ACCSCIENCE PUBLISHING

Journal of Clinical and Translational Research

REVIEW ARTICLE

Harnessing the gut microbiome for therapeutic interventions

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Abstract

Background: Gut microbiome comprises a diverse microbial community, including bacteria, viruses, and fungi, which play a crucial role in human health. These microbes contribute to host well-being by producing beneficial compounds such as short-chain fatty acids and other metabolites that help maintain microbial homeostasis. Recent advancements in high-throughput sequencing techniques have identified key microbes crucial for human health and revealed that an imbalance in these communities—known as dysbiosis—can lead to various diseases, including inflammatory bowel disease (IBD), Crohn's disease, colorectal cancer, type 2 diabetes, and liver diseases. **Aim:** This review aims to provide a comprehensive overview of emerging microbiome-based therapeutic strategies, including fecal microbiota transplantation (FMT), prebiotics, probiotics, next-generation probiotics, synthetic microbiome transplantation, and microbiome editing therapies, as potential interventions to restore gut microbial balance and improve health outcomes. **Relevance for patients:** Microbiome-based therapies have emerged as promising tools for restoring gut homeostasis and managing microbiome-associated diseases. Approaches such as FMT have shown clinical benefits in conditions such as IBD, *Clostridium difficile* infection, and cancer immunotherapy. Understanding these therapies may guide future personalized treatments aimed at improving patient outcomes through modulation of the gut microbiome.

Keywords: Synthetic microbiome transplantation; Microbiome editing therapies; Inflammatory bowel disease; Next-generation probiotics

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Citation: Abbasi ZW, Ikram S, Ullah M, Ahmad A, Ali I, Naeem M. Harnessing the gut microbiome for therapeutic interventions. *J Clin Transl Res.* 2026;12(1):4-21. doi: 10.36922/JCTR025390067

Received: September 27, 2025

Revised: December 26, 2025

Accepted: January 19, 2026

Published online: February 6, 2026

1. Introduction

Humans have historically exploited microbes for a variety of purposes, from the fermentation of food to the heterologous synthesis of pharmaceutically useful substances such as insulin and antibiotics.[1-3] This long-lasting fascination eventually extended to the invisible microbial world within the human body, where the idea that microorganisms could shape human health sparked a new scientific frontier.[4] Reflecting how human curiosity often drives scientific discovery, this advancement led to a deeper understanding of the gastrointestinal (GI) tract, which was once viewed merely as the digestive system

but is now recognized as a significant contributor to human health and disease.[5] This shift in perspective stems from the recognition of the gut microbiome as a highly evolved and heterogeneous community of bacteria, fungi, viruses, and archaea that plays a major role in regulating physiological and metabolic processes by influencing both health maintenance and disease progression.[6]

Among the gut microbes, bacteria are the most prevalent, with the majority comprising obligate and facultative anaerobes. This dominant bacterial population is largely represented by four major phyla: Firmicutes (formerly Bacillota), Bacteroidetes (Bacteroidota), Actinobacteria (Actinomycetota), and Proteobacteria (Pseudomonadota), which together comprise approximately 90% of the total bacterial population in the gut.[7,8] These microbes perform diverse functions, ranging from digestion and nutrient metabolism to immune modulation and even the gut–brain axis communication. The metabolic capabilities of these microbes are particularly noteworthy, as they enable the breakdown of non-digestible carbohydrates to short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate.[9,10] SCFAs not only act as a source of energy but also play functions in gut integrity, immune system, cardiovascular system, metabolic homeostasis, and neurophysiological function. Beyond metabolic versatility, the gut microbiome also serves as a vital source of micronutrients essential for host physiology. It includes the synthesis of essential vitamins such as folate, riboflavin, cobalamin, niacin, pantothenate, and pyridoxine.[11-13] These micronutrients are important for essential processes, including DNA synthesis, energy metabolism, and neurotransmission, highlighting the vital role of the microbiome in sustaining health.[14]

Given the pivotal role of gut microbiota in maintaining homeostasis, any imbalance in its composition results in dysbiosis. Recent studies confirmed that dysbiosis is associated with the pathogenesis of numerous illnesses, including metabolic syndromes (obesity and diabetes), autoimmune diseases, GI disorders, and neuropsychiatric conditions.[15-17] This knowledge has brought a turnover in medicine, positioning the gut microbiome as a potential therapeutic target for the management and treatment of a variety of diseases. Scientists and clinicians have progressively discovered ways to harness this microbial community. Interferences range from simple strategies of dietary modifications and prebiotic or probiotic supplementation to complex approaches such as fecal microbiota transplantation (FMT) and microbiome-based drug development.[18,19] Whole genome analysis of bacterial species has recognized meanings attributed to strains, and integrating those strains in microbiome-based therapies has shown a noteworthy potential in enlightening health conditions.[20,21] Building on these discoveries, a major focus has shifted toward modified microbiome-based involvement. The probability of adapting treatments based on an individual's exceptional microbiome conformation heralds an era of precision medicine where interferences are custom-made to amplify efficiency and diminish side effects.[22,23]

The interaction between the host and the resident microorganisms has been increasingly elucidated with the advancement of molecular techniques, such as metagenomics, transcriptomics, and metabolomics, providing deeper insights into microbial communities and their molecular mechanisms.[24-27] Disruption in these microbial communities is characterized by alterations in microbial composition, including an increase in pro-inflammatory species and a decrease in anti-inflammatory species.[28-31] Restoration of a dysbiotic gut can be achieved through several approaches, including lifestyle modifications such as diet, exercise, and hygiene practices.[32] Beyond lifestyle modification, microbiome-based therapies have emerged as a promising candidate to restore microbial balance. These therapies involve the administration of prebiotics, probiotics, and post-biotics, as well as FMT.[33-35] Emerging therapeutic tools, such as the generation of probiotics and engineered microbial consortia, are gaining attention for their ability to more precisely target dysbiosis and modulate host health.[36-38] These innovative approaches represent a significant leap forward in tailoring microbiome intervention for specific health conditions. A general overview is illustrated in Figure 1. This review comprehensively overviews the microbiome-based therapies, signifying a transformative method in addressing some of the most interesting health problems. It aims to discuss the recent developments in the field of microbiome-driven therapeutics, highlight the challenges that must be overcome, and propose future directions. By addressing these gaps and fostering innovative approaches, microbiome-based therapies have the potential to become the keystone of precision medicine, offering personalized and sustainable solutions for a broad spectrum of diseases.

2. Microbiome-based therapeutic strategies

Microbiome-based strategies aim to restore microbial balance, enhance immunity, improve metabolism, and fight pathogens, moving toward personalized medicines. This leverages the gut–brain axis and immune system connections. Methods such as probiotics, prebiotics, and synbiotics administration, as well as FMT, gene editing,

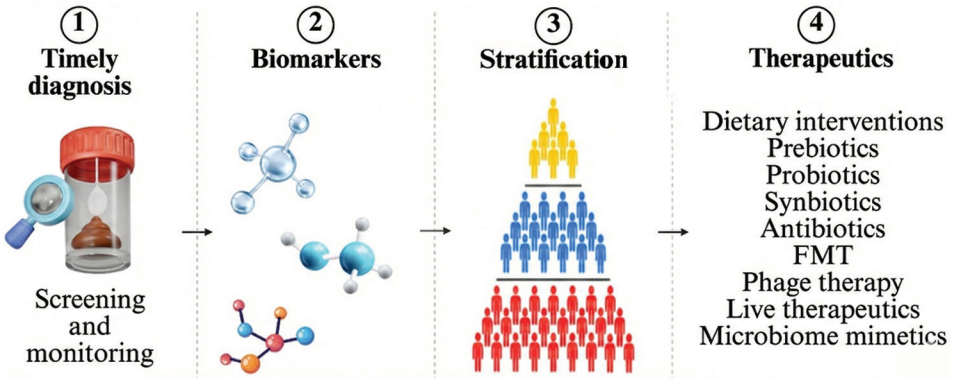

Figure 1. Summary of the various medical applications of the microbiome. Microbiota roles include serving as biomarkers for patient screening, monitoring, and stratification, as well as being used in therapeutic approaches. Created with BioRender.com. Ikram S. (2025).

engineered microbes, and personalized diets, aim to target specific diseases or enhance well-being.

2.1. Fecal microbiota transplantation

In recent studies, FMT has emerged as the ground-breaking therapy revolutionizing gut health by restoring microbial balance and offering hope where conventional treatment falls short. Originally rooted in traditional Chinese medicine, FMT was rediscovered by modern medicine in the 20th century.[39,40] This therapy involves transferring the entire fecal material from the donor to the patient through various routes, aiming to restore gut microbial diversity and treat various conditions.[41-43] It can be administered either through the upper GI tract, such as the duodenal tube, through oral capsule, or lower GI tract using colonoscopy or enema.[43,44] For FMT to be effective, the transplanted microbes must colonize and persist in the GI tract to achieve long-term therapeutic benefits. Donor selection and diet play a crucial role in determining microbial colonization, as a diverse and resilient microbiota enhances engraftment success.[45-47]

Studies on inflammatory bowel disease (IBD) patients have shown that FMT induces a significant shift in gut microbiota composition, increasing the abundance of *Bacteroides, Faecalibacterium*, and butyrate-producing bacteria, aligning the recipient microbiome more closely with that of the donor.[48] Butyrate, an SCFA produced by gut bacteria, plays a key role in gut health by exerting anti-inflammatory effects, strengthening gut-barrier integrity, and modulating immune response.[49-51] In patients with *Clostridium difficile* infection, a significant increase in alpha diversity is observed post-FMT. Notably, 92.1% of patients successfully resolved the infection, restoring normal bowel patterns. The microbial composition shifted toward the healthier state with a notable increase in key taxa, including *Bacteroides, Faecalibacterium, Blautia*, and *Enterobacter*, contributing to gut microbiome recovery.[52,53]

Beyond infections, gut dysbiosis can also promote tumorigenesis through multiple mechanisms, including chronic inflammation, DNA damage, and immune modulation.[54,55] Pathogenic bacteria such as *Escherichia coli* promote tumor progression by producing genotoxins (e.g., colibactin) and activating inflammatory pathways, including nuclear factor-kappa B (NF-κB), signal transducer and activator of transcription 3 (STAT-3), along with pro-inflammatory cytokines such as interleukin (IL)-17 and tumor necrosis factor-alpha (TNF-α).[56,57] These cations contribute to the creation of a tumor-promoting micro-environment through immune modulation, as represented in Figure 2.

Fecal microbiota transplantation has shown promise in cancer immunotherapy, particularly programmed cell death protein 1 (PD-1) inhibitors.[58,59] By modulating the gut microbiota, FMT enhances cytotoxic T-cells activation and their infiltration into the tumor microenvironment, thereby promoting anti-tumor immune response.[60-62] Phase 2 clinical trials have demonstrated that combining FMT with anti-PD-1 monoclonal antibody tislelizumab and vascular endothelial growth factor receptor (VEGFR) inhibitor fruquintinib improved survival in refractory microsatellite stable, metastatic colorectal cancer patients, with a median progression-free survival of 9.6 months and overall survival of 13.7 months.[63,64] Responders exhibited distinct gut microbiota signatures, including an abundance of Proteobacteria and Lachnospiraceae and lower levels of *Bifidobacterium* and Actinobacteriota, alongside unique T-cell receptor characteristics, highlighting FMT's potential to enhance immunotherapy efficacy.[65]

Preclinical studies have shown the effectiveness of FMT in treating cancer. One of the studies has demonstrated

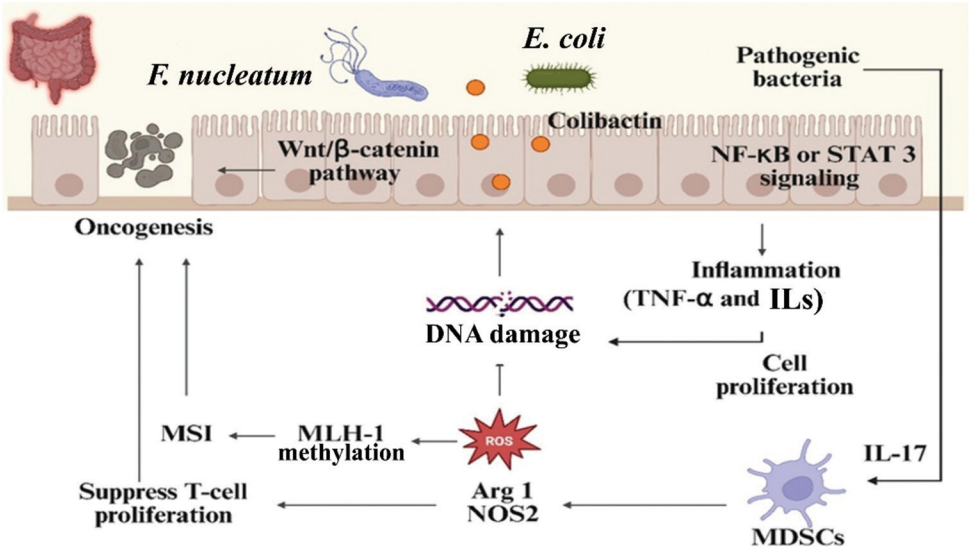

Figure 2. Mechanisms by which the gut microbiome drives cancer development and progression include activation of inflammatory pathways such as NF-κB and STAT-3, along with the induction of pro-inflammatory cytokines such as IL-17 and TNF-α. Created with BioRender. Ikram S. (2025). Abbreviations: Arg1: Arginase 1; *E. coli*: *Escherichia coli*; *F. nucleatum*: *Fusobacterium nucleatum*; IL: Interleukin; MDSC: Myeloid-derived suppressor cells; MLH-1: MutL homolog 1; MSI: Microsatellite instability; NOS2: Nitric oxide synthase 2; ROS: Reactive oxygen species; STAT3: Signal transducer and activator of transcription 3; TNF-α: Tumor necrosis factor-alpha.

that FMT reduced tumor size by nearly 40% and improved gut morphology in mice with colorectal cancer.[66] It restored microbial diversity along with downregulation of pro-inflammatory cytokines (e.g., IL-6 and TNF-α) and oncogenic markers (e.g., β-catenin and Ki-67), indicating suppressed tumor regression.[67] The therapeutic potential of FMT across various diseases is highlighted in Table 1.

One of the key challenges in this therapy is the selection of appropriate donors and the standardization of the FMT protocol. Significance and efficacy of FMT largely depend on the donor's microbiota composition, as transplants from different donors have resulted in varying clinical outcomes.[79] To improve FMT efficacy and consistency, standardized donor screening criteria and microbiome profiling should be established. In addition, long-term stability of FMT remains a concern, as it is unclear whether the transplanted microbes persist in the gut over an extended period or if periodic reinfusion is required to maintain therapeutic benefits.[80] While FMT is generally considered safe, potential risks include the transmission of opportunistic pathogens and unexpected immune responses of patients, underscoring the need for rigorous screening and regulatory oversight.

Table 1. Therapeutic potential of fecal microbiota transplantation across various diseases

Disease	Key outcomes	References
Ulcerative colitis	Clinical remission in 40–60% of patients, reduced pro-inflammatory cytokines	68,69
Immune checkpoint inhibitor-induced colitis	Clinical remission in 83–92% of patients, improved patient-reported outcomes	70,71
Graft-versus-host disease	Complete clinical response in 66–71% of patients, reduced immunosuppressant use	72,73
Colorectal cancer	Improved PFS and OS, increased beneficial bacteria, and enhanced anti-PD-1 efficacy	63,74
Metabolic syndrome	Improved insulin sensitivity and glucose metabolism	75,76
COVID-19	Alleviated diarrheal and depression symptoms	77,78

Abbreviations: OS: Overall survival; PD-1: Programmed cell death protein 1; PFS: Progression-free survival.

2.2. Probiotics

The World Health Organization defines probiotics as "live microorganisms which when administered in adequate amounts confer the health benefit to the host."[81(p22)] These microbes have been studied for their role in restoring gut microbiomes and have emerged as a keystone of microbiome-based therapies.[82,83] Probiotics help restore microbial balance by promoting beneficial microbes and maintaining gut homeostasis through the production of antimicrobial peptides, regulating inflammatory response by stimulating anti-inflammatory cytokines, and strengthening intestinal integrity to prevent

harmful substances from entering circulation.[55,84,85] These beneficial strains maintain intestinal homeostasis through competitive exclusion by promoting the growth of the endogenous desirable microbial population. Through competition, the probiotic strain uses the available nutrients and carbon source to reduce basic chlorine and oxygen in the microenvironment, helping them to occupy ecological niches and inhibit the growth of harmful bacteria (Figure 3). Certain probiotic strains, including *Lactobacillus* and *Bifidobacterium*, contribute to the biosynthesis of certain B vitamins, which are crucial for energy metabolism, immune regulation, and neurological function.[86,87] This vitamin production further enhances host health by preventing deficiencies and supporting metabolic processes. In addition, probiotics produce bioactive compounds such as SCFAs, bacteriocins, and neurotransmitters, supporting gut health and overall well-being.[88]

As a key component of the gut microbiome, probiotic strains are widely used to manage various health conditions, including GI disorders, metabolic diseases, neurodegenerative conditions, and immune dysfunction. Their influence on the gut–brain axis suggests potential therapeutic roles in cognitive health, including Alzheimer's disease and Parkinson's disease, by modulating gut inflammation and oxidative stress.[89] Probiotics influence both gut motility and mental health through modulation of microbiome-derived metabolites and serotonin pathways. The study on multistrand probiotics and sensi-biome (designed to target the sensitive and dynamic portion of the gut microbiome that responds rapidly to environmental changes) identified key microbiome-derived metabolites, including SCFAs (e.g., butyrate, iso-butyrate, propionate, and iso-valeric acid) for gut health, equal for anti-inflammatory benefits, and oleamide for potential neuroprotective effect.[90] The therapeutic potential of probiotics extends beyond GI disorders to metabolic and autoimmune disease. Probiotic strain *Klebsiella sp*. ARO112 treats IBD by displacing pathobiont adherent and invasive *E. coli* AIEC strain.[91,92] *Bifidobacterium* and *Lactobacillus*, termed as psychobiotic strains, have been shown to relieve symptoms of depression and anxiety through the production of neurotransmitters serotonin and dopamine, highlighting microbiome-based therapy as a promising approach for mental health disorders[93] (Table 2). The efficacy of probiotics is both disease-specific and site-specific, as different probiotic strains exhibit variable colonization, survival, and functional activities across the GI tract region, leading to different therapeutic outcomes in conditions such as irritable bowel syndrome, IBD, and antibiotic-associated diarrhea.[94] A pilot study using three probiotic strains (*Lactobacillus helveticus* MIMLh5, *Lacticaseibacillus paracasei* DG, and *Bifidobacterium bifidum* MIMBb23sg) revealed distinct colonization and site-specific effects of each strain on immune regulation, gut barrier integrity, and serotonergic signaling.[95] Further ongoing research continually uncovers new therapeutic potential.

2.3. Next-generation probiotics

Traditional probiotics, including *Lactobacillus* and *Bifidobacterium*, have been used to treat various diseases.

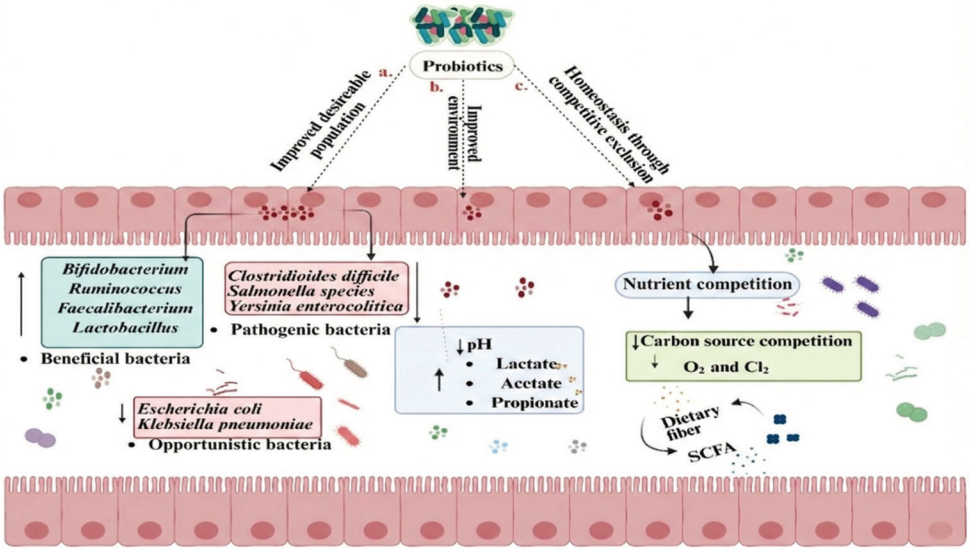

Figure 3. Probiotics maintain intestinal homeostasis by enhancing the growth of beneficial microbes, suppressing pathogenic and opportunistic bacteria, and promoting microbial balance through mechanisms such as nutrient competition and SCFA production. Created with BioRender. Ikram S. (2025). Abbreviation: SCFA: Short-chain fatty acid.

Table 2. Therapeutic applications of certain probiotic strains influencing gut motility and mental health

Probiotic strain	Therapeutic application/ diseases	References
Klebsiella sp. ARO112	Inflammatory bowel disease (IBD) and necrotizing enterocolitis	91
Lactobacillus rhamnosus	Gastrointestinal disorder and immune modulation	96
Akkermansia muciniphila	Metabolic disorder and obesity	97
Bifidobacterium animalis	Mental health, gut barrier function, and atopic dermatitis	98,99
Bifidobacterium longum	Gut–brain axis (reveals depression)	100
Pediococcus pentosaceus	Colorectal cancer therapy	101
Lactobacillus reuteri	Infantile colic	102
Lactobacillus rhamnosus, Lactobacillus plantarum, Escherichia coli Nissle 1917	IBD	103,104
Bifidobacterium spp., and Lactobacillus spp.	Irritable bowel syndrome, Parkinson's disease, Alzheimer's disease, type 2 diabetes, and functional constipation (pediatric)	105,106
Saccharomyces boulardii, Lactobacillus reuteri, and L. rhamnosus GG	Acute gastroenteritis (pediatric)	107
Lactiplantibacillus plantarum HY7712, Bifidobacterium animalis ssp. lactis HY8002, and Lacticaseibacillus casei HY2782	Inflammatory colitis, and atopic dermatitis	108

However, their effectiveness is limited by poor stability in harsh environments, lack of targeted action, and limited functionality (Table 3).[109] Advancements in genetic engineering and synthetic biology have led to the development of next-generation probiotics (NGP), designed to enhance viability, stability, and therapeutic potential, overcoming the limitations of traditional probiotics.[110,111] NGP employs advanced tools such as clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated proteins (Cas) system and synthetic gene circuits to create customizable therapies personalized for individual microbiome profiles. To overcome the challenge of harsh environments, such as nutrient limitation, encapsulation technologies and bioadhesion platforms enhance the adhesion and persistence of probiotic strains in the gut.[112] Advancement of high-throughput sequencing techniques, functional annotation, and metabolic modeling has further facilitated

Table 3. Comparison of traditional probiotics and next-generation probiotics

Features	Traditional probiotics	Next-generation probiotics	References
Stability	Limited stability in a harsh environment	Enhanced stability and viability	112
Targeted Action	Broad non-specific effect	Targeted delivery and sensitivity	114
Therapeutic potential	Primarily for gastrointestinal health	Wide range of applications, including mental health and cancer	110,115
Personalization	Limited personalization	Tailored to the specific disease state and individual	114
Genetic engineering	Not genetically modified	Engineered using synthetic biology tools	116

the identification of new NGPs in the gut microbiome with potential health benefits.[111,113]

Many probiotic bacterial strains have been identified from the intestinal microbiome using novel next-generation sequencing techniques, and these NGPs have become potential sources of innovative therapeutics for various diseases.[117] Notably, NGPs such as *Faecalibacterium prausnitzii*, *Akkermansia muciniphila*, and *Bacteroides fragilis* have an impact on cancer incidence.[118] It has been shown that these NGPs enhance GI immunity, maintain intestinal barrier integrity, improve immunotherapy efficacy, and reduce complications associated with chemotherapy and radiotherapy. To reduce inflammation in the gut and to alleviate symptoms of IBD, *Lactobacillus* bacteria have now been engineered to produce anti-inflammatory compounds such as IL-10 and transforming growth factor-β.[119] Furthermore, to overcome the challenges of a harsh environment, researchers have used CRISPR/Cas9 to delete genes in *Lactobacillus* species, making them resistant to stomach acid, thereby increasing their survival rate through the digestive tract.[120] In a study including *Akkermansia muciniphila*, CRISPR/Cas9 was used to enhance its ability to produce mucin-degrading enzymes.[109] These enzymes improve the bacterium's ability to strengthen the gut barrier and reduce inflammation, making it more effective in treating metabolic disorders such as diabetes and obesity.

2.4. Prebiotics

Prebiotics have emerged as a promising component in microbiome-based therapies in treating various conditions. Prebiotics are non-digestible dietary fibers that serve as a substrate for beneficial gut bacteria, encouraging

their growth and action, thereby improving gut health. The integration of prebiotics into therapeutic strategies is gaining attention due to their potential to enhance the efficacy of treatments by targeting gut microbiota dysbiosis. This approach is being explored in various contexts, from enhancing drug delivery systems to supporting the function of NGPs.

Prebiotics-based nanoparticles have advanced to target drug delivery to the colon, showing potential in treating colonic diseases such as ulcerative colitis and colorectal cancer. These systems utilize prebiotic shells that degrade in response to gut microbiota to release therapeutic agents directly at the site of inflammation.[121] The use of prebiotics in these systems not only aids in drug delivery but also maintains intestinal homeostasis in maintaining the gut microbiota.[104,122] Prebiotics have shown promise in managing IBD by altering the gut microbiota composition, reducing inflammation, and supporting immune function. They induce the growth of beneficial bacteria, which, in turn, produce anti-inflammatory metabolites.[123] Clinical trials have demonstrated variable but generally positive outcomes, suggesting that prebiotics can be a valuable adjuvant in IBD treatment.[123,124]

Moreover, prebiotics are crucial in enhancing the viability and function of probiotics, specifically, NGPs, which are more sensitive to GI conditions.[99] They help improve the antioxidant capacity and probiotics resistance, thereby enhancing their therapeutic potential.[125,126] The combination of prebiotics with probiotics, also called symbiotics, has been explored for various disorders, including metabolic syndromes and central nervous system disorders, by promoting the survival and growth of beneficial bacteria (Figure 4).[127] The novel approach to symbiotics emphasizes microbial metabolism as a key mechanism for therapeutic benefits, focusing on targeted metabolite–microbe interactions to enhance health outcomes.[128] While prebiotics offer a significant potential in microbiome-based therapies, challenges remain in understanding their precise mechanism and interaction with the host microbiome. The variability in individual response to prebiotic intervention highlights the need for personalized approaches in their application.

2.5. Synthetic microbiome transplantation

Synthetic microbiome transplantation (SMT) represents an innovative approach to microbiome therapy, aiming to overcome the limitations of traditional FMT.[129,130] This treatment involves the use of defined microbial communities, known as SynComs, to restore the microbiome in a controlled and safe manner. SynComs are composed of selected, well-characterized microbial

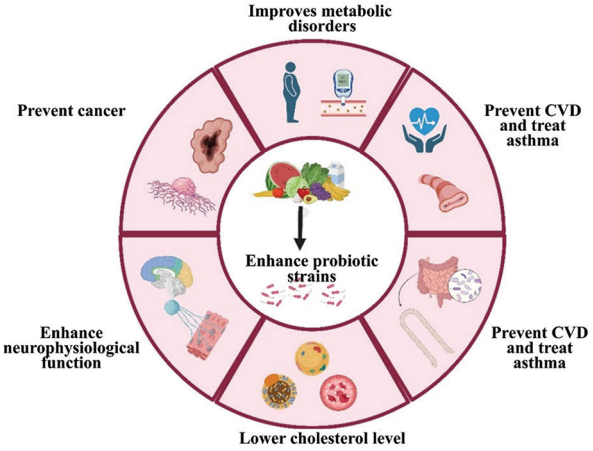

Figure 4. Prebiotics in combination with probiotics maintain overall body functions, from preventing cardiovascular disease (CVD), asthma, and cancer to enhancing neurological functions and lowering cholesterol levels. Created with BioRender. Ikram S. (2025).

strains, which can be derived from the mucosa and feces of human samples.[131] In the current era, the growing culturing capacity, along with reasonable sequencing and progressive computational modeling, has started a "golden age" for connecting the beneficial potential of SynComs to mitigate GI disorders such as infections and chronic IBD.[132,133] The development of SMT is driven by the need for more consistent, safe, and effective treatment for various diseases linked to microbiome dysbiosis. Some major advantages of SMT over FMT are its safety and consistency, which offer a controlled and known composition of microbial species, reducing the potential risk of infection and ensuring reproducibility in treatments.[134]

SynComs can be used in targeted therapeutics, such as restoring the microbial imbalance in conditions such as IBD and bacterial vaginosis, offering a more precise and personalized therapeutic approach. One of the studies has explored synthetic microbial consortia to combat bacterial vaginosis induced by *Gardnerella vaginalis* in germ-free mice to explore its effects on pro-inflammatory biomarkers in vaginal tissue.[135] It was found that key inflammatory regulator NF-κB and pro-inflammatory cytokines (IL-1 and IL-8) were suppressed by this treatment, along with increased abundance of *Lactobacillus* and reduction of *Escherichia*, *Shigella*, and *Vagococcus*. In addition, upregulation of anti-inflammatory cytokine (IL-10) suggests that SMT also helps modulate the immune system effectively. To combat the infection of multidrug-resistant *Klebsiella pneumoniae*, a SynCom of 15 microbial species isolated from the gut was tested across different settings. The successful engineering of this SynCom suppressed the resistant pathogen across various environments,

showcasing its versatility and robustness.[136,137] The engineered therapeutic microbes also act as therapeutic agents in reprogramming the microbial network to detect disease biomarkers and produce therapeutic molecules in response to the host's physiological state.[138,139] In conclusion, SynComs emerged as versatile and effective tools in addressing microbial imbalance, offering targeted therapeutic solutions across the range of conditions, showcasing their ability to restore microbial communities.

3. Microbiome-editing therapies

Recent progress in microbiome-editing therapies has opened new avenues for targeting microbial genes in the human gut with specificity. The new tools, primarily CRISPR and base editing, provide promising ways of editing the microbial populations they target with high accuracy and efficiency, and have immense potential to cure many diseases.[140] These *in situ* approaches edit the microbiome in its natural environment. Microbiome transplants can make dramatic changes, but are not specific; *in situ*-engineered microbes target specific bacteria with little effect on the rest of the microbial community. Base editing is a tool that can make single-base, precise modifications without inducing double-strand breaks or requiring homologous recombination.[141,142] A hybrid base-editing approach has been proposed that uses a catalytically impaired CRISPR-associated protein together with a nucleobase deaminase enzyme. A guide RNA directs the complex to the target DNA sequence, where the deaminase makes chemical modifications and introduces a point mutation. This approach enables precise genetic modifications with less likelihood of unwanted genomic alterations. These novel approaches offer a new means of manipulating the microbiome and have immense potential for addressing the challenges of antibiotic resistance and complex microbial communities.

Many research teams have proposed new gene-editing technologies for gut bacteria, including CRISPR-Cas9 and CRISPR interference. Moreover, scientists have designed viruses that infect bacteria with CRISPR-Cas systems to specifically target antibiotic-resistant bacteria, offering a new tool to address antibiotic resistance.[143] Clinical trials have recently tested whether microbiome modification can cure infections. Locus Biosciences has run a Phase 2 trial of CRISPR-enhanced viruses in urinary tract infection (UTI) patients caused by *E. coli*. Reported results indicated reductions in bacterial levels together with improvement in UTI symptoms, supporting the potential of CRISPR-enabled approaches for targeted antimicrobial strategies. Furthermore, scientists at the University of California have used CRISPR tools to edit the gut microbiota and alleviate childhood asthma by altering the composition of the microbiome.[21,144,145] These studies are promising for disease prevention by fixing microbial imbalances through microbiome modification.

Despite these encouraging steps forward, several challenges remain with microbiome-edited therapies. It is of the highest importance that genome-editing technologies are precise and safe to prevent unwanted side effects that would upset the sensitive balance of the microbiome. Moreover, the understanding of the intricate interactions of microbial communities and their influence on human health is critical to implement these therapies successfully. Future research should address these issues with better editing technologies and delivery strategies. The Innovative Genomics Institute is developing new CRISPR-based technologies to improve microbiome editing, making it safer and more precise, thereby allowing these therapies to reach their potential.[146] The Berkeley Initiative for Optimized Microbiome Editing is developing better CRISPR technologies to edit microbiomes in their natural environment,[146] aiming to identify safe and effective solutions to difficult problems by understanding and controlling the microbial ecosystems.

4. Multi-omics approaches in microbiome research

The human microbiome is a dynamic complex community of fungi, viruses, bacteria, small eukaryotes, and archaea that differ between individuals and locations.[147] The gut microbes help in vitamin synthesis, metabolism, immune system regulation, and resistance to infection.[148,149] Dysbiosis, or microbial imbalance, has been associated with metabolism, inflammation, and nervous system issues.[150]

Multi-omics has given insightful data on host–microbiome interaction, especially through diet. Deehan *et al.*[151] proved that higher fermentable fiber intake elevates propionate-producing bacteria, satiates the subject, and decreases obesity risk. Wang *et al.*[152] recognized lithocholic acid, a secondary bile acid derived from gut microbiota, as powerfully activating the body's heat production, supporting fat metabolism through farnesoid X receptor and Takeda G-protein-coupled receptor 5. However, Zeb *et al.*[78] and Caradonna *et al.*[153] reported that trimethylamine, a gut microbiota-derived metabolite generated from a protein-rich diet, contributes to atherosclerosis and cardiovascular disease. Likewise, Nageswaran[154] recognized imidazole propionate, a microbial metabolite, as a factor that impairs insulin signaling and exacerbates type 2 diabetes. Luo *et al.*[155] associated the production of toxic metabolites 2-butanone and 4-methyl-2-pentanone by microorganisms with non-alcoholic fatty liver disease,

whereas Tan *et al.*[156] delineated *K. pneumoniae*, an ethanol-producing bacterium, as perpetuating liver damage and inflammation.

New functional omics technologies have accelerated microbiome research. Ferrocino *et al.*[157] demonstrated how metagenomics and meta-transcriptomics profiling may reveal dysbiosis and gene expression changes in inflammatory and metabolic diseases. Meta-proteomics has the potential to yield absolute functional information but is limited by sampling depth. Han *et al.*[158] highlighted the function of metabolomics in identifying metabolites derived from the microbiome. They suggested that proton nuclear magnetic resonance spectroscopy can be used to identify common compounds, including short-chain fatty acids (SCFAs). Singer *et al.*[159] reported, however, that although many metabolite features are detected in microbial samples, more than 90% cannot be confidently annotated or assigned to known metabolites, thereby limiting our understanding of microbial functions.

These findings have driven the development of microbiome-directed therapies. Probiotics, prebiotics, and symbiotics have been highlighted by Kadam *et al.*[160] as a central part in restoring the balance of microbes. FMT has shown great success in the treatment of *C. difficile* infection and is additionally being researched into metabolic and inflammatory diseases.[15,161] Recent developments in precision microbiome medicine, such as engineered probiotics and targeted post-biotic treatments, offer potential for the prevention and treatment of diseases.

Scientists are striving to develop tailored treatments through enhanced functional omics approaches and improved interventions from the microbiome. These treatments aim to harness the power of the microbiome in promoting human health and combating disease.

5. Limitations and risks of microbiome-based therapies

Like most new technologies and therapies, microbiota transplants and treatments create challenges for regulators and raise ethical concerns for researchers and practitioners. Nonetheless, scientific research attempts to balance the safety of patients against promoting innovation and medical advancements.

5.1. Variability impact of an individual's microbiome

Our gut microbiome is influenced by factors such as what we eat, where we live, how we live, and even how tidy we are. Ethnicity is one factor, but geography, culture, routine, lifestyle, and exposure to environmental toxins or pathogens all shape the microbiome in different ways.[162] This variability made it complicated to develop universal microbiome-targeted treatments. More recent research suggests that a one-size-fits-all approach to diet therapies for metabolic diseases is likely to fail, as gut microbes play a major role in controlling how individuals metabolize key nutrients.[163] With all such variations, it is difficult to identify reliable microbial biomarkers to predict treatment outcomes. Individuals with the same illness respond differently to the same treatment due to the uniqueness of their microbiome.

5.2. Knowledge gaps in microbiome research

Even though microbiome information is important for treatment, it is still challenging to analyze and understand due to several reasons, including composition, which causes negative bias, sparsity, and collinearity.[164,165] The complexity of microbial communities has made it difficult to explore certain interactions between microbes and their hosts. At present, the effects of probiotics and symbiotics are not fully understood. The human microbiome has a complex mixture of microbes, and we still lack comprehensive data on the specific roles each species plays in human health. Our understanding remains limited regarding how effectively these microbes perform their functions and how they communicate with the host and with each other. Closing this knowledge gap through focused research is essential to unravel the complicated relationships within the microbiome.

5.3. Ethical and regulatory issues in microbiome research

Study of the human microbiome must justify a favorable risk–benefit ratio, indicating potential benefits outweigh disadvantages. However, balancing these benefits and risks is not always straightforward. Therapies involving living organisms, such as FMT, probiotics, and prebiotics, are subject to regulatory oversight regarding their safety and effectiveness.[166] Choosing the appropriate regulatory category (e.g., drug, biological product, or dietary supplement) can be difficult, as it governs the requirements and approval processes. Developers need to position their products within regulatory frameworks based on their function and biological nature.

To quantify safety and efficacy, thorough preclinical and clinical testing is essential, including assessments of adverse effects on the microbiome and host physiology. The manufacture, distribution, and storage of live biotherapeutic products must comply with Good Manufacturing Practice guidelines.[167] Ethical considerations, particularly for FMT, are critical to ensure patient protection and informed consent. Rigorous donor screening and careful recipient selection help minimize the risk of transmitting infections or diseases.[168] Informed consent remains a fundamental

element, involving the participant's voluntary agreement to clinical trial participation with full knowledge of the study's aims, risks, potential benefits, and safety measures. Ultimately, a comprehensive evaluation of safety and risk–benefit ratio is necessary to prevent adverse effects and ensure therapies are safe and effective.

6. Conclusion

The fast-growing area of microbiome-based therapies holds tremendous potential to revolutionize the treatment of various health conditions. From FMT to SMT, and the application of probiotics, prebiotics, and engineered microbial consortia, these approaches aim to restore microbial balance and treat diseases once considered difficult to treat. The research covered in this review emphasizes the various potent means through which manipulation of the gut microbiome can enhance health, influence disease prognosis, and even modulate immune responses, including in cancer therapy.

Treatments such as FMT and Syncoms, along with personalized and precision medicine, are leading the way for microbiome-based therapy. The ability to engineer microbial communities targeted specifically to correct dysbiosis provides new opportunities for treating multifactorial diseases, ranging from metabolic diseases to GI and neuropsychiatric disorders. Synthetic microbial consortia are particularly promising due to their controlled composition, which allows for more predictable and safer restoration of microbial communities compared to conventional FMT. However, challenges remain in fully understanding the complex interactions between the microbiome and the host.

In the future, microbiome-based treatments are poised to unlock some gripping prospects. Advances in genetic engineering, synthetic biology, and computational modeling will enhance the design and performance of NGPs and SMT. In addition, integrating microbiome data into personalized medicine strategies could result in more targeted and effective treatments, optimizing therapeutic benefits while reducing side effects. In summary, microbiome-based therapies are a revolutionary breakthrough in medical science, offering a promising new direction for the management of various diseases. Continued research, development, and deeper understanding of microbial dynamics will be critical to realize the potential of these therapies, enabling their widespread implementation in healthcare, personalized medicine, and disease prevention in the future.

Acknowledgments

The author would like to acknowledge the National University of Medical Sciences, Islamabad, Pakistan, for providing a guidance and supportive research environment.

Funding

None.

Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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