gastrointestinal disorders

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Review

Microbiome-Driven Therapeutics: From Gut Health to Precision Medicine

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Abstract: The human microbiome, a complex ecosystem of microorganisms residing in and on the body, plays a pivotal role in the regulation of a wide range of physiological processes, including digestion, immune responses, and metabolic functions. In recent years, the rapidly growing field of microbiome-driven therapeutics has garnered significant attention owing to its potential to revolutionize healthcare. This review explores the evolving landscape of microbiome-based therapies, with a particular focus on the gut microbiome and its implications for both gut health and precision medicine. We highlight recent advances in understanding how microbial communities influence disease pathogenesis and treatment outcomes, spanning conditions such as inflammatory bowel disease (IBD), metabolic disorders, neurological diseases, and even cancer. This article also discusses emerging therapeutic strategies, including probiotics, prebiotics, fecal microbiota transplantation (FMT), and microbial-based drugs, as well as the challenges associated with their clinical implementation. Additionally, we examined how the integration of microbiome profiling and metagenomic data is advancing the field of precision medicine, paving the way for personalized and effective treatments. This review serves as a comprehensive resource that synthesizes current knowledge, identifies key gaps in microbiome research, and offers insights into the future direction of microbiome-driven therapeutics, thus providing a valuable framework for clinicians, researchers, and policymakers seeking to harness the potential of microbiomes to advance personalized healthcare solutions.

Keywords: microbiome-driven therapeutics; gut microbiota; precision medicine; probiotics; prebiotics; fecal microbiota transplantation (FMT); microbial-based therapies; personalized healthcare; microbiome profiling; disease modulation

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1. Introduction

Microbiome-driven therapeutics have emerged as a transformative field in medicine, utilizing complex interactions between microbial communities and host biological functions to address various health problems [1]. The human microbiome, often called the "second genome", is involved in crucial processes, such as regulation of the immune system, metabolic activities, and maintenance of gut homeostasis. Disruption of the microbiome, known as dysbiosis, has been associated with numerous health disorders, including inflammatory bowel disease (IBD), neurological diseases such as autism and Parkinson's,

metabolic conditions such as obesity and diabetes, and certain cancers [2]. Despite significant advances, some notable gaps remain in our understanding of the mechanisms underlying host–microbiome interactions. Understanding these interactions is essential to develop more effective microbiome-based therapies.

Current therapeutic strategies, such as fecal microbiota transplantation (FMT), probiotics, and treatments based on microbial metabolites, have shown varying degrees of success. However, their clinical application is often hindered by factors such as the high inter-individual variability of microbiomes, the complexity of microbial interactions, and significant gaps in our mechanistic understanding of how these therapies work at the molecular level. Moreover, regulatory hurdles and the lack of standardized protocols further complicate their widespread clinical adoption. These challenges underscore the urgent need for advanced research to uncover the underlying mechanisms of host–microbiome interactions and refine microbiome-based interventions for more consistent and predictable clinical outcomes [3–5].

One promising direction is the development of personalized microbiome therapies tailored to the specific microbial profiles of individual patients. Precision-based approaches that consider the genetic, environmental, and lifestyle factors that shape the microbiome could enhance therapeutic efficacy and reduce variability. Although interventions such as FMT and probiotics have demonstrated potential in clinical settings, their inconsistent results highlight the need for more targeted and individualized treatments [6,7]. Another key area of exploration is the engineering of synthetic microbiomes, such as customized microbial consortia, designed to modulate the host physiology in a controlled manner. Recent advancements, particularly in CRISPR-based microbiome editing technologies, offer exciting possibilities for precise microbial interventions. However, these technologies are still in their infancy and face challenges related to stability, delivery, and safety that need to be addressed before they can be translated into widespread clinical use [8,9].

The therapeutic potential of the microbiome extends beyond the gut, with emerging research highlighting its role in diverse areas such as cancer immunotherapy, neuroimmune modulation, and the gut–brain axis [10]. These findings underscore the need for interdisciplinary research that integrates microbiology, genomics, immunology, and personalized medicine. However, translating microbiome-based therapies into clinical practice requires the establishment of robust regulatory frameworks and ethical guidelines to ensure patient safety and treatment efficacy [11,12]. Simultaneously, a comprehensive exploration of under-studied microbiome niches, such as those in the skin, oral cavity, and respiratory tract, is essential and holds promise for novel therapeutic applications [12,13]. This review discusses recent developments in the field of microbiome-driven therapeutics, highlights the challenges that must be overcome, and proposes future directions for research and clinical implementation. By addressing these gaps and fostering innovative approaches, microbiome-based therapies have the potential to become the cornerstone of precision medicine, offering personalized, effective, and sustainable solutions for a broad spectrum of diseases.

2. Microbiome and Disease Connections

Human microbiome imbalance or dysbiosis, which is increasingly associated with various health disorders, ranges from gastrointestinal diseases such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) to systemic diseases such as metabolic syndrome, cardiovascular diseases, neurological diseases, and immune-related diseases. Evidence now points to its role in cancer, especially colorectal cancer, in which some microbial species contribute to inflammation and DNA damage (Figure 1).

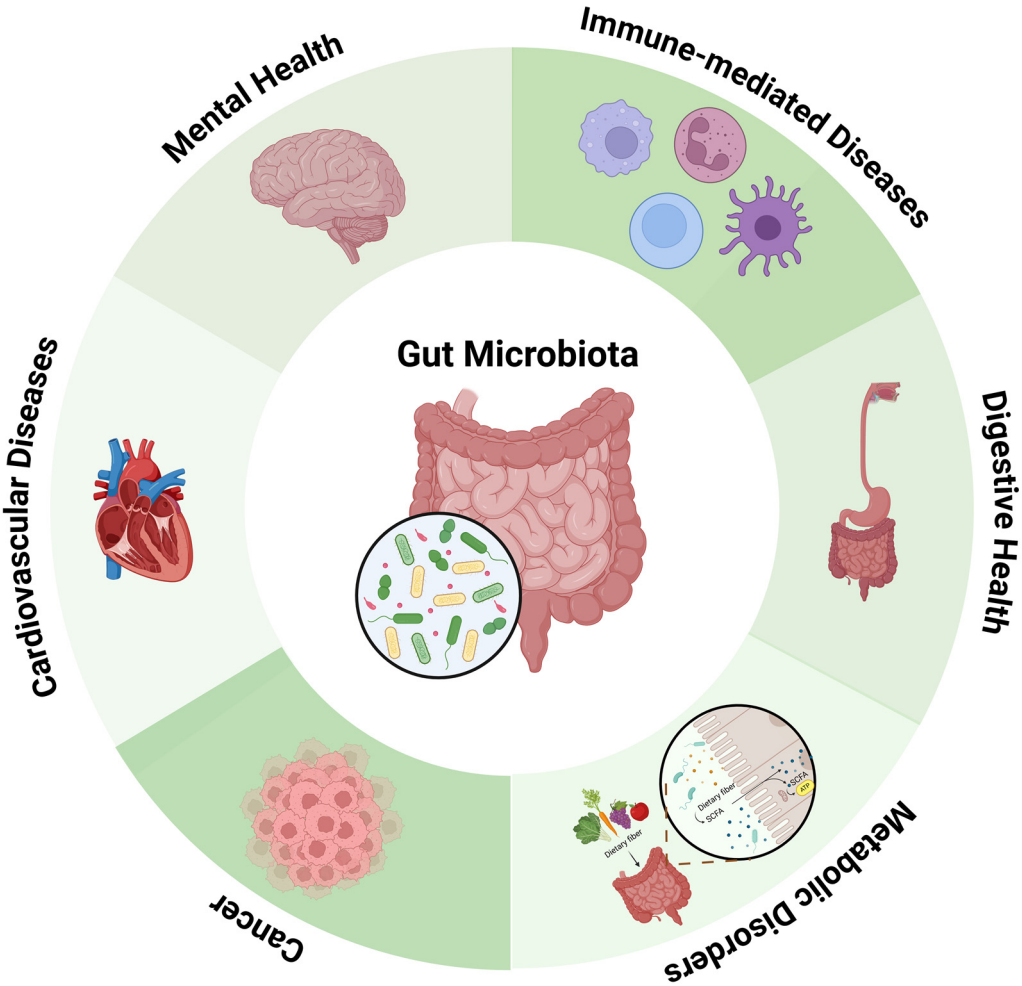

Figure 1. Gut microbiota and disease connections (Created in https://BioRender.com).

2.1. Gastrointestinal Disorders

2.1.1. Irritable Bowel Syndrome (IBS)

IBS is a common functional gastrointestinal disorder with a variety of symptoms, including abdominal pain, bloating, and altered bowel habits, such as diarrhea, constipation, or a combination of both. Although the exact cause of IBS remains unclear, several studies have consistently demonstrated that individuals with IBS have distinct changes in their gut microbiota compared with healthy individuals [13–15]. A comprehensive meta-analysis revealed a significant reduction in bacterial diversity among IBS patients, particularly a noticeable decrease in beneficial bacteria such as *Bifidobacterium* and members of the reclassified *Lactobacillus* genera, including *Lacticaseibacillus* and *Limosilactobacillus*, which are known to support gut health and maintain microbial balance [16]. This loss of microbial diversity can disrupt the overall harmony of the gut ecosystem, potentially leading to the overgrowth of pathogenic bacteria such as those belonging to the Enterobacteriaceae family [17,18]. These shifts in bacterial composition may worsen IBS symptoms through mechanisms such as increased intestinal permeability (also known as "leaky gut") and altered immune responses [19]. Elevated levels of pro-inflammatory cytokines in IBS patients trigger inflammation in the gut, leading to pain perception and more severe abdominal discomfort [20,21]. IBS symptomatology is also linked to gut bacterial fermentation of undigested carbohydrates. When these carbohydrates are not properly absorbed, they become substrates for bacterial fermentation, leading to increased gas production and symptoms such as bloating and abdominal distension [22]. In addition to gut dysbiosis and immune dysregulation, IBS is also related to abnormal gut–brain communication [23],

and changes in the gut microbiota can affect neurotransmitter levels, potentially leading to emotional disorders in patients with IBS [23].

2.1.2. Inflammatory Bowel Disease (IBD)

IBD is a chronic inflammatory condition affecting the gastrointestinal tract (GIT), primarily in Crohn's disease (CD) and ulcerative colitis (UC), leading to damage to the intestinal lining [24]. Recent studies have highlighted significant alterations in the gut microbiota of IBD patients, shedding light on its potential role in disease development and progression [25]. One of the most consistent findings is the depletion and imbalance of the beneficial bacterial populations. A study by Sokol et al. (2008) demonstrated that one of the beneficial bacteria, *Faecalibacterium prausnitzii*, is significantly depleted in patients with IBD, particularly those with CD [26]. *F. prausnitzii* is known for producing short-chain fatty acids (SCFAs), particularly butyrate, which is crucial for maintaining intestinal barrier function and regulating immune responses [27,28]. Its depletion has been linked to increased intestinal permeability, which allows harmful substances and bacteria from the gut lumen to cross the epithelial barrier, leading to immune activation and chronic inflammation [26]. Another protective role of *F. prausnitzii* is that it can inhibit the secretion of pro-inflammatory cytokines, such as TNF-α and IL-6, which are major contributors to the inflammatory cascade in IBD patients [29]. This ability to dampen inflammation underscores the importance of maintaining a balanced gut microbiota to prevent disease exacerbation.

In addition to the loss of beneficial bacteria, the microbiota of patients with IBD is often characterized by an overrepresentation of pathogenic bacteria such as *Escherichia coli*. Adherent-invasive *E. coli* (AIEC) strains have been implicated in mucosal inflammation [30]. These pathogenic strains adhere to and invade the epithelial cells of the gut, producing virulence factors that trigger and sustain inflammation. A meta-analysis found that AIEC strains are significantly more prevalent in individuals with CD, supporting the idea that microbial dysbiosis, in the form of pathogenic overgrowth, contributes to disease pathogenesis [31]. Given the strong association between gut microbiota alterations and IBD, therapeutic strategies for restoring microbial balance are gaining significant attention.

2.2. Metabolic Disorders

Emerging evidence suggests that the gut microbiota significantly influences metabolic health and is crucial for the development of metabolic disorders such as obesity and type 2 diabetes [32]. The microbiota composition of obese individuals tends to differ from that of lean individuals, with a higher proportion of *Firmicutes* and a lower proportion of *Bacteroidetes*. This altered microbial composition may affect energy extraction from dietary sources, leading to increased fat storage and weight gain [33]. The gut microbiota regulates host metabolism by producing metabolites, particularly SCFAs [34]. For instance, certain bacterial taxa, such as *F. prausnitzii*, are associated with increased SCFA production, which has been linked to improved insulin sensitivity and anti-inflammatory effects [35]. Conversely, dysbiosis can lead to reduced SCFA levels and promote insulin resistance, creating a vicious cycle that exacerbates metabolic disorders [27]. Moreover, the gut microbiota affects lipid metabolism and cholesterol homeostasis by influencing energy balance and insulin sensitivity. Some intestinal bacteria metabolize bile acids, which play a vital role in the digestion and absorption of fat. Alterations in bile acid metabolism, influenced by gut microbial composition, can affect lipid profiles and potentially lead to disorders such as hyperlipidemia and fatty liver disease [36]. Furthermore, the microbiota influences the host response to dietary interventions [37]. For example, individuals with diverse and balanced microbiota tend to respond better to dietary changes aimed at weight

loss than those with dysbiosis [38]. This finding underscores the importance of considering the microbiota composition in the development of personalized dietary recommendations for weight management and metabolic health.

2.3. Mental Health

Emerging research has focused on the complex relationship between the gut and brain, known as the gut–brain axis [39]. The gut–brain axis represents a bidirectional communication pathway between the gastrointestinal tract and central nervous system, mediated by various signaling mechanisms, including hormonal, neural, and immune pathways [40]. Research has uncovered significant connections between the gut microbiota and mental health conditions such as depression, anxiety, and neurodegenerative diseases [41]. Gut microbiota can influence brain function by producing neurotransmitters and neuroactive compounds that directly affect central nervous system (CNS) function, influencing gastrointestinal motility and pain perception [39,42]. For instance, certain bacteria can synthesize gamma-aminobutyric acid (GABA) and serotonin, both of which are critical for mood regulation [43]. Dysbiosis may disrupt this process and potentially contribute to the onset of mood disorders. Moreover, the gut–brain axis is thought to play a role in neurodegenerative diseases such as Alzheimer's and Parkinson's [44]. Research has indicated that changes in gut microbiota composition may precede the onset of neurodegenerative symptoms, suggesting that microbial intervention may be a novel approach to preventing or mitigating these conditions [45]. The role of microbial metabolites, such as SCFAs, which are produced through the fermentation of dietary fibers, has also been shown to affect gut–brain signaling pathways by interacting with the nervous system, potentially affecting gut motility, inflammation, and visceral sensitivity—key factors in the manifestation of IBS symptoms [46].

2.4. Immune-Mediated Diseases

Gut microbiota plays a pivotal role in regulating the immune system, and its interactions with immune cells are critical for maintaining immune homeostasis [47]. The gut houses a large proportion of the body's immune cells, particularly within gut-associated lymphoid tissue (GALT). It is a major interface between the microbiota and the immune system [48]. Microbiota can influence innate and adaptive immune responses, particularly by shaping the functions of T-cells, dendritic cells, and macrophages. Studies have shown that specific microbial populations are involved in the differentiation of T helper (Th) cells and regulatory T cells (Tregs), which are key to maintaining immune tolerance and preventing autoimmunity and chronic inflammation [49]. For example, *Lactobacillus* genera (e.g., *Lacticaseibacillus* and *Limosilactobacillus*) and *Bifidobacterium* strains have been shown to promote Treg differentiation, which can help prevent inflammatory diseases such as IBD and reduce excessive immune responses [50]. Dysbiosis, or an imbalance in microbial composition, has been implicated in a range of autoimmune and inflammatory diseases, including rheumatoid arthritis (RA) and IBD [51]. In IBD, the microbial diversity is often reduced, causing an increased abundance of pro-inflammatory bacteria such as *E. coli* and *Fusobacterium* [52]. This dysbiosis contributes to the inappropriate activation of the immune system, leading to chronic inflammation and tissue damage in the gut [53]. Similarly, altered gut microbiota composition in RA has been associated with increased intestinal permeability and systemic inflammation, highlighting the role of the gut in modulating joint health [54].

Dysbiosis, or microbial imbalance, is increasingly recognized as a driver of various immune-mediated diseases, including IBD, rheumatoid arthritis, and autoimmune disorders such as type 1 diabetes and multiple sclerosis. Disruptions in the gut microbial

diversity or overgrowth of pathogenic bacteria can lead to a dysregulated immune response, resulting in chronic inflammation and tissue damage. For instance, reduced microbial diversity in the gut has been observed in patients with IBD, with an overabundance of pro-inflammatory bacteria and the depletion of anti-inflammatory species [54]. The gut microbiota influences systemic immune responses by producing metabolites, such as SCFAs, which have potent anti-inflammatory effects. SCFAs produced through fiber-fermenting, particularly butyrate bacteria, can modulate immune function by promoting Treg activity and inhibiting the activation of pro-inflammatory cytokines [52].

2.5. Cardiovascular Diseases

The relationship between the microbiome and cardiovascular disease (CVD) has emerged as a prominent area of research, highlighting the critical role of the microbiome in systemic health. However, significant gaps remain in our understanding of the precise mechanisms and the multifactorial nature of these interactions. A foundational study has shown that gut bacteria can metabolize dietary phosphatidylcholine to produce trimethylamine-N-oxide (TMAO), a metabolite associated with atherosclerosis. These findings indicate a correlation between elevated TMAO levels and cardiovascular events [55]. Tang et al. (2013) suggested that a more diverse gut microbiota might counteract the harmful effects of TMAO, further highlighting the importance of overall microbial diversity in maintaining cardiovascular health [56]. Chronic inflammation is another critical mechanism linking the microbiome to cardiovascular diseases (CVDs). Cani et al. (2009) demonstrated that dysbiosis increases intestinal permeability, allowing bacterial endotoxins to enter the bloodstream and provoke systemic inflammation. This pathway, involving glucagon-like peptide-2 (GLP-2), has been implicated in developing atherosclerosis and other cardiovascular conditions [57].

The impact of the microbiome on key cardiovascular risk factors such as obesity and diabetes has also been extensively studied. A recent study found that specific microbial communities are associated with obesity and insulin resistance, suggesting that the microbiome may influence metabolic pathways contributing to cardiovascular risk [58]. However, the translational potential of these findings remains unclear. For instance, a systematic review by Dixon et al. (2020) reported mixed outcomes in clinical trials assessing the efficacy of probiotics in reducing cardiovascular risk factors, highlighting the need for standardized protocols and clearer definitions of success in these studies [59]. Moreover, the literature often overlooks the individual variability inherent to microbiome composition. Genetics, age, sex, and ethnicity can significantly influence microbiome diversity and its interactions with cardiovascular health [60].

2.6. Cancer

Colorectal cancer (CRC) is one of the most prevalent cancers worldwide, and growing evidence suggests a critical link between the composition of gut microbiota and the development of this malignancy [61]. Research has shown that certain bacterial profiles, particularly those enriched in pathogenic species, are associated with an increased likelihood of CRC development [62,63]. *Fusobacterium nucleatum* is one of the most notable bacteria associated with colorectal cancer [64]. It is known to activate oncogenic signaling pathways, thereby facilitating tumor growth and progression. Specifically, the bacterium produces virulence factors such as adhesins and inflammatory mediators, which can alter the tumor microenvironment by promoting chronic inflammation [65]. Rubinstein et al. (2013) demonstrated that *F. nucleatum* plays a key role in colorectal tumorigenesis by interacting with colorectal cells and inducing an inflammatory response through the modulation of E-cadherin/catenin signaling [64]. In turn, this inflammation contributes to the initia-

tion and progression of cancer. Clinical studies have shown that patients with elevated *F. nucleatum* levels have poorer prognoses and increased tumor metastasis, suggesting that this pathogen may contribute not only to tumor development but also to disease progression [66]. This highlights *F. nucleatum* as a potential biomarker for CRC severity and as a target for therapeutic interventions to reduce bacterial load and inflammation in the tumor environment.

Polimeno et al. (2019) conducted a pilot study comparing the anaerobic gut microbiota in stool samples from patients with sporadic colorectal adenomas/polyps (SCA/P) and healthy controls. Their findings revealed distinct differences in the microbial composition between the two groups. Notably, *Bacteroides fragilis* and *Prevotella melaninogenica* were present exclusively in SCA/P patients, whereas *Bacteroides stercoris* and *Parabacteroides distasonis* were found only in controls. Among Gram-positive bacteria, *Clostridium clostridioforme*, *Propionibacterium avidum*, and *Pediococcus pentosaceus* were identified solely in controls, whereas *Eubacterium limosum*, *Clostridium innocuum*, and *Corynebacterium xerosis* were unique to patients with SCA/P. These findings suggest that specific alterations in gut microbiota may create a microenvironment conducive to the development of proliferative lesions, highlighting the potential of microbiota manipulation as a future target for personalized CRC treatments [67].

Dysbiosis in colorectal cancer is an overrepresentation of pathogenic bacteria and the depletion of beneficial anti-inflammatory bacteria [68]. In particular, there was a reduction in butyrate-producing bacteria such as those belonging to the phylum Firmicutes. Butyrate, an SCFA, plays a crucial role in maintaining the integrity of the intestinal epithelium, protecting it against DNA damage, and regulating immune responses [69,70]. Studies have shown that butyrate has anticancer properties, including the ability to induce apoptosis (programmed cell death) in cancer cells [71]. Sanchez-Alcoholado et al. (2020) also reported that CRC patients exhibited significantly reduced levels of butyrate-producing bacteria, which may contribute to compromised gut barrier function and increased susceptibility to colorectal cancer [72]. Li et al. (2022) analyzed the gut microbiota across different colorectal mucosal sites (tumor, para-cancerous, normal) and feces in CRC patients. They observed significant variations between the tumor and normal mucosal microbiota, with the para-cancerous mucosal microbiota representing a transitional state between the two. Six key genera, *Fusobacterium*, *Gemella*, *Campylobacter*, *Peptostreptococcus*, *Alloprevotella*, and *Parvimonas*, were consistently overrepresented in the tumor mucosa compared with normal mucosa and/or in mucosa compared with feces. These genera may contribute to the topographic variances in the microbiota of tumor-bearing colorectum, underscoring the importance of considering microbial composition at specific colorectal sites when studying CRC pathogenesis [73].

In addition to colorectal cancer, the human microbiome appears to be involved in the development and progression of several other types of cancers. For example, *Helicobacter pylori* infection is a well-known risk factor for gastric cancer, and chronic inflammation of the stomach lining increases the risk of malignancy [74]. Similarly, some oral microbiota have been associated with an increased pancreatic cancer risk, suggesting that oral pathogens may influence pancreatic carcinogenesis [75,76]. Moreover, lung microbiota have been found to differ between individuals with lung cancer and healthy controls, suggesting a potential role in lung tumorigenesis [77,78]. Additionally, the oral microbiota exhibits a close relationship with the intestinal microbiota through the oral–gut axis, impacting not only local conditions but also systemic health. Talapko et al. (2024) highlighted how dysbiosis in the oral microbiome contributes to the pathogenesis and progression of oral cancer, emphasizing the importance of microbial balance in maintaining oral health [79]. Santacroce et al. (2023) further underscored the broader systemic implications of the oral

microbiota, linking its dysbiosis to conditions such as cardiovascular diseases, diabetes, and gastrointestinal disorders [80]. McCune et al. (2024) also revealed compositional differences in the gut and oral microbiota among women with breast cancer, indicating that microbial imbalances in these niches might influence cancer development [81]. These findings reinforce the integral role of the oral microbiota in human health and disease, warranting further exploration of its therapeutic potential.

The complex connections between the microbiome and various disease states underscore the potential of microbiome-driven therapeutics in clinical practice [82]. Understanding the mechanisms underlying these associations may lead to novel treatment strategies aimed at restoring the microbial balance and improving health outcomes across a spectrum of conditions. Table 1 summarizes the bacterial strains implicated in gastrointestinal and other diseases, including their alterations and their clinical significance.

Table 1. Key bacterial strains and clinical implications of microbiome-related disorders.

Disorder	Associated Bacterial Strains	Alterations	Clinical Implications	References
Irritable Bowel Syndrome (IBS)	*Bifidobacterium* spp., *Lactobacillus* genera (e.g., *Lacticaseibacillus*, *Limosilactobacillus*), *Methanobrevibacter smithii*, *Escherichia coli*	Decreased *Bifidobacterium* and members of the reclassified *Lactobacillus* genera; increased *Methanobrevibacter* and *E. coli*.	Increased gas production, altered motility, and inflammation.	[83]
Inflammatory Bowel Disease (IBD)	*Faecalibacterium prausnitzii*, *Roseburia* spp., *Eubacterium rectale*, *Akkermansia muciniphila*, *Escherichia coli*	Depletion of anti-inflammatory species (*F. prausnitzii*, *Roseburia*); overgrowth of pathogenic *E. coli*.	Loss of gut barrier integrity, chronic inflammation.	[84]
Clostridioides difficile Infection	*Clostridioides difficile*, reduced *Bacteroidetes* and *Firmicutes* diversity	Overgrowth due to disrupted microbiota (e.g., post-antibiotics).	Severe diarrhea and colitis.	[84]
Helicobacter pylori Infection	*Helicobacter pylori*	Colonizes the stomach lining, reduces protective microbial diversity.	Gastritis, ulcers, increased gastric cancer risk.	[85]
Colorectal Cancer (CRC)	*Fusobacterium nucleatum*, *Bacteroides fragilis*, *Escherichia coli*	Enrichment of *F. nucleatum* and *B. fragilis*.	Promotes tumorigenesis via inflammation and DNA damage.	[86]
Diverticulitis	*Bacteroides fragilis*, *Escherichia coli*, *Enterococcus* spp.	Altered microbial diversity, increased inflammation.	Pain, fever, abscess formation.	[87]
Metabolic Disorders	*Akkermansia muciniphila*, *Bacteroidetes* spp., *Firmicutes* spp.	Reduced *Akkermansia*; altered Firmicutes/Bacteroidetes ratio.	Obesity, insulin resistance, increased inflammation.	[88]
Celiac Disease	*Bifidobacterium* spp., members of the reclassified *Lactobacillus* genera (e.g., *Lacticaseibacillus*, *Limosilactobacillus*), increased *Enterobacteriaceae*.	Reduced beneficial bacteria; increased pathogenic strains.	Triggers inflammatory responses in the gut.	[89,90]
Autism Spectrum Disorders (ASD)	*Bacteroides* spp., *Clostridium* spp., *Prevotella* spp.	Decreased *Prevotella*; increased *Clostridium*.	Altered gut–brain axis signaling, behavioral symptoms.	[91,92]
Cardiovascular Diseases	Members of the reclassified *Lactobacillus* genera (e.g., *Lacticaseibacillus*, *Limosilactobacillus*), *Bifidobacterium* spp., *Firmicutes*	Increased trimethylamine-N-oxide (TMAO)-producing species.	Links to atherosclerosis and hypertension.	[93,94]

3. Current Microbiome-Driven Therapies

3.1. Fecal Microbiome Transplantation

One of the most promising interventions in microbiome-driven therapy is fecal microbiota transplantation (FMT), a procedure in which fecal matter from a healthy donor enters the recipient's gastrointestinal tract to re-establish a healthy microbial composition (Figure 2) [95]. This is most often accomplished using colonoscopies, enemas, or capsules. The aim of transplanting healthy fecal matter is to restore gut balance by repopulating it with bacteria that are beneficial to the body and eliminating harmful viruses [96]. The procedure begins by selecting a donor with no family history of autoimmune, metabolic, or malignant diseases, followed by infection testing of the donor. The fecal matter from the donor is suspended in a solution containing either water or saline and is strained to eliminate particulate matter. The resulting concoction may be delivered to the recipient using numerous means, such as a nasogastric or nasojejunal tube, esophagogastroduodenoscopy, colonoscopy, or retention enema [97,98].

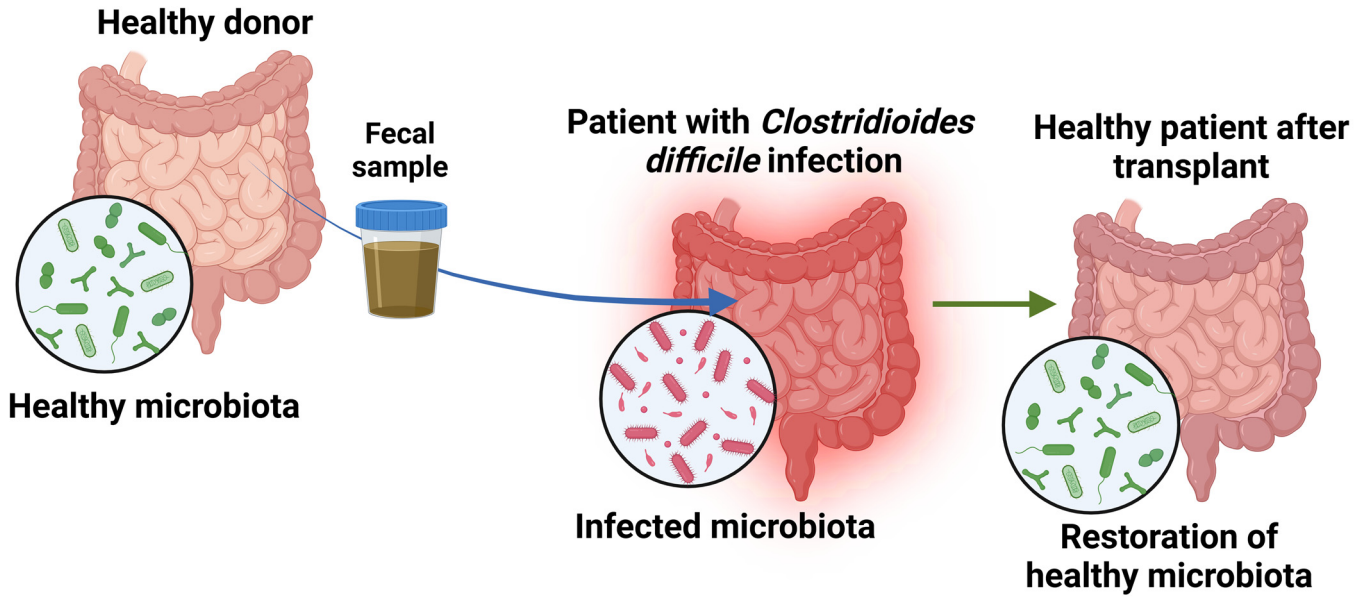

Figure 2. Gut microbiota restoration through fecal microbiota transplantation (FMT) in patients with *Clostridioides difficile* infection (Created in https://BioRender.com).

Fecal microbiota transplantation (FMT) has a rich history in ancient Chinese medicine, predating modern scientific understanding of the microbiome. The earliest records of fecal therapy in China, dating back to the 4th century AD, were attributed to physician Ge Hong. He described the use of a fecal slurry known as "yellow soup" to treat severe gastrointestinal issues, including diarrhea and food poisoning. This practice has been noted for its effectiveness in protecting patients from critical conditions [99,100]. Currently, FMT is being studied in various patients in North America. The participating investigators entered de-identified data into an online platform, including the FMT protocol, baseline patient characteristics, *Clostridioides difficile* infection (CDI) cure and recurrence, and short- and long-term safety outcomes. FMT has demonstrated a 90–92% success rate in resolving recurrent CDI after a single treatment [4,101]. A systematic review and meta-analysis showed that fecal microbiota transplantation had a clinical cure rate of 76.1% after the first administration. It also revealed that open-label studies had high cure rates of 82.7% compared with 67.7% in randomized trials [102].

Several studies have reported that FMT can lead to significant clinical improvement in patients with IBD. IBD is closely linked to disruptions in the gut microbiota, characterized

by the depletion of beneficial bacteria and overgrowth of pathogenic strains. The primary goal of FMT in IBD is to restore a balanced gut microbiota and improve the interaction between the microbiota and the host immune system [103]. A randomized controlled trial by Moayyedi et al. (2015) found that FMT successfully induced remission in a subset of patients with UC, providing strong evidence that restoring microbiome balance can positively affect disease outcomes [104]. According to a comprehensive study, FMT can alleviate symptoms in approximately 76% of IBD patients, with 63% exhibiting disease improvement. However, recent large-scale meta-analyses have reported decreased efficacy rates, with approximately 36% of patients with UC and 50.5% of patients with CD receiving symptomatic relief after FMT [95,105].

3.2. Probiotics, Prebiotics, and Synbiotics

Probiotics, prebiotics, and synbiotics have become key interventions for restoring and maintaining a balanced gut microbiota [106]. Probiotics are live microorganisms that provide health benefits to their hosts when consumed in sufficient quantities. Commonly used probiotic strains include members of the reclassified *Lactobacillus* genera (e.g., *Lacticaseibacillus* and *Limosilactobacillus*), *Bifidobacterium*, and *Saccharomyces boulardii*. These beneficial bacteria enhance intestinal health by inhibiting pathogenic microorganisms, modulating immune responses, and strengthening the intestinal barrier. Next-generation probiotics (NGPs) represent an innovative class of beneficial bacteria derived directly from the human gut microbiota, offering enhanced adaptability to the intestinal environment compared with traditional probiotics. NGPs have shown promise in modulating the gut microbiome to address various health conditions. For instance, *Faecalibacterium prausnitzii* and *Akkermansia muciniphila* have been studied for their anti-inflammatory properties and potential roles in managing chronic diseases such as inflammatory bowel disease and metabolic disorders [107]. The therapeutic potential of NGPs extends beyond gastrointestinal health. Research indicates that certain NGP strains may influence the gut–brain axis, thereby affecting mental health outcomes. Additionally, NGPs are being explored for personalized probiotic therapies, synthetic biology applications, and targeted delivery methods, highlighting their versatility in precision medicine [108]. Incorporating NGPs into clinical practice requires rigorous research to establish their efficacy and safety profiles. Nonetheless, their emergence marks a significant advancement in microbiome-based therapeutics, potentially offering more tailored and effective interventions for various health conditions.

Clinical applications of probiotics have successfully managed conditions such as IBS, IBD, and antibiotic-associated diarrhea. For instance, certain strains, such as *Bifidobacterium infantis*, have been found to reduce IBS symptoms, particularly bloating and abdominal pain [109,110]. Although probiotics have been associated with symptom relief in IBD, evidence supporting their role in remission is limited. According to some studies, they may be advantageous in sustaining remission in UC but less effective in Crohn's disease [111,112]. Probiotics have been explored for their ability to modulate the immune responses against allergic diseases. Research has indicated that early life administration of probiotics reduces the incidence of eczema during infancy, suggesting its preventative role in allergic diseases [113]. The gut–brain axis was another focus of this probiotic research, where results from a randomized controlled trial showed that a multispecies probiotic supplement reduced symptoms of depression in patients with a major depressive disorder, indicating a potential adjunctive treatment for the management of mood disorders [114]. Animal studies have demonstrated that altering the gut microbiome through diet or probiotics can affect behavior and cognitive function [115]. For example, germ-free mice, which lack gut microbiota, exhibit increased anxiety-like behavior. Clinical studies have shown that

probiotics can improve anxiety and depression symptoms, highlighting the therapeutic potential of targeting the gut microbiome for mental health treatment [116].

Prebiotics are non-digestible food components that selectively stimulate the growth and activity of beneficial intestinal bacteria. Common prebiotics include dietary fibers, such as inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS). Prebiotics act as substrates for beneficial microorganisms, promoting a beneficial intestinal environment and increasing microbial diversity and metabolic activity. This may lead to enhanced digestion, an improved immune response, and reduced inflammation. Research has shown that prebiotic consumption promotes the growth of Bifidobacterium and members of the reclassified *Lactobacillus* genera (e.g., *Lacticaseibacillus* and *Limosilactobacillus*), thereby enhancing overall gut health. Additionally, supplementation with prebiotic inulin-type fructans improves insulin sensitivity and reduces body weight in overweight adults, emphasizing the role of prebiotics in metabolic health [117].

Synbiotics are combinations of probiotics and prebiotics that have synergistic advantages. The rationale behind synbiotics is that the prebiotic component provides a specific substrate that supports the growth and activity of probiotic strains. This would eventually lead to an increase in the therapeutic outcome because the prebiotics guarantee that the beneficial bacteria not only survive the gastrointestinal transit but also become active and start exerting their health-promoting effects [106]. Clinical research on synbiotics has investigated their potential applications in various health areas, including gastrointestinal diseases, metabolic disorders, and immune system modulation. Specific synbiotic formulations are being investigated for their potential to reduce the incidence of necrotizing enterocolitis in preterm infants, most of which show positive results [85]. Synbiotics have been evaluated as adjunctive therapies for IBD. Randomized controlled trials have demonstrated that the synbiotic combination of *Bifidobacterium breve* and prebiotic GOS improves the clinical outcome of patients with UC, suggesting a possible synergistic effect in modulating gut inflammation [118]. The effects of synbiotics on cardiovascular health have also been investigated. A meta-analysis showed that synbiotic supplementation significantly lowered systolic and diastolic blood pressure levels in patients with hypertension, suggesting a positive impact on blood pressure regulation [119].

3.3. Microbial Metabolite-Based Therapies

Microbial metabolite-based treatments offer a way to capitalize on the positive effects of gut microbiota on host health, marking a new chapter in the treatment of illness. Their use includes the treatment of neurological illnesses, metabolic diseases, and inflammatory bowel diseases. Further research is needed to improve and incorporate these treatments into routine clinical practice. Microbial metabolites are small molecules produced by gut bacteria during the fermentation of dietary fibers and other substrates. These metabolites, including SCFAs, bile acids, and other signaling molecules, play crucial roles in host physiology and health [120]. Metabolites can influence various biological pathways, including immune response, inflammation regulation, and metabolic processes. For instance, SCFAs, such as butyrate, are known to enhance gut barrier integrity, modulate immune function, and exert anti-inflammatory effects [121,122].

Microbial metabolites play an important role in the gut–brain axis. SCFAs, such as butyrate, produced by the intestinal microbiota modulate cognitive function and behavior. Butyrate exhibits neuroprotective effects and can modulate immune responses, suggesting great therapeutic applications for neurodegenerative diseases, including Alzheimer's and Parkinson's diseases [123]. SCFAs also have potent effects on host metabolism. They provide energy to colonocytes, regulate glucose and lipid metabolism, and modulate appetite via hormonal actions. Restoring the healthy levels of these metabolites improves

insulin sensitivity and reduces inflammation. This opens up new prospects for the treatment of metabolic disorders such as obesity and type 2 diabetes [124]. In IBD, intestinal dysbiosis leads to changes in the microbial metabolite profile, which contributes to chronic intestinal inflammation. Treatments to re-establish beneficial metabolites, such as butyrate, have shown promise for reducing inflammation and facilitating mucosal healing. For instance, butyrate enemas are used to reduce the symptoms in patients with UC [125].

Microbial metabolite-based and probiotic treatments are two distinct approaches to modulating the gut microbiome for health benefits. Table 2 shows microbial metabolite-based and probiotic treatments.

Table 2. Comparative overview of microbial metabolite-based treatments and probiotic treatments.

Aspect	Microbial Metabolite Based Therapies	Probiotic Treatment
Definition	Utilizes metabolites produced by gut microbiota (e.g., SCFAs) to exert therapeutic effects [126].	Involves the administration of live microorganisms that confer health benefits when consumed in adequate amounts [127].
Mechanism	Directly modulates host signaling via metabolites, influencing immune responses and gut health [126,127].	Restores or maintains a healthy gut microbiota, inhibiting pathogenic bacteria and enhancing mucosal barrier function [127].
Efficacy in Disease Treatment	Effective for conditions like IBD, metabolic disorders, and neurological conditions through targeted action [126].	Variable efficacy; beneficial for gastrointestinal disorders like diarrhea and IBD, but effectiveness can be strain-specific [127].
Advantages	Provides targeted therapy; may overcome limitations of probiotics related to colonization and individual microbiomes [126].	Generally safe; can restore gut flora balance effectively in many individuals [127].
Limitation	Less research on long-term effects; potential need for personalized approaches based on specific metabolites.	Variable efficacy based on strain and individual microbiome composition; may pose risks for immunocompromised individuals.
Safety Profile	Generally low toxicity; fewer risks associated with live organisms.	Safe for most; caution advised in immunocompromised individuals or those with severe underlying conditions.
Administration	Can be administered as stable compounds (e.g., supplements).	Requires viable organisms; may have storage and viability issues.

3.4. Emerging Microbiome Editing Therapeutics

Recent breakthroughs in microbiome editing therapeutics have paved the way for innovative treatments that precisely target the microbial genes in the human gut. These emerging techniques, mostly CRISPR and base editing, offer promising approaches for manipulating microbial communities in situ with high specificity and efficacy, thus showing great potential for treating various diseases. This in situ technique manipulates the microbiome in its native setting. Although microbiome transplants can create large-scale changes but lack specificity, in situ-engineered microbiomes are designed to target specific bacteria, limiting their impact on the rest of the microbial community [128]. Base editing is a genome-editing technique that enables precise modification of specific DNA bases without causing double-strand breaks or relying on homologous recombination, without introducing double-strand breaks or homologous recombination. This fusion technology combines a catalytically weakened CRISPR-associated nuclease (Cas) protein and nucleobase deaminase enzyme. The guide RNA guides these complexes to the target DNA sequence, where the deaminase catalyzes chemical alterations and produces a point mutation. This method allows for accurate genetic modifications with a lower risk of unintended genomic changes [129]. Together, these approaches represent a new paradigm in microbiome manipulation and have tremendous potential for addressing the challenges associated with antibiotic resistance and the complex populations of microbes.

Several research groups have developed new gene editing tools specifically for individual gut bacteria or entire communities. Techniques such as CRISPR-Cas9 and inducible CRISPR interference (CRISPRi) have been used to effectively modify bacterial genetic materials [130]. For example, researchers have engineered bacteriophages and viruses that infect bacteria using CRISPR-Cas systems that selectively target antibiotic-resistant bacteria, thereby providing a new approach to combating antibiotic resistance. Recently, clinical trials have tested whether microbiome modification can be used as a therapeutic agent for infection. Locus Biosciences performed a phase 2 trial of CRISPR-enhanced bacteriophages against *E. coli* in patients with urinary tract infections (UTIs). The results showed significant reductions in both bacterial numbers and symptoms of UTIs, suggesting that CRISPR may be useful in treating bacterial infections [124,131]. In addition, researchers at the University of California have used CRISPR gene-cutting tools to modify the gut microbiota and prevent childhood asthma by changing the structure of the microbiome. This shows a promising avenue in which diseases related to microbial dysbiosis can be prevented through microbiome modification [132].

Despite these promising improvements, several challenges still remain in the field of microbiome-edited therapeutics. Specificity and safety must be guaranteed for genome-editing techniques to avoid off-target effects that may disrupt the sensitive balance of the microbiome. Moreover, knowledge of the complex interactions between microbial communities and their consequences on human health is essential for the successful application of such therapies. Ongoing research on the development of more precise editing tools and delivery methods aims to overcome these challenges. For instance, the Innovative Genomics Institute (IGI) is developing new CRISPR-based strategies to increase both the safety and accuracy of microbiome editing, which could improve the therapeutic potential of such interventions. The Berkeley Initiative for Optimized Microbiome Editing (BIOME) is dedicated to advancing CRISPR technologies to edit microbiomes within their natural environments. The goal is to develop safe and effective solutions to complex problems by understanding and manipulating the microbial communities [133].

4. Microbiome-Based Drug Development

4.1. Microbiome as a Drug Target and Modulator

Recent microbiome research has opened avenues for novel strategies to develop drugs that precisely target specific microbial metabolic pathways for treating infections and as a weapon against antibiotic resistance. Understanding and manipulating these pathways will help devise therapeutic interventions that inhibit or modulate selective microbial functions without damaging the host. One strategy involves targeting vital bacterial processes, including the synthesis of cell walls, proteins, nucleic acids, and other metabolic processes. For example, antibiotics in the β-lactam family inhibit cell wall biosynthesis by attaching penicillin-binding proteins, leading to bacterial cell lysis. Similarly, drugs such as tetracyclines and macrolides disrupt bacterial protein synthesis by binding to ribosomal subunits, thereby hindering bacterial proliferation [134]. Another promising strategy is the inhibition of bacterial fatty acid biosynthesis. This pathway provides membrane production and energy storage for the bacteria. Compounds that target the essential enzymes in this pathway, such as enoyl-acyl carrier protein reductase (FabI), have demonstrated potent activity against *Staphylococcus aureus*, including strains resistant to methicillin [135]. The application of genomics has enabled the discovery of new drug targets in microbial metabolic pathways. Studies on bacterial genomes have enabled researchers to identify unique enzymes or mechanisms that are not present in human cells as drug targets, facilitating the design of highly specific drugs with low toxicity. For example, targets include two-component signal transduction systems (TCSTSs) and histidine kinases, which play

crucial roles in bacterial adaptation and virulence [136]. Furthermore, the integration of synthetic biology and metabolic engineering has enabled the production of antimicrobial drugs through engineered microbial pathways [137].

The gut microbiota, referred to as the second human genome, is critically important in drug metabolism and significantly influences therapeutic efficacy and adverse effects. Recent research has shown that the microbiota itself is responsible for several drug modifications, such as activation, inactivation, and even toxification. Variations in the gut microbiota of different individuals may result in divergent microbe-drug interactions, underscoring the importance of personalized approaches in pharmacotherapy [138–140]. Emerging evidence has highlighted the role of the gut microbiota in determining the efficacy and toxicity of anticancer drugs. Lam et al. (2021) explored the potential of gut microbes to predict the efficacy and toxicity of combined immune checkpoint blockade therapies. Their findings underscore the importance of gut microbiota composition in modulating host immune responses to cancer therapies, suggesting that microbial profiles could be used as predictive biomarkers for treatment outcomes [141]. Furthermore, Sadeghi et al. (2024) discussed the role of gut microbiota in gastrointestinal cancer resistance to treatment. Their study demonstrated that microbiota-mediated mechanisms, such as drug metabolism, immune modulation, and the creation of a tumor-promoting microenvironment, can affect the efficacy of cancer therapies. These findings highlight the potential for microbiota-targeted strategies to enhance the effectiveness of anticancer treatments [142].

4.2. Engineered Microbiomes

Engineered microbiomes, or synthetic microbial communities, are designed to perform specific functions in a host or environment for precise interventions in health and disease management. Researchers have assembled defined microbial consortia with tailored functionalities to modulate the host physiology, enhance therapeutic outcomes, and mitigate disease processes. The development of synthetic microbiomes involves the careful selection and integration of microbial species with specific traits to achieve targeted effects. This process can be achieved through two approaches: bottom-up and top-down approaches. The bottom-up approach isolates and assembles specific microbial strains into an organized community with defined functions. This method allows for the complete and precise control of the community, composition, and interactions. The top-down approach involves altering existing microbial communities by adding or deleting members of the community to change community behavior and function [143]. Advances in genetic engineering and synthetic biology have enabled the programming of microbial consortia to execute complex tasks, including biosensing, metabolic production, and immune modulation [144].

Engineered microbiomes have significant potential in precision medicine by facilitating treatments customized to each patient's unique characteristics. In disease therapy, engineered microbiomes can modulate metabolic pathways, generate therapeutic compounds, or outcompete pathogenic microbes to treat conditions such as IBD, infections, and metabolic disorders [144]. Engineered gut microbiota composition also controls drug metabolism, thereby improving efficacy and decreasing adverse effects [7]. In addition, engineered microbial communities modulate immune responses, thus offering potential treatments for autoimmune diseases and allergies [144]. Despite their promise, engineered microbiomes face several challenges, such as stability in the host, avoidance of off-target interactions, and ethical and regulatory concerns. Ongoing studies are focused on areas such as developing strategies to control engineered microbes and prevent horizontal gene transfer to native microbiota [145], altering synthetic microbiomes to individual genetic and microbiome profiles to maximize therapeutic benefits [7], and establishing regulations for the clinical use of engineered microbiomes to confirm safety and efficacy [146].

5. Challenges and Limitations

5.1. Individual Microbiome Variation

Research has demonstrated a significant correlation between gut microbiome diversity and factors such as food, demographics, health problems, and hygiene [147]. While ethnicity has an impact on the microbiome, other factors such as geographic location, culture, tradition, dietary pattern, lifestyle, and exposure to toxins and diseases largely contribute to differences in microbiomes among different populations of humans, which poses challenges in microbiome-driven therapy [148]. Recent research indicates that a "one size fits all" approach to dietary interventions for treating metabolic disorders could be insufficient because the gut microbiota plays a critical role in inter-individual variability in the metabolism of key nutrients [149]. Despite considerable heterogeneity, identifying reliable microbiological biomarkers that predict therapeutic responses is challenging because each individual's microbiome is unique; individuals with similar symptoms may show divergent reactions to identical treatments [150].

5.2. Mechanistic Gaps in Microbiome Research

Although microbiome data have enormous therapeutic potential, they are still difficult to analyze and interpret owing to several factors, including compositional structure, which introduces a negative correlation bias, sparsity, and collinearity [151]. The complexity of microbial ecosystems has led to a lack of understanding of specific microbial-host interactions. Consequently, the effects of probiotics and synbiotics are not yet fully understood [152]. The human microbiome comprises a complex array of microorganisms, and our knowledge of their individual roles in human health remains limited. There is a lack of a comprehensive understanding of how successfully these microbial species perform their roles, their interactions with the host and other microbial species, and their specific locations within the host where they exert their influence. This knowledge gap highlights the need for further research to better understand these complex relationships.

5.3. Regulatory and Ethical Considerations

According to research ethics, the potential societal benefits of conducting a study must be weighed against the potential risks. Studies on the human microbiome must explain the favorable risk-benefit ratio. However, this can be extremely challenging because of several unresolved microbiological, clinical, and social problems. Balancing potential risks and benefits is often difficult and nearly impossible in some cases [153]. To ensure safety and effectiveness, therapies involving live organisms such as FMT, probiotics, and prebiotics are under strict regulatory oversight. Selecting the right regulatory category, such as drug, biological, or dietary supplement, can be challenging, as it profoundly affects the requirements and approval process. Depending on their functions and characteristics, developers must classify their products under regulatory frameworks as biological goods, medications, or medical devices. Preclinical studies, clinical evaluations, and assessments of adverse effects on the microbiome and host physiology should be performed to determine both safety and efficacy. The manufacturing, distribution, and storage of live biotherapeutic products (LBPs) follow standard good manufacturing practice (GMP) guidelines [11]. Ethical considerations in FMT include the major elements necessary to protect patients and to ensure informed participation. Rigorous screening and precise selection can reduce the risk of transferring novel diseases to recipients via FMT. Informed consent was another crucial component of this study. It is a voluntary agreement to participate in clinical trials based on knowledge of the research goals, risks, potential advantages, and safety issues. Also, a proper assessment of safety issues and benefit-to-risk ratio should be carried out to avoid adverse effects and ensure the therapy is safe and effective overall [154].

6. Future Directions

Microbiome-driven therapeutics are advancing rapidly, with future research focusing on addressing these challenges and broadening their therapeutic applications. Precision medicine will play a key role by utilizing individual microbial profiles to develop personalized treatments that enhance efficacy and reduce side effects [155]. Progress in synthetic biology and computational modeling is expected to improve the design of engineered microbiomes and predictive tools, thereby increasing their stability and functionality. Additionally, the integration of microbiome profiling and metagenomic data is transforming the field of precision medicine. These tools provide deep insights into the functional and genetic attributes of microbial communities, enabling the identification of individual-specific microbial signatures associated with health and disease. By combining metagenomic data with advanced computational frameworks and clinical information, researchers can identify novel biomarkers and therapeutic targets. This integration fosters the development of tailored interventions, including personalized probiotics, microbiota-targeted drugs, and predictive models for disease risk. As metagenomic technologies continue to advance, they promise to bridge the gap between microbial research and individualized healthcare, paving the way for innovative diagnostic and therapeutic solutions [156,157]. Understanding the gut–brain axis and immune modulation promises new therapies for neurological diseases and autoimmune disorders [158]. Future research has also highlighted the potential of microbiome modulation in cancer therapy to improve responses to immunotherapy and reduce side effects through targeted interventions such as probiotics or engineered microbiomes [10,159]. Therefore, one of the critical avenues that will ensure the safe and effective translation of these therapies into the clinic is the creation of strong regulatory frameworks and ethical guidelines [11]. This will be accelerated through public education, access equality, and expansion into understudied areas, including research on the skin and oral microbiomes [160–162]. Together, these efforts will establish microbiome therapeutics as the cornerstone of precision medicine and improve health outcomes worldwide.

7. Conclusions

Microbiome-driven therapeutics are a next-generation approach to treating complex diseases, highlighting host-microbial community interplay. This review covers the current developments in FMT, probiotics, and engineered microbiomes, each of which holds promise for meeting unmet medical needs. However, the remaining challenges, such as individual variability, knowledge gaps, and regulatory hurdles, are significant. However, with interdisciplinary approaches, innovation, and adherence to ethical standards, microbiome-based treatments can revolutionize healthcare by providing targeted, effective, and sustainable solutions for numerous conditions.

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