

GUT MICROBIOTA IMPACT ON HUMAN HEALTH AND DISEASES

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ABSTRACT

The human gastrointestinal microbiota, an intricate consortium of microorganisms, profoundly impacts numerous facets of health, encompassing digestion, metabolic processes, immune functionality, and even psychological well-being. These microbial entities facilitate the degradation of food substances, biosynthesize vital nutrients, and modulate immunological reactions. A shift in the gut microbiome linked to several clinical conditions such as Dysbiosis including inflammatory bowel disease (IBD), obesity, hyperglycaemia, cardiovascular disease, autoimmune diseases, irritable bowel syndrome (IBS) and certain malignancies. Furthermore, burgeoning research has elucidated the association between intestinal bacteria and psychological well-being via the gut-brain axis, impacting emotional states, stress reactivity, and disorders such as anxiety and depression. Nutritional determinants, particularly a diet rich in fiber and derived from plant sources, can foster robust microbiota, whereas suboptimal dietary practices may lead to dysbiosis. Interventional approaches, such as probiotics, prebiotics, and fecal microbiome implants are currently being investigated as viable therapeutic modalities aimed at reinstating microbial equilibrium and enhancing health outcomes.

KEYWORDS: Gut Microbiome, Inflammatory bowel disease, obesity, hyperglycaemia, cardiovascular disease, irritable bowel syndrome etc.

INTRODUCTION

The microorganisms known as bacteria inhabit various parts of the human body. However, within the human abdomen, exists an assorted population of approximately 300 to 500 distinct bacterial species, collectively harboring around 2 million genes. These microorganisms significantly influence human health; in conjunction with other minuscule entities such as viruses and fungi, they constitute what is termed the Microbiota or Microbiome. The quantity of bacteria residing in the gut is estimated to be roughly tenfold that of all cells present in the human body, and the aggregated bacterial genome is substantially more extensive than the human genome. The composition of an individual's microbiome is inherently unique.

These bacteria are distributed throughout the entirety of the digestive system. The majority are localized within the intestines and the colon. They influence a wide array of physiological processes, including metabolic function, emotional state, and immune response.

The human gastrointestinal microbiota has its origins in the colonization by environmental microorganisms at the time of parturition, and it coexists in a symbiotic

relationship with host association throughout its lifespan. The intestinal tract harbors trillions of microorganisms, which significantly contribute to both health and illness by engaging with the host through numerous metabolic, defense system, neural, and endocrine pathways (1). The investigation of the gut microbiota about human health and illness continues to show several challenges (2). The gut microbiota constitutes a complex and adaptive assemblage, shaped by a myriad of influencing factors. Various populations of gastro-intestinal bacteria exert their significant effects on health through the fermentation of dietary fibers, resulting in the production of volatile fatty acids, which serve as endogenous signals playing critical roles in lipid equilibrium and the attenuation of inflammation (3).

Common gut microbiota and its positive impact on human wellness:

Human health and illness are greatly impacted by the microbiota; in fact, it is frequently called our "forgotten organ." In addition to performing several metabolic tasks like digesting and absorbing undigested carbohydrates, the gut microbiome is intricate in energy harvesting and deposit. This

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characteristic has most likely been a major evolutionary factor in the development of bacteria as human symbionts. More significantly, the gut microbiome communicates with the defense system by sending indications that support immune cell maturation and the proper development of immunological activities (4).

Below is a description of several common bacteria and their impact on human health are :

Bifido bacteria

Bifidobacteria are characterized by their V- or Y-shaped branched morphology, exhibiting a rod-like form, and are classified as immobile, non-spore-forming, Gram-positive, anaerobic probiotics that are catalase-negative and members of the family Bifidobacteriaceae within the Actinobacteria phylum. These microorganisms are predominantly located in the intestinal microbiota of neonates and within the uterine environment of expectant mothers.

The genus Bifidobacterium was initially recognized from fecal samples of breast-fed infants; however, it has since been isolated from different ecological environments like sewage, dairy products, and anaerobic digestion systems. Nonetheless, the majority of isolations are predominantly linked to the gastrointestinal systems of both humans and various animal species (5). Certain strains of the Bifidobacterium genus are extensively utilized as probiotic agents and are intricately associated with human health, being particularly recognized for their roles in enhancing the immune, digestive, and metabolic systems (6). In addition to reducing inflammation and oxidative stress, it also enhances intestinal barrier function and controls the metabolites produced by intestinal microbes (7).

Bacteroides

Bacteroides is a Gram-negative, non-spore-producing, obligatorily anaerobic, bacillary bacteria. A significant portion of the intestinal bacterial community in vigorous adults is composed of Bacteroidota, called as Bacteroidetes a significant phylum of the gut microbiota. Intestinal homeostasis and general human health profile depend on several genera in this phylum, including Bacteroides, Parabacteroides, Prevotella, and Alistipes. According to studies, bacteroidota can comprise 20–80 percent of the gut microbiota, indicating its significance in the gastrointestinal habitat (8).

Bacteroidota is essential for the breakdown of complex carbohydrates, which results in the synthesis of butyrate and other volatile acids that have anti-inflammatory, gut barrier-maintenance, and

colonocyte-energy-related functions. By affecting immune cell maturation and cytokine production, this phylum contributes to the modulation of the host defense system. Immunological tolerance and pathogen protection depend on such modulation (9).

Lactobacillus

A taxonomic group of rod-shaped, facultatively anaerobic, Gram-positive, non-sporing bacteria classified within the phylum of Firmicutes is designated as Lactobacillus (10). Lactobacilli constitute the predominant genus within the lactic acid bacteria (LAB) classification due to their capability to metabolize carbohydrates and synthesize lactic acid as a metabolic by-product (11). Various anatomical regions of the human organism, notably the female reproductive system and the gastrointestinal tract, including the oral cavity, have been inhabited by lactobacilli (12).

Certain strains of Lactobacillus are good for human health because they affect metabolic processes (like the production of vitamins, lactase activity, and cholesterol assimilation) and immune responses (13). They have also been shown to enhance the function of the gastrointestinal barrier by promoting the growth of pathogenic bacteria in IBD and non-alcoholic fatty acid liver disease.

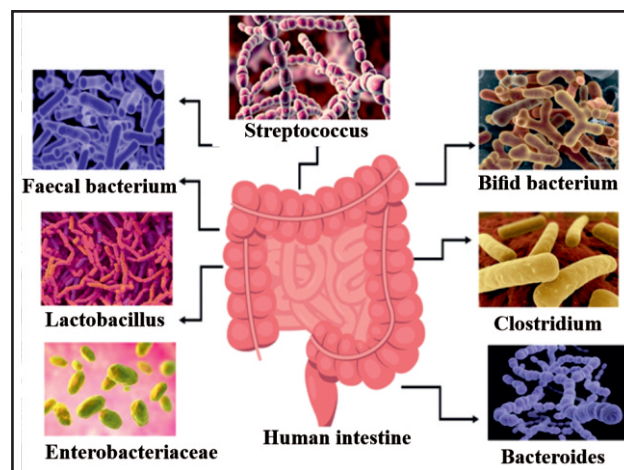


Fig. 1: Some common Bacteria Living in Gut and influence Gut Health accordingly

Clostridium

The microorganisms classified within the genus Clostridium exhibit a rod-like morphology, possess Gram-positive characteristics, and are capable of forming spores as obligate anaerobes. Their presence is noted in various environments including soil, the intestinal tracts of fauna, aquatic systems, and other ecological niches. These bacteria are categorized as chemoorganotrophs, demonstrating the ability to ferment an array of substrates such as carbohydrates, proteins,

organic acids, and various other organic compounds, leading to the production of metabolic derivatives including butyric acid, propionic acid, acetic acid, and certain solvents like acetone and butanol. Within the animals and humans' intestinal system, species of *Clostridium* predominantly metabolize indigestible polysaccharides. Furthermore, the metabolic by-products generated by these organisms confer numerous advantages to the health of the gut bacteria (14).

Clostridium butyricum enhances the immune system's efficacy by strengthening the gut barrier, thereby inhibiting the colonization of harmful pathogens within the gastrointestinal tract. Additionally, it mitigates inflammation in the bowel, known as colitis, and is modulated with a reduced risk of developing colorectal cancer (15).

Faecal bacterium

Faecal bacterium is a rod-shaped, nonmotile, Gram-positive, strictly anaerobic, extremely oxygen-sensitive (EOS), and non-spore-forming bacteria (16). It is one of the most functionally active elements of the microbiome, as evidenced by the modification of eight urine metabolites of various structures linked to population variance (17). One of the most important functions of *Faecalibacterium* is energy production for the colonocytes, and anti-inflammatory metabolites collaborate to maintain gut health. The primary contribution of this microbiota metabolism is thought to be the prebiotic fermentation process, a non-digestible dietary complex that defines and stimulates the healthy microbiota inhabitants (18).

Streptococcus

Streptococci are classified as Gram-positive, nonmotile, nonspore-forming, and catalase-negative cocci that manifest in pairs or chains, possessing considerable relevance in both medical and industrial contexts. Various species of streptococci play a crucial ecological role as constituents of the normal microbial flora in both animals and humans (19). The genus *Streptococcus* is extensively utilized in dairy fermentation processes for the production of yogurt and cheese. These microorganisms confer benefits to human gastrointestinal health and are primarily linked to the alleviation of diarrhoea symptoms as well as the prophylaxis of irritable bowel diseases. Furthermore, they possess the capacity to synthesize thermophilins, which are a class of bacteriocins—small peptides that can inhibit the proliferation of or eliminate closely related bacterial strains (20).

Streptococcal species are not only pivotal for gastrointestinal health but also serve as a critical determinant of oral health. Subsequent to parturition, members of the genus *Streptococcus* are among the initial inhabitants of the oral cavity and they significantly

contribute to the foundational organization of the oral microbiota. This underscores the rationale for the selection of specific streptococcal species for their potential influential components used as oral probiotics (21).

Among the Streptococcal strains, *S. salivarius* is also detected in human breast milk, which constitutes a critical reservoir of the bacteria during the initial stages of life, it is recognized as a remarkable and seemingly significantly constituent of the gastro microbiome (22).

Enterobacteriaceae

Enterobacteriaceae constitute a significant family of gram-negative, non-spore-producing bacterium. In the context of gut homeostasis, these bacteria play a precarious role in resisting the colonization of foreign pathogens. The gastro-intestinal microbiota offers protection through various mechanisms, such as immune system activation, engagement for nutrients, synthesis of antimicrobial substances, and maintenance of the integrity of the epithelial barrier (23).

Gut Microbiota influence in Disease

The human gut microbiome, along with its contributions to both health and disease, has been a focal point of considerable scholarly investigation, thereby delineating its integral role in host metabolism, nutrition, physiology, and defense responses. Disruptions in the equilibrium of the gut microbiota have been correlated with several irritable bowel syndrome, gastrointestinal disorders, inflammatory bowel disease including broader systemic disease manifestations such as obesity and chronic diabetes and cardiac disease to colorectal cancer (24).

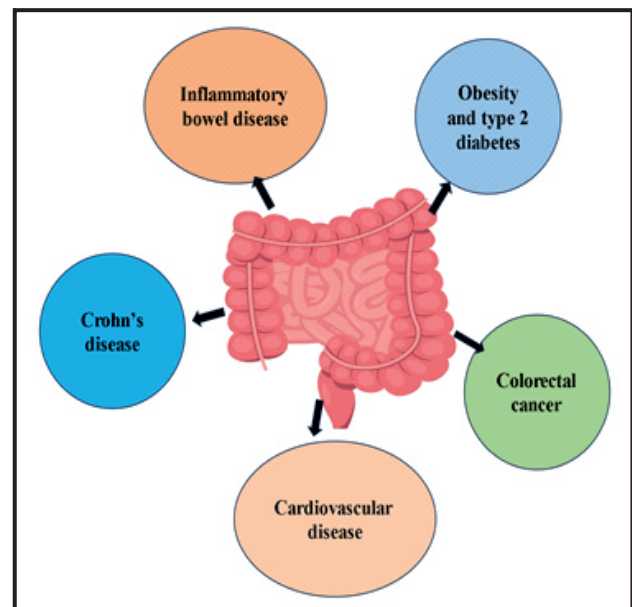


Fig. 2: In the negative environment Gut Microbiota can cause Disease in Intestine

Inflammatory Bowel Disease is a persistent gastrointestinal disorder i.e. demarcated by an exaggerated immune reaction to the gut microbiome. This condition, which is both severe and incapacitating, adversely contribute progress and improvement in pediatric populations, heightens the likelihood of colorectal malignancies, and has the potential to result in life-threatening sequelae(25). IBD manifests in two distinct forms, namely ulcerative colitis and Crohn's disease which are differentiated through the specific regions of the intestine that are inflamed (26).

Typically, anaerobic microorganisms residing in the gastrointestinal tract acquire their sustenance through the fermentation of non-digestible oligosaccharides and other carbohydrates that evade proximal digestion. The repercussion of the gut microbiome on individual health has prompted researchers to explore novel therapeutic interventions for a variety of health issues, including obesity or fats. A bidirectional interaction occurs between gut microbiota and nutritional habits, in which dietary components modulate the composition and functionality of the microbiota. Microorganisms present in the human digestive tract significantly affect the processes of nutrient assimilation, degradation, and deposition, which may have profound implications for host physiological functions (27). Further, overuse of antimicrobial medication has been linked to the onset of weight gain or obesity (28).

Individuals with type 2 diabetes experience metabolic dysfunctions that are related with imbalances in gut flora. The population of gut flora in humans is over 10 times greater than the number of human tissues and they are crucial for metabolic processes and defence system regulation. In T2D, the dysbiosis of gut microbiota leads to abnormal intestinal metabolites and interrupts the gastro-intestinal barrier, letting pathogenic bacteria and their metabolites to enter the blood vessels. This abnormal entry can cause damage to various organs by impairing insulin sensitivity, glucose metabolism, and immune balance (29).

The microflora may significantly participate to the functioning of the brain and the central nervous system, thereby elucidating the intricate interaction between gut microbiome and overall health profile. The gastrointestinal tract, often labelled as the 'second brain', comprises trillions of microorganisms that exert direct influence on both brain activity and neural signalling, thereby modulating stimuli associated with appetite or hunger. The variety and configuration of the gut flora are subject to modulation by several aspects, including mode of birth, eating practices, the administration of antibacterial and other suppositories,

the aging process, and additional ecological influences. The colonization of human microbes initiates at the moment of birth and subsequently undergoes progression and alteration in species abundance over a period of three years, culminating in the establishment of a mature microbiota (30).

Furthermore, within the realm of respiratory pathologies, the gut microflora is acknowledged to use a substantial influence. The gastrointestinal and respiratory systems exhibit a shared epithelial framework, having both developed from a unified ancestral lineage that can be traced back to the foregut, and they display the presence of secretory immunoglobulin A (IgA) alongside goblet cell. Respiratory diseases encompass a myriad of disorders that impact both the upper and lower respiratory tracts. These conditions are characterized by elevated mortality rates and may arise from physiological or immunological dysregulations or from pathogenic microorganisms. Chronic respiratory conditions include asthma, cystic fibrosis and chronic obstructive pulmonary disease , while pneumonia and tuberculosis serve as examples of diseases induced by microbial agents (31). Respiratory diseases represent a substantial burden on global healthcare infrastructures; projections indicate annual fatalities of 3.9 million individuals worldwide. The effect of gut micro flora in the establishment of pulmonary immunity, particularly during the initial stages of life, has been well-documented. This correlation between the gastrointestinal tract and the respiratory system is further illustrated by the observation that perturbations in gut microbiota during early life can precipitate enduring respiratory complications(27).

Mechanism for disease:

The initial phase in elucidating the symbiotic interactions between gastrointestinal microbiota and their hosts necessitates a inclusive characterization of the equilibrated configuration of gut microbiota alongside variations associated with disease (32).

Alterations in gut microbiota and immune responses in intestinal disorders are critical. The gut microbiome, surrounding bacteria, viruses, and fungus, besides with dysregulated immune responses involving regulatory T cells (Tregs), T-helper type 1 cells, and T-helper type 17 cells, are recognized as pivotal factors in the pathogenicity of inflammatory bowel disease. Under homeostatic conditions, gut microbiota foster an immune tolerance phenotype within the host, whereas in inflammatory states such as IBD, antigens derived from dysbiotic microbiota activate Th1 and Th17 cells, leading to tissue damage, a reduction in the mucus layer, and the penetration and tenacity of microbiotas

within intestinal nerves. The resultant mucosal barrier injury facilitates the further absorption of microbial antibodies, Toll-like receptor (TLR) ligands, and viable creatures, thereby sustaining the defensive responses.

Therapeutic Interventions that targets the Gut Microbiota

The utilization of gut microbiota as probiotics for the amelioration of diseases has been a longstanding practice. Furthermore, their incorporation into the food and feed industries as dietary supplements has experienced significant growth, attributable to their beneficial effects on gut homeostasis.

Probiotics participate to the enhancement of intestinal hemorrhage, the fortification of intestinal barrier functionality, immunomodulation, and the regulation of the production and secretion of metabolites and small reactive molecules associated with intestinal microbiome, such as volatile acids, tryptophan and its by-products, gamma-aminobutyric acid, bile acids (Bas), amino acids (AAs), trimethylamine (TMA), sphingolipids, and bacteriocins, as well as extracellular polysaccharides (EPS), thereby facilitating the alleviation or management of a variety of diseases, including metabolic disorders, neurological conditions, inflammatory bowel diseases, cardiovascular ailments, and tumorigenesis (33).

Dysregulation of gut microbiota is frequently correlated with a multitude of immune system disorders. Subsequently, these microorganisms have been shown to modulate the efficacy of immunotherapeutic interventions for diseases. Evidence from preclinical and clinical investigations indicates that the gut microbiota may markedly affects the success of cancer immunotherapy. The observed diminished response to immunotherapy in patients who received antibiotic treatment further substantiates the critical role of the microbiota in this context (34).

Conclusion

The human gastrointestinal microbiome represents a composite and dynamic ecological entity that fulfills a perilous role in the maintenance of health is crucial for promoting overall well-being and the reduction of disease incidence. The interaction between gut microbiota and human health is bidirectional, with gut microorganisms influencing a broad spectrum of physiological processes, which encompass, but are not limited to, digestion, immune modulation, and even mental health. The maintenance of a well-regulated gut microbiota through nutritional strategies, the implementation of probiotics, and various therapeutic measures may provide considerable benefits in the anticipation and management of innumerable diseases.

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