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REVIEW

Unlocking the secrets of the human gut microbiota: Comprehensive review on its role in different diseases

Jibon Kumar Paul, Mahir Azmal, ANM Shah Newaz Been Haque, Meghla Meem, Omar Faruk Talukder, Ajit Ghosh

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Abstract

The human gut microbiota, a complex and diverse community of microorganisms, plays a crucial role in maintaining overall health by influencing various physiological processes, including digestion, immune function, and disease susceptibility. The balance between beneficial and harmful bacteria is essential for health, with dysbiosis - disruption of this balance - linked to numerous conditions such as metabolic disorders, autoimmune diseases, and cancers. This review highlights key genera such as *Enterococcus*, *Ruminococcus*, *Bacteroides*, *Bifidobacterium*, *Escherichia coli*, *Akkermansia muciniphila*, *Firmicutes* (including *Clostridium* and *Lactobacillus*), and *Roseburia* due to their well-established roles in immune regulation and metabolic processes, but other bacteria, including *Clostridioides difficile*, *Salmonella*, *Helicobacter pylori*, and *Fusobacterium nucleatum*, are also implicated in dysbiosis and various diseases. Pathogenic bacteria, including *Escherichia coli* and *Bacteroides fragilis*, contribute to inflammation and cancer progression by disrupting immune responses and damaging tissues. The potential for microbiota-based therapies, such as probiotics, prebiotics, fecal microbiota transplantation, and dietary interventions, to improve health outcomes is examined. Future research directions in the integration of multi-omics, the impact of diet and lifestyle on microbiota composition, and advancing microbiota engineering techniques are also discussed. Understanding the gut microbiota's role in health and disease is essential for formulating personalized, efficacious treatments and preventive strategies, thereby enhancing health outcomes and progressing microbiome research.

Key Words: Gut microbiota; Cancer; Diabetics; Autoimmune disease; Dysbiosis

Core Tip: The human gut microbiota, a complex and diverse community of microorganisms, plays a critical role in maintaining health by influencing digestion, immune function, and disease susceptibility. Dysbiosis, an imbalance in this microbial community, is linked to conditions such as metabolic disorders, autoimmune diseases, and cancers. Key genera, including *Enterococcus*, *Ruminococcus*, and *Bacteroides*, are essential for immune regulation and metabolic health. Microbiota-based therapies, including probiotics and fecal microbiota transplantation, offer the potential to restore balance and improve health outcomes. We herein discuss the intimate correlations between gut microbiota and human health, predominantly associated with function, regulation, and management strategies.

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INTRODUCTION

The human gastrointestinal tract harbors a complex ecosystem of microorganisms, inclusively known as the gut microbiota. This microbial community, dominated by bacteria but also viruses, fungi, and archaea, profoundly influences host physiology, metabolism, and vulnerable function[1]. They play a pivotal part in maintaining gut barrier integrity and regulating vulnerable responses, impacting immune system development and function[2]. The human gastrointestinal tract harbors an essential ecosystem of bacteria that profoundly impacts health and disease susceptibility. *Enterococcus*, *Ruminococcus*, *Bacteroides*, *Bifidobacterium*, *Prevotella*, *Escherichia coli* (*E. coli*), *Akkermansia muciniphila*, *Firmicutes* (including *Clostridium* and *Lactobacillus*), and *Roseburia* are important genera that support vulnerable regulation and metabolic processes, which are essential for gut health and general well-being[3]. It is important to recognize that other bacteria, such as *Clostridioides difficile*, *Salmonella*, *Helicobacter pylori*, and *Fusobacterium nucleatum*, are also involved in various diseases. Dysbiosis of the gut microbiota is implicated in a spectrum of diseases ranging from metabolic disorders such as obesity and diabetes, to autoimmune conditions and cancers, emphasizing their profound impact on overall health[4]. Certain gut bacteria, such as *E. coli*, O157 and *Bacteroides fragilis* produce toxins, *Fusobacterium nucleatum* is involved in colorectal cancer, *Helicobacter pylori* in gastric cancer, and *Prevotella* in seditious bowel complaints, contributes to inflammation and cancer progression by damaging skin and dismembering host vulnerable responses[5]. These bacteria demonstrate the intricate relationship between gut microbiota composition and disease development, emphasizing the need for targeted interventions in disease forestallment and treatment strategies[6].

The composition and diversity of the gut microbiota are influenced by various factors such as diet, lifestyle, genetics, and environmental exposures[7]. The link between gut microbiota dysbiosis and disease development has prompted ferocious exploration into understanding microbial species and their relations with the host. Understanding the gut microbiota's role in health and disease is an area of intense scientific interest, with implications for developing novel therapeutic strategies[8]. Researchers are investigating how alterations in the gut microbiota contribute to these conditions and exploring ways to restore a healthy microbial balance[9]. The gut microbiota interacts with the host immune system, influencing immune development and responses. They can also produce metabolites that can affect host physiology, highlighting the intricate crosstalk between the gut microbiota and the host[10].

To delve deeper into the composition and function of the gut microbiota, advanced sequencing technologies and computational tools are paving a better understanding[11]. As the field of gut microbiota research continues to evolve, there is a growing interest in developing microbiota-based therapies, such as probiotics, prebiotics, fecal microbiota transplantation (FMT), and microbiota engineering[12]. These approaches hold promise to prevent and treat diseases by modulating gut microbiota. However, challenges remain in understanding the complex interactions between the gut microbiota and the host, as well as in developing safe and effective microbiota-based interventions[13]. The influence of gut bacteria on carcinogenesis is of particular interest, both within the gastrointestinal tract and on distant organs. Studies have linked microbial signatures associated with increased cancer threat, mechanisms by which gut bacteria modulate inflammation, and vulnerable responses[14]. This comprehensive review aims to explore the current understanding of human gut microbiota in association with disease and cancer development. It summarizes crucial findings from epidemiological studies, mechanistic exploration, and clinical observations to interpret the complex interplay between microbial communities and host health. By addressing gaps in knowledge and proposing future exploration, this review seeks to contribute to the broader issue of employing microbiota-based therapies for disease prevention and treatment.

GUT BACTERIAL DIVERSITY

The human gut microbiota consists of different bacteria essential for digestion, metabolism, and immune function. Beneficial bacteria like *Bifidobacterium* and *Lactobacillus* aid in carbohydrate breakdown, vitamin production, and immune support[15]. *Bifidobacterium*, for instance, plays a crucial role in digesting dietary fiber and producing short-chain fatty acids (SCFAs) such as acetate, which provide energy to gut cells and help maintain a healthy gut environment[16]. *Lactobacillus* is known for its ability to ferment lactose into lactic acid, aiding in lactose digestion and preventing the

growth of harmful pathogens by lowering the pH of the gut[17]. *Lactobacillus* species also produce antimicrobial substances such as bacteriocins, which inhibit the growth of harmful bacteria, contributing to a balanced gut microbiome. Moreover, these bacteria are involved in the production of bioactive peptides that can modulate the immune system and reduce inflammation[18]. *Akkermansia muciniphila* maintains gut barrier integrity by degrading mucin, the main component of mucus, which fortifies the gut lining and prevents pathogens from invading the gut wall. This bacterium has been linked to metabolic health, with studies showing its association with reduced inflammation, improved glucose metabolism, and protection against obesity and diabetes. The ability of *Akkermansia* to interact with the host's immune system and promote the production of anti-inflammatory molecules highlights its therapeutic potential[19]. *Faecalibacterium prausnitzii* produces anti-inflammatory butyrate, a SCFA that nourishes colon cells, reduces inflammation, and enhances gut barrier function, playing a significant role in preventing conditions such as inflammatory bowel disease (IBD). This bacterium is one of the most abundant and important in the human gut, contributing to overall gut health by modulating immune responses and promoting a balanced inflammatory environment. Low levels of *Faecalibacterium prausnitzii* have been associated with various inflammatory conditions, making it a key target for probiotic and dietary interventions[20].

In contrast, harmful bacteria such as pathogenic *E. coli* and *Clostridium difficile* produce toxins causing gut damage and severe illnesses like diarrhea. Pathogenic *E. coli* strains can produce *Shiga* toxin, leading to bloody diarrhea and potentially life-threatening hemolytic uremic syndrome[21]. *Clostridium difficile*, often triggered by antibiotic use, can cause severe colitis and life-threatening diarrhea through the production of potent toxins that damage the intestinal lining[22]. *Salmonella* causes foodborne illnesses, characterized by symptoms such as diarrhea, fever, and abdominal cramps, by invading intestinal cells and triggering an inflammatory response[23]. *Fusobacterium nucleatum* contributes to colorectal cancer by promoting inflammation and tumor growth. This bacterium adheres to and invades epithelial cells, facilitating a pro-inflammatory environment and providing a conducive setting for cancer development[24]. *Helicobacter pylori* increases gastric cancer risk through chronic inflammation and the production of cytotoxins that damage stomach lining cells, leading to ulcers and malignancies[25]. *Bacteroides fragilis* produces a toxin that disrupts the tight junctions between epithelial cells, leading to chronic inflammation and an increased risk of tumor formation[26]. These diverse bacterial communities with their harmful activities, highlight the intricate role of gut microbiota in maintaining health. Understanding these interactions further underscores the potential of targeted microbiome therapies to enhance beneficial bacteria and mitigate the effects of harmful ones, contributing to improved health outcomes (Figure 1).

GUT MICROBIOTA LINKED TO DIFFERENT DISEASES

Human gut microbiota, a complex community of trillions of microorganisms residing in our intestines, has garnered significant attention due to its profound impact on various aspects of health and disease. This intricate microbial ecosystem influences a range of physiological processes, from digestion and metabolism to immune system function and even brain health. Recent research has elucidated the role of gut microbiota in numerous diseases, highlighting its potential as a therapeutic target and its significance in maintaining overall health (Figure 2).

Microbiota and mental health: Exploring the gut-brain axis

One of the most fascinating areas of research is the gut-brain axis, which refers to the bidirectional communication between the gut microbiota and the brain. This connection is mediated through neural, endocrine, and immune pathways. Studies have shown that alterations in gut microbiota composition can influence brain function and behavior, potentially contributing to mental health disorders such as depression, anxiety, and autism spectrum disorders[27]. Certain gut bacteria can produce neurotransmitters like serotonin and γ-aminobutyric acid, which are crucial for regulating mood and anxiety levels[28]. Moreover, microbial metabolites such as SCFAs can affect the brain by modulating inflammation and the integrity of the blood-brain barrier[29]. Associations between gut microbiota composition and emotion-related brain functions suggest potential links to anxiety and depression, with regions such as the insula and amygdala - key players in emotional processing - frequently connected to microbial diversity[30]. A recent review underscores the significant association between gut microbiota and brain connectivity, with specific genera such as *Bacteroides*, *Prevotella*, and *Ruminococcus* consistently linked to brain networks like the default mode network and frontoparietal network[31]. These findings underscore the therapeutic potential of targeting gut microbiota to alleviate symptoms of mental health disorders. This evolving understanding suggests that probiotic and prebiotic treatments, alongside dietary modifications, could offer new avenues for managing and treating mental health conditions, thus integrating mental health care with dietary and microbiota-based strategies (Table 1)[32-44].

Microbiota linked to autoimmune and inflammatory diseases

The gut microbiota plays a critical role in the development and modulation of the immune system. Dysbiosis, or an imbalance in the gut microbial community, has been implicated in various autoimmune diseases, where the body's immune system mistakenly attacks its own tissues[45]. Conditions like rheumatoid arthritis, multiple sclerosis, and IBD have been linked to alterations in gut microbiota[46]. Studies have shown that certain pathogenic bacteria can trigger inflammatory responses, while beneficial microbes can help to maintain immune tolerance[47]. This delicate balance is essential for preventing autoimmune reactions. Understanding the specific microbial changes associated with these diseases can lead to new strategies for prevention and treatment[48]. This line of research opens promising avenues for using microbiota modulation as a form of immunotherapy, offering hope for better management of autoimmune diseases through non-invasive and dietary-based approaches (Table 2)[49-61].

Table 1 Gut bacteria and their mechanisms of involvement in various disorders

Sl No.	Disease	Mechanism of involvement	Key bacteria implicated	Ref.
1	Alzheimer's disease	Gut microbiota influences neuroinflammation and cognitive function; modulation of SCFA production affects brain health	*Lactobacillus spp., Bifidobacterium spp.*	[32]
2	Anxiety and depression	Dysbiosis, inflammation, cytokine release, HPA axis dysregulation	*Bifidobacterium, Lactobacillus*	[33]
3	Anxiety disorders	Gut microbiota-induced alterations in neurotransmitter levels and stress response pathways; modulation of vagus nerve activity	*Campylobacter jejuni, Lactobacillus rhamnosus*	[34]
4	Autism spectrum disorders	Interaction between *Candida albicans* and bacterial metabolites	*Candida albicans*	[35]
		Changes in gut microbiota affecting neurodevelopment and behavior; disruption in SCFA metabolism affecting microglial function	*Bacteroides spp., Firmicutes spp.*	[36]
5	Cognitive impairment	Gut microbiota affecting cognitive control and executive function networks such as the FPN and DMN	*Bacteroides, Prevotella, Ruminococcus*	[37]
6	Depression	Dysbiosis leading to increased intestinal permeability and systemic inflammation; alterations in serotonin and other neurotransmitter levels	*Lactobacillus spp., Bifidobacterium spp.*	[38]
		Chronic low-grade inflammation and altered neuroplasticity; influence on HPA axis and neurotransmitter metabolism	*Lactobacillus spp., Bifidobacterium spp.*	[39]
7	Emotional and interoceptive awareness	Gut microbiota composition associated with brain areas involved in emotional and visceral interoception	*Roseburia, Bacteroides*	[40]
8	Irritable bowel disease	Disruption in the balance of gut microbiota leads to chronic inflammation and dysbiosis affecting mood and stress responses	*Faecalibacterium prausnitzii, Bacteroides spp.*	[41]
9	Irritable bowel syndrome	Gut microbiota-induced inflammation and dysregulation of the enteric nervous system; alterations in gut motility and visceral hypersensitivity	*Bifidobacterium spp., Lactobacillus spp.*	[42]
10	Mood disorders	Alterations in gut-brain communication affecting mood-related brain networks	*Bifidobacterium, Collinsella*	[43]
11	Neurological disorders	Influence on neuroinflammation, gut-brain axis communication	*Lactobacillus, Bacteroides*	[44]

SCFA: Short-chain fatty acid; HPA: Hypothalamic-pituitary-adrenal; FPN: Frontoparietal network; DMN: Default mode network.

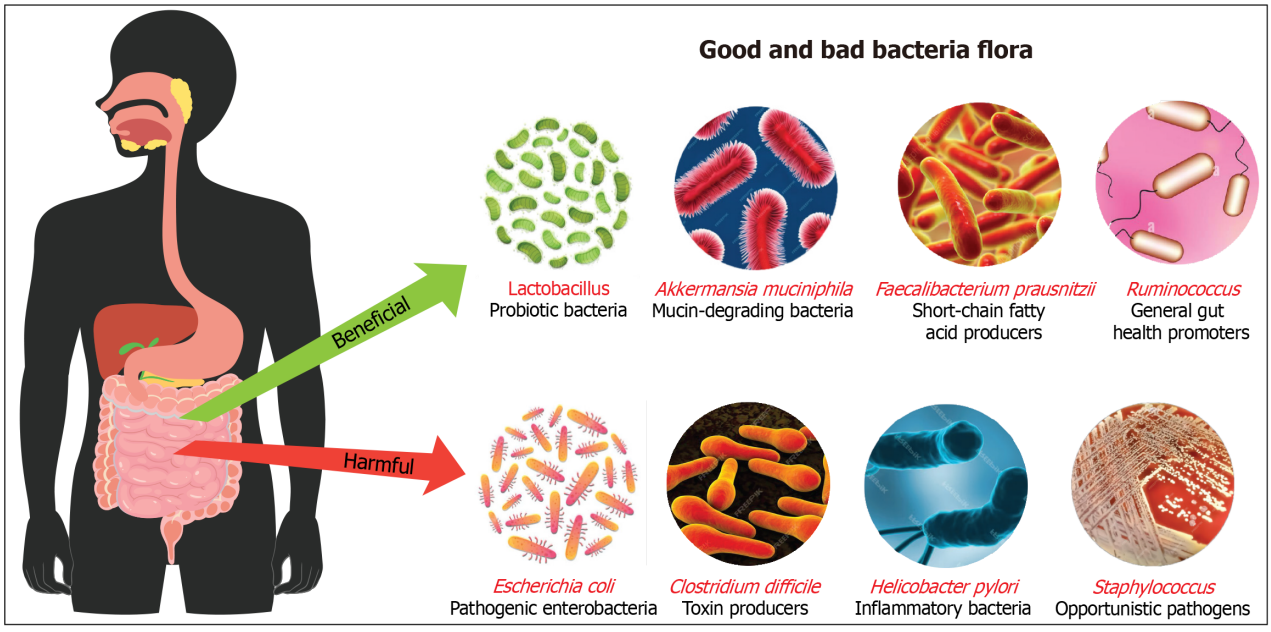

Figure 1 Illustration to distinguish between beneficial and harmful gut bacteria. Beneficial bacteria include *Lactobacillus*, which are probiotics supporting digestion and immunity; *Akkermansia muciniphila*, which maintains gut lining integrity; *Faecalibacterium prausnitzii*, short-chain fatty acid producers with anti-inflammatory effects; and *Ruminococcus*, which aid in digesting complex carbohydrates. In contrast, harmful bacteria such as *Escherichia coli* can cause infections, *Clostridium difficile* produce toxins linked to severe diarrhea, *Helicobacter pylori* are associated with stomach ulcers, and *Staphylococcus* can be opportunistic pathogens. This highlights the critical role of a balanced microbiome in health maintenance and disease prevention.

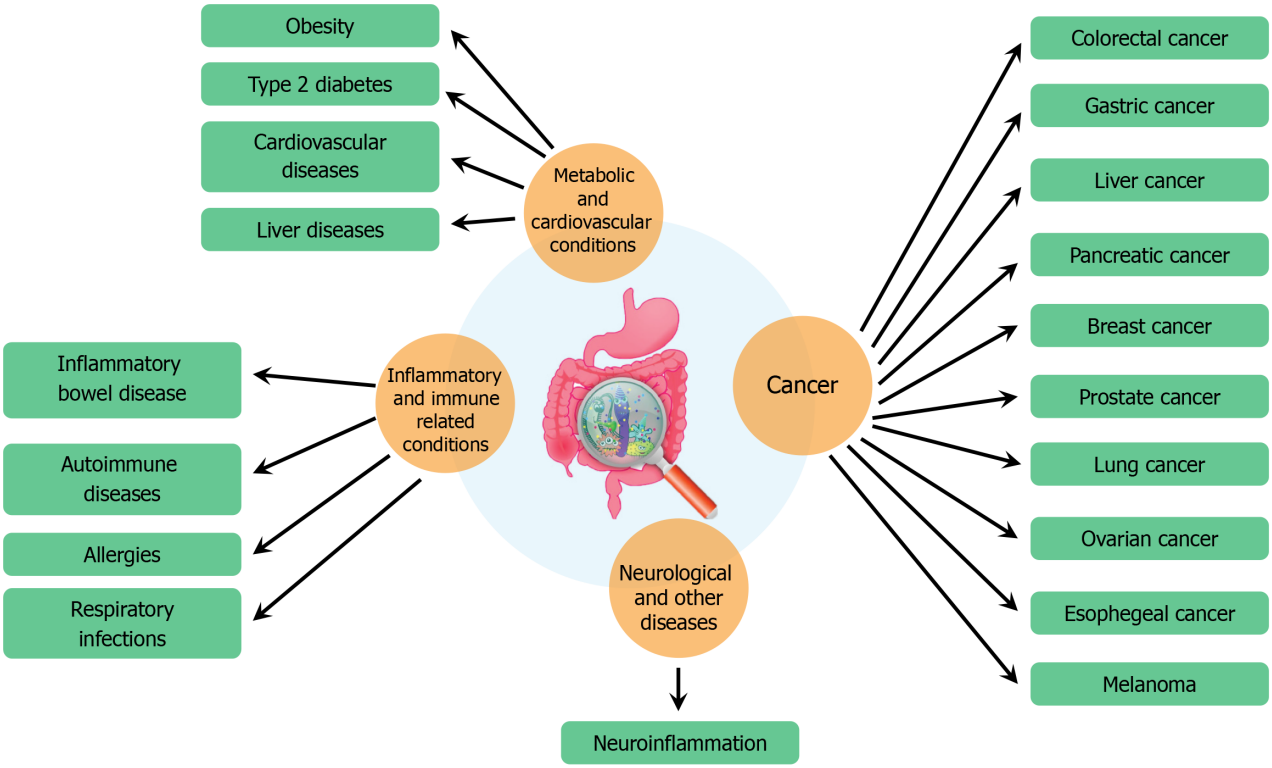

Figure 2 The relationship between human health and various diseases. It highlights how poor gut health is linked to a range of conditions across different categories. Metabolic and cardiovascular conditions associated with gut health include obesity, type 2 diabetes, cardiovascular diseases, and liver diseases. Inflammatory and immune-related conditions affected by gut health include inflammatory bowel disease, autoimmune diseases, allergies, and respiratory infections. Gut health also plays a role in the development of cancer, with potential links to colorectal, gastric, liver, pancreatic, breast, prostate, lung, ovarian, esophageal cancers, and melanoma. Additionally, gut health is connected to neurological and other diseases, notably through neuroinflammation, emphasizing the extensive impact of gut microbiota on overall health.

Gut microbiota linked to diabetes

Type 2 diabetes (T2D) is another condition where gut microbiota has been shown to play a significant role. Individuals with T2D often exhibit distinct gut microbiota profiles compared to healthy individuals[62]. Dysbiosis in T2D is characterized by a reduced diversity of gut bacteria and an increase in opportunistic pathogens[63]. These microbial changes can influence glucose metabolism, insulin resistance, and chronic inflammation, all of which are key factors in the development and progression of diabetes[64]. Certain gut bacteria can affect the production of SCFAs, which in turn influence insulin sensitivity[65]. Moreover, the gut microbiota can interact with dietary components to modulate the host's metabolic response. These insights highlight the potential of manipulating gut microbiota through diet, probiotics, or other interventions as an approach to diabetes management[66]. Future therapeutic strategies could involve personalized nutrition plans and microbiota-based treatments to improve insulin sensitivity and metabolic health, providing a more tailored approach to diabetes management (Table 3)[67-82].

Role of gut microbiota in cancer progression

The role of gut microbiota in cancer progression is a dynamic and multifaceted area of exploration that continues to evolve. Dysbiosis is implicated in various conditions, including metabolic diseases such as obesity and diabetes, where altered microbial metabolism affects host energy balance and systemic inflammation[83]. Specific microbial taxa and their metabolites have been linked to cancer initiation and progression, especially in colorectal cancer, through mechanisms involving inflammation, genotoxicity, and modulation of tumor microenvironments[84]. Certain bacterial species have been found to promote colorectal cancer by producing toxins that damage DNA or by inducing chronic inflammation [85]. Conversely, other microbes may have protective effects by enhancing immune surveillance and inhibiting tumor growth. Gut microbiota can affect the efficacy and toxicity of cancer treatments, such as chemotherapy and immunotherapy[86]. Personalized modulation of the gut microbiome could therefore represent a promising strategy for improving cancer treatment outcomes and reducing side effects[87]. This underscores the potential of integrating microbiota analysis into oncological care, paving the way for precision medicine approaches that consider the individual's microbial composition in developing treatment protocols (Table 4)[88-104].

Role of gut microbiota in chronic kidney disease

The gut microbiota plays a crucial role in the development and progression of chronic kidney disease (CKD). It comprises trillions of microorganisms that influence various physiological processes, including metabolism, immune function, and inflammation[105]. In CKD, the composition and diversity of gut microbiota are often altered, leading to dysbiosis, which

Table 2 Microbiota-associated mechanisms in autoimmune and inflammatory diseases: Insights and implications

Sl No.	Disease	Mechanism of involvement	Key bacteria implicated	Ref.
1	Allergies	Modulation of immune responses, allergic inflammation	*Clostridium*, *Bifidobacterium*	[49]
2	Autoimmune diseases	Dysregulated immune responses, inflammation	*Prevotella*, *Bacteroides*	[50]
3	Cardiovascular diseases	Production of trimethylamine N-oxide, systemic inflammation	*Prevotella*, *Firmicutes*	[51]
4	Inflammatory bowel disease	Dysregulated immune responses against microbiota lead to chronic inflammation in the GI tract. Reduced anti-inflammatory microbes and increased potentially inflammatory microbes. SCFAs and dietary factors influence disease progression	Decreased *Bacteroidetes*, *Lachnospiraceae*, *Faecalibacterium prausnitzii*. Increased *Proteobacteria*, *Ruminococcus gnavus*. Key producers: *Faecalibacterium prausnitzii*, *Roseburia hominis*. Pathogens: Vancomycin-resistant *Enterococcus*	[52]
		Associated with reduced anti-inflammatory response. Increased pro-inflammatory activity	Reduced abundance of *Faecalibacterium prausnitzii*. Overgrowth of *Escherichia coli*	[53]
5	Liver diseases	Regulation of bile acid metabolism, inflammation	*Enterococcus*, *Ruminococcus*	[54]
6	Multiple sclerosis	Microbiota interaction: Dysbiosis with increased *Euryarchaeota* and *Verrucomicrobia*. Microbial impact: Modulation of T cell responses and inflammation in the central nervous system. Protective effects: Certain bacteria and metabolites have protective effects against disease	Increased: *Methanobrevibacter smithii*, *Akkermansia muciniphila*. Decreased: *Clostridia* clusters XIVa and IV, *Bacteroidetes*. Protective: *Lactobacillus reuteri*, *Lactobacillus murinus*	[55]
		Akkermansia muciniphila and *Acinetobacter calcoaceticus* induce pro-inflammatory responses. *Parabacteroides* distasonis stimulates anti-inflammatory Tregs	Decreased abundance of *Lachnospiraceae* and *Faecalibacterium*. Increased abundance of *Akkermansia spp.*	[56]
7	Respiratory infections	Modulation of respiratory immune responses, inflammation	*Streptococcus*, *Haemophilus*	[57]
8	Rheumatoid arthritis	Dysbiosis contributes to systemic inflammation and joint symptoms; gut barrier dysfunction affecting overall immune response	*Prevotella spp.*, *Fusobacterium spp.*	[58]
		Microbiota interaction: Oral and intestinal dysbiosis linked to disease severity and immune responses. Microbiota influence: Microbial DNA and peptidoglycan-polysaccharide complexes found in joints. Microbial-induced immunity: Certain bacteria drive inflammation through immune cell activation	Oral dysbiosis: *Porphyromonas gingivalis*, *Lactobacillus salivarius*. Intestinal dysbiosis: Increased Gram-positive bacteria, *Prevotella copri*. Exacerbation: *Prevotella copri*, *Segmented filamentous bacteria*	[59]
		Pro-inflammatory molecule production. Autoreactive immune cell activation. Linked to RA susceptibility with specific HLA-DRB1 alleles	Overgrowth of *Prevotella spp.*, reduction in *Bacteroides*, *Bifidobacterium*, butyrate-producing bacteria, and high abundance of *Ruminococcus gnavus*	[60]
9	Systemic lupus erythematosus	Microbiota interaction: Dysbiosis in oral and gut microbiota contributes to disease through molecular mimicry and bacterial antigen recognition. Metabolic factors: Bacterial metabolites impact disease severity	Increased: *Lactobacillaceae*, *Ruminococcus gnavus*. Decreased: *Bifidobacteria*, *Clostridiales*. Specific antigens: *Propionibacterium propionicum*, *Bacteroides thetaiotaomicron*	[61]

SCFA: Short-chain fatty acid; GI: Gastrointestinal; Treg: Regulatory T cell.

exacerbates the disease[106]. This dysbiosis can result in the overproduction of uremic toxins, which accumulate in the blood due to impaired renal function and contribute to inflammation and further kidney damage[107]. Additionally, changes in diet and medication use in CKD patients can further impact the gut microbiome, highlighting the potential for dietary interventions and probiotics to restore microbial balance and potentially slow CKD progression[108]. Understanding the complex interactions between the gut microbiota and CKD could lead to novel therapeutic approaches for managing the disease and improving patient outcomes (Figure 3).

A recent study explored the relationship between gut microbiota and CKD, revealing a significant reduction in microbial diversity in CKD patients compared to healthy individuals[109]. This reduction is linked with inflammation and metabolic alterations typical of CKD. The study highlights specific bacterial genera, such as *Bacteroides* and *Prevotella*, that are associated with inflammatory markers and metabolic imbalances. It emphasizes the role of dietary intake in influencing gut microbiota composition and suggests that nutritional interventions could modulate gut microbiota to potentially alleviate CKD symptoms. The findings propose that targeting gut microbiota through dietary modifications or probiotic treatments could be a promising therapeutic strategy for managing CKD, advocating for further research to understand the underlying mechanisms and develop effective interventions.

Another study found significant alterations in gut microbiota composition and diversity in CKD patients compared to healthy controls, with an increase in *Proteobacteria* and a decrease in synergies, especially in advanced stages[110]. Specific bacterial genera, such as *Escherichia-Shigella*, were identified as potential biomarkers for distinguishing CKD patients from healthy individuals. Functional analysis indicated enriched metabolic pathways related to fatty acid and inositol

Table 3 Overview of gut microbiota's role in diabetes and mechanistic insights

Sl No.	Disease/drug target	Mechanism of involvement	Key bacteria or drug implicated	Ref.
1	GLP-1 receptor agonists	Mimic the incretin GLP-1, enhancing insulin secretion, slowing gastric emptying, and altering gut microbiota composition	Decreased: *Allobaculum*, *Turicibacter*, *Anaerostipes*, *Blautia*, *Lactobacillus*, *Butyricimonas*, *Desulfovibrio*, *Clostridiales*, *Bacteroidales*. Increases: *Akkermansia muciniphila*	[67]
2	Insulin	Improves glycemic control by increasing glucose uptake into cells. Minimal direct impact on gut microbiota	Minimal direct effect on humans. In rats, it increased *Norank_f_Bacteroidales_S24-7* and decreased *Lactobacillus* and *Peptostreptococcaceae*, suggesting possible effects on gut bacteria in animal models. Effect on T2DM: Influences microbiota dysbiosis in T2DM patients, potentially regulating inflammation and gut health	[68]
3	Metabolic syndrome	Increased intestinal permeability leading to systemic inflammation; effects on metabolic pathways and mood	Increased: *Lactobacillus spp*., *Bacteroides spp*.	[69]
4	Obesity	Gut microbiota affecting metabolic processes and inflammatory responses; alterations in appetite regulation and mood	Increased: *Firmicutes spp*., decreased: *Bacteroidetes spp*.	[70]
		Metabolic dysregulation, energy extraction from diet	Increased: *Bacteroides*, *Firmicutes*	[71]
5	SGLT2 inhibitors	Inhibit SGLT2 in the proximal tubule, preventing glucose reabsorption and promoting glucose excretion in urine. Limited impact on gut microbiota reported	Dapagliflozin is used as drug. *Ruminococcaceae*, *Proteobacteria* (Desulfovibrionaceae); Sotagliflozin changes in *Firmicutes*/*Bacteroidetes* ratio with high-sucrose diet	[72]
6	Type 1 diabetes	Altered microbiota composition influencing the immune system and glucose metabolism	Decrease: *Prevotella*, *Akkermansia*. Increase: *Actinobacteria*, *Bacteroidetes*, *Proteobacteria*, *Lactobacillus*, *Lactococcus*, *Bifidobacterium*, *Streptococcus*	[73]
		Increased abundance of certain bacteria linked to inflammation and immune responses. Decreased abundance of beneficial bacteria	Increase: *Clostridium*, *Bacteroides*, *Veillonella*. Decrease: *Lactobacillus*, *Bifidobacterium*, *Blautia coccoides/Eubacterium rectale*, *Prevotella*	[74]
		Insulin resistance, inflammation	Decreased: *Akkermansia muciniphila*, *Bifidobacterium*	[75]
		Microbial composition influences immune responses and disease onset	Decreased: *Bifidobacteria*, *Lachnospiracea*	[76]
7	Type 2 diabetes mellitus	Changes in bile acid metabolism affecting glucose metabolism	Involvement of *Clostridium*, *Eubacterium*, *Bacteroides*, *Lactobacillus*, *Bifidobacterium*	[77]
		Correlation between gut microbiota composition and inflammatory markers influencing diabetes progression	Increased: *Bacteroidetes*, *Proteobacteria*. Decreased: *Roseburia*, *Firmicutes*, *Clostridiaceae*	[78]
		Imbalance in microbiota affecting glucose metabolism and insulin sensitivity	Decrease: *Firmicutes*. Increase: *Bacteroidetes*, *Proteobacteria*, *Lactobacillus*, *Faecalibacterium prausnitzii*, *Blautia*, *Serratia*	[79]
		Increased abundance of certain bacteria linked to metabolic dysfunction and inflammation	Increase: *Faecalibacterium prausnitzii*, *Blautia*. Decrease: *Verrucomicrobia phylum*	[80]
		Influence of SCFA production on insulin sensitivity and glucose metabolism	Increase: *Bacteroides*, *Ruminococcus*, *Akkermansia muciniphila*. Decrease: *Roseburia*, *Clostridium*	[81]
		Inhibit the enzyme DPP-4, which prolongs the action of incretins (*e.g.*, GLP-1), enhancing insulin secretion and reducing glucose levels. Effects on microbiota include changes in diversity and composition	Sitagliptin and Blautia used as drug. *Blautia* increases, while changes in *Roseburia*, *Clostridium*, *Bacteroides*, *Erysipelotrichaceae*, and *Firmicutes* are variable and require more research	[82]

T2DM: Type 2 diabetes mellitus; SCFA: Short-chain fatty acid; GLP-1: Glucagon-like peptide-1; DPP-4: Dipeptidyl peptidase-4; SGLT2: Sodium-glucose cotransporter 2.

phosphate in CKD, while amino acid and oxidative phosphorylation pathways were more active in healthy controls. These microbiota changes could aid in early CKD diagnosis and monitoring[111].

There is a consistent alteration in the gut microbiota composition in patients with CKD, marked by a decrease in beneficial bacteria like *Bifidobacterium* and *Lactobacillus* and an increase in potentially harmful bacteria such as *Enterobacteriaceae* and *Enterococcus*[112]. Dysbiosis in CKD patients is associated with increased production of uremic toxins, such as indoxyl sulfate and p-cresyl sulfate, which are linked to the progression of kidney disease and cardiovascular complications. Dietary interventions, probiotics, and prebiotics show potential in modulating gut microbiota composition, reducing uremic toxins, and improving CKD outcomes, although more clinical trials are needed to confirm these effects [113].

Table 4 Gut microbiota's role in cancer progression: mechanistic insights and key bacterial implications

Sl No.	Disease	Mechanism of involvement	Key bacteria implicated	Ref.
1	Breast cancer	Modulation of systemic inflammation, hormone metabolism	*Lactobacillus*, *Prevotella*	[88]
		Gut microbiota impacts hormone levels and immune responses. Microbiota may modulate estrogen levels and immune cell infiltration in breast tissue, affecting cancer risk and progression	*Clostridium*, *Bifidobacterium*	[89]
2	Colorectal cancer	Chronic inflammation, carcinogen metabolism	*Fusobacterium nucleatum*, *Escherichia coli*	[90]
		Gut microbiota influences chemotherapy efficacy. Microbial dysbiosis can affect drug metabolism and immune responses, altering treatment outcomes	*Fusobacterium nucleatum*, *Bacteroides*	[91]
3	Esophageal cancer	Dysbiosis in esophageal microbiome, inflammatory pathways	*Prevotella*, *Fusobacterium*	[92]
		Dysbiosis in esophageal microbiota is associated with cancer. Microbial-induced inflammation and changes in the esophageal microenvironment can contribute to cancer development	*Prevotella*, *Streptococcus*	[93]
4	Gastric cancer	Disruption of gastric mucosa, inflammation	*Helicobacter pylori*	[94]
		Helicobacter pylori is a major risk factor for gastric cancer. Chronic infection with *Helicobacter pylori* causes inflammation and genetic alterations leading to cancer	*Helicobacter pylori*	[95]
5	Liver cancer	Modulation of liver inflammation, bile acid metabolism	*Enterococcus*, *Bacteroides*	[96]
		Gut microbiota can contribute to liver cancer development. Microbiota produced metabolites and inflammation can promote liver cancer progression	*Enterococcus faecalis*, *Bacteroides*	[97]
6	Lung cancer	Impact on lung microbiome, immune response modulation	*Streptococcus*, *Bacteroides*	[98]
		Oral and gut microbiota are linked to lung cancer risk. Inhaled microbiota or systemic effects from gut microbiota can influence lung inflammation and carcinogenesis	*Streptococcus*, *Veillonella*	[99]
7	Melanoma	Systemic immune modulation, tumor microenvironment	*Bifidobacterium*, *Lactobacillus*	[100]
8	Ovarian cancer	Role in local inflammation, metabolic influences	*Ruminococcus*, *Clostridium*	[101]
9	Pancreatic cancer	Alteration of pancreatic microenvironment, immune modulation	*Akkermansia muciniphila*, *Bifidobacterium*	[102]
		Microbiota composition affects pancreatic cancer development. Specific bacteria may modulate inflammation and immune responses in the pancreas	*Porphyromonas gingivalis*, *Fusobacterium nucleatum*	[103]
10	Prostate cancer	Influence on androgen metabolism, immune modulation	*Clostridium*, *Firmicutes*	[104]

A recent systematic review indicated that patients with CKD exhibit distinct changes in their gut microbiota composition, characterized by a decrease in beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, and an increase in pathogenic bacteria like *Enterobacteriaceae* and *E. coli*. These alterations are associated with CKD progression and systemic inflammation, suggesting a potential link between gut microbiota dysbiosis and CKD pathophysiology. Additionally, interventions targeting gut microbiota, such as probiotics and prebiotics, have shown promise in modulating these microbial imbalances and improving CKD outcomes[114]. However, the findings across studies are often inconsistent and lack replication, with variations in methodologies and target populations complicating the ability to draw definitive conclusions about microbiota-connectivity associations across different diseases.

This underscores the complexity of gut-brain interactions and the need for more standardized research approaches to better understand these relationships[115]. Another recent original study identified significant differences in gut microbiota diversity and composition between stage 4 and 5 CKD patients and healthy controls[116]. Patients with stage 4 and 5 CKD exhibited lower species richness and diversity, with a notable reduction in beneficial bacteria such as *Faecalibacterium* and *Roseburia* and an increase in potential pathogens like *Escherichia-Shigella*. Alpha and beta diversity analyses confirmed these disparities, highlighting a strong correlation between gut microbiota alterations and CKD severity[116].

Linear discriminant analysis effect size analysis revealed distinct microbial and metabolic pathway profiles between the two groups, suggesting that these microbial changes could have functional implications in CKD progression[17]. A study in end-stage renal disease patients from southern China found a reduction in total gut bacteria. Beneficial butyrate-producing bacteria (*Roseburia, Faecalibacterium*, and *Prevotella*) were reduced in end-stage renal disease patients, while *Bacteroides* were more prevalent. These changes were associated with increased inflammation and worsened renal function, as indicated by markers like cystatin C and estimated glomerular filtration rate, suggesting that gut microbiota alterations may play a role in CKD progression[117].

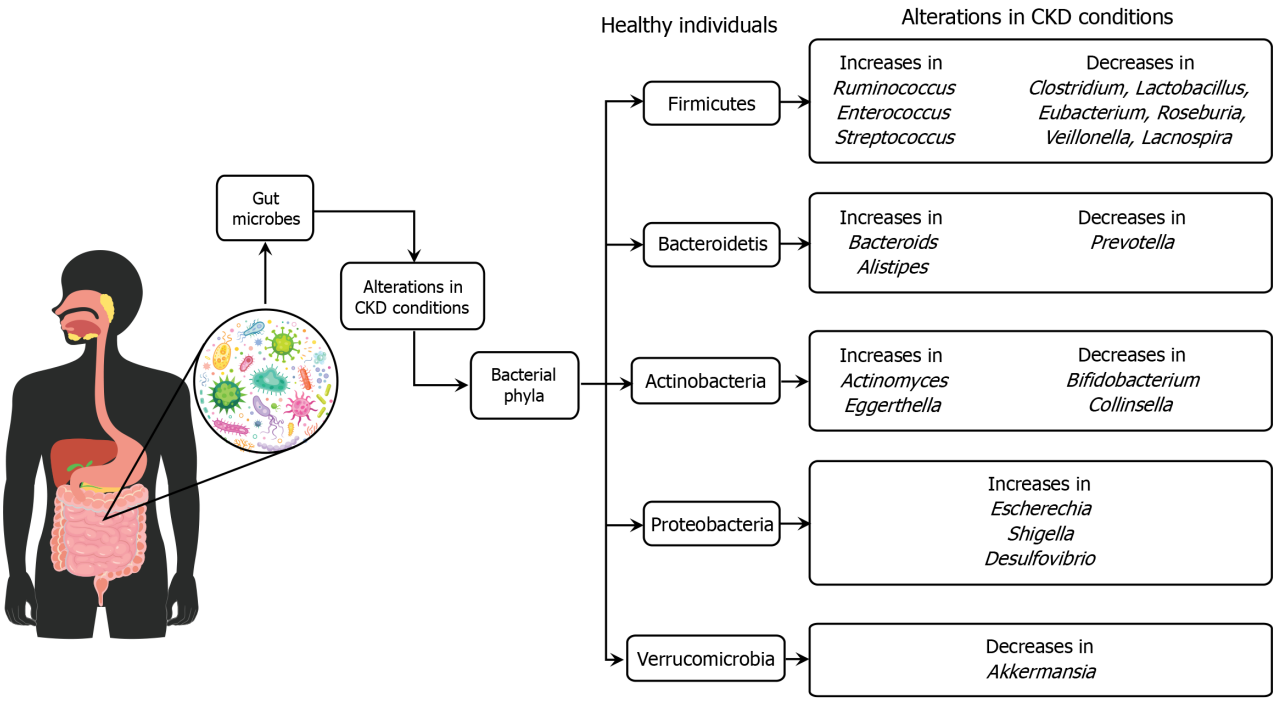

Figure 3 The alterations in gut microbiota are associated with chronic kidney disease conditions compared to healthy individuals. In chronic kidney disease, there is a notable shift in the abundance of various bacterial phyla. Specifically, certain bacteria, such as *Ruminococcus* and *Enterococcus* from the *Firmicutes* phylum, are increased, while beneficial bacteria like *Clostridium* and *Lactobacillus* are decreased. Similar patterns are observed in other phyla, with increases in some bacteria and decreases in others, indicating a state of dysbiosis. This microbial imbalance is important as it may influence chronic kidney disease progression and related complications, highlighting the role of gut microbiota in disease mechanisms and potential therapeutic targets. CKD: Chronic kidney disease.

CLINICAL IMPLICATIONS AND THERAPEUTIC STRATEGIES

Therapeutic strategies targeting the gut microbiota encompass a range of approaches aimed at restoring microbial balance and improving host health. Probiotics, live microorganisms that benefit health by colonizing the gut, are widely used to restore diversity post-antibiotic therapy and support gut health. Prebiotics, non-digestible fibers that promote beneficial bacteria growth, play a crucial role in reducing inflammation, particularly in conditions like IBD. FMT is highly effective in treating *Clostridium difficile* infections by restoring microbial diversity. Dietary modifications, such as high-fiber or Mediterranean diets, manage symptoms in conditions like irritable bowel syndrome. Postbiotics, metabolites produced by probiotics, are studied for their therapeutic potential in metabolic disorders. Antibiotics are used cautiously to avoid disrupting beneficial microbes. Phage therapy targets harmful bacteria, offering an alternative to antibiotics (Figure 4). Microbial ecosystem therapeutics engineer microbial communities to enhance gut health and treat inflammatory diseases, highlighting personalized microbiota-based therapies in disease prevention and treatment (Table 5)[118-137].

IMPACT OF ANTIBIOTICS AND OTHER MEDICATIONS ON GUT MICROBIOTA

Antibiotics and other medications can significantly impact the composition and function of gut microbiota, leading to various health consequences. The use of antibiotics, while essential for treating bacterial infections, often results in the disruption of the gut microbiome's balance, causing a reduction in microbial diversity and the proliferation of resistant strains[138]. This disruption can have short-term and long-term effects on health, including increased susceptibility to infections, antibiotic-associated diarrhea, and the potential for developing chronic conditions such as IBD and obesity [139].

Other medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), and antipsychotics, also influence gut microbiota. NSAIDs, for example, can cause intestinal inflammation and mucosal damage, which in turn alters the gut microbiota composition[140]. PPIs, commonly used to treat acid reflux, have been shown to decrease microbial diversity and promote the growth of potentially harmful bacteria, such as *Enterococcus* and *Streptococcus* species[141]. Antipsychotic medications have been linked to changes in gut microbiota that may contribute to metabolic side effects, including weight gain and insulin resistance[142]. The interactions between medications and gut microbiota are complex and influenced by multiple factors, including the type of medication, dosage, duration of treatment, and individual patient characteristics[143]. Understanding these interactions is crucial for developing strategies to mitigate negative effects on the gut microbiome and enhance overall health outcomes.

Table 5 Clinical implications and therapeutic strategies targeting the gut microbiota

Sl No.	Therapeutic strategy	Description	Clinical application	Ref.
1	Antibiotics	Targeted use to treat dysbiosis or specific bacterial infections affecting gut health	Used in severe cases of gut dysbiosis	[118]
2	Biofilm disruptors	Compounds that disrupt bacterial biofilms in the gut, enhancing susceptibility to treatment	Investigated for their potential in chronic infection treatments	[119]
3	Butyrate supplementation	Providing the short-chain fatty acid butyrate to support gut barrier function and reduce inflammation	Studied for efficacy in treating ulcerative colitis	[120]
4	Colonization resistance	Strategies to enhance the gut's ability to resist colonization by harmful bacteria	Investigated in preventing infections in hospitalized patients	[121]
5	Dietary modifications	Including high-fiber diets, Mediterranean diet, and low fermentable oligosaccharides, disaccharides, monosaccharides and polyols diet to support gut microbiota	Management of symptoms in irritable bowel syndrome	[122]
6	Enteral nutrition	Providing nutrients directly into the gastrointestinal tract to support gut health	Used in patients unable to tolerate oral intake	[123]
7	Fecal microbiota transplantation	Transfer of fecal microbiota from a healthy donor to restore microbial diversity in the recipient	Effective treatment for recurrent *Clostridium difficile* infection	[124]
8	Gut microbiota modulators	Pharmaceuticals that target specific pathways or microbes within the gut	Studied for their potential in precision medicine approaches	[125]
9	Microbial consortia therapy	Using multiple species of bacteria to restore healthy microbial balance	Investigated in treating recurrent bacterial infections	[126]
10	Microbial ecosystem therapeutics	Engineered microbial communities designed to restore or enhance gut health	Investigated for potential in treating inflammatory diseases	[127]
11	Microbiota-targeted dietary interventions	Specific diets aimed at altering the composition and function of gut microbes	Used in managing metabolic syndrome and obesity	[128]
12	Phage therapy	Using bacteriophages to selectively target harmful bacteria in the gut microbiota	Potential alternative to antibiotics in treating infections	[129]
13	Postbiotics	Metabolites produced by probiotic bacteria have beneficial effects on host health	Investigated for potential in treating metabolic disorders	[130]
14	Prebiotics	Non-digestible fibers that promote the growth of beneficial bacteria in the gut	Improve gut health and reduce inflammation in IBD patients	[131]
15	Probiotics	Live microorganisms that confer health benefits by colonizing the gut and influencing microbial balance	Used to restore gut microbiota after antibiotic therapy	[132]
16	Protein therapeutics	Engineered proteins designed to modulate microbial activity in the gut	Investigated for their role in targeted microbiota treatments	[133]
17	Proton pump inhibitors	Medications that alter gastric acidity and impact gut microbiota composition	Used to manage symptoms of gastroesophageal reflux disease	[134]
18	Stool substitutes	Synthetic or cultured microbial communities for fecal microbiota transplantation when donor stool is unavailable or impractical	Investigated as a potential treatment for chronic infections	[135]
19	Symbiotics	Combination of probiotics and prebiotics to enhance gut health	Used in enhancing gut health and immune function	[136]
			Studied for efficacy in treating diarrhea in children	[137]

IBD: Inflammatory bowel disease.

The impact of antibiotics and medications on gut microbiota and disease is increasingly clear, with antibiotic use significantly altering microbiota composition. This disruption can lead to conditions such as antibiotic-associated diarrhea, *Clostridioides difficile* infection, and the development of antibiotic-resistant infections[144-146]. Recent research has highlighted the critical role of gut microbiota in influencing drug metabolism, efficacy, and safety[147]. Gut bacteria can chemically modify drugs, affecting their bioavailability and activity, with some species activating or deactivating drugs through enzymatic actions. Specific bacterial strains such as *Gammaproteobacteria* have been found to metabolize chemotherapy drugs like gemcitabine into inactive forms, reducing its effectiveness in cancer treatment[147]. Conversely, commensal bacteria such as *Enterococcus hirae* and *Barnesiella intestinihominis* have been shown to enhance the efficacy of other drugs like cyclophosphamide by stimulating immune responses in cancer therapies. These microbiota-related interactions offer promising potential for using specific bacterial markers as indicators of therapeutic outcomes, guiding the development of personalized treatments based on an individual's microbiome composition[148].

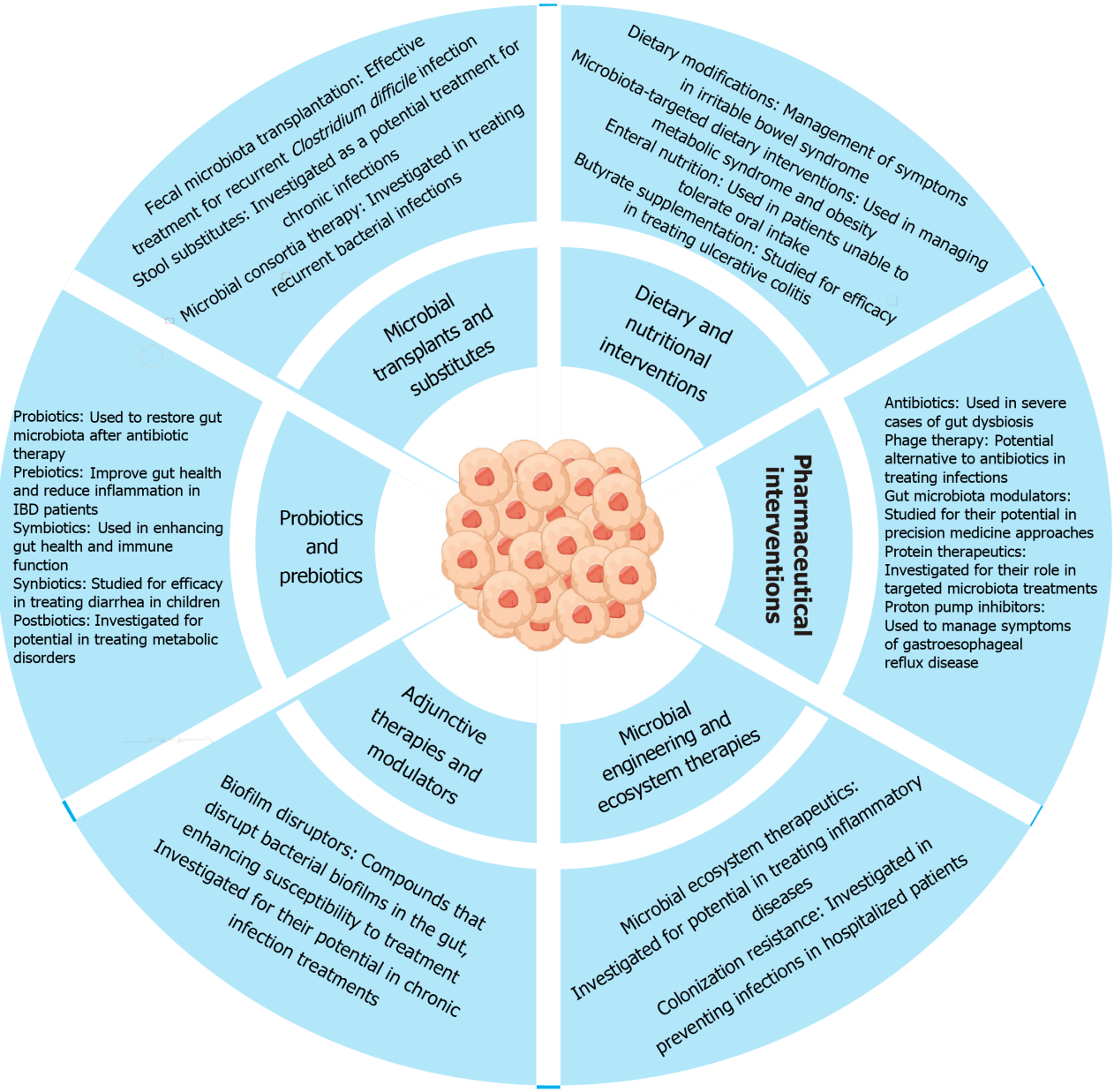

Figure 4 Therapeutic strategies aimed at improving gut health through different interventions. The section on "Microbial transplants and substitutes" highlights the use of fecal microbiota transplantation stool substitutes, and microbial consortia for treating recurrent infections and metabolic disorders. "Probiotics and prebiotics" are emphasized for restoring and enhancing gut microbiota, improving gut health, and reducing inflammation, with specific applications for inflammatory bowel disease and metabolic disorders. "Dietary and nutritional interventions" include dietary modifications, microbiota-targeted diets, enteral nutrition, and butyrate supplementation for managing conditions like irritable bowel syndrome and ulcerative colitis. The "Pharmaceutical interventions" segment lists antibiotics, phage therapy, gut microbiota modulators, protein therapeutics, and proton pump inhibitors for treating dysbiosis and other gut-related conditions. "Adjunctive therapies and modulators" feature biofilm disruptors for treating chronic infections, while "Microbial engineering and ecosystem therapies" focus on microbial ecosystem therapeutics and colonization resistance to prevent infections and manage inflammatory diseases.

Long-term antibiotic use has been linked to chronic conditions like IBD, Crohn's disease, and metabolic syndrome by disrupting microbial balance[149,150]. Dysbiosis, or an imbalance in the gut microbiota, is implicated in obesity, asthma, allergies, cardiovascular disease, and depression, where altered microbiota affect metabolism, immune function, and neurotransmitter production[151-153]. Non-antibiotic medications, such as NSAIDs and PPIs, also contribute to intestinal inflammation, dysbiosis, and conditions like ulcerative colitis, small intestinal bacterial overgrowth, and lactose intolerance[154-156]. In diseases like celiac disease, CKD, and colorectal cancer, gut microbiota alterations influence inflammation, uremic toxin production, and cancer progression[157,158]. Additionally, early-life antibiotic exposure is associated with increased risks of asthma, allergies, autism spectrum disorder, eczema, and psoriasis, highlighting the critical role of gut microbiota in immune regulation and disease susceptibility across various conditions[159].

Table 6 Current research gaps in understanding the gut microbiota's role in disease and cancer

Sl No.	Aspect	Description	Ref.
1	Crosstalk with immune system	Microbiota interact with the immune system. Research should focus on how these interactions influence autoimmune diseases, allergies, and cancer	[160]
2	Impact of antibiotics and therapeutics	Antibiotics and medications alter microbiota. Understanding these effects is important for assessing long-term health consequences	[161]
3	Interaction with host genetics	Host genetics influence microbiota. Understanding these interactions is key to linking genetic predispositions with microbiota and disease risk	[162]
4	Mechanistic understanding	While correlations between microbiota and diseases exist, the mechanisms remain unclear. Future studies should explore specific microbial influences on disease	[163]
5	Microbial metabolites and signaling	Microbial metabolites affect host physiology. Identifying these metabolites and their role in disease modulation is crucial	[164]
6	Microbiota and cancer immunotherapy	Gut microbiota impact cancer immunotherapy efficacy, but mechanisms are poorly understood. Identifying beneficial microbial profiles is necessary	[165]
7	Microbiota in early life and development	Early microbiota establishment affects long-term health. Research should examine its impact on immune and metabolic development	[166]
8	Microbiota in extraintestinal diseases	Gut microbiota may influence non-gut diseases like cardiovascular and neurological disorders. Research is needed to explore these associations	[167]
9	Need for longitudinal studies	Most studies are cross-sectional; longitudinal research is needed to track microbiota changes over time in relation to disease	[168]
10	Role of diet and lifestyle	Diet and lifestyle significantly influence microbiota. Research should focus on how these factors affect microbiota and disease risk	[169]
11	Gender differences in microbiota	Gender-specific microbiota differences influence disease outcomes. Research should explore how these variations impact health between males and females	[170]
12	Variability in microbiota composition	Challenges arise due to factors like diet, genetics, and lifestyle. Research lacks comprehensive large-scale studies on these interactions	[171]

GAPS IN THE CURRENT UNDERSTANDING

Current research on the involvement of gut microbiota in disease and cancer has several key gaps. One major challenge is the substantial variability in microbiota composition among individuals, influenced by factors such as diet, genetics, and lifestyle. This variability complicates efforts to establish clear causal relationships between specific microbial profiles and disease states. Mechanistic understanding also remains limited; while correlations exist between microbiota composition and diseases like colorectal cancer, the precise biological mechanisms underlying these associations are often unclear (Table 6)[160-171]. Many studies are cross-sectional, providing snapshots rather than longitudinal insights into how microbiota changes over time and correlate with disease progression. Addressing these gaps requires large-scale, longitudinal studies that integrate multi-omics data to elucidate microbiota-host interactions comprehensively.

FUTURE RESEARCH DIRECTIONS

Future research directions should focus on integrating multi-omics data to better understand the intricate interactions between gut microbiota and disease. This approach will help identify microbial biomarkers and therapeutic targets, facilitating personalized medicine strategies tailored to individual microbiota profiles. Exploring the impact of diet and lifestyle interventions on microbiota composition and disease outcomes is crucial. Investigating microbiota engineering techniques, such as precision microbiome editing and synthetic ecology, holds promise for developing novel therapies. Ethical considerations surrounding microbiota-based therapies also demand attention, including issues of informed consent, privacy protections for microbiota data, and equitable access to emerging treatments.

To advance our understanding of the role of gut microbiota in health and disease, it is crucial to integrate multi-omics data, including genomics, transcriptomics, proteomics, metabolomics, and microbiomics. This comprehensive approach allows for the study of interactions between gut microbiota and disease, helping to identify microbial biomarkers, therapeutic targets, and molecular pathways that underlie disease mechanisms[172,173]. Investigating the impact of dietary patterns, prebiotics, probiotics, dietary fibers, and lifestyle factors such as exercise and stress management on gut microbiota composition and function is essential[145]. Understanding these impacts can lead to personalized dietary and lifestyle recommendations tailored to individual microbiota profiles, ultimately aiding in disease prevention and management[174,175].

The exploration of advanced microbiota engineering techniques, including precision microbiome editing, synthetic biology, and microbial ecosystem engineering, offers promising avenues for manipulating microbiota composition and

function to promote health or treat diseases[176]. These innovative approaches have the potential to provide novel therapeutic interventions based on microbial modulation. Alongside these scientific advancements, it is important to address ethical considerations in microbiota-based therapies[177]. This includes ensuring informed consent for research and therapy participation, protecting privacy related to microbiota data, and ensuring equitable access to emerging treatments. Ensuring transparency, safety, and fairness in the implementation of microbiota-related interventions is crucial for maintaining ethical standards and public trust in these healthcare innovations[178].

CONCLUSION

Human gut microbiota plays a critical role in maintaining overall health, influencing various physiological processes, and modulating disease susceptibility, including cancer. The complex ecosystem of beneficial and harmful bacteria within the gut impacts digestion, immune function, and systemic health through intricate mechanisms involving microbial metabolites and interactions with the host immune system. Dysbiosis, or the disruption of this microbial balance, is implicated in a wide range of diseases, from metabolic and autoimmune disorders to various cancers. Current research has highlighted the profound impact of specific gut bacteria on disease progression and cancer development, underscoring the importance of maintaining healthy microbiota for disease prevention and management. Therapeutic strategies such as probiotics, prebiotics, FMT, dietary modifications, and emerging approaches like phage therapy and microbial ecosystem therapeutics offer promising avenues for restoring microbial balance and improving health outcomes. Despite significant advancements, gaps in understanding remain, particularly concerning the variability in microbiota composition, the precise mechanisms by which microbiota influence disease, and the long-term effects of therapeutic interventions. Future research directions should focus on integrating multi-omics data to unravel the complex interactions between microbiota and host, exploring the impact of diet and lifestyle interventions, and advancing microbiota engineering techniques. Ethical considerations must also be addressed to ensure informed consent, privacy protection, and equitable access to microbiota-based therapies. By continuing to investigate the role of gut microbiota in health and disease, we can develop personalized, effective treatments and preventive measures, ultimately contributing to better health outcomes and advancing the field of microbiome research.

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FOOTNOTES

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