# GUT MICROBIOTA AND THEIR IMPACT ON DISEASE PATHWAYS AND INTERVENTIONS

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# Gut Microbiota and their Impact on Disease Pathways and Interventions

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# FOREWORD

Embark on an illuminating exploration into the intricate universe thriving within us: the realm of gut microbiota. This comprehensive book unravels the profound interplay between these microscopic inhabitants and human health, unveiling their pivotal roles in various physiological processes and disease states.

The human gut hosts a vibrant ecosystem, populated by trillions of microorganisms encompassing bacteria, viruses, fungi, and archaea. Collectively, they constitute the gut microbiota—a dynamic community with far-reaching impacts on our well-being. From facilitating digestion and nutrient uptake to modulating our immune responses and influencing mood and cognition, the gut microbiota is a cornerstone in nearly every facet of human health.

Initially, the book establishes a robust groundwork, defining the gut microbiota and examining its multifaceted composition. It explores the varieties of prebiotics that nourish these microbial communities and the metabolites generated by probiotics, illuminating the intricate biochemical processes occurring within our intestines.

Venturing further, the book uncovers the critical role of gut microbiota in conditions such as inflammatory bowel diseases (IBD), obesity, cardiovascular diseases, Type 2 diabetes, and even ocular ailments. Each segment offers an in-depth examination of the respective condition, elucidating the intricate links between gut microbiota dysbiosis and disease development. Additionally, cutting-edge treatment modalities, ranging from microbiota-targeted therapies to innovative interventions were discussed.

A particularly fascinating facet of gut microbiota research is its relevance to neurological disorders, underscoring the profound connection between gut health and brain function. Through the gut-brain axis, the microbiota exerts influence over neurological well-being, potentially unlocking novel therapeutic avenues for conditions like Alzheimer's disease, Parkinson's disease, and depression.

The book also delves into diverse strategies for modulating the gut microbiota, encompassing probiotics, prebiotics, faecal microbiota transplantation, and dietary modifications. These interventions present promising opportunities for fostering a balanced gut microbiome and reducing disease risk.

Exploring the realm of gut microbial metabolites reveals their potential as diagnostic markers and therapeutic targets. From advancing drug development to enabling personalized medicine, these metabolites hold transformative potential for healthcare and disease management.

In the concluding chapters, the future trajectory of gut microbiota research, spotlighting emerging trends, untapped frontiers, and the challenges and prospects on the horizon has been contemplated. The ongoing pursuit to decode the intricacies of the gut microbiota promises to yield fresh insights into human health and disease, catalysing innovative interventions and personalized therapeutic strategies.

I ardently hope that this book serves as an invaluable resource for researchers, healthcare professionals, and anyone captivated by the profound impact of gut microbiota on human health. May it kindle curiosity, stimulate discussions, and guide us towards a deeper appreciation of the microbial cosmos dwelling within us.

**Sreenivas Patro Sisinthy**
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# PREFACE

The phrase "gut microbiota" has become widely used among scientists and researchers over time. The diverse population of microorganisms directly involved in the body's normal homeostasis and illness states resides in the human gastrointestinal tract. A man's diet and the frequency of infectious diseases determine how much of the microbiota population remains in adulthood after it has grown in the body during infancy.

Before its role in drug absorption was discovered, it was thought that the microbiome was mostly involved in food digestion. Over time, it became clear that the microbiome system is crucial to the body's ability to fight against illness. The particular products of the microbiome are essential to the process of digestion. However, as science advanced and human curiosity grew, it became interesting to see how the microbiota was linked to a number of disorders. After extensive investigation, it was shown that the majority of the diseased state develops as a result of variety in the gut's microbial community.

The idea for writing this book came about as a result of the knowledge regarding the significance of microbiota in human health. The "gut microbiota" plays a role in controlling various systems and is not limited to the alimentary canal. The book's chapters go into greater detail about the role that gut microbes play in the development of conditions like Inflammatory Bowel Disease, Type 2 Diabetes, obesity, cardiovascular problems, neurological disorders, and other conditions. The tactics that would provide an appropriate microbe are also covered here, as the proliferation of the microbiome has become vital in the body.

By reading the book, academics and researchers will gain a grasp of the fundamental physiology and homeostatic changes associated with specific diseases caused by the "gut microbiota," as well as the potential implications of the microbiome and its metabolites for human health.

We sincerely hope that the book will pique readers' curiosity, assist the medical community recognise the significance of the human microbiome in illness prevention and maintaining homeostasis, and provide a natural means of preserving good health for all.

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# CHAPTER 1

# Exploring the Microbial Universe: An Overview of Gut Microbiota

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**Abstract:** The gut microbiota, a diverse assemblage of microorganisms inhabiting the gastrointestinal tract, profoundly influences human health and disease. Comprised of bacterial taxa such as Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria, this intricate ecosystem engages in symbiotic interactions with the host, exerting regulatory effects on various physiological processes. Prebiotics, indigestible dietary fibers including inulin, oligosaccharides, and resistant starches, selectively nourish beneficial gut bacteria, promoting their proliferation and metabolic activity. Through fermentation, prebiotics yield short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, pivotal in supporting intestinal health and function. Probiotics, live microorganisms administered in sufficient quantities, confer health benefits through producing metabolites such as vitamins, enzymes, and SCFAs during fermentation. These bioactive compounds contribute to immune modulation, nutrient absorption, and the preservation of gut epithelial integrity. The profound importance of gut microbiota extends beyond gastrointestinal health, impacting metabolic, immune, and neurological functions. Dysbiosis, characterized by perturbations in microbial composition, has been implicated in a spectrum of disorders, including inflammatory bowel diseases, obesity, and neurodegenerative conditions. Understanding the diversity of gut microbiota and their metabolites is pivotal for devising targeted interventions to modulate microbial communities and optimize health outcomes. Metagenomic investigations have unveiled distinct microbial signatures associated with dietary habits, diseases, and physiological states, underscoring the dynamic nature of the gut microbiome and its potential as a therapeutic avenue.

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**Keywords:** Dietary metabolites, Gut-brain axis, Gut microbiome, Immune modulation, Probiotics, Prebiotics, Short-Chain Fatty Acids (SCFAs), Vitamin metabolites.

## INTRODUCTION

The gut microbiota, which includes bacteria, viruses, fungi, and archaea, is a complex and varied collection of microorganisms that live in the human gut. This microbial ecology affects many body processes, including digestion, immunological response, and even mental health, and is essential to preserving general health and well-being. The complex link between the gut microbiota and human health has been made clear by developments in microbiology and genetics over the last several decades. These developments have highlighted the gut microbiota's potential influence on various ailments, including autoimmune diseases, metabolic disorders, and gastrointestinal disorders. It is becoming increasingly obvious that comprehending this microbial universe is essential to developing novel approaches to the prevention and treatment of a range of medical disorders. The gut flora plays a crucial role in nutrient absorption. These microbes are needed for metabolizing or breaking down necessary components so that the host may absorb them more easily [1].

Beyond its involvement in digestion and nutrient absorption, the gut microbiota also helps to support our body's immunity. The microbial community serves as a barrier to stop dangerous bacteria from colonizing. These beneficial bacteria are added to various vegetable juices, creating what are known as probiotic juices (Fig. **1**). These probiotic juices offer various advantages, as they combine the benefits of a plant-based diet with the presence of beneficial bacteria and high nutritional value.

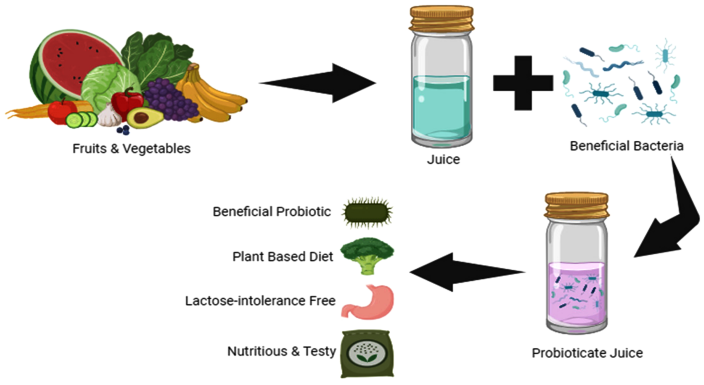


**Fig. (1).** Stage in probiotic action of fruits and vegetable juice

The gut microbiome's structure is dynamic and influenced by a number of internal and external factors. The microbial community is mostly determined by nutrition, with various dietary habits affecting the variety and abundance of certain bacteria. Poor lifestyle choices, such as stress and inactivity, may change how the gut microbiota functions. Additionally, while antibiotics are often required to cure infections, their usage might upset the delicate balance of the microbial population [2].

## What is Gut Microbiota?

A varied population of bacteria called the gut microbiome (MB) inhabits the gastrointestinal tracts of all animals, including humans. This intricate ecosystem is crucial for maintaining health and influencing a variety of physiological activities [3]. The bacteria that live in the human gut are mostly bacteria, with thousands of different species living together. These microbes play an important role in processes including vitamin production, nutrition absorption, and digestion. Additionally, the gut microbiota plays a critical role in maintaining intestinal equilibrium, protecting against dangerous invaders, and strengthening the immune system. Dysbiosis, or an imbalance in the gut's microbial ecology, may lead to many health issues, such as metabolic irregularities, autoimmune diseases, and gastrointestinal disorders [4].

Maintaining a diverse and well-balanced microbial community is important to maintain good complex relationships between general human health and gut microbiota.

## COMPOSITION OF GUT MICROBIOTA

A diverse range of bacteria, viruses, fungi, and other microorganisms comprise the gut microbiota, a complex microbial population that resides in the digestive system. The gut microbiota is composed primarily of hundreds of distinct bacterial species and is dynamically influenced by a variety of factors (Detailed impact of different microbes is described in Table **1**).

Individual genetic differences contribute to the early colonization and stability of these bacteria. The quantity and diversity of gut microorganisms are influenced by nutrition, with dietary fiber, probiotics, and prebiotics being important factors. An emerging field of study that holds promise for tailored healthcare methods and possible therapies to support optimum well-being is the recognition of the intricate interactions between the makeup of the gut microbiota and external factors [5].

CHAPTER 2

# Inflammatory Bowel Diseases and Gut Microbiota

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**Abstract:** Inflammatory Bowel Diseases are a type of intestinal chronic inflammation affecting the gastrointestinal tract generally developed due to environmental susceptibility, immune-mediated susceptibility, gene-mediated susceptibility, and gut microbiota. These heterogeneous complex immune disorders have two subtypes commonly known as Crohn's Disease and Ulcerative Colitis. Most studies of gut dysbiosis are concerned with various forms of IBD. The gut microbiome consists of up to 100 trillion microorganisms with about $10^{11}$–$10^{12}$ cells/ml density comprising viruses, protozoa, fungi, and most abundantly different bacterial strains. Bacteria belonging to *Firmicutes*, *Bacteroides*, *Proteus*, and *Actinomycetes* phyla are the most dominant ones in the gut microbiome and any change in the combination can cause an abundance of pathogenic bacteria. A dysbiosis in the gut environment regarding the above-mentioned bacterial and other microorganism compositions may lead to gastrointestinal inflammation leading to CD and UC. Alteration in microbiota also causes an abundance of fungi like *Candida spp.* and yeast, *Malassezia spp.* especially *M. restricta* and *M. globosa* in the gut, which has been linked to severe colitis and CD. Different drug-based therapies have been used for short-term relief of symptomatic complications in IBD for the last two decades. But to avoid the side effects due to the chronic use of conventional drugs alternative strategies such as prebiotics, probiotics, and synbiotics have evolved in the past few years as effective treatment regimens. In this chapter, the abnormalities of the gut microbiome are linked with IBD, and the mechanism of the gut microbiome associated with the disease is discussed along with the novel therapies.

**Keywords:** Chron's disease, Dysbiosis, Gut microbiota, Inflammatory Bowel Diseases, IBD therapy, Short-chain fatty acids, Ulcerative colitis.

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# INTRODUCTION

## Definition and Overview

The incidence rate of Inflammatory Bowel Diseases (IBD) has been found to be progressive and emerged as a major public health challenge globally. The need for early identification is underscored by the fact that millions of individuals across the globe from developed to developing nations are impacted by IBD [1]. It is an intestinal chronic inflammation affecting the gastrointestinal tract (GIT) generally developed due to environmental susceptibility, immune-mediated susceptibility, gene-mediated susceptibility, and gut microbiota. Side-by-side etiopathogenesis of IBD depends on the consumption of plant-based or animal-based processed diets, smoking, antibiotic administration, etc [2]. In 1859, Samuel Wilks suspected microbes as a potent cause of IBD in the 19th century. These heterogeneous complex immune disorders have two subtypes commonly known as Crohn's Disease (CD) and Ulcerative Colitis (UC), which could be characterized by a disrupted mucosa structure, systemic biochemical abnormalities, and altered gut microbial composition affecting 0.3% to 0.5% people [3]. Developed countries, *viz.* North America, Australia, New Zealand, and Europe faced the highest incidents and it has also increased in developing countries *viz.* Brazil, South Korea, and China. The incidence of UC and CD was found to be 11.6 cases/lakh and 1.4 cases/lakh per year, respectively in China [4, 5]. Chronic inflammation of the colonic mucosa is observed in UC, whereas CD often involves the GI tract from the mouth to the anus and could be patchy, and transmural. Diarrhea, bloody stools, and abdominal spasms are the clinical manifestations of IBD [6]. If the gut microbial composition of healthy individuals and IBD patients is compared, prominent differences will link IBD with the gut microorganisms. Experimental IBD models using chemicals or genetic modulation abolish disease development or attenuate effectively under germ-free conditions mentioning the microbes as a major factor in IBD where any mismatches in host-microbe interactions promote the disease. The gut microbiome consists of up to 100 trillion microorganisms with about $10^{11}$–$10^{12}$ cells/ml density comprising viruses, protozoa, fungi, bacteriophage, and archaea being the most abundantly different bacterial strains [7]. It should be noted that most studies on altered gut microbiota, *i.e.*, gut dysbiosis associated it with various forms of IBD (Fig. **1**). In the gut microbiome, these microorganisms actively participate in nutritional absorption, immunity modulation, and combating pathogens and metabolize short-chain fatty acids (SCFAs) namely propionic acid, butyric acid, *etc.* which provide energy to the intestinal epithelium [8, 9]. The immunosuppressive potential of these beneficial bacteria regulates host immune cells. Immune cell interactions with pathogenic bacteria and bacterial metabolites can increase GI damage by inducing inflammatory cytokines.

Bacteria belonging to *Firmicutes* and *Bacteroides* are the most dominant ones among *Firmicutes*, *Bacteroides*, *Proteus*, and *Actinomycetes* phyla, which cumulatively comprise 90% of gut bacterial flora in healthy individuals. *Ruminicoccus*, *Lactobacillus*, *Bacillus*, *Clostridium*, and *Enterococcus* are the primary genus from *Firmicutes* phylum [10]. In the gut microbiome, pathogenic bacteria such as *Bacteroides fragilis*, *Ruminococcus torques*, *and Ruminococcus* are found with relatively higher growth rates in UC and CD, whereas the levels of beneficial bacteria *viz. Bifidobacterium longum*, *Faecalibacterium prausnitzii*, *Roseburia intestinalis*, and *Eubacterium rectale*, *etc.* were found to be prominently reduced [11, 12]. In CD patients, there is a rise in *Actinomyces*, *Escherichia coli*, and *Veillonella* spp. families whereas the *Coriobacteriaceae* and *Christensenellaceae* families, and *Clostridium leptum* in particular, decrease. Bacteriophages and archaea appear to be less abundant in an active disease in the human GIT [13, 14]. On the other hand, fungi like *Candida albicans* display an increased abundance but *Saccharomyces cerevisiae* has a decreased count during the pathogenesis of IBD. *Malassezia* especially *M. restricta* and *M. globosa* has also been linked to severe colitis caused by yeast in animals and the intestinal mucosa of CD patients [15]. Generally, corticosteroids, amino-salicylates, immunosuppressive, and biological agents have been used for short-term relief of symptomatic complications in IBD for the last two decades but prominent side effects like immunodeficiency and resistance of drugs have taken place. Novel therapeutic strategies *viz.* synbiotics, prebiotics, and probiotics have evolved in the past few years. Other than that, surgical therapies, gene-mediated therapies, and other related future therapies are now adopted and exposed to clinical trials [16]. In this chapter, the abnormalities of the gut microbiome linked with IBD and the mechanism associated with the disease are discussed. In a nutshell, the population, classification, and diagnosis of the GIT microbiome along with its contribution to the pathogenesis of IBD, and respective therapies were demonstrated.

## *Effect of Gut Microbiota on Ibd and its Mechanism*

In the human body, a symbiotic relationship is consistent between a host and gut bacteria where the host provides residence and nutrients, but gut bacteria contribute by producing SCFAs and vitamins in the host [9]. Different species including bacteria, fungi, and viruses constitute the human gut microbiome where over 90% of beneficial bacteria are from diverse subspecies of a few major phyla *i.e.*, *Bacteroidetes*, *Actinobacteria*, *Firmicutes*, and *Proteobacteria*. *Ruminicoccus*, *Lactobacillus*, *Bacillus*, *Enterococcus,* and *Clostridium (Clostridium XIVa* and *IV* groups*)* are the primary genera of the *Firmicutes* phylum [10]. Existing beneficial bacteria get reduced and pathogens may increase, which could be referred to as dysbiosis. The beneficial and pathogenic

CHAPTER 3

# Obesity and the Gut Microbiome

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**Abstract:** The gut microbiota (GM) comprises a complicated community of bacteria within the human intestinal tract. Nutrient absorption, immune reaction, energy metabolism, and various other physiological functions are all greatly impacted by the extensive and dynamic population of microbes found in the human gut. Scientific study indicates that a disorder in the configuration and role of the gut microbiota known as dysbiosis plays a major part in the development of inflammation leading to the development of obesity and illnesses associated with it like metabolic syndrome, non-alcoholic fatty liver, and the development of type 2 diabetes mellitus and cancer. There is a common interactive relationship between the microbiota in the gut with all the organs in the body including the brain. Food addiction along with dysfunctional eating patterns reflect changes in the interrelationship between the brain- gut-microbiota (BGM), along with a tipping point in this balance towards hedonistic pathways that result in obesity. Research supports the belief that the pathophysiology of obesity is influenced by bidirectional transmission in the gut-brain axis (GBA), which is assisted by the immune system, neurological, endocrine, and metabolic mechanisms. This study discusses the roles played by the gut microbiota in promoting obesity, the comorbidities that go along with it, and how microbial manipulation can assist in avoiding or alleviating weight gain and related comorbidities. It also encompasses the various strategies used to address the issue, including diet modifications to address individual microflora or the use of probiotics, prebiotics, synbiotics, and fecal microbiota transplants (FMT).

**Keywords:** Brain-gut microbiota (BGM), Diet modification,endocrine regulation, Fecal microbiota transplants (FMT), Food addiction, Gut-brain axis (GBA), Gut microbiota, Hedonistic pathways, Microbial dysbiosis.

## INTRODUCTION

The incidence of obesity, a complicated metabolic disease spurred on by an array of genetic and nongenetic causes, is increasing rapidly in both developed and

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developing nations. Though the exact definition varies by nation, the World Health Organization (WHO) describes the condition of obesity as having a body mass index (BMI) of more than thirty. Based on comprehensive studies all over the world, approximately 35% of the community is considered to have body mass more than BMI, and 11% are obese [1]. Besides its outward manifestations, obesity has been linked with metabolic issues such as deposition of fat and glucose, oxidative stress, chronic inflammation, and an increased risk of several ailments, including cancer, type 2 diabetes, and cardiovascular disorders [2]. Within the gut resides a community of symbiotic microbes known as the gut microbiota, which can number up to 100 trillion and is ten times more numerous than all the cells in the body. The bacterial genome that comprises the gut microbiota, or microbiome, influences nutrition uptake, energy management, and fat accumulation whose imbalance can lead to obesity. To sustain its robust population, the gut microbiota relies on a supply of deceased cells for nutrients, along with mucus secreted by the gut and undigested remnants from the diet that are inaccessible to the human body for absorption [3, 4].

The gut microbiota among human beings is a complicated and constantly changing ecological system that has developed with its host and makes up about one kilogram of total body weight. The idea that the communities of microbes that live in our stomachs work similarly to an organ and affect several facets of human health by way of immunological, metabolic, and endocrine processes is becoming a growing consensus. A significant portion of gut bacteria remains unculturable, thus impeding our comprehension of this microbiota due to technical limitations. In the 1980s, Pace and colleagues pioneered a novel culture-independent approach for bacterial identification, centered on sequencing the 16S rRNA gene. The implementation of 16S ribosomal RNA (rRNA)-based, culture-independent molecular techniques in the 1990s included competitive PCR, real-time PCR, fluorescent in situ hybridization, and denaturing/temperature gradient gel electrophoresis, supported the understanding that *Bacteroidetes and Firmicutes* bacteria are most prevalent in the gut microbiome of human [5]. In addition to producing various biologically active compounds such as SCFAs and vitamins, the dynamic gut microbiota can generate both potentially harmful substances like neurotoxins, carcinogens, and immunotoxins, as well as beneficial compounds such as antioxidants, pain relievers, and anti-inflammatory agents [6]. Obesity is often classified into two main types: visceral and subcutaneous. A known biomarker for obesity is an elevated *Firmicutes/Bacteroidetes* ratio. But in cases of extreme obesity, there is a positive link between the relative abundance of *Firmicutes* and indicators of brown adipocytes in subcutaneous adipose tissue as opposed to visceral adipose tissue. This implies that browning of white adipose tissue may assist the maintenance of a healthy obesity pattern, suggesting a potential benefit of a larger relative abundance of *Firmicutes* for subcutaneous

obesity [7]. Thus, the maintenance of the body's metabolism and energy equilibrium relies on the presence of a healthy gut flora. Metabolic complications and elevated central appetite could originate from an imbalance in the gut flora, which might lead to obesity [8]. Moreover, obesity is recognized to hurt the quality of life and increase the likelihood of experiencing psychological conditions such as depression and anxiety disorders. The gut-brain axis (GBA), which serves as a shorthand for the bidirectional connection that exists between the gut microbiome and the brain, is mediated by immunological, endocrine, and neurological pathways [9, 10]. Signals from the central nervous system regulate several gastrointestinal processes, such as the mucus transition and secretion of fluid motility. These signals are transmitted along the autonomic nervous system *via* the hypothalamic-pituitary-adrenal (HPA) axis [11]. Recent research has linked obesity to the gut microbiota due to its influence on hormones regulating appetite, such as ghrelin, leptin (LEP), and glucagon-like peptide 1 (GLP-1). Furthermore, studies have shown that modifying eating behaviors and appetite heavily depends on the gut-brain axis's neuronal connection with the vagus nerve. A unique approach to obesity management involves targeting the gut-microbiot--brain axis, as it plays a crucial role in regulating behaviors and physiological processes associated with obesity. Fecal microbiota transplantation and probiotic, prebiotic, and synbiotic supplements constitute some of the GBA-based therapies [12].

## THE GI TRACT AND IT'S MICROBIOME

### The Development and Robustness of the Gut Microbiome

While there may be limited bacterial translocation through the placental circulation contributing to a basic microbiota before birth, fetuses are commonly believed to be devoid of microbes while in the womb [13]. An infant's gut rapidly gets colonized by germs on delivery from the mother as well as from the surroundings. Breastfeeding compared to antibiotic therapy, delivery method (cesarean section vs vaginal delivery), and hygiene in the environment all affect the makeup of this microbiota. The host's genotype, growth modifications to the gut environment, and the consumption of solid foods represent a few of the factors that impact these microbiotas during the first few years of life [14]. Around the age of three, a more robust and intricate community that is similar to the adult microbiota develops. The "core microbiome," consisting of a vast array of shared microbial genes, illustrates the evolutionary convergence among diverse bacterial species [15].

# CHAPTER 4

# Cardiovascular Diseases and Gut Microbial Metabolites

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**Abstract:** Cardiovascular diseases (CVDs) continue to be the world's leading cause of death, and their aetiology is influenced by a complex interaction of lifestyle, environmental, and genetic variables. There is growing evidence that the billions of microorganisms and their metabolites that make up the gut microbiota may be crucial in regulating cardiovascular health. This chapter sheds insight on the possible mechanisms of action and therapeutic consequences of the complex link between gut microbial metabolites and cardiovascular disorders.

The gut microbiota produces a wide range of metabolites, including lipopolysaccharides (LPS), bile acids, trimethylamine N-oxide (TMAO), and short-chain fatty acids (SCFAs), by fermenting food substrates. These metabolites have the ability to affect a number of physiological processes that are important for cardiovascular health, including inflammation, lipid metabolism, endothelial function, and blood pressure management. They can also have systemic effects.

Certain gut microbial metabolites have been linked in recent research to the pathophysiology of heart failure, hypertension, atherosclerosis, and other CVDs. For example, a greater risk of atherosclerosis and severe cardiovascular events has been linked to elevated levels of TMAO, whereas the anti-inflammatory and potential atherogenic properties of SCFAs may offer cardioprotective advantages. Comprehending the function of gut microbiota metabolites in cardiovascular well-being presents opportunities for the creation of innovative treatment approaches and tailored therapies. Using dietary changes, prebiotics, probiotics, or microbial-based treatments to target the gut microbiota may present novel strategies for managing and preventing CVD. However, further research is warranted to elucidate the complex interactions between gut microbial metabolites, host physiology, and cardiovascular outcomes, paving the way for more effective strategies to combat CVDs in the future.

**Keywords:** Atherosclerosis, Bile, Hypertension, Inflammation, Lipids, LPS, Metabolites, Microbiota, Prevention, Probiotics, Prebiotics.

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## INTRODUCTION TO CARDIOVASCULAR DISEASES AND GUT MICROBIAL METABOLITES

Cardiovascular diseases (CVDs) contribute to morbidity and death globally and constitute a substantial global health burden. These ailments cover a wide range of conditions that affect the heart and blood vessels, including coronary artery disease, heart failure, peripheral artery disease, and stroke. Despite advances in medical management, CVDs continue to pose substantial challenges to public health systems and individuals alike [1].

Recent years have seen an increase in interest in the function of gut bacteria in cardiovascular health and disease. Trillions of bacteria that live in the gastrointestinal system make up the gut microbiota, which is essential for regulating several physiological processes and preserving host homeostasis. Notably, interactions between gut microbial communities and host metabolism have garnered significant attention, with mounting evidence suggesting a link between gut microbiota dysbiosis and the development of cardiovascular diseases [2].

The intricate relationship between gut microbiota and cardiovascular health underscores the pivotal role of microbial metabolites in shaping physiological processes. Through the synthesis of various metabolites, gut bacteria exert profound effects on host biology, particularly in modulating immunological responses, metabolic homeostasis, and vascular function. This symbiotic interplay between the gut microbiota and the host extends beyond mere digestion; it serves as a dynamic nexus where dietary substrates and host-derived compounds converge to generate a diverse array of bioactive molecules.

The microbial metabolites produced by the fermentation of dietary fibres, proteins, and other nutrients are at the forefront of this interplay. Acetate, propionate, and butyrate are examples of short-chain fatty acids (SCFAs), which are important metabolites generated by gut bacteria when dietary fibres are broken down. SCFAs play multifaceted roles in cardiovascular health, exerting anti-inflammatory effects, enhancing insulin sensitivity, and influencing lipid metabolism. Moreover, these metabolites have been shown to regulate blood pressure and endothelial function, thereby impacting vascular health and reducing the risk of cardiovascular diseases.

Beyond SCFAs, gut microbial metabolism also yields a plethora of bioactive compounds with diverse physiological functions. Trimethylamine-N-oxide (TMAO), for example, has attracted a lot of interest since it is linked to cardiovascular events and atherosclerosis. It is produced by microorganisms that metabolise dietary choline, phosphatidylcholine, and carnitine. Elevated levels of

TMAO have been linked to increased platelet aggregation, promotion of foam cell formation, and impairment of reverse cholesterol transport, all of which contribute to the progression of cardiovascular pathology.

Conversely, certain microbial metabolites exhibit cardioprotective properties and contribute to the maintenance of cardiovascular homeostasis. For example, bile acids, which are mostly produced in the liver and then altered by gut microbes, are essential for the absorption of lipids and the metabolism of cholesterol. Certain bile acids, such as ursodeoxycholic acid and lithocholic acid, have been shown in recent research to have a part in lowering the development of atherosclerotic plaque, enhancing endothelial function, and decreasing inflammation. The regulation of host immune responses highlights the reciprocal link between gut microbiota and cardiovascular health. Secondary bile acids (SBAs) and other microbial metabolites control the development and activity of immune cells, such as macrophages and T regulatory cells, to provide immunomodulatory effects. By modulating the balance between pro-inflammatory and anti-inflammatory signaling pathways, these metabolites influence the progression of cardiovascular diseases, such as atherosclerosis and hypertension. Moreover, the metabolic activity of gut bacteria can directly impact systemic metabolism, thereby influencing cardiovascular risk factors such as dyslipidemia, insulin resistance, and obesity. The development of metabolic illnesses and cardiovascular diseases has been linked to dysbiosis, which is typified by changes in the makeup and functionality of the gut microbiota. Restoration of microbial balance through dietary interventions, probiotics, or fecal microbiota transplantation represents a promising therapeutic approach for ameliorating cardiovascular risk factors and improving overall health outcomes [3].

This chapter aims to provide an overview of the relationship between cardiovascular diseases and gut microbial metabolites.

## THE GUT-HEART AXIS: LINKING GUT MICROBIOTA AND CARDIOVASCULAR HEALTH

The gut-heart axis serves as a conceptual framework to explain the complex relationship between gut microbiota and cardiovascular health, which is becoming widely acknowledged as a basic component of human physiology. This axis represents a bidirectional communication system between the gut microbiota and the cardiovascular system, wherein changes in gut microbial composition and activity can profoundly influence cardiovascular function and vice versa. Understanding this axis can help prevent and treat cardiovascular diseases (CVD), which continue to be the world's leading cause of morbidity and death. The gut

**CHAPTER 5**

# Gut Microbiota in Type 2 Diabetes

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**Abstract:** Type 2 Diabetes mellitus (T2DM), a chronic metabolic disorder characterized by insulin resistance and relative insulin deficiency, has emerged as a significant public health challenge globally due to its rapidly increasing prevalence. Growing evidence, as demonstrated by various studies, show that there is a significant association between the development of T2DM and disturbance in the composition profile of gut microbiota, which has generated interest in establishing the roles played by various metabolites derived from the gut microbiota in the development of T2DM. New approaches to treat T2DM by regulating the gut microbiota using probiotics, prebiotics, synbiotics, and fecal microbiota transplantation have generated significant interest.

**Keywords:** Farnesoid X Receptor (FXR), Gut microbiota, Gut permeability, Gut microbial metabolites, Probiotics, Prebiotics, Type 2 diabetes mellitus.

## INTRODUCTION

### Type 2 Diabetes Mellitus (T2DM)

Type 2 diabetes mellitus (T2DM), which accounts for most of all diabetes (about 90%), is a chronic metabolic disorder characterized by insulin resistance and relative insulin deficiency. It has emerged as a significant public health concern globally due to its increasing prevalence, particularly in developed and developing countries.

In 2021, every tenth adult, or just above half a billion adults in the world (537 million) were reportedly suffering from diabetes. The prevalence has nearly tripled in the last two decades (from 2020) and if allowed to grow unchecked at the current rate, it is projected to reach an alarming level of more than three-quarters of a billion within the next two decades (783 million by 2045). A large

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proportion of that, about half of those adults suffering from diabetes (240 million), are not diagnosed and, therefore, unaware of their disease condition. Equally alarming is the estimate that a further half a billion adults (541 million) have impaired glucose tolerance which increases the risk of developing type 2 diabetes [1].

## Gut Microbiota and Microbiomes

There is a complex ecosystem of microorganisms consisting of bacteria, archaea, fungi, viruses, and protozoa living inside and on the human body, and they are collectively called microbiota. The exact composition of the microbiota, both in number and type, changes from site to site like gut microbiota, oral microbiota, etc. The genomic information from this community of microorganisms including their microbial structural elements and metabolites is referred to as the Microbiome. The term 'human microbiome' was first defined by a Nobel Laureate Joshua Lederberg in 2002 as an "ecological community of commensal, symbiotic and pathogenic microorganisms that collectively share our body space" [2].

The gut microbiota, weighing about 1.5 kg in a healthy adult, is a collection of trillions of microorganisms (mostly bacteria, with a small minority of viruses, fungi, and eukaryotic) from more than a thousand species from 6 phyla namely *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria,* and *Verrucomicrobi*. Of these, *Firmicutes* and *Bacteroidetes* make up the largest portions of the gut microbiota (64% and 23% respectively), followed by *Proteobacteria* (8%) and *Actinobacteria* (3%). Gut microbiota is well reported for a variety of symbiotic functions such as breakdown and absorption of complex carbohydrates, absorption of some electrolytes and minerals as well as effect on bowel movement, and synthesis of micronutrients. Additionally, the gut microbiota interacts with the immune system by sending signals that promote immune cell maturity and normal functions while preventing colonization by harmful bacteria [3].

## EFFECT OF GUT MICROBIOTA ON TYPE 2 DIABETES AND ITS MECHANISM

A child at birth is introduced to the microbiota from the mother during birth and this plays a crucial role in developing the initial immunity of the child. After birth, breastfeeding also enriches the immune system of the by further contribution from the mother. Those born by Cesarean section are more prone to be colonized with microbiota of epidermal origin, while infants born naturally tend to have more microorganisms from the maternal vaginal flora (Table **1**). Formula-fed infants are known to show higher Proteobacteriaceae. This abundance leads to dysbiosis,

which increases the probability of acquiring T2DM and obesity in the future [4 - 9].

**Table 1. Gut microbiota acquisition during the first three years.**

| Influencing Factors | Species | References |
|---|---|---|
| **MODE OF BIRTH** | - | - |
| a. Normal Delivery | *Bifidobacteriaceae*, *Lactobacillus*, and *Prevotella spp*. | [4] |
| b. Cesarean | *Enterobacter hormaechei/ E. cancerogenus, Haemophilus parainfluenzae/ H. aegyptius/ H. influenzae/ H. haemolyticus, Staphylococcus saprophyticus/ S. lugdunensis/ S. aureus, Streptococcus australis, and Veillonella dispar/ V. parvula, Enterococcus and Klebsiella spp* | [5] |
| **TYPE OF FEEDING** | - | - |
| c. Breast milk | *L. gasseri, L. salivarius, Lactobacillus reuteri, L. fermentum, or Bifidobacterium breve* | [6] |
| d. Non-breastfed | *Prevotella* | [7] |
| e. Formula-fed | *Proteobacteriaceae* | [8] |
| f. Solid foods | *Fecal bacilli and Rosebacterium. R. intestinalis* | [9] |

The adult gut is dominated by two phyla, namely *Firmicutes* and *Bacteroidaceae*. These phyla are involved in maintaining homeostasis in the gut and the host. Any change in their population and proportion may lead to a loss of that balance. A close correlation has been found between higher *Firmicutes* to *Bacteroidaceae* ratio and the development of T2DM [2, 3]. An investigation by Gurung *et al.* showed that administrating *Bacteroides uniformis* and *Bacteroides acidifaciens* in diabetic mice improved insulin resistance and glucose intolerance. This suggests that the *Bacteroides* play an advantageous role in glucose metabolism [10].

*Bifidobacteriaceae* is one of the most commonly reported genera negatively associated with T2DM [10 - 13]. Certain species, such as *Bifidobacterium adolescentis, Bifidobacterium dentium, Bifidobacterium pseudocatenulatum, Bifidobacterium bifidum* and *Bifidobacterium longum* are negatively associated with T2DM when metformin is administered [14 - 16]

*Streptococcus mutans* and *Eggerthela lenta* can trigger insulin resistance through mTORC1-p38γ by producing propionic acid imidazole [17].

*Lactobacillus* abundance in T2DM portrayed a positive association with fasting blood glucose and HbA1c [18]. Certain species, such as *Lactobacillus gasseri* [19], *Lactobacillus acidophilus* [20] and *Lactobacillus salivarius* [10] increased in T2DM patients. *Clostridium*, a genus belonging to phyla *Firmicutes*, is negatively

# CHAPTER 6

# The Role of Gut Microbiota in Ocular Diseases

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**Abstract:** The adaptive environment that is crucial to the host's health is the microbiome. Several research works have revealed that dysbiosis, or changes in the gut microbiota of humans can have an involvement in the etiology of a number of prevalent ailments, including diabetes, cancer, and neuropsychiatric disorders. Nonetheless, recent findings indicate the potential for a gut-eye axis, in which gut dysbiosis suggests a crucial role in the progression and development of an array of ocular conditions, that include uveitis, diabetic retinopathy, glaucoma and age-related macular degeneration. Current therapeutic strategies include probiotic and prebiotic supplementation, which seems to be the most economical and practical way to avoid ocular diseases and return the gut microbiome to a healthy state. In this chapter, we discuss the present understanding of gut dysbiosis linked with the pathophysiology of common eye disorders along with potential therapeutic implications for future translational studies in this research area.

**Keywords:** Age-related macular degeneration, Bacteriophage Therapy, Diabetic Retinopathy, Dysbiosis, Fecal transplant, Glaucoma, Gut-Eye Axis, Keratitis, Microbial-derived metabolites, Ocular disease, Retinal artery occlusion.

## INTRODUCTION

The gut microbiome (GM), producing numerous small molecules, and shaping mammalian physiology profoundly in health and disease [1], stands out as the largest, with a predominance of bacteria whose quantity ($3.8 \times 10^{13}$) closely matches the count of cells in the human body ($3.0 \times 10^{13}$) [2]. The gut microbiome

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contributes to digestion, short-chain fatty acids (SCFA) synthesis, vitamin production, and immune system development, while SCFAs from microbes like *Bacteroides* regulate Treg and Th17 cells systemically [3]. The dynamic interplay between the host's immune system and the GM is crucial for preserving intestinal balance and suppressing inflammatory responses. Numerous studies have found a connection between changes in gut bacteria and eye diseases. A precise understanding of the gut microbiome is critically important for maintaining host health and managing disease. The eye is equipped with unique anatomic structures to maintain a highly regulated and confined environment for its function. There are mainly two blood-ocular barriers present in the human eye *i.e.* blood-aqueous barrier (BAB) and blood-retinal barrier (BRB) [4]. The endothelial cells lining the blood vessels in the iris, along with the non-pigmented cell layer of the ciliary epithelium, collectively constitute the BAB. Additionally, tight junctions between the non-pigmented epithelial cells further limit drug movement from the ciliary processes into the posterior chamber. Compared to immunocompetent tissue, privileged sites like the eye are particularly susceptible to inflammatory diseases resulting from changes in the gut microbiome. As people age, changes in the microbiome occur, potentially contributing to degenerative diseases like age-related macular degeneration (AMD) through altered ratios of Bacteroidetes to Firmicutes, as noted by Mariat *et al.* [5, 6]. In this manuscript, we summarized the association between gut microbiota and common eye diseases, including autoimmune uveitis, diabetic retinopathy, AMD, keratitis, glaucoma, and retinal artery occlusion, sheds light on the microbial involvement in ocular disease pathogenesis.

## GUT MICROBIOME FUNCTIONS

The gut microbiome is beneficial for human health in numerous ways. Complex carbohydrates, fibres, and other indigestible substances that the human body is unable to handle on its own are broken down by gut bacteria. Furthermore, gut bacteria produce enzymes that help the body absorb nutrients like vitamins, minerals, and short-chain fatty acids. Theinteraction between the gut microbiota and the immune system helps regulate the functions of the immune system. It aids in the formation and upkeep of a well-balanced immune response, which is necessary to protect the body from infections while preventing detrimental inflammation or autoimmune reactions.

## GUT MICROBIOME AND ITS AGE-DEPENDENT FEATURES

The microbiome in infancy undergoes significant changes influenced by various factors including the method of birth (cesarean section or vaginal delivery), feeding practices (breastfeeding or formula feeding, and introduction to solid

foods), family lifestyle, location, genetic factors, and antibiotic usage [7]. Between approximately 3 to 4 years of age, the microbiome undergoes dynamic alterations, eventually transitioning to a more stable adult state [8]. As individuals age, the microbiome composition shifts due to senescence, with some degenerative diseases being linked to these changes in the aging microbiome. Research conducted by Mariat *et al.* revealed a modified ratio of Bacteroidetes to Firmicutes in older age groups, characterized by a higher proportion of Bacteroidetes among the elderly [5]. This ratio has demonstrated implications for various diseases, including AMD, which affects eye health [6]. Hence, to uphold a high quality of life and mitigate age-related ailments, it becomes imperative to comprehend the dynamics of the gut microbiome in older individuals. A recent study demonstrated that individuals aged 65 years and above (n = 145) differed from those below 65 years (n = 133) in both taxonomic and functional aspects of their gut microbiome [9]. These modifications could have a considerable impact on overall health, an elevated presence of *Proteobacteria* may serve as a potential indicator of an unstable gut microbiome and heightened susceptibility to diseases [10]. These discoveries carry significance for preventative strategies against age-related degenerative ailments and conditions such as AMD and retinal artery blockages. Utilizing interventions that target the microbiome, such as antibiotic or probiotic treatments, may offer promising avenues for preventive strategies.

## INTERDEPENDENT REGULATION OF THE HOST IMMUNE SYSTEM AND GUT MICROBIOME

The interplay between the host immune system and gut microbiome has an important role in preserving intestinal balance and preventing inflammation. Acting as a barrier, the epithelial layer of the gut forms a biochemical and physiological shield that separates the host from commensal microbes, food antigens, pathogens, and toxins. Overlaying this epithelial barrier is a mucin layer composed of heavily glycosylated mucins, forming a gel-like substance, and containing various molecules like immunoglobulin A and antimicrobial agents such as lactoferrin [11]. Furthermore, another barrier to microbial invasion is the immunological defense system composed of specialized lymphoid structures known as Peyer's patches and lymphoid follicles. These follicles house a diverse array of immune cells like neutrophils, T cells, B cells, and dendritic cells. Goblet cells, predominantly found in the small intestine, facilitate the presentation of acquired luminal antigens to CD103+ dendritic cells, forming goblet cell-associated antigen passages [12]. The gut microbiota generates a multitude of metabolites, known as gut microbiota-derived metabolites, including short-chain fatty acids (SCFAs) and lipopolysaccharides (LPS), which facilitate communication between immune cells and gut epithelium, further playing a crucial role in inflammatory signalling. SCFAs have a direct binding affinity for

CHAPTER 7

# Neurological Disorders and the Gut-Brain Axis

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**Abstract:** The term "gut microbiota" refers to the group of microbes that reside in the GI tract, which extends from the mouth to the rectum. The term "microbiome," which refers to the substance of these microbes, is also used to describe this collection of microorganisms. A complex and reciprocal relationship between the stomach and the central nervous system (CNS), the gut-brain axis influences both health and disease. The hypothalamic-pituitary-adrenal (HPA) axis, sympatho-adrenal axis, autonomic nervous system (ANS), enteric nervous system (ENS), and descending monoaminergic pathways are the routes that are engaged in this communication. Mesenteric lymphoid tissues can become translocated with compounds produced by gut bacteria and molecular patterns associated with microbes due to dysbiosis in the gut and a weakened gut barrier. The complex immunological interaction between the gut bacteria and host cells allows for their mutually beneficial existence. When commensal bacteria are present, the gut's immune system must gently maintain equilibrium in order to continue performing its essential defensive role. Our goal is to understand how gut microbes relate to neurological conditions, particularly anxiety, depression, Parkinson's disease, autism spectrum disorders, and Alzheimer's disease. Further nutritional therapies can be utilized to improve overall gut health, induce eubiosis, and alter the composition of the gut microbiota and associated metabolites in addition to current medicinal approaches.

**Keywords:** Autism spectrum disorders, Alzheimer's disease, Anxiety, Depression, Eubiosis, Gut microbiota, Homeostasis, HPA axis, Immunological interaction, Microbiome, Metabolites, Nutritional, Parkinson's disease.

## INTRODUCTION

The collection of microorganisms that live in the GI tract, from the mouth to the rectum is known as the gut microbiota. This group of microorganisms is also refe-

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rred to as the microbiome, which represents the material of these microbes [1]. The makeup of the microbes, in the system varies in parts like the stomach, small intestine, and colon. These microbes and bacteria have a relationship with the host. While archaea, yeast, and fungi are also present in the GI tract, our knowledge about them is still limited. Previously thought to start after birth, it now appears that the establishment of gut microbiota begins during development [2]. The gut microbiota's composition is influenced by a range of factors, including antibiotic use, age, obesity, gastrointestinal disorders, and environment and nutrition. The bacteria, viruses, eukaryotic organisms, and archaea that make up the human body's enormous microbial ecosystem are between 10 and 100 trillion in number, individually [3]. Numerous environmental elements, including pH and oxygen content, are present in the body's habitat and have an impact on the ability of different bacteria to colonize. As a result, the exact anatomical site of colonization greatly influences the composition of the microbiota. In the human gut, microorganisms belonging to the families Firmicutes and Bacteroidetes predominate. Actinobacteria, Proteobacteria, Verrucomicrobia, Fusobacteria, Cyanobacteria, and Tenericutes are also present, albeit in fewer amounts [4].

The complex interactions that gut microorganisms have with each other and the host are a result of their direct and indirect interactions. The dynamics of the gut microbiome are closely related to the health of the gastrointestinal tract and other organ systems, including the brain [5]. Dietary materials such as fiber are used by gut microorganisms in greater quantities than the host can absorb. These microorganisms produce a wide range of compounds that have recently been dubbed “postbiotics.” These include lactic acid, ammonia, volatile fatty acids (VFAs, sometimes called short-chain fatty acids), and gases like hydrogen, carbon dioxide, and methane [6].

The gut microbiome is essential for promoting adult development and preserving bodily equilibrium. Its influence on human metabolic processes is one of its primary functions since it breaks down complex polysaccharides included in meals. Furthermore, these microorganisms help regulate gut motility, the gut barrier, and the body's fat distribution. By controlling the growth of gut-associated lymphoid tissue and halting the colonization of dangerous pathogens, they also contribute to immune function. They may also have an impact on the host's mitochondrial and energy metabolism [7]. Comprehending the variety of gut microbes and their functions in physiology has been the focus of recent research. By changing these bacteria' makeup, this understanding may someday help prevent and cure illnesses. Certain gut floras, for example, have been found in trials to improve the efficacy of conventional chemotherapy medications [8]. Diet and age have a big impact on the makeup of the gut microbiota. Various studies, involving both humans and animals, have demonstrated that dietary practices can

cause substantial changes in the microbiome. For example, due to their different diets, people in rural Africa and Europe have quite different gut bacterial compositions [9]. Wu *et al.* found that a diet high in animal fats and proteins was linked to greater levels of Bacteroides, whereas a diet high in carbohydrates was linked to higher levels of Prevotella after analyzing stool samples from 98 people [10]. Disease and infection can also upset the balance of the gut flora, potentially leading to adverse effects on the host. The human body and bacteria cohabit symbiotically to produce a complex micro-ecological system. Variations in the number and kind of gut microbes can affect how well the gut barrier functions, secrete more toxic compounds and less helpful ones, and perhaps cause several gastrointestinal and systemic illnesses [11]. Three basic approaches are usually used to identify gut microorganisms: high-throughput sequencing technologies, conventional molecular biology methods that do not require culture and bacterial culture. In contrast, the latter two techniques, on the other hand, extract bacterial DNA for quick identification from stool samples and provide a more thorough understanding of the types of bacteria present [12].

Emotional dysregulation, dementia, developmental disorders, and other immune-related neurological illnesses are linked to changes in the gut microbiota and the creation of microbial metabolites as described in Fig. (**1**). The brain is made up of several neuronal and non-neuronal cell types that are connected by complex structural networks [13]. The brain is the organ that controls all behavior. More than 98% of the bacteria in the body reside in the gastrointestinal (GI) tract; these bacteria are referred to as gut microbiota [14]. The rise of omics approaches has allowed us to better understand the role of the gut microbiota in regulating gut-brain connections. Research on both human and animal gut microbiota has shown that the microbiota may affect immune responses, metabolites, hormone synthesis, and brain behavior and development [15, 16]. This implies that improving or maybe treating brain disorders could be possible by altering the gut flora. Additionally, through intricate neurohumoral networks, messages from the brain can affect the sensory and secretory processes of the stomach [17]. Similarly, signals from the gastrointestinal tract that are visceral afferents can influence brain activity. As a significant factor in controlling normal brain function and contributing to the development of neuropathological illnesses, recent research has brought attention to the gut-brain axis [18]. The processes relating gut microbiota to brain diseases still require comprehensive confirmation. There are new technologies that can go beyond correlation to find biological pathways that could lead to effective treatments. As a significant factor in controlling normal brain function and contributing to the development of neuropathological illnesses, recent research has brought attention to the gut-brain axis [19]. The processes relating gut microbiota to brain diseases still require comprehensive confirmation, though. There are new technologies that can go

**CHAPTER 8**

# Gut Microbiota Modulation Strategies

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**Abstract:** The gut microbiota plays a fundamental role in human health, influencing various physiological processes and contributing to overall welfare. This book chapter synthesizes current knowledge on the modulation of gut microbiota through key interventions, including prebiotics, probiotics, faecal microbiota transplantation (FMT), and dietary strategies. Prebiotics act as non-digestible fibers that selectively stimulate the growth and activity of primary three enterotypes like *Firmicutes*, *Bacteroidetes* and *Actinobacteria* that have emerged as promising contributors to gut health. Probiotics which are live microorganisms provide considerate health benefits and offer simultaneously, a direct means of manipulating microbial composition. FMT, a therapeutic approach involving the transfer of faecal material from a healthy donor to a recipient, has gained attention for its potential to restore gut microbiota equilibrium. Additionally, dietary interventions, such as high-fibrous diets, polyphenolic-rich foods, omega-3 fatty acids, and restricted sugar intake can exert profound effects on the gut microbial community. Understanding the intricate interplay between these interventions and the gut microbiota provides valuable insights into developing targeted strategies for promoting gastrointestinal health and managing various health conditions like obesity, IBD, and Type 2 diabetes. This chapter highlights recent advancements, challenges, and future directions in harnessing the potential of prebiotics, probiotics, FMT, and dietary interventions for modulating the gut microbiota and improving human health.

**Keywords:** Dietary intervention, Enterotypes, Fatty acids, Gastrointestinal health, Gut, Human health, Live-microorganisms, Microbiota, Obesity, Polyphenol-rich foods.

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# INTRODUCTION

## Probiotics and Promoting a Healthy Gut Microbiome

A probiotic is defined as "a live microbial food ingredient that is beneficial to health" [1]. The probiotics extensively investigated to date are predominantly from the *Lactobacillus* and *Bifidobacterium* genera [2]. Probiotic therapy has shown great effectiveness in contrast to a wide range of alimentary diseases and ailments [2] as they colonise the human intestines and modify the composition of the gut flora in specific parts of the host thus, inhibiting the colonisation of pathogenic bacteria in the intestine. They assist the host in preserving a robust protective layer for the intestinal mucosa, thereby reinforcing immunity [3]. Probiotics also help enhance the bioavailability of micronutrients like calcium and iron from the ingested food [4]. This process is achieved by the release of short-chain fatty acids (SCFAs) from these probiotics during fermentation. Consequently, it leads to a reduction in intestinal pH, enhancing mineral solubility and expanding the surface area for enterocyte absorption [5]. Moreover, dairy products that we consume act as an outstanding food medium thus ensuring their stability, feasibility, and ideal expression of probiotic function [6].

## Probiotics as a Relieving Agent Against Lactose Intolerance

Africans and Asians constitute the primary demographic population who experience such intolerance, while in Europe, the prevalence ranges from 2% to 70% [7]. Commonly observed symptoms include bloating, stomach pain, flatulence, loose stools, nausea, and borborygmi whereas, those with lactose intolerance can effectively tolerate and digest alternative sources of lactose, such as yogurt, kimchi, or sauerkraut, but struggle with the digestion of raw milk [8]. Yogurt and lactic acid bacteria in probiotics contain elevated levels of lactase, that are secreted into the enteric lumen. In this environment, lactase undergoes lysis facilitated by bile secretions [9]. Subsequently, lactase interacts with ingested lactose, alleviating symptoms associated with malabsorption. Additionally, fermented foods, including yogurt, contribute to a prolonged intestinal transit time, allowing for slower digestion of lactose and consequently mitigating symptoms.

## Probiotics Help to Combat Diarrhoea

In instances of acute infantile diarrhoea, commonly associated with rotavirus infection, *Lactobacillus rhamnosus GG* consistently demonstrates the ability to decrease the period of diarrhoea by around 50% [10]. The potential mechanism through which this bacterium operates involves strengthening mucosal integrity and triggering the immune response, potentially through increased production of

anti-rotavirus-specific immunoglobulin (Ig)A [10]. Another notable finding involves *Bifidobacterium bifidum*, administered alongside *Streptococcus thermophilus* present in standard milk formula, which has proved to be effective in reducing the occurrence of rotaviral diarrhoea [11].

Diarrhoea is a more prevalent issue in individuals undergoing antibiotic treatment [8]. Antibiotics can proximately disturb the native gut microbiota thereby diminishing colonization resistance and establishing a conducive environment for the development of disease-causing microorganisms like *Clostridium difficile* and *Klebsiella oxytoca* [12]. Probiotics are also advantageous in alleviating the complications linked to the 'triple therapy,' which entails the use of antibiotics to eradicate Helicobacter pylori from the stomach [13]. In particular, the administration of *Lactobacillus rhamnosus GG* has demonstrated effectiveness in reducing the frequency of diarrhoea, nausea, and alterations in taste among individuals undergoing *H. pylori* eradication with rabeprazole, clarithromycin, and tinidazole [13].

## Probiotics for the Treatment of Inflammatory Bowel Disease (IBD)

Extensive research has been conducted on probiotics to explore their capacity to alleviate symptoms associated with chronic conditions such as Inflammatory Bowel Disease (IBD) and Colorectal Cancer. Inflammatory Bowel Disease (IBD) is a term that refers to a group of chronic inflammatory conditions of the gastrointestinal tract. The administration of probiotics either regulates or modulates the composition of the gut microbiome, providing relief from symptoms associated with IBD and preventing the recurrence of such inflammation [14]. The non-pathogenic strain E. coli Nissle 1917 and S. boulardii have demonstrated efficacy in individuals with Crohn's disease, showing a reduction in stool frequency and the severity of relapses when compared to a placebo [15]. VSL#3, a blend of four *Lactobacilli* (*L. acidophilus, Lactobacillus bulgaricus, Lactobacillus casei, and Lactobacillus plantarum*), three *Bifidobacteria* (*Bifidobacterium breve, Bifidobacterium infantis,* and *Bifidobacterium longum*), and *S. thermophilus* [16]. This combination has proven to be efficient in reducing the recurrence of chronic relapsing pouchitis [17]. VSL#3, given at a daily dosage of 6 g, exhibited a substantial decrease in the recurrence of relapses (15%) when contrasted with a placebo group (100%) throughout a 9-month duration [18]. Additionally, it was successful in preventing the onset of pouchitis in individuals who had undergone ileo-pouch anal anastomosis for ulcerative colitis (UC). Understanding the mechanisms underlying probiotic activity in treating inflammatory bowel disease (IBD) has primarily been derived from animal model studies. The suggested mechanism involves the engagement of probiotics with mucosal regulatory T cells and the

**CHAPTER 9**

# Gut Microbial Metabolites as Diagnostic Biomarkers

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**Abstract:** Metabolites that originate from the human host and microbiota significantly alter host physiology and metabolism, which is a key factor in disease susceptibility and development. The gastrointestinal tract's gut microbiota, a community of bacteria, produces vital signalling metabolites that are essential to the hosts' physiological well-being. However, disruptions in the production of these metabolites can result in a variety of diseases, including cancer, neurological diseases, gastrointestinal disorders, metabolic diseases, and cardiovascular diseases. The understanding of gut microbiota metabolites, encompasses their various forms and mechanisms of action on targets. Furthermore, we enumerate their physiological and pathologic roles in both health and illness, including influencing the gut microbiota's composition and providing nourishment. In order to fight microbial-driven disorders and promote health, this study can be useful in understanding the roles of gut microbiota metabolites as it provides suggestions for designing appropriate therapeutic options. Many of these metabolites may be used in conjunction with intestinal microbiota dysbiosis as diagnostic biomarkers to track disease states.

**Keywords:** Autoimmune disease, Cancer, Cardiovascular disease, Diabetes, Food interaction, Gut microbiota, Immune response, Metabolites, Metabolite profiling, Neurological disorders.

## INTRODUCTION

The gastrointestinal system of humans houses a wide range of microorganisms, including viruses, bacteria, fungi, archaea, and protozoa. This group of organisms (gut microbiota) has a significant adaptable genome that benefits the host and res-

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ponds to the intestinal environment and also located both inside and outside the body, such as the conjunctiva, saliva, oral, vaginal, and cutaneous mucosa [1]. The extensive range of roles that the microbiome has provided includes the metabolism of xenobiotics, vitamin synthesis, pathogen defence, fermentation of dietary fibres, and immune maturation. These functions demonstrate how the microbiome is intricately linked to human biology [2]. In the human digestive system, the microbial parasitic organ that lives in the gut is called the microbiota [3]. Ninety-five percent of the human microbiota is found in the gastrointestinal system, and each person has a different microbiota composition that may operate as a fingerprint [4].

A wide range of biological tissues, including the liver, kidney, urine, faeces, and cerebrospinal fluid, are frequently reported to contain microbial metabolites [2]. With 10 microbial cells and more than 22 million microbial genes, the gut microbiota can produce an extensive number of flexible enzymes to ferment many kinds of substances that are indigestible or difficult for human enzymes to break down, such as fibres. Thus, the gut microbiota is capable of producing a wide spectrum of metabolites with various bioactivities.

Based on their origin, the gut microbiota's metabolites can be broadly classified into three categories (a) Microbiota produced directly from diets, like SCFAs and indole derivatives; (b) Host and the gut microbiota that perform modification , like secondary bile acids, and (c) Produced de novo, like polysaccharide A [5].

Byproducts produced by the gut bacteria have a role in mediating their systemic effects. These microbial metabolites can either diffuse easily or are absorbed by the gut mucosa. The gut liver, gut brain, gut bone, gut kidney, gut lung, and gut heart axes are the channels *via* which the gut microbiota and various organs communicate with one another in a bidirectional fashion. Certain groups of metabolites derived from microbiota, including branched-chain amino acids, short-chain fatty acids, trimethylamine N-oxide, and tryptophan derivatives, have been linked to the etiology of neurological and cardiovascular diseases, metabolic disorders, and lifespan [3] as indicated in Fig. (**1**). There may be two ways in which these differential metabolites and disease are related: a) Metabolites from the gut microbiota change as the result of disease. Thus, these modified metabolites can serve as disease biomarkers. b) Because gut microbes produce chemicals that promote disease, they are considered risk factors for specific illnesses [6].

The biomedical literature provides data that the physiological and compositional shifts of gut flora may have a close relationship with variations in host immunity [4]. A biomarker can identify a disease's kind or identify and verify the existence

of an illness [7]. Biomarkers might originate from imaging data or biological material. Artificial intelligence and machine learning are capable of identifying highly predictive illness biomarkers [8].

Gut microbiota has been linked to both the promotion of health and the development or maintenance of various gastrointestinal and non-gastrointestinal disorders, in part because of high-resolution observational studies that have made use of next-generation sequencing technologies and metabolite profiling.

As we approach the post-metagenomic era, we must shift from using basic observations to distinguish between causal relationships and correlations and concentrate our efforts and resources on the latter. The goal is to include a person's microbiota in some type of customized healthcare and, *via* a deeper comprehension of its function, more effectively and precisely treat a person's illnesses. One will be able to classify various disease states more precisely and ascertain whether or not the gut microbiota is a viable therapeutic target that we may modify to treat particular diseases if we have a deeper understanding of the disease process [9]. Many studies demonstrate that treatments including medication, nutrition, and surgery alter gut microbial populations, which in turn influences the development and course of the disease. Investigators have shown an intense curiosity in the involvement of gut microorganisms and diseases related to the digestive system recently to understand the processes by which these microbes affect intestinal homeostasis and human diseases [10].

From the metabolic viewpoint, studies have shown that dysbiosis of gut microbes can cause or exacerbate many diseases such as tumors, gastrointestinal diseases, metabolic diseases, cardiovascular diseases, and neurobiological diseases; likewise, the supplement of beneficial commensals may relieve symptoms. Trimethylamine N-oxide (TMAO), a metabolite produced from gut microbes, was found to be a novel biomarker for independently predicting the incidence of poor prognosis of cardiovascular disease. In addition, *Faecalibacterium prausnitzii*, one of the most abundant bacterial species found in the gut, is reduced in different intestinal diseases, which means that *F. prausnitzii* may therefore assist as a biomarker for intestinal disease diagnostics [11 - 13].

Ageing is characterized by an ongoing decrease in homeostasis, diminished function, and increased mortality risk. Fundamentally, the cellular and molecular characteristics of mammals are shown at age 25, but this coincides with alterations in the microbiome, which change in turn, thus, influencing the speed at which age-related decline occurs. Studies on the gut microbiome of the elderly can be broadly divided into two groups, those highlighting changes in the microbiome of the elderly that are connected to specific illnesses associated with

CHAPTER 10

# Therapeutic Approaches Targeting Gut Microbial Metabolites

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**Abstract:** In recent years, there has been a lot of interest in studying gut microbial metabolites and their potential medicinal applications. This chapter gives a detailed review of therapeutic techniques that target gut microbial metabolites, including their role in health and illness, research methodologies, clinical applications, obstacles, and future directions. We begin with an overview of gut microbial metabolites, emphasizing their many roles and relevance in sustaining host physiology. We then investigate the complex link between gut microbiota and metabolism, explaining the processes by which microbial metabolites affect human health. The taxonomy of gut microbial metabolites, such as short-chain fatty acids, amino acid derivatives, bile acids, biogenic amines, and others, is thoroughly investigated, focusing on their functions and therapeutic possibilities.

To give insights into the instruments used in this discipline, methods for researching gut microbial metabolites are presented, including analytical techniques, metabolomics approaches, and microbiota profiling. The therapeutic potential of gut microbial metabolites is investigated, including targeting metabolites for disease management, modifying gut microbiota composition, and individualized treatments suited to particular patients. Clinical applications and case studies emphasize the importance of gut microbial metabolites in gastrointestinal problems, metabolic diseases, and neurological and immune system issues.

Challenges and future objectives in the area are discussed, highlighting the need to understand the complexities of gut microbial metabolite interactions, develop targeted therapeutics, and realize the translational potential of research discoveries. To summarize, pharmaceutical techniques targeting gut microbial metabolites provide intriguing options for enhancing human health and combating illness.

**Keywords:** Clinical applications, Gut microbial metabolites, Gut microbiota, Metabolomics, Personalized medicine, Short-chain fatty acids, Therapeutic approaches.

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## INTRODUCTION TO GUT MICROBIAL METABOLITES

Gut microbial metabolites are critical in maintaining the delicate balance of the gut microbiome and impacting different physiological processes within the host. These metabolites, generated by the varied microbial community that lives in the gastrointestinal system, include a wide range of substances such as short-chain fatty acids (SCFAs), bile acids, trimethylamine N-oxide (TMAO), and neurotransmitters. SCFAs, notably acetate, propionate, and butyrate, are essential energy sources for colonic epithelial cells and have anti-inflammatory properties, which contribute to gut health. Bile acids, which are predominantly generated in the liver and then changed by gut bacteria, are essential for lipid metabolism and cholesterol balance. Furthermore, growing research demonstrates the importance of gut microbial metabolites in systemic health, including their role in metabolic disorders, immunological modulation, and even brain function. Understanding the complicated interplay between gut microbial populations and their metabolites has enormous therapeutic potential for treating a variety of health issues by targeted therapies that modulate these metabolites [1].

## OVERVIEW OF GUT MICROBIOTA AND METABOLISM

The human gut microbiota, a complex ecology of billions of bacteria that live in the gastrointestinal tract, is critical for controlling host metabolism. Recent research has shown the complicated interplay between gut bacteria and many metabolic systems, providing light on their significant effect on human health and illness. Gut microorganisms create a wide range of metabolites from dietary components, including short-chain fatty acids (SCFAs), bile acids, and amino acid derivatives, all of which have different impacts on host physiology. These microbial metabolites act as signaling molecules, regulating immunological responses, energy metabolism, and neurobehavioral processes. Furthermore, the makeup and activity of the gut microbiota are regulated by a variety of factors, including nutrition, antibiotics, and host genetics, demonstrating the symbiotic relationship's dynamic character [2].

## ROLE OF GUT MICROBIAL METABOLITES IN HEALTH AND DISEASES

The scientific community has given the function of gut microbial metabolites in health and illness a great deal of attention lately. Through complex metabolic interactions, the billions of bacteria that make up the human gut microbiota are essential to the preservation of host homeostasis. There is growing evidence that the microbial metabolites that are generated when food ingredients ferment play a major role in host physiology. Protonate, butyrate, and acetate are a few examples of short-chain fatty acids (SCFAs) that are produced by gut bacteria. The effects

of these SCFAs on immunological response, intestinal barrier integrity, and host metabolism are varied. For example, butyrate has anti-inflammatory qualities and is an essential energy source for colonic epithelial cells, which helps to prevent inflammatory bowel disorders (IBD). Furthermore, some physiological processes, including lipid metabolism, immunological regulation, and neuronal function, have been linked to additional microbial metabolites, such as bile acids, derivatives of amino acids, and polyphenol metabolites.

Microbial metabolites resulting in various diseases are shown in Fig. (**1**).

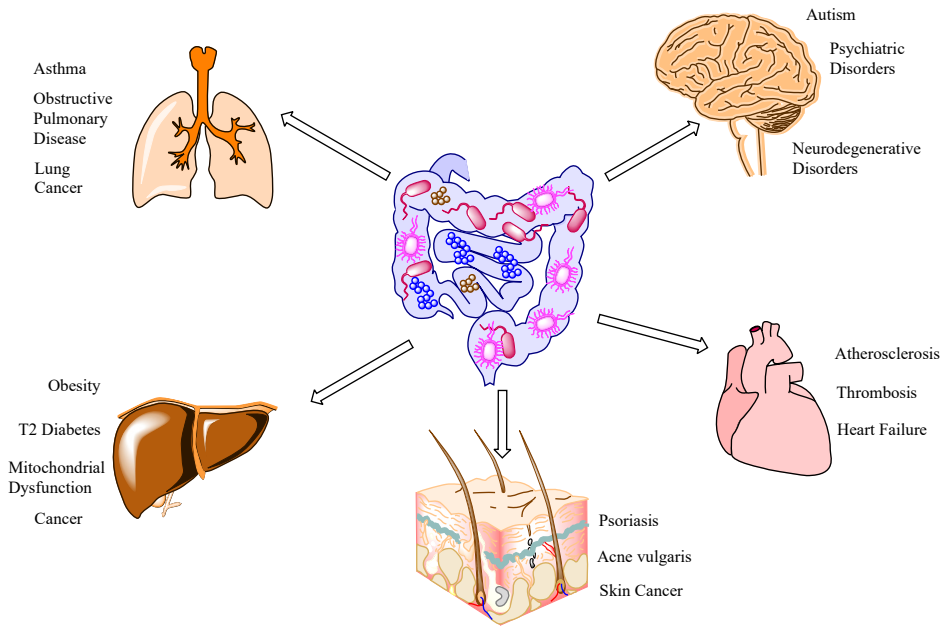


**Fig. (1).** Microbial metabolites and their association with various diseases.

Novel treatment approaches that target gut microbial metabolites have been made possible by recent research that has clarified the complex relationship between these metabolites and human health. The use of probiotics, prebiotics, or dietary modifications to alter the makeup of the gut microbiota has become a viable strategy for modifying microbial metabolite profiles and improving disease conditions. For example, it has been demonstrated that giving certain probiotic strains to people with IBD increases SCFA synthesis and improves gut barrier function. Additionally, dietary treatments high in fermentable fibers encourage gut bacteria to produce SCFAs, which protect against metabolic diseases including type 2 diabetes and obesity. Moreover, novel approaches to the

CHAPTER 11

# Gut Microbiota and Future Research Directions

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**Abstract:** The human intestines anchorage a complex of bacterial communities called gut microbiota. Gut microbiota is a prime regulator that preserves homeostasis in the intestine and the extra-intestine host-microbial interface. By contrast, the dysregulation of gut microbiota is accompanied by the assembling of various toxic substances and oncogenic proteins, which encourage several inflammatory responses and tumorigenesis. Moreover, gut microbiota correlates with the pathogenesis and progression of many disease conditions, including diabetes, obesity, inflammatory bowel diseases, cardiovascular disease, and neurological disorders. Besides that, different approaches have been intimated for the modulation of gut microbiome characteristics including treatment with antibiotics, prebiotic and probiotic supplements, nutritional interventions, and fecal microbiota transplantation (FMT) to control normal homeostasis of gut microbiota. Recently, it has been shown that gut microbiota has a significant connection to the regulation of the immune system in pathogenic conditions, and it has been identified as a potent therapeutic biomarker in the context of immunotherapy. This review emphasized the potential role of gut microbiome in the regulation of disease pathogenesis and therapeutic approaches. In connection with this, the recent study has elucidated emerging technologies for gut microbiome research, immunotherapeutic strategies, and the effects of nanomedicines on gut microbiota as a future perspective.

**Keywords:** Culturomics, Fecal microbiota transplantation, Gut microbiota, Homeostasis, Host-microbial interface, Immunotherapy, Immunomodulation, *In-vitro* holobiont system, Metagenomics, Nanomedicines.

## INTRODUCTION

Human gut microbiota is considered a complex bacterial community in the gastrointestinal arena. The intestinal community mainly consists of $10^{13}$ microbes, primarily obtained from the phyla *Bacteroidetes* and *Firmicutes* [1, 2]. Microorganisms in the gut microbiota interact with various host cells, which can significantly regulate physiological function in response to nutrient metabolisms and gut barrier regulation. The diversity of gut microbiota mainly depends upon several factors such as age, diet, environmental factors, and human lifestyle [3]. In addition, the gut microbiome is in charge of controlling how the host and microbiome interact and how they talk to immune, hormonal, neural, endocrine,

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and metabolic pathways. The gut microbiota can help improve the interactions between the host and microbiome, which could boost the host's immune system to fight off pathogens. Dysbiosis of the gut microbiome is significantly correlated with the manifestation and progression of many disease conditions, like cardiovascular disease, diabetes, anxiety, depression, obesity, inflammatory bowel syndrome, and cancer [4, 5].

Intriguingly, the gut microbiota contributes to the relationship to maintain immune homeostatic conditions, demonstrated in germ-free animals resulting in the impairment of regulatory T-cells (Tregs) development as well as the downregulation of gut-associated lymphoid tissues (GALT) proliferation. Besides that, host-immune responses are substantially accompanied by the control of the gut microbiome environment [6]. For instance, IgA (Immunoglobulin A) is secreted by gut plasma cells and shows reactivity to a wide spectrum of microbes, whereas this immunoglobulin A may increase the translocation of specific commensals into the lymphoid tissue to promote the antigenic appearance and uphold the gut microbiome diversity [7, 8]. The alteration of the gut microbiota environment causes the downregulation of good bacterial survival and function with upsurges of bad bacterial activities. Therefore, fecal microbial transplantation and prebiotic management significantly increase the magnitude of beneficial bacterial restoration in the intestine, changing this dysregulation and combating disease prevalence [9].

The immune surveillance theory identifies the evasion of tumor immuneresponses as a fundamental mechanism within the tumor microenvironment. This is because gut microbiota interacts directly with human immune systems, stopping tumor immune escape through their structures and byproducts. These factors play a pivotal role in facilitating disease progression and poor prognosis. Additionally, the microbiota in the gut can effectively change the immune system by producing metabolites [6, 10]. This recent article has reviewed the potential mechanistic understanding of gut microbiota in response to disease progression as well as the correlation with recent therapeutic strategies. Furthermore, this study also described the emerging technologies associated with gut microbiome research, as well as the potential role of immunotherapy and the effect of nanomedicines on gut microbiota.

## Microbiota in Health

The intestinal-gut microbial balance is directly associated with human health and disease progression. The human digestive tract is home to a large community of microbes that play a big role in breaking down nutrients, extracting them, and immune system regulation [11]. Extensive studies have suggested that microbiota

can significantly interact with several biological processes *via* several mechanistic pathways. Furthermore, the biosynthesis of bioactive molecules like amino acids, vitamins, and lipids also depends upon gut microbial regulation [12].

In healthy conditions, the gut microbiome elicits resilience, stability, and symbiotic interactions with the hosts. The gut microbial community consists of bacteria, yeasts, and viruses. The healthy microbial community often exhibits higher taxonomical diversity, stable core microbiota, and high microbial gene prosperity [13]. Moreover, it has been reported that the relative distribution of microbiomes is different between individuals, which may be associated with age and environmental factors like pH and medicine usage. Additionally, the presence of gut microbiota may also vary in different anatomical parts of the gastrointestinal tract. For instance, *Proteobacteria* like *Enterobacteriaceae* are found in the small intestine and *Bacteriodetes* like *Bacteroidaceae*, *Prevotellaceae* and *Rikenellaceae* are present in the colonic environment [14]. These changes depend on the environment. For example, the small intestines have a short transit time and a high concentration of bile, while the colon has slower flow rates, a lighter pH, and large communities of anaerobic microbes [15]. Moreover, gut microbiota could differ by age. Normally, we observe a significant microbiota diversity between childhood and adulthood, which decreases at an older age [13]. Children's gut microbiota diversity increases due to the presence of *Akkermansia muciniphila*, *Bacteroides*, *Veillonella*, *Clostridium coccoides spp*., and *Clostridium botulinum spp* [16]. An adult's gut microbial community consists of three dominant microbial phyla, such as *Firmicutes*, *Bacteroidetes* and *Actinobacteria*. The dietary and immune systems remarkably change in older age people, which can affect the healthy gut microbial composition. Especially, elder people have been shown to have increased *Clostridium* and *Proteobacteria* and decreased *Bifidobacterium* microbiota [17]. In the last two decades, extemporaneous efforts in biomedicine have been undertaken to develop the interplay of commensal bacteria living in and on the human body with their own human physiology. Also, Laudes and his colleagues reported some examples of future clinical applications in several entities, which suggest the microbiome-based molecules as potential targets for intervention studies, either as a standalone therapy or in addition to disease-specific drugs to make them work better [18].

## Microbiota in the Development of Diseases

The gut microbiota communities encompass trillions of microorganisms, utilizing advanced sequencing technologies and bioinformatics [5]. These microorganisms have a significant impact on our physiology, both healthy and diseased. They facilitate multiple functions, some of which include modulating metabolic activities, defending against potential infections, bolstering the immune system,

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## Sandipan Dasgupta

Sandipan Dasgupta is an experienced pharmaceutical professional specializing in Pharmacology, drug delivery systems, and Pharmaceutical Sciences. He holds a PhD in Pharmaceutical Sciences from Dibrugarh University, Assam, India. Presently, he is the Head of the Department at Department of Pharmaceutical Technology, Maulana Abul Kalam Azad University of Technology, West Bengal, India.

With over 17 years of combined experience in academia and the pharmaceutical industry, he brings a wealth of real-world expertise to his work. He has contributed to over 25 research and review publications in peer-reviewed journals, focusing on medication formulation optimization, cancer immunotherapy, lipid nanoparticles, nanoemulsion technology, and other neoplastic treatment techniques. His innovative contributions are further reflected in his involvement in seven book chapters and patents.

Beyond research, his diverse skill set is reinforced by his active participation in seminars and extracurricular activities, including bioinformatics and animal research management. This positions him as a versatile pharmaceutical expert committed to advancing research, education, and industry practices. Currently, he is working on anti-obesity drugs and alternative treatment approaches.

## Moitreyee Chattopadhyay

Moitreyee Chattopadhyay is a highly skilled and experienced professional in the field of Pharmaceutical Sciences, specializing in Pharmacology. A gold medalist from Nagpur University, Maharashtra, India, in her master's program and a recipient of the IDMA award, she later earned her PhD in Pharmaceutical Technology from Maulana Abul Kalam Azad University of Technology, West Bengal, India.

After gaining industrial experience in research and development, she transitioned into academia. She is currently an Associate Professor at Maulana Abul Kalam Azad University of Technology, West Bengal, India. Her expertise spans neuropharmacology, pharmacokinetic studies, various in-vitro and in-vivo models, safety assessment studies, and toxicology.

Her contributions to research articles, book chapters, and patents have significantly enriched the field of health sciences. Currently, her research focuses on the mechanistic pathways of neurological disorders, molecular approaches, and potential treatment strategies.