©IDOSR PUBLICATIONS

ISSN: 2550-7931

International Digital Organization for Scientific Research IDOSRJAS1030000
IDOSR JOURNAL OF APPLIED SCIENCES 10(3):93-103, 2025.
https://doi.org/10.59298/IDOSRJAS/2025/103.93103

Microbiome Engineering: A Narrative Review

Ahabwe Edwina

Email: edwina.ahabwe@studwc.kiu.ac.ug
Department: Industrial pharmacy and pharmacognosy Kampala International University Uganda

ABSTRACT

The human microbiome is a dynamic ecosystem essential for host physiology, metabolism, and immunity. Advances in microbiome engineering have opened new opportunities to prevent and treat disease by modulating microbial communities. Two principal approaches are synbiotics and fecal microbiota transplantation (FMT). Synbiotics, which combine probiotics and prebiotics, promote the growth and activity of beneficial microorganisms, thereby supporting intestinal barrier integrity, immune regulation, and metabolic balance. FMT, a practice with roots in traditional Chinese medicine and now a validated therapy for recurrent *Clostridium difficile* infection, aims to restore microbiome diversity and function through transplantation of donor stool. Beyond *C. difficile*, both strategies show promise in managing metabolic disorders, autoimmune diseases, and even neurological conditions, though long-term safety and mechanisms remain incompletely understood. Challenges include interindividual variability, limited mechanistic insights, and regulatory and ethical barriers, particularly around donor screening, informed consent, and commercialization of microbiome-based therapies. Innovations such as targeted synbiotic formulations and metabiotic approaches offer potential for precision interventions. Future research integrating systems biology, clinical trials, and regulatory frameworks will be crucial to harness microbiome engineering for personalized medicine and broader public health. Overall, synbiotics and FMT represent transformative tools at the interface of microbiology, immunology, and clinical practice, with potential to redefine therapeutic strategies for diverse human diseases.

Keywords: Microbiome engineering; Synbiotics; Fecal microbiota transplantation; Gut health; and Precision medicine.

INTRODUCTION

The human microbiome shapes multiple physiological processes, and engineering these trillions of microbes and the molecules they produce can shape immunity, prevent and treat disease, and even target pathogens. Two widely used microbiome engineering approaches are highlighted: synbiotics and fecal microbiota transplantation. Synbiotics combine probiotics and prebiotics to synergistically promote the growth and activity of beneficial microorganisms. This approach can modulate the gut microbiome through several microbiota-dependent mechanisms that support barrier integrity, improve metabolism, and promote immune function. Fecal microbiota transplantation has a long history, with its use described in Chinese medicine during the Dong-jin era (AD 318-589). Its use in Western medicine has been demonstrated in Clostridium difficile infection and shows potential to address metabolic disorders, autoimmune conditions, and neurological diseases; however, unanswered questions about long-term safety and mechanisms persist.

Understanding the Human Microbiome

The human microbiome constitutes a dynamic ecosystem consisting of trillions of microorganisms influencing host physiology, metabolism, nutrition, and immune function. The human gut microbiome is the most complex and functionally diverse in nature, with well over 1,700 different species-level phylotypes identified, with more than half still unknown. Its composition remains largely stable during adulthood but changes markedly during infancy, childhood, and old age. Microbiome communities are shaped by diet, age, host genetics, and life history. The term microbiome refers to the collection of microorganisms inhabiting the human body and is associated with various health and disease states. Techniques to precisely control microbiome composition or activity could deepen understanding of host-microbe interactions and open new avenues for disease intervention and diagnosis [1].

Composition of the Microbiome

The human body is colonized by trillions of microorganisms that constitute the microbiome, which encompasses a broad diversity of bacteria, viruses, and fungi. These microbial populations primarily inhabit body cavities and various epithelia, including the gastrointestinal, respiratory, and urogenital tracts. Research to date has identified over 1,000 unique species at the population level and more than 200 species per individual [2]. Individual-specific variations occur, as do regional variations within an individual, dictated by tissue or organ of origin [3]. Environmental factors, mode of delivery, age, diet, and drug administration influence the diversity and temporal colonization of the microbiome. Microbial cells comprise the majority of the biomass within the normal gastrointestinal tract. The functions attributed to the gastrointestinal tract are mediated by a combined host-microbe superorganism. This system aids the host in extracting energy and nutrients from otherwise indigestible polysaccharides, modifying and detoxifying xenobiotics. Microbes also influence the development of several physiological systems, such as the gut-associated lymphoid tissue and the intestinal epithelium; they affect the metabolism of enterocytes and can directly inhibit competing pathogens through the production of bacteriocins and by competing with pathogens for the available niche space. Microbial metabolism contributes to the fermentation of many dietary polysaccharides into essential metabolites, including short-chain fatty acids such as butyrate, acetate, and propionate [2, 3].

Functions of the Microbiome

The microbiome resides in the human gut, airway, skin, oral cavity, and genitourinary tract. Once defined as an ecological community of commensal, symbiotic, and pathogenic microorganisms, the microbiome should now refer to not only microorganisms but also the relevant spectra of materials upon which the microbes act or interact [1]. The collection of genomes and genes of the microbiota, host environmental conditions, and diet all shape human microbial composition and function. The microbiome plays an important role in defending against environmental aggression, metabolizing carbohydrates, and educating the innate and adaptive immune system. The microbiome affects fat storage and biliary cirrhosis functions and influences a variety of diseases such as diabetes, obesity, and atherosclerosis. Conversely, various factors can influence the stability of microbiota, and consequently affect homeostasis. Such factors include age, the environment, processed food, and the medical use of antibiotics [1].

Factors Influencing Microbiome Composition

Microbiomes populate every environment on earth, influencing diverse phenomena, from human health to soil fertility. Yet, our ability to modulate microbiome composition or activity remains limited. Microbiome engineering aims to design and build microbial communities that address fundamental questions in host-microbe interactions, synthetic biology, and microbial consortia, with applications in human health, agriculture, and basic science [2]. Communities of microbes living in and on the human body, the human microbiome, provide critical functions essential for proper mammalian growth and development. The microbiome begins to assemble at birth and is predominantly fixed by three years of age; it remains generally constant throughout adulthood, but fluctuates substantially at the extremes of life, following infections, or as a result of antibiotic treatment. Several factors have been identified that contribute to the overall variation in the composition of the microbiota. Among them are: diet, antibiotics, host genetics, hygiene, stress, environment, and smoking [4]. Microbiome phenotypes and responses to perturbations vary across age, geography, and ethnicity, making universal microbiome engineering approaches difficult to establish without further fundamental understanding. Modulating gut communities via probiotics, prebiotics, and other factors alters composition and/or function that modulates disease risk. Schaubeck et al. detail a broad spectrum of conditions tied to dysbiotic microbial communities, and discuss how gut communities might be rationally manipulated for health gains [5].

Synbiotics: Definition and Mechanisms

Synbiotics are a class of compounds aimed at adjusting and preserving microbiome activity by stimulating intrinsic microbes, thereby improving host health and resilience through dietary inputs [1]. Observations that combined administration of probiotics and prebiotic fibers yields greater benefits than isolated applications gave rise to the conception of synbiotics [6]. The original definition characterizes synbiotics as mixtures of live organisms and substrates selectively utilized by host microorganisms, intending to confer health advantages on the host. Despite widespread acceptance, practical challenges persist in fulfilling all aspects of this definition and comprehending the interactions among the components involved [2]. Introducing the term "synergistic synbiotics" to encompass combinations where microbial constituents benefit from the co-administered substrate, the scope of synbiotics is broadened to include mixtures that support either the exogenous or endogenous microorganisms. Analyses employing a set of assays quantifying substrate metabolism among human fecal microbes afford a metabiotic perspective to inform the design of targeted synbiotic formulations tailored to specific metabotypes or functional aims. Synbiotic interactions center on the capacity of gut microbiota to metabolize given substrates within the whole system, extending tendencies observed in prebiotic species utilization. Accordingly, a survey of relevant substances comprises those promoting probiotic growth, activity, and engraftment; precursors for active ingredient generation; metabolites modulating physiological functions; and compounds detoxified by probiotics from toxins or allergens. Establishing a functionally active and compositionally diverse microbiota alongside a well-balanced diet constitutes the foundation for health maintenance and disease prevention that can be further optimized with deliberate, targeted synbiotic interventions [2]. Although classified as food or dietary components, formulations operating through these mechanisms may exhibit pharmacological activity, highlighting the proximity of related concepts and blurring conventional distinctions between food and medicine. Applying the expanded framework within precision nutrition and individual therapy contexts promises more predictable microbiome-targeted effects and facilitates the generation of clinically reproducible outcomes. By diminishing interindividual variability, this approach represents a crucial advance for microbiome interventions under widespread evaluation. Continued development and comparative evaluation of novel synbiotics against traditional prebiotic and probiotic superiorities remain necessary to substantiate these benefits [1, 6, 2].

Components of Synbiotics

Synbiotics consist of live microorganisms and substrates that beneficially affect the host by selectively stimulating the growth or activity of one or a limited number of health-promoting bacteria in the microbiota [6]. Probiotic-based components include strains of beneficial bacteria accompanied by functional compounds such as carbohydrates, proteins, minerals, and antioxidants that protect the microbial cells during storage and gastrointestinal transit [7]. Encapsulating agents, often hydrocolloid biopolymers, are used to ensure sufficient release and survival of these probiotic cells at the target site in the gut. A substrate is considered prebiotic if it is selectively utilized by host microorganisms to confer a health benefit to the host. Common prebiotics are mainly carbohydrate compounds, such as inulin and fructooligosaccharides (FOS), but also include a variety of oligosaccharides, disaccharides, monosaccharides, and sugar alcohols. Plant-based materials, such as certain seeds and roots, have demonstrated potential prebiotic effects, along with polyphenols, which are proposed to modulate the gut microbiota composition. Synbiotics may therefore act independently and/or synergistically, whereby the substrate is selectively utilized by the co-administered live microbes to achieve the intended health benefit [6].

Mechanisms of Action

The mechanisms of action in microbiome engineering involve modulation of the commensal gut microbiome through administration of live microorganisms, substrates, or donor fecal material. Microbiome engineering interrogates the complex webs of microbe–microbe, microbe–host, and microbe–environment interactions, providing a means to characterise microbial functions and therapeutic mechanisms within the host [8]. Synbiotics are mixtures of live microorganisms and substrates that selectively promote the growth or survival of specific microbial genera or species already present in the host. One mechanism involves the production of inhibitory substances such as organic acids or bacteriocins. Another is competition with competing organisms for adhesion sites or intestinal receptors. A third mechanism is the enhancement of intestinal barrier integrity through increased mucin production, encouragement of epithelial-cell repair, and stimulation of tight-junction proteins. Finally, synbiotics modulate the immune system locally in the gastrointestinal tract by influencing production of secretory IgA, cytokines, and inflammation-regulating receptors [8]. Microbiome engineering through fecal microbiota transplantation (FMT) uses a suspension of microbiota from a healthy donor to restore diversity and alter the metabolic functions of the recipient's colonic microbiota. The exact mechanisms of action are uncertain, though FMT reliably restores diversity and metabolic functions. Potential modes of action include introduction of competing microbes that displace pathogens, reestablishment of the natural balance of commensal microbial communities, and restoration of colonisation resistance. Anecdotal and investigational reports have resolved disease states linked to cryptosporidiosis and inflammatory bowel disease, reflecting the broad immunologic and metabolic impact of the technique [28].

Applications of Synbiotics

A healthy gut microbiome influences metabolism, disease development, and individual response to medical interventions [8]. Synbiotics are a strategic methodology to promote healthy gut microbiota, and are defined as "a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host" [6]. Synbiotics therefore consist of a selective substrate, such as fibres or oligosaccharides, to stimulate the growth of a specific microorganism and of a probiotic with beneficial effects, such as lactic acid bacteria. Synbiotics are beneficial in preventing infections from pathogens like Helicobacter pylori, reducing the concentration of undesirable compounds, supporting immunity, preventing atopy in infants, increasing mineral absorption, and reducing the risk of several cancers. They are also beneficial in supporting metabolic diseases such as diabetes, hyperlipidemia, and hepatic cirrhosis, and may assist recovery after bariatric surgery. Applications, therefore, highlight the centrality of synbiotics in modulating gut health and their potential as therapeutic adjuncts in metabolic and immune-related conditions [6].

Gut Health and Disease Prevention

When researchers examine the human microbiome's role in gastrointestinal health beyond the oral cavity, they trace a path from small-molecule metabolites such as nitric oxide, hydrogen sulfide, and short-chain fatty acids (SCFA) through prebiotics/probiotics/synbiotics to fecal microbiota transplantation (FMT) [9]. The scientific community is forging ahead with innovative approaches to rebalance the microbiome and restore homeostasis, including FMT, probiotics, prebiotics, and synbiotics [10]. A central mission in microbiome engineering is to establish clinical protocols that employ these tools to prevent or cure chronic gastrointestinal diseases such as inflammatory bowel disease, irritable bowel syndrome, and colorectal cancer [9].

Impact on Metabolic Disorders

The human gut microbiota comprises a vast and diverse array of microorganisms that colonize the gastrointestinal tract shortly after birth and continue to maintain a symbiotic relationship with the host throughout life. The composition of the microbiota varies in space and time, remaining relatively stable within an individual over time and in close relatives, yet profoundly influenced by a wide range of intrinsic and extrinsic factors such as host genetics, diet, and lifestyle [9]. A growing body of evidence has implicated gut microorganisms in several metabolic pathways that affect local and systemic homeostasis as well as the development of various pathologic conditions. Due to the direct connection between the gut microbiota and health status, microbiota-engineering strategies such as synbiotic development and faecal microbiota transplantation have been employed to restore microbial balance and offer potential therapeutic interventions, especially for metabolic disorders [10]. A comprehensive understanding of the mechanisms governing the physiological effects of the gut microbiota remains indispensable to fully exploit the potential of microbiome engineering.

Role in Immune Modulation

The commensal microbiome plays a fundamental role in immune modulation [11]. The trillions of microbes colonizing the host modulate immune cells through the expression of components and effector molecules, influencing local and systemic immunity. Co-evolution of the microbiome with its host has established a complex mutualism. But external influences, such as antibiotics, can cause microbial imbalance or dysbiosis, which is linked to many diseases including diabetes, cancer, and neurological disorders [12]. Altered microbiomes have been characterized in these disease states, and many studies have focused on restoring homeostasis as a therapeutic intervention. Intestinal bacteria, for example, are potent regulators of the immune system, promoting processes such as immune education and resistance to pathogens. Several species have been described, including segmented filamentous bacteria that drive T helper 17 (TH17) cell differentiation to promote intestinal barrier integrity; Bacteroides fragilis, which induces T helper 1 (TH1) cells and maintains a TH1/TH2 balance through its capsular polysaccharide A; and many species within the Firmicutes phylum particularly Clostridia that promote regulatory T (Treg) cell development through the production of short-chain fatty acids. These microbial interactions are central to the idea that the microbiome can be conceptualized as an organ system that influences host physiology across numerous axes. Microbial dysbiosis is therefore a form of organ failure, and microbiome transplants represent organ replacements. Microbiome transplantation has indeed demonstrated therapeutic benefits in a wide variety of inflammatory and infectious diseases [13]. Hundreds of studies examining interactions between microbiome transplants and the immune system further indicate that the crosstalk between the two is a principal determinant of transplant success.

Fecal Microbiota Transplantation (FMT)

Fecal microbiota transplantation (FMT) is the procedure of transferring healthy donor stool into the gastrointestinal tract of another person to treat or prevent disease. The first report describing this approach was published in 1958 by Eiseman et al., who successfully rescued four patients with pseudomembranous colitis after failing other treatments. Currently, interest in FMT has been renewed because of its outstanding cure rate against recurrent Clostridium difficile infection (CDI) and its potential in other digestive and non-digestive diseases. The precise mechanism by which FMT cures refractory CDI remains unknown; however, effective fecal transplantation usually coincides with enhanced fecal microbiota diversity in recipients, reestablishing bile acid and short-chain fatty acid (SCFA) metabolisms and restoring gut barrier function [1]. Research indicates that FMT efficacy goes beyond CDI resolution by modulating metabolic, immunologic, and neuroendocrine pathways. Although clinical studies report FMT as a safe procedure, several ethical considerations demand attention. A cornerstone of FMT practice must therefore focus on the patient's understanding of the technique and reverse engraftment. The human gut microbiota comprises trillions of microorganisms, mainly bacteria in the colon, originating from the colonization of the intestine at birth and evolving throughout life. Its composition and function depend on numerous factors, including genetic profile, neonatal determinants like delivery and breastfeeding, diet, exposure to xenobiotics, and the interaction with other microbiotas cohabiting in other body niches. Its main role is to protect the host against different pathogens through the production of antimicrobial substances; engagement with the immune system, promoting immunoglobulin production; supporting metabolism by fermenting indigestible foods and transforming some xenobiotics; and contributing to the development and function of specific tissues and organs. Given that synbiotics act on the modulation of microbiota composition and activity, findings on synbiotic-induced gut microbiota alterations in health and disease are discussed here [1].

History and Development of FMT

Interest in FMT can be traced back to the fourth century in China, when the physician Ge Hong used it to treat gastrointestinal disorders. Full clinical use can be traced back to 1958, when a group of physicians performed it to treat recurring pseudomembranous enterocolitis. The modern era began with the use of FMT in patients with Clostridium difficile infection (CDI), with the first randomized controlled trial following a decade later. Since then, in-depth study of the human intestine and its microbial role has opened new possibilities for altering the microbiome of patients with other disorders [1, 3]. The main use of FMT is in C. difficile colitis, with methods of administration varying among nasal tubes, gastroscopy, colonoscopy, and enema. For other diseases, such as inflammatory bowel disease and metabolic syndrome, patients with short-bowel syndrome have received intestinal microbiota not from feces but from a healthy donor's ileostomy, based on the assumption that the stool of a healthy subject acts as a fecal surrogate for gut colonization or realimentation. Patient follow-up ranges from several weeks for CDI to several months for colitis. FMT effectiveness in CDI has been shown to reach approximately 90%, remaining stable in the mid-80% range at one, four, and six months, both in first and recurrent episodes. Although it is a generally safe technique, certain precautions are necessary to avoid possible adverse effects; for example, in patients with colitis, it can cause flare-ups, and in immunosuppressed patients, it must be administered carefully. To prevent transmission of infectious diseases, donor screening is mandatory. However, perhaps the most important point related to FMT is providing thoroughly informed consent, as the procedure is still considered experimental by most hospitals and healthcare authorities [15].

Indications for FMT

The most prominent FMT indication is recurrent Clostridium difficile infection (CDI), defined as multiple episodes occurring within 8 weeks [14]. FMT yields a cure rate as high as 90%, far superior to conventional vancomycin treatment [15].In 19 studies comprising 305 patients, FMT led to CDI cure rates of 92%. Treatment failure was 8%, but a single repeat FMT cured 70% of these cases. A randomized controlled trial found a 27% recurrence risk for each vancomycin alone treatment, versus 3.8% recurrence among once-treated FMT patients and an identical 3.8% for alternate vancomycin-FMT treatments. Consequently, guidelines endorse FMT at the second recurrence of CDI, following the initial vancomycin treatment as standard protocol [16]. Currently, Th1-T17 immune responses and systemic inflammation in recurrent CDI owe to the dysbiotic, low-diversity, C. difficile-dominated gut ecosystem. FMT restores the diverse community and microbiota-accessible carbohydrates, leading to secondary-bile acid production that inhibits C. difficile vegetative growth. Successful FMT is therefore linked to the return of a healthy, metabolically functional microbiome [14, 15, 16].

Procedure and Safety Considerations

FMT has a long history, spanning millennia. The first report of FMT was in the 4th century in China, where the practice subsequently gained widespread recognition in the 16th century. Physicians used a fecal suspension to treat food poisoning, severe diarrhea and other illnesses [8]. The underlying mechanism of FMT remains unknown. However, theory dictates that a diseased gut microbiome can be restored to its healthy state through the infusion of a healthy microbiota. Once successful engraftment of healthy microbiota is achieved, the single abnormal bacterial strain that caused the disorder is inhibited and healthy bacteria proliferate once more. This theory was demonstrated in 1958 as Bacteroides species were shown to restore the normal balance of intestinal bacteria, in turn suppressing the growth of Clostridium difficile in hamsters. Clinical application currently utilizes FMT for the treatment of C. difficile infection, a health complication that occurs after extensive use of antibiotics. FMT is shown to be highly effective for the treatment of recurrent cases of this infection [8].

Mechanisms of Fecal Microbiota Transplantation

FMT confers colonization resistance by maintaining a diverse gut microbiota through complex mechanisms, including nutritional competition, antimicrobial production, and immune modulation. These mechanisms facilitate a swift and complete normalization of fecal physiology compared with antibiotics alone [17]. The factors involved in the restoration of microbiome diversity include niche exclusion, prevention of the establishment of pathobiont species, and modulation of the host's immune responses. Most likely, both the microbiota and the immunological processes converge to provide host protection [18]. FMT also significantly increases the intestinal production of short-chain fatty acids, which can suppress the expansion of pathogenic bacteria [19].

Restoration of Microbiome Diversity

Microbial ecosystems provide essential biogeochemical and ecological functions that sustain life over a wide range of scales, from global-level climate change to ecosystem-level soil fertility and organism-level health. Biotic or abiotic perturbations can degrade ecosystems by disrupting these functions and their underlying microbial communities. Microbiome restoration aims to bring back these functions by improving community structure and is an emerging approach for engineering microbial ecosystems. For example, fecal-microbiota transplantation, applied for more than 1,700 years, has been used in clinical settings to treat diseases and conditions related to the gut microbiome. However, limited knowledge of the mechanisms has hindered its broader application. Microbiome-engineering technologies and their corresponding substrates (e.g., probiotics and prebiotics) have shown promise in fostering a balanced microbial ecosystem through complimentary, tuned perturbations, and ongoing developments are expected to improve applications for sustainable ecosystems, including novel therapies for microbiome-related diseases and degraded environments [20]. The investigation of microbiota and microbiome dynamics during microbiota-transplantation–based restoration of degraded ecosystems has provided insights into how transplanted species coevolve with indigenous species and how the structure and function of microbial communities are restored. Transplantation of microbiota into ecosystems such as the gut, soil, and water has enabled limited restoration of ecosystem structure and function. Nevertheless, the mechanisms by which transplanted microbiota enhances ecosystem succession and stability remain unclear. These mechanisms must be elucidated through simplified-model ecosystems, microbial-ecology principles, and molecular-technology approaches to guide design principles and advance microbiome-engineering technologies. A thorough understanding of the ecological mechanisms underpinning restoration across diverse habitats will reveal novel strategies for restoring degraded systems, including the human gut and contaminated environments [20].

Reestablishment of Metabolic Functions

The microbiome contributes to the host metabolome through the actions of primary and secondary metabolites that fulfill various biological functions, such as nitrogen fixation, antimicrobials, and carotenoid production. Alterations in microbiome composition can significantly affect microbial metabolic activities and, consequently, a variety of functional parameters [20]. In addition to the immune system and bile acid metabolism, the reestablishment of the microbiome's metabolic functions is a prerequisite for successfully treating Clostridioides difficile infection (CDI). After a single fecal microbiota transplantation (FMT), patients show restored microbial transcriptional activity of carbohydrate- and amino acid-utilization pathways and upregulation of key genes in both oxidative and anaerobic carbohydrate metabolism. Alongside the upregulation of these pathways, higher levels of fermentation end products, including short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate, as well as secondary bile acids like lithocholate and deoxycholate, are observed [21].

Clinical Outcomes of FMT

Fecal microbiota transplantation (FMT) has emerged as a highly successful therapy for microbiome-associated diseases [22], noting its extensive history of use and ongoing investigation through nearly 400 randomized clinical trials involving almost 100 distinct conditions in the past five years. The initial indication for therapeutic FMT was pseudomembranous colitis caused by Clostridium difficile infection (CDI), with the approach subsequently adopted as the standard of care for recurrent CDI following demonstration of its clinical efficacy.

Evidence from randomized clinical trials and meta-analyses of controlled clinical studies of FMT has been compiled in an umbrella review to consolidate information, evaluate the strength of identified associations, and assess the methodological quality and potential biases of the original investigations in order to delineate the most reliable outcomes [22]. The results of therapeutic FMT have also been evaluated with respect to clinical success and modulation of gut bacterial communities in order to characterize the mechanism of action [23]. The accumulated data indicate effective resolution of infection by week 8 post-transplant, with nonresponse or disease recurrence associated with administration to the upper gastrointestinal tract. Although the primary indication remains refractory CDI, follow-up studies exploring extension of the technique to other diseases involving gut dysbiosis have demonstrated promising results, and additional clinical trials for FMT have been registered in recent years.

Success Rates in Clostridium difficile Infection

Clostridium difficile infection (CDI) precipitates 15,000–20,000 deaths annually [24], presenting a major health threat highlighted by the European Centre for Disease Prevention and Control and the U.S. Centers for Disease Control and Prevention. Following initial antibiotic-induced disturbance and colonisation, a recovery period precedes either resolution or a relapse, usually during the first 8 weeks [25]. Antibiotics remain the standard firstline treatment but only achieve primary cure rates around 66 %. At the first recurrence, a similar or slightly reduced cure rate justifies continued antibiotic use for the majority of patients, but subsequent recurrences generally prompt FMT intervention. FMT success rates are high: even among patients receiving it after multiple recurrences as a last resort, around 85–90 % achieve sustained clearance [26]. Consequently, in clinical practice FMT is often reserved until one or two prior episodes have occurred. Administration methods include oral capsules, endoscopic duodenal infusion, and retention enema. Efficacy is high regardless of delivery mode, though oral capsules are preferred for convenience and lower invasiveness. Outcomes from capsule FMT meet or exceed previously reported efficacy, underscoring its strengths.

Emerging Indications for FMT

Further indications for FMT continue to emerge [15]. Despite the potential to recover a healthy microbiome, the precise mechanisms remain largely unknown. The restoration of intestinal microbial diversity and metabolic composition likely plays a key role in FMT. The administration of a eubiotic faecal formulation markedly improves bacterial diversity, correcting imbalances related to the pathogenesis of intestinal and extraintestinal chronic inflammatory disorders 16. Highly beneficial effects have been observed in the treatment of rCDI, where FMT proves more effective than standard antibiotic regimens, and several studies currently evaluate its use in other clinical settings. Various reports indicate a microbiota-driven mechanisms of action [15].

Ethical Considerations in Microbiome Engineering

Microbiome can be a powerful tool in cancer immunotherapy, yet concerns remain with regards to ethical decision-making. Morally, researchers should strive to ensure that patients are properly informed of associated risks while employing guidelines to best inform researchers as to how this information should be delivered [27]. Other difficult questions in relationship to the microbiome in general relate to commercial ownership, agricultural and industrial usage, as well as modifications to the functional properties of the microbiome.

Informed Consent for FMT

Fecal microbiota transplantation (FMT) involves the transfer of stool from a healthy individual to a diseased one, making the donor's stool the central focus of the transplant. The first documented clinical use of FMT was by Eiseman et al. in 1958, preceding the recognition of Clostridium difficile as the cause of pseudomembranous colitis. Today, FMT is a well-established treatment for recurrent C [1]. difficile infection, with cure rates exceeding 90% reported during randomized controlled trials. Although FMT is generally considered safe with mild and infrequent adverse events, serious complications such as infections and disease flare-ups have been documented. Informed consent is therefore essential, and if the procedure is conducted within a research protocol, institutional review board approval is mandatory. Despite its long history of use, a formal professional organization has yet to define a consensus on the specific elements required in the informed consent process [1, 27].

Regulatory Challenges

Engineering the microbiome holds considerable potential to promote various facets of human health, yet the field must address a range of regulatory challenges and ethical considerations to optimize clinical benefit and minimize adverse effects. Investigational new drug (IND) applications impose constraints on fecal microbiota transplantation (FMT), creating barriers that limit access to what is arguably one of the most effective developed therapies [3]. These barriers may lead some patients to pursue unsupervised, at-home FMT, presentations to emergency departments with adverse effects, or use of government-funded health care resources to access FMT abroad, resulting in continued health risks without the benefit of oversight. Additionally, the increasing use of microbiome engineering in diverse applications, including human therapeutics, complicates regulatory decisions as mechanisms of action and clinical outcomes are not well defined [3]. FMT introduced a distinct set of regulatory challenges that illustrate the policy gaps in microbiome therapeutics and demonstrate the need for innovative solutions. Reconceptualizing FMT as a foundational therapy and proposing regulatory pathways to facilitate the development of both established and emerging microbiome-directed therapies may offer a framework that more effectively supports innovation and patient access. If microbiome engineering is to continue achieving meaningful advancements in human health, clinical development must proceed rapidly, with careful oversight and transparent communication, to build meaningful standards while maintaining focus on the ultimate beneficiaries: patients [27].

Future Directions in Microbiome Engineering

Human gut bacteria comprise a complex community whose perturbation is linked to a variety of diseases. Approaches to manipulate these species and their function would offer new therapeutic strategies. While fraught with significant challenges, manipulation of the gut microbiome remains a promising avenue for intervention. One approach uses prebiotics and probiotics, also known as synbiotics, to increase the representation of health-promoting organisms, particularly those that manufacture beneficial metabolites. Clinical studies have documented some efficacy in specific conditions, but they are limited by a general lack of mechanistic understanding, and the field awaits larger and more rigorous trials on well-defined microbial enrichments to demonstrate clear clinical efficacy [1]. Alternatively, the fecal microbiota transplant (FMT) has seen widespread clinical use and regulatory approval in certain jurisdictions for treatment of recurrent Clostridium difficile infection. The ability to manipulate this community will provide opportunities for sustained delivery of a wide variety of products [8]. Engineering the microbiomes of humans and their environment provides an emerging strategy to combat modern threats to health and food security. The microbiome has provided the capability to recycle nutrients and occupy specific niches during host colonization. The ability to cherry pick strains both compatible with existing communities and carrying desirable functions could present a broadly-applicable strategy to deliver a variety of compounds. Metagenomic studies have identified distinct microbiome configurations, or enterotypes that are generally preserved after long periods of time, and an individual's enterotype determines their susceptibility to colonization by new strains [3]. High strain-level heterogeneity within the microbiome and the lack of widely-shared strains have limited studies to top-level analyses of global composition without interrogation of the specific factors shaping these communities. There is an urgent need to expand the suite of approaches to alter microbial community composition in human health, agriculture, and natural ecosystems [1, 3, 8].

Innovations in Synbiotic Development

Whereas most established probiotics have rather broad mechanisms of action, there is still a lack of targeted synbiotic compositions acting on the microbiome with a defined and reliable mode of action. A major source for missing efficacy and replicability lies in the absence of knowledge to design synbiotics specifically for groups of the population with a shared metabolic phenotype (metabotype) or related mode of action. The clear relation between metabolism of substances and development of health effects supports a metabiotic approach by following the interaction of specific microbes and a distinct substrate with the gut and the brain. Studying the effect of substrate–microbe combinations on the overall gut microbiome function and host physiology can lead to the desired combination of prebiotic and probiotic ingredient. This metabiotic approach takes the majority of modulating and confounding factors into account and represents a unique strategy to develop synbiotic compositions with specific modes of action [6]. The development of well-defined compositions requires an improved understanding of the conversion of prebiotic substrate and the interaction with the microbiota. Studies along these lines can identify metabolic indicators and reveal momentary efficacy under standardized conditions. Systematic investigation of specific prebiotics combined with taxonomically defined microbes also leads to transferable insights into behaviour and robustness of the entire synbiotic composition. Metabolism-based combination studies suggest that substrate–microbe combinations remain stable across quite some range of interacting parameters and that adding a similar probiotic can fully restore prebiotic activity under unfavourable conditions [6]. Systematic testing of substrate–microbe combinations thus repeatedly yields versatile and robust synbiotic choices even with regard to complex substrate–microbe interactions. The metabiotic approach provides knowledge to design next-generation synbiotics with a metabiotic rationale [6].

Research on Personalized Microbiome Therapy

Personalized microbiome therapy strives to modulate the microbiome to preserve eubiosis and reduce the risk of microbiome-associated diseases. Microbiome engineering offers the opportunity to alter the microbial composition of a community. In this context, altering the microbiome allows restoration from a dysbiotic state to a healthy configuration [28].

Challenges and Limitations

Microbiome engineering encompasses a diverse set of techniques with the shared goal of manipulating the complex and dynamic communities of symbiotic microbes that inhabit living hosts. These microbes confer numerous benefits nutritional, metabolic, and immune that are critical to host fitness [2]. Consequently, if the diverse assemblages of microbes can be engineered in a rational and controlled manner to perform specific functions and develop desired compositions, microbiome engineering will constitute a powerful therapeutic and diagnostic arena. The overarching goal of microbiome engineering is to control microbial communities and their functions, thus allowing for in-depth characterization of host-microbe interactions in an iterative fashion. Such iterative characterization would inform the manner in which a specific microbiome could be manipulated to affect host phenotype, which in turn could lead to new techniques for both disease diagnosis and treatment. Moreover, these tools could lead to prevention or mitigation of pathogen invasion [2]. Such fine control would further allow relevant synthetic communities to be generated, enabling the identification of minimal microbiomes that would allow for survival and growth of both the microbial community as well as the host. Microbiome engineering techniques can be classified based on application mode and desired outcome. Top-down approaches start with a microbiome and seek to modify its structure or function by removing, adding, or amplifying specific constituents. Bottom-up approaches endeavor to selectively add genetically modified microbes or impose genetic circuits on the existing community to achieve a desired function. Both strategies face the challenge of functional and compositional resilience observed in microbiomes. Natural probiotics (beneficial microbes added to a community) serve as top-down agents that can replace or supplement existing microbiome members. Engineered probiotics offer a bottom-up approach, capable of producing specific molecules or exhibiting new regulatory properties for therapeutic or preventative purposes. Training existing microbes to perform new functions is also a bottom-up strategy and can be implemented using "kill switches" or "stabilizing circuits" to modulate community dynamics and maintain desired compositions [2]. Current microbiome engineering tools are limited in their ability to introduce precise changes at both compositional and functional levels. Subtractive techniques such as bacteriophages and selective antimicrobials are impactful but lack specificity among related organisms and the capability to target specific strains or genes. Additive methods also fall short in delivering complex molecules capable of nuanced ecosystem modulation. Standalone approaches are often insufficient, suggesting that hybrid methods, combining subtractive, additive, and modulatory techniques may offer enhanced control and specificity [2].

Variability in Microbiome Responses

The human microbiome exhibits unique functional properties and quantitatively dynamic interaction networks that determine community stability and resilience, responses to perturbations, and ultimately host health [29]. Bacterial communities assembled in different ways from an environment are inherently unpredictable even when initial conditions are highly controlled. Individualized microbiota formation is favored by high initial diversity, stochasticity during colonization, and a prolonged colonization period. For a complex community such as the healthy human gut, replicating the exact strain complements formed during early childhood is therefore highly challenging. Once matured and highly diverse, the human microbiome gains stability, robustness toward perturbations, and high functional redundancy. If sufficiently perturbed, a tipping point can be reached after which a new dynamic equilibrium may be established, a process that is individual dependent and has been clearly documented in dysbiotic gut microbiomes of inflammatory bowel disease (IBD) patients, for example [29]. Interindividual differences are amalgamations of location, sociocultural traditions, and population migrations, but are variable and difficult to tease apart. Geography still dominates as the main discriminator of microbiome β-diversity at a global scale, followed by ethnicity and lifestyle [4]. The construction of a pan microbiome of human populations worldwide may assist in defining the full extent of the human microbiome repertoire and provide more detailed insights into population-specific variations. Variability is often overlooked in small-scale studies and ignored in disease association analyses, resulting in missing valuable mechanistic insights and generalizable microbiome-based therapeutics that would benefit global populations. Community coalescence during fecal microbiota transplantation (FMT) therefore remains a crucial determinant for therapeutic success. The human genotypic and phenotypic individuality highlights the futility of one treatment serving all, encouraging highly tailored donor-recipient matching in microbiome engineering [27].

Long-term Effects of Interventions

Engagement of microbiota through synbiotic administration and fecal microbiota transplantation (FMT) has opened promising opportunities for microbiome restoration and alteration. However, multiple limitations should be overcome before exploiting these for widespread clinical use [21]. The microbiome of individual hosts varies depending on genetics, diet, lifestyle, and many other factors, yet it remains to be explored whether a framework for universal synbiotic mixtures applicable to all hosts can be identified or whether streamlined selection of parameters can make customized therapy feasible. Of particular importance are the long-term effects of microbiome engineering, which are only just starting to be unveiled, together with the duration of therapy and the extensive definition of end targets needed to monitor the treatment course [21].

CONCLUSION

The human microbiome is increasingly recognized as a fundamental determinant of health and disease. Engineering this ecosystem through synbiotics and fecal microbiota transplantation (FMT) represents a frontier in biomedicine with far-reaching implications. Synbiotics combine probiotics and prebiotics to synergistically promote beneficial microbial activity, improve intestinal barrier function, and support immune modulation. Clinical applications extend to gastrointestinal, metabolic, and immune-related disorders, although reproducibility and efficacy are limited by interindividual variability and incomplete mechanistic understanding. FMT has revolutionized the treatment of recurrent *Clostridium difficile* infection, achieving cure rates exceeding 85–90%. Its potential in autoimmune, metabolic, and neurological conditions is being actively explored, with evidence suggesting broad immunological and metabolic benefits. However, safety, donor variability, and regulatory hurdles remain significant challenges, underscoring the need for standardized protocols and ethical frameworks. Looking forward, precision microbiome engineering, incorporating targeted synbiotic formulations, metabiotic strategies, and next-generation FMT approaches, holds promise for more predictable and individualized outcomes. Success will require integrating metagenomic insights, mechanistic studies, and clinical validation within responsible regulatory and ethical boundaries. Ultimately, microbiome engineering exemplifies the convergence of synthetic biology, clinical medicine, and public health. By restoring microbial balance and harnessing microbial functions, synbiotics and FMT have the potential to transform prevention, diagnosis, and therapy, advancing the paradigm of precision medicine.

REFERENCES

1. Zhang Y, Zhou L, Xia J, Dong C, Luo X. Human microbiome and its medical applications. Frontiers in Molecular Biosciences. 2022 Jan 13;8:703585.
2. McClure S, Enam F, Arnold J, Mimee M. Proceedings from the 3rd international conference on microbiome engineering. Biotechnology Progress. 2022 May;38(3):e3241.
3. Chitayat Levi L, Rippin I, Ben Tulila M, Galron R, Tuller T. Modulating gene expression within a microbiome based on computational models. Biology. 2022 Aug 31;11(9):1301.
4. Gupta VK, Paul S, Dutta C. Geography, ethnicity or subsistence-specific variations in human microbiome composition and diversity. Frontiers in microbiology. 2017 Jun 23;8:1162.
5. Hasan N, Yang H. Factors affecting the composition of the gut microbiota, and its modulation. PeerJ. 2019 Aug 16;7:e7502.
6. Speckmann B, Ehring E, Hu J, Rodriguez Mateos A. Exploring substrate–microbe interactions: a metabiotic approach toward developing targeted synbiotic compositions. Gut Microbes. 2024 Dec 31;16(1):2305716.
7. Kouhounde S, Adéoti K, Mounir M, Giusti A, Refinetti P, Otu A, Effa E, Ebenso B, Adetimirin VO, Barceló JM, Thiare O. Applications of probiotic-based multi-components to human, animal and ecosystem health: concepts, methodologies, and action mechanisms. Microorganisms. 2022 Aug 24;10(9):1700.
8. Arnold J, Glazier J, Mimee M. Genetic engineering of resident bacteria in the gut microbiome. Journal of Bacteriology. 2023 Jul 25;205(7):e00127-23.
9. Shang Z, Pai L, Patil S. Unveiling the dynamics of gut microbial interactions: a review of dietary impact and precision nutrition in gastrointestinal health. Frontiers in Nutrition. 2024 May 30;11:1395664.
10. Kho ZY, Lal SK. The human gut microbiome–a potential controller of wellness and disease. Frontiers in microbiology. 2018 Aug 14;9:356589.
11. Lee C, Lee H, Park JC, Im SH. Microbial components and effector molecules in T helper cell differentiation and function. Immune Network. 2023 Feb 22;23(1):e7.
12. Kabat AM, Srinivasan N, Maloy KJ. Modulation of immune development and function by intestinal microbiota. Trends in immunology. 2014 Nov 1;35(11):507-17.
13. Reens AL, Cabral DJ, Liang X, Norton Jr JE, Therien AG, Hazuda DJ, Swaminathan G. Immunomodulation by the commensal microbiome during immune-targeted interventions: focus on cancer immune checkpoint inhibitor therapy and vaccination. Frontiers in Immunology. 2021 May 13;12:643255.
14. Borody TJ, Paramsothy S, Agrawal G. Fecal microbiota transplantation: indications, methods, evidence, and future directions. Current gastroenterology reports. 2013 Aug;15(8):337.
15. König J, Siebenhaar A, Högenauer C, Arkkila P, Nieuwdorp M, Norén T, Ponsioen CY, Rosien U, Rossen NG, Satokari R, Stallmach A. Consensus report: faecal microbiota transfer–clinical applications and procedures. Alimentary pharmacology & therapeutics. 2017 Jan;45(2):222-39.
16. Borody TJ, Brandt LJ, Paramsothy S. Therapeutic faecal microbiota transplantation: current status and future developments. Current opinion in gastroenterology. 2014 Jan 1;30(1):97-105.
17. Biazzo M, Deidda G. Fecal microbiota transplantation as new therapeutic avenue for human diseases. Journal of clinical medicine. 2022 Jul 15;11(14):4119.
18. Zhang F, Cui B, He X, Nie Y, Wu K, Fan D, FMT-standardization Study Group. Microbiota transplantation: concept, methodology and strategy for its modernization. Protein & cell. 2018 May;9(5):462-73.
19. Xiao Y, Angulo MT, Lao S, Weiss ST, Liu YY. An ecological framework to understand the efficacy of fecal microbiota transplantation. Nature communications. 2020 Jul 3;11(1):3329.
20. Song L. Toward understanding microbial ecology to restore a degraded ecosystem. International Journal of Environmental Research and Public Health. 2023 Mar 6;20(5):4647.
21. Laudes M, Geisler C, Rohmann N, Bouwman J, Pischon T, Schlicht K. Microbiota in health and disease—potential clinical applications. Nutrients. 2021 Oct 29;13(11):3866.
22. Li Y, Zhang T, Sun J, Liu N. Fecal Microbiota transplantation and health outcomes: an umbrella review of meta-analyses of randomized controlled trials. Frontiers in Cellular and Infection Microbiology. 2022 Jun 27;12:899845.

23. Dave AA, Robson R. Clinical Utility and Alterations in Bacterial Flora in Fecal Microbiome Transplantation. International Journal of Medical Students. 2015 Dec 31;3(3):140-50.
24. Kachrimanidou M, Tsintarakis E. Insights into the role of human gut microbiota in Clostridioides difficile infection. Microorganisms. 2020 Jan 31;8(2):200.
25. Hirsch BE, Saraiya N, Poeth K, Schwartz RM, Epstein ME, Honig G. Effectiveness of fecal-derived microbiota transfer using orally administered capsules for recurrent Clostridium difficile infection. BMC infectious diseases. 2015 Apr 17;15(1):191.
26. Shankar V, Hamilton MJ, Khoruts A, Kilburn A, Unno T, Paliy O, Sadowsky MJ. Species and genus level resolution analysis of gut microbiota in Clostridium difficile patients following fecal microbiota transplantation. Microbiome. 2014 Apr 21;2(1):13.
27. Lange L, Berg G, Cernava T, Champomier-Vergès MC, Charles T, Cocolin L, Cotter P, D'hondt K, Kostic T, Maguin E, Makhalanyane T. Microbiome ethics, guiding principles for microbiome research, use and knowledge management. Environmental microbiome. 2022 Sep 30;17(1):50.
28. Yadav M, Chauhan NS. Microbiome therapeutics: exploring the present scenario and challenges. Gastroenterology report. 2022;10:goab046.
29. Chen J, Siliceo SL, Ni Y, Nielsen HB, Xu A, Panagiotou G. Identification of robust and generalizable biomarkers for microbiome-based stratification in lifestyle interventions. Microbiome. 2023 Aug 8;11(1):178.

**CITE AS: Ahabwe Edwina (2025). Microbiome Engineering: A Narrative Review. IDOSR JOURNAL OF APPLIED SCIENCES 10(3):93-103.
https://doi.org/10.59298/IDOSRJAS/2025/103.93103**