IJMCM 14(1) (2024) 1970-1980 Doi: 10.22034/ijmcm.2024.2008780.1302

International Journal of
Molecular and Clinical Microbiology

Review Article

The impact of gut microbiota in human health and disease: a comprehensive review

Farhad Mashayekhi* and Zivar Salehi
Department of Biology, Faculty of Sciences, University of Guilan, Rasht, Iran

ARTICLE INFO

Article history:
Received 15 May 2024
Accepted 29 June 2024
Available online 1 July 2024

Keywords:
Gastrointestinal Microbiome;
Autism Spectrum Disorder;
Cardiovascular Diseases;
Immune System Diseases;
symbiosis.

ABSTRACT

Numerous studies have been emphasizing the role of microbiota in health and diseases. The intestinal microbial flora, referred to as the second gene pool of the human body, plays a crucial part in immune function, nutrient absorption, and various activities of host cells, as well as in human disease. These microbial communities exist in symbiosis with the host, contributing to homeostasis, regulating immune function, and playing a significant role in the development of certain organs. However, dysbiosis of the microbiota can result in the dysregulation of bodily functions and the occurrence of diseases such as cardiovascular diseases (CVDs), cancers, autism, dementia, inflammatory bowel disease (IBD), and respiratory diseases. This review delves into the recent understanding of how the microbiota is linked to the health or pathogenesis of the host. First, we outline the findings on the transmission of gut microbiota and the functions of microbiota in maintaining good health, such as their involvement in the development of the immune system, formation of bones, and influence of bacteria on brain function and behavior. Next, we discuss the contribution of the gut microbiome to various human illnesses, including immune system imbalances, osteoporosis, and autism spectrum disorder. Extensive research has focused on the gut microbiome and its impact on both health and disease, demonstrating its influence on human metabolism, nutrition, physiology, and immune function. Changes in the composition of the gut microbial community, known as dysbiosis, have been associated with gastrointestinal conditions like inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), as well as broader systemic effects including obesity, type 2 diabetes, Autism, Parkinson's disease, dementia, and cancer.

1. Introduction

The term "microbiota" has its roots in the early 1900s. It is believed that around 90% of the cells in our bodies are prokaryotic. Although the exact number is challenging to pinpoint, it is suggested that the human intestinal tract could harbor up to 100 trillion microorganisms, which is roughly 10 times the number of cells present in our eukaryotic "human" cells. Furthermore, the human microbiota, also referred to as "the hidden organ," contributes more than 150 times the amount of genetic information compared to the entire human genome (Grice and Segre, 2012). The human intestinal system harbors a community of approximately 500–1000 diverse bacterial species. It is challenging to provide a more precise calculation, partly due to the fact that many of these bacteria have not been

*Corresponding author: Prof. Farhad Mashayekhi
Tel: 0098-9113330017
E-mail: mashayekhi@guilan.ac.ir

successfully grown in a lab setting; in fact, only around 7% have been cultured *in vitro*.

The human gut microbiome weighs approximately 2 kg, surpassing the weight of the brain. It is equally active metabolically as the liver and contains a hundred times more unique genes compared to the human genome (Rawls et al., 2006).

The terms "microbiota" and "microbiome" are often used interchangeably, but there are specific distinctions between the two. Microbiota refers to the living microorganisms present in a specific environment, such as the oral and gut microbiota. On the other hand, microbiome encompasses the collection of genomes from all microorganisms in the environment, not only including the microorganism community, but also the microbial structural components, metabolites, and environmental conditions (Berg et al., 2020). Therefore, microbiome covers a wider range than microbiota. This review primarily focuses on the role of microbiota in human health and diseases.

The gut bacteria and the microbial cells both exhibit the ability to change their characteristics. In order to survive in the intestinal microbiome, the gut bacteria create biofilms, which are interconnected communities of microbes that can withstand forces that could otherwise dislodge and remove them (Sonnenburg et al., 2004). When bacteria become part of a biofilm, they activate different genes and develop new traits (Macfarlane et al. 2005). These genes are triggered by the gut's epithelial cells and mucus, enabling the bacteria to stick together and modify how they take in nutrients. Interestingly, the presence of biofilms in the human appendix, and the location and narrow aperture of this structure, suggests that the normal appendix acts as a "safe house," harboring a reserve of the gut commensals that typically colonize the healthy colon; this normal gut microbiome of the colon aids in the immune regulation and native immunity of the gut. In cases of diarrhea or other severe evacuation of the gut, the appendix would be able to maintain its bacterial population to serve as a culture that can repopulate the bowel during its recovery (Yap et al., 2024).

The attachment of gut microbes to intestinal mucus helps to clarify why the gut bacteria composition varies in different parts of the intestine. The thickness and composition of intestinal mucus differ in various gut regions, allowing different bacteria to form biofilms in distinct areas. This segregation of bacteria enables specialization. For instance, in one gut region, various bacteroides species produce products that are subsequently metabolized by Escherichia coli, another gut resident, in a more distant gut region (Sonnenburg et al., 2004). The link between the gut microbiome and gene expression in the host has been established through numerous studies in model organisms and humans. In the gut, bacteria trigger gene expression in the host's tissue, while the gut tissue also stimulates new gene expression in the microbes. For instance, in mice, gut bacteria are responsible for triggering the expression of intestinal Cytochrome P450 (Cyp) 3a sub-family and transporter genes (Fu and Cui, 2017). Several molecular mechanisms facilitate the communication between the microbiome and host gene expression. Transcription factors are host proteins that bind to DNA and regulate the transcription of genes. Elements of the microbiome bind directly to transcription factors (Krautkramer et al. 2017). It has been found that the microbiome suppresses the transcription factor hepatocyte nuclear factor 4A (HNF4α), preventing the regulation of host inflammatory pathways, potentially leading to an inflammatory state (Davison et al., 2017). Studies on the skin microbiome of mice showed that colonization of the skin microbiome regulates the expression of several key transcription factors (Klf4, AP-1 and SP-1), albeit via an unknown mechanism (Meisel et al., 2018).

2. Inheritance of the gut bacteria

The gut microbiome and the immune system co-develop around the time of birth, well after genetic information has been passed from the parents to the offspring. Recent observations suggest that maternal factors encountered both in utero and after birth can directly or indirectly impact the development of the offspring's gut microbiome and immune system (Knoop et al., 2018). It is believed that human babies acquire the beginnings of such communities largely from the reproductive and digestive tracts of their mothers. In support of this idea, babies born through Caesarean section have been found

to have an altered bacterial colonization pattern early in life compared with vaginally delivered babies (Ley et al., 2006) It appears that the gut microbiota are an epigenetic inheritance from the mother.

3. Gut bacteria and normal mammalian organ development

The enteric bacteria have been shown to induce or regulate the expression of many genes in the gut. In other words, products of the bacterial cells can induce gene expression in the mammalian intestinal cells. Additionally, normal gut development requires this gene expression. Fucosyl transferase, an enzyme characteristic of mouse intestinal villi, was shown to be induced by bacteria. More recent studies have shown that the intestines of germ-free mice (i.e., mice bred in sterile facilities and having no contact with bacteria or fungi) can initiate, but not complete, their differentiation. For complete development of the mouse gut, the microbial symbionts are needed. Microarray analyses of mouse intestinal cells have shown that normally occurring gut bacteria can upregulate the transcription of numerous mouse genes, including those encoding colipase, which is important in nutrient absorption; angiogenin-4, which helps form blood vessels; and Sprr2a, a small, proline-rich protein that is thought to fortify matrices that line the intestine, Nucleotide-binding oligomerization domain-containing protein 2 (NOD2) and Human Leukocyte Antigens (HLAs) genes which involves in inflammatory bowel disease (IBD) (Cohen et al., 2019). Thus, the “normal” amount of gene expression in the gut is regulated by the microbes. In human cultured colon cells, bacteria (through their flagellin proteins) are responsible for activating the synthesis of transcription factors that are necessary for several intestinal functions (Nichols and Davenport, 2021). Thus, we develop as holobionts.

Mammals are not the sole vertebrates whose intestinal and immune system growth relies on microbial symbionts. Zebrafish intestinal tracts harbor a wide variety of microorganisms, and these microbial partners utilize the Wnt/β-catenin signaling pathway to trigger cell division in the stem cells of the intestine. In the absence of this cell division, germ-free mice have smaller intestines and a deficiency of enteroendocrine and goblet cells (Jemielita et al., 2014). Studies have shown that without specific intestinal microbes, the capillaries of the small intestinal villi do not develop their complete vascular networks. *Bacteroides thetaiotaomicron* is crucial for stimulating host angiogenesis. Mice raised without any gut bacteria, known as germ-free mice, were found to have a reduced gut capillary network formation compared to normal mice (Schirbel et al., 2013). However, when the intestines of germ-free mice were colonized with either a sample of bacteria from conventionally raised mice or with *B. thetaiotaomicron* alone, the capillary network formation was completed within 10 days. It was observed that this outcome was not affected by the age of the mouse, as even adult mice were able to complete capillary growth quickly in the presence of the necessary symbiotic bacteria.

The presence of Paneth cells, which are essential gut cells located in the intestinal glands, was found to be necessary for the development of the capillary network. Mice lacking Paneth cells did not properly form the capillary network even after being exposed to B. thetaiotaomicron or regular gut bacteria. Further tests demonstrated that Paneth cells react to B. thetaiotaomicron by producing the gene that encodes angiogenin-4, a protein that is known to stimulate the formation of blood vessels. This suggests that when exposed to intestinal flora and microbiota-derived elements, Paneth cells secrete not just antimicrobial peptides but also pro-angiogenic signaling molecules, which in turn encourage intestinal and mesenteric angiogenesis (Hassan et al., 2022). Ang4 disrupts the integrity of bacterial membranes by targeting critical basic amino acid residues with different functionalities, rather than relying on overall electrostatic interactions. This mechanism potentially allows Ang4 to maintain gut microflora both in vivo under physiological conditions and in pathophysiological conditions, as demonstrated in the study by Sultana et al., 2022. The experiments clearly showed that the presence of a specific environmental factor, such as *B. thetaiotaomicron* in this case, is essential for inducing the expression of important factors needed for the formation of capillary networks in the host's gut.

3.1. Maturation of gut-associated lymphoid tissue by symbionts

The gut microbiota play a crucial role in maintaining the balance of various interconnected metabolic and immune systems in the body. In mice, delayed initial microbial colonization results in the failure of gut-associated lymphoid tissues (GALT) to develop, leading to long-term immune system dysregulation (West et al., 2015). Research has demonstrated that the combination of Bacteroides fragilis and Bacillus subtilis is capable of inducing GALT (Rhee et al., 2004). The presence of microbial colonization is essential for the development of T- and B-cells in the intestinal mucosa (Wesemann et al., 2013). Therefore, symbiotic bacteria play a critical role in the differentiation of mammalian immune system lymphocytes.

3.2. Impact of bacteria on brain and behavior

The human physiology is greatly influenced by the gut microbiome, including its impact on the nervous system. The colonization of the microbiome during fetal development occurs at the same time as the development of the nervous system, and it happens in a well-coordinated manner. Recent research indicates that the microbiome and its metabolic by-products play an active role in controlling early brain development. Any disruption during this early developmental process can have a negative effect on brain function, and it can lead to various neurodevelopmental and neuropsychiatric disorders (NPD) (Dash et al., 2022).

Studies have indicated that symbiotic bacteria can promote the postnatal growth of the mammalian brain (Wang and Kasper, 2014). Germ-free mice exhibit reduced levels of NGF1-A and BDNF in relevant brain areas compared to normal mice. Research has demonstrated that specific Lactobacillus strains contribute to the regulation of emotional behavior through the vagus nerve–dependent control of GABA receptors (Forsythe et al., 2012). The gut microbiota has the potential to influence brain development and modify the structure of specific brain regions linked to social behavior, stress response, and internal balance. The gut microbiota can impact the amygdala, a brain region that significantly influences social behavior and anxiety (Awe et al., 2024).

Furthermore, introducing gut bacteria to mice at an early age normalized many of these behavioral traits. Studies with mice demonstrated that being exposed to *Bacteroides fragilis* could result in social and behavioral impairments, particularly in males, emphasizing the microbiome's influence on neurodevelopment. This innovative study paves the way for gaining a better grasp of the complexities of autism spectrum disorder (ASD) and creating potential interventions (Carmel et al., 2023). The gut microbiota might play a role in causing damage to the blood-brain barrier (BBB) and leading to the development of neurodegenerative diseases. However, even germ-free mice have a BBB that is not completely impermeable to proteins, whether they are young or mature. This issue can be resolved by reintroducing normal gut bacteria to the pups' guts. It seems that substances from the mother's beneficial gut bacteria control the permeability of the blood-brain barrier while it is forming in the fetal mice. It is probable that both our brains and our behaviors cannot develop properly without the right symbiotic organisms (Parker et al., 2020).

4. Gut bacteria and human disease

The presence of gut bacteria can significantly impact our health. An imbalance in our symbiotic microbes is now recognized as a medical condition known as dysbiosis. This condition is linked to various human diseases such as anxiety, depression, hypertension, cardiovascular diseases, obesity, diabetes, inflammatory bowel disease, and cancer. Studying the role of gut bacteria in human obesity and bowel inflammation has become a priority due to the increasing obesity rates in developed countries and the associated health issues. Furthermore, there are theories suggesting that certain diseases like asthma, rectal cancer, and gastric cancer may be caused by imbalances in gut microbes (Afzaal et al., 2022).

4.1. Gut microbiome and immune system

The gastrointestinal tract is home to the gut microbiota, which plays a crucial role in maintaining the host's health by balancing the immune system. Recent findings indicate that

changes in these microbial communities can lead to immune imbalances and subsequent autoimmune conditions. *H. hepaticus* has the ability to trigger an immune response in the host, leading to inflammatory bowel disease (IBD), while Bacteroides can prevent this response. This beneficial effect of *Bacteroides* is achieved through the action of Polysaccharide A (PSA). *Bacteroides* strains lacking the ability to produce PSA are unable to protect susceptible mice from IBD, and administering PSA to susceptible mice via a feeding tube can prevent Helicobacter-induced IBD. *Bacteroides* secretes a PSA that can inhibit the inflammatory response triggered by Helicobacter, particularly the interleukins. This suppression occurs due to the activation of gut CD4+ T lymphocytes, which produce IL-10, an interleukin that hinders the inflammatory immune reaction (Danne et al., 2017).

Many documented reports show direct evidence that highlights the crucial role of the gut microbiota in controlling the development of Antigen presenting cells (APCs). Germ-free (GF) animals displayed a decreased count of intestinal dendritic cells (DCs) but not systemic ones, and introducing Escherichia coli into GF animals was adequate to attract DCs to the intestines. GF mice also lacked macrophage activation markers like major histocompatibility complex class II (Wu and Wu, 2012). The regulation of neutrophils by the microbiota's systemic influence has been demonstrated, and one notable phenotype of GF rats is their neutropenia. NK cells, a type of innate lymphocytes, can identify and remove transformed and infected cells by secreting interferon-γ (IFNγ) or perforin. Research has distinguished two categories of NK cells expressing the NKp46 receptor in the gut mucosa (Satoh Takayama et al., 2008). One type of gut NKp46+ cell closely resembles conventional NK cells while the other type, unlike classical NK cells, shows limited IFNγ production and lacks perforin. Moreover, these atypical gut NKp46+ cells differ from classical NK cells by their expression of the nuclear hormone receptor retinoic acid receptor-related orphan receptor gamma t (RORγt) and interleukin-22 (IL-22). As GF mice lack IL-22-producing $NKp46^{+}$ cells, this suggests that the gut microbiota may play a crucial role in promoting IL-22+NKp46+ cell differentiation (Sanos et al., 2009).

4.2. Gut microbiome and bone formation

The presence of gut microbiota contributes to various processes impacting bone health. Genetic variation is closely linked to gut microbes, and the regulation of genes significantly influences the onset of bone-related ailments like osteoporosis. Gut microbiota can disturb the equilibrium between bone formation and resorption by indirectly stimulating or inhibiting osteoblasts and osteoclasts. Furthermore, intestinal microorganisms impact bone metabolism by controlling growth factors or modifying bone immune status, and they can also influence the metabolism of serotonin, cortisol, and sex hormones, ultimately affecting bone mass in mice (Zhang et al., 2023). Osteoporosis is characterized by reduced bone mass and mineral density, leading to alterations in bone microstructure. The influence of genetics and environmental factors predominately contributes to this condition, and numerous research studies have verified the existence of a correlation between the intestinal microbial flora and osteoporosis (Marini et al., 2016). Osteoporosis results from estrogen deficiency causing bone loss, and the absence of estrogen in mice is induced by surgical ovarian resection (OVX) or inhibition of sexual hormones. Treatment of OVX mice with *Lactobacillus acidophilus* resulted in decreased levels of bone resorption markers and inhibition of osteoclast formation (Ohlsson et al., 2014). Furthermore, *Lactobacillus reuteri* reduced the number of T lymphocytes in OVX mice, leading to inhibition of osteoclast formation (Britton et al., 2014). Type I diabetes may lead to osteoporosis as well. According to a study, L. reuteri was found to inhibit the expression of tumor necrosis factor (TNF) and Wnt10b, which helps prevent bone loss and bone marrow adiposity in a mouse model with type I diabetes (Zhang et al., 2015). Numerous research studies have demonstrated that the intestinal microflora can regulate the insulin-like growth factor (IGF)-1 levels, thereby influencing bone formation and absorption in young and middle-aged mice. The use of antibiotics to eliminate the intestinal microflora in young mice resulted in decreased levels of IGF-1. Furthermore, it was discovered that intestinal microbes can impact bone metabolism by altering the immune status of the bone (Yan et al., 2016).

4.3. Gut microbiome in Autism Spectrum Disorder

ASD, or autism spectrum disorder, is a neurological condition that impacts the normal development of the brain. The growing number of ASD diagnoses is causing concern, with statistics revealing that 1 in 68 individuals worldwide are affected. ASD is a prevalent neurodevelopmental disorder characterized by impaired communication skills, deficient reasoning, and repetitive and obstructive behavioral patterns (Taniya et al., 2022). Multiple studies indicate that genetic factors such as chromosomal abnormalities, gene polymorphisms, and environmental factors like diet and stress play a role in the onset and progression of ASD (Matsuzaki et al., 2012; Hosseinpour et al., 2017; Mashayekhi et al., 2021; Lord et al., 2022). Throughout numerous years, parents have documented that their children who have been diagnosed with ASD experience gastrointestinal (GI) issues such as constipation, abdominal pain, diarrhea, and vomiting. Recently, researchers have highlighted the gut microbiome as a potential factor contributing to the development of ASD, as individuals with ASD often experience digestive issues and exhibit a distinct composition of intestinal microbes (Peralta-Marzal et al., 2024). During prenatal development inside the mother's womb, in the placenta, and amniotic fluid, microbial colonization initiates as indicated by numerous pieces of evidence. It has been observed that the gut microbiota of children with ASD differs from that of neurotypically developed children (Korteniemi et al., 2023). The colonization of bacteria in the maternal-fetal unit may have positive or negative effects on pregnancy and/or fetal development. Infants receive colonization of certain bacterial species like *Lactobacillus, Enterococcus, Streptococcus, Peptostreptococcus, Corynebacterium, Escherichia,* and *Staphylococcus* passed through breast milk from lactating mothers (Senn et al., 2020). The commencement of pioneer microbial colonization inside the GI tract of preterm infants begins at birth. Around the age of 2-3 years, the microbiota stabilizes after 1 year of development. The period during pregnancy and after birth can critically impact infant microbiome development and have lasting effects on overall health (Lee, 2020). Numerous research studies indicate that infants delivered vaginally harbor a greater abundance of beneficial bacteria compared to infants delivered via cesarean section. Infants born through vaginal delivery come into contact with the mother's vaginal bacteria, while those born via C-section are primarily exposed to the mother's skin flora and environmental microorganisms. Throughout pregnancy, the baby's gastrointestinal tract is colonized by a diverse array of bacteria from the mother through breastfeeding and exposure to vaginal and intestinal microorganisms (Groer et al., 2015). At the time of birth, the baby's microbiota closely resembles that of the mother's microbiome (Forssberg, 2019). A significant population-based study involving 5 million births from Norway, Sweden, Denmark, Finland, and Western Australia observed each participant for 36–42 weeks. The study confirmed more than 31,000 cases of ASD, supporting the hypothesis that C-section birth delivery carries a higher risk of ASD compared to vaginal delivery (Yip et al., 2016). It has been proposed that the gut microbiome can influence an individual's sociability. Understanding the connections between gut microbiota, the brain, and sociability could enhance our comprehension of psychiatric diseases and neurodevelopmental disorders that affect sociability, as well as potential microbial interventions to alleviate their symptoms. The communication between the brain and the gut microbiome involves complex, two-way pathways. One extensively studied pathway involves the vagus nerve (Forsythe et al., 2014), which transmits chemical signals from the gut to the brain and also influences the central nervous system (CNS) (Bravo et al., 2011) and the immune system (Belkaid and Hand, 2014). The neuropeptide hormone oxytocin, crucial for forming social bonds and functioning as an anti-inflammatory factor (Panaro et al., 2020), is an important target of this communication. Several studies indicate that an imbalance in the gut microbiota, with an excess of unhealthy microorganisms, can disrupt the communication pathways between the gut and brain, leading to abnormal characteristics. According to previous studies, an unhealthy gut microbiome is causally related to conditions such as depression, anxiety, and ASD (Warner, 2019). One of the distinct features of these conditions, particularly ASD, is abnormal

social behavior. Research conducted in the past decade indicates that these conditions emerge early in an individual's life and can be influenced by the mother's health and gut microbiome during pregnancy, implying a multigenerational aspect in the development of these conditions (Di Gesu et al., 2022). Furthermore, research has demonstrated that probiotic therapy, whether administered before or after birth, can help reduce gastrointestinal and social interaction issues commonly associated with ASD (Abdellatif et al., 2020).

4.4 Gut microbiome and cancer

Recent evidence has shown that the human microbiome is associated with cancer development and progression. Microbes have been implicated in indirectly affecting many types of cancer. For example, gut microbes have been shown to impact cancer stem cells, or cancer cells that become quiescent and are thought to be responsible for disease relapse (Artusa et al., 2023). The gut microbiota composition can affect the tumor microenvironment and its interaction with the immune system, thereby having implications for treatment predictions (Roy and Singh, 2024). The intake of fermented dairy products reduces the risk of cancer by inducing immune responses and creating balanced and healthy gut microbiomes to support all therapies. A detailed, 12-year-long study conducted to determine the effect of yogurt consumption on cancer prevention in volunteers of the EPIC-Italy cohort suggested the protective role of yogurt against colorectal cancer (CRC). This finding suggests that yogurt should be part of a diet to prevent the disease (Pala et al., 2011). It has been shown that gastrointestinal cancer can be caused by a dysregulation of the expression of non-coding RNA (ncRNA) through the gut microbiome (Ağagündüz et al., 2023).

Conclusion

It should be clear by now that most organisms are not “individuals,” nor do they develop as individuals. It might be better to think of each of us as a team, or as a collection of ecosystems. It is suggested that gut microbiome and its role in both health and disease has been the subject of extensive research, establishing its involvement in human metabolism, nutrition, physiology, and immune function. An alteration in the gut microbial community or dysbiosis have been linked with gastrointestinal conditions such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), and wider systemic manifestations of disease such as obesity, type 2 diabetes, Autism, Parkinson's disease, dementia and cancers.

Authors’ contributions

Both authors wrote and reviewed the manuscript. The authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The author declares that he has no competing interests.

The authors declare that no support from any organization for the submitted work; no financial relationships with any organizations.

Refereces

Abdellatif B, McVeigh C, Bendriss G, Chaari A. The Promising Role of Probiotics in Managing the Altered Gut in Autism Spectrum Disorders. Int J Mol Sci. 2020 Jun 10;21(11):4159. doi: 10.3390/ijms21114159.

Afzaal M, Saeed F, Shah YA, Hussain M, Rabail R, Socol CT, Hassoun A, Pateiro M, Lorenzo JM, Rusu AV, Aadil RM. Human gut microbiota in health and disease: Unveiling the relationship. Front Microbiol. 2022 Sep 26;13:999001. doi: 10.3389/fmicb.2022.999001.

Ağagündüz D, Cocozza E, Cemali Ö, Bayazıt AD, Nanì MF, Cerqua I, Morgillo F, Saygılı SK, Berni Canani R, Amero P, Capasso R. Understanding the role of the gut microbiome in gastrointestinal cancer: A review. Front Pharmacol. 2023 Jan 24;14:1130562. doi: 10.3389/fphar.2023.1130562.

Artusa V, Calabrone L, Mortara L, Peri F, Bruno A. Microbiota-derived natural products

targeting cancer stem cells: Inside the gut pharma factory. Int J Mol Sci. 2023;24(5):4997. doi: 10.3390/ijms24054997.

Awe T, Fasawe A, Sawe C, Ogunware A, Jamiu AT, Allen M. The modulatory role of gut microbiota on host behavior: exploring the interaction between the brain-gut axis and the neuroendocrine system. AIMS Neurosci. 2024 Mar 31;11(1):49-62. doi: 10.3934/Neuroscience.2024004.

Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell. 2014 Mar 27;157(1):121-41. doi: 10.1016/j.cell.2014.03.011.

Berg G, Rybakova D, Fischer D, Cernava T, Vergès MC, Charles T, et al. Microbiome definition re-visited: old concepts and new challenges . Microbiome. 2020 Jun 30;8(1):103. doi: 10.1186/s40168-020-00875-0.

Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci U S A. 2011 Sep 20;108(38):16050-5. doi: 10.1073/pnas.1102999108.

Britton RA, Irwin R, Quach D, Schaefer L, Zhang J, Lee T, Parameswaran N, McCabe LR. Probiotic L. reuteri treatment prevents bone loss in a menopausal ovariectomized mouse model. J Cell Physiol. 2014 Nov;229(11):1822-30. doi: 10.1002/jcp.24636.

Carmel J, Ghanayem N, Mayouf R, Saleev N, Chaterjee I, Getselter D, et al. Bacteroides is increased in an autism cohort and induces autism-relevant behavioral changes in mice in a sex-dependent manner. NPJ Biofilms Microbiomes. 2023 Dec 18;9(1):103. doi: 10.1038/s41522-023-00469-2.

Cohen LJ, Cho JH, Gevers D, Chu H. Genetic Factors and the Intestinal Microbiome Guide Development of Microbe-Based Therapies for Inflammatory Bowel Diseases. Gastroenterology. 2019 Jun;156(8):2174-2189. doi: 10.1053/j. gastro.2019.03.017.

Danne C, Ryzhakov G, Martínez-López M, Ilott NE, Franchini F, Cuskin F, Lowe EC, Bullers SJ, Arthur JSC, Powrie F. A Large Polysaccharide Produced by Helicobacter hepaticus Induces an Anti-inflammatory Gene Signature in Macrophages. Cell Host Microbe. 2017 Dec 13;22(6):733-745.e5. doi: 10.1016/j.chom.2017. 11.002.

Dash S, Syed YA, Khan MR. Understanding the Role of the Gut Microbiome in Brain Development and Its Association With Neurodevelopmental Psychiatric Disorders. Front Cell Dev Biol. 2022 Apr 14;10:880544. doi: 10.3389/fcell.2022.880544.

Davison JM, Lickwar CR, Song L, Breton G, Crawford GE, Rawls JF. Microbiota regulate intestinal epithelial gene expression by suppressing the transcription factor Hepatocyte nuclear factor 4 alpha. Genome Res. 2017 Jul;27(7):1195-1206. doi: 10.1101/gr.220111.116.

Di Gesù CM, Matz LM, Bolding IJ, Fultz R, Hoffman KL, Gammazza AM, Petrosino JF, Buffington SA. Maternal gut microbiota mediate intergenerational effects of high-fat diet on descendant social behavior. Cell Rep. 2022 Oct 11;41(2):111461. doi: 10.1016/j.celrep.2022.111461.

Forssberg H. Microbiome programming of brain development: implications for neurodevelopmental disorders. Dev Med Child Neurol. 2019 Jul;61(7):744-749. doi: 10.1111/dmcn.14208.

Forsythe P, Bienenstock J, Kunze WA. Vagal pathways for microbiome-brain-gut axis communication. Adv Exp Med Biol. 2014;817:115-33. doi: 10.1007/978-1-4939-0897-4_5.

Forsythe P, Kunze WA, Bienenstock J. On communication between gut microbes and the brain. Curr Opin Gastroenterol. 2012;28(6):557-62. doi: 10.1097/MOG.0b013e3283572ffa.

Fu ZD, Cui JY. Remote Sensing between Liver and Intestine: Importance of Microbial Metabolites. Curr Pharmacol Rep. 2017

Jun;3(3):101-113. doi: 10.1007/s40495-017-0087-0.

Grice EA, Segre JA. The human microbiome: our second genome. Annu Rev Genomics Hum Genet. 2012;13:151-70. doi: 10.1146/annurev-genom-090711-163814.

Groer MW, Gregory KE, Louis-Jacques A, Thibeau S, Walker WA. Birth Defects Res C. The very low birth weight infant microbiome and childhood health. Embryo Today. 2015 Dec;105(4):252-64. doi: 10.1002/bdrc.21115.

Hassan M, Juanola O, Keller I, Nanni P, Wolski W, Martínez-López S, Caparrós E, Francés R, Moghadamrad S. Paneth Cells Regulate Lymphangiogenesis under Control of Microbial Signals during Experimental Portal Hypertension. Biomedicines. 2022 Jun 25;10(7):1503. doi: 10.3390/ biomedicines10071503.

Hosseinpour M, Mashayekhi F, Bidabadi E, Salehi Z. Neuropilin-2 rs849563 gene variations and susceptibility to autism in Iranian population: A case-control study. Metab Brain Dis. 2017 Oct;32(5):1471-1474. doi: 10.1007/s11011-017-0024-2.

Jemielita M, Taormina MJ, Burns AR, Hampton JS, Rolig AS, Guillemin K, Parthasarathy R. Spatial and temporal features of the growth of a bacterial species colonizing the zebrafish gut. mBio. 2014 Dec 16;5(6):e01751-14. doi: 10.1128/mBio.01751-14.

Knoop KA, Holtz LR, Newberry RD. Inherited nongenetic influences on the gut microbiome and immune system. Birth Defects Res. 2018 Dec 1;110(20):1494-1503. doi: 10.1002/bdr2.1436.

Korteniemi J, Karlsson L, Aatsinki A. Systematic review: Autism spectrum disorder and the gut microbiota. Acta Psychiatr Scand. 2023 Sep;148(3):242-254. doi: 10.1111/acps.13587.

Krautkramer KA, Dhillon RS, Denu JM, Carey HV. Metabolic programming of the epigenome: host and gut microbial metabolite interactions with host chromatin. Transl Res. 2017 Nov;189:30-50. doi: 10.1016/j.trsl.2017.08.005.

Lee SC. mSphere of Influence: the Mycobiota in Human Health and Disease. mSphere. 2020 Jan 22;5(1):e00974-19. doi: 10.1128/mSphere.00974-19.

Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell. 2006 Feb 24;124(4):837-48. doi: 10.1016/j.cell.2006.02.017.

Lord JR, Mashayekhi F, Salehi Z. How matrix metalloproteinase (MMP)-9 (rs3918242) polymorphism affects MMP-9 serum concentration and associates with autism spectrum disorders: A case-control study in Iranian population. Dev Psychopathol. 2022 Aug;34(3):882-888. doi: 10.1017/S0954579420002102.

Macfarlane S, Woodmansey EJ, Macfarlane GT Colonization of mucin by human intestinal bacteria and establishment of biofilm communities in a two-stage continuous culture system. Appl Environ Microbiol. 2005 Nov;71(11):7483-92. doi: 10.1128/AEM.71.11.7483-7492.2005.

Marini F, Cianferotti L, Brandi ML. Epigenetic Mechanisms in Bone Biology and Osteoporosis: Can They Drive Therapeutic Choices? Int J Mol Sci. 2016 Aug 12;17(8):1329. doi: 10.3390/ijms17081329.

Mashayekhi F, Mizban N, Bidabadi E, Salehi Z. The association of SHANK3 gene polymorphism and autism. Minerva Pediatr (Torino). 2021 Jun;73(3):251-255. doi: 10.23736/S2724-5276.16.04539-4.

Matsuzaki H, Iwata K, Manabe T, Mori N. Triggers for autism: genetic and environmental factors. J Cent Nerv Syst Dis. 2012 Feb 22;4:27-36. doi: 10.4137/JCNSD.S9058.

Meisel JS, Nasko DJ, Brubach B, Cepeda-Espinoza V, Chopyk J, Corrada-Bravo H, et al. Current progress and future opportunities in applications of bioinformatics for biodefense and pathogen detection: report from the Winter Mid-Atlantic Microbiome Meet-up, College Park, MD, January 10, 2018. Microbiome. 2018 Nov 5;6(1):197. doi: 10.1186/s40168-018-0582-5.

Nichols RG, Davenport ER. The relationship between the gut microbiome and host gene expression: a review. Hum Genet. 2021 May;140(5):747-760. doi: 10.1007/s00439-020-02237-0.

Ohlsson C, Engdahl C, Fåk F, Andersson A, Windahl SH, Farman HH, Movérare-Skrtic S, Islander U, Sjögren K. Probiotics protect mice from ovariectomy-induced cortical bone loss. PLoS One. 2014 Mar 17;9(3):e92368. doi: 10.1371/journal.pone.0092368.

Pala V, Sieri S, Berrino F, Vineis P, Sacerdote C, Palli D, Masala G, Panico S, Mattiello A, Tumino R, Giurdanella MC, Agnoli C, Grioni S, Krogh V. Yogurt consumption and risk of colorectal cancer in the Italian European prospective investigation into cancer and nutrition cohort. Int J Cancer. 2011 Dec 1;129(11):2712-9. doi: 10.1002/ijc.26193.

Panaro MA, Benameur T, Porro C. Hypothalamic Neuropeptide Brain Protection: Focus on Oxytocin. J Clin Med. 2020 May 19;9(5):1534. doi: 10.3390/jcm9051534.

Parker A, Fonseca S, Carding SR. Gut microbes and metabolites as modulators of blood-brain barrier integrity and brain health. Gut Microbes. 2020;11(2):135-157. doi: 10.1080/19490976.2019.1638722.

Peralta-Marzal LN, Rojas-Velazquez D, Rigters D, Prince N, Garssen J, Kraneveld AD, Perez-Pardo P, Lopez-Rincon A. A robust microbiome signature for autism spectrum disorder across different studies using machine learning. Sci Rep. 2024 Jan 8;14(1):814. doi: 10.1038/s41598-023-50601-7.

Rawls JF, Mahowald MA, Ley RE, Gordon JI. Reciprocal gut microbiota transplants from zebrafish and mice to germ-free recipients reveal host habitat selection. Cell. 2006 Oct 20;127(2):423-33. doi: 10.1016/j.cell.2006.08.043.

Rhee KJ, Sethupathi P, Driks A, Lanning DK, Knight KL. Role of commensal bacteria in development of gut-associated lymphoid tissues and preimmune antibody repertoire. J Immunol. 2004 Jan 15;172(2):1118-24. doi: 10.4049/jimmunol.172.2.1118.

Roy R, Singh SK. The Microbiome Modulates the Immune System to Influence Cancer Therapy. Cancers (Basel). 2024 Feb 14;16(4):779. doi: 10.3390/cancers16040779.

Sanos SL, Bui VL, Mortha A, Oberle K, Heners C, Johner C, Diefenbach A. RORgammat and commensal microflora are required for the differentiation of mucosal interleukin 22-producing NKp46+ cells. Nat Immunol. 2009 Jan;10(1):83-91. doi: 10.1038/ni.1684.

Satoh-Takayama N, Vosshenrich CA, Lesjean-Pottier S, Sawa S, Lochner M, Rattis F, Mention JJ, Thiam K, Cerf-Bensussan N, Mandelboim O, Eberl G, Di Santo JP. Microbial flora drives interleukin 22 production in intestinal NKp46+ cells that provide innate mucosal immune defense. Immunity. 2008 Dec 19;29(6):958-70. doi: 10.1016/j.immuni.2008.11.001.

Schirbel A, Kessler S, Rieder F, West G, Rebert N, Asosingh K, McDonald C, Fiocchi C. Pro-angiogenic activity of TLRs and NLRs: a novel link between gut microbiota and intestinal angiogenesis. Gastroenterology. 2013 Mar;144(3):613-623.e9. doi: 10.1053/j.gastro.2012.11.005.

Senn V, Bassler D, Choudhury R, Scholkmann F, Righini-Grunder F, Vuille-Dit-Bile RN, Restin T. Microbial Colonization From the Fetus to Early Childhood-A Comprehensive Review. Front Cell Infect Microbiol. 2020 Oct 30;10:573735. doi: 10.3389/fcimb.2020.573735.

Sonnenburg JL, Angenent LT, Gordon JI. Getting a grip on things: how do communities of bacterial symbionts become established in our intestine? Nat Immunol. 2004 Jun;5(6):569-73. doi: 10.1038/ni1079.

Sultana MF, Suzuki M, Yamasaki F, Kubota W, Takahashi K, Abo H, Kawashima H. Identification of Crucial Amino Acid Residues for Antimicrobial Activity of Angiogenin 4 and Its Modulation of Gut Microbiota in Mice. Front Microbiol. 2022 Jun 6;13:900948. doi: 10.3389/fmicb.2022.900948.

Taniya MA, Chung HJ, Al Mamun A, Alam S, Aziz MA, Emon NU, Islam MM, Hong SS, Podder BR, Ara Mimi A, Aktar Suchi S, Xiao J. Role of Gut Microbiome in Autism Spectrum Disorder and Its Therapeutic Regulation. Front Cell Infect Microbiol. 2022 Jul 22;12:915701. doi: 10.3389/fcimb.2022.915701.

Wang Y, Kasper LH. The role of microbiome in central nervous system disorders. Brain Behav Immun. 2014 May;38:1-12. doi: 10.1016/j.bbi.2013.12.015.

Warner BB. The contribution of the gut microbiome to neurodevelopment and neuropsychiatric disorders. Pediatr Res. 2019 Jan;85(2):216-224. doi: 10.1038/s41390-018-0191-9.

Wesemann DR, Portuguese AJ, Meyers RM, Gallagher MP, Cluff-Jones K, Magee JM, Panchakshari RA, Rodig SJ, Kepler TB, Alt FW. Microbial colonization influences early B-lineage development in the gut lamina propria. Nature. 2013 Sep 5;501(7465):112-5. doi: 10.1038/nature12496.

West CE, Jenmalm MC, Prescott SL. The gut microbiota and its role in the development of allergic disease: a wider perspective. Clin Exp Allergy. 2015 Jan;45(1):43-53. doi: 10.1111/cea.12332.

Wu HJ, Wu E. The role of gut microbiota in immune homeostasis and autoimmunity. Gut Microbes. 2012 Jan-Feb;3(1):4-14. doi: 10.4161/gmic.19320.

Yan J, Herzog JW, Tsang K, Brennan CA, Bower MA, Garrett WS, Sartor BR, Aliprantis AO, Charles JF. Gut microbiota induce IGF-1 and promote bone formation and growth. Proc Natl Acad Sci U S A. 2016 Nov 22;113(47):E7554-E7563. doi: 10.1073/pnas.1607235113.

Yap M, O'Sullivan O, O'Toole PW, Sheehan JJ, Fenelon MA, Cotter PD. Seasonal and geographical impact on the Irish raw milk microbiota correlates with chemical composition and climatic variables. mSystems. 2024 Apr 16;9(4):e0129023. doi: 10.1128/msystems.01290-23.

Yip BHK, Leonard H, Stock S, Stoltenberg C, Francis RW, Gissler M, Gross R, Schendel D, Sandin S. Caesarean section and risk of autism across gestational age: a multi-national cohort study of 5 million births. Int J Epidemiol. 2017 Apr 1;46(2):429-439. doi: 10.1093/ije/dyw336.

Zhang J, Motyl KJ, Irwin R, MacDougald OA, Britton RA, McCabe LR. Loss of Bone and Wnt10b Expression in Male Type 1 Diabetic Mice Is Blocked by the Probiotic Lactobacillus reuteri. Endocrinology. 2015 Sep;156(9):3169-82. doi: 10.1210/EN.2015-1308.

Zhang YW, Cao MM, Li YJ, Sheng RW, Zhang RL, Wu MT, Chi JY, Zhou RX, Rui YF. The Preventive Effects of Probiotic Prevotella histicola on the Bone Loss of Mice with Ovariectomy-Mediated Osteoporosis. Microorganisms. 2023 Apr 6;11(4):950. doi: 10.3390/microorganisms11040950.