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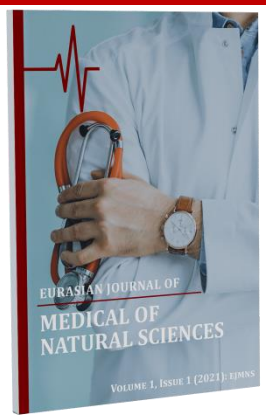


# THE HUMAN MICROBIOME AND ITS IMPACTS ON HEALTH

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**ABSTRACT**

*The human microbiome consists of bacteria, archaea, viruses, and eukaryotes that inhabit both the internal and external surfaces of the body. These microorganisms play a significant role in human physiology, influencing health and disease by enhancing or impairing metabolic and immune functions. Different microorganisms colonize various body sites, each adapting to the unique characteristics of its environment. Facultative anaerobes are more common in the gastrointestinal tract, while strict aerobes dominate areas like the respiratory tract, nasal cavity, and skin. The immune system and these indigenous microbes have evolved together, leading to a balanced biological interaction. Disruptions in the gut microbial community, often influenced by lifestyle or underlying diseases, contribute to various health issues. Such dysbiosis increases susceptibility to infections, which vary depending on the affected anatomical site. The diversity of the human microbiota is responsible for the specific metabolic functions at each body site. Thus, understanding the composition and activities of the human microbiome is crucial for insights into its role in health and disease.*

## 1. Introduction

The human microbiota refers to the collection of microorganisms that inhabit and interact with the human body [1]. These interactions can be commensal, mutualistic, or pathogenic in nature. The term "human microbiome" refers to the genetic material of these microorganisms living at specific sites within the body. Microorganisms colonize various anatomical areas, including the skin, mucosa, gastrointestinal tract, respiratory system, urogenital tract, and mammary glands, forming complex ecosystems adapted to the specific conditions of each niche [2]. From birth, a symbiotic relationship between the human body and its native microbiota begins, playing a crucial role in maintaining overall health and well-

being. Through coevolution, the organisms within the microbiota have adapted to their specific habitats, occupying distinct niches within the body [3–5].

The biological activities of these organisms become an integral part of the body, with their effects evolving from conception to death. The human microbiome continuously changes in response to host factors such as age, diet, lifestyle, hormonal shifts, genetic inheritance, and underlying diseases. However, disruptions in the balance of the microbiota (dysbiosis) can lead to serious health issues [2]. A well-balanced microbiota is essential for sustaining health [2]. The gut harbors the highest concentration of microorganisms, and these organisms are critical for maintaining human health. Research from the Human Microbiome Project has demonstrated that changes in the immune environment may be directly linked to dysbiotic gut flora. Conditions such as cancer, cardiovascular diseases, inflammatory bowel disease, and antibiotic-resistant bacterial infections have also been associated with dysbiosis [6, 7].

This review aims to explore the role of the human microbiome in both the development of diseases and the maintenance of health.

## 2. The Human Microbiome and Disease

### 2.1. Cancer

The gut microbiota plays a crucial role in influencing the health of its host [8]. Research into the interactions between microbial communities and their hosts suggests that these microorganisms perform biochemical activities that impact carcinogenesis, tumor growth, and response to immunotherapy, as illustrated in Figure 1 [8]. A well-established model indicates that factors contributing to gut dysbiosis—such as persistent intra-abdominal infections and antimicrobial drug use—can increase the risk of colorectal cancer. Additionally, the metabolic by-products of gut bacteria can either promote carcinogenesis or inhibit tumor growth by affecting intestinal cell linings [9].

Beyond colorectal cancer, the gut microbiota is also implicated in cancers outside the intestinal tract, such as hepatocellular carcinoma, through the systemic spread of microbes to other organs (Figure 2) [2]. In addition, *Helicobacter pylori* is a known contributor to the risk of gastric cancer. Recent studies have found that certain bacterial species, like *Fusobacterium* and *Clostridium*, are overrepresented in individuals with gastric cancer [10].

In breast cancer, while environmental and host factors play a key role in cancer progression, bacterial communities may also contribute. Individuals with breast cancer have been found to have a higher prevalence of *Bacillus*, *Enterobacteriaceae*, and *Staphylococcus* in breast tissue compared to healthy individuals. Furthermore, *Escherichia coli* and *Staphylococcus epidermidis*, isolated from breast cancer patients, were shown to induce DNA double-strand breaks in HeLa cells. Interestingly, *Lactobacillus spp.*, which is known for its health benefits, was absent in the breast tissue of patients with breast cancer [11].

Prostate cancer has also been associated with an increased population of *Bacteroides massiliensis*. Changes in the composition of the human microbiota are thought to play a role in the complex interactions between cancer and the microbial communities of the body [10].

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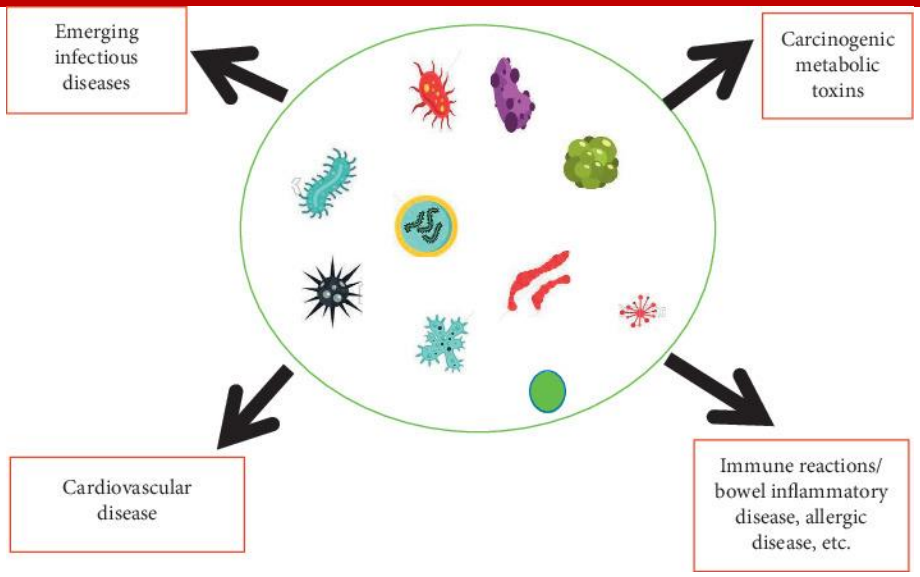


Figure 1

Dysbiotic flora and its impact on human health. Carcinogenic metabolic toxins produced from dysbiotic flora may trigger the progression of cancer and immune reaction in the gastrointestinal tract. In addition, hepatic oxidation of trimethylamine to trimethylamine N-oxide contributes to cardiovascular and emerging diseases.

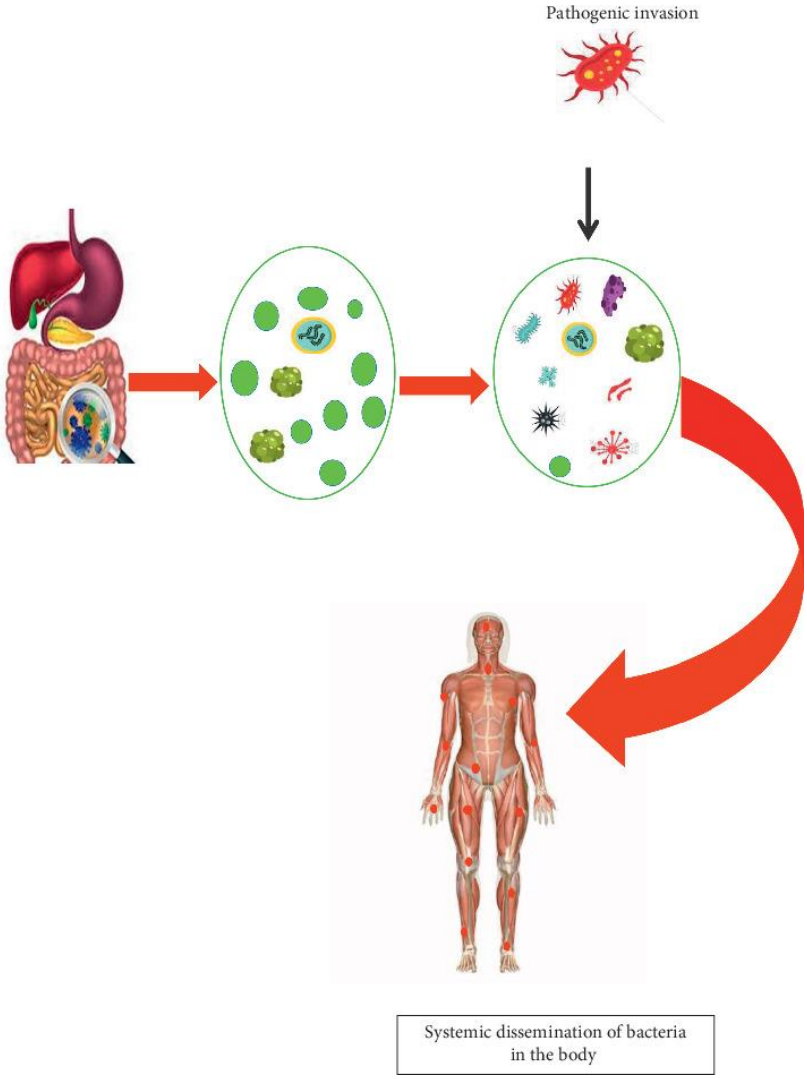

Figure 2

An alteration in the gut microbiota leads to systemic translocation of organisms from damaged gut epithelium to other extraintestinal sites.

**2.2. Inflammatory Bowel Disease (IBD)**

The accumulation of pathogenic microorganisms can trigger an abnormal immune response against the body's tissues, contributing to the development of autoimmune diseases, including inflammatory bowel disease (IBD) and other serious conditions [12]. The human microbiota has coevolved with the immune system, resulting in a balanced interaction over time. However, disturbances in the host-microbiota relationship can disrupt this balance, impairing immune responses and potentially leading to inflammatory disorders [13].

Sunil et al. [14] describe how the gut microbiome plays a role in compromising the integrity of the gastrointestinal barrier in IBD. The epithelial barrier forms tight junctions that separate tissue spaces and regulate the movement of solutes across the epithelium. Damage to the intestinal mucus layer can impair this barrier, resulting in defective cell attachment [15]. A reduction in gut *Firmicutes* has been linked to increased levels of pro-inflammatory cytokines (IL-12, IFN-γ) and decreased levels of the anti-inflammatory cytokine IL-10 [14]. Additionally, certain helminth infections have been associated with anti-inflammatory organisms, which help prevent inflammatory bowel disease in IBD-susceptible mice [10].

**2.3. Cardiovascular Diseases**

The metabolites produced by the gut microbiota not only influence the gastrointestinal system but also have systemic effects. One such metabolite, trimethylamine N-oxide (TMAO), produced by certain gut bacteria, has been implicated in heart disease [16]. The gut microbiota metabolizes trimethylamine—derived from diets high in L-carnitine, choline, and phosphatidylcholine—into TMAO via hepatic flavin-containing monooxygenase. TMAO plays a role in lipid transport and promotes the release of precursors that contribute to foam cell formation and atherosclerosis in animal models [16].

Intestinal dysbiosis has been associated with cardiovascular diseases. A clinical study by Kho and Lal compared two groups—those with low cardiovascular disease risk and those at high risk. Their findings revealed that individuals with a higher cardiovascular risk had more disrupted gut flora [17, 18]. Additionally, overrepresentation of specific organisms, such as *Prevotella* and *Klebsiella*, was linked to cardiovascular disease. Fecal transplants from hypertensive patients with elevated levels of these bacteria increased blood pressure in germ-free mice. Further research also showed that hypertensive mice exhibited a significant increase in the Firmicutes-to-Bacteroidetes ratio in their stool [18, 19].

**2.4. Systemic Infections Resulting from Bacterial Translocation**

Systemic infections occur when bacteria move continuously from the intestinal mucosa to other extraintestinal sites in the body, as illustrated in Figure 2. The risk of developing a systemic infection due to bacterial translocation is particularly high in immunocompromised individuals, such as those who are hospitalized, undergoing surgery, or recovering from trauma [19]. Disruption of the gut epithelium, coupled with the overuse of antibiotics, can disturb the balance of the microbiota, leading to an increase in facultative anaerobes and compromised host immune responses. Bacterial species that are often involved in

translocation and associated with systemic infections include E. coli, K. pneumoniae, Enterobacter spp., P. mirabilis, Enterococcus spp., Streptococcus spp., and C. albicans [19].

Additionally, microbial translocation can lead to systemic infections through the production of uremic toxins. This process suggests that changes in the gut microbiota may result in the synthesis of nitrogenous compounds, which compromise the integrity of epithelial tight junctions, allowing the translocation of bacteria and their toxins to other parts of the body. Uremic toxins produced by dysbiotic gut flora activate systemic inflammatory responses, contributing to the onset of various diseases [15]. A clinical study conducted in 2015 found a link between gut microbiota and chronic kidney disease, revealing the presence of translocating gut microbes in individuals undergoing hemodialysis [16].

**3. The Human Microbiome and Allergic Diseases**

The potential role of the human microbiome in the development of allergic diseases has been identified, although there is still limited knowledge about how lung microbiota regulate immune responses in the respiratory tract [20]. It is known, however, that a balanced gut microbiome significantly influences lung mucosa health. Dysbiosis in the gut can directly impact lung microbiota through microaspiration, increasing the risk of respiratory diseases. Renz et al. demonstrated this effect in germ-free mice, showing that the absence of an immune regulatory network in these mice led to respiratory and allergic diseases [21].

Cesarean (CS) delivery has also been identified as a risk factor for allergic diseases. The absence of maternal flora transfer during CS delivery increases children's susceptibility to such diseases [22]. Studies have shown that children born via CS have lower levels of healthy gut bacteria (*Bacteroidetes*), which are crucial for anti-inflammatory activity. This reduction contributes to local tissue inflammation, such as asthma and allergic rhinitis, exacerbated by genetic and environmental factors [12]. A recent epidemiological study found a significant association between gut dysbiosis and increased production of allergic antibodies (IgE), contributing to airway diseases in children [23]. Additional studies have shown that children with lower microbial diversity—particularly of *Bifidobacterium*, *Akkermansia*, and *Faecalibacterium*—are more prone to multiple allergen sensitivities (polysensitization) and may develop asthma by age 4 [24].

Further supporting this, Huang et al. observed that germ-free mice were more susceptible to allergic airway diseases. However, once their microbiota was restored, their allergen sensitivity decreased. Studies on allergies in Europe revealed that children raised in farming environments, which feature diverse microbial exposure, had lower rates of airway allergies [25]. The proposed mechanism involves activation of the innate immune system in the epithelial cells of the respiratory tract. Exposure to farm dust containing microbial strains like *Acinetobacter lwoffii* F78 and *Lactococcus lactis* G121 has been shown to reduce respiratory inflammation in mice [25, 27].

**4. The Human Microbiome in Health Maintenance**

**4.1. Maintenance of Homeostasis**

The human microbiome plays a crucial role in the development and maintenance of the human body (Figure 3). These microorganisms are essential for initiating the immune system and regulating inflammatory responses, especially in neonates and young children [14]. A study by Melli in 2015 found that children who developed allergies later in life had higher

levels of *Bacteroidaceae* and anaerobic bacteria, with reduced counts of *Bifidobacterium adolescentis*, *Bifidobacterium bifidum*, and *Lactobacillus spp.* [26, 27].

Ongoing research has also shown that these microorganisms interact with and degrade external contaminants, such as heavy metals, polycyclic aromatic hydrocarbons, pesticides, ochratoxins, plastic monomers, and other organic compounds [28]. After the kidney filters toxins from the bloodstream, these substances are stored in the bladder, creating a suitable environment for the urinary tract microbiota to deactivate harmful toxins [29]. The activity of these organisms can influence the outcome of infections. In the female genital tract, indigenous microbial flora provide a protective mechanism by triggering innate immune responses, including the secretion of cytokines, antimicrobial peptides, and inhibitory substances [29].

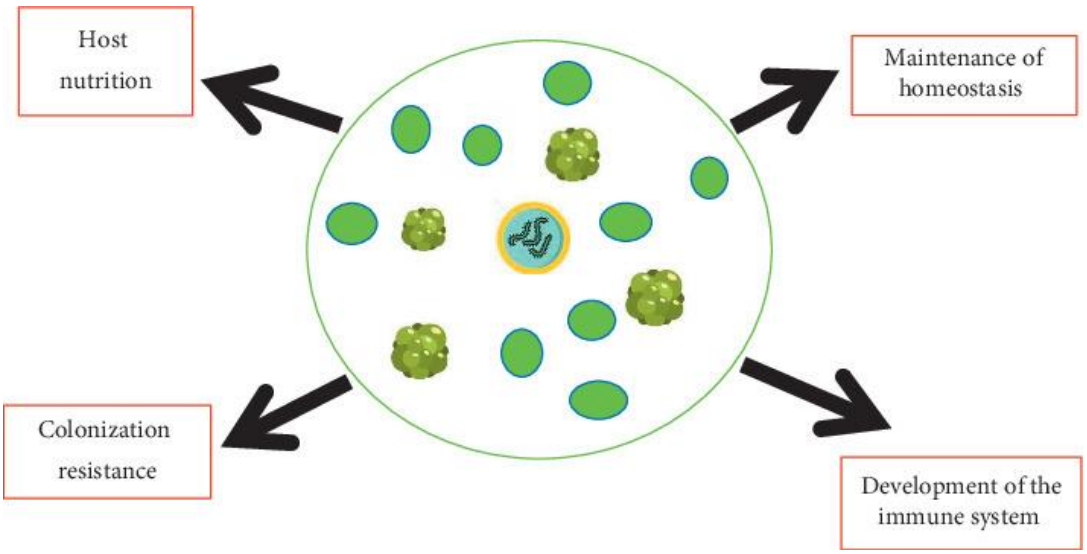


Figure 3

Symbiotic interaction between eubiotic flora and the human body results in the maintenance of homeostasis, regulation, and development of the immune system, hosts nutrition, and colonization resistance.

**4.2. Development of Host Immune System**

The coevolution of the indigenous microbiota and the immune system has played a critical role in the development and enhancement of immune responses. This relationship enables the immune system to distinguish between harmful pathogens and beneficial commensal organisms that need to be maintained [30]. In the gut, the composition of the microbiota influences the development of the adaptive immune system, which helps control microorganisms. Consequently, the human microbiota plays a significant role in shaping the mammalian immune system [13].

Recent research has shown that the absence or early disruption of commensal organisms can lead to an overactive type II immune response and the development of allergies due to abnormal immune function. For instance, factors such as cesarean delivery, a sedentary lifestyle, environmental pollution, and Western-style diets have been linked to an increase in childhood allergic rhinitis [7, 22]. Interventions such as probiotics, breastfeeding, lifestyle modifications (like outdoor play to boost vitamin D levels), and allergen-specific

immunotherapy have been suggested to promote immune system development and prevent atopy in children [22].

The gut microbiota also plays a vital role in regulating the activation of proinflammatory Th17 cells and regulatory T-cells (Tregs) in the intestines [10]. Additionally, the microbiota influences innate immunity, such as in the case of neutrophil aging, which reduces the body's proinflammatory responses [30]. These organisms trigger neutrophil aging through Toll-like receptor (TLR) and MyD88 signaling pathways. Disruptions in microbial balance reduce the circulation of aged neutrophils, which can result in inflammation-related organ damage, as seen in models of sickle cell disease and endotoxin-induced septic shock. Thus, the microbiota actively controls disease-promoting neutrophils, which are crucial in inflammatory diseases [30].

Moreover, the intestinal microbiota defends against pathogens by promoting colonization resistance and synthesizing antimicrobial compounds. For example, a balanced gut microbiome can regulate CD8 T-cells and CD4 cells that respond to respiratory infections, such as the influenza virus [12]. Additionally, the microbiota helps improve and maintain gastrointestinal function [31]. The high concentration of microorganisms in the gut presents a challenge to the immune system, which must tolerate commensal bacteria and dietary antigens while retaining the ability to eliminate harmful pathogens. The activation of colonic regulatory T-cells (Tregs) is essential for maintaining immune homeostasis [14]. These Tregs are classified into two types: thymus-derived and peripherally-derived (pTregs). While the differentiation between these two types is complex, both play crucial roles in immune regulation, with pTregs specifically requiring microbiota for activation in the colon.

**4.3. Host Nutrition**

The colonic microbiota plays a crucial role in meeting the nutritional needs of the host [32]. These microorganisms break down complex dietary components, such as carbohydrates, that are otherwise indigestible by intestinal cells, making these nutrients more accessible for absorption. The main by-products of this process are short-chain fatty acids (SCFAs), including acetic, propionic, and butyric acids [33]. Upon absorption by the colonic mucosa, these SCFAs serve as energy sources and precursors for mucosal lipid synthesis and promote the growth of epithelial cells, thereby maintaining gut integrity [19]. Additionally, the production of butyrate from the fermentation of complex dietary materials helps protect the large intestine from cancer [9]. These microbial activities provide essential nutrients that are vital for sustaining colonic health, but are otherwise inaccessible [33].

Studies have found that African mothers and infants have higher levels of *Bacteroidetes* and SCFAs in their stool compared to European infants, whose mothers consume a Western diet low in SCFAs. This suggests that traditional diets rich in fermentable carbohydrates contribute to a healthier gut microbiome [12]. Another key function of the colonic microbiota is the synthesis of vitamins needed for host development. Intestinal bacteria, such as *Bifidobacterium spp.*, *Bacteroides spp.*, and *enterobacteria*, are responsible for producing vitamins like vitamin K and folic acid [32]. Vitamin K is essential for synthesizing clotting factors, including prothrombin, while folic acid is a precursor for DNA and RNA synthesis, and both are involved in red and white blood cell production [19].

Probiotics containing *Lactobacillus* or *Bifidobacterium* are increasingly used to treat allergic diseases. Research shows that probiotics have an immunomodulatory effect by reducing antigen-induced T-cell activation and suppressing the production of tumor necrosis factor (TNF), a protein involved in systemic inflammation [12].

**5. Conclusion and Recommendation**

The study of the human microbiome is crucial for gaining a deeper understanding of the relationship between humans and their indigenous microbiota. It provides valuable insights that could pave the way for optimizing these microorganisms in the fight against life-threatening diseases. However, the overuse of broad-spectrum antibiotics can disrupt the balance of the microbiome, leading to an increased risk of pathogen invasion. To address this, the use of prebiotics and probiotics should be encouraged as a treatment strategy. Future research should focus on the therapeutic potential of probiotics in combating infectious diseases. Additionally, further investigation is needed to explore the impact of the human microbiome on mental health, as well as the roles of the mycobiome and virome in contributing to microbial imbalances (dysbiosis).

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