatory cytokines [45]. While release of these cytokines in systemic circulation may contribute to the proinflammatory state in COVID-19, diminution of Tregs may give rise to secondary infections [45,49]. A disrupted gut barrier in the setting of dysbiosis supports migration of microbes and their toxins in circulation, which further deteriorates the septic state [50].

Increased expression of ACE2 corresponds to higher propensity of SARS-CoV-2 entry in host cells [51]. This is evident from the greater risk of developing severe COVID-19 disease among people with diabetes, hypertension and cardio-respiratory disorders as they typically show higher expression of ACE2 [52]. In contrast, gut microbiota such as *B.dorei, B.thetaiotaomicron, B.massiliensis*, and *B.ovatus h*ave been found to reduce ACE2 expression in animal models [33]. Lesser faecal SARS-CoV-2 load have been observed in patients with high faecal abundance of these species [33]. This is likely due to diminished viral entry in enterocytes as a result of downregulation of ACE2 by beneficial gut microbiota. Dysregulation of Renin-Angiotensin-Aldosterone System (RAAS) is implicated in pulmonary fibrosis and acute lung injury in COVID-19 [53]. During the course of infection SARS-CoV-2 downregulates ACE2 in pulmonary tissue [54]. This shifts the balance towards ACE-Angiotensin II-AT1R pathway by diminishing ACE2-Ang1-7-MasR axis activity leading to endothelial injury, vascular permeability, prothrombotic state, ARDS, myocardial fibrosis, nephropathy, pancreatitis, and Insulin Resistance (IR) [55]. Furthermore, ACE2 expressed on intestinal cells can trigger disturbance in gut microbiota homeostasis [56]. ACE2 determines normal amino acid transport in intestine. In an animal study, it was observed that lack of tryptophan due to ACE2 downregulation in intestine of mice was related to reduced production of anti-microbial peptides leading to altered GI microbiome [56].

Potential Therapies and Applications of Gut Microbiota in COVID-19

The research data on microbiome in health and disease have increased exponentially over last few years. Thus, it is now possible to determine and quantify the deviations of normal human microbiome in various disease conditions. Several studies provided consistent evidence of alteration of gut as well as lung microbiota in COVID-19 and the role of specific microbial taxa are being investigated. The relative abundance of specific microbial species has been found in correlation with higher infectivity, severity and complications of COVID-19. Hence, these microbial signatures may be employed as diagnostic or prognostic markers in COVID-19 [57].

Beneficial gut microbiota has the potential to be used as a novel therapeutic agent or as an adjunct or supplement to the standard therapy in COVID-19. Gut microbiome have been found to accord protection against respiratory infections through Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) mediated activation of alveolar macrophages in mice [58]. In addition, it was associated with cellular and humoural immune responses and colonisation resistance. Lung microbiota in mice also reduced lung injury by influenza through secretion of anti-inflammatory cytokines [59]. These evidences suggest modulation of gut microbiota may confer protection against SARS-CoV-2 or may hasten the recovery. This gut microbiota modulation is possible either by administration of "live microorganisms" into GIT in the form of probiotic or faecal microbiota transplantation or by administration of prebiotics (non-viable, non-digestible food components or dietary fibres) [60,61]. Probiotic strains such as *Lactobacillus*, *Bifidobacterium* and *Saccharomyces boulardii* exert their anti-inflammatory, anti-cancer, anti-microbial and immunomodulatory actions directly [62]. However, prebiotics such as inulin and non-digestible oligosaccharides indirectly confer health benefits by promoting the growth or activity of certain beneficial gut microbiota [63]. For example, dietary fibres (prebiotic) are metabolically inert substances. These are fermented by gut microbes to produce SCFA such as acetate, propionate, and butyrate and this SCFA performs multiple functions as it diffuses into intestinal and extra intestinal tissues. *Faecalibacterium prausnitzii, Eubacterium rectale, E. hallii, Coprococcus comes* and *C. eutactus* are the major butyrate producers [64]. Whereas, *Bacteroidetes, Lachnospiraceae* and *Negativicutes* produce propionate [64]. Diminished abundance of these microbiota has been linked to intestinal dysbiosis. Maintaining GI epithelium integrity, reducing gut inflammation, increasing production of mucin and IgA and activation of macrophage and DC signalling are the critical functions of SCFA in intestine [24]. SCFA diffuses into bone marrow and regulate the production and differentiation of haematopoietic cells [24]. DAT is another bioactive microbial metabolite produced by *Clostridium orbiscindens* [65]. Researchers have found DAT to confer resistance against influenza in mice through type I interferon signalling [65]. Similarly, a group of beneficial intestinal bacteria named as Segmented Filamentous Bacteria (SFB) have been found to boost respiratory mucosal immunity [66]. Gauguet S et al., investigated the role of SFB and gut microbiome in staphylococcal pneumonia in mice [66]. They observed that SFB reduced the susceptibility to staphylococcal pneumonia by activating T-helper type 17 cell-immune response. While pre-and probiotics have been already in use as adjunctive therapy against diarrhoea associated with dysbiosis, faecal microbiota transplantation is popularly utilised for antibiotic-associated diarrhoea. Taking these findings into consideration, probiotics, prebiotics and their synergistic combinations (i.e., synbiotics) as well as faecal microbiota transplantation are likely to show protective effects in prevention and treatment of SARS-CoV-2 [45]. Moreover, beneficial gut microbiota may also be used to prevent SARS-CoV-2 associated secondary infections and diarrhoea associated with prolonged use of antibiotics, especially in people with high risk of developing severe disease and complications [67].

Immunomodulatory activity is an essential property in probiotics [62]. Gut microbiome is also known to modulate immune response through interaction with innate and adaptive immune system [68]. The variations in rotavirus vaccine efficacy in different populations have been attributed to difference in gut microbiota [69]. Pre- and probiotics and recombinant probiotic strains are being explored to improve vaccine efficacy. *Lactobacillus rhamnosus* GG, *Bifidobacterium animalis*, and *Lactobacillus paracasei* have shown to boost immunogenicity of influenza vaccine [70]. Likewise, specific gut microbiota or probiotic species may be utilised as adjuvants for COVID-19 vaccine.

CONCLUSION(S)

The intricate interplay between the lung microenvironment and the gut-lung axis in COVID-19 infection has been explored in the light of currently available research. It is apparent that multifaceted connections and communication pathways exist between these two systems during COVID-19 infection. These may have potential implications on disease progression, immune responses, and clinical outcomes. A holistic understanding of how the lung

microenvironment and gut-lung axis contribute to the pathogenesis of COVID-19, is imperative to develop innovative preventive measures and therapeutic strategies. Modulation of gut-lung axis through personalised nutrition in the form of probiotics and prebiotics have been explored in the context of COVID-19. It can be employed as an adjunctive therapy to impart immunomodulatory action and antiviral effect in lungs and to enhance efficacy of COVID-19 vaccine. Despite these promising implications, microbiome modulation in COVID-19 currently have several challenges, such as paucity of specific data and translational research. Like any therapeutic agent, the composition, route, and dosage of microbiome-modulating agents need to be standardised and its indications, contraindications, precautions, safety and adverse effects must be characterised through clinical trials. Moreover, the findings of basic research on microbiome need to be utilised efficiently in clinical practice and decision making by means of translational research.

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