



GUT MICROBIOME AND HUMAN HEALTH: THERAPEUTIC APPLICATIONS

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Abstract:

*The human gut microbiome is an ecological community comprising bacteria, archaea, fungi, viruses, and their genetic elements that interact with the host. This ecosystem contributes to intestinal barrier maintenance, nutrient transformation, immune regulation, colonization resistance, and metabolic signalling. Microbial disturbance, or dysbiosis, is associated with gastrointestinal, metabolic, inflammatory, neurological, and malignant diseases. Consequently, research is transitioning toward microbiome therapeutics to modify microbial functions and improve clinical outcomes. Current approaches include dietary modification, prebiotics, probiotics, synbiotics, postbiotics, fecal microbiota transplantation, live biotherapeutic products, and engineered microorganisms. Microbiota restoration demonstrates strong clinical evidence in recurrent *Clostridioides difficile* infection, whereas applications in inflammatory bowel disease, metabolic disorders, and cancer remain heterogeneous. Advances in synthetic biology and multi-omics now enable defined consortia development. However, translation is limited by inter-individual variation, unclear causality, safety concerns, and regulatory uncertainty. This review examines these biological interactions, therapeutic platforms, evidence gaps, and future precision opportunities.*

Keywords Gut Microbiome, Dysbiosis, Probiotics, Fecal Microbiota Transplantation, Live Biotherapeutic Products, Next-Generation Probiotics.

1. Introduction

The gastrointestinal tract contains one of the most densely populated microbial ecosystems in the human body. The collective microbial community, its genetic repertoire and its metabolic potential are commonly described as the gut microbiome. Rather than functioning as passive passengers, intestinal microorganisms participate in digestion, fermentation, bile-acid transformation, vitamin metabolism, epithelial signalling, immune maturation and resistance to invading pathogens. These activities create a dynamic host-microbe system in which microbial functions can influence physiology well beyond the intestinal lumen [1,2].

Modern microbiome research has substantially changed the way human health is understood. Early investigations frequently focused on identifying which bacterial taxa were increased or decreased in a disease. More recent research emphasizes that taxonomic composition alone may not explain biological activity. Two individuals may contain different bacterial species but produce similar metabolites and maintain similar physiological functions. Conversely, apparently similar microbial communities can behave differently because of strain-level differences, gene expression, substrate availability or host factors [1,2].

One of the most important developments in the field is the movement from association toward causality. Observational studies have linked dysbiosis with many disorders, but disease itself can change diet, intestinal physiology, medication exposure and immune activity, which can then change the microbiome. Therefore, a microbial signature is not automatically a therapeutic target. Intervention studies, mechanistic experiments and randomized clinical trials are needed to determine whether modifying the microbiome changes disease outcomes [3].

The therapeutic potential of the gut microbiome is particularly evident when a disease is strongly influenced by loss of microbial ecological functions. Recurrent *C. difficile* infection is the clearest example. Antibiotic treatment can reduce *C. difficile* but also disrupt protective microbial communities. Restoration of microbial functions can therefore reduce the ecological opportunity for recurrence. This principle has encouraged development of FMT and more standardized microbiota-derived products [4,5].

At the same time, the field is expanding beyond gastrointestinal infections. Microbiome-directed interventions are being studied in inflammatory bowel disease, metabolic syndrome, diabetes, obesity, cancer immunotherapy, neurological disorders and other conditions. However, the strength of evidence differs considerably among diseases. A major objective of modern microbiome research is therefore to determine which intervention, for which patient, at what stage of disease, and through which microbial function is most likely to be beneficial [4].

The concept of microbiome therapeutics also extends beyond adding microorganisms. Dietary substrates can alter microbial metabolism; probiotics can introduce defined strains; postbiotics can deliver microbial components or metabolites; FMT can transfer complex microbial communities; LBPs can deliver controlled microbial preparations; and engineered microorganisms can be designed to perform specific functions. These approaches form a therapeutic continuum from broad ecological manipulation to highly targeted biological engineering [5,6]. This review focuses on recent literature and evaluates the therapeutic applications of gut microbiome modulation. Particular attention is given to mechanisms, clinical evidence, comparative advantages, limitations, safety, standardization and future development. The aim is to provide a critical rather than purely descriptive overview of how gut microbiome science is being translated into therapeutic biotechnology.

2. The gut microbiome: Composition, ecology and functional diversity

2.1 Composition of the gut microbial ecosystem

The human gut contains bacteria from numerous phyla together with archaea, fungi, bacteriophages and other viruses. The relative abundance of individual organisms varies substantially between people and along the gastrointestinal tract. Factors such as oxygen availability, pH, bile acids, nutrient availability, intestinal transit and host secretions create distinct ecological niches. Consequently, the microbiome should be viewed as a spatially organized ecosystem rather than a single uniform community. At the species level, microbial diversity can provide functional redundancy: different organisms may perform related metabolic functions. At the strain level, however,

major functional differences can exist. This is one reason why simply reporting bacterial abundance may not be sufficient to predict therapeutic response. Modern microbiome therapeutics increasingly emphasize strain characterization, genome content, metabolic capacity and safety rather than relying only on genus-level identification [5,7].

Microbial communities are also shaped by ecological interactions. Competition for nutrients, cross-feeding, production of inhibitory compounds and bacteriophage predation can influence community stability. These interactions may contribute to colonization resistance, a protective property in which resident microorganisms limit establishment or expansion of pathogens.

2.2 Microbial functions relevant to human health

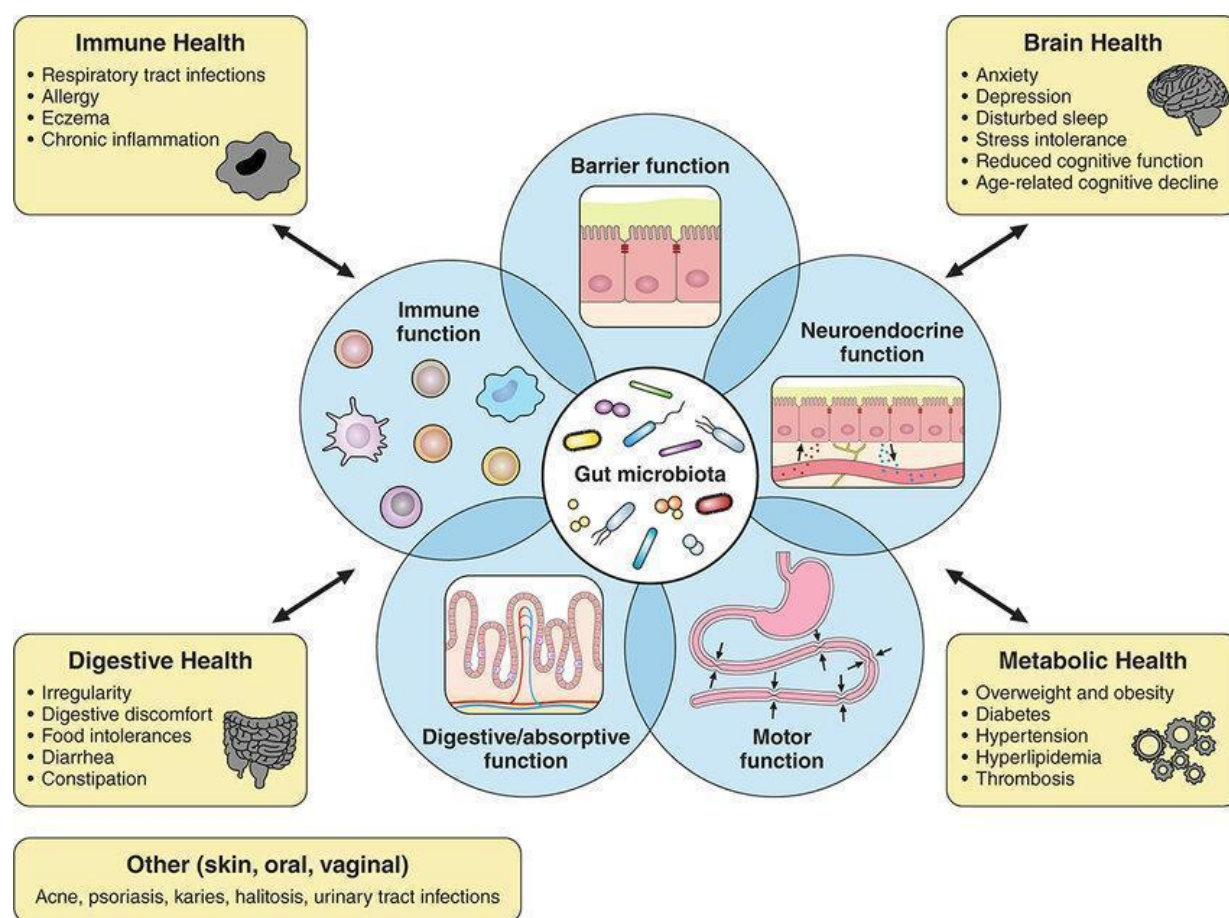


Figure 1: Microbial functions in human health

One major function of the gut microbiome is fermentation of dietary components that escape digestion in the upper gastrointestinal tract. Fermentation can produce short-chain fatty acids such as acetate, propionate and butyrate. These metabolites can influence epithelial energy metabolism, barrier function, immune signalling and systemic metabolic pathways [2].

Microorganisms also modify primary bile acids into secondary bile-acid derivatives. Bile-acid signalling involves host receptors and can influence metabolic regulation and immune function. Microbial metabolism of tryptophan and other dietary compounds generates additional molecules capable of interacting with host receptors and signalling pathways.

Microbial functions therefore connect diet, intestinal ecology and host physiology. This functional perspective explains why therapeutic interventions may work through changes in metabolites even when large shifts in bacterial abundance are not observed.

2.3 Factors shaping the gut microbiome

Factor	Potential influence
Diet	Provides substrates, fibre, fats, proteins and phytochemicals that shape microbial metabolism.
Age	Associated with changes in microbial diversity, immune function and metabolic environment.
Medication	Antibiotics and other drugs can directly or indirectly alter microbial communities.
Lifestyle	Physical activity, sleep, stress and environmental exposure may influence microbial ecology.
Host genetics	Can influence immune responses, mucosal environment and available nutrients.
Disease	Inflammation, altered motility, surgery and dietary changes can reshape the microbiome.
Geography	Food patterns, environment and cultural practices contribute to population differences.

3. Gut Dysbiosis and human disease

3.1 Concept of dysbiosis

Dysbiosis is a broad term used to describe alterations in microbial composition, diversity, abundance or function. It is not a single pathological state. Dysbiosis can involve loss of beneficial functions, expansion of potentially harmful organisms, changes in microbial interactions, altered metabolite production or reduced ecological resilience. In clinical research, dysbiosis is frequently identified through comparisons between patients and healthy controls. However, such comparisons can be misleading if confounding variables are not considered. Hospitalization, antibiotics, diet, disease severity and medication can all affect the microbiome. Consequently, interpretation requires careful study design and longitudinal sampling [3,4].

A more useful therapeutic concept is therefore functional dysbiosis: a state in which specific microbial activities relevant to host health are impaired. This approach allows researchers to ask whether a missing function can be restored, whether an excessive function can be suppressed, or whether a harmful microbial metabolite can be redirected.

3.2 Dysbiosis and gastrointestinal disease

Inflammatory bowel disease is associated with altered microbial composition, reduced ecological stability and changes in microbial metabolites. Whether these changes are causes, consequences or both remains an active research question. Microbiota therapeutics in IBD are therefore being evaluated with attention to disease phenotype, inflammatory status and response heterogeneity [8].

Recurrent *C. difficile* infection provides a different biological situation. Repeated antibiotic exposure can create a profound ecological disturbance, reducing colonization resistance. Restoration of microbial communities or functions has a clearer mechanistic rationale and stronger clinical evidence [5,9].

3.3 Dysbiosis and metabolic disease

Metabolic disorders including obesity, type 2 diabetes and metabolic syndrome have been associated with changes in gut microbial composition and microbial metabolite profiles. Proposed mechanisms include altered energy harvest, intestinal permeability, endotoxin exposure, bile-acid signalling, SCFA production and low-grade inflammation [4, 10].

A 2024 systematic review and meta-analysis of randomized controlled trials reported that microbiota-targeted interventions can improve several glucose and lipid parameters, although heterogeneity remained across studies. Probiotic and synbiotic interventions showed relatively consistent benefits, while FMT results were more mixed [11]. These findings support therapeutic potential but also demonstrate that microbiome intervention effects are not uniform.

3.4 Dysbiosis, immunity and cancer

The gut microbiome can influence systemic immunity through microbial metabolites, antigenic stimulation and regulation of innate and adaptive immune cells. This has become particularly relevant to cancer immunotherapy. Multiple studies indicate that microbiome composition and function can influence response to immune-checkpoint inhibitors, although exact predictive signatures vary between cohorts [12,13].

Antibiotic exposure around immunotherapy has also been associated in several studies with poorer outcomes, supporting the possibility that disruption of microbial ecology can influence treatment response. However, antibiotics may also be clinically necessary, and observational associations do not prove that microbiome manipulation alone will improve cancer survival.

4. Biological mechanisms underlying microbiome therapeutics

4.1 Colonization resistance

Resident microorganisms can inhibit pathogen establishment through nutrient competition, production of antimicrobial compounds modification of environmental conditions and occupation of ecological niches. Loss of these functions can increase susceptibility to opportunistic organisms. Microbiota restoration therefore aims to rebuild ecological barriers rather than simply eliminate a pathogen.

4.2 Short-chain fatty acids

SCFAs are major products of microbial fermentation. Butyrate can serve as an energy source for colonocytes and influence epithelial barrier function. Acetate and propionate participate in metabolic signalling and can influence immune pathways. Therapeutic strategies that increase beneficial SCFA production may therefore affect multiple host processes simultaneously [2, 10].

4.3 Bile-acid transformation

Microorganisms convert primary bile acids into secondary forms that interact with host receptors. Changes in microbial bile-acid metabolism may influence intestinal immunity and metabolic physiology. This pathway is being investigated as a functional target rather than merely a taxonomic marker.

4.4 Immune modulation

Microbial components and metabolites can influence dendritic cells, macrophages, T cells and regulatory immune pathways. A balanced microbiome may promote controlled immune activation and tolerance, whereas dysregulated microbial signals may contribute to chronic inflammation. Probiotics, postbiotics and microbial metabolites are being investigated as tools for modifying this immune interface [8].

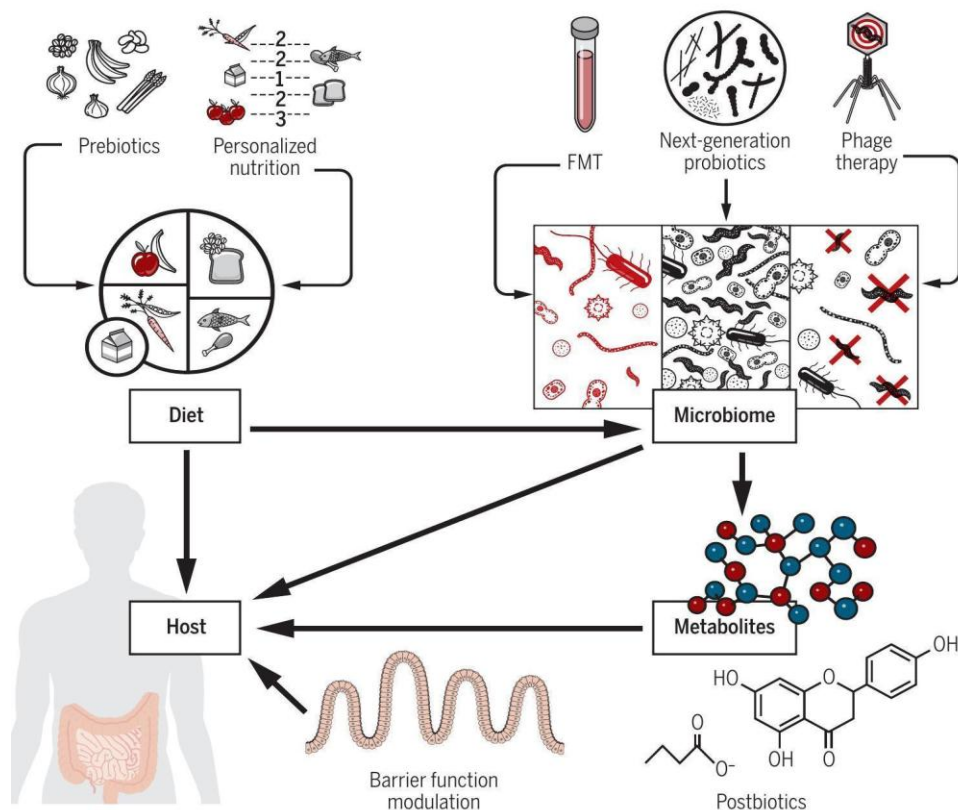
4.5 Gut barrier integrity

The intestinal epithelial barrier limits movement of microbial products into systemic circulation. Microbiome-derived metabolites can support epithelial integrity, while inflammation, altered diet and microbial imbalance may weaken barrier function. Therapeutic interventions that restore barrier-supportive functions may reduce inflammatory signalling and systemic metabolic disturbances.

4.6 Microbial metabolites as therapeutic targets

The therapeutic value of the microbiome may depend more on microbial chemistry than on the identity of individual taxa. Metabolomics can identify functional products associated with treatment response and may help design interventions that increase beneficial molecules or decrease harmful ones. This is one reason multi-omics approaches are becoming central to precision microbiome medicine.

5. Therapeutic strategies for modulating the gut microbiome



5.1 Dietary interventions

Diet is the most direct environmental factor influencing the microbiome. Fibre-rich foods provide substrates for microbial fermentation, whereas dietary patterns high in processed foods can alter substrate availability, bile-acid metabolism and microbial ecology. The therapeutic advantage of dietary intervention is accessibility, but the major limitation is variability in response.

Precision nutrition seeks to overcome this limitation by integrating baseline microbiome composition, metabolic phenotype and dietary response. Rather than prescribing the same dietary pattern to every patient, future approaches may predict which substrates are most likely to promote beneficial microbial functions in a particular individual [2].

5.2 Prebiotics

Prebiotics are selectively utilized substrates that confer a health benefit. They can increase growth or activity of selected microbial groups and promote metabolite production. Their effects depend on substrate chemistry, dose, baseline microbiome and the ecological context. A prebiotic may therefore be effective in one population but less effective in another.

5.3 Probiotics

Probiotics are live microorganisms administered in adequate amounts to confer a health benefit. Commonly studied genera include *Lactobacillus*-related taxa, *Bifidobacterium* and other lactic-acid bacteria. Proposed mechanisms include competitive exclusion of pathogens, production of antimicrobial molecules, modulation of epithelial signalling and immune responses.

Recent literature emphasizes that probiotic effects are strain-specific. A positive result obtained with one strain should not automatically be generalized to another strain of the same species. Differences in dose, viability, formulation and treatment duration further complicate comparisons [14].

Another limitation is colonization. Many administered probiotic strains may pass through the gastrointestinal tract without stable colonization. This does not necessarily eliminate their biological effect, but it highlights why exposure, persistence and functional activity should be measured in clinical studies.

5.4 Synbiotics

Synbiotics combine live microorganisms with substrates that are intended to support microbial activity. The rationale is to create a coordinated intervention in which the introduced organism and its substrate complement each other. However, efficacy depends on the exact combination, making product-level evidence more important than category-level claims.

5.5 Postbiotics

Postbiotics are preparations of inanimate microorganisms and/or their components that confer a health benefit. Depending on the production process, they may contain cell components, metabolites, enzymes, peptides or other microbial-derived molecules. Because they do not require viable cells, postbiotics may offer advantages in stability, storage and formulation [15]. Postbiotics are being investigated for gut barrier support, inflammatory conditions and metabolic disease. In IBD, proposed mechanisms include modulation of inflammatory signalling, improvement of barrier integrity and alteration of microbial-host interactions [16]. However, clinical evidence remains less mature than the evidence base for some FMT/LBP applications.

6. Fecal microbiota transplantation

FMT involves transfer of processed fecal material from a screened donor to a recipient. The treatment aims to restore a complex microbial ecosystem rather than introduce one or two selected strains. This ecological breadth is a major theoretical advantage but also a major challenge because the composition of the transferred community is difficult to standardize. Recurrent *C. difficile* infection remains the strongest clinical indication. Current guidelines and reviews describe microbiota-based therapies as an important option for selected patients after appropriate antibiotic management [5,17]. The mechanism is believed to involve restoration of colonization resistance, microbial metabolism and ecological stability.

FMT has nevertheless produced variable results outside recurrent CDI. In IBD, clinical responses can depend on donor characteristics, preparation, route of administration, dosing frequency and patient phenotype. In metabolic disorders, controlled studies have produced mixed outcomes. These differences indicate that transferring a microbiome is not equivalent to transferring a single therapeutic molecule.

Safety is another central issue. Donor screening is required to reduce transmission of pathogens and potentially harmful microbial traits. Antimicrobial-resistance genes and unexpected microbial effects are additional concerns. Long-term follow-up is therefore important, particularly when FMT is considered for chronic diseases.

An additional issue is the negative result of some controlled trials. For example, a randomized controlled trial reported in 2024 did not show a reduction in CDI recurrence or death at 56 days with the studied FMT capsule strategy compared with placebo [18]. Such results highlight that microbiome therapy is formulation-, population- and protocol-dependent rather than universally effective.

7. Live biotherapeutic products

LBP are biological products containing live microorganisms developed to prevent, treat or cure disease. They differ from conventional probiotics because they are developed as therapeutic products with defined composition, characterization, manufacturing and clinical indications [7].

The development of LBPs represents a major step toward standardization. Instead of transferring an entire donor ecosystem, researchers can select microorganisms with specific functions and manufacture them under controlled conditions. This may improve reproducibility and facilitate regulatory evaluation.

Clinical development has been most advanced for recurrent *C. difficile* infection. Reviews of recent clinical trials indicate that microbiota-derived LBPs can reduce recurrence in appropriately selected patients after antibiotic treatment [9]. These products demonstrate that microbiome science can produce regulated therapeutics rather than remaining limited to nutritional supplements.

However, LBP development is technically demanding. Candidate organisms must be identified, cultured or otherwise produced consistently, genetically and phenotypically characterized, tested for virulence and antimicrobial-resistance features, and formulated to maintain viability. Expert consensus has emphasized rational strain selection, preclinical evaluation and careful preparation for clinical studies [7].

Future LBPs may involve single strains, defined consortia or engineered communities. The design objective is likely to shift from maximum diversity toward a reproducible combination of organisms that delivers a defined therapeutic function.

7.1 FMT versus LBP

Feature	FMT	Live biotherapeutic product
Source	Screened donor material	Defined cultured/processed organisms
Community complexity	High	Low to moderate, depending on product
Standardization	Difficult	Higher potential
Donor dependence	High	Low or controlled
Manufacturing	Variable	Controlled process
Quality control	Donor and preparation based	Product and batch based
Strongest current application	Recurrent <i>C. difficile</i> infection	Recurrent <i>C. difficile</i> infection
Main concern	Transmission and variability	Safety, manufacturing and regulation
Future direction	Defined microbiota transplantation	Targeted and personalized microbial therapy

8. Therapeutic applications

8.1 Recurrent *Clostridioides difficile* Infection

Recurrent CDI is the leading clinical proof of concept for microbiome therapeutics. Standard antibiotics can eliminate *C. difficile* but also disturb commensal organisms. The resulting ecological instability may permit recurrence. Microbiota restoration attempts to rebuild the community functions that suppress *C. difficile* expansion.

Recent reviews of LBPs and microbiota-based products describe meaningful clinical efficacy and support the development of regulated microbiome therapeutics [9,19]. The field has progressed from donor-derived FMT toward more standardized products with defined manufacturing processes.

Despite strong evidence, therapy should not be interpreted as universally interchangeable across products. Different products may contain different organisms, spore fractions or microbial communities and may have different dosing schedules. Comparative effectiveness and long-term outcomes remain important areas of study.

8.2 Inflammatory bowel disease

IBD includes Crohn's disease and ulcerative colitis, both characterized by chronic intestinal inflammation. Microbial alterations have been reported in IBD, including changes in diversity, abundance and metabolite production. However, the microbiome of an IBD patient is influenced by inflammation, medication, diet and disease activity, making causal interpretation complex.

Microbiota therapeutics investigated in IBD include FMT, probiotics, prebiotics, synbiotics and postbiotics. Recent reviews emphasize that the field is moving toward rationally designed interventions and better patient selection rather than assuming that every patient will respond to the same microbial manipulation [8].

Postbiotics may be attractive in IBD because they can deliver microbial-derived functional molecules without requiring viable organisms to colonize the gut. Experimental and early translational studies suggest effects on inflammatory pathways and epithelial barrier function, but larger controlled trials are needed [16].

The major scientific challenge is defining the therapeutic endpoint. Increasing diversity alone may not be sufficient. A successful therapy may need to restore particular metabolic functions, reduce inflammatory metabolites, or rebuild a specific ecological interaction. Functional biomarkers may therefore be more informative than simple taxonomic diversity.

8.3 Obesity and metabolic syndrome

Obesity and metabolic syndrome are associated with chronic low-grade inflammation, insulin resistance and altered energy metabolism. Gut microbes may contribute through SCFA production, bile-acid transformation, intestinal permeability and immune signalling [10].

Microbiota-targeted interventions have produced encouraging but heterogeneous outcomes. A 2024 systematic review and meta-analysis of randomized trials found significant improvements in fasting glucose, HbA1c, HOMA-IR, total cholesterol, LDL cholesterol and triglycerides across microbiota-targeted interventions, with probiotic and synbiotic approaches showing relatively consistent benefits and FMT showing mixed results [11].

These results suggest that microbiome modulation may function as an adjunct to conventional metabolic management. However, microbial therapy should not be considered a replacement for established dietary, pharmacological and lifestyle interventions. The optimal strategy may be to combine microbiome modulation with metabolic phenotyping and precision nutrition.

8.4 Type 2 diabetes

Type 2 diabetes is characterized by hyperglycemia and insulin resistance and is influenced by diet, adiposity, inflammation and host genetics. Microbial metabolites can interact with these pathways. Prebiotics and probiotics have been investigated for effects on glycemic control and inflammatory markers.

Potential mechanisms include increased SCFA production, improved barrier integrity, reduced endotoxin exposure and altered bile-acid signaling. Nevertheless, clinical effects are generally modest and heterogeneous. Future trials should use standardized metabolic endpoints and characterize baseline microbiome function.

8.5 Cardiometabolic disease

Beyond glucose regulation, the microbiome may influence lipid metabolism, blood pressure, vascular inflammation and cardiovascular risk. Microbial metabolites such as trimethylamine and its hepatic product TMAO have been investigated as links between diet, microbial metabolism and cardiovascular physiology.

Therapeutic manipulation is challenging because metabolic pathways involve multiple microbial species and host organs. Precision dietary interventions may be more feasible than broad microbial transplantation in this setting. Microbiome measurements may also become useful as biomarkers for metabolic risk and treatment response.

8.6 Cancer and immunotherapy

The interaction between the gut microbiome and cancer treatment is one of the most rapidly developing areas of microbiome therapeutics. Immune-checkpoint inhibitors such as anti-PD-1 and anti-PD-L1 antibodies depend on effective host immune responses. Microbial signals can influence antigen presentation, T-cell activity and systemic immune tone. Recent reviews summarize evidence linking microbiome composition and microbial metabolites with response to immune-checkpoint inhibitors [12, 13,20]. Some studies have also suggested that FMT or other microbiome-directed interventions may improve response in selected patients with immunotherapy-resistant disease, although the field remains experimental. Antibiotics are particularly relevant because they can reduce microbial diversity and alter metabolic pathways. Several observational studies associate antibiotic exposure with poorer immunotherapy outcomes, but clinical necessity must take priority and antibiotic use cannot simply be avoided in patients who require treatment. The most promising future direction is probably not indiscriminate probiotic supplementation. Instead, researchers are investigating defined microbial consortia, donor selection, diet, microbial metabolites and engineered organisms that may deliver specific immune-modulating functions.

8.7 Colorectal cancer

The gut microbiome may influence colorectal carcinogenesis through microbial metabolites, inflammatory pathways, epithelial interactions and genotoxic compounds. Microbiome-directed approaches are being studied both for prevention and for improving responses to treatment. Reviews have highlighted the potential of microbiome modulation as a biomarker and therapeutic target, while emphasizing that clinical translation requires stronger causal evidence [21].

8.8 Neurological disorders and the gut-brain axis

The gut-brain axis involves bidirectional communication among the gut, microbiota, immune system, endocrine pathways and nervous system. Microbial metabolites can affect host signaling, while stress and neurological states can alter gastrointestinal physiology and microbial ecology.

Interest in microbiome therapeutics has expanded to neurological and psychiatric disorders. Potential interventions include diet, probiotics, prebiotics, postbiotics and FMT. However, clinical evidence is less mature

than for recurrent CDI. Many studies remain small or heterogeneous, and placebo effects can be substantial in symptom-based neurological outcomes.

Future research should prioritize objective biomarkers, longitudinal microbiome profiling and mechanistic endpoints. The aim should be to identify specific microbial functions associated with neural or immune pathways rather than assuming that broad changes in diversity will produce neurological benefit.

8.9 Liver disease and the gut-liver axis

The gut-liver axis connects intestinal microbial products with hepatic metabolism and immune function. Changes in intestinal permeability and microbial metabolites may contribute to metabolic dysfunction-associated steatotic liver disease and other liver disorders. Microbiome-targeted strategies are being explored, but clinical translation requires careful distinction between association and therapeutic causality.

9. Next-generation probiotics

Next-generation probiotics (NGPs) are selected from microorganisms that may have strong links to human health but are not necessarily traditional food-associated probiotic strains. Candidates discussed in recent literature include Akkermania, Faecalibacterium, Bacteroides and selected Clostridia-related organisms [22].

The attraction of NGPs is functional specificity. Instead of using a microorganism simply because it survives in a fermented food, researchers may select an organism because it produces a beneficial metabolite, interacts with the intestinal barrier, modulates immunity or influences a disease-associated pathway. However, NGPs may also carry greater safety uncertainty. Some candidate organisms are less well characterized and may have pathogenic potential under particular conditions. Risk assessment must therefore include genome analysis, antimicrobial-resistance screening, virulence assessment and careful evaluation in vulnerable patients [22,7].

The regulatory boundary between probiotics, NGPs and LBPs is also important. A microorganism used as a food supplement may be regulated differently from a defined medicinal product. Therapeutic claims require stronger evidence than general nutritional claims.

10. Engineered probiotics and synthetic biology

Synthetic biology has created the possibility of designing microorganisms with therapeutic functions that do not naturally occur or are not sufficiently strong in conventional probiotic strains. Engineered probiotics can be programmed to sense molecules, produce therapeutic proteins, consume disease-associated metabolites or respond to environmental signals [6]. Potential applications include intestinal inflammation, metabolic disorders, pathogen detection, cancer and delivery of biological molecules. Engineered strains can theoretically combine sensing, decision-making and therapeutic output in a single living system.

However, the gut is a challenging environment for engineered microorganisms. Nutrient limitation, bile acids, pH changes, immune pressure and competition with resident microorganisms can reduce survival and activity. Genetic stability is another concern because engineered traits must remain functional during passage through the gut. Containment is essential. Researchers have developed biological safeguards such as nutrient dependencies and genetic circuits designed to limit survival outside the intended environment. Nevertheless, horizontal gene transfer, ecological effects and long-term persistence require careful evaluation.

Recent reviews emphasize that engineered microbial therapeutics are moving toward clinical translation but remain an emerging technology [6]. Their success will depend on integrating synthetic biology with microbiology, pharmacology, manufacturing and regulatory science.

11. Microbiome-drug interactions and pharmacology

The relationship between drugs and the microbiome is bidirectional. Drugs can alter microbial communities, while microorganisms can modify drug molecules and influence their absorption, metabolism or activity. This concept has expanded microbiome pharmacology beyond antibiotics [23].

Microbial enzymes can transform pharmaceutical compounds before or after systemic absorption. This may contribute to differences in drug response among patients with different microbiomes. Conversely, chemotherapy, proton-pump inhibitors, metformin and other commonly used medications can alter microbial ecology.

Microbiome therapeutics may therefore eventually be integrated with pharmacological decision-making. Companion diagnostics could identify microbial features associated with response or toxicity, allowing clinicians to select interventions more precisely. This concept remains developing and requires standardized microbiome assays and prospective clinical validation.

12. Critical discussion of recent literature

The recent literature reveals a clear progression from descriptive microbiome studies toward therapeutic manipulation. This progression is scientifically important because therapeutic claims require evidence that changing the microbiome changes clinical outcomes. The strongest evidence currently comes from selected indications, particularly recurrent *C. difficile* infection [5,9]. A second major trend is the movement from complex FMT toward defined LBPs. FMT has the advantage of transferring an entire ecological community, but this complexity also makes it difficult to identify active components. LBPs offer greater control and reproducibility, although the optimal number and identity of strains remain uncertain [4,5,7].

A third trend is the shift from taxonomy to function. A simple statement such as “beneficial bacteria increased” may be less informative than evidence that butyrate production, bile-acid metabolism or colonization resistance was restored. Multi-omics studies can therefore provide mechanistic evidence linking treatment to function.

A fourth trend is personalization. Microbiome interventions can produce highly variable responses because individuals differ in diet, baseline microbial composition, immune status and medication exposure. Future therapies will likely use baseline microbiome and metabolomic data to predict responders and non-responders. The evidence for metabolic disease is promising but heterogeneous. The 2024 meta-analysis of 41 randomized controlled trials supports improvements in several metabolic parameters, yet heterogeneity remains substantial [11]. This suggests that microbiome interventions may have measurable benefits but that effect sizes and clinical relevance need to be evaluated carefully.

In IBD, the evidence is similarly complex. Microbiota therapeutics are biologically attractive because the disease occurs directly in the intestine, but inflammation itself alters the microbial environment. This creates a feedback loop in which the intervention may fail if the host inflammatory environment is not simultaneously controlled [8]. Cancer immunotherapy presents another opportunity but also a major methodological challenge. Microbiome signatures associated with response can vary between populations and cancer types. A taxon that predicts response in one study may not be sufficient in another. Functional signatures and metabolite profiles may prove more reproducible than single bacterial taxa [12,13,20].

An important lesson from recent negative or mixed clinical trials is that microbiome therapy is not a universal intervention. The outcome depends on disease, product, route, dose, patient selection and ecological context. This reinforces the need for well-designed randomized trials with standardized microbiome endpoints.

Another limitation is that many studies focus on short-term changes in microbial composition. A therapeutic intervention may alter the microbiome temporarily without producing durable clinical benefit. Longitudinal studies should therefore measure whether the desired microbial function persists after treatment.

Overall, recent evidence supports the gut microbiome as a therapeutic system but does not justify broad claims that microbiome modulation can treat all chronic diseases. The field is strongest when there is a clear mechanistic pathway, a defined intervention and clinically meaningful endpoints.

13. Comparative analysis of major therapeutic approaches

Approach	Mechanism	Evidence	Safety considerations	Therapeutic potential	Main limitation
Dietary intervention	Changes substrate availability and microbial metabolism	Broad human evidence	Low	High	Response variability
Prebiotics	Selective microbial substrate utilization	Developing	Low	Moderate	Baseline microbiome dependence
Probiotics	Introduces live beneficial strains	Condition/strain specific	Generally low in healthy adults	Moderate	Strain-specific efficacy
Synbiotics	Combines live strains with substrate	Developing	Generally low	Moderate	Product-specific evidence
Postbiotics	Delivers non-viable microbial components/metabolites	Emerging	Potentially favorable	Moderate	Definition and dose standardization
FMT	Transfers complex donor microbiota	Established in selected CDI	Donor-related risk	High in selected CDI	Variability
LBP	Defined live microbial therapeutic	Advanced in recurrent CDI	Requires rigorous screening	High in selected indications	Manufacturing/regulatory
NGP	Functionally selected organisms	Early clinical development	Requires strain-level safety	Potentially high	Safety and colonization
Engineered microbes	Designed therapeutic functions	Emerging/preclinical-to-early clinical	Requires containment	Potentially high	Genetic stability/regulation

14. Challenges in clinical translation**14.1 Inter-individual variability**

The microbiome differs among individuals because of diet, age, genetics, geography, medication, lifestyle and disease. This creates a major source of variability in treatment response. Standardized interventions may therefore need to be accompanied by patient stratification.

14.2 Standardization of microbiome measurements

Different laboratories can obtain different results because of differences in sample collection, DNA extraction, sequencing platforms, reference databases and bioinformatic pipelines. Clinical translation requires validated analytical methods and consistent reporting.

14.3 Safety and antimicrobial resistance

Microbiome therapeutics can potentially transfer microorganisms, resistance genes or other biological traits. Safety assessment must include pathogen screening, genome analysis, antimicrobial-resistance profiling and monitoring for unexpected adverse effects.

14.4 Manufacturing

Live microbial products are biologically complex. Manufacturing must maintain identity, purity, viability and potency while controlling contamination and batch-to-batch variation. Defined consortia can be especially challenging because each organism may grow differently and interact during production.

14.5 Regulatory complexity

Microbiome products can occupy different regulatory categories depending on composition and intended use. Clear definitions are important because a food supplement, probiotic product and medicinal LBP cannot be evaluated using identical standards.

14.6 Long-term effects

The microbiome is an ecological system, so introducing or removing microorganisms may have effects beyond the immediate treatment period. Long-term studies should evaluate persistence, ecological shifts, antimicrobial resistance, immune consequences and delayed adverse events.

14.7 Clinical trial design

Clinical trials should use standardized endpoints and include microbiome measurements before, during and after treatment. Randomization, adequate sample size, appropriate control groups and clinically meaningful outcomes are essential. Trials should also report antibiotic exposure, diet and concomitant medications because these factors can strongly influence microbiome outcomes.

15. Future perspectives**15.1 Precision microbiome medicine**

Precision microbiome medicine aims to match a specific microbial intervention to a specific patient phenotype. A future clinical workflow may include baseline stool metagenomics, metabolomics, host inflammatory markers and dietary assessment, followed by selection of a targeted microbial intervention.

15.2 Multi-omics integration

Metagenomics identifies genetic potential, transcriptomics indicates active pathways, proteomics describes proteins and metabolomics measures functional products. Integrating these layers may reveal mechanisms that cannot be identified by taxonomic sequencing alone.

15.3 Artificial intelligence and predictive models

Machine-learning models may identify combinations of microbial, dietary and clinical variables that predict response. However, models must be externally validated and interpreted cautiously because microbiome datasets can be highly population-specific.

15.4 Defined microbial consortia

Defined consortia may provide a compromise between FMT and single-strain therapy. A small number of selected organisms can be combined to reproduce a desired ecological function while allowing better manufacturing and quality control.

15.5 Engineered microbial therapeutics

Synthetic biology can add sensing, metabolic and therapeutic functions to microorganisms. The long-term goal is a living therapeutic capable of detecting a disease signal and producing a controlled response. Biosafety mechanisms will be essential for clinical implementation [6].

15.6 Precision nutrition

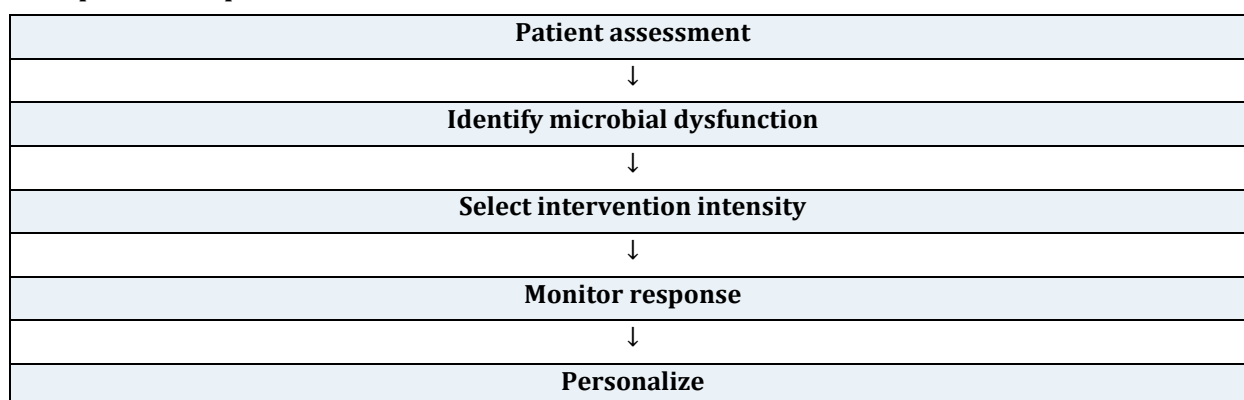
Dietary interventions can be personalized according to microbial metabolic capacity. Instead of assuming that a fibre source benefits everyone equally, future approaches may identify the substrate most likely to promote a desired microbial metabolite profile in an individual [2].

15.7 Microbiome as a companion diagnostic

Microbial signatures may eventually help predict treatment response, adverse effects or disease recurrence. Such applications require validated biomarkers and prospective clinical studies before routine clinical use.

16. Evidence strength across therapeutic applications

Application	Current evidence	Major approaches	Critical limitation
Recurrent C. difficile infection	High relative evidence	FMT/LBP	Repeated clinical evidence; product-specific differences remain
IBD	Moderate/emerging	FMT, postbiotics, probiotics	Heterogeneous response; patient selection important
Obesity/metabolic syndrome	Moderate/emerging	Diet, probiotics, synbiotics	Meta-analyses show modest metabolic improvements
Type 2 diabetes	Moderate/emerging	Pro/prebiotics	Potential glycemic benefit; strain and protocol heterogeneity
Cancer immunotherapy	Emerging	Diet, FMT, defined microbes	Strong mechanistic rationale; clinical standardization needed
Neurological disorders	Early/emerging	Diet, probiotics, FMT	Evidence limited by small and heterogeneous studies
Engineered microbial therapeutics	Early	Engineered probiotics	High theoretical potential; safety and regulation remain barriers

17. Proposed therapeutic decision framework**18. Safety, ethical and regulatory considerations**

Microbiome therapeutics challenge conventional ideas about medicines because the active agent may be a community rather than a single molecule. This creates unique ethical and regulatory questions. Donor-derived products require informed consent, screening and traceability. Engineered microorganisms require additional safeguards. Patient selection is particularly important. Immunocompromised or medically complex patients may face higher risks from live microorganisms. Risk-benefit assessment should therefore be indication-specific rather than based on assumptions about general probiotic safety. Regulatory agencies also need standardized definitions for probiotics, postbiotics, FMT-derived products, LBPs and engineered microorganisms. Product identity, potency, purity, stability and biological activity should be measurable and reproducible.

Ethically, microbiome interventions should be evaluated with the same rigor as other medical treatments. Claims should be proportional to evidence, and patients should be informed when an intervention remains experimental.

19. Limitations of current evidence

Despite rapid progress, the microbiome literature has several limitations. First, studies use different sequencing methods, sample types, definitions of dysbiosis and statistical approaches. This makes direct comparison difficult. Second, many studies have small sample sizes and short follow-up. Chronic diseases require long-term assessment because microbial changes may be temporary. Third, diet and medication are sometimes incompletely recorded even though they can substantially influence microbiome composition. Future trials should treat these variables as core clinical data. Fourth, publication bias may favour positive results. Negative microbiome interventions are important because they help identify where the therapeutic hypothesis is insufficient. Finally, taxonomic associations do not necessarily identify therapeutic targets. Functional validation and mechanistic studies are essential for moving from correlation to intervention.

20. Conclusion

The gut microbiome has emerged as a biologically active component of human physiology and a promising target for therapeutic intervention. Its influence on intestinal barrier function, immunity, metabolism, microbial competition and systemic signalling provides multiple opportunities for disease prevention and treatment.

Therapeutic strategies now extend from dietary manipulation and prebiotics to probiotics, synbiotics, postbiotics, FMT, LBPs, next-generation probiotics and engineered microbial therapeutics. The most clinically established application is recurrent *C. difficile* infection, where microbiota restoration has progressed into standardized therapeutic products. In other conditions, particularly IBD, metabolic disease, cancer and neurological disorders, the evidence is promising but heterogeneous.

The next phase of microbiome research should focus on function, causality and personalization. Rather than asking only which bacteria are present, researchers should determine which microbial pathways are altered, whether those pathways contribute to disease, and whether targeted correction improves clinical outcomes.

Integration of multi-omics, synthetic biology, computational modelling and precision nutrition may enable microbiome-based therapies to become more reproducible and patient-specific. Defined microbial consortia and engineered organisms could provide therapeutic functions that are difficult to achieve using conventional probiotics or FMT. Ultimately, the clinical success of microbiome therapeutics will depend on rigorous randomized trials, standardized manufacturing, validated biomarkers, robust safety monitoring and transparent regulation. With these developments, the gut microbiome has the potential to become an important platform for next-generation biotechnology and precision medicine.

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