Review

Gut Microbiota and Human Health: Physiological Functions, Host Interactions, and Modulatory Factors

Carla Gimena Escudero , Macarena Herrera , Gaston Aguilera , Guillermina Belmonte-Giannetti , Eduardo Agüero , Julieta Juri , Gonzalo Lucero , Abigail Rojas-Aguilar , Ailen Victoria Maugeri , Gino Martin Binotto , Facundo Nahuel Escudero , Guadalupe Orozco , Agustina Lucía Diaz , Francesco Rino Binotto Ferrero , Stefano Bilo , Morena da Silva , Lucia Alejandra Elias , Cristobal Frustaglia-Vignolo , Vanesa Silvana Bazzocchini *

Posted Date: 17 March 2026

doi: 10.20944/preprints202603.1264.v1

Keywords: human gut microbiota; microbial diversity; short-chain fatty acids; immune modulation; gut–brain axis; dysbiosis; diet and lifestyle

 doi:10.20944/preprints202603.1264.v1

Review

Gut Microbiota and Human Health: Physiological Functions, Host Interactions, and Modulatory Factors

Carla Gimena Escudero [1], Macarena Lorena Herrera [2], Gaston Aguilera [1], Guillermina Belmonte-Giannetti [1], Eduardo Agüero [1], Julieta Gabriela Juri [1], Gonzalo Valentín Lucero [1], Abigail Micaela Rojas-Aguilar [1], Ailen Victoria Maugeri [1], Gino Martin Binotto [1], Facundo Nahuel Escudero [1], Guadalupe Orozco [1], Agustina Lucía Díaz [1], Francesco Rino Binotto Ferrero [1], Stefano Bilo [1], Morena da Silva [1], Lucía Alejandra Elías [1], Cristóbal Frustaglia-Vignolo [1] and Vanesa Silvana Bazzocchini [1,*]

[1] Cátedra de Fisiología, Facultad de Ciencias Médicas, Universidad de Mendoza, Paseo Dr. Emilio Descote 720, 5500 Mendoza, Argentina

[2] School of Pharmacy and Biomolecular Sciences; Department of Physiology & Medical Physics; FutureNeuro, SFI Research Centre for Chronic and Rare Neurological Diseases, RCSI University of Medicine and Health Sciences, Dublin D02 YN77, Ireland

* Correspondence: vanesa.bazzocchini@um.edu.ar; Tel.: +54 9 261 598-3067

Highlights

- The human gut microbiota exhibits regional variation in composition and density, with the colon hosting the most diverse and abundant microbial communities.
- Beyond bacteria, the virome and archaeome contribute to microbial ecosystem stability and metabolic cooperation.
- Gut microbes play essential roles in immune regulation, intestinal barrier integrity, metabolic homeostasis, and neurotransmitter signaling, forming critical host–microbiota axes.
- Diet, lifestyle, exercise, sleep, and aging profoundly modulate microbial composition and functional output, influencing systemic health and disease risk.
- Understanding host–microbiota interactions offers opportunities for therapeutic interventions, including probiotics, prebiotics, and personalized nutrition, to restore eubiosis and promote health across the lifespan.

Abstract

The human microbiota is a diverse and dynamic ecosystem of microorganisms that inhabit the gastrointestinal tract and other body sites, playing a central role in host physiology. Microbial composition and density vary along the gastrointestinal tract, with the oral cavity and colon representing regions of highest diversity and microbial load, respectively. Beyond bacteria, gut virome and archaeome contribute to ecosystem stability and metabolic cooperation. The microbiota performs essential physiological functions, including maintenance of the intestinal barrier, modulation of the immune system, fermentation of dietary components into short-chain fatty acids (SCFAs), vitamin biosynthesis, and regulation of systemic metabolic and neuroendocrine pathways. Host–microbiota communication is mediated by microbial metabolites, pattern recognition receptors, immune cells, and neuroimmune interactions involving the enteric nervous system, forming the basis of the gut–brain, gut–liver, and other organ axes. Dysbiosis, caused by stress, aging, antibiotics, or an unhealthy diet, disrupts these interactions, contributing to inflammatory, metabolic, and neurodegenerative disorders. Environmental factors, including diet, physical activity, and sleep, profoundly shaped microbial composition and functional output. Diets rich in fiber, plant-based foods, and Mediterranean patterns promote microbial diversity and SCFA production, whereas Western diets predispose dysbiosis and systemic inflammation. Understanding the mechanisms by which microbiota influences host physiology provides opportunities for targeted interventions, including probiotics, prebiotics, and lifestyle modifications, aimed at restoring microbial balance and

 doi:10.20944/preprints202603.1264.v1

improving health outcomes. This review integrates current knowledge on the composition, function, and modulators of the human microbiota, emphasizing its central role in maintaining intestinal and systemic homeostasis across the lifespan.

Keywords: human gut microbiota; microbial diversity; short-chain fatty acids; immune modulation; gut–brain axis; dysbiosis; diet and lifestyle

1. Introduction

The human gut microbiota constitutes a highly complex and dynamic ecosystem that harbors trillions of microorganisms, predominantly bacteria, but also archaea, viruses, and eukaryotic microbes [1]. Over the past decade, growing scientific interest in this microbial community has been driven by mounting evidence linking dysbiosis to a wide range of chronic non-communicable diseases [2,3]. The intricate interplay among the gut microbiota, its derived metabolites, and the host immune system is fundamental to maintaining physiological homeostasis [4–6]. Disruption of this equilibrium may contribute to the development of inflammatory, metabolic, and neuropsychiatric disorders [3,7]. Accordingly, the gut microbiota is increasingly conceptualized as a metabolically active organ that participates in systemic regulation [8]. This review aims to provide a comprehensive overview of the human gut microbiota, integrating current knowledge into its spatial organization, composition, physiological functions, mechanisms of host interaction, and modulatory factors. In addition, the review examines how diet, lifestyle, aging, and environmental influences shape microbial communities and their functional output, with implications for health and disease. By synthesizing findings across microbiology, immunology, metabolism, and neurobiology, the review highlights the central role of the gut microbiota in maintaining homeostasis and presents potential strategies for targeted interventions. Importantly, despite its growing relevance, there is a notable lack of dedicated material and structured curricula on this topic in health sciences careers, underscoring the need for increased educational resources to prepare future professionals for microbiota-informed clinical practice.

1.1. Search Strategy and Selection Criteria

Peer-reviewed articles were systematically searched using the PubMed database, the Google Scholar search platform, and Elsevier DataSearch. The literature search aimed to identify relevant studies addressing the relationship between gut microbiota and human health outcomes. To ensure methodological rigor and transparency in the selection process, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist was applied to evaluate the quality and eligibility of the selected studies. This approach allowed for a structured screening process and improved the reliability and reproducibility of the literature included in this review. We considered articles including the most recent and remarkable studies in the field. The search terms for the introduction were "microbiota" AND ("gastrointestinal tract" OR "oral" OR "gastric" OR "intestinal") AND homeostasis NOT (disease OR pathology OR disorder OR cancer OR pathogenesis); for composition and development of gut microbiota were “microbiota” AND (oral microbiota OR gastric microbiota OR intestinal microbiota OR colonic microbiota) AND composition AND "healthy individuals"; for physiological functions were "microbiota" AND ("gastrointestinal tract" OR "oral" OR "gastric" OR "intestinal") AND ("neurotransmitters" OR "neuromodulation" OR " brain gut axis") NOT disease AND “immune system”; and for diet and lifestyle modulators were ("diet" OR "lifestyle") AND "gut microbiota composition" AND healthy NOT disease.

2. Composition and Development of the Gut Microbiota

The human gut microbiota is a complex and dynamic microbial community whose composition and structure are shaped by multiple host and environmental factors. Advances in sequencing

 doi:10.20944/preprints202603.1264.v1

technologies have enabled detailed characterization of the taxonomic diversity of intestinal microorganisms and the processes governing their establishment and maturation throughout the human lifespan. The composition of this microbial ecosystem varies considerably among individuals and evolves over time, particularly during early life when microbial colonization and immune system development occur simultaneously. Understanding both the taxonomic composition of the gut microbiota and the mechanisms that drive its early-life establishment is essential for elucidating its role in health and disease.

2.1. Taxonomic Composition

The human intestinal microbiota is predominantly composed of bacteria belonging to a limited number of major phyla. Among these, Firmicutes and Bacteroidetes represent the most abundant groups, followed by smaller proportions of Actinobacteria, Proteobacteria, and Verrucomicrobia [4]. Collectively, these microbial communities comprise a highly diverse ecosystem, with estimates suggesting that more than 1,500 microbial species may colonize the human gastrointestinal tract, although the specific composition varies substantially among individuals due to genetic, environmental, and lifestyle-related factors [9,10]. Advances in metagenomic sequencing have also led to the identification of distinct microbial community structures, commonly referred to as enterotypes. These enterotypes are characterized by the predominance of specific bacterial genera, most notably Bacteroides, Prevotella, or Ruminococcus, and are thought to be strongly influenced by long-term dietary patterns and lifestyle factors [9,11,12]. Although the phylum Firmicutes is typically the most abundant component of the intestinal microbiota, the genus Bacteroides has gained particular attention as a key ecological regulator [13]. These bacteria are considered keystone taxa, meaning that they play a disproportionately important role in maintaining the stability and functionality of the intestinal ecosystem [14]. Under physiological conditions, Bacteroides species contribute to essential processes such as polysaccharide digestion, pathogen exclusion, immune system modulation, and the regulation of host metabolic and neurological functions [15,16].

2.2. Early-Life Colonization

The establishment of the gut microbiota begins at birth and represents a critical window in human development. Initial microbial colonization is influenced by several perinatal and environmental factors, including the mode of delivery, maternal microbiota composition, early nutrition, and exposure to antibiotics [17]. Infants delivered vaginally are typically colonized by microbial communities resembling the maternal vaginal and intestinal microbiota, whereas those born by cesarean section tend to acquire microbial profiles more closely associated with maternal skin and the hospital environment [5,9]. These early differences in microbial exposure may have lasting effects on microbiota composition and immune system development.

Postnatal nutrition further shapes microbial succession during infancy. In particular, breast milk plays a fundamental role in promoting the growth of beneficial bacterial taxa. Human milk oligosaccharides (HMOs), complex carbohydrates present in breast milk, act as selective substrates for microbial fermentation and preferentially stimulate the proliferation of genera such as *Bifidobacterium* and *Lactobacillus* [18]. Early microbial colonization is closely linked to the maturation of the host immune system, contributing to the development of regulatory T cells, the establishment of mucosal immune tolerance, and the strengthening of long-term immune resilience [19].

2.3. Metabolic and Endocrine Functions

The intestinal microbiota plays a fundamental role in host metabolism through the fermentation of complex carbohydrates that escape digestion in the upper gastrointestinal tract. This fermentation process generates short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate, which serve as key energy sources for colonocytes and exert anti-inflammatory, immunomodulatory, and potential antitumor effects [4,5]. Butyrate, in particular, supports intestinal epithelial integrity,

 doi:10.20944/preprints202603.1264.v1

regulates gene expression through histone deacetylase inhibition, and promotes intestinal barrier function. In addition to SCFA production, gut microorganisms contribute to the biosynthesis of several essential micronutrients, including B-group vitamins (such as folate, riboflavin, and biotin) and vitamin K. These microbial metabolic activities supplement host nutritional requirements and influence systemic metabolic pathways [20,21]. Furthermore, the microbiota participates in the production and modulation of various bioactive compounds, including neurotransmitters such as serotonin, gamma-aminobutyric acid (GABA), and dopamine precursors, which contribute to signaling within the gut–brain axis [22]. Another important metabolic function of the microbiota involves the transformation of dietary components into bioactive metabolites. For example, dietary choline and carnitine are metabolized by gut bacteria into trimethylamine (TMA), which is subsequently converted in the liver to trimethylamine-N-oxide (TMAO), a compound associated with increased cardiovascular risk [23,24]. Additionally, microbial metabolism regulates bile acid transformation, producing secondary bile acids that influence lipid absorption, glucose metabolism, and host metabolic signaling pathways. These findings highlight the complex interaction between diet, microbial metabolism, and systemic metabolic health.

2.4. Immunological Regulation and Barrier Function

The gut microbiota plays a crucial role in maintaining intestinal barrier integrity and regulating immune homeostasis. Commensal microorganisms stimulate epithelial cells to produce mucins and antimicrobial peptides, which reinforce the mucosal barrier and prevent colonization by pathogenic organisms [25,26]. In parallel, microbial signals interact with immune cells in the intestinal mucosa to promote the development of regulatory T cells and stimulate the production of secretory immunoglobulin A (IgA), a key component of mucosal immunity. The gut-associated lymphoid tissue (GALT), which represents approximately 70% of the human immune system, relies heavily on microbial stimulation for its development and functional maturation. Continuous interaction between commensal microbes and immune cells promotes immune tolerance to beneficial microorganisms while maintaining the capacity to respond to pathogens [27]. Alterations in microbial composition can disrupt this balance. A reduction in beneficial SCFA-producing bacteria, such as *Faecalibacterium prausnitzii*, has been associated with inflammatory bowel diseases and colorectal cancer, highlighting the importance of microbial diversity in maintaining intestinal health [28]. Dysbiosis can impair epithelial barrier integrity, increase intestinal permeability, and promote chronic inflammation, thereby contributing to the development of several immune-mediated and metabolic diseases [29].

2.5. Key Factors Modulation the Gut Microbiota

The diversity and composition of the gastrointestinal microbiota are shaped by a variety of host and environmental factors. Local physiological conditions such as pH gradients, oxygen concentration, nutrient availability, and intestinal motility strongly influence microbial colonization patterns along the digestive tract. In addition, host-related factors, including genetics, immune activity, age, diet, and medication exposure, play important roles in determining microbial diversity and stability [12,30]. Dietary patterns are considered one of the most influential determinants of microbiota composition. Diets rich in plant-derived fiber promote microbial diversity and support the growth of short-chain fatty acid–producing bacteria, whereas diets high in saturated fats and refined carbohydrates are associated with reduced diversity and increased susceptibility to dysbiosis [31–33].

2.6. Dysbiosis and Disease

Dysbiosis refers to an imbalance in microbial composition characterized by the loss of beneficial microorganisms and the expansion of opportunistic pathogens. This condition has been linked to numerous chronic diseases, including inflammatory bowel diseases, obesity, type 2 diabetes,

 doi:10.20944/preprints202603.1264.v1

allergies, cardiovascular disease, and colorectal cancer [4,34,35]. In ulcerative colitis, for example, reduced microbial diversity and the depletion of butyrate-producing bacteria contribute to chronic intestinal inflammation and impaired mucosal healing [5]. In surgical contexts, dysbiosis may increase susceptibility to surgical site infections and postoperative complications, particularly in patients exposed to prolonged antibiotic therapy [3].

2.7. Therapeutic Strategies

Several strategies have been developed to restore microbial balance and improve health outcomes: 1) **Probiotics and prebiotics:** These compounds promote the growth and activity of beneficial microorganisms and enhance intestinal barrier function [36]; 2) **Synbiotics:** Combinations of probiotics and prebiotics have demonstrated beneficial effects in inflammatory conditions such as ulcerative colitis [37]; 3) **Fecal microbiota transplantation (FMT):** This approach has shown high efficacy in treating recurrent *Clostridioides difficile* infections and is being explored for other metabolic and gastrointestinal disorders [3,38]; 4) **Dietary modulation:** Increased consumption of fermentable fiber and functional foods, such as fermented brown rice or germinated barley, may exert anti-inflammatory effects and promote microbial diversity [5]; 5) **Optimized surgical protocols:** Evidence-based strategies such as chlorhexidine skin preparation and Enhanced Recovery After Surgery (ERAS) protocols may help preserve microbiome homeostasis and reduce postoperative complications [3]

3. Spatial Distribution of the Gut Microbiota Along the Gastrointestinal Tract

While the overall composition of the gut microbiota has been extensively characterized, it is important to recognize that microbial communities are not uniformly distributed throughout the gastrointestinal tract. Instead, they exhibit marked spatial variation driven by differences in local physicochemical conditions, including pH, oxygen availability, nutrient gradients, host secretions, and intestinal motility. These environmental factors create distinct ecological niches along the gastrointestinal tract, allowing specific microbial populations to colonize and thrive in particular regions. Understanding spatial organization is therefore essential for interpreting the functional roles of the gut microbiota and its interactions with host physiology [39].

The human gastrointestinal (GI) tract hosts a highly structured microbial ecosystem whose composition and density vary markedly along its anatomical length. These spatial variations are primarily determined by physicochemical factors such as pH, oxygen availability, nutrient gradients, bile acids, immune defenses, and intestinal transit time. As a result, microbial density and diversity increase progressively from the upper to the lower gastrointestinal tract, with each compartment supporting distinct microbial communities adapting to its environmental conditions [39,40].

The oral cavity represents one of the most microbially diverse environments in the human body, harboring more than 1,000 identified microbial taxa. This ecosystem is characterized by complex multispecies biofilms that form on dental surfaces, the tongue, and mucosal tissues. Dominant bacterial genera include *Streptococcus*, *Prevotella*, *Fusobacterium*, and *Veillonella*, which interact through metabolic cross-feeding and coaggregation processes that stabilize oral microbial communities [41,42]. These microbial biofilms play essential roles in maintaining oral health but can also contribute to dental caries and periodontal disease when ecological balance is disrupted.

The esophagus harbors a microbial community that closely resembles that of the oral cavity due to the continuous passage of saliva and swallowed microorganisms. The esophageal microbiota is typically dominated by genera such as *Streptococcus*, *Prevotella*, and *Haemophilus*. However, local conditions such as transient oxygen exposure, epithelial turnover, and peristaltic movement limit extensive microbial colonization. Despite its relatively lower microbial density compared with distal gut regions, the esophageal microbiome has gained attention for its potential role in esophageal diseases, including gastroesophageal reflux disease and Barrett's esophagus [43].

The stomach presents one of the most challenging environments for microbial survival due to its highly acidic pH, which can reach values as low as 1–2. Consequently, microbial density in the

 doi:10.20944/preprints202603.1264.v1

stomach is substantially lower than in other gastrointestinal compartments. Nevertheless, several acid-tolerant microorganisms are able to persist in this environment, including members of the families *Streptococcaceae* and *Enterobacteriaceae*. A key microbial inhabitant of the stomach is *Helicobacter pylori*, a bacterium capable of colonizing the gastric mucosa by neutralizing gastric acid through urease activity. Colonization by *H. pylori* can profoundly alter the gastric microbial ecosystem, often leading to reduced bacterial diversity and contributing to the development of chronic gastritis, peptic ulcers, and gastric cancer [44].

In the small intestine, microbial density remains relatively low compared with the colon but increases gradually along its length. The proximal small intestine, including the duodenum and jejunum, contains relatively sparse microbial populations due to the presence of bile salts, digestive enzymes, antimicrobial peptides, and rapid luminal flow. These conditions favor the growth of facultative anaerobes and fast-growing bacteria, with genera such as *Lactobacillus*, *Streptococcus*, and members of the phylum *Proteobacteria* being commonly detected. As intestinal contents move distally toward the ileum, environmental conditions become more conducive to microbial colonization, including reduced oxygen levels and slower transit times. Consequently, microbial diversity and density increase substantially, and the microbial composition begins to resemble that of the colon [45,46].

The colon represents the most densely populated microbial habitat in the human body, containing up to 10^{14} microbial cells and accounting for the majority of the gut microbiota. The colonic microbiome is dominated by the bacterial phyla *Firmicutes*, *Bacteroidetes*, and *Actinobacteria*, with smaller contributions from *Proteobacteria* and *Verrucomicrobia* [4]. The anaerobic conditions and prolonged transit time in the colon facilitate extensive microbial fermentation of dietary substrates that escape digestion in the upper gastrointestinal tract. These substrates include complex carbohydrates, resistant starch, and dietary fiber, which are converted into short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate. These metabolites serve as important energy sources for colonocytes and play key roles in regulating host metabolism, immune function, and intestinal barrier integrity. In addition to luminal microbial populations, the colonic mucosal layer hosts specialized microbial communities adapted to the mucus-rich environment. Mucin-degrading bacteria such as *Akkermansia* and *Ruminococcus* contribute to the turnover and remodeling of the mucus barrier, thereby supporting mucosal homeostasis and host–microbe interactions [44]. The spatial organization of these microbial communities, distinguishing luminal from mucosa-associated populations, represents an additional level of ecological complexity that influences gut health and disease susceptibility.

4. Integration of the Birome and Archaeome

Although the spatial organization of bacterial communities along the gastrointestinal tract represents a key aspect of gut microbial ecology, bacteria are not the only microorganisms inhabiting this environment. Advances in high-throughput sequencing and metagenomic technologies have revealed that the intestinal ecosystem also contains diverse viral and archaeal communities that interact closely with bacterial populations. These additional microbial domains contribute to the overall complexity, stability, and functional capacity of the gut microbiome. Consequently, a comprehensive understanding of the intestinal microbial ecosystem requires consideration of not only bacterial populations but also the virome and archaeome that coexist within the gut environment. In recent years, advances in metagenomic sequencing have revealed that the intestinal ecosystem also includes diverse viral and archaeal communities. These microbial domains, collectively referred to as the virome and archaeome, contribute significantly to the ecological stability, metabolic functionality, and evolutionary dynamics of the gut microbiome.

The intestinal virome consists predominantly of bacteriophages, viruses that infect bacteria, and represents a highly diverse and dynamic component of the gut ecosystem. Among the most abundant viral groups identified in the human gut are members of the orders *Caudovirales*, *Microviridae*, and the recently characterized *Assphages* [47]. Bacteriophages play a fundamental role in shaping bacterial

 doi:10.20944/preprints202603.1264.v1

community structure through both lytic and lysogenic replication cycles. During the lytic cycle, bacteriophages infect and lyse bacterial cells, thereby regulating bacterial population sizes. In contrast, during the lysogenic cycle, phage genomes integrate into bacterial chromosomes as prophages, potentially altering bacterial gene expression and metabolic capabilities [48].

Through these mechanisms, bacteriophages act as important regulators of microbial diversity and ecological balance. They also facilitate horizontal gene transfer between bacterial hosts, contributing to the dissemination of genes involved in metabolic pathways, antibiotic resistance, and virulence. This process can drive rapid microbial adaptation within the intestinal environment. Beyond their regulatory effects on bacterial populations, bacteriophages contribute to the ecological resilience of the gut microbiome [48]. Environmental perturbations such as dietary changes, infections, or antibiotic exposure can disrupt microbial community structure. Viral communities may help restore ecological balance by selectively targeting dominant bacterial populations and promoting microbial turnover. Studies have suggested that greater viral diversity is associated with increased ecosystem stability, whereas reduced virome diversity has been linked to dysbiosis and several disease states, including inflammatory bowel disease and obesity [49].

The archaeome represents another important yet historically underexplored component of the gut microbiota. Although archaea are generally less abundant than bacteria and viruses, they play a critical role in intestinal microbial metabolism. The human gut archaeome is dominated by methanogenic archaea, particularly *Methanobrevibacter smithii*, which are specialized in utilizing hydrogen and carbon dioxide generated during bacterial fermentation to produce methane [50]. This metabolic interaction illustrates a key example of microbial syntrophy within the gut ecosystem. During bacterial fermentation of dietary carbohydrates, hydrogen gas is produced as a metabolic byproduct. Excess hydrogen can inhibit bacterial fermentation processes by shifting redox balance and reducing metabolic efficiency. Methanogenic archaea alleviate this constraint by consuming hydrogen, thereby maintaining favorable thermodynamic conditions for bacterial metabolism. As a result, the removal of hydrogen enhances bacterial fermentation efficiency and promotes increased production of beneficial short-chain fatty acids. Through this metabolic cooperation, methanogenic archaea indirectly influence host energy harvest and intestinal metabolic activity [51,52]. Variations in archaeal abundance have been associated with several physiological and pathological conditions. For example, elevated levels of *Methanobrevibacter smithii* have been linked to constipation-predominant irritable bowel syndrome, likely due to methane-mediated slowing of intestinal transit. Conversely, alterations in archaeal populations have also been implicated in metabolic disorders such as obesity (Borrel et al., 2020). Together, the bacterial microbiota, virome, and archaeome form a highly interconnected and dynamic microbial ecosystem. Understanding the interactions among these microbial domains is essential for developing a more comprehensive view of gut microbiome function and its influence on human health and disease.

5. Physiological Functions of the Human Microbiota

Beyond its compositional diversity and spatial organization along the GI tract, the human microbiota performs a wide range of physiological functions that are essential for maintaining host homeostasis. As discussed in the previous sections, the gut microbial ecosystem consists not only of bacteria but also of viruses and archaea that interact dynamically with each other and with the host. These microbial communities form a highly integrated biological system capable of influencing multiple physiological processes. The human microbiota colonizes several anatomical sites, including the gastrointestinal tract, skin, respiratory system, and urogenital tract. However, the intestine, particularly the colon, represents the most densely populated microbial habitat in the body. It is estimated that the total number of microbial cells in the human body is comparable to the number of human somatic cells, underscoring the close symbiotic relationship between the host and its resident microorganisms. Rather than functioning merely as passive colonizers, these microorganisms act collectively as a metabolically active organ that contributes to digestion, nutrient synthesis, immune regulation, and systemic metabolic balance. Advances in microbiome research have demonstrated

 doi:10.20944/preprints202603.1264.v1

that microbial communities regulate key metabolic pathways, participate in the development and modulation of the immune system, and mediate bidirectional communication between the gut and distant organs such as the liver, brain, and cardiovascular system. Through the production of metabolites, signaling molecules, and microbial-associated molecular patterns, the microbiota exerts both local and systemic physiological effects. The following sections summarize the principal physiological functions of the gut microbiota, focusing on its roles in maintaining intestinal barrier integrity, regulating metabolism and nutrient availability, shaping immune responses, and mediating communication between the intestine and other organs.

5.1. Maintenance of the Intestinal Barrier

One of the central physiological roles of gut microbiota is the maintenance of intestinal barrier integrity [1]. The intestinal barrier is composed of several structural and functional components, including the epithelial cell layer, tight junction proteins, the mucus layer, antimicrobial peptides, and immune defenses. Together, these elements form a selective barrier that separates luminal microorganisms and antigens from the underlying host tissues while permitting the absorption of nutrients and water. The microbiota actively contributes to the preservation and regulation of this barrier. Commensal microorganisms stimulate mucus production by goblet cells, enhance the expression and organization of tight junction proteins, and promote the secretion of immunoglobulin A (IgA), which helps neutralize pathogens and prevent their adhesion to epithelial surfaces. According to Wells et al. (2022), these interactions play a critical role in maintaining mucosal homeostasis and resistance to pathogen colonization [53]. Quirós and Nusrat (2018) describe the intestinal epithelium and lamina propria as a "selective barrier that separates luminal contents from host tissues," emphasizing the importance of microbiota–host interactions in maintaining epithelial integrity [54]. Experimental evidence further supports this concept. Studies in germ-free mice have demonstrated impaired epithelial regeneration and slower intestinal wound healing compared with animals colonized by commensal microbiota, indicating that microbial signals are essential for efficient epithelial repair. Certain bacterial taxa directly contribute to epithelial maintenance and regeneration. Species belonging to the genus *Lactobacillus*, for example, promote the proliferation of intestinal stem cells through signaling pathways involving reactive oxygen species [55]. Meanwhile, *Akkermansia muciniphila*, a mucin-degrading bacterium enriched in hypoxic regions of the intestinal mucus layer, contributes to mucosal remodeling and epithelial repair processes [54]. These interactions illustrate the essential role of microbiota in maintaining intestinal barrier stability and preventing microbial translocation.

5.2. Metabolic and Nutritional Functions

The gut microbiota plays a fundamental role in host metabolism by participating in the digestion of dietary components that cannot be processed by host enzymes alone. Complex carbohydrates such as dietary fiber, resistant starch, and certain oligosaccharides reach the colon largely undigested, where they are fermented by anaerobic microorganisms. This fermentation process generates short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, which represent key metabolic intermediates within the gut ecosystem [56].

SCFAs perform several important physiological functions. Butyrate serves as the primary energy source for colonocytes and supports epithelial barrier integrity, while propionate and acetate participate in hepatic gluconeogenesis, lipid metabolism, and systemic energy regulation. In addition to their metabolic role, SCFAs act as signaling molecules capable of modulating gene expression, immune responses, and inflammatory pathways through interactions with host receptors and epigenetic mechanisms. The microbiota also contributes to host nutrition through the synthesis of essential micronutrients, including vitamin K and several B-group vitamins. Furthermore, microbial metabolism influences the digestion and absorption of lipids and carbohydrates, thereby affecting overall energy balance [57,58]. Nicholson et al. (2012) describe the gut microbiota as a metabolic organ capable of extracting additional energy from dietary substrates that would otherwise remain

 doi:10.20944/preprints202603.1264.v1

inaccessible to the host [59]. Evidence supporting this concept comes from studies demonstrating that germ-free animals exhibit reduced fat storage and altered metabolic profiles compared with conventionally colonized animals. While this metabolic capacity is beneficial for energy harvest, alterations in microbial composition may also contribute to metabolic disorders such as obesity and metabolic syndrome.

5.3. Immune System Conditioning

Another essential function of the gut microbiota is the regulation and maturation of the immune system. From early life onward, interactions between microbial antigens and host immune cells shape both innate and adaptive immune responses [60]. This process promotes immune tolerance toward beneficial commensal microorganisms while maintaining the capacity to respond effectively to pathogens. Microbiota influences immune development through the production of metabolites, the presentation of microbial antigens, and the release of microbe-associated molecular patterns that interact with host pattern recognition receptors [61]. These interactions modulate immune signaling pathways and help establish appropriate immunological thresholds, a phenomenon described as "conditioned immunity" [62]. Early in life microbial exposure plays a particularly important role in immune maturation. During infancy, colonization by maternal microbiota and microbial metabolites contributes to the development of mucosal immune structures and regulatory pathways. Breast milk further supports this process by providing human milk oligosaccharides, which function as prebiotics that selectively stimulate the growth of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*. These microorganisms contribute to pathogen exclusion and promote the development of regulatory immune populations. Studies have shown that the gut microbiota stimulates the accumulation of regulatory T cells as well as unconventional T cell populations such as mucosal-associated invariant T (MAIT) cells and invariant natural killer T (iNKT) cells. Together, these immune populations help maintain long-term immune tolerance and homeostasis [18].

5.4. Gut-Organ Communication

Beyond its local effects in the intestine, the microbiota exerts systemic influence through bidirectional communication with distant organs. This interaction occurs through multiple pathways, including metabolic, endocrine, immune, and neural signaling mechanisms. Collectively, these interactions form several interconnected physiological axes, such as the gut–liver axis, gut–brain axis, gut–kidney axis, and gut–skin axis [63].

The gut–liver axis is one of the most extensively studied examples of microbiota-mediated organ communication. Microbial metabolites, microbial components, and bile acid derivatives produced in the intestine can enter the portal circulation and reach the liver, where they influence metabolic regulation, immune responses, and detoxification processes [64].

Similarly, the gut–brain axis represents a complex communication network linking the central nervous system, the enteric nervous system, and the intestinal microbiota. This interaction occurs through neural pathways such as the vagus nerve, as well as through circulating metabolites, hormones, and immune mediators. Through these mechanisms, the microbiota can influence appetite regulation, stress responses, and emotional behavior. As noted by Dicks (2024), human mental health is strongly influenced by the intrinsic interaction between the central nervous system, the enteric nervous system, and intestinal microbial communities [65].

5.5. Microbiota and the Nervous System

The microbiota also plays an important role in regulating both the enteric and central nervous systems. Microbial metabolites and signaling molecules influence neuronal activity, neuroimmune interactions, and the production of neurotransmitters. Several gut microorganisms are capable of producing or modulating neurotransmitters, including serotonin, dopamine, gamma-aminobutyric acid (GABA), and noradrenaline. For instance, *Bacteroides thetaiotaomicron* has been shown to

 doi:10.20944/preprints202603.1264.v1

influence neuronal density and glial cell activity within the enteric nervous system [66]. Meanwhile, species of the genus *Lactobacillus* stimulate acetylcholine production, which is important for regulating intestinal motility [65]. It is estimated that approximately 80–90% of the body's serotonin is produced in the gastrointestinal tract, largely under the influence of microbial activity. Alterations in this microbial regulation can affect intestinal permeability and contribute to disturbances in mood and emotional regulation [67]. In addition, certain bacteria such as *Enterococcus faecalis* participate in dopamine synthesis from L-DOPA, linking microbial metabolism with neurological processes related to motivation, cognition, and behavior [68].

5.6. Metabolic Homeostasis

Finally, the gut microbiota plays a central role in systemic metabolic homeostasis [21]. Microbial communities regulate energy extraction from food, influence lipid and glucose metabolism, and modulate insulin sensitivity. Short-chain fatty acids derived from microbial fermentation act as key metabolic regulators that influence hepatic gluconeogenesis, adipose tissue metabolism, and appetite signaling. Nicholson et al. (2012) emphasize that microbial metabolites function as metabolic mediators between the host and its environment, reinforcing the concept of the microbiota as a metabolic organ [59]. Additionally, the interaction between intestinal microbes and hepatic metabolism forms the basis of the gut–liver axis, which is essential for maintaining hepatic metabolic balance [64]. An important example of microbiota-mediated metabolic regulation involves bile acids. Gut microorganisms convert primary bile acids into secondary bile acids, which influence lipid absorption and regulate signaling pathways involved in glucose and lipid metabolism. Dysregulation of these processes has been associated with the development of metabolic diseases, including non-alcoholic fatty liver disease, type 2 diabetes, and atherosclerosis [69].

6. Mechanisms of Host-Microbiota Interaction

The physiological functions described in the previous section arise from a complex network of molecular interactions between the host and the intestinal microbiota. These interactions involve metabolic signaling, immune modulation, neuroendocrine communication, and epithelial regulation. Through these mechanisms, the microbiota contributes to maintaining intestinal homeostasis while simultaneously influencing systemic physiological processes.

The commensal microbiota of the gastrointestinal tract plays a central role in regulating immune responses, maintaining epithelial barrier integrity, and controlling inflammatory processes. Clinical and experimental studies have shown that microbial metabolites, including SCFAs, polyamines, and tryptophan derivatives, act as key mediators in host–microbiota communication. These molecules strengthen epithelial defenses, modulate inflammatory signaling pathways, and promote immune tolerance [70]. Because of this metabolic and immunological influence, strategies capable of modifying microbial composition, such as dietary interventions, prebiotics, probiotics, and fecal microbiota transplantation, have emerged as promising approaches for restoring beneficial metabolic profiles and preventing chronic inflammatory diseases [4,10].

6.1. Immune System Interactions

A fundamental mechanism of host–microbiota interaction involves the bidirectional communication between intestinal microorganisms and the host immune system. In mammals, the immune system maintains continuous surveillance of intestinal microbial communities while simultaneously tolerating beneficial commensal organisms [71]. This communication is mediated primarily through interactions involving T lymphocytes, particularly Th17 cells, and B lymphocytes. These immune cells facilitate signal transmission between the microbiota and host tissues while promoting the secretion of antimicrobial peptides and immunoglobulin A (IgA). IgA plays a critical role in mucosal immunity by neutralizing pathogens and preventing microbial adherence to epithelial surfaces [72]. Through these mechanisms, a local immune defense circuit is established that

 doi:10.20944/preprints202603.1264.v1

complements the mechanical protection provided by the epithelial layer and intestinal mucus barrier [70]. In the intestinal mucosa, commensal bacteria release SCFAs that stimulate mucus secretion and the production of antimicrobial molecules. These responses enhance immune protection against pathogens while preventing the absorption of harmful substances into intestinal lymphatic vessels. In addition to IgA-mediated protection, microbial metabolites regulate immune cell differentiation. Certain bacterial taxa, such as segmented filamentous bacteria and species like *Akkermansia muciniphila*, induce differentiation of Th17 cells, $CD8^+$ T cells, and B cells, thereby strengthening immune responses and immunoglobulin production. Conversely, *Lactobacillus reuteri* promotes the development of tolerogenic intraepithelial lymphocytes, contributing to immune tolerance toward commensal microorganisms [73].

6.2. Pattern Recognition Receptors and Molecular Signaling

Host epithelial and immune cells detect microbial signals through pattern recognition receptors (PRRs), particularly Toll-like receptors (TLRs) and NOD-like receptors (NLRs). These receptors recognize microbial-associated molecular patterns derived from commensal microorganisms and initiate controlled signaling responses that regulate immune activation and epithelial homeostasis. Microbial metabolites and structural components interact with TLRs expressed on intestinal epithelial cells, including specialized enteroendocrine cells that establish direct connections with neurons of the submucosal plexus. For example, bacterial metabolites can activate TLR2 signaling pathways, triggering regulated inflammatory responses that stimulate epithelial proliferation and contribute to the maturation of the enteric nervous system (ENS) [74]. These interactions illustrate how microbial signals influence both immune and neural development within the intestine. Importantly, the development of the ENS occurs largely during the postnatal period and is strongly influenced by maternal microbiota transmitted through breastfeeding. Experimental models have demonstrated that maternal milk contains cytokines and neurotrophic factors that contribute to enteric neuronal maturation and immune regulation [75].

6.3. Dysbiosis and Host Neuroendocrine Regulation

Disruption of host–microbiota interactions can lead to dysbiosis, a condition characterized by the loss of beneficial microorganisms, increased abundance of potentially pathogenic species, and reduced microbial diversity. Dysbiosis has been associated with numerous inflammatory, metabolic, and neurological disorders [12]. Host physiological factors, particularly stress, can significantly influence microbial composition. Stress activates neuroendocrine pathways that release hormones such as glucocorticoids, adrenocorticotropic hormone (ACTH), and catecholamines. These hormones reach the intestinal lumen and directly affect bacterial physiology. Experimental studies have demonstrated that stress hormones can stimulate bacterial proliferation, alter bacterial gene expression through microbial receptors, influence bacterial motility in a dose-dependent manner, and promote biofilm formation and epithelial adhesion [76]. These findings highlight the strong influence of host neuroendocrine activity on microbial ecology.

6.4. The Microbiota–Gut–Brain Axis

Another important level of host–microbiota interaction involves communication between the gut microbiota and the central nervous system (CNS). This communication occurs through multiple interconnected pathways, including neural, endocrine, immune, and metabolic mechanisms, and forms the basis of the microbiota–gut–brain axis. Intestinal microorganisms interact with the CNS through vagal nerve signaling, circulating metabolites, immune mediators, and microbial neurotransmitter production. Through these mechanisms, the microbiota can influence gastrointestinal motility, emotional behavior, and cognitive function [77]. CNS also exerts reciprocal regulation over the gut environment by modulating sympathetic and parasympathetic activity, which influences intestinal motility, secretory functions, and immune responses. In addition, stress-

 doi:10.20944/preprints202603.1264.v1

related mediators released by the nervous system can alter microbial gene expression and community composition [7,22]. This bidirectional communication supports the concept of a host–microbiome mutualistic relationship in which the host provides nutrients and protective mechanisms while the microbiota generates beneficial metabolites and supports immune tolerance.

6.5. Regulation of Hematopoiesis and Immune Cell Development

The microbiota also influences systemic immune development by stimulating myelopoiesis through TLR signaling and microbial metabolites. These signals promote the maturation of neutrophils and basophils in the bone marrow. Although microbiota does not directly alter the development of hematopoietic stem cells, it influences their functional adaptation within specific tissues [78]. Additionally, intestinal dendritic cells play an essential role in translating microbial signals into systemic immune responses. These cells capture microbial antigens and present them in mesenteric lymph nodes, thereby activating adaptive immune responses [79]. Commensal microorganisms can enter immune surveillance pathways through epithelial damage, direct sampling by dendritic cells, or transport through specialized M cells located in Peyer's patches. Once activated, immune responses are regulated by mechanisms including expansion of T cells with dual receptors, cytokine-mediated activation, and molecular mimicry involving microbial antigens that resemble host molecules [61]. MicroRNAs further contribute to these regulatory processes. Molecules such as miR-21 and miR-31 influence intestinal permeability and epithelial proliferation during inflammatory responses, thereby modulating host–microbiota interactions at the molecular level [73].

6.6. Neuro–Immune–Epithelial Coordination

The coordination between intestinal macrophages and enteric neurons represents another important mechanism of host–microbiota interaction. This neuroimmune network regulates intestinal motility, tissue repair, and immune surveillance. The enteric nervous system influences microbial composition through peristalsis and secretion patterns, while microbial metabolites regulate neuronal function and density within the intestinal wall [75]. Macrophages and enteric neurons communicate through signaling molecules such as bone morphogenetic protein-2 (BMP2) and colony-stimulating factor-1 (CSF1), which coordinate intestinal motility and immune responses. Stress can disrupt this regulatory network by increasing intestinal permeability [80]. Hormonal effects on epithelial and immune cells, along with mast cell activation, weaken tight junctions and allow microbial translocation across the epithelial barrier. This process activates TLR signaling in macrophages and triggers inflammatory cascades characterized by the release of proinflammatory cytokines. As a result, a pathological cycle involving epithelial dysfunction, dysbiosis, and systemic inflammation may develop [76].

6.7. Microbiota and Intestinal Angiogenesis

The intestinal microbiota also influences vascular development within the gut. Microbial ligands can activate TLRs expressed on endothelial cells, triggering intracellular signaling pathways such as MAPK and NF-κB that stimulate angiogenic factor production. Dietary factors strongly modulate this process. High-fat diets increase intestinal permeability and promote proinflammatory responses that stimulate angiogenesis. These vascular changes may contribute to the progression of metabolic and inflammatory disorders [81].

6.8. Aging and Microbiota-Driven Inflammation

With aging, the intestinal mucosa undergoes progressive functional decline characterized by reduced epithelial regeneration, increased intestinal permeability, decreased IgA production, and reduced microbial diversity. In addition, the production of protective microbial metabolites, particularly SCFAs, declines. These alterations contribute to a chronic low-grade inflammatory state known as inflammaging, which has been associated with metabolic disorders, cardiovascular

 doi:10.20944/preprints202603.1264.v1

diseases, and neurodegenerative conditions. The central role of the gut microbiota in these processes highlights the intestine as a key regulatory hub in age-related physiological decline [60,82].

7. Microbiota, Diet, and Lifestyle

The composition and metabolic activity of the intestinal microbiota are highly dynamic and influenced by multiple environmental and host-related factors, including antibiotic exposure, dietary habits, lifestyle, age, and geographic location. The importance of this microbial ecosystem lies in the fact that approximately 95% of microbial products, particularly metabolites derived from fiber fermentation, are directly linked to gastrointestinal physiology, blood pressure regulation, circadian rhythm control, and neurological and immune function. Among these factors, diet represents one of the most powerful modulators of microbiota composition and function.

7.1. Dietary Patterns and Microbial Composition

As for unfavorable dietary patterns, the Western diet, characterized by high consumption of red meat, refined carbohydrates, processed foods, and sugars, has been associated with microbial dysbiosis. This dietary pattern disrupts bile acid metabolism and alters microbial metabolic pathways, promoting systemic inflammation [33,83]. These alterations may contribute to neuroinflammatory processes, including microglial activation and reduced neuroplasticity, which are associated with cognitive decline and neurodegenerative diseases. In contrast, healthy dietary patterns rich in fiber, fruits, vegetables, whole grains, and nuts are associated with increased microbial diversity and beneficial metabolic activity, i) Plant-Based and Vegan Diets: this type of diet promotes the growth of carbohydrate-fermenting bacteria and increases the production of SCFAs such as propionate and butyrate. These metabolites regulate metabolic pathways and reduce inflammatory signaling, thereby lowering the risk of cardiovascular disease and type 2 diabetes [31]; ii) Mediterranean Diet: it is widely recognized for its beneficial effects on microbiota composition. This dietary pattern promotes microbial production of SCFAs, including acetate, propionate, and butyrate, which exert anti-inflammatory and metabolic regulatory effects. Additionally, adherence to the Mediterranean diet increases microbial diversity, reduces oxidative stress markers, and decreases proinflammatory cytokines while increasing anti-inflammatory mediators. These changes contribute to the prevention and management of chronic diseases such as obesity and type 2 diabetes [84].

Across the life course, maternal diet during pregnancy strongly influences maternal microbiota composition and microbial metabolite production. Diets rich in fruits and vegetables increase microbial diversity and SCFA production, and these metabolites can cross the placenta, exerting anti-inflammatory and metabolic effects on the developing fetus. Breast milk further contributes to microbiota development by providing both probiotics (such as *Bifidobacterium* species) and prebiotics in the form of human milk oligosaccharides (HMOs). These compounds support immune development and protect infants against infections and inflammatory conditions. In older adults, dietary modulation of microbiota has been associated with improvements in inflammation, frailty, and cognitive function. Studies have shown that centenarians with preserved physical health exhibit higher fecal concentrations of SCFAs compared with younger elderly individuals, supporting the protective role of microbial metabolites in healthy aging [85–87].

7.2. Exercise and the Gut Microbiota

Physical activity represents another important host factor influencing microbiota composition and metabolic activity. Exercise promotes a favorable microbial metabolic profile characterized by increased production of SCFAs, particularly butyrate [88]. Butyrate plays multiple physiological roles, including energy supply for colonocytes, regulation of gene expression, maintenance of intestinal barrier integrity, and modulation of immune responses [89,90]. Through activation of signaling pathways such as AMP-activated protein kinase (AMPK), microbial metabolites influence skeletal muscle metabolism and energy utilization. Additionally, exercise-induced myokines exert

 doi:10.20944/preprints202603.1264.v1

anti-inflammatory effects that indirectly support microbial homeostasis. However, excessive or prolonged physical activity, such as ultra-endurance exercise, may temporarily disrupt microbiota balance and induce transient immunosuppression. For this reason, nutritional strategies including prebiotic and probiotic supplementation are sometimes recommended for high-performance athletes [91,92].

7.3. Sleep and Microbial Rhythms

Sleep patterns also influence microbiota composition and metabolic activity. Acute sleep deprivation has been shown to alter microbial richness and beta diversity, contributing to systemic inflammation and disruption of the blood–brain barrier. Chronic sleep deprivation further activates the hypothalamic–pituitary–adrenal (HPA) axis and increases intestinal permeability, which may exacerbate inflammatory responses and cognitive impairment [93].

8. Conclusion

The human gut microbiota represents a highly dynamic and spatially organized ecosystem, whose composition extends beyond bacteria to include viruses, archaea, and fungi, collectively shaping the metabolic, immunological, and neuroendocrine landscape of the host. Its physiological contributions are multifaceted, encompassing maintenance of intestinal barrier integrity, modulation of immune responses, fermentation of dietary substrates into bioactive metabolites, and participation in critical organ–microbiota axes such as the gut–brain and gut–liver pathways. Host–microbiota interactions are orchestrated through molecular signals, pattern recognition receptors, immune cells, and neuroimmune circuits, creating a reciprocal network essential for homeostasis. Environmental factors, including diet, exercise, sleep, and aging, exert profound influence on microbial composition and functional output, with dysbiosis linking directly to metabolic, inflammatory, and neurodegenerative disorders. The accumulating understanding of these interactions underscores the potential of microbiota-targeted interventions, including probiotics, prebiotics, dietary strategies, and fecal microbiota transplantation, to restore eubiosis and improve systemic health. As research advances, integrating multi-omics approaches and mechanistic studies will be crucial to unravel the complexity of host–microbiota crosstalk and enable personalized strategies for disease prevention and therapy. Ultimately, the gut microbiota emerges not merely as a microbial community but as a central regulator of human health, whose preservation and modulation are pivotal across the lifespan.

Despite substantial advances in understanding the gut microbiota, many aspects of host–microbiome interactions remain unexplored, particularly the functional roles of the virome, archaeome, and mycobiome. Future research integrating multi-omics, spatial mapping, and longitudinal studies will be essential to delineate causal relationships between microbial communities, metabolites, and systemic health. Personalized interventions tailored to an individual's microbiota profile, combined with dietary and lifestyle optimization, hold promise for preventing and treating metabolic, immune, and neurodegenerative disorders. Furthermore, elucidating the mechanisms underlying microbiota-driven modulation of the gut–brain and other organ axes may open new avenues for therapeutic strategies targeting cognition, mood, and overall resilience.

Funding Source: This study was funded by the Facultad de Ciencias Médicas, Universidad de Mendoza, through the 2025-2026 Chair Research Projects Program, under the direction of Dr. Bazzocchini.

References

1. Colella M, Charitos IA, Ballini A, Cafiero C, Topi S, Palmirotta R, et al. Microbiota revolution: How gut microbes regulate our lives. World J Gastroenterol [Internet]. 2023 Jul 28 [cited 2026 Mar 13];29(28):4368. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10415973/

 doi:10.20944/preprints202603.1264.v1

2. Woźniak D, Cichy W, Przysławski J, Drzymała-Czyż S. The role of microbiota and enteroendocrine cells in maintaining homeostasis in the human digestive tract. Adv Med Sci. 2021 Sep 1;66(2):284–92.
3. Reynolds T, Noorbakhsh S, Smith R. Microbiome Contributions to Health. Surg Infect (Larchmt) [Internet]. 2023 Apr 1 [cited 2026 Mar 13];24(3):213–9. Available from: https://scholar.google.com/scholar_url?url=https://journals.sagepub.com/doi/pdf/10.1089/sur.2023.002&hl=en&sa=T&oi=ucasa&ct=ufr&ei=2pCzaYzJPIS4ieoPqaao0As&scisig=AFtJQiy4CdWzTXtGhPcA39xQ1nsp
4. Gomaa EZ. Human gut microbiota/microbiome in health and diseases: a review. Antonie van Leeuwenhoek 2020 11312 [Internet]. 2020 Nov 2 [cited 2026 Mar 13];113(12):2019–40. Available from: https://link.springer.com/article/10.1007/s10482-020-01474-7
5. Kataoka K. The intestinal microbiota and its role in human health and disease. J Med Investig. 2016 Apr 1;63(1.2):27–37.
6. Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. Nat Rev Immunol 2016 166 [Internet]. 2016 May 27 [cited 2026 Mar 13];16(6):341–52. Available from: https://www.nature.com/articles/nri.2016.42
7. Anand N, Gorantla VR, Chidambaram SB. The Role of Gut Dysbiosis in the Pathophysiology of Neuropsychiatric Disorders. Cells 2023, Vol 12, Page 54 [Internet]. 2022 Dec 23 [cited 2026 Mar 13];12(1):54. Available from: https://www.mdpi.com/2073-4409/12/1/54/htm
8. Vernocchi P, Chierico F Del, Putignani L. Gut Microbiota Metabolism and Interaction with Food Components. Int J Mol Sci [Internet]. 2020 May 2 [cited 2026 Mar 13];21(10). Available from: https://pubmed.ncbi.nlm.nih.gov/32456257/
9. Álvarez J, Fernández Real JM, Guarner F, Gueimonde M, Rodríguez JM, Saenz de Pipaon M, et al. Microbiota intestinal y salud. Gastroenterol Hepatol [Internet]. 2021 Aug 1 [cited 2026 Mar 13];44(7):519–35. Available from: https://www.sciencedirect.com/science/article/pii/S0210570521000583?via%3Dihub
10. Ma Z, Zuo T, Frey N, Rangrez AY. A systematic framework for understanding the microbiome in human health and disease: from basic principles to clinical translation. Signal Transduct Target Ther [Internet]. 2024 Dec 1 [cited 2026 Mar 13];9(1):237. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11418828/
11. Arumugam M, Raes J, Pelletier E, Paslier D Le, Yamada T, Mende DR, et al. Enterotypes of the human gut microbiome. Nat 2011 4737346 [Internet]. 2011 Apr 20 [cited 2026 Mar 13];473(7346):174–80. Available from: https://www.nature.com/articles/nature09944
12. Van Hul M, Cani PD, Petitfils C, De Vos WM, Tilg H, El-Omar EM. What defines a healthy gut microbiome? Gut [Internet]. 2024 Nov 1 [cited 2026 Mar 13];73(11):1893–908. Available from: https://gut.bmj.com/content/73/11/1893
13. Pan X, Raaijmakers JM, Carrión VJ. Importance of Bacteroidetes in host–microbe interactions and ecosystem functioning. Trends Microbiol [Internet]. 2023 Sep 1 [cited 2026 Mar 13];31(9):959–71. Available from: https://www.cell.com/action/showFullText?pii=S0966842X23001075
14. Banerjee S, Schlaeppi K, van der Heijden MGA. Keystone taxa as drivers of microbiome structure and functioning. Nat Rev Microbiol 2018 169 [Internet]. 2018 May 22 [cited 2026 Mar 13];16(9):567–76. Available from: https://www.nature.com/articles/s41579-018-0024-1
15. Wong JPH, Chillier N, Fischer-Stettler M, Zeeman SC, Battin TJ, Persat A. Bacteroides thetaiotaomicron metabolic activity decreases with polysaccharide molecular weight. MBio [Internet]. 2024 Mar 1 [cited 2026 Mar 13];15(3). Available from: /doi/pdf/10.1128/mbio.02599-23?download=true
16. McMath AL, Aguilar-Lopez M, Cannavale CN, Khan NA, Donovan SM. A systematic review on the impact of gastrointestinal microbiota composition and function on cognition in healthy infants and children. Front Neurosci. 2023 Jun 14;17:1171970.
17. Suárez-Martínez C, Santaella-Pascual M, Yagüe-Guirao G, Martínez-Graciá C. Infant gut microbiota colonization: influence of prenatal and postnatal factors, focusing on diet. Front Microbiol [Internet]. 2023 [cited 2026 Mar 13];14:1236254. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10478010/
18. Ansaldo E, Farley TK, Belkaid Y. Control of Immunity by the Microbiota. Annu Rev Immunol [Internet]. 2021 Apr 26 [cited 2026 Mar 13];39(Volume 39, 2021):449–79. Available from: https://www.annualreviews.org/content/journals/10.1146/annurev-immunol-093019-112348

 doi:10.20944/preprints202603.1264.v1

19. Asanuma M, Miyazaki I, Ogawa N. Dopamine- or L-DOPA-induced neurotoxicity: the role of dopamine quinone formation and tyrosinase in a model of Parkinson's disease. Neurotox Res [Internet]. 2003 [cited 2022 Nov 4];5(3):165–76. Available from: https://pubmed.ncbi.nlm.nih.gov/12835121/
20. Chen W, Ma Q, Li Y, Wei L, Zhang Z, Khan A, et al. Butyrate Supplementation Improves Intestinal Health and Growth Performance in Livestock: A Review. Biomolecules [Internet]. 2025 Jan 1 [cited 2026 Mar 13];15(1):85. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11763988/
21. Kalkan AE, BinMowyna MN, Raposo A, Ahmad MF, Ahmed F, Otayf AY, et al. Beyond the Gut: Unveiling Butyrate's Global Health Impact Through Gut Health and Dysbiosis-Related Conditions: A Narrative Review. Nutrients [Internet]. 2025 Apr 1 [cited 2026 Mar 13];17(8):1305. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC12029953/
22. Ramadan YN, Alqifari SF, Alshehri K, Alhowiti A, Mirghani H, Alrasheed T, et al. Microbiome Gut-Brain-Axis: Impact on Brain Development and Mental Health. Mol Neurobiol 2025 628 [Internet]. 2025 Apr 15 [cited 2026 Mar 13];62(8):10813–33. Available from: https://link.springer.com/article/10.1007/s12035-025-04846-0
23. Zhen J, Zhou Z, He M, Han HX, Lv EH, Wen PB, et al. The gut microbial metabolite trimethylamine N-oxide and cardiovascular diseases. Front Endocrinol (Lausanne). 2023 Feb 7;14:1085041.
24. Liu Y, Dai M. Trimethylamine N-Oxide Generated by the Gut Microbiota Is Associated with Vascular Inflammation: New Insights into Atherosclerosis. Mediators Inflamm [Internet]. 2020 [cited 2026 Mar 13];2020:4634172. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7048942/
25. Takiishi T, Fenero CIM, Câmara NOS. Intestinal barrier and gut microbiota: Shaping our immune responses throughout life. Tissue Barriers [Internet]. 2017 Oct 2 [cited 2026 Mar 13];5(4):e1373208. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC5788425/
26. Chen Y, Xiao L, Zhou M, Zhang H. The microbiota: a crucial mediator in gut homeostasis and colonization resistance. Front Microbiol. 2024 Aug 6;15:1417864.
27. Bemark M, Pitcher MJ, Dionisi C, Spencer J. Gut-associated lymphoid tissue: a microbiota-driven hub of B cell immunity. Trends Immunol [Internet]. 2024 Mar 1 [cited 2026 Mar 13];45(3):211. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11227984/
28. Benameur T, Porro C, Twfieg ME, Benameur N, Panaro MA, Filannino FM, et al. Emerging Paradigms in Inflammatory Disease Management: Exploring Bioactive Compounds and the Gut Microbiota. Brain Sci [Internet]. 2023 Aug 1 [cited 2026 Mar 13];13(8):1226. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10452544/
29. Shen Y, Fan N, Ma S xia, Cheng X, Yang X, Wang G. Gut Microbiota Dysbiosis: Pathogenesis, Diseases, Prevention, and Therapy. MedComm [Internet]. 2025 May 1 [cited 2026 Mar 13];6(5):e70168. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC12006732/
30. Sommer F, Bäckhed F. The gut microbiota — masters of host development and physiology. Nat Rev Microbiol 2013 114 [Internet]. 2013 Feb 25 [cited 2026 Mar 14];11(4):227–38. Available from: https://www.nature.com/articles/nrmicro2974
31. Egas-Montenegro E, Echeverria-Chilla J, García-Ulloa M, Aizaga-Benalcazar C, Ordoñez-Araque R. The influence of a plant-based diet on the composition and functions of the human gut microbiota: a review. Front Nutr. 2026;13.
32. Muigano MN, Liu J, Liu X, Luo P, Li Z, Li J. The Impact of Dietary Patterns on the Human Gut Microbiome and Its Health Significance: A Review. FASEB J. 2025 Oct 15;39(19).
33. Soldán M, Argalášová Ľ, Hadvinová L, Galileo B, Babjaková J. The Effect of Dietary Types on Gut Microbiota Composition and Development of Non-Communicable Diseases: A Narrative Review. Nutrients [Internet]. 2024 Sep 1 [cited 2026 Mar 14];16(18):3134. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11434870/
34. Safarchi A, Al-Qadami G, Tran CD, Conlon M. Understanding dysbiosis and resilience in the human gut microbiome: biomarkers, interventions, and challenges. Front Microbiol. 2025;16.
35. Kasar GN, Rasal PB, Upaganlawar AB, Pagar DS, Surana KR, Mahajan SK, et al. Navigating dysbiosis: Insights into gut microbiota disruption and health outcomes Gaurav. Community Acquir Infect [Internet]. 2025 Jun 20 [cited 2026 Mar 14];12. Available from: https://www.hksmp.com/journals/cai/article/view/778/1252

 doi:10.20944/preprints202603.1264.v1

36. Latif A, Shehzad A, Niazi S, Zahid A, Ashraf W, Iqbal MW, et al. Probiotics: mechanism of action, health benefits and their application in food industries. Front Microbiol [Internet]. 2023 [cited 2026 Mar 14];14:1216674. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10470842/
37. Wang S, Yu L, Tian F, Zhao J, Zhai Q, Chen W. Mechanism of synbiotic in alleviating inflammatory bowel disease: Gut microbiota metabolic pathways and treg differentiation. Food Biosci. 2025 Dec 1;74.
38. Wortelboer K, Nieuwdorp M, Herrema H. Fecal microbiota transplantation beyond Clostridioides difficile infections. EBioMedicine. 2019 Jun 1;44:716–29.
39. Donaldson GP, Lee SM, Mazmanian SK. Gut biogeography of the bacterial microbiota. Nat Rev Microbiol 2015 141 [Internet]. 2015 Oct 26 [cited 2026 Mar 14];14(1):20–32. Available from: https://www.nature.com/articles/nrmicro3552
40. Suzuki TA, Nachman MW. Spatial Heterogeneity of Gut Microbial Composition along the Gastrointestinal Tract in Natural Populations of House Mice. PLoS One [Internet]. 2016 Sep 1 [cited 2026 Mar 14];11(9):e0163720. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0163720
41. Radaic A, Kapila YL. The oralome and its dysbiosis: New insights into oral microbiome-host interactions. Comput Struct Biotechnol J [Internet]. 2021 Jan 1 [cited 2026 Mar 14];19:1335. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7960681/
42. Rajasekaran JJ, Krishnamurthy HK, Bosco J, Jayaraman V, Krishna K, Wang T, et al. Oral Microbiome: A Review of Its Impact on Oral and Systemic Health. Microorganisms [Internet]. 2024 Sep 1 [cited 2026 Mar 14];12(9):1797. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11434369/
43. Jinyu K, Jian W, Yiwen L, Ruonan L, Shegan G. Role of Oral and Esophageal Microbiota in Esophageal Squamous Cell Carcinoma. Clin Med Insights Oncol [Internet]. 2025 Jan 1 [cited 2026 Mar 14];19:11795549251350184. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC12227878/
44. Ruan W, Engevik MA, Spinler JK, Versalovic J. Healthy Human Gastrointestinal Microbiome: Composition and Function After a Decade of Exploration. Dig Dis Sci 2020 653 [Internet]. 2020 Feb 18 [cited 2026 Mar 14];65(3):695–705. Available from: https://link.springer.com/article/10.1007/s10620-020-06118-4
45. Piewngam P, De Mets F, Otto M. Intestinal microbiota: The hidden gems in the gut? Asian Pacific J allergy Immunol [Internet]. 2020 [cited 2026 Mar 14];38(4):215. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10988648/
46. Kastl AJ, Terry NA, Wu GD, Albenberg LG. The Structure and Function of the Human Small Intestinal Microbiota: Current Understanding and Future Directions. Cell Mol Gastroenterol Hepatol [Internet]. 2019 Jan 1 [cited 2026 Mar 14];9(1):33. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6881639/
47. Li Y, Handley SA, Baldridge MT. The dark side of the gut: Virome-host interactions in intestinal homeostasis and disease. J Exp Med [Internet]. 2021 May 3 [cited 2026 Mar 14];218(5). Available from: https://dx.doi.org/10.1084/jem.20201044
48. Naureen Z, Dautaj A, Anpilogov K, Camilleri G, Dhuli K, Tanzi B, et al. Bacteriophages presence in nature and their role in the natural selection of bacterial populations. Acta Bio Medica Atenei Parm [Internet]. 2020 [cited 2026 Mar 14];91(Suppl 13):e2020024. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC8023132/
49. Tiamani K, Luo S, Schulz S, Xue J, Costa R, Mirzaei MK, et al. The role of virome in the gastrointestinal tract and beyond. FEMS Microbiol Rev [Internet]. 2022 Nov 2 [cited 2026 Mar 14];46(6). Available from: https://dx.doi.org/10.1093/femsre/fuac027
50. Borrel G, Brugère JF, Gribaldo S, Schmitz RA, Moissl-Eichinger C. The host-associated archaeome. Nat Rev Microbiol [Internet]. 2020 Nov 1 [cited 2026 Mar 14];18(11):622–36. Available from: https://pubmed.ncbi.nlm.nih.gov/32690877/
51. Gaci N, Borrel G, Tottey W, O'Toole PW, Brugère JF. Archaea and the human gut: New beginning of an old story. World J Gastroenterol [Internet]. 2014 Nov 21 [cited 2026 Mar 14];20(43):16062. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4239492/
52. Dirks B, Davis TL, Carnero EA, Corbin KD, Smith SR, Rittmann BE, et al. Methanogens are associated with altered microbial production of short-chain fatty acids and human-host metabolizable energy. 2025 Jan 2 [cited 2026 Mar 14]; Available from: http://biorxiv.org/lookup/doi/10.1101/2024.12.31.630929

 doi:10.20944/preprints202603.1264.v1

53. Wells JM, Gao Y, De Groot N, Vonk MM, Ulfman L, Van Neerven RJJ. Babies, Bugs, and Barriers: Dietary Modulation of Intestinal Barrier Function in Early Life. Annu Rev Nutr [Internet]. 2022 Aug 22 [cited 2026 Mar 14];42(Volume 42, 2022):165–200. Available from: https://www.annualreviews.org/content/journals/10.1146/annurev-nutr-122221-103916
54. Quirós M, Nusrat A. Contribution of Wound-Associated Cells and Mediators in Orchestrating Gastrointestinal Mucosal Wound Repair. Annu Rev Physiol [Internet]. 2019 Feb 10 [cited 2026 Mar 14];81(Volume 81, 2019):189–209. Available from: https://www.annualreviews.org/content/journals/10.1146/annurev-physiol-020518-114504
55. Alam A, Neish A. Role of gut microbiota in intestinal wound healing and barrier function. Tissue Barriers [Internet]. 2018 Jul 3 [cited 2026 Mar 14];6(3):1539595. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6389125/
56. Rowland I, Gibson G, Heinken A, Scott K, Swann J, Thiele I, et al. Gut microbiota functions: metabolism of nutrients and other food components. Eur J Nutr [Internet]. 2017 Feb 1 [cited 2026 Mar 14];57(1):1. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC5847071/
57. Liu M, Lu Y, Xue G, Han L, Jia H, Wang Z, et al. Role of short-chain fatty acids in host physiology. Anim Model Exp Med [Internet]. 2024 Oct 1 [cited 2026 Mar 14];7(5):641–52. Available from: /doi/pdf/10.1002/ame2.12464
58. Lange O, Proczko-Stepaniak M, Mika A. Short-Chain Fatty Acids—A Product of the Microbiome and Its Participation in Two-Way Communication on the Microbiome-Host Mammal Line. Curr Obes Rep [Internet]. 2023 Jun 1 [cited 2026 Mar 14];12(2):108. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10250490/
59. Nicholson JK, Holmes E, Kinross J, Burcelin R, Gibson G, Jia W, et al. Host-gut microbiota metabolic interactions. Science [Internet]. 2012 Jun 8 [cited 2026 Mar 14];336(6086):1262–7. Available from: https://pubmed.ncbi.nlm.nih.gov/22674330/
60. Walrath T, Dyamenahalli KU, Hulsebus HJ, McCullough RL, Idrovo JP, Boe DM, et al. Age-related changes in intestinal immunity and the microbiome. J Leukoc Biol [Internet]. 2021 Jun 1 [cited 2026 Mar 14];109(6):1045–61. Available from: https://dx.doi.org/10.1002/JLB.3RI0620-405RR
61. Bayer F, Dremova O, Khuu MP, Mammadova K, Pontarollo G, Kiouptsi K, et al. The Interplay between Nutrition, Innate Immunity, and the Commensal Microbiota in Adaptive Intestinal Morphogenesis. Nutr 2021, Vol 13, Page 2198 [Internet]. 2021 Jun 26 [cited 2026 Mar 14];13(7):2198. Available from: https://www.mdpi.com/2072-6643/13/7/2198/htm
62. Graham DB, Xavier RJ. Conditioning of the immune system by the microbiome. Trends Immunol [Internet]. 2023 Jul 1 [cited 2026 Mar 14];44(7):499–511. Available from: https://www.cell.com/action/showFullText?pii=S1471490623000832
63. Balakrishnan R, Kang S Il, Lee JY, Rho YK, Kim BK, Choi DK. Gut Microbiota-Immune System Interactions in Health and Neurodegenerative Diseases: Insights into Molecular Mechanisms and Therapeutic Applications. Aging Dis [Internet]. 2024 Dec 1 [cited 2026 Mar 14];16(6):3421. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC12539548/
64. Hsu CL, Schnabl B. The gut–liver axis and gut microbiota in health and liver disease. Nat Rev Microbiol [Internet]. 2023 Nov 1 [cited 2026 Mar 14];21(11):719. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10794111/
65. Martinez R, Dicks LMT. Our Mental Health Is Determined by an Intrinsic Interplay between the Central Nervous System, Enteric Nerves, and Gut Microbiota. Int J Mol Sci 2024, Vol 25, Page 38 [Internet]. 2023 Dec 19 [cited 2026 Mar 14];25(1):38. Available from: https://www.mdpi.com/1422-0067/25/1/38/htm
66. Aktar R, Parkar N, Stentz R, Baumard L, Parker A, Goldson A, et al. Human resident gut microbe Bacteroides thetaiotaomicron regulates colonic neuronal innervation and neurogenic function. Gut Microbes [Internet]. 2020 Nov 1 [cited 2026 Mar 14];11(6):1745–57. Available from: https://www.tandfonline.com/doi/pdf/10.1080/19490976.2020.1766936
67. Alhusain F. Microbiome. Saudi Med J [Internet]. 2021 Feb 1 [cited 2026 Mar 14];42(2):146–50. Available from: https://smj.org.sa/content/42/2/146

 doi:10.20944/preprints202603.1264.v1

68. Wachsmuth HR, Weninger SN, Duca FA. Role of the gut–brain axis in energy and glucose metabolism. Exp Mol Med 2022 544 [Internet]. 2022 Apr 26 [cited 2026 Mar 14];54(4):377–92. Available from: https://www.nature.com/articles/s12276-021-00677-w
69. Cox TO, Lundgren P, Nath K, Thaiss CA. Metabolic control by the microbiome. Genome Med 2022 141 [Internet]. 2022 Jul 29 [cited 2026 Mar 14];14(1):80-. Available from: https://link.springer.com/article/10.1186/s13073-022-01092-0
70. Gasaly N, de Vos P, Hermoso MA. Impact of Bacterial Metabolites on Gut Barrier Function and Host Immunity: A Focus on Bacterial Metabolism and Its Relevance for Intestinal Inflammation. Front Immunol [Internet]. 2021 May 26 [cited 2026 Mar 14];12:658354. Available from: www.frontiersin.org
71. Wang Q, Meng Q, Chen Y, Liu Y, Li X, Zhou J, et al. Interaction between gut microbiota and immunity in health and intestinal disease. Front Immunol [Internet]. 2025 [cited 2026 Mar 14];16:1673852. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC12641010/
72. Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. Cell Res [Internet]. 2020 Jun 1 [cited 2026 Mar 14];30(6):492. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7264227/
73. Bi K, Zhang X, Chen W, Diao H. MicroRNAs Regulate Intestinal Immunity and Gut Microbiota for Gastrointestinal Health: A Comprehensive Review. Genes (Basel) [Internet]. 2020 Sep 1 [cited 2026 Mar 14];11(9):1–17. Available from: https://pubmed.ncbi.nlm.nih.gov/32932716/
74. Fung C, Vanden Berghe P. Functional circuits and signal processing in the enteric nervous system. Cell Mol Life Sci 2020 7722 [Internet]. 2020 May 18 [cited 2026 Mar 14];77(22):4505–22. Available from: https://link.springer.com/article/10.1007/s00018-020-03543-6
75. Joly A, Leulier F, De Vadder F. Microbial Modulation of the Development and Physiology of the Enteric Nervous System. Trends Microbiol [Internet]. 2021 Aug 1 [cited 2026 Mar 14];29(8):686–99. Available from: https://pubmed.ncbi.nlm.nih.gov/33309188/
76. Beurel E. Stress in the microbiome-immune crosstalk. Gut Microbes [Internet]. 2024 Dec 31 [cited 2026 Mar 14];16(1). Available from: https://www.tandfonline.com/doi/pdf/10.1080/19490976.2024.2327409
77. Gershon MD, Margolis KG. The gut, its microbiome, and the brain: connections and communications. J Clin Invest [Internet]. 2021 Sep 15 [cited 2026 Mar 14];131(18). Available from: https://doi.org/10.1172/JCI143768.
78. Tuganbaev T, Honda K. Non-zero-sum microbiome immune system interactions. Eur J Immunol [Internet]. 2021 Sep 1 [cited 2026 Mar 14];51(9):2120–36. Available from: /doi/pdf/10.1002/eji.202049065
79. Ost KS, Round JL. Communication between the Microbiota and Mammalian Immunity. Annu Rev Microbiol [Internet]. 2018 Sep 8 [cited 2026 Mar 14];72(Volume 72, 2018):399–422. Available from: https://www.annualreviews.org/content/journals/10.1146/annurev-micro-090817-062307
80. Muller PA, Koscsó B, Rajani GM, Stevanovic K, Berres ML, Hashimoto D, et al. Crosstalk between Muscularis Macrophages and Enteric Neurons Regulates Gastrointestinal Motility. Cell [Internet]. 2014 Jul 17 [cited 2026 Mar 14];158(2):300. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4149228/
81. Solari E, Marcozzi C, Negrini D, Moriondo A. Interplay between Gut Lymphatic Vessels and Microbiota. Cells 2021, Vol 10, Page 2584 [Internet]. 2021 Sep 28 [cited 2026 Mar 14];10(10):2584. Available from: https://www.mdpi.com/2073-4409/10/10/2584/htm
82. Santoro A, Martucci M, Conte M, Capri M, Franceschi C, Salvioli S. Inflammaging, hormesis and the rationale for anti-aging strategies. Ageing Res Rev [Internet]. 2020 Dec 1 [cited 2022 Nov 3];64. Available from: https://pubmed.ncbi.nlm.nih.gov/32814129/
83. Clemente-Suárez VJ, Beltrán-Velasco AI, Redondo-Flórez L, Martín-Rodríguez A, Tornero-Aguilera JF. Global Impacts of Western Diet and Its Effects on Metabolism and Health: A Narrative Review. Nutrients [Internet]. 2023 Jun 1 [cited 2026 Mar 14];15(12):2749. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10302286/
84. Bacaloni S, Agrawal DK. Nutrition, Gut Microbiota, and Epigenetics in the Modulation of Immune Response and Metabolic Health. Cardiol Cardiovasc Med [Internet]. 2025 [cited 2026 Mar 14];9(3):111. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC12121961/

 doi:10.20944/preprints202603.1264.v1

85. Aulia B, Ermamilia A, Sundjaya T, Pratiwi D. MATERNAL GUT MICROBIOME AND ITS IMPACT ON FETAL OUTCOMES: A FOCUS ON MATERNAL NUTRITION. J Indones Spec Nutr [Internet]. 2025 Jul 30 [cited 2026 Mar 14];3(2):125–46. Available from: https://jisn.org/index.php/jisn/article/view/46
86. Fontaine F, Turjeman S, Haib M, Collado MC, Callens K, Koren O. Programming the Infant Gut: How Maternal and Early Life Nutrition Shape the Infant Microbiome and Long-term Health—A Narrative Review. Mol Nutr Food Res [Internet]. 2026 Jan [cited 2026 Mar 14];70(2):e70385. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC12816947/
87. Jovandaric MZ, Babic S, Milincic M, Medjo B, Raus M, Krstic M, et al. Microbiome, Epigenetics, and Nutritional Factors in Shaping Perinatal Pregnancy Outcomes. Int J Mol Sci 2026, Vol 27, Page 1622 [Internet]. 2026 Feb 7 [cited 2026 Mar 14];27(4):1622. Available from: https://www.mdpi.com/1422-0067/27/4/1622/htm
88. Clarke SF, Murphy EF, O'Sullivan O, Lucey AJ, Humphreys M, Hogan A, et al. Exercise and associated dietary extremes impact on gut microbial diversity. Gut [Internet]. 2014 Dec 1 [cited 2026 Mar 14];63(12):1913–20. Available from: https://gut.bmj.com/content/63/12/1913
89. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From dietary fiber to host physiology: Short-chain fatty acids as key bacterial metabolites. Cell [Internet]. 2016 Jun 2 [cited 2026 Mar 14];165(6):1332–45. Available from: https://www.cell.com/action/showFullText?pii=S009286741630592X
90. Venegas DP, De La Fuente MK, Landskron G, González MJ, Quera R, Dijkstra G, et al. Short chain fatty acids (SCFAs)mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Front Immunol [Internet]. 2019 Mar 11 [cited 2026 Mar 14];10(MAR):424615. Available from: www.frontiersin.org
91. Aykut MN, Erdoğan EN, Çelik MN, Gürbüz M. An Updated View of the Effect of Probiotic Supplement on Sports Performance: A Detailed Review. Curr Nutr Rep [Internet]. 2024 Jun 1 [cited 2026 Mar 14];13(2):251. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11133216/
92. Ahsan M, Garneau L, Aguer C. The bidirectional relationship between AMPK pathway activation and myokine secretion in skeletal muscle: How it affects energy metabolism. Front Physiol [Internet]. 2022 Nov 21 [cited 2026 Mar 14];13:1040809. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC9721351/
93. Lin Z, Jiang T, Chen M, Ji X, Wang Y. Gut microbiota and sleep: Interaction mechanisms and therapeutic prospects. Open Life Sci [Internet]. 2024 Jan 1 [cited 2026 Mar 14];19(1):20220910. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11260001/