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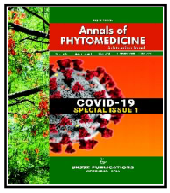

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Current understanding of gut microbiota in tackling COVID-19

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Abstract

SARS-CoV-2 is a global pandemic that mainly affects the respiratory system by binding to host cell transmembrane protease serine-2 (TMPRSS-2) and ACE2 (angiotensin-converting enzyme) receptors on alveolar epithelial cells. The gut microflora plays an important role in maintaining human health and of greatest concern in covid affected individuals. Dysbiosis may be a consequence for lung infection that has been linked to the severity of SARS-CoV-2. Recent studies identified the presence of SARS-CoV-2 RNA in the faeces of COVID-19 patients, which has been associated with several gastrointestinal tract ailments and multiorgan dysfunction. Diet, lifestyle, and genetics plays a vital role in determining the gut microbiota and immune compromise to the virus infection. COVID-19 is attributed to the variations in gut microbiota diversity which often decreases with age and, hence the lethality in elderly patients. Intestinal microbiota profile can be enhanced by improved diet and supplementation, which has been shown to increase immunity in elderly and immune-compromised patients. Diet has an incredible impact on the gut microbiome, allowing for a new state of homeostasis to be achieved through intake timing, frequency, and duration. This review article focuses on gut, lung microbiota, and immunomodulation, with an emphasis on gut microbiota-induced immune activation.

1. Introduction

The gut microbiota is a complex species of commensal bacteria that lives in the human gastrointestinal (GI) tract. The number of microorganisms present in the GI tract is estimated to be greater, with 100 times the amount of genomic content (microbiome) as the human genome. Depending on environmental and genetic factors, the gut microbiome comprises 1000 species of bacteria, with an individual containing approximately 160 species. In the gut, Firmicutes and Bacteroidetes predominate, while in the lungs, Proteobacteria, Bacteroidetes, and Firmicutes predominate (Wang *et al*., 2020). Gut microbiota has provided numerous benefits to its host over time, including direct pathogen inhibition, gut integrity maintenance, metabolizing undigested substances, particularly certain carbohydrates, and the production of tolerant mucosal barrier and intestinal epithelium. Since the gut contains 70-80 % of the body's immune cells, the immune system and gut microbiota have a complex interplay and relationship that controls and supports each other (Xiao *et al*., 2020). Dysbiosis, characterized as changes in gut microbiota that result in microbial imbalance, has been linked to the pathogenesis of many inflammatory diseases and also plays a role in a variety of infections. Viruses are one of the most common pathogens that cause strong interactions between viruses and the commensal microbiota (Li *et al*., 2019).

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The severe global burden of disease caused by COVID-19 infection has prompted almost unparalleled levels of rapid activity across various disciplines by the international scientific community in an effort to understand pathogenesis and establish therapeutic options for this novel virus, with an emphasis on slowing and preventing its transmission (Shen *et al*., 2020). The marked heterogeneity of clinical presentation in COVID-19 infection is particularly intriguing, with certain infected individuals being asymptomatic while others progress to multiorgan damage and death. A comparison of clinical, molecular, and immunological data from a large Chinese cohort of COVID-19 patients revealed that viral genetic diversity did not even appear to be correlated with disease severity, whereas host factors (such as age and inflammatory response) appeared to play a much prominent role (Kalantar Zadeh *et al*., 2020).

The gastrointestinal (GI) tract has been implicated in a variety of emerging clinical and scientific strands of research as a significant organ for the susceptibility to, and intensity of COVID-19 infections. In addition to normal respiratory and constitutional symptoms, GI symptoms (such as nausea, vomiting, and diarrhoea) have been consistently identified as common clinical features of infection (Wu *et al*., 2019). COVID-19 has also been found in tissues from throughout the GI tract, and virus shedding in stool has been observed in a significant proportion of patients, with shedding often enduring for long periods of time; raised faecal calprotect in has also been reported in association with infection (Cai *et al*., 2020). Further more, evidence from organoid models suggests that COVID-19 can specifically infect the GI tract; the SARS-CoV-2 virus, for example, uses angiotensin converting enzyme 2 (ACE-2), which is highly expressed on differentiated enterocytes, as a receptor for cell entry before inducing a viral response program (Fang *et al*., 2020).

In this study, we have discussed how the gut microbiome plays a role in the pathogenesis of COVID-19 infection and the effects of the SARS-CoV-2 virus's interaction with the gut microbiome.

2. Dysbiosis and COVID-19

The human gastrointestinal (GI) tract contains up to 2000 bacterial species divided into 12 phyla, with the *Proteobacteria* (Gram-negative), *Firmicutes* (Gram-positive), *Actinobacteria* (Gram-positive) and *Bacteroidetes* (Gram-negative), phyla being the most common (>90%) (Hugon *et al.*, 2015; Li *et al.*, 2014). With the diversity of microbes, a new concept of "gut virome" has emerged, which is need to be considered as a significant aspect of a healthy human microbiota (Scarpellini *et al.*, 2015). The human gut virome almost shares the vital information with all microbial components and may have an effect on overall human health by shaping gut community structure and function (Cani, 2018; Garmaeva *et al.*, 2019). Gut eukaryotic viruses that are most commonly seen during viral gastrointestinal infections include Norwalk, Rotaviruses, Enteroviruses (the well-known agents of gastroenteritis in humans) and in recent time, SARS-CoV-2 infection (Scarpellini *et al.*, 2015).

Dysbiosis, characterised as changes in gut microbiota that result in microbial instability, has been linked to the pathogenesis of many inflammatory diseases and also plays a role in a variety of infections. Dysbiosis of the gut microbiota causes abnormal immune response in the respiratory epithelium and mucosa, which may cause immune responses to be compromised for respiratory viral infections (Musa, 2020). Many studies have documented the gastrointestinal symptoms as one of the major clinical features during the course of the illness (Zhang *et al.*, 2020a), and perhaps even the presence of viral RNA in faeces (Ng and Tilg, 2020; Xiao *et al.*, 2020). SARS-CoV-2 requires the presence of transmembrane protease serine-2 (TMPRSS-2) and angiotensin converting enzyme-2 (ACE-2) receptor in enterocytes from the colon and ileum to enter and infect the cells (Hoffmann *et al.*, 2020; Zhang *et al.*, 2020b). These gastrointestinal changes in COVID-19 may be a consequence of the major pulmonary changes, or SARS-CoV-2 may be engulfing enterocytes, causing gut dysbiosis and increased negativity of lung homeostasis. The gut microbiota of the elderly (in particular those with age-related pathologies, *e.g.*, cardiovascular, metabolic, renal diseases) is normally less oriented (Shen, 2017), which could be related to the more severe effect of SARS-CoV-2 infection among elderly people that share the common phenomena of gut microbiome dysbiosis. As a result, there appears to be a bidirectional relationship between SARS-CoV-2 infection and dysbiosis, not only as a result of SARS-CoV-2 infection, but also as a possible risk factor for Covid-19 negative consequences (Kalantar-Zadeh *et al.*, 2020).

Intestinal gut microbiome is regulated by innate and adaptive immunity through certain mechanisms of antimicrobial peptides and IgA antibodies. Imbalance in the microbiome alters the innate and adaptive immunity, thereby affecting the colonization of microbiota (Xu *et al.*, 2020). A recent study from China showed that COVID-19 patients had gut dysbiosis with lower levels of *Bifidobacterium* and *Lactobacillus*, both are probiotic strains (Kuba *et al.*, 2005). ACE2 controls the expression of amino acid transporter B(0)AT1, which is responsible for the intake of tryptophan (Zhao *et al.*, 2018) and also the antimicrobial peptides' mRNA expression is controlled by tryptophan *via* the mTOR pathway (Lie´vin-Le Moal and Servin, 2006) which can impact the composition of the gut microbiota. During infection, ACE2 receptor expression becomes downregulated, thereby as a consequence, normal absorption of tryptophan by intestine is reduced and also affects the normal mechanism of antimicrobial peptides, resulting in greater pathogen sustenance and gut dysbiosis (Zuo *et al.*, 2020a). Figure 1 shows the influence of gut microbiota in COVID-19 immune homeostasis.

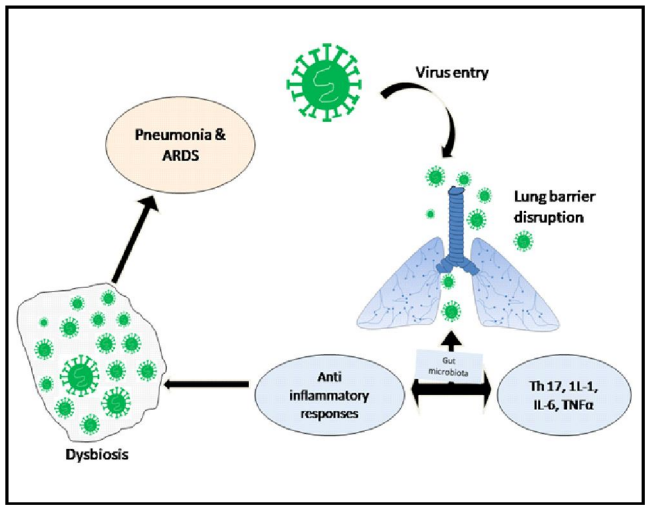

Figure 1: Influence of gut microbiota in COVID-19 immune homeostasis.

A shotgun metagenomic analysis of COVID infected patients' faecal samples reported a decrease in beneficial microflora and an increase in pathogenic strains. This gut dysbiosis was observed even after the clearance of respiratory illness. *Clostridium hathewayi* and *Clostridium ramosum* are responsible for bacteremia and clinical severity (which includes pneumonia along with fever and respiratory tract symptoms; respiratory ratee ≥ 30/min, oxygen saturationd ≥ 93%) and the genus *Coprobacillus* has been shown to strongly upregulate colonic ACE-2 receptor (Yang *et al.*, 2020). Due to the severity of infection by SARS-CoV-2, the *Faecalibacterium prausnitzii*, *Alistipes onderdonkii*, *Roseburia* and *Lachnospiraceae*, which are involved in maintaining gut and inflammatory homeostasis might decline, leading to dysbiosis. A study conducted in SARS-CoV-2 individuals showed that *Bacteroides thetaiotaomicron*, *Bacteroides dorei*, *Bacteroides ovatus* and *Bacteroides massiliensis* were found to have a strong negative association with faecal viral load (Elsayed and Zhang, 2004) and they are all attributed to a decrease in ACE-2 expression in the colon (Yang *et al.*, 2020). There was a higher rate of increase in pathogenic organisms including *Actinomyces*, *Rothia*, *Sterptococcus*, and *Veillonllea* as well as a decrease in beneficial microflora in covid infected patients was reported (Gu *et al.*, 2020). Multiple bacterial flora that are beneficial to host immunity, such as *Faecalibacterium prausnitzii*, *Lachnospiraceae bacterium*, *Eubacterium rectale*, *Ruminococcus obeum* and *Dorea formicigenerans* showed a further decline in SARS-CoV-2 infected people (Zuo *et al.*, 2020a).

A study from Wuhan, China studied the association between dysbiosis and covid infection severity (Gou *et al.*, 2020). Elevated levels of proinflammatory bacterial strains, such as *Klebsiella*, *Streptococcus* and *Ruminococcus gnavus* were associated with the higher levels of proinflammatory cytokines and expanded disease

severity. These microbes had previously been discovered to be enriched in the proinflammatory intestinal tract of patients with diabetes, obesity, irritable bowel disease (IBD), and high blood pressure. Most of the inflammatory cytokines studied have a clear positive association with *Ruminococcus gnavus*. *R. gnavus*, in particular, produces a proinflammatory glucorhamnan polysaccharide that powerfully induces TNF (tumor necrosis factor) secretion by dendritic cells *via* Toll-like receptor 4 (Henke *et al.*, 2019). *R. gnavus* can also destroy mucin to be used as a carbon source (Png *et al.*, 2010; Bell *et al.*, 2019), causing the disintegration of mucus layer and its intestinal barrier function. A dysbiotic gut microbiome with high levels of *Streptococcus* and lower incidence of *Lactobacillus* species was identified in Kawasaki disease (Esposito *et al.*, 2019), a disorder similar to multisystem inflammatory syndrome in children (MIS-C) that is increasingly identified as a complication in young children diagnosed with COVID-19 (Jones *et al.*, 2020). As a result, changes in the gut microbiome caused by COVID-19 may play a role in this complication.

Han *et al.* (2020) looked into whether the SARS-CoV-2 infection has an effect on lung microflora, which could lead to COVID-19 complications. The findings suggest that SARS-CoV-2 infection has a significant impact on the lung microbiota. COVID-19 subjects had severe microbiota dysbiosis, with elevated levels of pathogenic bacteria like *Klebsiella oxytoca*, Lactic acid Bacteria, *Faecalibacterium prausnitzii* and Tobacco Mosaic Virus (TMV). In the lungs, a harmful inflammatory atmosphere was discovered, which was linked to *Rothia mucilaginosa* and SARS-CoV-2. This preliminary evidence suggests that the lung microbiota plays a role in the SARS-CoV-2 infection process and may help researchers better understand the virus prevention and complications.

A mice model study proved the modulation of gut microbiota or an induction of dysbiosis by ACE2 receptor from colon (Yang *et al.*, 2020). *Fusicatenibacter, Romboutsia, Intestinibacter, Actinomyces* and *Erysipelato clostridium* were also found to be a differentiating factor of symbionts or a biomarker between the COVID-19 community and the healthy individuals. A shotgun metagenomics analysis with baseline stool samples from COVID-19 patients revealed a reduction in *Faecalibacterium prausnitzii* species and altered host immune response (Geva-Zatorsky *et al.*, 2017). *Erysipelotrichaceae* bacterium, responsible for GI tract inflammation was found to be a strong hausser of SARS-CoV-2 infection in the host gut. Another metagenomic analysis of faecal samples from virus infected patients showed a significant variation in their microflora enriched with *Candida albicans, Candida auris, Aspergillus flavus* and a heterogenous mycobiota (Zuo *et al.*,2020a). Viral RNA metagenomic sequencing of faecal samples from SARS-CoV-2 patients showed the active viral load for 6 days even after the clearance of nasopharyngeal SARS-CoV-2 with high incidence of *Collinsella aerofaciens, Collinsella tanakaei, Streptococcus infantis* and *Morganella morganii* (Zuo *et al.*, 2020b). Another study suggested the impact of gut bacteria on colonic ACE2 expression and systemic inflammation in their hosts. Yang *et al.* (2020) found a reduction in colonic ACE2 expression, when gut microbiota is re-established in germ-free rats. Higher levels of tryptophan metabolites, kynurenic acid, and hydroxykynurenine, were discovered in serum metabolome research, implying that these metabolites are involved in ACE2 control. This suggested that the gut microbiota may influence intestinal ACE2 expression and contribute to dysbiosis in SARS-COV-2 infected host (Yang *et al.*, 2020).

3. Respiratory viruses and gut microbiome

Bradley *et al.* (2019) recently found that influenza virus highly influence the gut microbiota which is highly responsible for the viral infection of respiratory tract. Type 1 IFN-1 is target driven signal of gut microbiome and it fights against premature viral infections (Steed *et al.*, 2017). Influenza virus multiplies in the respiratory tract of COVID-19 patients, this viral infection was considered as a clinical spectrum (Pan *et al.*, 2020). Viral infection has changed the composition of gut microbiome with the help of type 1 IFN-I molecules. Remarkably, IFN-I molecules induced by influenza virus supports the reduction of anaerobic bacteria and improve the *Entero bacteriaceae* in the gut which inactivate viral mechanism (Pan *et al.*, 2016).

Proinflammatory gut microbiome modification has happened because of the influence of respiratory viruses like adenovirus. In adenovirus infection in lemur model, the count of essential healthy gut microbiome was very low whereas the count of genera contain pathogen like Nessieria genera was high (Wasimuddin *et al.*, 2019).

In these cases, gastrointestinal symptoms where seen to show the severity of COVID-19 infection (Li *et al.*, 2019). Dysbiotic gut microbial condition and epithelial swelling boosts the angiotensin-converting enzyme 2 (ACE2) level, which is the cell surface receptor molecule involved in the dietary amino acid homeostasis, innate immunity, and gut microbial ecology (Hashimoto *et al.*, 2012). Target of SARS-CoV-2 was ACE2 (Chan *et al.*, 2020), elevated level of ACE2 from patients were characterized by proinflammatory gut microbiome highly supports the coronavirus infections like SARS-CoV (Wang *et al.*, 2020). In that, SARS-CoV could spread throughout the human body (Zhou *et al.*, 2017). Researchers have identified viral RNA from the feces of many COVID-19 positive patients. With this, they identified development of infection in the gastrointesinal tract (Xiao *et al.*, 2020).

Digestive symptoms and respiratory symptoms of COVID-19 patients were compared for the confirmation and presence of viral load in the fecal sample (Han *et al.*, 2020). Extended digestive clinical spectrum like diarrhea is not connected with the composition and richness of gut microbiota. So, the modification of gut microbiota is directly related to immune dysfunction (Vandeputte *et al.*, 2016). This finding supports the redesigning the gut microbiota would be adjuvant therapy for those who are suffering from digestive symptoms associated with COVID-19.

The connection between patients's with unbalanced microbial composition and healthy individual microbial population was confirmed (Gou *et al.*, 2020). Higher level of *Lactobacilllus* species associated to increased proportion of anti-inflammatory interleukin-10 enhanced the disease prediction. High level of proinflammatory bacterial species like *Streptococcus, Klebsiella* and *Ruminococcus gnavus* correlated with the proinflammatory cytokines and enhanced the disease seriousness. The above mentioned organisms were enriched in gut microbiota of those who are suffering from diabetes, obesity, irritable bowel syndrome and high blood pressure.

Kawasaki disease is a one of the complication in children associated with COVID-19 (Jones *et al.*, 2020), is characterized by a dysbiotic gut environment including high count of *Streptococcus* and lesscount of *Lactobacillus* compared to healthy children (Esposito *et al.*, 2019). These studies show that COVID-19 stimulates the alteration in composition of gut microbiome mayroute to this barrier.

4. Disruption of the gut microbiome and COVID-19

SARS-CoV-2 enters the host *via* the angiotensin converting enzyme 2 (ACE2) receptor, which is strongly expressed in the respiratory and gastrointestinal tracts. Intestinal inflammation and gut microbial environment, both are regulated by ACE2 (Hill *et al*., 2020). The gut microbiome, which contains trillions of different bacteria, has a wide range of impacts on gene regulation, immune response, and metabolism. Invading viruses can manipulate the commensal microbiota environment in the gut to facilitate a stimulatory or suppressive response. Respiratory virus infections have been linked to changes in the gut microbiome, which may predispose patients to secondary bacterial infections, according to research (Mendes *et al*., 2019). Pathogens or oral and upper respiratory commensal bacteria dominated the microbiota in SARS-CoV-2 infected patients, according to recent meta-transcriptome sequencing of bronchoalveolar lavage fluid. Furthermore, changes in bacteria taxa from the phyla Bacteroidetes and Firmicutes, which have been shown to control ACE2 expression in rodents, have been linked to co-morbidities usually associated with extreme COVID-19. Understanding the host microbial disturbances that cause SARS-CoV-2 infection is critical because it could affect infection response and the effectiveness of potential immune interventions such as vaccines (Hagan *et al*., 2019).

Loss of beneficial species in COVID-19 persisted in the number of people despite SARS-CoV-2 virus clearance, indicating that SARS-CoV-2 infectionand/or hospitalization could be linked to a longer-term negative impact on the gut microbiome. Respiratory viral infections, such as influenza and respiratory syncytial virus (RSV), have been shown in studies to modify the gut microbiome (Zimmermann *et al*., 2019). Patients with viral infections are more likely to develop secondary bacterial infections, which have a more serious clinical path. *Clostridium hathewayi*, *Bacteroides nordii*, and *Actinomyces viscosus* was the opportunistic pathogens found in the gut microbiome of COVID-19 patients, and a higher baseline abundance of *Clostridium hathewayi* was linked to more extreme COVID-19. The majority of these bacteria are bacteraemia-associated bacteria, implying a risk of a serious disease path due to secondary viral infection (Matson *et al*., 2018). *Actinomyces viscosus*, an opportunistic pathogen of the oral cavity and upper respiratory tract, has been found in the guts of COVID-19 patients. Its existence indicates that extraintestinal microbes have passed through or been transmitted through the gut (Wei *et al*., 2018).

SARS-CoV-2 can bind to human ACE2 as a host entry point, according to a study published recently. ACE2 regulates amino acid transport, microbial ecology, and inflammation in the gut and is highly expressed in the intestine, especially in colonocytes of healthy subjects and patients with inflammatory bowel disease. Bacteroidetes species have been shown to suppress ACE2 expression in the murine colon, while Firmicutes species modulate ACE2 expression in a variety of ways (Doan *et al*., 2019). Bacteroidetes species *Alistipes onderdonkii* and *Bacteroides ovatus* had a negative association with COVID-19 intensity, and four species from the phylum Bacteroidetes (*Bacteroides dorei*, *Bacteroides thetaiotaomicron*, *Bacteroides massiliensis*, and *Bacteroides ovatus*) had an inverse correlation with SARS-CoV-2 fecal viral load. *Bacteroides dorei* is one of them, and it has been shown to suppress colonic ACE2 expression and calibrate the host immune response. Older patients and those with underlying chronic conditions associated with inflammation, such as hypertension, obesity, diabetes mellitus, and coronary artery disease, had the highest SARS-CoV-2 mortality and morbidity. Surprisingly, these individuals were found to have a lower abundance of Bacteroides species than healthy people. All of these results lead to the fact that a person's gut microbiome configuration influences their vulnerability and response to SARS-CoV-2 infections (Strathdee *et al*., 2020).

Increased interferon-inducible protein and other cytokines were included in the cytokine profile correlated with hyperinflammation in extreme COVID-19. Understanding host cytokine pathways and microbiota interactions with cytokine reactions in SARS-CoV-2 infection is critical in developing new therapeutic methods, given the lack of proven treatments for COVID-19 (Bradley *et al*., 2019). The use of empirical antibiotics (which was common during the initial SARS-CoV-2 outbreak when secondary bacterial infection was a challenge) resulted in further loss of beneficial symbionts and exacerbation of gut dysbiosis in COVID-19 patients, and our findings support the avoidance of unnecessary antibiotics in the treatment of viral pneumonitis, as antibiotics can eliminate beneficial bacteria and weaken the immune system. In addition, antibiotic-induced changes in the gut microbiome can affect human vaccine immunity. In order to combat COVID-19, it is necessary to consider improving the effectiveness of potential immune treatments such as vaccines by modulating the gut microbiome (Baud *et al*., 2020). One approach for promoting a healthy microbiome may include measures to enhance intestinal butyrate production through the promotion of microbial interactions by dietary changes, and reduction of pro-inflammatory states. These data highlight a new concept that novel and targeted approach of modulation of the gut microbiota may represent a therapeutic avenue for COVID-19 and its co-morbidities (McIlroy *et al*., 2020).

5. Microbiome as a barrier to virus infection

The micro-organism population has greatly evolved the human species over many millions of years. Because of the bacterial coevolution, eukaryotic cells could produce genomic functional complementarity with genetic disease (Zilber-Rosenberg and Rosenberg, 2008). Cells and microbes interact in environments that are based on fluctuating competitive and collaborative patterns in and between species. Cells receive and transmit chemical messages that modify expression of genes and cellular activities, transmit biomolecules and metabolites that strengthen the community's persistence and feasibility, and trigger defense mechanisms to regulate species contending for same important resources in order to sustain these balances (Caruana and Walper, 2020). RNA plays an essential role in biological processes, the link between both the genome and the proteome, among various molecules that could be used to communicate information.

Non-coding RNAs can be used by eukaryotic and prokaryotic cells to transmit signals *via* extra cellular cables to the target site, where they can be converted into a regulatory response by a detailed molecular apparatus (Leito *et al*., 2020). Bacterial non-coding RNAs control the expression of host genes, while eukaryotic miRNAs control the expression of bacterial genes (Duval *et al*., 2016). The replication of SARS-CoV-2 in a human host has been found to be hampered by host miRNA defensive lines (Hosseini and AD, 2020).

Epitranscriptomic alteration is another type of interaction with both commensal bacteria and their host. Difference in the gut microbiota is linked to N6-methyladenosine (m6A) alterations (Jabs *et al*., 2020). Sometimes, it is essential to allow a drastic change in order to com-

pletely interrupt the communication between pathogenic bacteria and the host in the pathophysiological process. It's no surprise, then, that faecal transplantation has become one of the most successful therapies in recent years (Aas *et al*., 2003; Polák *et al*., 2015). The composition of the microbiome can be modulated to be protected from viral infections, as demonstrated by the probiotic intervention (Yitbarek *et al*., 2018).

The higher the dose for healthy volunteers of influenza virus, the worse are the symbols of this virus (Memoli *et al*., 2015). The viral load alone does not, however, clearly forecast the outcome of the disease. Some asymptomatic patients were found to have similar viral loads as patients with COVID-19 symptoms (Lee *et al*., 2020). In patients with asymptomatic or very low forms of disease, T cell reactions played an important role. Unknowingly, these patients are often the major carriers of the disease (Budden *et al*., 2017). They demonstrated that in the absence of significant circulating antibodies, a large number of activated/cycling T-cells were functionally complete and specific for SARS-CoV-2 (Sekine *et al*., 2020). Variations in the intestines and in the lungs are associated with changes in the immune response and the development of the disease (Belkaid and Hand, 2014).

Interleukin IL-6 is one of the substances that is significantly elevated in patients with SARS-CoV-2 disease, particularly in those who do not survive. The removal of this pro-inflammatory interleukin could contribute to patient survival (Zhou *et al*., 2020).

He *et al*. (2020b) published an article that directly designates the intestinal microbiota as a potential strategy to fight SARS-CoV-2 infection. However, there is no clear scientific proof that can modulate the intestinal flora and has implications on the prevalence of COVID-19, we argue in the following section that targeting the intestinal microbiota could be a promising pharmacological choice or at the very least an adjuvant treatment of choice. A better and healthier microbiome could be one of the reasons for COVID-19 patients having a lower case fatality ratio. Obesity is one of the strong factors for COVID-19 infection, which has a more severe course (Dietz and Santos-Burgoa, 2020). In many cases, we can partially compensate for the lack of symbiotic organism diversity together with fermented foods in our diet, which contain essential probiotics for intestinal health.

6. Potential mechanisms underlying the role of the gut microbiome in COVID-19 infection

Coronaviruses are enveloped, single-stranded RNA viruses with a positive single-stranded RNA genome that can infect humans and animals. Coronaviruses and microbiota (particularly the microbiota of the lungs) have close interrelations and they are regulated by viral pathogens in terms of susceptibility to viral infections (Shen *et al*., 2020). SARS-CoV-2 infection, on the other hand, decreases the expression of ACE2 in the gut tract. As a result, the number of circulating angiogenic cells (CACs) decreases, endangering the endothelium and potentially leading to intestinal dysbiosis (Gheblawi *et al*., 2020). The lung microbiota can exacerbate infection by altering several factors, including local or systemic inflammatory response, host immune response, mucosal layer protection, and finally unleashing secondary bacterial infections (Shen *et al*., 2020; Gao *et al*., 2020).

The viral spike protein of SARS-CoV-2 binds to the cell surface receptor angiotensin converting enzyme 2 and infect the host system. When virus enters the host, the spike protein is cleaved by a type 2 transmembrane serine protease (TMPRSS2 - an enzyme found in the epithelial cells of the small intestine), which makes the fusion of spike protein into the cell membrane (Matsuyama *et al*., 2010; Hoffmann *et al*., 2020; Zhou *et al*., 2020a) and an additional furin protease enzyme could prime SARS-CoV-2 (Coutard *et al*., 2020). In enterocytes, the oesophagus, and the lungs, there was a plethora of co-expression of ACE2 and TMPRSS2. High expression of ACE2 and TMPRSS2 in epithelial cells makes the lung, the most susceptible target during coronavirus infection.

ACE2 is a negative regulator of renin-angiotensin-aldosterone system (RAAS) homeostasis, thereby has a key response towards pathology (Gheblawi *et al*., 2020). ACE2 is a coreceptor for uptake of nutrient and protein absorption in the intestine (Hashimoto *et al*., 2012). Infection with SARS-CoV-2 causes an inflammatory reaction in the intestine, as noticed by increased calprotectin (biomarker expressed by neutrophils) levels in the faeces (Effenberger *et al*., 2020) and also the virus entry marks several gastrointestinal disorders. Loss of RAAS homeostasis by ACE2 negatively impacts the inflammatory reactions. Loss of function of ACE2, modifies the B(0) AT1 amino acid transporter expression and thus reduces the tryptophan microbiota-derived metabolites. This causes an imbalance in the gut homeostasis (Hashimoto *et al*., 2012; Agus *et al*., 2018). Reduced expression of antimicrobial peptides and modified intestinal microbial components have been observed in ACE2 knockout mice, which can be restored by administering tryptophan (Hashimoto *et al*., 2012). Explicit cellular damage caused by viral replication and spread can also play a role in gut epithelial injury and inflammation.

Furthermore, in humans, disturbance of the ACE/ACE2 network during pulmonary hypertension (loss of ACE2) is linked to changes in the gut microbiota (Santisteban *et al*., 2016; Kim *et al*., 2020). Reduced availability of ACE2 during SARS-COV-2 infection could be enough to understand its effect on change in gut microbiota's composition, but the effect of SARS-CoV-2 on the metabolic activity of the gut microbiota is also unexplained. Mouse model study involving impaired gut microbiota related with ACE2 deficiency endorses inflammatory responses and imparts susceptibility to colitis, when transmitted to wild-type organisms (Hashimoto *et al*., 2012). In patients with pre-existing coronary heart disease and other risk factors, a RAAS-ACE2 deficit in COVID-19 can worsen tissue inflammation and lead to more negative COVID-19 outcomes.

Gut microbiota can favour byboosting the immune system, however, dysbiosis can lead to several health ailments. The results of experiments with antibiotic treatment (to deplete the residual microbiota) in the setting of influenza infections have shown that the gut microbiota is critical for regulating viral replication (Ichinohe *et al*., 2011; Abt *et al*., 2012; Steed *et al*., 2017; Bradley *et al*., 2019). The development of type I interferons and inflammasome-dependent cytokines by pulmonary cells is favoured by bacterial cell wall components and bacterial metabolites (such as desaminotyrosine). Additionally, the gut microbiota improves CD8 + T cell effector activity, which aids in viral clearance (Ichinohe *et al*., 2011). But treatment with antibiotics makes the infection worse and it can be overcome by using dietary supplements (Trompette *et al*., 2018). Gut dysfunction-related complications are common in patients with respiratory infections, and they exacerbate the clinical path. Evidence indicates that SARS-CoV-2 infection disrupts the gut-blood barrier, allowing bacteria, endotoxins, and microbial metabolites to spread

across the body (Wang *et al.*, 2020; Huang *et al.*, 2020; Guan *et al.*, 2020). This could impact the host's initial response to SARS-CoV-2 outbreak, leading to multisystem dysfunction, septic shock, and the systemic cytokine storm that occurs in the second phase of SARS-CoV-2 infection, which probably results in death (Guan *et al.*, 2020; Huang *et al.*, 2020; Wang *et al.*, 2020c).

Murine model has shown that the gut microbiota regulates colonic ACE-2 receptors (Yang *et al.*, 2020) and suggesting that it may have a key role in the infectivity as well as the severity of SARS-CoV-2. Various mechanisms of entry have been proposed when considering particular sites of ACE-2 expression inside the intestinal lumen. It has been shown that the ACE-2 receptor in the duodenum increases with age, implying a possible entry mechanism *via* microbiome interactions (Vuille-dit-Bille *et al.*, 2020). Single-cell transcriptomic study showed a strong expression of ACE2 in oesophageal upper and stratified epithelium and also in enterocytes from the ileum and the colon (Zhang *et al.*, 2020). It was only recently discovered that the gut microbiota plays a part in the extent of viral respiratory tract infections, including those caused by the influenza virus (Bradley *et al.*, 2019). Stromal cells in human lung have been identified as the target of microbiota-driven type 1 interferon (IFN-1) signals, that sets up the defence reaction against early viral load (Steed *et al.*, 2017). Gastrointestinal (GI) symptoms as noted for virus infected patients may be resulted from altered gut microflora composition through IFN-1 mechanism. Noticeably, infection stimulated IFN-1 causes reduction in anaerobic bacteria and enrich the *Entero bacteriaceae* in the gut environment, resulting to proinflammatory dysbiosis condition (Deriu *et al.*, 2016) and, thus prompting the severity of infection. Adenovirus respiratory infection in a lemur model showed a decrease in abundance of many commensal flora important for a healthy gut microbiome, whereas genera of infectious agents, such as *Neisseria*, increased (Wasimuddin *et al.*, 2019).

Antigenic presentation to naive T cells by dendritic cells and antigens derived from commensal species facilitate Treg (regulatory T-cell) cell differentiation, triggering the secretion of anti-inflammatory cytokines (*e.g.*, IL-10) and reinforcing immune responses (Barko *et al.*, 2018; Kamada *et al.*, 2013). Pathogenic bacteria, on the other hand, can elicit pro-inflammatory immune responses; as naive T cells differentiate into Th1 and Th17 cells. In such circumstances, increased bacterial component translocation across the gut epithelium can occur, resulting in gut epithelial damage and, eventually, disruption of the gut–blood barrier and systemic endotoxemia. These altogether compromises the immune function and an interconnection between dysbiosis, immune cells imbalance and mucosal and systemic inflammation was noticed in Covid-19 patients (Weiss and Henne, 2017).

The gut microbiota was shown to influence lung health through interactions between the gut and the lungs, a phenomenon known as the "gut lung axis" (Pan *et al.*, 2020). Immune cells or the gut microbiota and its metabolites are primarily responsible for possible interactions between cells during the gut-lung axis. Antigen presenting cells phagocytose microbiota and their products that reach the intestinal mucosa, allowing them to be transported to the mesenteric lymph nodes, where they may activate B and T cells and these activated cells return to its own site of intestinal mucosa or to another site, for instant, lungs. The second underlying strategy involves transfer of flow of residual bacteria or bacterial products to the lungs through the bloodstream or lymphatic system, resulting in a local or general immunological response that causes further lung damage (Bingula *et al.*, 2017). A study involving mice with lack of gut microbiota showed a lower microbial clearance in the lungs (Fagundes *et al.*, 2012) and the intratracheal lipopolysaccharide (LPS) dosage was found to impair the lung microbiota, which could contribute to disturbance of the intestinal microbiota and an increase in microbial load (Sze *et al.*, 2014). Transition experimental studies with dysbiotic microbiota (Sencio *et al.*, 2020) showed that infections, inflammation, and metabolic disorders can induce dysbiosis, which can alter disease outcomes in distant organs such as the respiratory tract, forming a negative feedback loop.Viral proteins, which vary in structure and fold, can interact with bacterial surfaces such as lipopolysaccharides and peptidoglycans. Microflora has an effect on virus biology both directly and indirectly, and eukaryotic viruses can manipulate bacterial biology (Neu and Mainou, 2020). Surfactin is a cyclic lipopeptide (CLP) that was reported to inhibit CoV like enveloped viruses (Johnson *et al.*, 2019). Figure 2 shows the potential role of SARS-CoV-2 in gut-lung axis dysfunction.

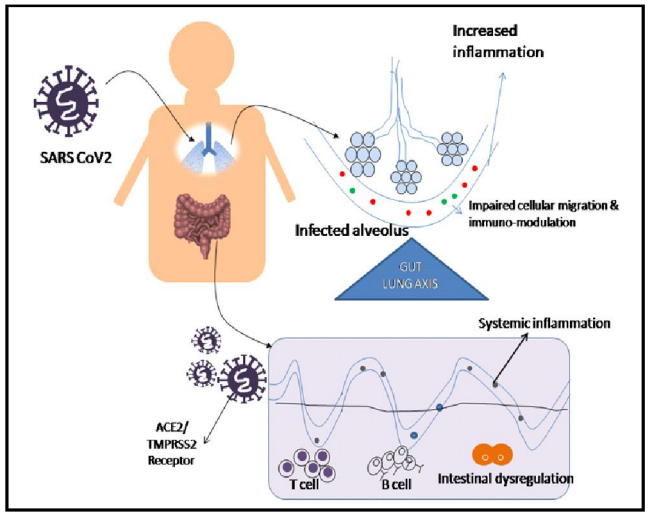

Figure 2: Potential role of SARS-CoV-2 in gut-lung axis dysfunction.

Acute respiratory distress syndrome and pneumonia are two of the most common symptoms of COVID-19. Shen *et al.* (2020) examined the differences in the composition of the lung microflora in SARS-CoV-2-infected patients and showed that the bronchoalveolar lavage fluid (BALF) had varied microbial composition when compared to healthy individual (Shen *et al.*, 2020). Interestingly, a subsection of the core species is associated with the serum levels of proinflammatory cytokines, such as TNF-α, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13.

Furthermore, the risk factors like obesity, high blood pressure, diabetes, age-related and auto-immune disease conditions increases the severity in virus affected patients with disturbances in the gut microbiota, but however, the role of dysbiosis in intestine is need to be elucidated (Badawi *et al.*, 2018; Honce and Schultz-Cherry, 2019). Angiotensin-converting enzyme 2(ACE2), a cell surface receptor involved in dietary amino acid homeostasis, innate immunity, and gut microbial ecology, is increased by a dysbiotic gut environment and epithelial proinflammation; thereby an increased ACE2 creates a potential site for SARS-CoV-2 infection (Wang *et al.*, 2020), from where it can invade to other parts of the body (Zhou *et al.*, 2017).

Many COVID-19 patients, including those who tested negative by PCR with their respiratory secretions, developed GI infections and had viral RNA detected in their faeces (Xiao *et al.*, 2020). Long-term digestive health issues, especially diarrhoea, are accompanied by changes in gut microbiota composition and diversity (Vandeputte *et al.*, 2016), which are related to immune dysfunction and may explain the late clearance of viral load. This suggests that reforming the gut microbiota could be used as an adjuvant treatment in patients with COVID-19 related digestive symptoms.

In terms of intestinal permeability, a leaky gut exports its microbiota to the lungs, causing pulmonary microbiota to shift. This causes leakage of lipopolysaccharide (LPS) into the circulating system and, thus aggravates the severity of infection by inducing the viral replication and transmission (Robinson and Pfeifer, 2014). This could result in the release of immunosuppressive cytokines, which reduces the immunoregulatory effects of regulatory T cells and dendritic cells. Both of these modifications cause the virus to evade immune responses and promote viral infection (Anderson, 2020). Some studies reported the activation of NF-κB signalling by flagellin (microbiota particle that act as damage-associated molecular patterns) toll-like receptor 5 (TLR5) promotes lentiviral pseudovirus binding on lung epithelial cells and that may implicate SARS-CoV-2 infection and lead to harmful inflammatory responses (Golonka *et al.*, 2020).

The human intestine contains a remarkable mechanism for immune system development. Intestinal homeostasis is accomplished by the interaction and synchronisation of innate and adaptive immunity in the gut, which has a mutually beneficial relationship. Antigen-presenting cells, such as dendritic cells in the Peyer's patches of the intestine, Langerhans cells, and macrophages, play a role in the regulation of innate immunity through the gut microbiota (Smythies *et al.*, 2005). These cells have certain immune-tolerance properties against the gut microbiome, similar to that of inflammation anergy by macrophages (Sanos *et al.*, 2009). Mast cells and natural killer cells are two other cells in the innate system that communicate with the gut microbes. The mouse gut microbiota study was found to be critical in expanding the development of IL-22-producing NKp46 cells (Ivanov *et al.*, 2009). Mainly B and T lymphocytes are involved in interaction of gut microbiota and B cells attributed to the gut are typically located in the peyer's patches (Mazmanian *et al.*, 2005). T cells are also essential in the adaptive system and its differentially regulatory T-cells maintain the immune homeostasis of gut lung axis which establishes the anti-inflammatory response (Dhar and Mohanty, 2020). Several microbial metabolites involved in the immune responses, such as *Bacteroides fragilis* and *Clostridia* have an impact on cytokine production in the gut, whereby microbiome impairs the interferon signalling and increases the threshold of chronic state protein. According to one theory, COVID-19's interaction with the microbiome can influence cytokine development, possibly leading to an overproduction of pro-inflammatory cytokines like IFNc, MCP-1, IP10, and IL1B (Nagano *et al.*, 2012; Rooks *et al.*, 2016), as a result, there's a high probability that COVID-19 can bind with gut microbes, resulting in increased immune cell induction.

Elevated serum levels of lipocalin-2, also regarded as neutrophil gelatinase-associated lipocalin, which is involved in innate immunity, and a greater proportion of CD11b+ granulocytes were also associated with conventionalization. This research suggests that the gut flora may influence intestinal ACE2 expression and contribute to covid immune dysregulation (Yang *et al.*, 2020). The rise in a blood proteomic risk score (PRS) was linked to a higher risk of developing a clinically serious infection in COVID-19 patients. The C-reactive protein (CRP) are exacerbated during systemic inflammation. The magnitude of COVID-19 can be interconnected to the relationship between PRS and the intestinal microbiome (Gou *et al.*, 2020).

ACE2 deprivation is probably a crucial factor for the negative outcomes in COVID-19 patients with pre-existing comorbidities, and it explores a potential correlation between gut microbiota dysbiosis and the disease conditions. To summarise, the gut microbiota plays a prominent role in host immunity, and SARS-CoV-2 can interfere with the gut microbiota and infect enterocytes, causing gastrointestinal symptoms.

7. Gut microbiome, immunity and COVID-19

Coronavirus has infected millions of people and caused many deaths worldwide. The primary site of infection is an airway epithelium where ACE2 receptors, which are necessary for SARS-CoV-2 infection, are in abundance (Fadai *et al.*, 2021). ACE2 receptors are also present in multiple organs including gastrointestinal tracts. ACE2 deficiency causes the modulation of composition of intestinal bacterial population and affects immune system (Chhibber-Goel *et al.*, 2021). Early reports had shown that 2%-10% of COVID-19 patients had gastrointestinal symptoms including diarrhea, but a recent report suggests that about 20% of the COVID-19 patients has gastrointestinal symptoms. Also, faecal calprotectin, which is responsible for the indication of inflammatory response in gut, was found to be increased in the COVID-19 patients with diarrhea. These evidences indicate that the digestive tract might be an extra pulmonary site for corona-virus infection (Zuo *et al.*, 2021). During COVID-19 infection, the pro-inflammatory cytokines IFN, TNF-α, IL-6 and IL-10 are raised in critical patients. This is termed as 'cytokine storm'. It is notable that some of those cytokines are often correlated with the gut bacterial population. The immune system tries to respond to cytokine storm but affects itself which leads to further multiorgan failure (Morais *et al., 2020*; Yazdanpanah *et al.*, 2020). It is also noteworthy that the data from China shows that there is no death of children under age 9 because of COVID-19 cytokine storm, even though children have immature immune system. This shows that cytokine storm will not trigger the immature immune system. However, infants can be severely affected by COVID-19 (Yu, 2021).

The immune system protects the body by employing various mechanisms against invading pathogens. They exhibit three types of immunity. Innate immunity, adaptive immunity and passive immunity. There are two types in passive immunity: natural immunity, which is received from maternal side (breast milk) and artificial immunity, which is received through medicines (Chaplin, 2010; Chowdhury *et al.*, 2020). When a pathogenic microorganism enters a human body, it must get close to the cells to develop infection. The mucous membrane and skin makes this interaction difficult by providing innate immunity (Nicholson, 2016). Adaptive immunity is based on the antigen specific receptor which is expressed on the surface of B lymphocytes and T lymphocytes (Chaplin, 2010). Immune system keeps the body healthy by providing a fine balance between the eradication of invading pathogen and the maintenance of normal healthy tissues. Gut microbial community play a pivotal role in regulating immune system (Wu and Wu, 2012). The human gut microbiota consists of 10^{14} microbes including bacteria, virus, fungi and archae, these microorganisms get nourishment from the

host and in turn regulates the various physiological functions of the host which includes imparting protective immunity against pathogens (Dhar and Mohanty, 2020).

COVID-19 infection affects both the immune system directly and indirectly on (Yazdanpanah *et al.*, 2020). Due to COVID-19 infection around the world, people are experiencing stress and fear about the future consequences of COVID-19. Social distancing is one of the effective methods to prevent the spread of this infection. But, social distancing decreases the access to family and friends which leads to mental stress, anxiety and depression. This indirectly influences on the immune system (Morais *et al.*, 2020). Intestinal microbial population is involved in host metabolism and nutrient absorption and it has a major role in human health. Several studies indicate that intestinal microflora was closely associated with respiratory virus diseases as it occurs through gut-lug axis and it leads to lung damage (Gu *et al*., 2020). It is observed that gut microbiome composition of COVID-19 patients has altered significantly comparing with healthy individuals even after receiving medications (Yeoh *et al*., 2021). COVID-19 also causes in depletion of beneficial commensals such as *Faecalibacterium prausnitzii* (anti-inflammatory bacterium), *Bacteroides dorei*, *Bacteroides massiliensis* and *Eubacterium ventriosum* which correlate with disease severity and down regulates the ACE2 receptors (Morais *et al.*, 2020; Villapol, 2020). A study shows that the significant decrease in the *Lachnospiraceae* family (*Anaerostipes, Fusicatenibacter, E.hallii* and *Agathobacter*) COVID 19 patients comparing with healthy individuals (Gu *et al*., 2020). Another study conducted with 10 COVID-19 hospitalized patients shows that there are 14 species of gut bacteria are associated with fecal SARS-CoV-2 load across all fecal samples (Villapol, 2020).

Probiotics can help to maintain the gut microbiome by restoring the beneficial microbes and strengthen the immune system against pathogens. Researchers around the world have shown that microorganisms which are having the ability to modulate the immune response could be used to treat the viral and bacterial respiratory infections. The most commonly used probiotic microorganisms are *Lactobacillus* and *Bifidobacterium*. Some studies have shown that COVID-19 patients have lower level of *Lactobacillus* and *Bifidobacterium* bacterias.These bacterias can be used as probiotics in COVID-19 infection. Probiotic microorganisms are mostly from the gut and can be consumed as isolated form or incorporated in food. *Lactobacillus gasser*i can be used as probiotic against respiratory viral infection. So, it could possibly use in COVID-19 infection (Morais *et al*., 2020).

8. Gut microbiome, diet and COVID- 19

The gut microbiome of healthy adult harbor more than 1000 species of bacteria belonging to few known bacterial phyla (*Bacteroidetes* and *Firmicutes* are being the dominant phyla) (Shreiner *et al*., 2015). COVID-19 can interact with one or more of those 1000 species of gut microbiota (Kalantar-Zadeh *et al*., 2020). The gut microbiome forms a dynamic environment which can be controlled by dietary habits and probiotic treatments. The amount of food consumed has been reported to shape the microbiome. Several studies shows that proper diet gives an optimal immune response against pathogens including COVID-19 (Hullar and Fu, 2014; Villapol, 2020). The dietary patterns are associated with the differences in the distribution of bacteria and this influences host exposure to microbial metabolites. Dietary intervention studies shows that gut microbiome responses hastily to changes in diet. These changes are often transient (Hullar and Fu, 2014). Besides dietary habits, the gut microbiota is shaped by a combination of extrinsic and intrinsic factors such as medication, lifestyle and host, genetic, metabolic and immune regulations (Leeming *et al*., 2019). Carbohydrates play a vital role in influencing the gut microbiome (Avila-Nava *et al.*, 2017). It is a known fact that the modern Western diet which contains processed, canned and frozen foods has less fiber content comparing with the diet consumed by developing countries like India. It has also observed that the Western diet tends to increase in the abundance of bacteria belonging to *Firmicutes* phylum with the simultaneous drastic decrease in the bacteria of *Bacteroidetes* phylum (Senghor *et al.*, 2018). Protein intake is essential for the production of antibodies (Villapol, 2020).

Children in Africa are reported to have high *Bacteroidetes* population and low *Firmicutes* population in the gut as their diet include high-fiber content. It was also observed that increased short chain fatty acids (SCFA) in their feces when compared to the children of European origin. SCFAs are important in immunoregulation and it alleviates type 2 diabetes mellitus (De Filippo *et al*., 2017; Rishi *et al.*, 2020; Yu, 2021). Plant-based high fiber diet was found to elevate the *Bifidobacterium* and reduces the *Firmicutes* to *Bacteroidetes* ratio (Avila-Nava *et al*., 2017). A study observed in India shows that *Prevotella* are the dominant species in the gut of North-central Indians whose diet mostly contains carbohydrate rich plant-based food. Whereas, it has been observed that *Fecalibacteria, Ruminococci* and *Bacteroidetes* species of bacteria are dominant in the gut of South Indians who majorly consume omnivorous diet (Dhakan *et al.*, 2019). During COVID-19 pandemic till 31st May 2020 in India, it was observed that the fatality rate in India was the lowest in comparison with the Western countries. It may be inferred that plant-based, fiber rich, home cooked diet during lockdown in India might increase the population of symbiotic microflora, which is resulted in eliciting anti-inflammatory responses and production of SCFAs (Rishi *et al.*, 2020).

Hairy morphology of the intestine can be maintained by branched-chain amino acids and these amino acids help to increase intestinal immunoglobulin levels which improves intestinal barrier. High protein intake improves anti-inflammatory property. Omega 3 fatty acids are the excellent source of anti-inflammatory and antioxidant capacity (Villapol, 2020). The dietary intake of iron, zinc and selenium promotes immunity to fight against COVID-19 (Rishi *et al.*,2020). Food sources of fiber (example: whole grains) are suggested to have a prebiotic-like effect on the gut microbiome. Along with fiber, the dietary intake of polyphenols, magnesium, vitamin C, vitamin D and vitamin E exert a beneficial effect on microbiota composition. Polyphenols are found higher levels in foods such as vegetables, cereals, tea, coffee and wine (Leeming *et al*., 2019). Foods such as dark chocolate, whole greens, black beans and avocados are some of the good dietary sources of magnesium. soaked almonds, sunflower seeds, hazel nuts and peanut butter are the major sources of vitamin E. vitamin C rich foods include lemon, spinach and broccoli. Egg and fish are some sources of Vitamin D (Arshad *et al.*, 2020; Rishi *et al.*, 2020).

9. The gut microbiome and suggested treatments for COVID-19 infection

Parallel to attempts to understand the pathogenesis of COVID-19 disease, the pandemic has caused an unprecedented number of

investigational treatment trials to be developed and initiated. Over 3800 clinical trials targeting COVID-19 have been reported around the world as of October 2020. The gut microbiome has been shown to modulate a broad variety of therapeutic compounds used in clinical practice, including antivirals, antihypertensives, and antidiabetic drugs, and baseline gut microbiome profiles can predict cancer therapy responses. It is clear that inter-individual variation in gut microbiome will affect the effectiveness of COVID-19 treatments (Zhang *et al*., 2020). To combat COVID-19, a variety of drugs are being tested, with some showing signs of interaction with the gut microbiome. Azithromycin, a macrolide antibiotic, is being studied extensively as a COVID-19 treatment, primarily in conjunction with hydroxychloroquine. The action of azithromycin on gut bacteria is well known, therefore, it is used to treat Campylobacter disease in many regions of the world. A 3-day course of azithromycin (10 mg/ kg) was shown to reduce alpha diversity of the gut microbiota in a blinded, randomized, placebo-controlled study in young children, with loss of the genus bifidobacterium at 14 days (Vikse and Henry, 2020).

Furthermore, functional study of the metagenomes of African children treated with azithromycin revealed that metabolic pathways involved in immune function and inflammation were under represented (Strangfeld *et al*., 2017). Antibiotic use has been common in COVID-19 patients, and there is increasing concern that antimicrobial resistance could improve. Antibiotic use prior to viral exposure has also been shown to predispose people to more serious respiratory infections. Animals given antibiotics had an abrogated interferon signature in the lung stroma, allowing early virus replication in the epithelia in a mouse model of influenza infection. Interestingly, faecal transplant following antibiotics recovered the interferon signature, indicating that the gut microbiome plays a significant role in deciding the integrity of barrier defenses against disease at sites distant to the GI tract (Barbara *et al*.,2017). If repeated in humans, this model may be appropriate to other viruses which enter through the respiratory epithelium, including SARS-CoV-2. As a result, a proposal has been made for intervention studies involving gut microbiota manipulation, such as probiotics and faecal transplant– with the goal of preventing or limiting the clinical extent of COVID-19 infection. Tocilizumab, a monoclonal anti-IL6 antibody, is the subject of several studies aimed at reducing the hyperinflammatory cytokine release storm seen in some COVID-19 patients (Hu *et al*., 2020). Concern was raised in some areas that tocilizumab, a drug to treat rheumatological conditions like rheumatoid arthritis, is proven to cause small gastrointestinal perforation (2-3 per 1000 patients). While patients with diverticular disease are thought to be at increased risk, the mechanism is unidentified. The existence of diverticular disease, regardless of effects, is linked to a microbial imbalance. It is important to note that IL-6-deficient mice have such a thinning mucus gel layer and a compromised gut-epithelial barrier. Bacteroidales bacteria promote intra-epithelial lymphocytes in the colon that generate IL-6, increasing the likelihood that the gut microbiota's composition or role is involved in the aetiology of tocilizumab-related perforation (Musa, 2020).

Eventually, there is clearly a massive clinical research need for such a vaccine against COVID-19, and a number of trials are currently in progress globally. Immune responses to vaccine management against viral and other pathogens are well known to vary significantly between patients; this variability may reflect the interaction of a variety of factors, including the compositionand/or functionality of the gut microbiome (Guan *et al*., 2020). Although, there is a lot of evidence from animal research that suggests immune response heterogeneity to vaccines, potential human data shows that antibiotic-mediated gut microbiome disturbance impairs the immune reaction to influenza vaccination in patients who have low pre-existing anti-influenza antibody titres. As a result, when recruiting participants for COVID-19 vaccine studies, recent use of antibiotics (or other factors that may disturb the gut microbiome) may be important to consider (Jin *et al*., 2020).

10. Conclusion

The diversity of the gut microbiota and the existence of beneficial microorganisms in the gut can play a key role in the progression of this disease.The gut microbiome is essential for human health and disease, and it may be important in the interaction between COVID-19 infection and the host. Microbiome research may aid our understanding of the pandemic and provide insight into prevention and treatment options. The long-term effects of COVID-19 infection on a number of organs are unclear at this time, although there is the possibility of long-term effects. The gut microbiota can affect immune response and, therefore disease progression. In COVID-19, both an overactive and underactive immune response, likely linked to gut microbiota status, may result in severe clinical complications. The unhealthiness of microbiota may then be a still-underappreciated risk factor. Since sufficient, effective, and inexpensive prebiotics and probiotics may help microbiota, their use should be regarded as an adjunctive treatment to reduce COVID-19 progression in infected individuals, or as a prevention measure for non-infected people at risk during COVID-19 spread. As we understand more about virus, it will be vital to understand the pandemic's impact on the gut microbiota, as well as the possible long-term consequences.

Conflict of interest

The authors declare that there are no conflicts of interest relevant to this article.

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