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**Review Article**

# Microbiome-Immune Dynamics: Insights into Infectious Diseases

**Nasim Rafinezhad***

*Department of Biotechnology, Amol University of Special Modern Technologies, Amol, Iran.*

***Corresponding Author:** Nasim Rafinezhad, Department of Biotechnology, Amol University of Special Modern Technologies, Amol, Iran.*

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## Abstract

Infectious diseases and infections continue to be a leading cause of death in low-income countries and pose a significant risk to vulnerable populations, such as infants and the elderly. The immune system is crucial in determining susceptibility, persistence, and resolution of these infections. With 70-80% of immune cells located in the gut, there is a complex interaction between the intestinal microbiota, the intestinal epithelial layer, and the local immune system. Beyond the local immune responses in the gut, it is increasingly acknowledged that the gut microbiome also influences systemic immunity. Clinicians are increasingly leveraging the growing understanding of these complex interactions between the immune system, the gut microbiome, and human pathogens. The now well-established influence of nutrition on the gut microbiota composition and the immune system underscores the role that nutrition can play in enhancing health. This review explores the mechanisms that maintain the intricate balance between the microbiota, gut health, the local immune response, and systemic immunity, linking this to infectious diseases throughout life, and emphasizes the impact of nutrition in the prevention and treatment of infectious diseases.

***Keywords:*** *Gut Microbiota, Probiotics, Immune System, Infectious Diseases*

## Introduction

The microbiota is a diverse microbial community residing in a specific environment, interacting synergistically with the host organism. It comprises not only bacteria but also fungi, archaea, and protozoans [1,2], along with viruses, which appear to be more numerous than microbial cells [3]. The gastrointestinal tract (GIT), with an epithelial barrier covering an area of 400 $m^2$, is a complex and integrated ecosystem that is highly exposed to external influences. The diversity of the GIT microbiota is influenced by various factors, including host genetics, gender, age, immune system, anthropometric parameters, health status, geographical and socioeconomic conditions, treatments, and diet [4,5]. Recent metagenomic studies have shown that most microbial species are not consistently present in the same individual at the same time, although some species are commonly found in healthy individuals while others are less prevalent [6,7]. The GIT microbiota also varies across different segments of the digestive tract and among three distinct microhabitats: cells floating in the intestinal lumen, cells adhering to the mucus layer, and cells on the epithelial surface [3].

This active microbial community interacts beneficially with the host, contributing to energy harvest and storage. Its unique metabolic pathways and enzymes extend the host's metabolic potential, exerting evolutionary pressure to establish bacteria as human symbionts [8]. The GIT microbiota plays a crucial role in normal gut development by influencing epithelial cell proliferation and apoptosis. While the precise interactions between the microbiota and host cells remain largely unknown, short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate, produced from the fermentation of indigestible polysaccharides, are believed to play a significant anti-inflammatory role. SCFAs also promote intestinal homeostasis by aiding in intestinal repair through cellular proliferation and differentiation, and they inhibit the proliferation of cancerous cells. Butyrate, in particular, is vital for intestinal homeostasis as it serves as a primary energy source for colonocytes [9,10].

Furthermore, the GIT microbiota stimulates the development of both nonspecific and specific immune system components from birth and throughout life. It acts as an anti-infectious barrier by preventing pathogen adherence and colonization and producing bacteriocins and other toxic metabolites [11]. This review aims to highlight these physiological roles, with a particular focus on the GIT microbiota's contribution to the development and education of the immune system.

## 1. Infections

In Western countries, the incidence of infectious diseases has significantly decreased over the past decades due to improved hygiene, vaccination, and the use of antibiotics [12]. However, in developing nations, nearly one-third of deaths are still linked to infectious diseases. Infections also remain a considerable risk for vulnerable groups such as infants and the elderly. Upper respiratory tract infections are the most common reason people seek medical care, and in older adults, both influenza and pneumonia continue to be common causes of death [13]. The World Health Organization reports that infectious enteric diseases are among the leading causes of death, and according to the Global Burden of Diseases, Injuries, and Risk Factors Study of 2015, infectious diarrhea is a major cause of mortality worldwide, with a significant percentage of these deaths occurring in children under the age of five [13,14].

## 2. Defense Mechanisms in the Gastrointestinal Tract: The Role of Gut Microbiota and the Epithelial Barrier

Pathogens face three primary obstacles when attempting to cause an infection in the gastrointestinal (GI) tract: the intestinal microbiota, the intestinal epithelial layer, and the mucosal immune system [15]. The gut microbiota is a diverse microbial community, comprising bacteria, fungi, and viruses that coexist in harmony with the host [16]. This coevolution of gut microbes and mammals allows microbes to thrive in a habitat while they regulate various host physiological functions, including protective immunity against pathogens [17]. The composition of the gut microbiota is affected by numerous factors, such as genetics, gender, age, socio-economic status, diet, stress, and environmental influences like pollutants and antibiotics, collectively known as the exposome [18]. Disruptions to the microbial community structure and function, such as those caused by antibiotic use, can allow opportunistic pathogens to colonize, proliferate, and persist [19].

The microbiota employs several mechanisms to prevent pathogen colonization, overgrowth, and subsequent infection. One such mechanism is colonization resistance, where commensal microbiota and invading microbes compete for resources or niche space, whether nutritional or functional [19–21]. Bacterial cells continuously monitor their environment through signaling molecules accumulated during replication, adjusting their gene expression in response, a process known as quorum sensing [16,22]. These chemical signals lead to phenotypic changes in bacteria, affecting adherence, motility, intestinal density, and the secretion of protective compounds. Quorum sensing is used by commensals to maintain gut homeostasis, and by pathogens to evade host immune responses and enhance their pathogenicity [15].

Changes to the microbiota's community structure, or a harmful microbiota composition potentially caused by diet, stress, antibiotics, and other drugs, can alter the overall dynamics between the microbiota and host. This may result in low-grade inflammation, reduced colonization resistance, and increased susceptibility to infections [23].

In addition to the gut microbiota, the gut epithelial barrier is vital in safeguarding the host from pathogenic infections [24]. This physical barrier, composed of a single layer of cells linked by tight-junction-protein complexes, separates the commensal bacteria in the gut from the underlying tissues. The formation of these tight-junction complexes is a dynamic process that certain bacteria can disrupt by releasing toxins [19]. Additionally, the epithelial cell layer is protected by a mucus layer, which is one of the primary defense mechanisms of the intestinal epithelium against bacterial invasion, preventing direct interaction between luminal and mucosal microbes and epithelial cells [15]. Besides acting as a physical barrier, mucus also serves as a reservoir for host-produced antimicrobial molecules such as secretory IgA and defensins [25].

The production and degradation of mucus are controlled by a complex interaction between the host and microbes, regulated through the host's recognition of microbe-associated molecular patterns (MAMPs) and bacterial metabolites. This interaction makes mucus production susceptible to changes in the indigenous microbiota's composition [26].

There is a reciprocal relationship between mucus and microbes, where changes in the host's inflammatory state and microbiota composition can affect mucus production and composition, increasing susceptibility to infections [27]. The ongoing interaction between the gut microbiota and the intestinal epithelium results in constant immune signaling [28]. The regulation of this immune response, along with maintaining epithelial barrier integrity and permeability in the presence of commensal bacteria and invading pathogens, is crucial for sustaining intestinal homeostasis. Any disruption in this process can lead to inflammation and infection.

## 3. Defense against Infections: The Interaction of Gut Microbiota with the Local Immune System

The immune response is pivotal in determining susceptibility to, persistence of, and clearance of infections. The immune system is composed of two main components: the innate immune system and the adaptive immune system [29]. The innate immune system provides nonspecific protection through various defense mechanisms, including physical barriers like skin and mucous membranes, chemical barriers such as enzymes and antimicrobial proteins, and innate immune cells like granulocytes, macrophages, and natural killer cells [30]. T- and B-lymphocytes of the adaptive immune system recognize and respond to specific foreign antigens. T cells target infectious agents that have infiltrated host cells, a process termed cellular immunity due to the direct involvement of cells. T cells also play a crucial role in regulating B cells, which secrete antibodies that recognize specific antigens, a process known as humoral immunity because the antibodies circulate through body fluids [31].

The development and efficacy of the immune response are closely linked to the development and composition of the gut microbiota. Evidence for this comes from studies comparing age- and sex-matched germ-free mice, which lack commensal microflora, with conventionally raised mice and germ-free mice colonized with a defined microbiota, known as gnotobiotic mice. These studies have advanced our understanding of the effects of single bacterial strains, consortia of strains, specific microbe-expressed genes, and microbial metabolites on intestinal homeostasis and local and systemic immunity [32]. Research highlights that innate immunity plays a crucial role in the initial recognition and response to microbiota-derived products. Innate immunity in the gut begins with the single layer of intestinal epithelial cells (IECs) directly exposed to luminal contents and microbial products. The balance between host and microbes is maintained through the recognition of microorganisms via pattern-recognition receptors (PRRs). PRRs include a variety of extracellular and intracellular receptors that detect specific microbe-associated molecular patterns (MAMPs), such as TLRs, C-type lectin receptors (CLRs), nucleotide binding oligomerization domain (NOD)-like receptors (NLRs), and sensors for cytosolic DNA and RNA. Activation of PRRs induces the production of chemokines and cytokines necessary for orchestrating a protective immune response [33]. MyD88, an important adaptor molecule in PRR signaling, links PRR activation to the activation of NF-kB, a key regulator of inflammation. A deficiency in MyD88 can lead to a compromised immune response and increased susceptibility to infections [34–37]. However, inappropriate activation of PRRs can lead to excessive immune responses, potentially causing inflammatory diseases and autoimmunity. Hence, PRR responses are tightly regulated through feedback loops and cross-regulation [38].

IECs also secrete antimicrobial peptides (AMPs), which are key innate immune effectors with bactericidal, anti-inflammatory, and anti-endotoxic properties [39]. AMPs are vital for limiting pathogen interaction with the epithelium. Their expression can be down-regulated by certain pathogens and enhanced by specific microorganisms, highlighting the importance of microbiota composition in shaping the innate immune response [15,19]. Another way the microbiota influences the immune response is through metabolites produced from dietary components, host products, or other microbial metabolites [39]. These microbial metabolites, such as short-chain fatty acids (SCFA), tryptophan metabolites, and bile acid derivatives, have immunoprotective abilities. SCFAs enhance the production of antimicrobial peptides and mucus by specialized intestinal epithelial cells and stimulate the maturation and expansion of colonic regulatory T cells, which reduce local inflammatory responses to the microbiota [40]. SCFAs also support intestinal homeostasis by modulating the epithelial barrier and promoting the repair of intestinal cells through inducing cell proliferation and differentiation [16]. Furthermore, SCFAs are crucial for the proliferation of innate lymphoid cells (ILC3), which secrete IL-22, a cytokine important for inducing antimicrobial molecules in epithelial cells [41]. Tryptophan metabolites, particularly indoles derived from the commensal fermentation of dietary tryptophan, act as ligands for the aryl hydrocarbon receptor (AhR), which is essential for maintaining intestinal homeostasis. A loss of these metabolites is linked to inflammatory bowel disease [42,43]. Bile acid derivatives contribute to intestinal homeostasis and affect various host functions through the activation of farnesoid X receptor (FXR) and G protein-coupled bile acid receptor (TGR5) [44].

These derivatives are metabolically produced from bile acids by bacterial bile salt hydrolases (BSHs), expressed by specific bacterial phyla. A decrease in BSH gene abundance is associated with inflammatory bowel disease [45].

In summary, mucosal homeostasis in the gut is a delicate balance between gut microbiota, microbial metabolites, and host factors. This continuous interaction results in a tightly regulated low-grade inflammatory state, maintaining optimal host defense and influencing susceptibility to infections [46,47].

## 4. Defense against Infections: Impact of Gut Microbiota on Systemic Immune Response

The immune response is integral to the susceptibility, persistence, and clearance of infections, and comprises the innate and adaptive immune systems [29]. The innate immune system provides nonspecific defense through mechanisms such as physical barriers (skin, mucous membranes), chemical barriers (enzymes, antimicrobial proteins), and innate immune cells (granulocytes, macrophages, natural killer cells) [30]. The adaptive immune system, featuring T- and B-lymphocytes, recognizes and responds to specific foreign antigens. T cells target infectious agents within host cells, a process known as cellular immunity, and regulate B cells that secrete antibodies, part of humoral immunity [31].

Development and efficacy of the immune response are closely linked to the gut microbiota. Studies comparing germ-free mice with those colonized by defined microbiota (gnotobiotic mice) have shown the significant impact of the gut microbiota on intestinal homeostasis and immunity [32]. The gut microbiota influences systemic immune responses through various mechanisms, including the release of microbial soluble products into the circulation that affect peripheral immune cells [40]. Immune cells in distant organs can sense these microbial factors, and the absence of microbiota-derived signals alters immune function, increasing susceptibility to systemic infections [16].

One well-characterized mechanism is the microbiome's impact on T cells of the adaptive immune system, affecting their differentiation into T-helper (Th1, Th2, Th17) and regulatory phenotypes [48-51]. Butyrate, a short-chain fatty acid (SCFA), promotes differentiation of regulatory T cells, inhibiting systemic inflammation [52]. SCFAs also reprogram cell metabolism, inducing regulatory B cells and inhibiting Th17 cells, which is relevant for inflammatory and autoimmune diseases [53]. Other microbial products, such as ATP, tryptophan metabolites, and polysaccharides, influence immune cell populations and modulate inflammatory responses [54,55].

Commensal activation of memory T cells is necessary for protection against bacterial pathogens [56]. Control of IL-10-mediated anti-inflammatory responses by commensals enhances infection resistance by improving bacterial clearance and appropriate inflammatory responses [57]. Microbiota-derived signaling molecules can enter circulation, influencing immune cell development during hematopoiesis and affecting infection responses [1,58]. For instance, butyrate promotes differentiation of bone marrow monocytes to a tolerogenic phenotype [59]. Bone marrow cells express PRRs and respond to circulating MAMPs, with effects varying by PRR expression [60]. Activation of different PRRs on hematopoietic stem and progenitor cells (HSPCs) can induce trained immunity or generate tolerized macrophages [61-63]. AhR ligands can lead to the production of myeloid-derived suppressor cells, which suppress immune responses [64].

Gut microbiota-derived signals also modulate innate immune defenses, influencing lymphoid stimulation in the spleen, neutrophil migration and function, macrophage activation, and NK cell maturation [40,50,51,58,65]. Specific bacterial species can regulate inflammatory responses by reducing plasma corticosterone levels, an anti-inflammatory steroid [66]. Dysbiosis in the gut microbiota can impair local and systemic immune responses, leading to inflammatory diseases both locally and in distant sites like the airways, highlighting the gut-lung axis [67-69]. Alterations in the gut microbiota, often due to antibiotics, have been linked to atopic manifestations, allergic airway disease, and asthma [70-74]. The gut microbiota is also crucial in protecting against respiratory infections by directing immune responses [75-77]. Probiotic use has been associated with lower incidence and better outcomes of respiratory infections in clinical trials [76-80].

The common mucosal immune system further links gut and lung health, with gut-primed antigen-specific B cells migrating to the lungs via the thoracic duct [68]. Determining whether changes in the gut microbiota cause or result from disease is challenging, and longitudinal studies are needed to better understand its impact on lung disease severity and progression [67].

## 5. Gastrointestinal Microbiota and Infections from External or Internal Sources

### *5.1 Interactions Between Microbiota and Pathogens*

The intestinal microbiome, often called "the last undiscovered human organ," plays a critical role in the development and differentiation of the immune system. It is also essential in the initiation and progression of infectious diseases [69]. By colonizing mucosal entry sites, microbiota can directly prevent the invasion of pathogens through a process known as colonization resistance. This occurs by competing with pathogenic bacteria for adhesion sites and nutrients and by releasing toxic molecules that counteract pathogen colonization. Indirectly, microbiota stimulate the immune response as well. The gut microbiota send signals that promote the normal development of the immune system and the maturation of immune cells [70-72].

The microbiota stimulate the secretory IgA response, which inactivates rotaviruses, competes with *Clostridium difficile* colonization, and neutralizes cholera toxin [73]. Additionally, signaling molecules from the microbiota actively shape the host's systemic immune response by regulating hematopoiesis, thereby enhancing the response to infections [74]. Microbiota-derived signals trigger the development of granulocyte/monocyte progenitors in the bone marrow, influencing tissue-resident innate immune populations and promoting an early innate response. In the absence of these signals, tissue-resident myeloid populations alter, increasing susceptibility to systemic infections by *Staphylococcus aureus* and *Listeria monocytogenes* [75].

Pathogens can also exploit the interactions between the innate immune system and microbiota to evade the mucosal barrier. For example, the oral bacterium *Porphyromonas gingivalis* escapes the host immune response by modulating the TLR2 signaling pathway, leading to dysbiosis and subsequent inflammation [76]. Some viruses interfere with the interplay between bacteria and the innate immune system, such as the TLR4 signaling pathway, to ensure efficient transmission [77]. It has been shown that the antiviral host response improves with antibiotic depletion of commensal microbiota. Intestinal antiviral innate immunity involves the induction of IL-18, interferon (IFN)-λ, or IL-22 pathways, promoting the expression of signal transducer and activator of transcription 1 (STAT1) and antiviral genes. While IL-22 and IL-18 are stimulated by commensal bacteria, IFN-λ expression is inhibited by the microbiota, allowing viral persistence.

Interactions between gut epithelial cells and microbiota are crucial for maintaining barrier defenses and gut homeostasis. For instance, the microbiota help maintain tight junction integrity, limiting *Salmonella typhimurium* invasion [78]. Conversely, *S. typhimurium* induces IL-22 production, targeting commensal bacteria and creating a niche for its own colonization. Generally, the anti-infectious barrier is most effective when the microbiota are complex and stable, in a eubiotic state. However, dysbiosis—caused by factors such as poor colonization, antibiotic therapy, unhealthy diet, or conditions leading to secondary immunodeficiencies—weakens this barrier, making the host more susceptible to infections by various environmental pathogens. Additionally, certain microbiota species that become enriched in the new dysbiotic conditions can exploit their pathogenic potential, leading to opportunistic infections. For instance, antibiotics used to treat certain gastrointestinal tract (GIT) diseases can disrupt the intestinal microbiota, resulting in metabolic disturbances such as increased intestinal permeability and heightened susceptibility to infections, including fungal infections and *Clostridium difficile* infections (CDIs). Recent studies have demonstrated a clear link between microbiome composition and the risk of infectious diseases. For example, the composition of the microbiota can influence the risk of *Plasmodium falciparum* infection and play a crucial role in various vaccine responses [69].

Research focusing on the interactions between gut microbiota and the immune system in infectious diseases has mainly explored microbiome manipulation, through the administration of probiotics or fecal microbiota transplantation. Conditions like necrotizing enterocolitis, acute infectious diarrhea, antibiotic-associated diarrhea, CDIs, and ventilator-associated pneumonia, particularly prevalent in children, have shown improved outcomes, reduced mortality, and faster recovery rates with microbiota manipulation. Given that microbiota manipulation can balance health and infectious disease, alterations in intestinal microbiota by pathogens or pathobionts can lead to chronic diseases. For instance, in vivo studies have shown that the colonization of adherent-invasive *Escherichia coli* (AIEC), a pathovar associated with Crohn's disease, during microbiota acquisition led to chronic colitis in mice [79]. AIEC, *Yersinia enterocolitica*, and potentially other pathobionts can promote chronic inflammation in susceptible hosts by altering gut microbiota, thereby enhancing the activation of innate immunity and pro-inflammatory gene expression [80].

A recent study by Inoue et al. highlighted the impact of hepatitis C virus (HCV) infection on the gut microbiota. HCV-infected patients exhibited dysbiosis, characterized by decreased Clostridiales and increased *Streptococcus* and *Lactobacillus genera*, even in those with mild liver disease. This was evidenced by transient increases in Bacteroides and *Enterobacteriaceae* [81]. Members of the gastrointestinal tract microbiota can translocate from the digestive mucosa to the general circulation, indirectly stimulating IL-12 production by splenic macrophages and dendritic cells (DCs), which then regulates the Th1/Th2 balance toward a cell-mediated Th1 response [82].

Studies have shown that soluble products from *Lactobacillus fermentum* DSMZ 20052 can reduce IL-8 levels by inhibiting the NF-κB pathway, thereby mitigating the pro-inflammatory effects induced by *Yersinia enterocolitica* infection [83]. Other research supports the activation of the NF-κB signaling pathway by some probiotics, which subsequently triggers the activation of inflammatory genes. A hallmark of NF-κB activation is the production of IL-6 [84]. It has been demonstrated that colonizing the digestive tract of germ-free rats with the *Bifidobacterium lactis* BB12 strain stimulates IL-6 synthesis [85].

### *5.2 Interactions Between Microbes (Quorum Sensing)*

All bacteria communicate through signaling molecules, allowing them to sense their environment, monitor population density, and adjust gene expression accordingly. This communication provides bacteria with a significant advantage in surviving and spreading in highly competitive environments, such as the oral cavity and the intestine, which host numerous coexisting species. Intercellular communication among bacteria is categorized into two types based on the quorum-sensing (QS) mechanism. QS is a density-dependent molecular language that regulates cellular behavior in response to environmental changes. The first type is intraspecific cell-to-cell communication through specific QS molecules, while the second involves interspecific communication using a universal chemical "language" that facilitates signaling between bacteria and eukaryotic/host cells. QS operates via small, hormone-like organic molecules called autoinducers (AIs). In Gram-negative bacteria, AIs are diffusible molecules known as homoserine lactones (Acyl-HSL), whereas in Gram-positive bacteria, they are non-diffusible peptidic molecules (AIP). A universal interspecies signal, containing AIs common to both Gram-positive and Gram-negative bacteria, has been identified in 55 pathogens. These compounds, dependent on microbial density, play a crucial role in various niches, especially in highly colonized sites like the gut and oral cavity [86].

This communication mechanism regulates the expression of virulence genes in pathogens, significantly impacting infection. For example, low production of virulence factors by a small bacterial population may prompt a robust host response that neutralizes these molecules, whereas coordinated gene expression by high-density bacterial populations can lead to increased secretion of extracellular factors [87,88]. These molecules also have immunomodulatory effects, controlling inflammatory responses that can severely damage host tissues [89]. Recent studies suggest that these molecules might also have therapeutic potential as immunosuppressive drugs for autoimmune diseases [90]. The QS mechanism allows bacteria to regulate colonization by commensal bacteria and modulate the host response [91-93]. Although the exact mechanisms through which AIs influence mammalian cells remain unclear, modified immune responses have been observed. For instance, 3-oxododecanoyl homoserine lactone (HSL-C12) induces apoptosis and $Ca^{2+}$ release from endoplasmic reticulum stores. HSL-C12 also modulates inflammatory signaling, acting as an immunosuppressive agent at or below 10 μM concentrations but becoming pro-inflammatory and pro-apoptotic at 20 μM and above [94,95]. HSL-C12 operates through TLR- and Nod/Ipaf/caterpillar-independent signaling, activating multiple NF-κB-associated pro-inflammatory genes, including IL-1α, IL-6, IL-8, Cox2, mPGES, PGE2, and MUC5AC in various cell types. The pro-inflammatory effects may be mediated through the activation of MAPKs, extracellular signal-regulated kinases, inhibition of peroxisome proliferator-activated receptor γ, or $Ca^{2+}$ [96]. In the presence of pro-inflammatory molecules like lipopolysaccharides (LPS) or TNFα, HSL-C12 may inhibit NF-κB signaling and the expression of pro-inflammatory cytokines in macrophages and epithelial cells [97]. In vivo experiments have shown that direct injection of HSL-C12 into C57BL/6 mice leads to the expression of macrophage inflammatory protein-2 (MIP-2), the mouse analog of the human cytokine IL-8, and other cytokines. Notably, higher concentrations of MIP-2 were found in mice infected with QS-active microbial strains compared to those inoculated with QS-deficient bacteria [98].

Quorum-sensing is also used by microbiota members to detect the presence of similar microbes, contributing to their well-known anti-infectious barrier effect through antagonistic relationships with pathogens. It is known that probiotic strains can produce antimicrobial molecules and small QS inhibitors (QSIs) that interfere with the QS mechanism and virulence expression of pathogens [99-102].

Antimicrobial eosinophil-derived neurotoxin, cathelicidins, defensins, and AI2 signaling molecules play significant roles in intra- and interspecies communication. Some intestinal mammalian hormones mimic the action of bacterial signaling molecules, increasing the complexity of bidirectional communication between bacteria and the host [103]. Microbial endocrinology, which studies the exchange of molecular information between microorganisms and the host, reveals the ability of GIT microbiota to orchestrate bidirectional communication with the central nervous system by producing and sensing neurochemicals derived from either the microorganisms themselves or their host [104,105]. Steroid hormones like adrenaline and noradrenaline, due to their ability to pass through the plasma membrane, are involved in inter-kingdom communication between microorganisms and their mammalian host [106,107]. Although bacteria do not express adrenergic receptors, some studies indicate that bacterial cells respond to adrenaline and/or noradrenaline (NA), with recent research suggesting they significantly impact the homeostasis of gut microbiota [108]. Current data suggest that NA may function as a siderophore [109]. It is believed that NA contributes to the overexpression of enterobactin and the iron-chelating mechanism in *E. coli*, subsequently increasing bacterial growth rates. Conversely, gut microbiota can produce neurochemicals with hormonal activities that extend beyond the gut, influencing anxiety, depression, cognition, pain, inflammatory, autoimmune, and metabolic diseases [110-112].

## 6. Role of Probiotics

Lactic acid bacteria, including *Enterococcus* spp., *Lactobacillus* spp., *Bifidobacterium* spp., as well as various strains of *Bacillus*, *E. coli*, and *Streptococcus*, are among the most beneficial microbes identified in the human microbiota and are commonly utilized as probiotics. These probiotics are particularly valuable for addressing antibiotic-induced dysbiosis in critically ill patients. Many probiotic strains possess intrinsic resistance to antimicrobials, allowing them to be used alongside specific antibacterial treatments. For instance, *Lactobacillus rhamnosus* GG, which is naturally resistant to metronidazole and vancomycin, is frequently used for managing pseudomembranous colitis and antibiotic-associated diarrhea. Similarly, *Lactobacillus fermentum* ME-3 (DSM14241) can be administered with ofloxacin for treating infections caused by *Salmonella enterica* serovar Typhimurium [113].

Manges et al. employed a comparative metagenomic approach to demonstrate that CDI development in humans is associated with an increase in *Firmicutes* and a decrease in the *Bacteroidetes* phylum. Their study found that human probiotic infusion can correct dysbiosis in CDI by replenishing depleted bacterial species and restoring colonization resistance [114-116]. Additionally, Khodaii et al. examined the effects of cell-free supernatants from 16 strains of lactobacilli and bifidobacteria on the invasiveness of enteroinvasive *Escherichia coli* (EIEC). Their findings showed that these supernatants inhibited the invasion of EIEC strains into CaCo-2 and T84 cell lines. They proposed that probiotics prevent EIEC invasion into the intestines not by competing for adhesion sites but by producing metabolites that alter the environment, cell barriers, or gene expression [117].

Lactic acid bacteria produce bacteriocins through a cell density-dependent mechanism regulated by quorum sensing (QS). This production is inducible and requires the extracellular accumulation of specific chemical messengers, known as AI1 and AI2 [116]. Probiotics can therefore be used in various forms: live cells, dead cells, or soluble molecules like antimicrobials and QS inhibitors. Plants, too, can affect bacterial communication and processes controlled by QS mechanisms, representing an anti-infectious defense strategy. These plant-derived molecules have demonstrated in vitro efficacy and can be used alone or in combination as alternative or complementary anti-infectious treatments [117].

Probiotics confer health benefits by modulating both pro-inflammatory and anti-inflammatory responses. Research indicates that cell surface molecules of *Lactobacillus* strains can induce TNF-α production in macrophages via TLR2 signaling [118]. In vitro and in vivo studies suggest that *Propionibacterium* species offer numerous health benefits, including modulating gut microbiota composition and activities [119,120]. Dairy propionic bacteria can influence the gut microbiota by promoting the growth of beneficial bacteria like *Bifidobacteria* and inhibiting the adherence of pathogens such as *H. pylori* [121], *Salmonella enterica* serovar Enteritidis, and enteropathogenic *E. coli* to various cell lines [122,123]. Clinical studies have also highlighted the advantages of combining dairy propionibacteria with other probiotic strains to modulate the host immune system [124]. For example, *Propionibacterium freudenreichii* spp. shermanii (PJS) and *Lactobacillus rhamnosus* GG (GG) were tested for their immunomodulatory effects in fat-fed ApoE3Leiden mice. Mice receiving PJS and GG exhibited significantly lower intestinal mast cell counts compared to controls. Additionally, GG increased intestinal IL-10 levels, while PJS reduced intestinal TNF-α immunoreactivity.

Probiotics are also an effective preventive measure against necrotizing enterocolitis (NEC), with experimental evidence supporting their role. Oral administration of *Bifidobacterium bifidum* cells reduced ileal claudin-3 and occludin levels in neonatal rats with NEC [125]. Furthermore, bacteria-free conditioned media from probiotics such as *Bifidobacterium infantis*, *Lactobacillus plantarum*, and *Lactobacillus acidophilus*, whether used alone or in combination, may offer protection against NEC through their anti-inflammatory and cytoprotective properties and by enhancing intestinal barrier function [126,127].

A new frontier in probiotic therapy involves bioengineered probiotics, where strains are modified to express foreign genes. Culligan et al. explored the benefits of recombinant probiotics for treating enteric infections [128]. However, the use of genetically modified probiotics raises ethical concerns [129].

## Conclusions

As our understanding of the complex interactions between the gut microbiota and immune systems deepens, scientists and clinicians are increasingly leveraging this knowledge to develop strategies aimed at enhancing prevention and treatment of infectious diseases. Effective interventions must account for the considerable variability in microbiome composition and immune responses among individuals, necessitating a personalized approach.

Dietary modifications present a promising avenue for rapidly altering microbiome function and associated immune responses. Tailored nutritional strategies could therefore play a crucial role in influencing both the development and management of infectious diseases. Maintaining intestinal homeostasis involves a delicate equilibrium between the host and its microbiome. The host employs several physiological mechanisms to manage the microbiome, while the intestinal immune system relies on microbial interactions for proper development and regulation.

The application of macroecological concepts to the gut microbiota indicates that the microbiota biodiversity can serve as an important measure of eubiosis status. The easy access and possibility to modulate the microbiota makes it a good target for both establishing a link between certain patterns of gut microbiota and the physiological/pathological status. Due to the complexity and inter-individual differences of human microbiota, the identification of microbial colonization profiles specifically associated with certain disorders, as well as the characterization of microbial metabolic pathways related to health and disease state still remains a challenge. The human microbiota interacts at multiple levels with the immune system and the alteration of this crosstalk could be involved in the pathophysiological mechanisms of the host and can further be exploited to develop clinical therapies for some immunological disorders, such as inflammatory and autoimmune

## Conflict of Interest

The author declare no conflict of interest.

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