



Review Article

Therapeutic potential and clinical advances of fecal microbiota transplantation in disease management

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Abstract: Fecal microbiota transplantation (FMT) has become an important method for treating various diseases. This review explores the relationship between FMT and various diseases such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), metabolic disorders, neurological disorders, tumors, and cardiovascular diseases, and analyzes the key mechanisms by which FMT exerts therapeutic effects. The mechanism of FMT involves signaling pathways such as Toll-like receptor 4 (TLR4)/NF- κ B pathway, Aryl hydrocarbon receptor (AHR) pathway, NLR family pyrin domain containing 3 (NLRP3) inflammasome pathway, short chain fatty acid (SCFAs)-mediated pathway, and 5-hydroxytryptamine pathway. These pathways alleviate disease symptoms by synergistically regulating immune responses, inflammatory processes, and metabolic functions. In addition, this review also discusses different administration methods of FMT, including traditional colonoscopy or enema administration, oral FMT capsules, nasogastric/nasoduodenal tube administration, and rectal administration for pediatric patients. Although there are still technical and clinical challenges, FMT, as an individualized treatment strategy, has shown broad application prospects in the treatment of various diseases.

Keywords: fecal microbiota transplantation; gut microbiota; diseases; pathway; administration methods

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1 Introduction

Gut microbiota plays an essential role in human health and well-being by engaging in various physiological processes. These processes include nutrient absorption, utilization, immune regulation, and defense against pathogens^[1-4] (Fig. 1). Increasing evidence has demonstrated the systemic effects of gut microbiota, in addition to local effects, through the gut-brain axis (GBA), immune signaling, and metabolic processes, contributing to its designation as the “second genome” of the human body^[5,6]. Alterations to the form or function of the gut microbiota, often referred to as dysbiosis or ecological imbalance, has been associated with multiple diseases, including metabolic diseases, such as obesity and diabetes, neuropsychiatric disorders, including depression and Autism spectrum disorder (ASD), and immune-mediated diseases^[7-9]. Identification of these complex interconnections have positioned gut microbiota as a promising therapeutic target.

Fecal microbiota transplantation (FMT) has emerged as a successful method for restoring gut microbial homeostasis and balance by transferring fecal microbiota from a healthy donor to a recipient^[10]. After years of development, FMT has shown therapeutic promise for multiple diseases, such as ulcerative colitis (UC), Crohn’s disease (CD), metabolic syndrome (MetS), and

neurological diseases^[11-13]. While FMT has progressed and been applied clinically, the application of FMT in clinical practice is limited by challenges, including standardization of donor microbiota, safety, and variability in outcomes^[14]. Additionally, while short-term effectiveness of FMT has been well demonstrated, the long-term sustainability and mechanisms of host microbiota transplantation still requires further research^[15]. In recent years, advancements in high-throughput sequencing technologies, as well as the Human Microbiome Project (HMP), have stimulated further research into the gut microbiota, indicating the potential for diversity or function of gut microbiota to promote treatment of various diseases^[16-18]. However, despite the potential of FMT and challenges to standardized procedures and improvements in outpatient treatment, outcomes associated with FMT remain a challenge. This review aims to provide a comprehensive review of the current understanding of the relationship between FMT and disease across various disease mechanisms, while simultaneously transitioning to introduce recent advances, outstanding issues, and future directions in clinical intervention using this approach.

2 Microbiota transplantation and disease

Microbiota transplantation, including FMT has become an

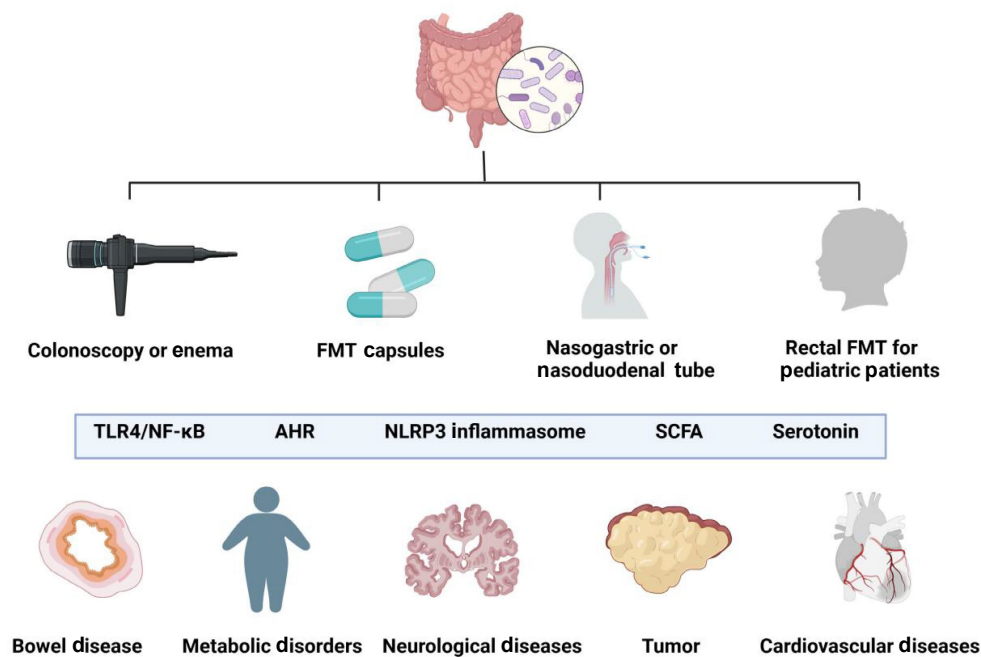


Figure 1 Overview of FMT modalities, mechanisms, and therapeutic applications. FMT can be administered via colonoscopy or enema, oral capsules, nasogastric or nasoduodenal tubes, and rectal delivery in pediatric patients. Mechanistically, FMT influences host health by modulating pathways such as TLR4/NF-κB signaling, AHR activation, NLRP3 inflammasome regulation, SCFAs production, and 5-HT metabolism. These mechanisms contribute to the therapeutic potential of FMT in various conditions, including bowel diseases, metabolic disorders, neurological diseases, tumors, and CVD. Created in <https://BioRender.com>.

important therapeutic strategy in various diseases, and its recognition for mitigating gut microbiota and general health outcomes is increasingly under investigation^[19]. In this next section we discuss the role of microbiota transplantation in the some major diseases, while reviewing the potential mechanisms of gut microbiota composition in diseases processes pathophysiologically.

2.1 Gut microbiota in inflammatory bowel disease (IBD)

The gut microbiota has essential roles in maintaining host immune homeostasis, energy metabolism, as well as, the integrity of the gut mucosa. The dysregulation (or gut dysbiosis) has also been strongly associated with the processes of IBD, including CD, and UC^[20]. Over the past two decades, extensive research have demonstrated the gut microbiota in contributing to host physiology and significantly affect immune lineage specificity to developmental processes, as well as the effects of microbiota metabolites on inflammation processes^[21]. Changes to the form, diversity, and function of gut microbiota, and/or the metabolic processes that modify microbiota, including bile acids and short-chain fatty acids (SCFAs) has also been associated with IBD processes^[22].

FMT has been utilized as a novel and appealing avenue to restore dysbiotic microbiota in patients with UC and IBD, driven by the recent burgeoning of clinical trials. Recent studies have reported that FMT could increase microbial α -diversity and species richness, and in some cases, the patient microbiome appeared to transition partially towards a donor-like profile^[23]. Accompanying these changes in the microbiome, a corresponding degree of clinical, endoscopic, and histological remission have been pre-reported. Wu *et al.*^[24] reviewed 27 clinical trials assessing FMT in the last decade, discovering that only some included prior gut microbiome profiling, immune response assessment, and metabolomic analysis, suggesting a paradigm for future studies. Further, although FMT is recognized for treating CD, its clinical outcomes are inconsistent, a function of differences in donor

selection, dose used, route of delivery, and/or other recipient factors^[25].

In addition to examining clinical results, mechanistic explanation of the immunomodulatory effects of FMT is gaining attention. For example, changes in the microbiome induced by FMT may impact either pro- or anti-inflammatory T cell functions, but these effects vary across studies^[26]. Microbial metabolites, such as SCFAs, bile acids, and tryptophan metabolites, have been identified as important mediators of these functions^[27]. SCFAs have demonstrated to augment regulatory T cell function and epithelial barrier function, while bile acid metabolism may alter mucosal inflammation through farnesoid X receptor (FXR) signaling^[28,29]. However, the lack of consistent mechanistic evidence linking changes in microbiota and metabolites to clinical outcomes is a critical barrier to the further uptake of FMT in practice. To address these questions, Lopetuso *et al.*^[30] convened an international panel of experts ($n = 25$) in the fields of IBD, immunology and microbiology to produce evidence-based recommendations regarding the use of FMT. Their consensus recommendations address donor screening, biobanking, FMT procedures, and future research agendas, with the intention to standardize practice and promote the clinical use of FMT. The interest in FMT as a therapy for IBD is increasing, and the use of FMT clinically continues to be complicated and will require further investigations. Furthermore, pilot studies suggest FMT may be an effective therapeutic approach for mild-moderately active UC; however, currently, there is limited evidence to suggest that FMT is effective for CD. While initial studies show positive outcomes for those with UC, limitations include short follow-up times and methodological variability making the clinical interpretation difficult. With respect to safety, FMT is generally well tolerated with mild and short-term adverse events typically limited to bloating and abdominal discomfort, however, long-term safety data is lacking. In addition, potential risks including transmission of an infectious agent or immune-mediated events need further research. Next steps to

optimize FMT clinically in IBD would be well-designed, rigorously powered randomized controlled trials (RCTs) with long-term follow up to assess the future safety and effectiveness of FMT. It's also important to consider location of disease, severity and behavior of a flare, as future use of FMT may be tailored to patients as a personalized therapy.

2.2 Gut microbiota in irritable bowel syndrome (IBS)

IBS is a chronic gastrointestinal disorder characterized by recurrent abdominal pain, bloating, and altered bowel habits in the absence of identifiable structural or biochemical abnormalities^[31,32]. Gut microbiota has recently been indicated to play an important role in the pathogenesis of IBS in particular related to the microbiota-GBA (MGBA)^[33]. The MGBA is a bilateral communication system between the gut and the central nervous system (CNS) that involves microbial metabolites, immune signaling, and neuroendocrine pathways^[34]. FMT is a therapeutic choice to restore microbiota diversity in addition to microbiota functioning, and is perhaps the most well-known therapeutic option for IBS.

FMT is thought to exert its therapeutic effects *via* several mechanisms. One important mechanism is restoration of microbiota diversity to address dysbiosis in IBS. Patients with IBS demonstrate a reduced abundance of beneficial bacteria, such as Bifidobacteria and *Lactobacillus*, and an increased abundance of associated inflammatory bacteria, such as Proteobacteria^[35]. Reintroduction of a diverse microbial community could enhance competitive exclusion of pathogenic bacteria, enhance the production of SCFAs, and modulate host immune activity. SCFAs, particularly butyrate, are important to maintaining colonic health by preserving epithelial barrier integrity, enhancing epithelial regulatory T cell activity, and suppressing the production of proinflammatory cytokines. Furthermore, FMT has been demonstrated to influence the communication between the microbiome and CNS in gut-brain-axis regulation through modulation of microbial metabolites, such as tryptophan-derived metabolites, gamma-aminobutyric acid (GABA), and precursors of serotonin (5-HT), all of which have effects on neural signaling^[36]. Modulation of these metabolites may reduce visceral hypersensitivity, which is a common feature of IBS, and improve IBS symptoms such as abdominal pain and mood alterations related to IBS^[37]. Intestinal barrier to lumen function is another target of interest for FMT. Intestinal barrier function is often compromised in the context of dysbiosis in patients with IBS^[38]. The increased intestinal permeability as a result of dysbiosis can facilitate the translocation of microbial products to the mucosa such as lipopolysaccharides (LPS), which activate mucosal inflammation and mucosal immune activation^[39]. Previous findings have shown that FMT improved intestinal barrier function by upregulating tight junction proteins and reducing elastase-driven mucosal inflammation resulting in improved gut homeostasis^[40].

While mechanistic insights into the therapeutic possibilities of FMT are promising, clinical outcomes related to FMT in IBS are variable. While a number of RCTs and observational studies associate improvement in symptoms and enhanced microbial diversity, there are contrary studies showing limited efficacy from FMT. A meta-analysis conducted more recently by Jamshidi *et al.*^[41] reported on a review of 7 studies, and did not find a significant difference in overall symptom improvement comparing FMT to placebo (odds ratio (OR) = 0.99, 95% confidence interval (CI): 0.39–2.50). In contrast, a subgroup

analysis for single-dose (1 day) multi-donor FMT at colonoscopy reported significantly improved symptoms *vs.* autologous placebo FMT (OR = 2.54, 95% CI: 1.20–5.37, *P* = 0.01), suggesting donor or dose or route of administration (e.g., duodenal) may all be important factors in determining the efficacy of FMT. Due to previous promising variations reported in clinical outcomes related to FMT for IBS, further inquiry is needed to elucidate the therapeutic potential for FMT for IB. Efficacy and safety of FMT for patients with IBS is still an area of active investigation. In fact, recent findings suggest that some IBS subtypes (especially diarrhea-predominant IBS (IBS-D)) may benefit from FMT by restoring a more favourable (optimal) composition of gut microbiota initially modulated by dysbiosis. One meta-analysis revealed that FMT results in a greater overall clinical response rate for the IBS population (risk ratio (RR): 1.56, 95% CI: 1.21–2.02), however significant heterogeneity existed across investigated studies. Additionally, FMT is generally well tolerated as a therapeutic strategy for patients with IBS, with most adverse events being mild to moderate in severity. Nevertheless, limited data regarding long-term safety have given rise to uncertainty in the sustainability of symptom relief from FMT following initial treatment. There is a need for additional, high-quality, large randomized controlled studies to select the best donor, delivery system, and long-term efficacy of FMT to treat IBS^[42].

There will be a need to understand the individual molecular mechanisms that underpin the beneficial actions of FMT on IBS health outcomes. Novel omics-derived methods, such as metagenomics, metabolomics, and transcriptomics, have the potential to identify microbial species and associated metabolites responsible for clinical improvement of IBS symptoms. Personalized treatment for IBS may be further enhanced with a tailored approach based on microbial profiles and IBS subtype. Finally, improving FMT protocols to address donor variability and standardization, and long-term treatment follow up are areas where further treatment optimization we be essential for FMT to become the standard of care for patients with IBS^[43].

2.3 The gut microbiome and disorders of metabolism

MetS is a group of metabolic disorders characterized by having abdominal obesity, dyslipidemia, high blood pressure, and impaired glucose metabolism, with insulin resistance and obesity being the primary pathophysiologies involved^[44]. In 2001, a national survey showed that the prevalence of MetS was 9.8% in men and 17.8% in women. By 2010–2012, there was a significant increase in the prevalence to 24.2% (24.6% in men and 23.8% in women)^[45]. Recent research has established the importance of the gut microbiome in the pathogenesis of MetS and linked the dysbiosis of the microbiome to metabolic disorders through changes in bile acid metabolism, SCFAs production, and systemic inflammation. For example, Molinaro *et al.*^[46] reported that mice with altered microbiota had changed the composition of bile acids suggesting that manipulation of the microbiota can be approached therapeutically towards the management of metabolic disorders. Overall, these observations suggest that microbiome-based therapy, such as FMT, may represent a novel metabolic therapeutic target.

Clinical trials have provided some evidence of FMT improving metabolic parameters in patients with metabolic syndrome (MetS). Vrieze *et al.*^[47] showed that in insulin resistant patients with MetS, lean donor FMT improved peripheral insulin sensitivity, and also had restored the relative abundance of butyrate-producing gut bacteria like *Faecalibacterium prausnitzii*.

Butyrate is an SCFAs that activates AMP-activated protein kinase (AMPK) and enhances intestinal barrier function to mitigate insulin resistance. Bustamante *et al.*^[48] demonstrated that lean deposit FMT improved insulin resistance and altered plasma levels of metabolites, including GABA, in obese patients. FMT improved metabolic function primarily through restoration of microbiome diversity, increasing SCFAs production, and altering bile acid signaling pathway activity which occurs *via* FXR and Takeda G protein-coupled receptor 5 (TGR5)^[49,50]. These pathways are integral to restoring insulin sensitivity, lipid metabolism, and mediating systemic inflammation. In spite of the encouraging results, variability in FMT efficacy has presented challenges in therapy, often resulting from donor selection and host microbiome composition. To understand the issues surrounding variability in FMT outcomes, Mocanu and colleagues^[51] evaluated the effectiveness and safety of single-dose oral FMT combined with fiber supplementation in subjects with severe obesity and MetS during a double-blind, randomized trial design. Participants ($n = 70$) were randomized to high-fermentable (HF) or low-fermentable (LF) fiber supplementation, with or without FMT. The primary outcome was based on the change in insulin sensitivity (homeostasis model assessment of insulin resistance (HOMA2-IR)); the FMT-LF group was the only group to demonstrate an improvement after 6 weeks ($P = 0.02$) while no significant change was observed in the FMT-HF, HF, or LF groups. Importantly, no serious adverse events were reported as a result of therapy. This study provides proof-of-concept for single-dose oral FMT combined with low fermentable fiber supplementation to improve insulin sensitivity in patients with severe obesity and MetS and may support the development of this therapeutic application for metabolic disorders.

2.4 Gut microbiome in neurological diseases

Emerging research indicates that gut microbiome contributes solitarily but significantly as a major functional link in bidirectional communication between the gastrointestinal tract and the CNS, otherwise known as the microbiome-GBA or GBA^[52]. This complex and functional pathway is involved in several brain-related functions, including neurodevelopment, neurotransmission, and behavior, and can initiate the progression of neurological, neurodevelopmental, and neuropsychiatric diseases. Gut dysbiosis, or an altered gut microbiome composition, has been implicated in Parkinson's disease (PD), Alzheimer's disease (AD), ASD, epilepsy, and schizophrenia^[53-56].

Microglia are considered the primary innate immune cells in the CNS and are vitally important for maintaining CNS homeostasis and responding to perturbations in the environment^[57]. Under normal physiological conditions, microglia contribute to neurogenesis, angiogenesis, synaptic pruning, myelination, and clearance of apoptotic cells and protein aggregates to maintain and preserve CNS integrity^[58]. However, when microglial behaviors and functions are disrupted and dysregulated, they contribute to the pathogenesis of neurodegenerative diseases such as AD, PD, amyotrophic lateral sclerosis (ALS), fronto-temporal dementia (FTD), and Huntington's disease (HD)^[59]. In AD, microglia are the first responders to amyloid-beta ($A\beta$) plaques. They will accumulate near $A\beta$ plaques and "eat or clear" these plaques^[60]. Similarly, in PD, microglial activation is associated with inflammation and the phagocytosis of aggregates of α -synuclein. However, in these diseases, the phagocytic age of microglia fluctuates and can significantly decline, which can lead to the continued presence of neurotoxic protein aggregates and disrupted neuronal functioning.

In addition, it is possible for excessive activation of microglia to cause phagocytosis unwanted or neurotoxic behaviors towards sick but viable neurons, which can contribute to even further neuronal loss of degenerative processes^[61]. Genome-wide association studies (GWAS) show that several genes expressed in microglia like *TYROBP*, *TREM2*, and *APOE* are significant in the pathogenesis of neurodegenerative disease^[62]. In addition, other regulatory pathways like the complement pathway or the purinergic pathway, and mechanosensors like Piezo1 in microglia, further complicate the neurodegenerative contributions of microglia^[63]. From these pathways, microglia can be described as neuroprotective to neurodegenerative pathways, thus contributing to a potential therapeutic target in reducing neurodegenerative. Emerging literature also suggests that gut microbiome composition can predict or has an additional effect on microglial behaviors that lead to neurodegenerative diseases like AD and PD. The gut microbiome produces SCFAs and tryptophan metabolites that can cross the blood-brain barrier and change microglial activation in both beneficial and harmful ways^[64]. These metabolites can potentially improve or mature microglial processes, and alter inflammation triggered by microglia or neuro-inflammation, or if dysbiosis occurs, lead to excessive overactivation in microglia, which then leads to neurodegenerative conclusions. Also, the neurodegenerative disease process can manipulate the gut microbiome, and create the vicious cyclic feedback of neuromodulation downstream from impaired microglia activation to influencing homeostasis and health of (the gut) microbe, and further deteriorate the neurodegenerative process^[65]. We highlight that the microglia, neurodegenerative diseases, and gut microbiome have a complex and dynamic bidirectional relationship.

The GBA is a complex bidirectional communication network between the CNS and the gastrointestinal tract. This communication occurs *via* several pathways, including the autonomic nervous system, enteric nervous system (ENS), vagus nerve, neuroendocrine system, hypothalamic-pituitary-adrenal (HPA) axis, immune system, and metabolic systems^[66-68]. In addition, the GBA transmits and produces various neurotransmitters and metabolites—such as SCFAs, secondary bile acids, essential vitamins, and amino acids—that affect cognition, behavior, learning, movement, and neurodegenerative diseases^[69]. Advances in technology—such as germ-free (GF) models, FMT, microbiome sequencing, and brain imaging—have increased our understanding of the MGBA. The gut microbiota is able to affect your CNS functions through endocrine, immune, and neuronal networks that influence neurodevelopment, behavior, and cognitive functions but there are still mechanisms that remain poorly understood; increasing evidence is revealing components of pathways such as autophagy and the endocannabinoid system^[70]. The gut microbiota's role and implications in immunoregulation systems and the gut on peripheral organs could further enhance our understanding of MGBA functions, neurodevelopmental, and mental health disorders. Optogenetics may be a powerful tool for studying the MGBA, but research remains in early phases^[71]. While evidence suggests that probiotics, prebiotics, and FMT may be a possible treatment for neurodevelopmental disorders, clinical evidence and use of personalized and standardized protocols and practices are limited.

2.5 Gut microbiota in tumor

FMT has shown promise, particularly, in enhancing

immunotherapy such as immune checkpoint inhibitors (ICIs), for treatment-resistant cancers (e.g., melanoma). Pre-clinical and clinical studies have shown that FMT can alter bile acid metabolism, increase anti-tumor immunity, and enhance the tumor-infiltrating CD8⁺ T cell density in the tumor microenvironment after FMT and treatment, which enhances outcome for treatment^[72]. For example, in esophageal squamous cell carcinoma (ESCC), higher gut and tumor *Streptococcus* was associated with improved clinical response to neoadjuvant chemioimmunotherapy and significantly longer disease free survival^[73]. This study demonstrates how the functions of specific bacterial species promote immune-mediated tumor regression and improve clinical outcomes.

Building on the complex interactions between the gut microbiome and immune response to cancer, some recent work has focused on the potential to use microbiome modulation to improve cancer immunotherapy. FMT is one such fast-moving and promising tactic that provides new opportunities to overcome ICIs resistance and improve patient outcomes^[74]. Gut microbiome composition is a key component in modulating cancer immune responses, which is directed by local and systemic mechanisms. The mucosal immune system (MIS) acts as the first line of protection against the gut microbiome, by utilizing the mucus layer and intestinal epithelial cells (IECs) to prevent microbial invasion, but also activating intraepithelial lymphocytes to produce pro-inflammatory effector cytokines. These effector cytokines modulated immune cells in the Peyer's patches and mesenteric lymph nodes, often acting in response to antitumor properties of microbiome. *Via* a more local mechanism, gut microbiome is involved in either antitumor or procarcinogenic mechanisms, which may also have extended effects to distal sites, due to translocation of bacteria into the host circulation through immune recognition, metabolism of microbial metabolites, and enterohepatic circulation. Systemic effects modulate immune pathways initiated through programmed cell death 1 (PD-1) interactions, as well as a programmed cell death ligand 1 (PD-L1) interaction with cytotoxic T-lymphocyte associated protein 4 (CTLA-4), creating another pathway for tumor immunity. In particular, microbiomes are associated with tumorigenesis, a result of specific bacteria, such as *Fusobacterium nucleatum* and enterotoxigenic *Bacteroides fragilis* (ETBF), which have been found to recruit suppressive immunosurveillance partners (such as myeloid derived suppressor cells) and target T cell proliferation, as well as evade cytotoxicity by NK cells. Clinical work by Davar *et al.*^[75] studied the safety and efficacy of FMT and anti-PD-1 therapy in PD-1-Refractory melanoma. Their investigation found that FMT and anti-PD-1 therapy was well tolerated, and that 6 of the 15 patients experienced durable clinical benefit. The patients who responded showed changes in gut-related microbes, with increased taxa of those who had previously shown an anti-PD-1 response. The responders also demonstrated increased CD8⁺ T cell activation and lower amounts of interleukin-8 (IL-8) expressing myeloid cells in circulation. Distinct proteomic and metabolomic signatures were also determined through further studies in responders, and the transkingdom network analyses showed that gut microbes dictated these changes from prior studies. These findings support the potential of using FMT as a method of improving ICIs in some cases of melanoma.

These findings stress the role of the gut microbiome in interacting with, or shaping the tumor microenvironment, which have ramifications for cancer progression^[76].

Finally, FMT could also be used to blunt treatment related

toxicities (perhaps through improvement of microbial metabolites), particularly those associated with chemotherapy and radiotherapy. In the case of chemotherapy, FMT has been suggested to limit gastrointestinal toxicity, and simultaneously improve therapeutic value of most anticancer agents^[77]. Similarly, FMT has also shown the ability to reduce radiation-induced toxicities through protection of gastrointestinal function and intestinal epithelial integrity. Preclinical studies have shown that FMT could increase survival rates, improve peripheral white blood cell counts, and independently affect gut microbial composition in mock irradiated animals, without promoting or skewing any cancer cell proliferation. However, while some microbial metabolites are involved in increasing treatment benefits, others can enhance treatment toxicity or counteract drug action (or efficacy) during treatments. The development of gut microbiota, and FMT methodologies have benefitted from systematic complexities associated with therapy induced effects, with recent technologies such as synthetic biology and phage therapy^[78]. Taken together these desires are showing evidence that FMT will grow in significance in the category of the microbiome.

2.6 Gut microbiota in cardiovascular disease (CVD)

Emerging data suggests a complex relationship between gut microbiota and CVD as we shift from a descriptive relationship to causative mechanisms. FMT has emerged as a novel method for evaluating the gut-heart axis because it can directly alter the gut microbial population, and as a consequence, the effect of gut microbiota on cardiovascular health^[79]. Dysbiosis, or an imbalance of beneficial versus harmful gut bacteria, is associated with hypertension, atherosclerosis, and other CVD. For example, uncovering the microbial metabolites trimethylamine-N-oxide and phenylacetylglutamine and their ability to affect vascular tone and other negative cardiovascular phenotypes through gut microbial interactions that directly affect host key receptors (adrenergic receptors) only furthers our understanding and exploration of CVD^[80].

FMT can also regulate hypertension through the restoration of gut microbiota homeostasis, while also improving gut barrier health and function^[81]. In hypertensive patient populations, dysbiosis is frequently characterized by a higher abundance of harmful gut bacteria and lipopolysaccharide, a lower abundance of beneficial gut bacteria and SCFAs, and increased permeability of the gut. Yang *et al.*^[82] systematically reviewed studies linking gut microbiota dysbiosis with hypertension pathogenesis, a primary risk factor for cardio-cerebral vascular diseases with major public health and economic impacts. Hypertension can promote gut microbiota dysbiosis and gut barrier dysfunction, including increases of harmful gut microbiota and metabolites (hydrogen sulfide (H₂S) and lipopolysaccharide), and decreases of beneficial gut microbiota, SCFAs, and gut barrier tight junction proteins. Many approaches to modulate the gut microbiota have been reported, including FMT, probiotics, antibiotics, dietary and exercise interventions, antihypertensive agents, and natural medicines which demonstrate important roles of gut microbiota across causation and intervention in hypertension. These findings illustrate the important role of gut microbiota for the pathogenesis and progression of hypertension, provide a novel understanding of the pathogenesis of hypertension, and point to important directions for novel approaches to prevention and treatment of hypertension.

The therapeutic implications of FMT in CVD extend beyond CVD to new approaches, including probiotics, diet and eating

patterns, and natural medicines as an adjunct or in combination with FMT^[83]. Yuan *et al.*^[84] reviewed the relationship between gut microbiota and cardiometabolic diseases (CMD), including conditions such as hypertension, atherosclerosis, heart failure, obesity, and type 2 diabetes. Their review suggests the progression of CMD, while dependent on the composition and metabolites, have been previously studied in human populations but have not definitively shown clinical benefits of dietary intervention or use of probiotics to demonstrate microbe modulation. However, new approaches (FMT and nanomedicine) suggest new avenues for potential treatment clinical avenues to modify CMD. Their review also addresses important areas of unknown, such as, a lack of consensus about the core composition of gut microbiota and metabolite classes that are directly affecting CMD, and as such new modeling and experimental designs need to be conducted to better establish the certainty and causal mechanisms of the gut microbiota and host disease phenotypic expression. The modulation of gut microbiota through some of these interventions demonstrate risk factor reduction and increased effectiveness of treatment. Future directions of FMT and gut microbiota studies in CMD will advance to modify, prevent, and improve cardiovascular risk in CMD population, including FMT in primary care and clinical settings.

3 Mechanisms linking gut microbiota transplantation and pathways in human diseases

3.1 TLR4/NF- κ B pathway

The TLR4/NF- κ B signaling pathway serves as a primary signaling cascade involved in innate immunity and inflammation, with gut microbiota being a contributing factor. Alterations in gut microbiota can raise intestinal barrier permeability and allow for the passage of microbial products like LPS into the systemic circulation. Microbial products activate TLR4 receptors on immune cells and trigger a subsequent NF- κ B signaling cascade that enhances the transcription of pro-inflammatory cytokines and chemokines. Such inflammatory responses can occur not only in the gut but also in peripheral organs and tissues^[85]. Tang *et al.*^[86] found that dysbiosis can worsen lipopolysaccharide-induced acute lung injury (ALI) through the TLR4/NF- κ B pathway leading to oxidative stress and inflammation. They also presented data suggesting that FMT helps restore gut microecology, decreases activation of the TLR4/NF- κ B pathway, and lessens lung injury. Li *et al.*^[87] assessed the therapeutic effect of FMT on neuroinflammation produced by AD. In this animal study, APP/PS1 transgenic mice (APPswe, PSEN1dE9) received FMT from healthy wild-type mice. The data revealed that FMT improved cognition and decreased expression of inflammatory mediators *via* modulation of the TLR4/MyD88/NF- κ B signaling pathway. Additionally, gut microbiota composition was restored from the dysregulated state in AD mice. In summary, it is evident that the gut microbiota is a fundamental regulator of the TLR4/NF- κ B signaling pathway and downstream events causing inflammation. In particular, following FMT, recovery of microbial composition was noted which strengthens the intestinal barrier and limits systemic exposure to LPS. Thus there is regulatory suppression of the TLR4/NF- κ B pathway that ultimately reduces inflammation^[88]. Furthermore, FMT can enhance production of protective factors such as secretory IgA (sIgA) that aid further by neutralizing microbial elements in the gut lumen to inhibit TLR4 activation. Overall, treatment with FMT may prove to be an

effective therapeutic target for shifting the homeostasis during ALI and AD by inhibiting both central and peripheral inflammatory responses.

3.2 Aryl hydrocarbon receptor (AHR) pathway

The AHR pathway operates as a ligand-activated transcriptional regulator, influenced by microbial metabolites, such as tryptophan derivatives. The gut microbiota produce endogenous AHR ligands, including indoles and kynurenine, with reports demonstrating that AHR activation can coordinately regulate immune responses, maintain epithelial barrier integrity, and facilitate detoxification pathways^[89]. An active and balanced gut microbiota maintains homeostasis through AHR events in the host; yet disturbance of gut microbiota can yield the insufficient or excessive activation of AHR, contributing to immune dysregulation and barrier dysfunction. FMT replenishes the AHR ligand-producing microbes (including indoles and kynurenine), normalizing the activation of this pathway. Increased activation of the AHR signal is hypothesized to strengthen the regulation of immune responses, detoxification pathways, and tissue repair when the gut microbiota is equilibrated, supporting the premise that the gut microbiota is crucial for AHR-dependent homeostasis in the gut. Wang *et al.*^[90] found evidence that FMT could reduce methamphetamine (Meth)-associated depression and anxiety through the AHR signaling pathway. They showed that the recipient mice receiving microbiota from the Meth withdrawal mice had a marked increase in depressive and anxiety-like behaviors with a concurrent population decrease in gut microbiota associated with tryptophan (TRP) metabolism (e.g., *Akkermansia*, *Bacteroides*, and *Faecalibaculum*). There were also significantly decreased levels of TRP-derived indole metabolites (e.g., indole-3-propionic acid (IPA), indole-3-acetic acid (IAA), and indole) notably in both individuals who abused Meth and in the Meth withdrawal model mice. Supplementation with these TRP-derived metabolites to the Meth abusing mice significantly improved Meth-related behavioral abnormalities, but those protective effects were abolished in AHR knockout mice. This suggests a role of the microbiota-indoles-AHR signaling axis in Meth-associated psychological disturbances and that FMT may offer some protective effects by restoring gut microbiota balance and augmenting TRP metabolism.

3.3 NLRP3 inflammasome pathway

The NLRP3 inflammasome forms an important aspect of the innate immune response and is activated by both microbial metabolites and environmental stressors. Its role in the initiation of inflammatory responses, shaped by gut microbiota, is paramount^[91]. Gut dysbiosis can increase NLRP3 inflammasome activation, which can increase the generation of pro-inflammatory cytokines (i.e., IL-1 β , IL-18), driving systemic inflammation and immune dysfunction^[92]. Therefore, gut microbiota regulation of the NLRP3 inflammasome is essential for immune homeostasis and inflammatory regulation.

Disrupting gut microbiota can drive overproduction of inflammasome-activating metabolites (e.g., trimethylamine N-oxide (TMAO)) that increase inflammasome activation and promote chronic inflammation. By restoring microbiota balance using interventions like FMT, levels of inflammasome-activating metabolites can be reduced, in turn decreasing NLRP3 inflammasome activation^[93]. Research shows that FMT can modulate gut microbiota composition, suppress inflammatory pathways, and restore immune homeostasis. This emphasizes the

role of gut microbiota in maintaining immune responses and in monosymptoms of inflammation-associated diseases.

Recent studies have additionally emphasized the efficacy of modulating gut microbiota, *via* NLRP3 inflammasome, for alleviating inflammation. For example, FMT has been shown to restore healthy microbiota and decrease NLRP3 inflammasome activation across various disease animal models^[94]. Modulating microbial balance reduces systemic inflammation and is seen as a potential therapeutic strategy for diseases related to chronic inflammation with psychiatric community interest in autoimmune disease and metabolic disruption. Xu *et al.*^[95] indicated that FMT may exert antidepressant-like effects in postpartum depression (PPD) models *via* the NLRP3 inflammasome signaling pathway. In their study, FMT from healthy mice to PPD model mice alleviated depression and anxiety-like behaviors and decreased NLRP3/caspase-1-mediated inflammation in both the gut and hippocampus. FMT led to increased SCFAs-producing bacteria and decreased *Akkermansia* in the gut microbiota in PPD models when compared to healthy models. Furthermore, decreased NLRP3 in the hippocampus decreased depression-like behaviors in PPD models; while NLRP3 overexpression in dentate gyrus of the hippocampus increased depressive behaviors in naive female mice. Moreover, FMT from healthy mice did not improve depressive-like symptomatology in PPD models with hippocampal NLRP3 overexpression. This data indicates a critical role for the NLRP3 inflammasome in GBA biology and suggests that FMT may mediate PPD symptomatology through the NLRP3 inflammasome pathway. The efficacy of gut microbiota modulation emphasizes its importance in immune function and inflammasome activity.

3.4 SCFAs-Mediated pathways

SCFAs, which include acetate, propionate, and butyrate, serve as important energy substrates for colonocytes and also act as key signaling molecules that modulate host physiology. SCFAs can alter immune responses by interacting with G-protein-coupled receptors (GPCRs) such as GPR41 and GPR43, and Olfr78, while

also regulating gene expression *via* histone deacetylase (HDAC) inhibition^[96]. In addition to the GPCR and HDAC pathways, SCFAs can also modulate system-wide immunity by regulating regulatory T cell (Tregs) differentiation, promoting anti-inflammatory signaling, and inhibiting the production of pro-inflammatory cytokines (e.g., IL-6, and TNF- α) (Fig. 2).

A healthy microbiota is essential for maintaining SCFAs signaling and production. Dysbiosis disrupts SCFAs-mediated signaling, in part by decreasing GPCR activation and inhibiting HDACs^[97]. Dysbiosis leads to a host of secondary consequences, including increased intestinal permeability and systemic inflammation, as well as metabolic dysregulation, which are all key components in the pathogenesis of chronic inflammatory diseases (e.g., IBD), metabolic diseases (e.g., diabetes), and CVD, among others. Additionally, as SCFAs levels decline, crosstalk between the gut and other organs may also be disrupted, contributing to the development of immune dysfunction and metabolic dysregulation. Tian *et al.*^[98] demonstrated in an animal model that FMT could improve the therapeutic effects of enteric neural crest cells (ENCC) transplantation, likely through modulation of SCFAs-mediated signaling and pathways. Their study showed that FMT improved outcomes in a rat model of hypoganglionosis by increasing the relative abundance of *Bacteroides*, *Clostridium*, and other SCFAs-producing bacteria. SCFAs promoted ENCC proliferation, migration, and functional integration in the gut. Transcriptomic analyses showed that SCFAs-mediated beneficial effects on ENCC outcomes likely occurred *via* MAPK signaling pathways, specifically MEK1/2 signaling. Importantly, when the MEK1/2 pathway was inhibited, the beneficial effects of SCFAs were lost, indicating that SCFAs and MAPK signaling specifically mediated the therapeutic effects of FMT. These findings suggest that FMT positively influences outcomes following ENCC transplantation, in part by improving SCFAs signaling.

Gut dysbiosis, which occurs due to the loss of SCFAs-producing bacteria, disrupts regulatory networks required for the maintenance of immune and metabolic homeostasis and contributes to the pathogenesis of inflammatory and metabolic

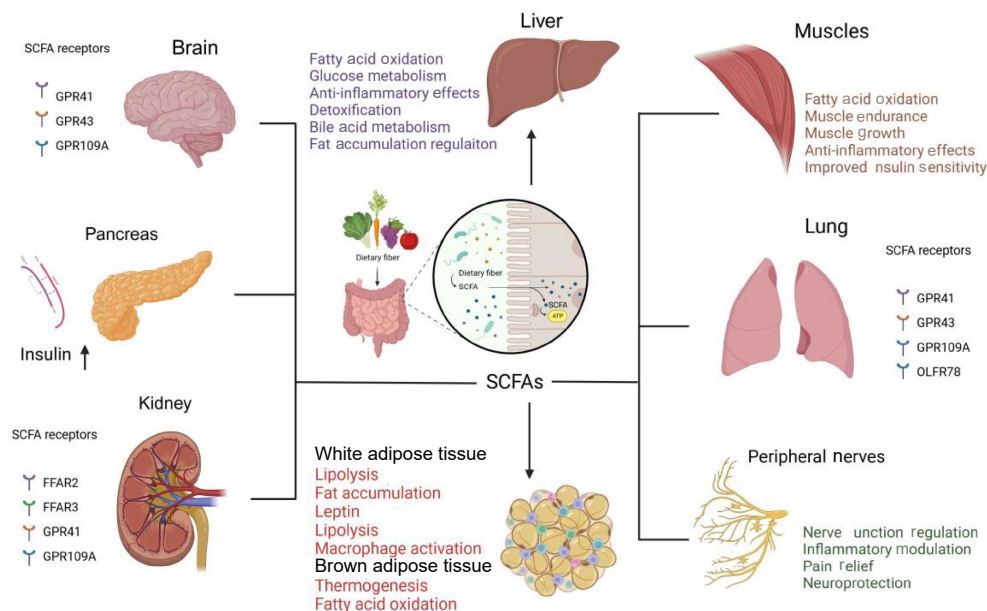


Figure 2 Biological effects of SCFAs on various organs. SCFAs can regulate the functions of various tissues and organs, such as the pancreas, brain, kidneys, heart, muscles, and adipose tissue, through multiple receptors, including free fatty acid receptor 2 (FFAR2) and G protein-coupled receptor 41 (GPR41), etc. Created in <https://BioRender.com>.

diseases. Microbiota-targeted therapies, including FMT and nutritional interventions, restore SCFAs-producing microbiota composition while also improving metabolic health. Increased butyrate production reduces the inflammatory response by promoting Treg differentiation, suppressing proinflammatory cytokine release, and strengthening the intestinal epithelial barrier to preserve immune tolerance and attenuate systemic inflammation^[99]. Overall, the gut microbiota and SCFAs play major roles in the preservation of host homeostasis and offer harness the therapeutic potential when addressing chronic inflammatory and metabolic conditions, including IBD, obesity, and neurodegenerative diseases (Fig. 3).

3.5 5-HT pathway

The gut microbiome is crucial in generating 5-HT as an approximate 90% of the body's 5-HT is produced in the gut^[100]. The enterochromaffin cells (EC), which are located in the intestinal mucosa, are the primary source of gut-derived 5-HT, which is made from the amino acid tryptophan by the enzyme tryptophan hydroxylase 1 (Tph1). Tph1 catalyzes the conversion of tryptophan to 5-hydroxytryptophan (5-HTP) and 5-HTP is subsequently transformed into 5-HT^[101]. The produced 5-HT then targets receptors on enteric neurons, smooth muscle cells, and immune cells in order to regulate several gut-related processes, including gut motility, gut secretion, and gut-brain cross talk.

The gut microbiome influences 5-HT synthesis primarily through microbial metabolites like SCFAs and secondary bile acids that enhance Tph1 expression in EC cells, which promotes the synthesis of 5-HT^[102]. GF mice studies demonstrate the role of gut microbes in regulating 5-HT levels, as GF mice have significantly lower gut 5-HT levels than controls. Derived from studies such as those featuring GF mice, there are specific gut microbial species that can metabolize tryptophan into tryptamine that also serves as a precursor to 5-HT^[103]. *Escherichia coli* and *Streptococcus* spp. are notable examples of such bacteria that can use tryptophan in this manner.

Along with influencing uptake and synthesis, the gut microbiome also influences the metabolism of 5-HT. The primary route of 5-HT metabolism is *via* monoamine oxidase (MAO), there have recently been some studies regarding an anti-inflammatory role of MAO through G-protein coupled receptor 35 (GPCR35)^[104]. At the level of 5-HT usage in the

gastrointestinal tract, dysbiosis of the gut microbiome can influence the reuptake of 5-HT through the 5-HT transporter (SERT). Disruptions in the normal functioning of SERT leads to disrupted intestinal 5-HT signaling which may contribute to gastrointestinal disorders, as well as the pathogenesis of neuropsychiatric diseases linked to dysregulation in 5-HT signaling^[105]. Jiang *et al.*^[106] and colleagues have demonstrated that FMT can alleviate or improve depressive behavior in mice that are not responsive to selective 5-HT reuptake inhibitors (SSRIs) and that this improvement may be associated with 5-HT usage. In the same study, FMT alleviated depressive behavior, and also partially restored diversity and structure of the gut microbiome. There were a panel of metabolites that were identified by their metabolomic analysis and these metabolites were linked to important metabolic pathways, which also indicated that there are microbiome metabolites that were responding to FMT. Most importantly, FMT increased the abundance of *Paraprevotella*, which was associated with lower levels of baicalin and increased expression of T-cell acute lymphocytic leukemia protein 2 (TAL2). Taken together, the authors demonstrated that gut microbiome and metabolites may directly modulate 5-HT pathways and help to mediate some antidepressant effects.

Therapies aimed at increasing 5-HT biosynthesis and transmission, including the clinical therapies FMT and probiotics as well as pharmaceutical agents like SSRIs, clearly represent an intersection between gut microbiota and 5-HT transmission and usage and provides useful frameworks for therapeutic approaches in disorders related to 5-HT dysregulation.

4 Therapeutic potential of key gut microbial strains and their mechanisms of action

The therapeutic capabilities of bacterial strains in FMT have become increasingly evident and various studies have emerged supporting their roles in disease modulation. Some bacterial taxa play a role in maintaining gut homeostasis, including enhancing the integrity of the gut barrier, regulating immune responses, managing energy metabolism, and the impact on the GBA. Table 1^[107-156] summarizes the therapeutic effects of some selected bacterial strains, the diseases they are related to, and the mechanisms that lead to their effects, which can be a basis for continued exploration of the strains in future clinical practice

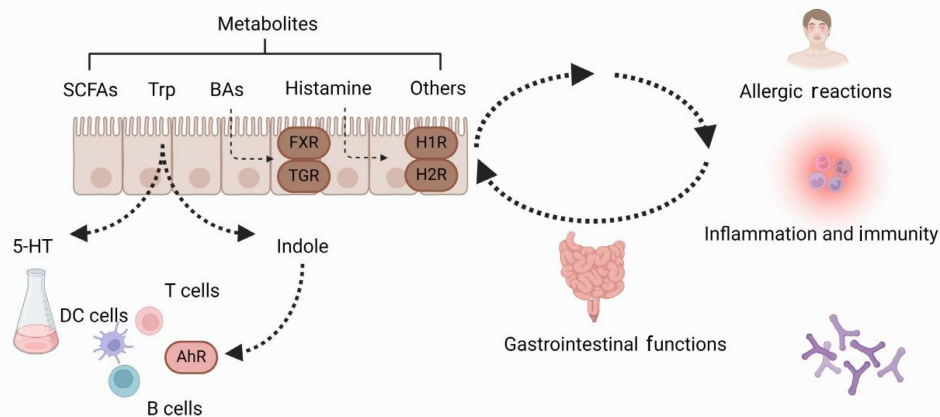


Figure 3 Metabolites and their role in gut and immune function regulation. Gut microbial metabolites, including SCFAs, tryptophan derivatives, bile acids, and histamine, interact with intestinal receptors (FXR, TGR5, histamine receptor 1 (H1R), histamine receptor 2 (H2R)) to regulate gastrointestinal functions, immunity, and allergic responses. Tryptophan metabolites, such as indole, activate the AhR in immune cells, influencing inflammation. Microbial activity also affects 5-HT production, contributing to immune regulation and gut-brain signaling. Created in <https://BioRender.com>.

Table 1 Therapeutic potential of selected gut microbial strains and their mechanisms of action

Bacterial strain	Therapeutic effect	Disease/Condition	Mechanism of action	References
<i>Akkermansia muciniphila</i>	Improved gut barrier function, enhanced insulin sensitivity, reduced insulinemia, improved cholesterol levels, slight reduction in body weight and fat mass	Obesity, type 2 diabetes, MetS, liver disorders	Enhanced gut barrier integrity, improved insulin sensitivity, reduced inflammation, modulation of energy metabolism	[107, 108]
<i>B. fragilis</i>	Modulates immune response, reduces neuroinflammation, regulates bile acid homeostasis	ASD, depression	Improves ASD behavior and gastrointestinal symptoms; reduces depressive behaviors and hippocampal neurogenesis impairment; decreases taurothiocholic acid (TLCA) and deoxycholic acid (DCA) levels via pregnane X receptor (PXR)-dependent pathway	[109-111]
<i>F. prausnitzii</i>	Reduces intestinal inflammation, prevents colitis, aids mucosal healing in IBD patients	IBD, CD	Anti-inflammatory properties, SCFA production, inhibits NF- κ B pathway, promotes IL-18 expression via HIF1 α pathway	[112-114]
<i>Clostridium butyricum</i>	Reduces intestinal inflammation, enhances gut barrier integrity, Improves overall IBS-D symptoms, quality of life, and stool frequency	UC, IBS	Regulates lamina propria dendritic cells (LPDCs), decreases IL-1 β and IL-6 expression, reduces T cell immunoglobulin and mucin domain-containing protein 3 (TIM3) on lamina propria dendritic cells (LPDCs), enhances NLRP6 expression	[115-117]
<i>Desulfovibrio</i> spp.	Adverse effect on renal function, improved anxiety/depression, possible negative impact on mental health	Chronic kidney disease (CKD), depression	Possible involvement in inflammatory pathways and oxidative stress, impacting renal microvascular function, potential modulation of GBA, overproduction of H ₂ S, alteration of neurotransmitter balance	[118-121]
<i>Lactobacillus rhamnosus</i> GG	Osteoporosis prevention, diarrhea management, UC treatment, allergy management, atopic dermatitis (AD) prevention, antibiotic-associated diarrhea (AAD) prevention	Postmenopausal osteoporosis, acute diarrhea, AAD, UC, cow's milk protein allergy, AD	Enhances bone microarchitecture, promotes osteogenesis, regulates Th17/Treg balance, prevents colonic tissue damage, inhibits TLR4-NF- κ B-NLRP3 axis activation, and suppresses pro-inflammatory cytokines, reduces AAD risk by stabilizing gut microbiota and reducing gut inflammation, promotes earlier acquisition of tolerance through immune modulation	[122-125]
<i>Bifidobacterium breve</i>	Enhances cognition and prevents brain atrophy, mitigates AD-like pathologies, neuroprotective effects, attenuates cognitive deficits and neuroinflammation, reduces brain inflammation and lipid droplet formation	AD, cognitive decline, PD, dementia	GBA modulation, Reduces A β levels, inhibits tau phosphorylation, and activates Akt/GSK-3 β pathway, reducing oxidative stress, decreases perilipin 4 expression and blocks oxidative stress-induced inflammation	[126-131]
<i>E. coli</i> Nissle	Reduces diarrhea frequency, stool consistency improvement, and shortens disease duration, induces remission and prevents relapse in UC, comparable to mesalazine in maintaining remission, lowers serum uric acid levels, reduces adenoma burden and enhances immunotherapy, potential for direct tumor injection or systemic administration, efficient delivery vehicle for therapeutic agents	Infectious diseases, IBD, UC, metabolic disorders, IBD, colorectal cancer, cancer therapy, drug delivery system	Competes with pathogenic bacteria, enhances immune response; regulates immune factor secretion, enhances host immunity; recombinant <i>E. coli</i> Nissle 1917 (EcN) expressing urate-degrading enzymes; selective tumor colonization, engineered to produce salicylate for screening or granulocyte-macrophage colony-stimulating factor (GM-CSF) and nanobody delivery for therapy; genetic engineering enhances colonization, stability, and targeted release of drugs	[132-139]
<i>Roseburia</i> spp.	Improves hepatic steatosis and inflammation; reduces inflammation, may slow CKD progression; potential biomarker for rheumatoid arthritis-associated interstitial lung disease (RA-ILD) and RA-non-ILD; improves gut health in histamine intolerance	Alcohol-related liver diseases (ALDs); CKD; RA-ILD and RA-non-ILD; histamine intolerance	Enhances gut barrier integrity via TLR5 recognition, upregulating Occludin and increasing IL-22 and REG3 γ expression; negatively associated with C-reactive protein (CRP) and cystatin C, positively associated with estimated glomerular filtration rate (eGFR); depletion observed in RA-ILD and RA-non-ILD patients; increased abundance associated with improved gut health after low-histamine diet and diamine oxidase (DAO) enzyme supplementation	[140-144]
<i>Ruminococcus bromii</i>	Favorable prognosis in colon cancer; early diagnostic marker for CKD; reduced risk of AD; enhanced resistant starch (RS) fermentation; improved ICI response	CKD; cancer immunotherapy resistance; AD; energy recovery and digestive health; general gut health	Reduces toxic metabolites; Increases butyrate levels and promotes beneficial microbial cross-feeding; facilitates resistant starch degradation and improves energy recovery; binds to castalagin, enriching immune-supportive bacteria; enhances immune response via tumor-enriched T cell clones and reduces neoantigen load	[145-150]
<i>Enterococcus faecium</i>	Infection improvement; Improvement of IBS symptoms (including abdominal pain, bloating, and stool consistency)	CDI; IBS; IBD; AAD, vancomycin-resistant enterococcus (VRE) infections	Competes with pathogens for nutrients and adhesion sites; inhibition of VRE clones; restoring gut flora protection; modulation of metabolic pathways (e.g., mineral absorption and metabolism of arachidonic acid, D-arginine, D-ornithine, phenylalanine, and vitamin B ₆)	[151-155]
<i>Veillonella</i> spp.	Enhanced athletic performance, improved fatigue resistance	Exercise-induced fatigue; decreased exercise performance	Lactate metabolism enhancement	[156]

FMT applications.

5 Therapeutic applications of FMT

5.1 Conventional FMT *via* colonoscopy or enema

Conventional FMT through enema or colonoscopy has been established as an effective intervention in conditions associated with gut dysbiosis, specifically *Clostridioides difficile* infection (CDI). This therapeutic intervention involves the introduction of fecal material from a healthy donor into the colonic environment of a recipient *via* colonoscopy or enema. This therapeutic modality has several strong advantages: it permits the transfer of the entire microbiota (bacteria, viruses, fungi) to the lower gastrointestinal tract, which is usually the site of dysbiosis in CDI or IBD patients^[157].

Colonoscopy aids in placing the fecal material precisely within the colon and a bonus benefit of colonoscopy is that it allows direct assessment of the colonic mucosa to determine if further pathology, such as lesions or active inflammation, is present. In patients with IBD, FMT has been demonstrated to restore microbial diversity, reduce inflammation, and in some patients, provide remission in those with limited response to conventional therapies. In recurrent CDI, FMT *via* colonoscopy has shown cure rates exceeding 90%, demonstrating superior efficacy compared to conventional antibiotics^[158]. However, this approach is invasive and presents risks of bowel perforation, infection, and discomfort, which may limit its viability for certain populations—largely the elderly or frail. Nonetheless, colonoscopic FMT is still the standard of care for severe CDI or recurrent CDI and is currently being studied for other indications, such as disease management for IBD or metabolic disorders.

5.2 Oral administration of FMT capsules

The development of oral FMT capsules is an important innovation in the delivery methods of FMT especially for recurrent *C. difficile* infection (rCDI). Oral FMT capsules provide a non-invasive and less burdensome option compared to conventional delivery methods such as enema or colonoscopy. It has the potential to enhance compliance and the accessibility of FMT as a therapy.

Currently, there is evidence showing that oral FMT capsules have an overall efficacy of 82.1% similar to colonoscopic FMT^[159]. Importantly, no significant differences have been identified in treatment outcomes related to capsule preparation (e.g., frozen vs. biopharmaceutical) or delivery method (capsule vs. enema). The safety of oral FMT capsules is also very favorable and there certainly have not been any severe adverse events that were directly attributable to FMT, which supports its clinical feasibility and reliability.

There are ongoing efforts to expand the indications for oral FMT capsules to include an even wider number of diseases beyond rCDI and further diseases in relation to gut dysbiosis. Preparing standardized capsules, establishing dosing regimens, and determining long-term efficacy and safety, are challenges that still exist. Future studies will be needed to further examine study protocols and standardize oral FMT capsules as a vetted treatment to be delivered more easily in microbiota-based therapies.

5.3 FMT *via* nasogastric or nasoduodenal tube

FMT has emerged as a recognized treatment option for gut dysbiosis-related conditions. Although traditional approaches such

as colonoscopy and enema applications are commonplace, interest has developed in delivery methods to patients who do not want to or cannot admit to invasive delivery methods. One such method is FMT *via* spiral nasojejunal tube (SNT). This procedure involves placing a tube in the patient's nostril, which leads into the small intestine where feces from a recognized healthy donor is then infused with the goal of restoring microbial homeostasis.

A recent prospective interventional trial examined clinical efficacy, comfort, and costs of SNT and mid-gut transendoscopic enteral tubing (TET) for washed microbiota transplantation (WMT) with 63 patients^[160]. Patients were divided into 2 groups: SNT ($n = 40$) and mid-gut TET group ($n = 23$). The clinical efficacy of WMT was found to be similar between the two groups, with the SNT group showing an efficacy of 90% and the mid-gut TET group showing 95.7% ($P = 0.644$). These treatments are both clinically efficacious, and SNT provides a good, alternative non-invasive option to mid-gut TET. In terms of the procedural aspects, SNT had several advantages: procedure time for SNT was significantly shorter than TET (120 s vs. 258 s, $P = 0.001$), and costs were significantly lower for SNT at an average of CNY 641.7 compared to CNY 1,702.1 for the TET group ($P = 0.001$). There were no significant differences in the comfort score or incidence of usual comfort symptoms (e.g., nausea, abdominal discomfort) between groups. Therefore SNT may be a more time and cost-effective method of FMT that appears to be equal in patient comfort and clinical outcomes.

5.4 Rectal FMT for pediatric patients

In pediatric patients, rectal administration of FMT is usually the preferred route, as it is simpler and less invasive than colonoscopy or oral capsules. FMT is an efficacious, safe, and minimally invasive procedure to restore the gut microbiota balance in children with allergic colitis. In this procedure, donor fecal matter is introduced into the rectum (such as *via* enema) to specifically, but not exclusively targeted the lower gastrointestinal (GI) tract. As a point of treatment, this may be preferable in children since it typically requires less preparation, is generally well-tolerated, and poses a lower risk than more invasive procedures like colonoscopy. In a cohort study of 19 pediatric patients with allergic colitis (AC), rectal FMT achieved a high clinical success rate, with 17 of those infants experiencing resolution of their symptoms quickly (typically within 2 days)^[161]. There were also no recurrences noted in the following 15 months of follow-up. Infants' gut microbiome composition had improved, showing greater diversity and microbial abundance shifts, including decreased Proteobacteria and increased Firmicutes, while important genera (*Bacteroides*, *Escherichia* and *Lactobacillus*) showed enrichment post-FMT.

Although rectal FMT has been shown to be a safe and effective treatment for AC in children, further studies are needed to assess the treatment's long-term safety, feasibility of repeated treatments, and for use across other pediatric gastrointestinal conditions. However, rectal FMT is already a promising alternative to invasive therapies with the potential of providing a non-invasive method to restore the microbial balance to pediatric patients.

6 Conclusion

FMT is a potentially effective treatment for restoring stable gut microbiome homeostasis and treating a number of diseases associated with dysbiosis. FMT has been shown to be beneficial in gastrointestinal, metabolic, and neurological disorders through

varied delivery modalities, including colonoscopy, oral capsules, and nasogastric tubes, but, several issues regarding donor material quality, microbiotic stability, and long-term efficacy still need to be addressed.

Synthetic microbial consortia are a promising and standardized alternative to traditional FMT, with great potential for reproducibility and scalability. Personalized methods of treatment such as autologous FMT may increase safety when considering more vulnerable patient populations (e.g., immunocompromised patients). Further research will result in expanded usage of FMT outside of gut-related diseases, with the potential to revolutionize useful therapies based on the microbiome.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

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