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Abdul Bari Hejran
(1) Department of Biology, Faculty of Education, Helmand University, Helmand, Afghanistan
(2) Department of Biotechnology, faculty of Biology and Biotechnology, Al-Farabi Kazakh National University, Almaty 050040, Kazakhstan

Atiqullah Sarwari
(1) Department of Biology, Faculty of Education, Helmand University, Helmand, Afghanistan
(2) Department of Biotechnology, faculty of Biology and Biotechnology, Al-Farabi Kazakh National University, Almaty 050040, Kazakhstan

Abdul Wahid Monib
(1) Department of Biology, Faculty of Education, Kandahar University, Kandahar, Afghanistan
(2) School of Environmental Sciences, Jawaharlal Nehru University, New Delhi, India

Mohammad Hassan Hassand
(1) Department of Biology, Faculty of Education, Kandahar University, Kandahar, Afghanistan
(2) Department of Biotechnology, faculty of Biology and Biotechnology, Al-Farabi Kazakh National University, Almaty 050040, Kazakhstan

Abdul Qadeer Baseer
Department of Biology, Faculty of Education, Kandahar University, Kandahar, Afghanistan

Sayedwali Sediqi
Department of Biology, Faculty of Education, Urozgan Institute of Higher Education, Urozgan, Afghanistan

Uzair Mohammad Kakar
(1) Department of Chemistry, Faculty of Education, Logar University, Logar, Afghanistan
(2) Department of Chemical-Physics and Material Sciences, Faculty of Chemistry and Chemical Technology, Al-Farabi Kazakh National University, Almaty 050040, Kazakhstan

Mustafa Rahime
(1) Department of Physics, Faculty of Education, Ghazni University, Ghazni, Afghanistan
(2) Faculty of Physics and Technology, Al-Farabi Kazakh National University, Almaty 050038, Kazakhstan

Parwiz Niazi
(1) Department of Biology, Faculty of Education, Kandahar University, Kandahar, Afghanistan
(2) Department of Plant Protection, Faculty of Agriculture, EGE University, Bornova, İzmir, Turkey

Corresponding Author:
Abdul Bari Hejran
(1) Department of Biology, Faculty of Education, Helmand University, Helmand, Afghanistan
(2) Department of Biotechnology, faculty of Biology and Biotechnology, Al-Farabi Kazakh National University, Almaty 050040, Kazakhstan

The influence of coronaviruses on the human gut microflora

Abdul Bari Hejran, Atiqullah Sarwari, Abdul Wahid Monib, Mohammad Hassan Hassand, Abdul Qadeer Baseer, Sayedwali Sediqi, Uzair Mohammad Kakar, Mustafa Rahime and Parwiz Niazi

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Abstract
The influence of coronaviruses on the human gut microflora is a topic of emerging interest within the scientific community. Coronaviruses, particularly those like SARS-CoV-2, which causes COVID-19, are primarily known for respiratory symptoms but have broader impacts on human health. Recent research suggests that coronaviruses can affect the gut microflora, the diverse community of microorganisms inhabiting the gastrointestinal tract, which plays a crucial role in human health and disease. Studies indicate that coronaviruses may disrupt the gut microflora directly or indirectly. Direct effects could occur through viral invasion of intestinal cells expressing the ACE2 receptor, which is the cellular entry point for coronaviruses. Indirect effects may arise due to systemic inflammation triggered by the viral infection, affecting gut microbial composition and function. Dysbiosis, an imbalance in gut microbial communities, has been observed in COVID-19 patients, indicating potential coronavirus-mediated alterations. Understanding these interactions is vital because the gut microflora influences immune responses, nutrient metabolism, and overall well-being. Altered microbial profiles due to coronavirus infections might contribute to the prolonged gastrointestinal symptoms reported in COVID-19 patients. Moreover, changes in gut microflora composition could impact the efficacy of therapies and vaccines, given the role of the microflora in modulating immune system function. Future research should explore the mechanisms underlying coronavirus-mediated alterations in gut microflora and their implications for health outcomes. This includes investigating how viral infections influence specific microbial species and their metabolic activities. Longitudinal studies are needed to assess whether these changes persist beyond the acute phase of infection and how they correlate with clinical outcomes. In summary, coronaviruses can exert significant influences on the human gut microflora, potentially disrupting microbial communities and functions essential for health. This understanding could inform therapeutic strategies targeting gut microflora to improve outcomes in coronavirus-infected individuals and enhance our broader understanding of host-microflora interactions in infectious diseases.

Keywords: Coronaviruses**,** gut microflora**,** ACE2 receptor, FMT, gastrointestinal symptoms**,** cytokine response

Introduction
The human gastrointestinal tract contains a complex community of commensal bacteria called the gut microbiota, with 1000–1500 species. The gut microbiota provides us with benefits which include amplifying the antibiotics properties, sustaining the health of the gut and working on digesting abnormal compounds. Dysbiosis which is descried as a microbial imbalance is found to be the root cause of infections and inflammatory diseases. Although digestion is not a primary mode of transmission in COVID-19, gastrointestinal symptoms like nausea, vomiting, diarrhea, and abdominal pain may be triggered by the virus [27]. The director of the World Health Organization announced COVID-19 as a global disaster right in the year 2020, and at the moment has a death toll record of 309,848 and affected 22,812,491 people. Symptoms of most importance, although not universal, are fever, cough, dyspnea, myalgia, fatigue, and sputum production [14]. The so-called microbiome, which is a community of trillions of cells, is heavily involved in functions such as development, injury repair, metabolism and the maintenance of systems like the immune, endocrine and nervous systems.

The COVID-19 virus has given rise to questions in regard to the effect of the changes in behavior and lifestyle on human microbiome, everybody assumption such events as the depletion of microbial diversity is presumably highly likely because of strict hygiene and social distancing practices [16]. The COVID-19 pandemic highlights immune responses and gut dysregulation, requiring investigation for novel treatment approaches. Gut microbiota disruption disrupts immune balance, highlighting the need for understanding immunopathology [37]. In Wuhan, China, COVID-19 outbreaks have been linked to the Omicron strain, with type 2 diabetes and gut dysbiosis contributing to higher mortality rates. Culture-based methods are cost-effective and suitable for low-income countries [25]. COVID-19, caused by SARS-CoV-2, has caused widespread health and economic damage, with over 175 million infected and 3.7 million dead. Symptoms include cough, fever, dyspnea, and a sore throat [21]. The COVID-19 pandemic has caused millions of deaths worldwide, with the US, Brazil, and India leading the way. Improving the intestinal microbiota could mitigate its impact on elderly and immunodeficient patients [36]. The COVID-19 pandemic persists due to emerging variants, with Omicron spreading globally, causing similar symptoms in younger populations, and limited gut microbiota composition in pediatric COVID-19 patients [38]. Microbiome-related measurements have the potential to identify patients at risk of infectious complications during chemotherapy in adult AML patients. Microbiome-related measurements have the potential to identify patients at risk of infectious complications during chemotherapy in adult AML patients [9]. Individuals with underlying diseases, particularly those living with HIV, are at higher risk for severe COVID-19 infection. Age, comorbidities, and a lack of viral control contribute to poor clinical outcomes [12]. SARS-CoV-2 infection, particularly in elderly and weakened immunes, may involve auxiliary proteins and the human microbiota, but its impact is controversial, necessitating further investigation [48]. Due to the virus SARS-CoV-2, the RNA one that is causing COVID-19, terribly disrupted the virome of human gut, the intestinal microbiome that is highly abundant in the human body compared to the rest. The digestive microbiome of the patients suffering from COVID-19 has significantly declined and lies in a direct correlation between disease progression and its symptoms. Researchers engineered RNA and DNA metagenomics to sense viral members in fecal samples and benchmarked the progressive diseases immune phenotypes [49].

The existence of fast-spreading novel coronavirus may become persistent, eventually infecting and affecting the gastrointestinal tract through the gut microbiota which regulates the immune system of the host and supports nutrients metabolism [45]. SARS-CoV-2 infection may influence gut microbiome, the effect of microbiome on immune function, and association of microbiome with the severity and the outcomes of COVID-19 [30]. In COVID-19 cases, gut microbiota analysis illustrates reduced diversity and possible overpopulated, prone-to-infections bacterial strains, a factor of scrutiny when it comes to understanding the factors related to the severity of the disease [42]. Gut dysbiosis from SARS-CoV-2 infection drives disease progression through bioactive metabolites, metabolism alterations, inflammation, and adaptive immunity modulation, affecting the susceptibility and severity of COVID-19 [37]. The bats' gut microbiota and SARS-CoV-2 interaction may help identify therapeutic targets for human infections, potentially addressing the public health emergency caused by bats' flight-induced immune suppression [20]. SARS-CoV-2 causes ARDS and SIRS, affecting the respiratory tract. The gut-lung microbiota's association with COVID-19 pathogenesis is crucial for effective diagnostics and management strategies [18, 6, 47, 1, 7]. The metagenome of gut microbiota has been used in the context of COPVID-19 a result of which its role in regulation of immune system has been unveiled, thereby the microbiota can become a useful diagnostic or prognostic biomarker in COPVID-19 patients [8]. A study on GM in children who have had the COVID-19 infection revealed a microbial disparity as compared to either a-diversity or b-diversity The GM profile of children with COVID-19 was characterized by the presence of Faecalibacterium, Fusobacterium, and Neisseria, and reduction in the level of some organisms namely Bifidobacterium, Blautia, Ruminococcus, Collinsella, Coprococcus, and Eggerthella across the entire population. The description of the gut microbiota of children infected with the SARS-CoV-2 virus in particular is based on one specific marker, the genus Faecalibacterium [31, 1]. Bats are potential reservoirs for emerging viruses, with gut bacteria potentially involved in DNA damage. Bat gut microbiota's antioxidant properties could prevent emerging diseases [26]. Despite increased vaccination rates and strategies, COVID-19 severity persists, with children and adolescents contributing to a small proportion of cases, potentially causing long-term complications [35]. Microbiota-focused treatments such as fecal microbiota transplantation (FMT), bacteriotherapy, and traditional Chinese medicine (TCM) show potential as effective therapies for managing COVID-19. By focusing on understanding and manipulating the gut-lung axis through microbiota modulation, new strategies could emerge for managing COVID-19 and enhancing patient outcomes. These approaches highlight the potential impact of microbiota-based therapies in the context of viral infections like COVID-19. This review underscores the importance of investigating the role of the gut microbiota in COVID-19 immunopathology and its implications for therapeutic interventions [37, 47].

Materials and Methods

The impact of coronaviruses on the human gut microflora was studied using a comprehensive methodology that incorporated findings from reliable scientific research conducted between 2020 and 2024. This investigation was conducted under the title "The Influence of Coronaviruses on the Human Gut Microflora," ensuring a thorough exploration of all essential aspects.

SARS-CoV-2 directly interacts with the gut microbiome.

The composition of the gut microbiota is responsible for the gravity symptoms and the severity of COVID-19 diseases since it controls innate and adaptive immune systems and keep steady gut immune homeostasis level. Disrupted gut microbiome leads to the communication link between the cells in the epithelium and inflammation. More ACE2 (angiotensin-converting enzyme 2) is present due to these phenomena which is a target of SARS-CoV-2. The increase of gut paracellular permeability will cause passage of inflammatory bacterial factors into the blood system later

leading to systemic inflammation. Gut microbiota composition could affect healthy individuals with chance severe infection by the high amount of pro-inflammatory bacterial species. The correlation between inflammatory cytokines and serious infection as well as the increased level of pro-inflammatory bacterial species, the severe disease may have occurred. Chronic inflammatory conditions like ulcerative colitis could be underlined by disturbances in interactions between microbiota and immune system, which may be associated with abnormal cytokine levels. Together with acute multi-organ dysfunction, these abnormal levels of cytokine may cause fatal degradations. A decrease in gut microbiome diversity could serve as a potential indicator of COVID-19 severity. SARS-CoV-2 RNA has been detected in the feces of COVID-19 patients, indicating possible fecal-oral transmission. Gastrointestinal symptoms are present in 17.6% of infected individuals, potentially linked to ACE2 receptors. The presence of the SARS-CoV-2 RNA in stool samples can be dated up to 14 days after the respiratory samples test negative. Some researches showed correlations between the level of infection and microbiome diversity in patients shifted to mechanics ventilation, perhaps it is also valid for COVID-19 cases needing ventilation support. Alongside these changes, it has become evident that there is a correlation between the microbiome modifications and some of the complications for COVID-19 patients like the acute respiratory distress syndrome (ARDS) which could impact the outcomes as well [3, 10, 4, 47].

The indirect impacts of the pandemic on an individual's or population's microbiome.

The pandemics of COVID-19 have fostered a lot of step towards the reduction of the spread of the virus, like the lockdowns, the improved hand cleanliness, and the decrease in social contact, travel, and remote work. However, few studies have evaluated the secondary consequences of such interventions and their effect on microbial communities in the gut. Authorities place greater emphasis on hand cleanliness, so people have started using more disinfectants and sanitizers as such products are now abundantly available in the society. The role of the environment in the microbiome is recognized and the constant usage of sanitizers may affect human, animal, and environmental microbiomes. The travel bans discourage person to person, national, and international travels, which consequently decrease the time that people spend outside and reduce their exposure to the external environmental microbes. Those changes could, in turn, determine microbes in both individual and population level microbiome, which may be a long-lasting trend if international and national travel restrictions are still in place. Remote work for an extended period of time is just one factor which has to be carefully thought about. The modifiable ones that have been changed by the pandemic such as diet, lifestyle, sport, and everyday behavior are responsible for both shift in eating patterns and influence of how people live. Increasing in remote work and bulk buying of groceries as alternative shopping options may be the reason that lead to diet changes resulting in microbiome affectation. The emotional and psychological responses may have stimulated dysfunctional or dominant eating habit altering patterns. Microorganisms which inhabit the gut are known to modify metabolic efficiency; and disproportions in gut bacteria and dysbiosis are observed in metabolic disorders, e. g. obesity and diabetes. Within low and middle-income countries, the financial straits, the food presented inflexions, and the interruptions in education, health care, and social services as the possible concerns of malnutrition in children have been raised. The disruptions might have the long-term health consequences which include by what ways will transform the gut microbiome and trigger the metabolic maladaptive responses, and also the immune systems will be weakened. Although scientists are still uncertain regarding the specific mental health effects of the pandemic, early research suggests an unprecedented transformation in everyday social interactions which might have long-term health repercussions as well. Isolation, financial insecurity, fear and uncertainty, as well as unwonted life difficulties as restrictive as some of these stressors, which are known to take a toll on individual and community wellness and mental health, thus might possibly play a role in gut microbiota dysregulation as well. a new review claims these changes under the hygiene hypothesis are exactly what could reduce microbiome diversity in a way that this diversity couldn't be balanced by a communal microbiome [3, 10, 47].

Table 1: The profile of the gut microbiota in individuals with COVID-19 [10]

Sample size	Microbioa Species	Geographic Location	Gut Microbiota Characteristics in COVID-19	Reference
15 individuals diagnosed with COVID-19, 6 patients with community-acquired pneumonia, and 15 individuals in good health as controls.	Bacterial	Hong Kong, China	The bacteria in the gut which are normally there for this symbiotic relationship are disrupted during the covid-19 infection thus opportunistic pathogenic bacteria flourish. Similarly, some bacterial abundances before COVID-19 are predictive of its severity as well.	Zuo *et al*., 2020b [51]
100 COVID-19 patients, 79 non-COVID-19 controls	Bacterial	Hong Kong, China	There is a depletion of gut microbiota that possesses immunomodulatory potential in individuals with COVID-19. Additionally, there is a negative correlation observed between certain bacterial species and the severity of the disease.	Yeoh *et al*., 2021 [50]
9 children diagnosed with COVID-19, ranging in age from 7 to 139 months, compared with 14 healthy controls of similar ages.	Bacterial	Not provided	In the gut of children with COVID-19, there is a higher abundance of Bacteroidetes and Firmicutes, along with a dominance of the pathogenic bacterium Pseudomonas.	Xu R. *et al*., 2021 [13]
36 COVID-19 patients, 23 suspected patients, 72 healthy controls	Bacterial	Henan, China	In COVID-19 patients, there is an enrichment of certain bacterial genera compared to healthy individuals, along with a depletion of other genera in the healthy population.	Ren *et al*., 2021 [52]
86 individuals diagnosed with COVID-19, 21 individuals who have	Bacterial	Germany	Several bacterial genera have been found to correlate with COVID-19 severity and associated complications.	Schult *et al*., 2022 [53]

recovered from COVID-19, 11 individuals with pneumonia (as controls), and 26 asymptomatic individuals (as controls).				
13 COVID-19 patients, 5 healthy controls	Bacterial	Beijing, China	COVID-19 patients exhibit both enrichment and depletion of specific bacterial species compared to healthy controls.	Cao *et al*., 2021 [54]
115 COVID-19 patients (mild: 19, moderate: 37, severe: 59)	Bacterial	Portuguese	The abundance of specific bacterial species varies depending on the severity of COVID-19 infection.	Moreira-Rosário *et al*., 2021
117 patients testing positive for SARS-CoV-2 and 95 patients testing negative for SARS-CoV-2.	Bacterial	German (98% Caucasian ethnicity)	There are observed alterations in the abundance of bacterial taxa in individuals who test positive for SARS-CoV-2.	Reinold *et al*., 2021 [30]
There were 62 patients diagnosed with COVID-19, 33 patients with seasonal flu, and 40 healthy individuals serving as controls.	Bacterial	Hefei, China	In COVID-19 patients compared to controls, there are notable changes in the abundance of certain bacterial genera.	Tao *et al*., 2020
30 individuals diagnosed with COVID-19, 9 individuals with community-acquired pneumonia, and 30 healthy individuals serving as controls.	Fungal	Hong Kong, China	There is evidence of opportunistic fungal pathogens becoming enriched during COVID-19 infection.	Zuo *et al*., 2020a [51]
There were 67 patients diagnosed with COVID-19, 35 patients infected with H1N1, and 48 healthy individuals serving as controls.	Fungal	Zhejiang, China	COVID-19 patients often experience an increased fungal load and enrichment of opportunistic pathogenic fungi.	Lv *et al*., 2021
There were 30 patients diagnosed with COVID-19, comprising 21 with non-severe cases and 9 with severe/critical cases, along with 23 healthy controls.	Fungal	German (mainly Caucasian ethnicity)	The abundance and diversity of fungi show differences based on the severity of COVID-19. Severe cases of COVID-19 exhibit an enrichment of specific bacteriophages and plant RNA viruses.	Reinold *et al*., 2021 [30]
13 COVID-19 patients, 5 healthy controls	Virome	Beijing, China	The abundance and diversity of fungi show differences based on the severity of COVID-19. Severe cases of COVID-19 exhibit an enrichment of specific bacteriophages and plant RNA viruses.	Cao *et al*., 2021 [54]
There were 98 patients diagnosed with COVID-19, compared with 78 controls who did not have COVID-19 but were matched for gender and co-morbidities.	Virome	Hong Kong, China	Variations in virome composition appear to be associated with COVID-19 severity.	Zuo *et al*., 2021b [50]
There were 15 patients diagnosed with COVID-19, 6 patients with community-acquired pneumonia, and 15 healthy individuals serving as controls.	Virome	Hong Kong, China	The gut DNA virome diversity is reduced in COVID-19 patients, characterized by a composition dominated by specific viral families.	Zuo *et al*., 2020b [51] (PRJNA624223)

Association of the gut microbiome with clinical symptoms during viral infections.

Viral pathogens damage not only the upper respiratory tract but the lungs, colon, liver and spinal cord, as well cervix cells, blood vessels and white cells. The mucosa is the main route of cellular entry from the environment, with three main lines of defense against pathogenic viruses: an effective mucous layer, the innate immune defenses, and the adaptive immune defenses. The microbiota in the mucosa of a gut is a key regulator of the immune response to the viral infection as it fine tunes both innate and adaptive immunity. Viral particles must, therefore, link with the host cells to allow viral entry into the cell. The microbiota is effective during this stage by preventing the virus variants from attaching to the host cells. The role of probiotics that bring about the steric hindrance like Lactobacillus and Bifidobacterium between the receptor and the virus, and the Lactobacillus that express CD4 receptors which bind to HIV and reduce virus transmissions. LPS exhibits antiviral mechanisms by priming the immune cells with its lipopolysaccharide, which leads to improved activation mediated by toll-like receptor 4 (TLR4). Microbial metalloproteases counter-act viruses, because they possess antiviral properties. Metabolites of bacteria, including SCFAs, are Imodulators of the host immune response and inhibit the IFN response. A basal level of secretion of classical IFN is a prerequisite for maintaining the immune system's general readiness to immediately respond with full power against infections. The host's nasal and pharyngeal microbiota protect against these infections. Staphylococci activate IFN, which gives the innate response an advantage against the viruses. Thus, the microbiota will form a better shield. The TLR4 receptor of colonic DCs are triggered by the glycolipids from Bacteroides fragilis leading to the induction of IFN-β. Besides, the Clostridium and Bacteroides elaboration of SCFAs and DAT promotes the influenza colitis CD8+ cell function and the macrophage type I IFN signaling [23, 39]. The protocol aims to explore the relationship between COVID-19 and intestinal flora, providing insights for therapy and prevention methods. It will involve a comprehensive review, including diverse participants, to minimize potential biases [15].

The infection caused by SARS-CoV-2 changes the metabolic activity of the gut microbiota.

To assess the functional implications of changes in fecal microbiota composition associated with infection, we employed a targeted metabolomics approach focusing on

three key categories of microbiota-derived metabolites: SCFAs, BAs, and tryptophan metabolites are a few examples. Some SCFAs such as acetate, propionate, and butyrate are a product of fibers fermentation by certain bacteria population and perform critical functions including restoration of intestinal barrier integrity, immune regulation, and metabolic control. To elaborate, a clear distinction in these main SCFAs' presence in cynomolgus macaques' feces was observed in the middle of SARS-CoV-2 infection on the third day up until the 13th day. BA (bile acids) are one of the primary ending products of the liver, conjugated state, which get further to deconjugation and degradation that start in the gut by the bacterial microbiota. FAs talk to the body by serving as signaling molecules within and beyond the seat of the digestive tract. Such effects are achieved mainly through G protein-coupled receptors, such as Takeda G protein receptor 5 and through nuclear receptors, e.g., farnesoid X receptor. Regardless of any sampling time, the main BAs identified in stool samples during both species was unconjugated secondary BAs especially DCA (deoxychoric acid) and less importantly LCA (lithocholic acid) in cynomologus macaques. This was an indication of the overall preserved capability of the microbiota to metabolize BAs. On the other hand, BA concentration of these BAs was remarkably increased at 10 and 13 days post-infection compared to 3 Day post-infection. Comparable alterations occurred as the totality of primary BAs and the primary BAs to secondary BAs ratio grew in the stool at day 10 post-infection [34, 39].

Angiotensin-converting enzyme 2: A bridge between the gut and lung

Angiotensin-converting enzyme 2 (ACE2) is a key target for various coronaviruses, including SARS-CoV-2, and plays a crucial role in preventing acute lung injury induced by respiratory viruses. This enzyme is highly expressed in human lung and small intestinal epithelial cells, suggesting a potential route for SARS-CoV-2 invasion. Studies have implicated ACE2 in regulating bradykinin levels through the renin-angiotensin system (RAS) and kinin-releasing enzyme kinin system (KKS), with implications for systemic inflammation affecting the lung and gastrointestinal systems. Notably, high ACE2 expression in the intestine of COVID-19 patients with gut microbiota dysbiosis hints at a potential link between ACE2 and the gut microbiota, although more evidence is needed to substantiate this relationship. ACE2's interactions with amino acid transporters like B0AT1 and collectrin impact antimicrobial peptide expression, mTOR pathway activity, and tryptophan levels, affecting gut microbiota composition. The gut microbiota's role in regulating ACE2 expression suggests its importance in COVID-19 severity, highlighting ACE2 as a potential target for severe COVID-19 prevention. Overall, ACE2 may contribute to inflammatory responses and gut microbiota imbalances associated with SARS-CoV-2 infection, linking the gut and lung environments [19, 17].

The reciprocal relationships between gut microbiota and COVID-19 vaccinations.

Specific to the gut area, there is a 10-fold more population of microbes than there are eukaryotic cells. Microbiota profoundly affects physiology, including intestinal immunity, metabolism, allergy inflammation, autoimmunity and interaction with the central nervous system. The balance of microbiome can serve as an aggravating or neutralizing factor for the efficacy of immune system interventions, such as COVID-19 vaccines. The connection between microbiota in the gut and the action of vaccines is a very serious research topic. The microbiota in the gut is very critical in the course of the immune response and the performance of the vaccine. Animal experiments, clinical interventional studies, as well as observational studies provide scientific evidence about interrelation between gut microbiota and COVID-19 vaccines [11, 28]. Asymptomatic COVID-19 carriers, often silent or presymptomatic, pose challenges to control. Identifying gastrointestinal symptoms and altering gut microbes may be therapeutic, and developing oral vaccines could help control the pandemic [5]. COVID-19 patients often experience gastrointestinal symptoms and gut microbiota alterations, which affect disease severity and susceptibility to long-term complications. Factors like sex, age, and genetics can affect gut microbiota composition, leading to individual differences and varying responses. Gut microbiota intervention through probiotics, prebiotics, and FMT is promising for future treatment [36, 40].

Discussion

The gut microbiota significantly contributes to both the imposition of human immune system and the achievement of balance, thus influencing human health and diseases. When the normal state of gut microbiota is altered, this can be followed by systemic inflammation and chronic inflammation even at remote sites like lungs, causing injury. The gut-lung axis couples the lung to the gut, and the microbes within the intestines may exhibit positive influence in the rehabilitation process. There have been studies to determine that gut microbiota in people with mental disorders, i.e. anxiety and depression, is affected by gut microbiota dysbiosis. An experiment found SCFA-producing proficient commensal bacteria are significantly reduced in RPs who did not improve (RPs), suggesting low levels of SCFAs and commensal bacteria not only slow down rehabilitation of pulmonary and psychiatric symptoms but also may have long-term COVID-19. These studies may have however some limiting factors for example that they take place in single centers, utilize cross sectional design, lack dynamic monitoring and there is a possibility that lifestyle and diet might affect gut microbiota. In a bid to look past the single-omics mostly employed, future studies should focus on a multi-omics approach in probing deep down the gut-lung axis mechanism [44]. The gut microbiome profile in COVID-19 patients undergoes alteration during the acute phase and recovery process, with decreased diversity linked to a pro-inflammatory response and increased susceptibility to opportunistic infections. Further studies are needed to understand the underlying mechanisms [2]. The study examines the impact of COVID-19 precautions on the gut microbiota and its potential influence on reducing nosocomial infections. It found a decrease in certain bacteria, such as Pseudomonas and Akkermansia, due to reduced transmission. The study emphasizes the need to understand these changes' durability and clinical consequences in outpatient settings and future treatment phases [29]. The gut microbiota in hamsters that is subjected to the COVID-19 severe form is shown to be affected promoting biomarkers of disease severity to be disrupted in this way. Utilizing the Syrian hamster model, one would be able to effectively study for the acute phase of COVID-19

infection and would be able to see the maximum of body weight loss upon the infection. Research results showed that changes in gut integrity were pronounced following SARS-CoV-2 infection in hamsters as developed by variations in the gene expression and minor changes of barrier functions. Intestine-lung axis gets provide more importance in the sense of viral respiratory infections. SARS-CoV-2 infection may be linked to a reduced abundance of the bacterial species with immunomodulatory potential [33]. Obesity and nonalcoholic fatty liver diseases significantly impact COVID-19 outcomes. Gut microbiota changes during infection provide insights into disease mechanisms. Animal models could help design gut-microbiota-targeting treatments [32, 11]. The gut microbiota diversity in COVID-19 patients and Type 2 diabetes patients may be influenced by antibiotic use and T2D. Metformin treatment may modulate gut microbiota and reduce oxidative stress, highlighting the importance of gut microbiota in T2D management [24]. A study confirms that SARS-CoV-2 infection is linked to antimicrobial resistance in the gut microbiota. It found an increase in Enterobacteriaceae in post-COVID individuals, despite the virus being mainly associated with moderate cases and hospitalization. The study also examined the impact of the post-COVID microbiota on the pulmonary immune system and pulmonary tissue damage in mice. Data revealed memory impairment in mice after transplantation and drop of acetate, propionic, and butyrate in stool production. This led to the functional changes such as increased TNF expression in the hippocampi of mice whose gut microbiota were changed after COVID infection and this trend revealed neuroinflammatory responses [22]. The study analyzed SARS-CoV-2 infections, GI microbiota, and host immune responses using the NHP model. It found similar GI microbiota and mucus in rhesus monkeys and humans, making the NHP model ideal for studying GI manifestations [4, 1]. COVID-19 patients' gut microbiome is disrupted, leading to opportunistic pathogens enriching and depleting beneficial commensals and causing long-lasting detrimental effects. Understanding microbiome changes is crucial for developing new treatment approaches [50]. The study reveals the gut microbiome community in COVID-19 patients has functional potential and metabolic output, potentially supporting microbiota-based therapy. It also found attenuated L-isoleucine biosynthesis and urea metabolism positively correlated with disease severity [46]. The COVID-19 pandemic significantly impacts the gastrointestinal tract, with airway exposure being a major infection route. Intranasal or intragastric inoculation causes infection, pathologic changes, and virus shedding. Further investigation is needed to understand the mechanisms [13]. Patients that consume nutritional fibers by and large see their strongly felt gastrointestinal symptoms alleviated as a consequence of structural changes in the fecal bacterial flora. It is essential for the progress that the project requires more research [39]. The COVID-19 pandemic has exerted a significant influence on the gut microbial ecology and induces atypical bacterial populations in the fecal matter, as well as makes individuals more likely to develop secondary infections. This process however is stimulated by the gut-lung axis, the direct infection by SARS-CoV-2, and some intervention procedures like mechanical ventilation which are needed in case of severe illness. The repercussions include compromised host immunity, increased inflammation, and an increased risk of systemic diseases [41, 17].

Conclusion

Relationship between coronaviruses and the human gut microflora represents a multifaceted and evolving area of research with significant implications for both infectious disease and overall health. The evidence suggests that coronaviruses, including SARS-CoV-2, can impact the gut microflora directly through viral invasion of intestinal cells expressing the angiotensin-converting enzyme 2 (ACE2) receptor, which may lead to dysbiosis and altered microbial composition. Indirect effects may occur due to systemic inflammation triggered by viral infection, further influencing gut microbial communities. The observed dysbiosis and changes in gut microbial composition in COVID-19 patients highlight the complex interplay between viral infections and the microbiome. Understanding these interactions is crucial, as the gut microflora plays essential roles in regulating immune responses, nutrient metabolism, and maintaining gut barrier integrity. Dysregulation of the gut microflora can contribute to the gastrointestinal symptoms reported in COVID-19, such as diarrhea and abdominal pain. Furthermore, alterations in the gut microflora could impact the efficacy of treatments and vaccines for coronaviruses. The microflora influences immune system function, and changes in microbial composition may affect immune responses to viral infections and vaccines. Therefore, optimizing the gut microflora could potentially enhance therapeutic outcomes in COVID-19 patients. Longitudinal studies are needed to assess whether these alterations persist beyond acute infection and whether they contribute to long-term health consequences, such as post-acute sequelae of SARS-CoV-2 infection (PASC). In summary, investigating the influence of coronaviruses on the human gut microflora is vital for comprehensively understanding the pathophysiology of COVID-19 and other coronavirus-related diseases.

Highlights

- **Altered Gut Microbiota Composition:** Coronaviruses, such as SARS-CoV-2, can impact the diversity and composition of the human gut microbiota. Studies suggest that COVID-19 patients may experience changes in microbial populations within the gut.
- **Potential Mechanisms:** The influence of coronaviruses on the gut microbiota could be mediated through systemic inflammation, immune responses, and alterations in gut barrier function. These factors can disrupt the balance of beneficial and harmful bacteria.
- **Implications for Health:** Changes in gut microbiota due to coronavirus infections may have implications for overall health beyond the acute phase of the illness. It could affect immune function, metabolism, and susceptibility to other diseases.
- **Long-Term Effects:** Understanding how coronaviruses impact the gut microbiota could shed light on potential long-term consequences of COVID-19, including post-infectious complications related to gut health.
- **Therapeutic Considerations:** Research into the influence of coronaviruses on the gut microbiota may inform future therapeutic strategies, such as probiotic interventions, to restore microbial balance and support recovery from COVID-19.

References

1. Ahlawat S, Sharma KK. Immunological co-ordination between gut and lungs in SARS-CoV-2 infection. Virus Res. 2020 Sep 1;286:198103. https://doi.org/10.1016/j.virusres.2020.198103
2. Brīvība M, Silamiķele L, Birzniece L, Ansone L, Megnis K, Silamiķelis I, *et al*. Gut Microbiome Composition and Dynamics in Hospitalized COVID-19 Patients and Patients with Post-Acute COVID-19 Syndrome. Int J Mol Sci. 2024 Jan 1;25(1):567. https://doi.org/10.3390/ijms25010567
3. Burchill E, Lymberopoulos E, Menozzi E, Budhdeo S, McIlroy JR, Macnaughtan J, *et al*. The unique impact of COVID-19 on human gut microbiome research. Front Med. 2021 Mar 16;8:652464. https://doi.org/10.3389/fmed.2021.652464
4. Chen H, Wang J, Ding K, Xu J, Yang Y, Tang C, *et al*. Gastrointestinal microbiota and metabolites possibly contribute to distinct pathogenicity of SARS-CoV-2 proto or its variants in rhesus monkeys. Gut Microbes. 2024 Dec 31;16(1):2334970. https://doi.org/10.1080/19490976.2024.2334970
5. Chen TH, Hsu MT, Lee MY, Chou CK. Gastrointestinal involvement in SARS-CoV-2 infection. Viruses. 2022 May 30;14(6):1188. https://doi.org/10.3390/v14061188
6. de Oliveira GL, Oliveira CN, Pinzan CF, de Salis LV, Cardoso CR. Microbiota modulation of the gut-lung axis in COVID-19. Front Immunol. 2021 Feb 24;12:635471. https://doi.org/10.3389/fimmu.2021.635471
7. Dhar D, Mohanty A. Gut microbiota and Covid-19-possible link and implications. Virus Res. 2020 Aug 1;285:198018. https://doi.org/10.1016/j.virusres.2020.198018
8. Farsi Y, Tahvildari A, Arbabi M, Vazife F, Sechi LA, Bonjar SAH, *et al*. Diagnostic, prognostic, and therapeutic roles of gut microbiota in COVID-19: a comprehensive systematic review. Front Cell Infect Microbiol. 2022 Mar 4;12:804644. https://doi.org/10.3389/fcimb.2022.804644
9. Galloway-Peña JR, Shi Y, Peterson CB, Sahasrabhojane P, Gopalakrishnan V, Brumlow CE, *et al*. Gut microbiome signatures are predictive of infectious risk following induction therapy for acute myeloid leukemia. Clin Infect Dis. 2020 Jun 24;71(1):63-71. https://doi.org/10.1093/cid/ciz777
10. Gang J, Wang H, Xue X, Zhang S. Microbiota and COVID-19: Long-term and complex influencing factors. Front Microbiol. 2022 Aug 12;13:963488. https://doi.org/10.3389/fmicb.2022.963488
11. Hong M, Lan T, Li Q, Li B, Yuan Y, Xu F, *et al*. A comprehensive perspective on the interaction between gut microbiota and COVID-19 vaccines. Gut Microbes. 2023 Dec 31;15(1):2233146. https://doi.org/10.1080/19490976.2023.2233146
12. Ishizaka A, Koga M, Mizutani T, Yamayoshi S, Iwatsuki-Horimoto K, Adachi E, *et al*. Association of gut microbiota with the pathogenesis of SARS-CoV-2 Infection in people living with HIV. BMC Microbiol. 2024 Jan 3;24(1):6. https://doi.org/10.1186/s12866-023-03157-5
13. Jiao L, Li H, Xu J, Yang M, Ma C, Li J, *et al*. The gastrointestinal tract is an alternative route for SARS-CoV-2 infection in a nonhuman primate model. Gastroenterology. 2021 Apr 1;160(5):1647-61. https://doi.org/10.1053/j.gastro.2020.12.001
14. Kaźmierczak-Siedlecka K, Vitale E, Makarewicz W. COVID-19–gastrointestinal and gut microbiota-related aspects. Eur Rev Med Pharmacol Sci. 2020 Oct 15;24(20). https://doi.org/10.26355/eurrev_202010_23448
15. Li F, Lu H, Li X, Wang X, Zhang Q, Mi L. The impact of COVID-19 on intestinal flora: A protocol for systematic review and meta analysis. Medicine. 2020 Sep 25;99(39):e22273. https://doi.org/10.1097/MD.0000000000022273
16. Li K, Methé BA, Fitch A, Gentry H, Kessinger C, Patel A, *et al*. Gut and oral microbiota associations with viral mitigation behaviors during the COVID-19 pandemic. Front Cell Infect Microbiol. 2022 Sep 9;12:966361. https://doi.org/10.3389/fcimb.2022.966361
17. Li S, Zhou Y, Yan D, Wan Y. An update on the mutual impact between SARS-CoV-2 infection and gut microbiota. Viruses. 2022 Aug 15;14(8):1774. https://doi.org/10.3390/v14081774
18. Liu TF, Philippou E, Kolokotroni O, Siakallis G, Rahima K, Constantinou C. Gut and airway microbiota and their role in COVID-19 infection and pathogenesis: a scoping review. Infection. 2021 Oct 20:1-33. https://doi.org/10.1007/s15010-021-01715-5
19. Liu Y, Kuang D, Li D, Yang J, Yan J, Xia Y, *et al*. Roles of the gut microbiota in severe SARS-CoV-2 infection. Cytokine & Growth Factor Reviews. 2022 Feb 1;63:98-107. https://doi.org/10.1016/j.cytogfr.2022.01.007
20. Luo J, Liang S, Jin F. Gut microbiota in antiviral strategy from bats to humans: a missing link in COVID-19. Science China Life Sciences. 2021 Jun;64:942-956. https://doi.org/10.1007/s11427-020-1847-7
21. Manosso LM, Arent CO, Borba LA, Ceretta LB, Quevedo J, Reus GZ. Microbiota-gut-brain communication in the SARS-CoV-2 infection. Cells. 2021 Aug 6;10(8):1993. https://doi.org/10.3390/cells10081993
22. Mendes de Almeida V, Engel DF, Ricci MF, Cruz CS, Lopes ÍS, Alves DA, *et al*. Gut microbiota from patients with COVID-19 cause alterations in mice that resemble post-COVID symptoms. Gut Microbes. 2023 Dec 18;15(2):2249146. https://doi.org/10.1080/19490976.2023.2249146
23. Moreno-Corona NC, López-Ortega O, Pérez-Martínez CA, Martínez-Castillo M, De Jesús-González LA, León-Reyes G, *et al*. Dynamics of the microbiota and its relationship with post-COVID-19 syndrome. Int J Mol Sci. 2023 Oct 1;24(19):14822. https://doi.org/10.3390/ijms241914822
24. Petakh P, Kamyshna I, Oksenych V, Kainov D, Kamyshnyi A. Metformin therapy changes gut microbiota alpha-diversity in COVID-19 patients with type 2 diabetes: the role of SARS-CoV-2 variants and antibiotic treatment. Pharmaceuticals. 2023 Jun 20;16(6):904. https://doi.org/10.3390/ph16060904
25. Petakh P, Kobyliak N, Kamyshnyi A. Gut microbiota in patients with COVID-19 and type 2 diabetes: A culture-based method. Front Cell Infect Microbiol. 2023 Feb 9;13:1142578. https://doi.org/10.3389/fcimb.2023.1142578

26. Popov IV, Mazanko MS, Kulaeva ED, Golovin SN, Malinovkin AV, Aleshukina IS, *et al*. Gut microbiota of bats: pro-mutagenic properties and possible frontiers in preventing emerging disease. Scientific reports. 2021 Oct 26;11(1):21075. Available from: https://doi.org/10.1038/s41598-021-00604-z
27. Rajput S, Paliwal D, Naithani M, Kothari A, Meena K, Rana S. COVID-19 and gut microbiota: a potential connection. Indian Journal of Clinical Biochemistry. 2021 Jul;36(3):266-77. Available from: https://doi.org/10.1007/s12291-020-00948-9
28. Ralli T, Saifi Z, Rathee A, Aeri V, Kohli K. Decoding the bidirectional relationship between gut microbiota and COVID-19. Heliyon. 2023 Mar 1;9(3). Available from: https://doi.org/10.1016/j.heliyon.2023.e13801
29. Rashidi A, Ebadi M, Rehman TU, Elhusseini H, Nalluri H, Kaiser T, *et al*. Effect of COVID-19 precautions on the gut microbiota and nosocomial infections. Gut microbes. 2021 Jan 1;13(1):1936378. Available from: https://doi.org/10.1080/19490976.2021.1936378
30. Reinold J, Farahpour F, Fehring C, Dolff S, Konik M, Korth J, *et al*. A pro-inflammatory gut microbiome characterizes SARS-CoV-2 infected patients and a reduction in the connectivity of an anti-inflammatory bacterial network associates with severe COVID-19. Frontiers in Cellular and Infection Microbiology. 2021 Nov 17;11:747816. Available from: https://doi.org/10.3389/fcimb.2021.747816
31. Romani L, Del Chierico F, Macari G, Pane S, Ristori MV, Guarrasi V, *et al*. The relationship between pediatric gut microbiota and SARS-CoV-2 infection. Frontiers in cellular and infection microbiology. 2022 Jul 8;12:908492. Available from: https://doi.org/10.3389/fcimb.2022.908492
32. Sencio V, Benech N, Robil C, Deruyter L, Heumel S, Machelart A, *et al*. Alteration of the gut microbiota's composition and metabolic output correlates with COVID-19-like severity in obese NASH hamsters. Gut microbes. 2022 Dec 31;14(1):2100200. Available from: https://doi.org/10.1080/19490976.2022.2100200
33. Sencio V, Machelart A, Robil C, Benech N, Hoffmann E, Galbert C, *et al*. Alteration of the gut microbiota following SARS-CoV-2 infection correlates with disease severity in hamsters. Gut Microbes. 2022 Dec 31;14(1):2018900. Available from: https://doi.org/10.1080/19490976.2021.2018900
34. Sokol H, Contreras V, Maisonnasse P, Desmons A, Delache B, Sencio V, *et al*. SARS-CoV-2 infection in nonhuman primates alters the composition and functional activity of the gut microbiota. Gut microbes. 2021 Jan 1;13(1):1893113. Available from: https://doi.org/10.1080/19490976.2021.1893113
35. Suskun C, Kilic O, Ciftdogan YD, Guven S, Karbuz A, Parlakay OA, *et al*. Intestinal microbiota composition of children with infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and multisystem inflammatory syndrome (MIS-C). European journal of pediatrics. 2022 Aug;181(8):3175-3191. Available from: https://doi.org/10.1007/s00431-022-04494-9
36. Usmani A, Baseer AQ, Rahimi BA, Jahid A, Niazi P, Monib AW, *et al*. Coronavirus disease 2019 (COVID-19) pandemic: What is the level of knowledge, attitude, and practice in Kandahar, Afghanistan? African Journal of Microbiology Research. 2020;14(9):465-470.
37. Vodnar DC, Mitrea L, Teleky BE, Szabo K, Călinoiu LF, Nemeș SA, *et al*. Coronavirus disease (COVID-19) caused by (SARS-CoV-2) infections: a real challenge for human gut microbiota. Frontiers in cellular and infection microbiology. 2020 Dec 9;10:575559. Available from: https://doi.org/10.3389/fcimb.2020.575559
38. Wang M, Zhang Y, Li C, Chang W, Zhang L. The relationship between gut microbiota and COVID-19 progression: new insights into immunopathogenesis and treatment. Frontiers in Immunology. 2023 May 2;14:1180336. Available from: https://doi.org/10.3389/fimmu.2023.1180336
39. Wang YZ, Zhou JG, Lu YM, Hu H, Xiao FF, Ge T, *et al*. Altered gut microbiota composition in children and their caregivers infected with the SARS-CoV-2 omicron variant. World Journal of Pediatrics. 2023 May;19(5):478-88. Available from: https://doi.org/10.1007/s12519-022-00659-6
40. Wang Y, Wu G, Zhao L, Wang W. Nutritional modulation of gut microbiota alleviates severe gastrointestinal symptoms in a patient with post-acute COVID-19 syndrome. MBio. 2022 Apr 26;13(2):e03801-21. Available from: https://doi.org/10.1128/mbio.03801-21
41. Xiang H, Liu QP. Alterations of the gut microbiota in coronavirus disease 2019 and its therapeutic potential. World Journal of Gastroenterology. 2022 Dec 12;28(47):6689. Available from: https://doi.org/10.3748/wjg.v28.i47.6689
42. Xiao Z, Pan M, Li X, Zhao C. Impact of SARS-CoV2 infection on gut microbiota dysbiosis. Microbiome Research Reports. 2024;3(1). Available from: https://doi.org/10.20517/mrr.2023.48
43. Xu X, Zhang W, Guo M, Xiao C, Fu Z, Yu S, *et al*. Integrated analysis of gut microbiome and host immune responses in COVID-19. Frontiers of medicine. 2022 Apr;16(2):263-75. Available from: https://doi.org/10.1007/s11684-022-0921-6
44. Yang Z, Liu Y, Wang L, Lin S, Dai X, Yan H, *et al*. Traditional Chinese medicine against COVID-19: Role of the gut microbiota. Biomedicine & Pharmacotherapy. 2022 May 1;149:112787. Available from: https://doi.org/10.1016/j.biopha.2022.112787
45. Zhang D, Zhou Y, Ma Y, Chen P, Tang J, Yang B, *et al*. Gut microbiota dysbiosis correlates with long COVID-19 at one-year after discharge. Journal of Korean Medical Science. 2023 Apr 4;38(15). Available from: https://doi.org/10.3346/jkms.2023.38.e120
46. Zhang F, Lau RI, Liu Q, Su Q, Chan FK, Ng SC. Gut microbiota in COVID-19: key microbial changes, potential mechanisms and clinical applications. Nature Reviews Gastroenterology & Hepatology. 2023 May;20(5):323-37. Available from: https://doi.org/10.1038/s41575-022-00698-4
47. Zhang F, Wan Y, Zuo T, Yeoh YK, Liu Q, Zhang L, *et al*. Prolonged impairment of short-chain fatty acid and L-isoleucine biosynthesis in gut microbiome in patients with COVID-19. Gastroenterology. 2022 Feb 1;162(2):548-61. Available from: https://doi.org/10.1053/j.gastro.2021.10.013

48. Zhang Y, Ma Y, Sun W, Zhou X, Wang R, Xie P, *et al*. Exploring gut–lung axis crosstalk in SARS-CoV-2 infection: Insights from a hACE2 mouse model. Journal of Medical Virology. 2024 Jan;96(1):e29336. Available from: https://doi.org/10.1002/jmv.29336
49. Zhou J, Yang X, Yang Y, Wei Y, Lu D, Xie Y, *et al*. Human microbiota dysbiosis after SARS-CoV-2 infection have the potential to predict disease prognosis. BMC Infectious Diseases. 2023 Nov 29;23(1):841. Available from: https://doi.org/10.1186/s12879-023-08784-x
50. Zuo T, Liu Q, Zhang F, Yeoh YK, Wan Y, Zhan H, *et al*. Temporal landscape of human gut RNA and DNA virome in SARS-CoV-2 infection and severity. Microbiome. 2021 Dec;9:1-6. Available from: https://doi.org/10.1186/s40168-021-01008-x
51. Zuo T, Zhang F, Lui GC, Yeoh YK, Li AY, Zhan H, *et al*. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. Gastroenterology. 2020 Sep 1;159(3):944-955. Available from: https://doi.org/10.1053/j.gastro.2020.05.048
52. Ren X, Wen W, Fan X, Hou W, Su B, Cai P, *et al*. COVID-19 immune features revealed by a large-scale single-cell transcriptome atlas. Cell. 2021 Apr 1;184(7):1895-1913.
53. Schult J, Mahler N, Fauth B, Lindner MA. Did students learn less during the COVID-19 pandemic? Reading and mathematics competencies before and after the first pandemic wave. School effectiveness and school Improvement. 2022 Oct 2;33(4):544-563.
54. Wang GL, Wang ZY, Duan LJ, Meng QC, Jiang MD, Cao J, *et al*. Susceptibility of circulating SARS-CoV-2 variants to neutralization. New England Journal of Medicine. 2021 Jun 17;384(24):2354-2356.