

Microbiota and their Influence in the Human Body

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Abstract

Scientists have invested considerable resources in the study of the microbiota of the human body. These microorganisms play pivotal roles in immunity and disease. Of which, probiotics are live beneficial microorganisms that keep your intestinal or lung microbiota healthy, and occupy a special role in combating the infections. Thus, it is critical to understand their contributions to these processes. Technology can facilitate advanced studies of the microbiota, including how it develops and its positive and negatives effects on the immune system. This paper investigates how several factors (e.g. birth delivery mode, metabolic activities, types of microorganisms, and immune system interactions) affect the microbiota, particularly in early life. The paper also discusses how gastrointestinal microbes in particular may be associated with certain disease processes, such as those related to schizophrenia, autism, and diabetes. Clinical studies show that certain probiotic strains, like *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* ssp. *lactis* help to prevent infection of pathogenic organisms (both bacterial and viral). This research may yield crucial contributions to disease prevention and public health. The dysbiosis may result in changes in the acquired immunity later on. The probiotic strains can prevent viral replication during SARS-CoV-2 or COVID-19 infection by reducing proinflammatory cytokines. There has been much interest into the intestinal flora as proposed by the diversity, volume, and proposed role in disease. Future research in the field of microbiome should be done in order to uncover their association to gut virome by noting both their influence on each other and relevant health and disease.

Keywords: COVID-19, Microbiota, Immune system, Crohn's disease, Schizophrenia

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INTRODUCTION

One of the most important symbiotic relationships in human beings involves the microbiota of the body, particularly in the intestinal tract. These benefits—and occasional negative effects—begin at the time of formation of the microbiota and continue until death. Many studies over the last century have shown the importance of the microbiota in humans, which begins forming in infancy and develops rapidly until the age of 2–3 years. During this period, the microbiota stabilises and forms the composition that will persist into adulthood¹⁻².

The microbiota affects early development of the immune system and offers long-term benefits to human health by providing antigens and antibodies that strengthen immunity. It also affects the development of distal organs, thus impacting the human body at the systemic level³⁻⁵. Studies have shown that the microbiota is involved in immune responses to various pathologies, such as high blood pressure, diabetes, and psychological diseases⁶⁻¹⁰. For example, faecal microbiota transplants have shown promising results for treating chronic gastrointestinal diseases and autism spectrum disorders¹¹⁻¹³. Other studies highlight the benefit of the microbiota in preventing or minimizing viral infections, including norovirus and coronaviruses¹⁴⁻¹⁶. In this review article, we discuss the importance of microbiota in treating, preventing, and reducing pathogenic disease, including viral diseases such as COVID-19.

Formation of Microbiota

Microbiota begin forming *in utero*, where the mother's gut and placenta play critical roles¹⁷⁻¹⁸. Factors that influence this process include the type of delivery (e.g. vaginal or Caesarean), the mother's lifestyle (e.g. diet and other habits) and health history (e.g. illness, antibacterial medications)¹⁹⁻²³. The dominant bacterial forms in an embryo include *Lactobacillus* and *Escherichia coli*²⁴. These microbes mostly colonize the gut of the foetus and can influence immunity and disease risk²⁵.

After delivery, a rapid shift in the microbiota composition occurs, and this shift depends on several factors, such as the delivery mode and feeding patterns of the infant²⁶⁻²⁷. The delivery method has significant implications on newborns' microbiota formation²⁸. For instance,

children who are born vaginally have higher levels of Lactobacilli than those born surgically, perhaps due to the abundance of Lactobacilli in the vagina²⁴. In contrast, children born via Caesarian section harbour less diverse microbiota, and normal colonization takes longer in these infants²⁹⁻³⁰. The most abundant microorganisms in babies born via C-section include the *Bacteroides* genus and other facultative anaerobic bacteria, such as the *Clostridium* species³¹. Compared to 72% of children born vaginally, only 41% of infants born via C-section exhibit a similar faecal structure to that of their mother³²⁻³³.

During the first month, the microbiota in a new-born is purely aerobic, limited in numbers, and low in diversity³⁴. After one month, the microbiota becomes anaerobic, allowing the growth of other bacterial forms³⁵. Several factors can affect this change, including antibiotic treatments, diet, and illness. In the first year, conditions in the body determine the growth and diversity of its microbiota³⁶⁻³⁷. Initially, the microbiota is mainly limited to two main bacterial phyla: Proteobacteria and Actinobacteria³³. By about two years of age, however, the child's microbial composition resembles that of an adult. This process is particularly affected by the introduction of solid foods around six months of age³⁸. The microbiota continues to develop into adulthood. The composition changes, shifting more to *Clostridium* and *Bacteroidetes* species. Other life events, such as illness, also affect the microbiota^{31,39}.

Benefits of the Microbiota

The microbiota protects the body from diseases and enhances metabolic activities. These microorganisms have important functions in the skin, oral cavity, gut, reproductive tract, and nasal cavity⁴⁰⁻⁴¹. The skin hosts a wide diversity of beneficial microbes that provide physical and immunological protection from pathogens. For example, *Staphylococcus epidermidis* is a common protective microbe on the skin that produces bacitracin, a toxic substance that acts as an antibiotic, ensuring that other harmful bacteria do not enter the body⁴²⁻⁴³. Enforcing constant use of antibiotics to treat severe infections like COVID-19 in hospitals can eventually lead to the antibiotic resistance. Phage therapy will help control diseases involving antibiotic resistance.

This is an insight into use of bacteriophages to control COVID-19 in a post-treatment–control era⁴⁴. Research shows that other microorganisms enhance the activities of T cells by increasing their ability to respond to pathogenic microorganisms⁴⁵. Thus, researchers discovered that phages targeting B16 melanomas in mice attracted tumor-associated macrophages to the tumor, which led to tumor regression and prolonged survival in mice⁴⁶.

The microbiota of the gastrointestinal tract contributes to metabolism, neuronal development, and physiology⁴⁷. The human gut hosts approximately 400–1,000 microbial species that participate in digestion, nutrient absorption, and protection against pathogenic microbes. Some of these species help strengthen and maintain the mucosal barrier, which protects cells from acids in the stomach and other digestive enzymes. In addition to their role in digestion, gut microbes interact with the mucosal immune system to facilitate disease detection and management⁴⁸⁻⁴⁹. They also contribute to enzyme production. For example, bacteria in the colon act as enzymes to facilitate fermentation of carbohydrates into metabolites⁵⁰. Different microbes in the gut produce propionate, acetate, and butyrate enzymes, which assist in apoptosis, differentiation, gene expression, and proliferation of epithelial cells⁵¹. Thus, the microbiota of the digestive tract has significant implications for immunity, digestion, cell development, and pathogenesis.

The reproductive system depends on a healthy microbiota. For instance, the female reproductive system has different microorganisms that participate in various aspects of fertility, such as menstruation, gametogenesis, pregnancy, and childbirth⁵². These microbiota boost immunity by preventing diseases, including HIV, urinary tract infections, yeast infections, sexually transmitted diseases, and bacterial vaginosis⁵³. In contrast to the female system, the upper parts of the male urinary tract do not have microbiota, although the lower genital region does⁵⁴. Dysbiosis could potentially contribute to a contributing cause of gut infection. It is difficult to know the connection between the gut and lung microbiome. Acute lung injury, mediated by gut microbiota, was associated with a shift in the microbial community in the lung, showing a co-relation between gut and lung⁵⁵. These strains exhibit anti-tumor or

immunomodulating activities, and some of them have also shown inhibitory effects on viruses⁵⁶.

Finally, the body's microbiome influences mental health due to its implications in the brain. Microbes of the gut can affect brain functioning by releasing molecular substances that trigger nerves and determine behaviour⁵⁷⁻⁵⁸. Research also indicates a relationship between microorganisms in the stomach and psychological conditions, such as autism and depression⁵⁹. Although microbiota often do not exhibit direct links to diseases, their regulatory roles contribute to complex pathogenesis processes⁶⁰. Changes in the composition of microbes may trigger or inhibit the development of asthma, depression, allergies, metabolic disorders, and autism⁶¹. Therefore, restoring or establishing a healthy microbial composition may represent a critical step for managing these conditions. Inflammatory mediators transported from the gut to the lungs by the blood can have detrimental effects on the lungs⁶².

Sources of the Microbiota

The human microbiota originates from numerous sources, including diet and supplementation. For example, prebiotics are mainly non-digestible food particles that enhance the stimulation, development, and growth of different microorganisms in the colon. They enhance digestion and provide an environment where healthy microbes can thrive. Humans can obtain prebiotics from numerous dietary substances, mainly carbohydrates⁶³. Certain foods are essential sources of prebiotics, including tomatoes, chicory, beans, wheat, sugar beets, onions, milk from cows and humans, and asparagus. According to research, breast milk supports the transfer of bacteria from the mother to child and contributes to the development of healthy microbiota in newborns⁶⁴.

There are several categories of prebiotics. For example, fructans contain inulin and activate the bacteria that produce lactic acid. Scientists have found that fructans stimulate the action of other beneficial bacterial strains. Galactooligosaccharides (GOS) are a class of prebiotics that play a significant role in stimulating Lactobacilli, Firmicutes, Enterobacteria, and Bifidobacteria. Oligosaccharides, which are primary prebiotics, can be derived from starch,

polysaccharides, glucose, and non-carbohydrate food substances⁶⁵⁻⁶⁶. In addition, they enhance immunity by improving the capacity of antibodies to respond and adapt to viral vaccinations. Studies also have shown that prebiotics reduce side effects of vaccinations⁶⁷. Diet is an important and regular lifestyle element that can influence a user's gut microbes, along with its viral species⁵⁸. Taking into account that the microbiota can be affected by diet, smoking, pre-and-probiotics, research continues into their use to restore health. Fermentation products of prebiotics decrease the gut pH which impact on the compositions and load of the intestinal microbiota⁶⁹. According to results of a study in 2006, supplementation with 15 grams of FOS for 3 weeks improved Crohn's disease symptoms and bifidobacteria population in the feces⁷⁰.

Probiotics are yeast or bacteria microorganisms that exhibit a positive role in the body. They can be particularly effective at restoring a microbiota that is damaged or lost due to illness or other lifestyle issues. Probiotics play a critical role in immunity by balancing harmful and healthy microbes. The two main types of probiotics are Lactobacilli and Bifidobacteria. Major sources of Lactobacilli include yogurt and other fermented foods⁷¹. These microbes improve digestion, particularly of lactose, and reduce diarrhoea. Foods that contain Bifidobacteria include yogurt, kefir, tempeh, and kimchi. These probiotic substances provide numerous benefits to the body, including the management of irritable bowel syndrome⁷². The primary mechanism of probiotics is mainly due to competitive exclusion, adhesion, immunomodulation, brain-gut interaction and enzymatic activity⁷³.

The Microbiota and Age Newborns

In newborns, the microbiota affects the immune system and thus may help prevent disease and improve immunity. Conversely, these same interactions can become pathogenic, causing different diseases in infants. According to research, infants who are exposed to a broad range of microbes in their early years are less likely to suffer from atopic diseases⁷⁴. Thus, reducing microbiota exposure during birth may help explain the increase in immunological disorders. During the early days of life, a balanced and

healthy development of microbiota leads to a robust innate and adaptive immune system that can tolerate pathogens. However, imbalance and poor development of microbes can be a primary predisposing factor for autoimmune diseases and atopic infections⁷⁵.

For instance, children with food allergies exhibit reduced levels of *Lactobacillus* and *Bifidobacterium* but excessive levels of enteric bacteria. Other studies indicate that newborns with protein allergies have excess *Clostridium coccooides* in their faecal matter⁷⁶. Additionally, the incidence of inflammatory bowel disease in newborns often depends on the composition of the microbiota. Studies show that reduced diversity and composition of *Bifidobacterium* is common among infants with necrotizing enterocolitis, a form of inflammatory bowel disease⁷⁷. Breast milk, which contains healthy microbiota, is especially critical in the prevention of diarrhoea and respiratory diseases⁷⁸. Overall, the microbiota is essential for newborns' immunity and even acts as an antibiotic against pathogenic bacteria.

The Elderly

A unique interaction exists between the microbiota and immunity among the elderly. As individuals age, their immune system undergoes deregulation, which reduces their ability to respond to mitogens. Additionally, maintaining homeostasis and balanced intestinal microbes is increasingly difficult with age, making the elderly more susceptible to conditions such as Alzheimer's disease. Malnutrition and poor diet among seniors further impairs the functionality of the microbiota, especially in the gastrointestinal tract. These changes can cause diseases, such as inflammatory and autoimmune disorders. For example, *Clostridium difficile* is a primary bacterial cause of diarrhoea among the elderly⁷⁹⁻⁸¹. This microbe is disproportionately present among the elderly due to environmental conditions (e.g. calorie restriction), medications (e.g. antibiotics), unhealthy intestinal microbiota, increased comorbidities, and changes in immunity. Overall, the features of the bacterium and the state of the immune system in the elderly determine the severity, mortality, and recurrence of *Clostridium difficile* infection in this population⁸²⁻⁸⁴.

The Microbiota and Disease

Interactions between the immune system and microbiota can affect overall health. For example, some interactions lead to better disease protection, whereas others may result in disease. Common disorders in the interaction between immunity and the microbiota include Crohn's disease, schizophrenia, autism spectrum disorder, obesity, and diabetes. Since COVID-19 does not have a safe method of treatment or prevention, it is best to focus on other strategies for its treatment.

Crohn's Disease

Crohn's disease is a condition caused by a dysfunctional interaction between the microbiota and the immune system. The disease is especially common among older adults. Studies with mice have shown that the urease enzyme and microbial activities may represent a major cause of this illness⁸⁵. Intestinal changes related to Crohn's disease interfere with the commensal relationship between the immune system and the gut microbiome, leading to pathological symptoms, such as inflammation of the digestive tract and tissue destruction⁸⁶.

Schizophrenia

Interactions between immunity and microbiota may cause schizophrenia⁸⁷. Research shows that variations in microbial diversity are likely to result in immune reactions or responses. Alternatively, microbial variations can increase production of mediators (e.g. inflammation), which then cross the brain-blood barrier and affect the brain, in turn leading to schizophrenia⁸⁸. Changes in the microbiota also may activate immunity and cause schizophrenia. Immune alteration sequences can include the activation of T cells and increased activities of chemokines, phase reactants, and plasma cytokines⁸⁹.

Autism Spectrum Disorder

Similar to schizophrenia, the microbiota in the digestive tract can produce metabolites that travel to the brain and affect its function. Changes in the microbiota may promote the production of metabolites that influence certain disease processes, such as those related to autism spectrum disorder. These metabolites include gamma aminobutyric acid, noradrenalin, and tryptamine⁹⁰. Research also has identified excessive levels of p-cresol and p-cresyl as causes

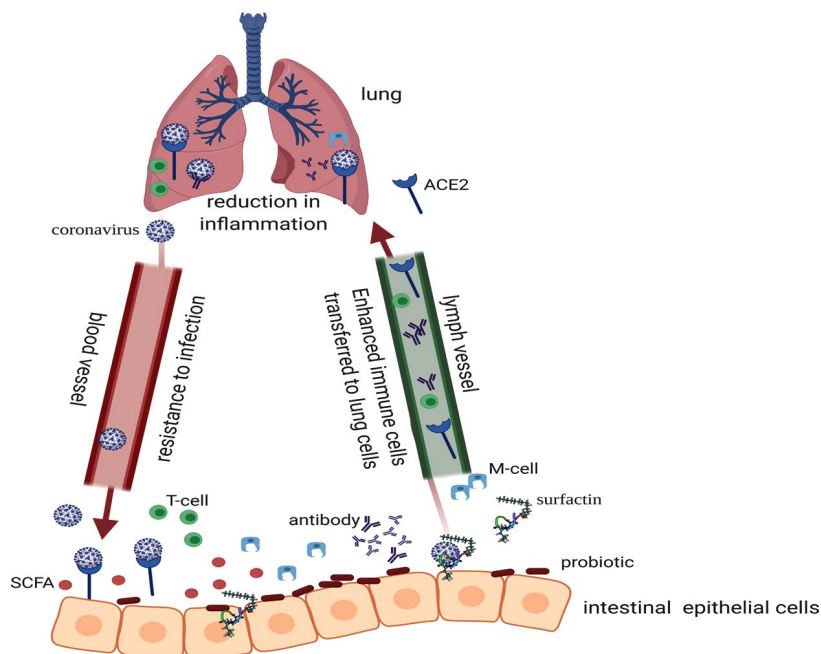


Fig. 1. The beneficial metabolites of probiotics and the enhancing antiviral immunity to provide protection to the lungs.

of cognitive disorders and behavioural variations in children with autism spectrum disorder. Gut microbiota in these children also may lead to obesity. Microbes can influence obesity in children by affecting energy extraction from food, hormonal functions, metabolism of lipids, and immune responses⁹¹⁻⁹².

Diabetes

Diabetes is a common condition among the elderly. The occurrence of pancreatic diseases, such as diabetes, may be synonymous with changes in the gut microbiota and in immune function. For instance, dysbiosis affects signalling pathways and reshapes the functions of the intestinal barriers. These activities have a direct implication on insulin resistance. Overall, these interactions between the immune system and microbiota vary according to age⁹³⁻⁹⁴.

Microbiota influence on Viruses like SARS-CoV-2

Viral infections include the common cold and flu, as well as the recently introduced COVID-19 virus. The interplay between the environment and biological host factors, such as regulation of the antiviral immune responses via intestinal bacteria, influences the outcome of these infections. The host immune system promotes the growth of beneficial microbes along the intestinal walls by producing molecular signals that support immune cell growth and targeted responses⁹⁵. Although the interactions between viruses and commensal microorganisms remain unclear, the microbiota likely has important immune system functions, including resisting viral invasions via direct and indirect mechanisms⁹⁶. Also, the diversity of gut bacteria is decreased in old age, and we learn that Covid-19 has mostly a deadly impact on elderly patients, which again suggests the role played by microbiota in this particular scenario⁹⁷. Recent studies demonstrate that *Acinetobacter* and *Klebsiella* bacteria have been observed in critical cases of COVID-19, who were in intensive care unit system set⁹⁸. It was reported that infection with COVID-19 infection can cause detrimental effects on the gastrointestinal system tract, which lead to a severe loss of immunity after recovery⁹⁹⁻¹⁰⁰.

The microbiota creates disease resistance by allowing bacterial membranes to develop tolerance to the immune system through an increase in anti-inflammatory cytokines, such as interleukin-10. The gut microbiota can promote

immunity against viral invasion via several mechanisms, such as binding of viruses to structural bacterial molecules. For example, the HIV-1 virus binds to lipopolysaccharides in the V3 loop to affect host cells. This process reduces the HIV-1 load and the inflammation caused by opportunistic Gram-negative bacteria. Segmented filamentous bacteria protect against vesicular stomatitis virus, reovirus, influenza A, and rotavirus^{101,96}. Moreover, viral infectivity can be reduced by bacterial products. For example, surfactin is produced by *Bacillus subtilis* and can disrupt the virion coronavirus and reduce the infectivity of different enveloped viruses (e.g. Crimean–Congo hemorrhagic fever, Dugbe, Ebola, influenza A, Mayaro, Nipah, Una, Zika, and Chikungunya)¹⁰²⁻¹⁰³. The conclusion of current research suggests that *L. plantarum* DR7 may be useful in the treatment of infection due to immunomodulation and release of IFN- γ , TNF- α pro-inflammatory cytokines¹⁰⁴. Some studies reveal a significant association between the microbiota composition and the ability of the host immune system to evade viruses. This association could be attributed to the mechanism through which viruses enter a host's system. For example, some viruses enter the host system through mucosal surfaces, and others evade the immune response to establish chronic infections, which could be the case with the new SARS-CoV-2 coronavirus. Therefore, although the gut microbiota is associated with several health benefits, these organisms also can interact with pathogens in various modes of transmission and infection to cause disease⁷³. Therefore, it seems that the gut microbiota impacts virus invasion via multiple mechanisms. It is recommended that the use of prebiotics, which assist in the growth of probiotic strains might flatten the curve in COVID-19²¹.

Scientific studies provide significant evidence on the interaction between the microbiota and viruses. Ample proof highlights how microbiota offer host protection against viruses and help regulate the mucosal immune system. Although none of these effects has been proven on the new SARS-CoV-2 virus, it should not outweigh considering this type of action, particularly, when there are probiotics capable of combating other coronavirus strains¹⁰⁵. Other evidence suggests that these microorganisms also

influence virus evasion. Therefore, microbiota may promote or limit viral infection, and in other instances they may have no effect at all, because they interact with each infection via different mechanisms¹⁰⁶⁻¹⁰⁷. It is suggested that increased permeability of the gut wall allows for increased transportation of bacteria to the lung, modifying the bacterial communities in the lung and thus modifying its immune function (Fig. 1)^{63,108}. Comparisons on recent studies need to be wisely followed. For example, immune system dysregulation in COVID-19 with severe respiratory distress has indeed been reported.

CONCLUSION

In conclusion, vast research has shown how some microorganisms lead to diseases and others enhance digestion, immunity, and metabolic activities. The microorganisms of the human microbiome play pivotal roles in immune activities and diseases. Development of the microbiota begins in utero and continues throughout life. Its composition and immune effectiveness depend on numerous factors, including the mode of delivery, environmental factors, and diet. The sources of microbiota range from food products to direct consumption of microbes. The possibility that the gut virome is an unidentified player in disease pathways is a plausible idea. Moreover, the human gut virome must be researched and studied in parallel with gut bacterial and fungal diversity. Future studies are necessary to understand better bacteria-virus interactions, cell-to-cell interactions, virus attachment sites, replication and the role probiotics on our gut when fighting against viral infections. Understanding how these microbes interact with disease processes may offer insight into treatment and prevention strategies for many illnesses, such as schizophrenia, autism, and diabetes.

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