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Fecal Microbiota Transplantation (FMT): Historical Perspectives, Expanding Therapeutic Applications, and Future Prospects in Human Health

Parameshwar Jakinala[1*], Harikrishna Naik Lavudi[1], Badithi Nani Babu[1], Doni Sri Lakshmi Angadala[2], Athoti Revanth[2], Kochera Rachel[2], Chintakrindi Chandra Sekhar[2], Anirudh Vivin Sabbi[2], Ushasree Ravula[1], Madhumohan Rao Katika[1*]

[1]Department of Microbiology, IG-Nomix and StemRegenex Bio Pvt Ltd., Hyderabad, India
[2]Department of Bio-Technology, Koneru Lakshmaiah Education Foundation, Vaddeswaram, India
Email: *jparamesh9@gmail.com, *maddycdfd@gmail.com

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Abstract

Fecal microbiota transplantation (FMT) has evolved from ancient Chinese medicine to a modern therapeutic intervention, gaining recognition in 1958 for treating pseudomembranous colitis. Today, recurrent *Clostridioides difficile* infection (rCDI) treatment is highly effective, and it has more than 90% success rate. Beyond rCDI, FMT shows promise in addressing metabolic disorders, autoimmune diseases, skin diseases, glaucoma and autism spectrum disorder, where it may enhance immune checkpoint inhibitor efficacy. However, challenges remain, including the lack of standardized protocols, donor-recipient matching complexities, long-term safety concerns, and ethical issues. Future advancements in personalized FMT, computational tools, and large-scale clinical trials are essential to overcome these limitations and expand its applications. This review highlights FMT's transformative potential in modern medicine while emphasizing the need for rigorous research, standardized protocols, and innovative strategies to optimize its therapeutic benefits across diverse diseases.

Keywords

Fecal Microbiota Transplantation, Gut Microbiome, Dysbiosis, *Clostridioides difficile*, Autoimmune Diseases, Metabolic Disorders

1. Introduction

The human gut microbiota, a complex ecosystem of trillions of microbes, plays a

pivotal role in maintaining host health by regulating digestion, immunity, metabolism, and even neurological functions [1] [2]. Disruption of this microbial balance, known as dysbiosis, has been implicated in various diseases, from gastrointestinal disorders like inflammatory bowel disease (IBD) and *Clostridioides difficile* infection (CDI) to systemic conditions such as obesity, diabetes, and neurodegenerative disorders [3] [4].

With the rising global burden of chronic diseases, there is increasing interest in therapeutic strategies that target the microbiome. Fecal microbiota transplantation (FMT)—the transfer of fecal matter from a healthy donor to a recipient has emerged as a promising intervention for restoring gut microbial homeostasis [5]-[7]. Initially established as a treatment for recurrent CDI, FMT is now being investigated for a broad range of conditions, including ulcerative colitis, obesity, diabetes, autoimmune diseases, and neurological disorders such as autism and epilepsy [8]-[12]. Advances such as washed microbiota transplantation (WMT), a refined FMT technique involving automated purification to enrich beneficial microbes and remove impurities like food residues, pathogens, and pro-inflammatory components, have improved the procedure's safety and efficacy [13] [14]. Compared to conventional FMT, WMT offers greater consistency and lower risk of adverse events, making it especially suitable for immunocompromised patients and standardized clinical applications.

The growing threat of antibiotic resistance has also spurred interest in FMT as an alternative or adjunct therapy [6]. Nevertheless, safety remains a key concern. A global review (2000-2020) reported adverse events (AEs) in 19% of FMT cases, most commonly diarrhea and abdominal discomfort, with serious adverse events (SAEs), including infections and deaths, occurring in 1.4%, particularly in patients with compromised gut barriers [14]. These findings underscore the need for standardized protocols in donor selection, recipient preparation, and FMT administration [5] [15] [16]. Technological advancements such as metagenomic sequencing and metabolomic profiling have deepened our understanding of FMT's therapeutic effects, which may involve restoring microbial diversity, modulating immune responses, and promoting production of short-chain fatty acids (SCFAs) [2] [17]-[20]. Meanwhile, methodological innovations like WMT continue to improve its clinical utility [13] [14].

This review presents a comprehensive examination of FMT, covering its historical background, clinical applications, methodological considerations, and emerging indications, including autoimmune and metabolic diseases, dermatological conditions, glaucoma, and neurodevelopmental disorders such as autism spectrum disorder (ASD). By synthesizing current evidence, we aim to clarify FMT's therapeutic potential and identify avenues for future research to optimize its clinical implementation.

2. Fecal Microbiota Transplantation (FMT): Historical Evolution

Fecal microbiota transplantation (FMT) is a therapeutic procedure that involves

transferring beneficial microorganisms from a healthy donor's feces into a recipient's gastrointestinal (GI) tract to restore and rebalance their gut microbiome (Figure 1). FMT has a long and fascinating history, with its origins tracing back to ancient China, where fecal suspensions referred to as "yellow soup" were used as early as AD 300 - 400 to treat severe diarrhea and food poisoning [6] [21]. These early practices align with modern criteria for FMT and highlight its enduring therapeutic potential [12]. The modern era of FMT began in 1958 when Eiseman and colleagues successfully treated patients with *pseudomembranous enterocolitis*, later identified as CDI, marking the first documented use of FMT in contemporary medicine [22]. Since then, FMT has gained widespread recognition, particularly for its remarkable efficacy in treating recurrent CDI with success rates exceeding 90% [23].

Similarly, Indian scriptures from 3000 years ago describe the therapeutic use of cow dung for gastrointestinal ailments [24]. By the 16th century, during the Ming Dynasty, fermented fecal preparations were applied to manage conditions such as diarrhea, constipation, and abdominal pain [5]. The term "transfaunation", coined by Italian surgeon Hieronymus Fabricius Aquapendente, later influenced veterinary practices involving gut microbiota transfer [21]. A landmark 2013 randomized trial demonstrated the superiority of FMT over antibiotics for recurrent *Clostridioides difficile* infection (rCDI), achieving symptom resolution in 90% of cases [25]. This pivotal study catalyzed the adoption of FMT for refractory CDI and spurred exploration into its use for non-infectious diseases. Borody *et al.* [26] first reported the efficacy of FMT in ulcerative colitis (UC), marking its transition toward treating autoimmune and metabolic disorders. Today, FMT is being studied for a wide range of conditions, including obesity, neuropsychiatric disorders, and metabolic diseases, reflecting the systemic influence of the gut microbiome [3] [14] [27].

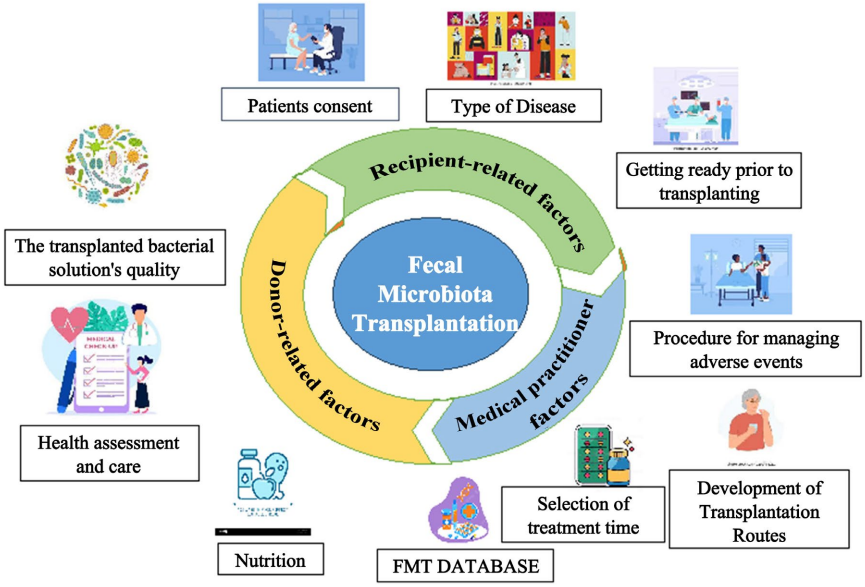

Figure 1. FMT treatment outcomes are influenced by a combination of donor, recipient, and medical practitioner factors.

FMT aims to restore microbial diversity or suppress pathogenic species by transferring donor microbiota to a recipient [12]. Pre-FMT colonic lavage may enhance engraftment by reducing residual pathogens [28]. The gut microbiome, shaped by factors such as genetics, early-life exposures, antibiotic use, and diet, exhibits functional redundancy across individuals. FMT introduces not only bacteria but also viruses, fungi, and donor-derived metabolites, complicating mechanistic studies [29]. Autologous FMT involves the use of an individual's own previously collected and stored stool, typically for microbiota restoration following medical treatments that disrupt gut flora. In contrast, allogeneic FMT uses stool from a healthy donor to treat another individual, aiming to correct dysbiosis or restore microbial diversity in the recipient. Autologous FMT involves re-transplanting a patient's own pre-collected healthy stool after microbiome disruption, such as following antibiotic use [3].

Autologous FMT involves re-transplanting a patient's own pre-collected healthy stool after microbiome disruption, such as following antibiotic use. This approach avoids the risks associated with allogeneic donor FMT and is particularly studied in allogeneic hematopoietic stem cell transplantation (allo-HSCT) to mitigate infections [3] [14]. Emerging evidence suggests that autologous FMT may counteract weight regain post-dieting and modulate autoimmunity in type 1 diabetes (T1D). While autologous FMT has demonstrated success in T1D patients, clinical trials remain limited, and further research is needed to establish guidelines for defining healthy autologous stool and determining optimal collection times. Allogeneic FMT uses donor stool to treat conditions such as CDI, inflammatory bowel disease (IBD), and metabolic disorders. Maternal FMT in caesarean-delivered infants has been shown to restore microbiome diversity akin to vaginal birth, potentially preventing autoimmune diseases [3].

In addition to bacteria, FMT introduces non-bacterial components such as viruses (particularly bacteriophages) and fungi, collectively referred to as the virome and mycobiome. These components may play therapeutic roles by influencing microbial community structure, modulating host immunity, and enhancing bacterial colonization resistance [30]. For instance, bacteriophages can selectively target pathogenic bacteria, while certain fungi may contribute to gut-immune interactions [31]. However, their presence also introduces confounding variables in mechanistic studies, as their individual and synergistic effects on the host and microbiota remain poorly understood. This complexity highlights the need for integrated multi-omics approaches to fully elucidate FMT's mode of action and optimize its composition for targeted therapies [32].

Despite its potential, standardizing FMT into a regulated clinical practice that aligns with expert consensus guidelines remains an ongoing challenge. The complexity of the gut microbiome, which includes bacteria, viruses, fungi, and metabolites, complicates mechanistic studies and the development of standardized protocols [30]. Additionally, the long-term safety and efficacy of FMT, particularly for non-infectious conditions, require further investigation. The historical evolu-

tion of FMT, from ancient remedies to modern therapeutic applications, underscores its potential to address a wide range of diseases. However, continued research is essential to optimize protocols, ensure safety, and expand its clinical use [23].

3. Fecal Microbiota Transplantation (FMT): Donor Screening and Standardization

Fecal Microbiota Transplantation (FMT) efficacy heavily depends on rigorous donor selection and screening to minimize infection risks. Prospective donors undergo comprehensive health evaluations, including questionnaires, clinical assessments, and stool and blood testing, guided by expert consensus [5] [16] (**Table 1**) (**Figure 2**). These protocols are updated to address emerging threats like COVID-19 and monkeypox [16]. Advances in sequencing have identified microbiota signatures such as richness, abundance, stability, and evenness linked to FMT success. However, stringent criteria result in low donor eligibility rates, e.g., 1.7% in a Chinese cohort and 3.9% in a U.S. study [31].

Table 1. Donor screening criteria and testing methods.

Category	Condition/Risk Factor	Method
General Exclusion Criteria	Age < 18 or >65 years	Questionnaire
	Recent (<6 months) blood product transfusion	Questionnaire
	Previous (<12 months) organ/tissue transplant	Questionnaire
	Recent (<6 months) needle stick accident	Questionnaire
	Alcohol consumption > 15 units/week (women) or >22 units/week (men)	Questionnaire
	Pregnant or breastfeeding women	Questionnaire
Infectious Disease Risk	Known HIV, Hepatitis B/C infections	Questionnaire
	High-risk sexual behavior	Questionnaire
	Use of illicit drugs	Questionnaire
	Recent (<6 months) travel to high-risk countries	Questionnaire
	Healthcare workers (risk of multidrug-resistant organisms)	Questionnaire
	Exposure to blood borne infections (HIV, HBV, HCV, syphilis, malaria)	Questionnaire
Gastrointestinal (GI) Conditions	History of IBD, IBS, chronic diarrhea/constipation, celiac disease	Questionnaire
	History of GI malignancy or polyposis	Questionnaire
	Major GI surgery	Questionnaire
	New GI symptoms (diarrhea, nausea, vomiting, jaundice)	Questionnaire
Metabolic & Autoimmune Disorders	Diabetes (FPG ≥ 126 mg/dL or 2-h PG ≥ 200 mg/dL)	Questionnaire
	Metabolic syndrome	Questionnaire
	Systemic autoimmunity (multiple sclerosis, connective tissue disease)	Questionnaire
	Atopic conditions (asthma, dermatitis, eczema)	Questionnaire

Continued

Neurological & Psychiatric Conditions	Parkinson's disease	Questionnaire
	Schizophrenia, delusion disorder, severe depression	Questionnaire
	Dementia or other psychiatric disorders	Questionnaire
	Chronic pain syndromes (fibromyalgia, chronic fatigue)	Questionnaire
Factors Affecting Gut Microbiota	Recent (<3 months) antibiotics	Questionnaire
	Major immunosuppressive medications	Questionnaire
	Chronic proton pump inhibitor use	Questionnaire
Blood Testing	Hepatitis A (HAV-IgM)	Blood test
	Hepatitis B (HBsAg, anti-HBc)	Blood test
	Hepatitis C (anti-HCV)	Blood test
	Hepatitis E (anti-HEV IgM)	Blood test
	HIV I & II (Anti-HIV)	Blood test
	Human T-cell lymphotropic virus (Anti-HTLV)	Blood test
	Treponema pallidum (RPR, VDRL, EIA)	Blood test
	Complete blood count	Blood test
	C-reactive protein	Blood test
	Liver function test	Blood test
	Renal function test	Blood test
Stool Testing for Viruses	*Rotavirus*	EIA
	Norovirus	PCR
Stool Testing for Bacteria	*Salmonella* sp.	Culture ± PCR
	Shigella sp.	Culture ± PCR
	Campylobacter sp.	Culture ± PCR
	Vibrio sp.	Culture ± PCR
	Clostridium difficile	PCR
	Helicobacter pylori	Stool antigen
Stool Testing for Multidrug-Resistant Bacteria	ESBL-producing *Enterobacteriaceae*	Culture
	VRE (Vancomycin-resistant *enterococci*)	Culture
	CRE (KPC, NDM, OXA 48)	Culture
	MRSA (Methicillin-resistant *Staphylococcus aureus*)	Culture
Stool Testing for Parasites	*Cyclospora* sp., *Isospora* sp., *Giardia* sp.	Microscopy ± Antigen
	Cryptosporidium sp., *Entamoeba histolytica*	Microscopy ± Antigen
	Ova and cysts	Light Microscopy
Additional Blood Tests	CMV (Cytomegalovirus) viral load	Blood test
	EBV (Epstein-Barr virus) viral load	Blood test
	Fasting Plasma Glucose (FPG), HbA1c	Blood test
	Liver enzymes (ALT, AST, ALP, Bilirubin)	Blood test
	Lipid profile (HDL, LDL, Triglycerides, Cholesterol)	Blood test

CRE: carbapenem-resistant *Enterobacteriaceae*; ESBL: extended-spectrum β-lactamase; MDR: multidrug resistant; MRSA: methicillin-resistant *Staphylococcus aureus*; VRE: vancomycin-resistant *enterococci*; HIV: human immunodeficiency virus; HBV: Hepatitis B; HCV: Hepatitis C; FPG: fasting plasma glucose; PG: 2-hour plasma glucose; RPR: rapid plasma regain; VDRL: venereal disease research laboratory test; ALT: alanine aminotransferase; ALP: alkaline phosphatase; AFP: alpha fetoprotein; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Figure 2. FMT donor screening.

Strict screening protocols are essential to reduce adverse events. U.S. and European guidelines recommend structured questionnaires, clinical interviews, and blood/stool tests within four weeks before donation [5]. While relatives were historically preferred for shared microbial traits [11], evidence shows no significant outcome differences between related and unrelated donors [5]. For conditions like inflammatory bowel disease (IBD), unrelated donors may be preferable due to genetic factors [31]. The FMT French Group advises a ≤21-day gap between screening and donation to minimize contamination risks [21]. Universal stool banks report < 3% donor eligibility after rigorous screening, excluding candidates with abnormal BMI, recent antibiotic use, or pathogens like *Dientamoeba fragilis* and *Blastocystis hominis* [5]. Preferred donors are typically aged 18 - 60, with protocols tailored to regional infectious threats. Autologous FMT, using a patient's pre-collected stool, avoids novel pathogen introduction [5] [15] [16].

Comprehensive blood and stool testing within four weeks before donation is mandatory to assess infectious risks [21]. Screening includes major pathogens, with additional tests based on geography, recipient condition, and donor history [3]. For example, donors in endemic regions are tested for human T-lymphotropic virus types I/II or *Strongyloides stercoralis*, while immunosuppressed recipients may require screening for cytomegalovirus (CMV) IgG and bacterial cultures for *Vibrio cholerae* and *Listeria monocytogenes* [5] [32]. Donor blood samples are archived per European guidelines [33], and stool is frozen at −80˚C within 8 hours if results are pending [10]. Validated preparations are delivered or cryopreserved

[33]. Multi-donor approaches enhance microbial diversity and response rates in IBD [23], but may reduce stability due to compositional fluctuations [21]. Innovations like germ-free animal colonization and gastrointestinal simulation devices aim to standardize production [31] [34]. Strain and spore-based therapies, such as MET-2 and SER-109, show >90% efficacy against recurrent *Clostridioides difficile* infection (rCDI), offering promising avenues for FMT standardization despite challenges like colonization antagonism [14] [23].

4. Collection, Preparation, and Storage of Fecal Material

4.1. Stool Collection

Stool samples should be collected within one month of initial donor screening, with pre- and post-donation screenings ensuring safety [5]. Donors collect stool in a clean, opaque plastic bag, which is sealed and placed in a larger storage bag. Samples can be donated on-site or transported in a cooler with ice packs within one hour. Stool remains viable at 4˚C for up to 8 hours, but prolonged storage leads to bacterial decline [35].

4.2. FMT Preparation

Fresh and frozen FMT show similar efficacy and fresh stool must be processed within six hours. A minimum of 50 - 80 g of stool is blended with 150 mL sterile saline, filtered, and loaded into 60-mL syringes for administration [21]. Frozen samples, processed under stringent protocols, are stored at −80˚C and thawed at 37˚C before use, maintaining a single-thaw policy [5] [35]. Higher infusion volumes (>50 g) improve treatment success, while lower volumes increase failure risk [5].

4.3. Cryopreservation

Frozen and fresh FMT show comparable CDI relapse prevention. Samples are cryopreserved at −80˚C or −196˚C, with refreezing prohibited due to bacterial viability loss [5]. Long-term storage at −20˚C leads to microbiota instability [36]. Recent studies have shown that long-term preservation at −20˚C can lead to microbiota instability, particularly affecting the *Actinobacteria* and *Bacteroidetes* phyla [36]. The recommended stool dose is ~80 g per treatment. Stool is homogenized in 0.9% saline, sequentially filtered, centrifuged, and resuspended in saline with 10% glycerol or trehalose before freezing [35]. Containers must allow for expansion, with aliquots reserved for analysis. A second donor screening occurs within one-month post-collection, with a four-week quarantine for retesting. The European Tissues and Cells Directive mandates traceability, and storage is limited to six months before disposal [5].

5. Recipient Preparation and Matching

5.1. Recipient Preparation

Patient education and preparation are critical steps before fecal microbiota trans-

plantation (FMT), regardless of the fecal material source or administration route [5]. To optimize microbiota engraftment, antibiotic treatment should be discontinued 12 - 48 hours before the procedure. A standard bowel preparation is also necessary to clear residual fecal material and create a favorable environment for donor microbiota colonization. Additionally, some protocols recommend administering loperamide one hour before FMT to enhance fecal retention for at least four hours, which may improve the efficacy of the transplant [5] [12].

5.2. Donor-Recipient Matching

The success of FMT is influenced by various host factors, including genetics, immune status, lifestyle, diet, smoking, alcohol consumption, and medication history, all of which shape the recipient's gut microbiota composition post-transplantation [23]. Key determinants of FMT outcomes include donor-recipient microbiome compatibility, microbial abundance, and the baseline composition of the recipient's microbiota [12]. To track the engraftment of donor bacterial strains, bioinformatics tools such as SameStr, Strainer, and Strain Finder have been developed [31]. However, the mechanisms underlying donor strain colonization remain poorly understood, with studies reporting inconsistent findings regarding donor strain persistence and its correlation with clinical outcomes [31] [33].

5.3. Computational Approaches to Donor-Recipient Matching

The development of advanced algorithms for donor-recipient matching is essential to improve FMT outcomes. Recent research has utilized hierarchical evaluation models based on microbiota diversity and bacterial composition to identify optimal donors [31]. For instance, one study achieved a donor-recipient matching success rate of over 70% by analyzing alpha-diversity, beta-diversity, and the presence of beneficial or pathogenic bacteria [6]. Enterotype classification has also emerged as a valuable tool for guiding donor selection. In a prospective clinical trial, a machine-learning approach incorporating microbiome profiles into a random forest model achieved a 93.3% matching accuracy [6]. Despite these advancements, further research is needed to refine computational models, particularly for applications in extraintestinal conditions.

6. Delivery Modes of Fecal Microbiota Transplantation (FMT)

Fecal microbiota transplantation (FMT) can be administered via multiple routes, including oral capsules, nasogastric/nasojejunal tubes, endoscopies, colonoscopies, and retention enemas (**Figure 3**). The choice depends on factors like patient preference, invasiveness, target site, cost, and risks [5]. Upper GI delivery (e.g., nasoduodenal tubes) benefits patients with inflamed colons but carries risks like aspiration pneumonia [3].

Mid-GI delivery via transendoscopic enteral tubes is minimally invasive and suitable for frail patients [23]. Lower GI methods, such as colonoscopy and retention enema, directly target the colon, with colonoscopy allowing mucosal assess-

ment but requiring bowel preparation [28]. Retention enema is less invasive and effective for recurrent *Clostridioides difficile* infection (CDI) [6].

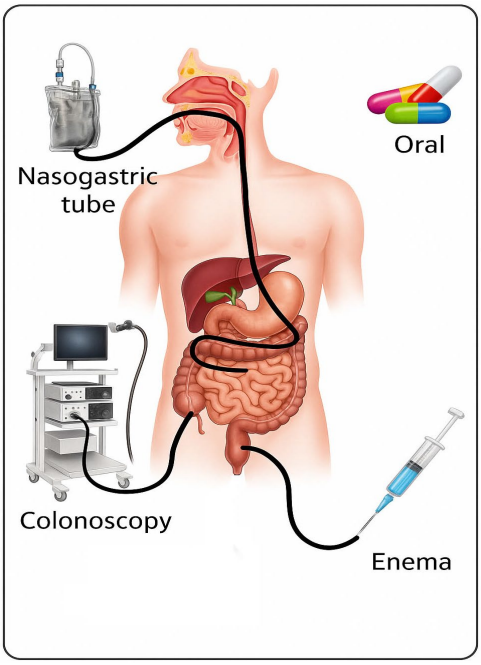

Figure 3. FMT delivery modes.

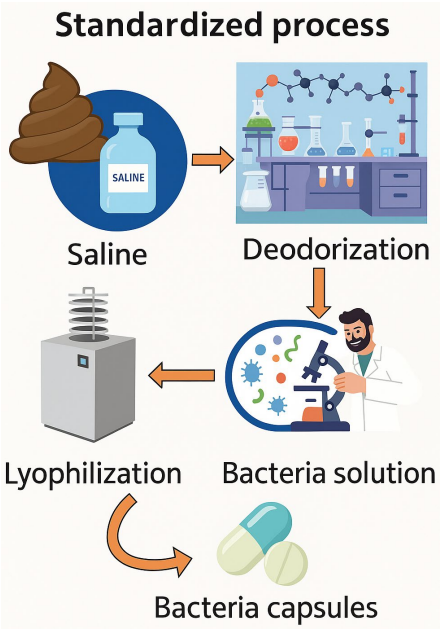

Figure 4. FMT oral capsules preparation procedure.

Oral capsules offer a non-invasive, patient-friendly option, showing efficacy comparable to colonoscopy for CDI (**Figure 4**) [3]. However, challenges include high production costs and the need for multiple capsules. Comparative studies show mixed results, with some suggesting lower GI routes may have higher effi-

cacy for CDI [28], while oral capsules are equally effective [35]. The optimal FMT delivery method remains patient-specific, with ongoing research needed to refine techniques, enhance microbial engraftment, and improve accessibility [12]. Both fresh and frozen FMT have demonstrated similar clinical efficacy in treating recurrent or refractory CDI [5] [36]. Frozen FMT is often preferred due to logistical advantages, such as ease of storage and transportation, which reduce donor dependency. Fresh FMT requires immediate administration within six hours after stool preparation, whereas frozen samples must be thawed in an ice bath for 2 - 4 hours before use [5] [35].

7. Fecal Microbiota Transplantation (FMT): Autoimmune Diseases

The gut microbiome plays a critical role in the pathogenesis of autoimmune diseases, with dysbiosis characterized by an imbalance in microbial composition being a common feature across conditions such as inflammatory bowel disease (IBD), multiple sclerosis (MS), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [31]. Dysbiosis is associated with distinct microbial signatures and functional changes, including impaired gut barrier integrity, molecular mimicry, altered microbial metabolites and aberrant immune activation, which collectively contribute to autoimmune pathogenesis.

7.1. Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), involves chronic gastrointestinal inflammation driven by dysregulated immune responses, altered gut microbiota, and environmental factors in genetically susceptible individuals. While immunosuppressive therapies are standard, they pose risks, prompting interest in microbiota-targeted interventions like dietary changes and fecal microbiota transplantation (FMT). Patients with CD show decreased levels of *Christensenellaceae*, *Coriobacteriaceae*, and *Faecalibacterium prausnitzii*, while exhibiting increased abundances of *Actinomyces*, *Veillonella*, and *Escherichia coli* [37]. Similarly, UC patients show decreased *Eubacterium rectale* and *Akkermansia* but increased *E. coli* [37]. FMT offers a direct approach to restoring gut microbial balance in IBD patients. Various case reports and cohort studies have explored FMT effects, but interpreting results remain challenging due to inconsistent study protocols, limited sample sizes and heterogeneity in outcome measures [31].

Randomized controlled trials (RCTs) have evaluated FMT efficacy in UC treatment [35]. Papanicolas *et al.* [38] reported a remission rate of 24% in the FMT group compared to 5% in the placebo group at week 7. However, Pittayanon *et al.* [39] found no significant differences in clinical remission between donor and autologous FMT groups, potentially due to variations in administration methods, sample sources and concurrent immunosuppressive therapies. Despite these inconsistencies, both trials indicated increased microbial diversity in FMT respond-

ers. Later studies using multi-donor intensive-dosing FMT [40] and lower-intensity FMT [31] suggested that treatment efficacy does not necessarily correlate with dose intensity. Additionally, lyophilized oral FMT capsules have shown promising results in UC remission [31]. FMT demonstrated superiority over placebo in achieving endoscopic and histological remission; however, its impact on steroid-free clinical remission was not statistically significant [41]. A 2020 randomized, sham-controlled pilot trial assessing FMT for remission maintenance in CD found that successful donor microbiota colonization (Sorensen index > 0.6) was not achieved at six weeks post-FMT [42]. Nonetheless, patients with higher donor microbiota colonization demonstrated better remission maintenance, highlighting its potential therapeutic role.

A pilot study evaluating the UC exclusion diet (UCED) suggested that diet alone was more effective than FMT integrated with dietary pre-conditioning of both donors and recipients [31]. Pediatric studies also suggest that FMT may benefit symptom control and inflammatory markers in UC patients [43]. Metagenomic analyses aid in microbiota profiling post-FMT, helping elucidate host-microbiome interactions. The remission in CD patients post-FMT correlated with engraftment of *Actinobacteria*, *Proteobacteria* and *Bacteroidetes* [44]. Specific bacteria, including *Eubacterium hallii* and *Roseburia inulivorans*, were enriched in FMT-responsive ulcerative colitis (UC) patients, whereas *Fusobacterium gonidiaformans* and *Escherichia* spp. were more prevalent in non-responders [45]. *Bacteroides* and *Streptococcus* spp. in donor stool were linked to patient response. Fungal and bacteriophage roles in FMT for IBD treatment remain underexplored but could significantly influence gut microbiota stability and inflammation regulation [31]. Future research should focus on refining donor selection, optimizing protocols and personalizing FMT strategies to maximize efficacy in IBD treatment.

7.2. Multiple Sclerosis (MS)

MS is marked by demyelination and axonal loss, resulting in acute inflammatory lesions and chronic inflammation in the central nervous system, ultimately causing tissue damage and disability [1] [28]. Progress in medical technology and disease-modifying therapies has deepened our understanding of MS prevalence, diagnosis, and treatment [31]. The intricate interaction between genetic and environmental factors is increasingly acknowledged as a key contributor to MS pathogenesis [12] [46]. MS patients exhibit increased abundances of *Methanobrevibacter* and *Akkermansia*, along with reduced levels of *Butyricimonas* [46]. The gut microbiota-gut-brain axis has garnered attention in MS research, given its role in immune, endocrine and nervous system interactions. Perturbations in this axis are associated with MS pathogenesis [47]. A proof-of-concept single-subject longitudinal study of a 48-year-old Caucasian male with relapsing-remitting MS (RRMS) revealed that FMT maintained normal gastrointestinal (GI) function without relapses during a 12-month follow-up period [48]. Clinical improvement

was associated with shifts in microbiota composition, elevated bacterial metabolite levels (such as SCFAs), and changes in serum brain-derived neurotrophic factor and inflammatory cytokines, including IL-8 [31] [48]. In experimental autoimmune encephalomyelitis (EAE) models, FMT reduced disease severity, delayed onset and modulated microglial and astrocyte activation, protecting myelin integrity [46] [47].

7.3. Rheumatoid Arthritis (RA)

RA is a systemic inflammatory autoimmune disease marked by polyarthritis, resulting in cartilage and bone damage while posing substantial health and economic burdens [49]. Mucosal immunity, influenced by gut microbiota-host interactions, is a hallmark of RA pathogenesis. The "gut-joint axis" suggests RA pathology originates at mucosal sites before affecting synovial joints [31]. In preclinical RA, there is a significant increase in *Prevotellaceae*, particularly *Prevotella* spp. [50]. A case study of a 20-year-old with a 5-year history of RA demonstrated beneficial outcomes following a 300-mL fecal suspension transplant via colonoscopy. The patient experienced reductions in the Disease Activity Score 28, Health Assessment Questionnaire Disability Index, and rheumatoid factor titer, with no reported discomfort [51]. While this suggests FMT therapeutic potential in RA, further RCTs are needed for validation.

7.4. Systemic Lupus Erythematosus (SLE)

SLE is an autoimmune disorder characterized by autoantibodies targeting nuclear components, resulting in systemic inflammation affecting multiple organs [52]. It predominantly affects women and non-white individuals, with complex clinical manifestations making diagnosis challenging [31]. SLE patients exhibit elevated levels of *Streptococcus intermedius* and *Streptococcus anginosus*, along with activation of bacterial pathways such as sulfur metabolism and flagella assembly [53].

While the role of gut microbiota dysbiosis in SLE remains unclear, emerging evidence highlights its significance in disease development. A single-arm pilot clinical trial involving 20 active SLE patients demonstrated that oral FMT capsules improved clinical parameters by restoring gut microbiota, increasing SCFA production and reducing IL-6 levels and circulating CD4+ memory/naïve T cell ratios [31]. These alterations persisted for 12 weeks without serious adverse effects. While promising, further large-scale, randomized, double-blind, placebo-controlled trials are necessary. Antibiotic-induced gut microbiota dysbiosis exacerbated SLE in MRL/lpr mice, which was reversed by FMT [54]. However, FMT also altered the therapeutic efficacy of glucocorticoids, such as prednisone, in lupus treatment, underscoring the need for clinical caution [31].

7.5. Type 1 Diabetes

T1D is an autoimmune disorder driven by T-cell-mediated destruction of pancre-

atic beta cells, resulting in insulin deficiency and hyperglycemia [3]. Its rising incidence, especially in youth, poses significant health challenges. While the exact mechanisms remain unclear, factors like molecular mimicry, infections, and immune dysregulation are implicated. TNF-alpha inhibitors show promise in preserving beta cell function, and residual beta cell activity persists even in long-standing T1D, offering potential for disease modification [55].

Preclinical studies show that gut microbiota influences disease onset, with T1D patients often exhibiting gut dysbiosis and reduced short-chain fatty acids (SCFAs). Autologous FMT may preserve insulin production, though placebo-controlled trials are needed for validation. Clinical trials indicate that autologous FMT may better preserve C-peptide levels compared to allogenic FMT, potentially due to unique microbiome transfer dynamics [56]. However, larger studies are needed to confirm these findings and explore alternative delivery methods. Placebo-controlled studies are crucial to validate FMT's therapeutic potential and elucidate its mechanisms in T1D pathogenesis [3].

7.6. Other Autoimmune Diseases

The effects of FMT have also been investigated in other autoimmune diseases. A case report of a 36-year-old patient with severe plaque psoriasis and IBS demonstrated symptom improvement following two FMT sessions via endoscopy and colonoscopy, with no adverse reactions [31]. However, an RCT found FMT inferior to sham treatment in patients with active psoriatic arthritis (PsA) undergoing methotrexate therapy [31]. Despite inconsistent results, qualitative studies suggest FMT is generally accepted and considered safe by participants [57]. FMT has been shown to attenuate autoimmune hepatitis by correcting gut dysbiosis and restoring follicular regulatory T-cell balance. In autoimmune myocarditis models, FMT increased *Bacteroidetes* abundance, reduced myocardial injury, and suppressed pro-inflammatory cytokine expression [31].

8. Fecal Microbiota Transplantation (FMT): Obesity

Obesity and its associated metabolic syndrome represent a global health crisis, contributing to significant morbidity, including type 2 diabetes (T2D) [58]. Despite available treatments for T2D, its prevalence continues to rise, necessitating novel therapeutic approaches. Emerging evidence suggests that obesity is linked to alterations in the gut microbiome, positioning FMT as a potential intervention [3]. The gut microbiome plays a critical role in host immunity, energy metabolism and nutrient processing. It facilitates the digestion of indigestible fibers, enhances energy harvest and produces essential metabolites such as short-chain fatty acids (SCFAs) [9]. Additionally, the microbiome modulates glucagon-like peptide-1 (GLP-1) release and bile acid metabolism, which are integral to lipid digestion and metabolic regulation [3]. Dysregulation of bile acid pathways has also been implicated in atherosclerosis, with interventions targeting these pathways showing promise in reducing atherosclerotic risk [59].

FMT may address obesity and metabolic syndrome by modulating these pathways, potentially reducing insulin resistance and improving lipid metabolism. For instance, FMT could counteract the heightened energy harvest observed in obese individuals, whose microbiomes are more efficient at extracting energy from food [60]. Conversely, FMT has been shown to promote weight gain in malnourished patients, as demonstrated in a case report of an anorexia nervosa patient [61]. Furthermore, animal studies indicate that certain microbiota can increase gut permeability, leading to systemic endotoxin exposure (e.g., lipopolysaccharide, LPS, which is associated with inflammation, hypertension, and metabolic dysfunction [62]. While gut permeability is typically assessed via biopsies, non-invasive methods like the 5-sugar absorption test offer a reproducible alternative [63].

Animal studies have demonstrated that obesity can be transferred from obese to lean germ-free mice via microbiome transplantation, suggesting the potential for reversing this process [64]. Clinical studies have shown mixed results: FMT from lean donors reduced insulin resistance in metabolic syndrome patients [65], while FMT from obese donors exacerbated insulin resistance in recipients [62]. Similarly, FMT has demonstrated potential in modulating the gut-brain axis and enhancing outcomes in metabolic syndrome, including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) [66] [67]. However, other studies, including those using post-bariatric surgery donors, have not demonstrated significant weight loss or improved insulin sensitivity despite changes in microbiome composition [68] [69]. These contradictory results emphasize the necessity for additional research to better understand FMT's role in managing obesity and metabolic syndrome.

Type 2 Diabetes

The gut microbiome has been implicated in the pathogenesis of insulin resistance and T2D, though causal evidence in humans remains limited. The microbiome influences low-grade inflammation, energy expenditure and lipid metabolism, all of which are relevant to T2D [3]. FMT from lean donors enhanced insulin sensitivity in individuals with metabolic syndrome, along with alterations in the duodenal and fecal microbiome composition [65] [70] [71]. While these changes were associated with reduced peripheral insulin resistance, they did not correlate with alterations in serum bile acids or incretions. The study also identified metabolic responders and non-responders, with greater clinical efficacy observed in recipients with low baseline gut microbiota diversity [72]. Further research is needed to define the characteristics of an optimal FMT donor and to standardize protocols for treating T2D and metabolic syndrome.

9. Fecal Microbiota Transplantation (FMT): Skin Diseases

Gut microbiota dysbiosis is increasingly linked to chronic inflammatory skin diseases, with fecal microbiota transplantation (FMT) emerging as a potential therapy to restore microbial balance and reduce inflammation [73]. However, chal-

lenges such as infection risks, adverse reactions, donor-recipient compatibility, and regulatory concerns hinder its widespread use. Standardization is complicated by donor variability, administration methods, and antibiotic preconditioning. Despite these issues, FMT's immune-modulatory properties show promise for treating conditions like atopic dermatitis (AD) and melanoma [74]. The gut microbiota, dominated by *Bacteroidetes* and *Firmicutes*, plays a key role in immune regulation. Research is exploring links between microbiota composition, disease susceptibility, and microbial metabolites' impact on health. FMT, successfully used for decades to treat recurrent *Clostridioides difficile* infections, is now being investigated for chronic inflammatory skin diseases [73] [74].

9.1. Atopic Dermatitis (AD)

Recent studies have identified a correlation between gut microbiota dysbiosis and the development of AD. Infants with AD often exhibit specific gut microbiota characteristics, such as an increased abundance of *Clostridium sensu stricto* and reduced microbial diversity [75]. AD patients also show decreased levels of beneficial bacteria like *Lactobacillus* and *Bifidobacterium*, alongside elevated levels of *Clostridium difficile*, *Escherichia coli* and *Staphylococcus aureus* [73] [76]. Additionally, reduced levels of short-chain fatty acids (SCFAs), which have anti-inflammatory properties, have been observed in AD patients, suggesting a role for gut microbiota dysbiosis in disease pathogenesis [74].

In mouse models, FMT has demonstrated promise in alleviating AD symptoms by restoring gut microbiota balance and immune regulation, such as rebalancing the Th1/Th2 response. For example, FMT from healthy mice reduced dermatitis severity and increased the abundance of butyrate-producing bacteria in AD-induced mice [77]. A pilot study conducted at Tel Aviv Medical Center reported significant improvements in AD symptoms following FMT, as measured by reductions in scoring atopic dermatitis (SCORAD) values. However, the study's limitations included a small sample size and the absence of a double-blind design. Further research is needed to confirm the efficacy and safety of FMT in AD, particularly given the compromised gut barrier function in these patients [73].

9.2. Psoriasis

Psoriasis is associated with reduced gut microbiota diversity and altered microbial composition, including increased *Firmicutes* and decreased *Bacteroidetes.* Compared to healthy controls, patients with psoriasis exhibit a distinct gut microbial composition characterized by a reduced abundance of the phyla *Bacteroidetes*, *Euryarchaeota*, and *Proteobacteria*, as well as the genera *Prevotella*, *Alistipes*, and *Eubacterium*, and an increased abundance of *Firmicutes*, *Actinobacteria*, *Verrucomicrobia*, *Faecalibacterium*, *Bacteroides*, *Bifidobacterium*, *Megamonas*, and *Roseburia* [78] [79]. Dysbiosis in psoriasis is linked to a weakened gut epithelial barrier, microbial translocation and systemic inflammation. Studies have shown that gut microbiota alterations can influence Th17 immune responses, which play

a key role in psoriasis pathogenesis. In mouse models, FMT from healthy donors reduced skin inflammation and restored immune balance, such as the Treg/Th17 ratio. Conversely, FMT from psoriasis patients exacerbated inflammation [80] [81].

A case report of a patient with severe psoriasis and IBD showed improvement in both psoriasis symptoms and gut health following FMT [78]. However, a randomized controlled trial found that FMT was not more effective than a placebo for psoriatic arthritis, although it was deemed safe [74]. Larger, well-designed studies are needed to evaluate the efficacy of FMT in psoriasis.

9.3. Alopecia Areata (AA)

AA is an autoimmune condition characterized by hair loss. While gut microbiota diversity does not significantly differ between AA patients and healthy controls, specific bacterial taxa, such as *Erysipelotrichaceae* and *Lachnospiraceae*, together with *Bacteroides eggerthii*, *Parabacteroides distasonis*, *Clostridiales vadin BB60 group*, *Holdemania filiformis*, and *Parabacteroides johnsonii* are more abundant in AA patients [82]. Reduced levels of SCFA-producing bacteria may contribute to immune dysregulation and decreased peripheral tolerance in AA [6]. FMT has shown promise in promoting hair regrowth in AA patients, particularly those with concurrent *C. difficile* infection or non-infectious diarrhea [73]. Further research is needed to establish the role of FMT in AA treatment and to elucidate the mechanisms underlying its potential benefits.

9.4. Sjögren's Syndrome (SjS)

A hypothesis suggests a "gut dysbiosis-ocular surface-lacrimal gland axis" may contribute to SjS pathogenesis [83]. Metagenomic sequencing reveals SjS patients have reduced operational taxonomic units (OTUs) and Shannon alpha-diversity compared to healthy controls [84]. Their gut microbiota (GM) is characterized by higher levels of *Pseudobutyrivibrio*, *Escherichia/Shigella*, *Blautia*, and *Streptococcus*, while *Bacteroides*, *Parabacteroides*, *Faecalibacterium*, and *Prevotella* are reduced [85]. In SjS patients with dry eye, *Firmicutes* is the dominant phylum, followed by *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* [86]. A study conducted in China identified *Bifidobacterium*, *Bacteroides*, *Escherichia-Shigella*, *Faecalibacterium*, and *Prevotella* as predominant in female SjS patients [73]. Primary SjS patients exhibit reduced microbial diversity, dominated by *Bacteroidetes*, with increased proinflammatory pathogens and fewer beneficial butyrate-producing bacteria. This dysbiosis correlates with elevated proinflammatory cytokines and reduced FOXP3 mRNA expression [73]. Severe GM dysbiosis is linked to higher disease activity (ESSDAI/ClinESSDAI scores), reduced complement component 4, and elevated fecal calprotectin [87]. In an open-label, non-randomized trial, FMT was assessed in 10 SjS patients with dry eye. Following FMT, gut microbiota profiles revealed a reduction in *Faecalibacterium*, *Prevotella*, and *Ruminococcus*, along with an increase in *Alistipes*, *Streptococcus*, and *Blautia.* No adverse events occurred,

and five patients reported improved dry eye symptoms, with some donor-like bacterial profiles persisting for three months [88]. While promising, larger studies are needed to confirm FMT's efficacy and safety.

9.5. Behçet's Disease (BD)

Behçet's disease (BD) pathogenesis is closely linked to gut microbiota (GM) dysbiosis, immune-mediated inflammation, and hyperactive neutrophil infiltration. Studies highlight the role of *Streptococcus sanguinis* and GM alterations in driving immune dysregulation and inflammation in BD. BD patients exhibit significant GM dysbiosis, characterized by reduced beneficial bacteria like *Roseburia* and *Subdoligranulum*, which are essential for butyrate production. This reduction may impair regulatory T cell (Treg) responses and activate pathogenic effector T cells (Teff), contributing to inflammation [89]. Specific microbial shifts in BD include increased *Bifidobacterium* and *Eggerthella* and decreased *Megamonas* and *Prevotella. Actinobacteria*, including *Bifidobacterium* and *Lactobacillaceae*, are more prevalent in BD. While alpha-diversity remains similar, beta-diversity shows slight variations, indicating distinct microbial community structures [73]. Patients with BD show increased levels of *Eggerthella lenta*, *Acidaminococcus* spp., *Lactobacillus mucosae*, *Bifidobacterium bifidum*, *Lactobacillus iners*, *Streptococcus* spp., and *Lactobacillus salivarius*, while *Megamonas hypermegale*, *Butyrivibrio* spp., *Streptococcus infantis*, and *Filifactor* spp. are found in lower abundance. Functional analyses reveal enriched pathways like the pentose phosphate pathway and inosine monophosphate biosynthesis, suggesting altered microbial metabolism influencing nucleic acid and fatty acid synthesis [90]. Elevated sulfate-reducing bacteria (*Bilophila* spp.) and opportunistic pathogens (*Parabacteroides* spp., *Paraprevotella* spp.), alongside reduced butyrate producers (*Clostridium* spp.) and methanogens (*Methanoculleus* spp., *Methanomethylophilus* spp.), further characterize BD dysbiosis. *Prevotella* is notably dysbiotic in neuro-BD [17] [91]. Cross-country analyses reveal geographic-specific beta-diversity clustering in BD, with reduced *Barnesiellaceae* and *Lachnospira* spp. and increased IgA-coating of *Bifidobacterium*, *Ruminococcus bromii*, and *Dorea* spp., suggesting mechanisms to retain anti-inflammatory species and neutralize pathosymbionts [92]. In Turkish studies, *Succinivibrionaceae* is a BD signature, while *Bacteroides* spp. are absent. Specific genera like *Actinomyces*, *Eggerthella*, and *Enterobacter* are enriched, whereas *Bacteroides*, *Akkermansia*, and *Coprococcus* are reduced. Clinical manifestations (e.g., uveitis, vascular involvement) show distinct microbial signatures, such as *Lachnospiraceae* NK4A136 in uveitis and *Gemella* in vascular involvement [73] [91] [93].

10. Fecal Microbiota Transplantation (FMT): Glaucoma

The gut microbiome influences retinal diseases like glaucoma through microbial metabolites and immune modulation. While *Lachnospiraceae*, producers of short-chain fatty acids (SCFAs), are generally beneficial [94], SCFAs may exacerbate glau-

coma by activating retinal microglia, causing neuroinflammation and retinal cell loss [83]. *Lachnospiraceae* UCG010, a key SCFA producer, is a potential therapeutic target for preserving optic nerve function in glaucoma. Toll-like receptor 4 (TLR4), which recognizes bacterial lipopolysaccharide (LPS), plays a role in glaucoma pathogenesis by triggering inflammatory cytokine production and disrupting lipid metabolism [83]. In glaucoma patients, TLR4 expression is elevated in retinal microglia, and LPS administration in animal models induces axonal degeneration and neuronal loss through TLR4 activation and complement-mediated damage [94].

Glaucoma patients exhibit a higher prevalence of Helicobacter pylori infection than healthy individuals [95]. Primary open-angle glaucoma (POAG) patients exhibit gut microbiota dysbiosis, with increased *Prevotellaceae*, *Enterobacteriaceae*, and *Escherichia coli*, and decreased *Megamonas* and *Bacteroides plebeius*, linked to distinct metabolic profiles and clinical phenotypes [96]. Mitochondrial DNA variants associated with glaucoma are enriched in patients with altered *Firmicutes* and *Proteobacteria* populations [83] [94].

The ocular surface and intraocular microbiota are increasingly studied in glaucoma, with microbial alterations linked to disease progression, often associated with preserved anti-glaucoma eye drops. Glaucoma patients using these drops exhibit a more diverse microbiome, with increased gram-negative bacteria and reduced tear film stability compared to healthy controls [97]. In uveitis glaucoma, *Paenibacillus* and *Dermacoccus* levels are elevated, while *Morganella* and *Lactococcus* are reduced [98]. *Rhodococcus* is more abundant in uveitis glaucoma than in POAG [99]. Glaucoma patients show a predominance of *Firmicutes* (61.1%) and *Verrucomicrobiota* (11.8%), with reduced *Actinobacteriota* [97]. The predominant genera include *Akkermansia*, *Corynebacterium*, *Faecalibacterium*, *Lachnospiraceae*, and *Blautia*. In glaucoma patients, there is an increase in anaerobic, gram-negative bacteria associated with lipopolysaccharide production and anaerobic metabolism, whereas healthy individuals have a greater abundance of gram-positive bacteria linked to carbohydrate synthesis and oxidative phosphorylation [94] [97].

Anti-glaucoma eye drops, particularly those with benzalkonium chloride (BAK), may alter the ocular surface microbiota, with BAK suppressing gram-positive organisms, though some studies suggest minimal impact [94] [97]. Bacterial presence in the intraocular environment, previously thought sterile, has been confirmed, with glaucoma patients showing increased *Propionibacterium acnes* and decreased *Staphylococcus warneri* [100]. *H. pylori* has been identified in trabecular meshwork and iris specimens, supporting its role in POAG pathogenesis [94].

Oral and gastric microbiota dysbiosis contribute to glaucoma through systemic inflammation. Severe periodontal disease and *H. pylori* infection are linked to increased POAG risk, with eradication improving IOP and visual fields [83] [94]. Glaucoma patients exhibit higher oral bacterial loads, with increased *Streptococci* and reduced *Lactococcus* [101]. Recent tooth loss is associated with a 1.45-fold

increased POAG risk [102]. *H. pylori* is histologically confirmed in 87.5% of chronic OAG and 88.9% of pseudoexfoliation glaucoma patients, with higher anti-*H. pylori* IgG in aqueous humor and serum [94]. Eradication slows POAG progression, reduces IOP, and improves visual fields [94] [103].

FMT introduces beneficial microbes from healthy donors, restoring gut microbiome balance and promoting short-chain fatty acid (SCFA) production, which enhances gut barrier integrity and reduces inflammation [104] [105]. FMT also regulates systemic immune responses through immune-modulatory compounds [106] [107]. The gut-eye axis underscores the link between gut microbiota and ocular health, with dysbiosis contributing to systemic inflammation, gut barrier disruption, and retinal damage (**Figure 5**) [108]. Preclinical studies show FMT may mitigate retinal inflammation and cell loss; mice receiving fecal samples from glaucoma patients exhibited increased retinal damage compared to those receiving healthy donor samples [94]. For example, mice receiving fecal samples from glaucoma patients exhibited increased retinal inflammation and cell loss compared to those receiving samples from healthy donors [109]. A clinical trial in Sjögren's syndrome patients demonstrated FMT improved dry eye symptoms in 50% of cases, highlighting its therapeutic potential for ocular diseases [88].

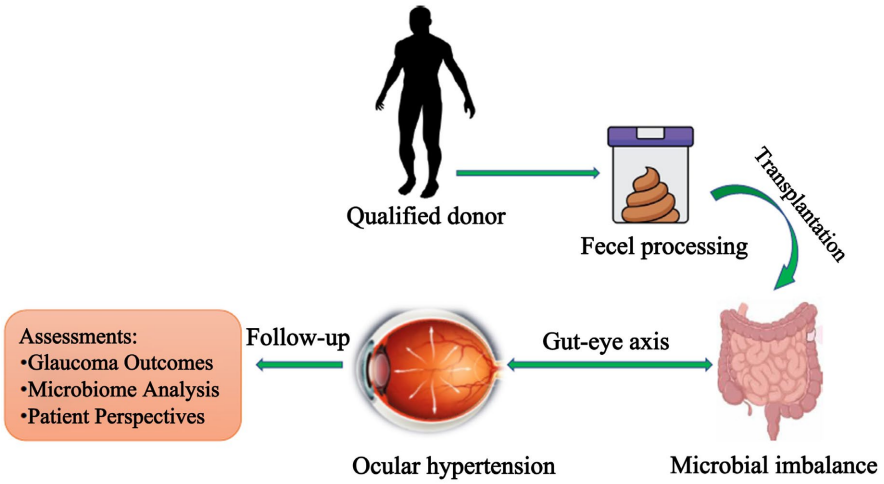

Figure 5. Schematic overview of fecal microbiota transplantation (FMT) as a potential glaucoma treatment targeting the gut-eye axis.

11. Fecal Microbiota Transplantation (FMT): Autism Spectrum Disorder (ASD)

The gut-brain axis, a two-way communication network connecting the gut and brain, is essential for neurodevelopment and behavior (**Figure 6**). This interaction begins in utero, with bacteria and their metabolites transported between mother and fetus via amniotic fluid. Postnatal factors such as delivery mode (vaginal or cesarean), maternal health, breastfeeding, diet and early antibiotic use significantly influence gut microbiota colonization [110] [111]. The gut microbiota is primarily composed of two major phyla: *Bacteroidetes* and *Firmicutes*. Maternal factors like

obesity, high-fat diets, and gestational diabetes can alter neonatal gut microbiota, potentially contributing to autism spectrum disorder (ASD) [11].

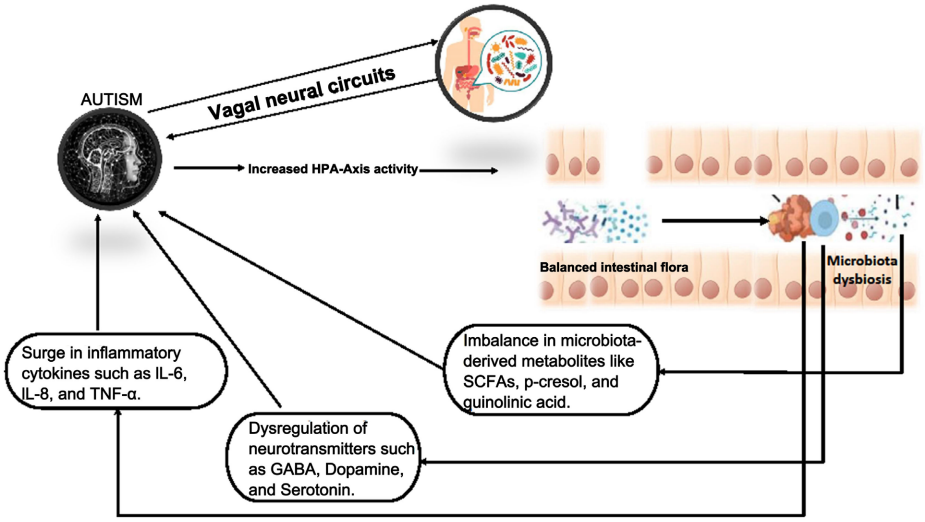

Figure 6. Exploring the link between gut dysbiosis, its metabolites, and autism.

The gut-brain axis operates through neuroendocrine, neuroimmune, and autonomic pathways, involving the hypothalamic-pituitary-adrenal (HPA) axis, the enteric nervous system (ENS), and the vagus nerve [11]. Dysregulation of this axis has been implicated in various diseases, including ASD, obesity and Alzheimer's disease [11]. Research using germ-free (GF) animals, probiotics and antibiotics has demonstrated the gut microbiota role in brain function. GF mice exhibit altered sociability, locomotor activity and repetitive behaviors, highlighting the microbiota importance in stress response, cognition and CNS homeostasis [112] [113]. Probiotics like *Bifidobacterium longum* 1714 have been shown to reduce stress and improve neurocognitive function in mice [114], while antibiotic-induced microbiota depletion in mice leads to anxiety, cognitive dysfunction and altered neuromodulator levels [115].

11.1. Dysbiosis in Gut Leading to ASD

Dysbiosis, an imbalance in gut microbiota composition, is strongly associated with ASD. Autistic individuals often exhibit altered gut microbiota, which disrupts immune function and increases the production of pro-inflammatory metabolites. This dysbiosis is linked to increased intestinal permeability ("leaky gut"), allowing bacterial products like lipopolysaccharide (LPS) to enter the bloodstream and modulate CNS activity, particularly in brain regions like the amygdala, which regulates emotions and behavior [116] [117].

Both the gut barrier and blood-brain barrier (BBB) are compromised in ASD. Increased expression of pore-forming claudins (e.g., CLDN-2, CLDN-10) and decreased levels of barrier-forming tight junction proteins (e.g., CLDN-1, occludin) contribute to impaired intestinal and BBB integrity [118]. Dysbiosis in ASD is also

associated with immune dysregulation, with elevated pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α) crossing the BBB and inducing neuroinflammation [11]. Specific microbial alterations in ASD patients include increased *Proteobacteria*, *Lactobacillus*, *Bacteroides*, *Desulfovibrio*, *Clostridium* and decreased *Bifidobacterium*, *Blautia*, *Prevotella* [119] [120]. *Clostridium* species produce neurotoxic metabolites like p-cresol, which reduce glutathione (GSH) levels and exacerbate ASD symptoms [11]. While antibiotic treatments targeting *Clostridium* show short-term symptom improvements, effects are often transient due to bacterial spore persistence [41]. Conflicting findings exist regarding *Akkermansia* and *Sutterella* in ASD. *Akkermansia*, associated with gut barrier integrity, is often reduced in ASD patients, suggesting impaired gut permeability [121]. *Sutterella* may influence mucosal metabolism and epithelial integrity, with its alterations potentially contributing to gut dysbiosis in ASD [122].

Dysbiosis in autistic children leads to immune over activation, releasing inflammatory cytokines like TNF-α, IL-8, and IL-6, which affect the CNS via the vagal system. Neuroinflammation is a key factor in autism pathophysiology, with elevated plasma levels of IL-8 and TNF-α observed in autistic children [123]-[125]. Mast cells, stimulated by neuropeptides like corticotropin-releasing hormone (CRH) and neurotensin (NT), release neurotoxic and inflammatory mediators, disrupting the BBB and causing microglial activation [126]. Gut microbes synthesize neuroactive molecules such as serotonin (5-HT), dopamine, GABA and histamine, which influence CNS neurons via the vagus nerve. Dysbiosis alters the levels of these neurotransmitters in autistic patients. Hyperserotonemia, characterized by elevated blood serotonin levels, is common in autism, with most serotonin synthesized in the GI tract [127]. GABA, an inhibitory neurotransmitter, is also affected by dysbiosis, as gut bacteria like *Lactobacillus brevis* and *Bifidobacterium dentium* produce GABA [128].

11.2. FMT in ASD

Given its potential, researchers are increasingly exploring FMT as a treatment for children with autism spectrum disorder (ASD). A modified version of FMT, called microbiota transfer therapy (MTT), has gained attention. MTT involves a 2-week antibiotic treatment, bowel cleansing, and FMT with a high initial dose of standardized human gut microbiota over 7 - 8 weeks. Clinical trials have demonstrated that MTT improves gastrointestinal (GI) symptoms such as constipation, indigestion, abdominal pain, and diarrhea in ASD patients. Additionally, MTT has been shown to ameliorate ASD-related symptoms and restore gut microbiota balance. A study by Kang *et al.* [129] conducted an open-label clinical trial involving 18 children with ASD to evaluate the effects of MTT on gut microbiota composition, GI symptoms, and behavioral outcomes. The study reported an 80% reduction in GI symptoms and significant behavioral improvements, with effects lasting up to 8 weeks post-treatment. However, concerns have been raised about potential side effects, such as new-onset obesity following FMT from an obese donor [130]. De-

spite these challenges, MTT shows promise as a therapeutic intervention for ASD, warranting further research to optimize protocols and assess long-term outcomes.

12. Challenges and Future Advancements in FMT

FMT is a highly successful therapy for recurrent *Clostridioides difficile* infection (rCDI), achieving cure rates above 90% [23]. FMT is FDA-approved for rCDI and is being explored for conditions such as IBD, irritable bowel syndrome (IBS), obesity, multiple sclerosis, and melanoma immunotherapy [3] [23] [47] [82]. While FMT is generally safe in immunocompetent individuals, short-term adverse effects such as diarrhea, constipation, bloating, and abdominal discomfort typically resolve within 48 hours [108] [131]. Reports of mortality are usually linked to pre-existing conditions rather than FMT itself [1]. Long-term risks remain unclear, emphasizing the need for rigorous patient screening and procedural adherence. Regulatory frameworks such as the European Union Tissues and Cells Directive (EUTCD) and FDA guidelines mandate stringent safety measures, including donor screening, adverse event reporting, and biobanking for retrospective analyses [5].

Large-scale studies in China have identified additional indications, including extraintestinal diseases linked to gut microbiota imbalances [105]. Emerging research suggests potential benefits for neurological and metabolic disorders such as Parkinson's disease, Alzheimer's disease, epilepsy, autism spectrum disorder, depression, diabetes, and fatty liver disease [4]. However, contraindications include active sepsis, severe immunosuppression, massive gastrointestinal bleeding, and toxic megacolon [132]. A key challenge in FMT is colonization antagonism, where donor-derived microbes face resistance from the recipient's native microbiota. Studies indicate that only 35% of post-FMT microbiota originates from the donor, with the rest deriving from the recipient or environmental sources [45]. Machine learning models, such as random forest and LASSO regression, have shown promise in predicting FMT success by considering donor-recipient compatibility and procedural factors [45].

FMT is generally safe, though concerns remain regarding pathogen transmission, particularly multi-drug-resistant bacteria, due to the heterogeneous nature of donor fecal material [132]. Rigorous donor screening, including serological and hematological assessments, helps mitigate infection risks, but the process is costly, with only 10% of candidates qualifying [40] [133] [134]. Long-term effects, such as potential links to autoimmune diseases, remain an area of concern [31]. European guidelines recommend an eight-week follow-up period to monitor adverse effects [5] [132]. To enhance safety, washed microbiota transplantation (WMT) has been developed, which removes impurities and reduces adverse events, particularly in IBD patients [14]. Future developments in personalised FMT techniques that make use of metagenomic analysis and bacterial ecosystem modelling might improve the way it is used in metabolic disorders, autism spectrum disorder and autoimmune

disease.

FMT expands beyond recurrent *Clostridioides difficile* infection (rCDI) into metabolic, autoimmune, and neurological disorders, both ethical and mechanistic considerations come to the forefront. Ethically, informed consent is vital, particularly in experimental indications where long-term risks and efficacy remain uncertain [135] [136]. Clear communication of benefits, limitations, and potential complications is essential. Donor compensation also raises concerns about undue inducement, potentially compromising disclosure of health risks; thus, regulatory frameworks must ensure voluntary, non-coercive participation and fair, transparent practices [137]. Furthermore, equity of access remains a pressing issue, as high costs associated with donor screening and microbiota processing may restrict availability to well-resourced populations. Scalable, cost-effective models are needed to ensure broader accessibility without sacrificing safety or efficacy [16].

From a biological standpoint, FMT exerts its effects across diverse conditions through shared core mechanisms: restoration of short-chain fatty acid (SCFA) production, which supports epithelial health and metabolic balance; immune modulation via expansion of regulatory T cells (Tregs), contributing to immune tolerance; and reinforcement of gut barrier integrity, which limits microbial translocation and systemic inflammation [21] [138]. These converging pathways reflect the gut microbiota's central role in maintaining homeostasis and support the rationale for FMT's use in a broad spectrum of diseases. However, to optimize outcomes and address ethical complexities, future research must integrate multi-omics analysis, patient stratification, and standardized clinical protocols.

13. Conclusion

The 21st century marks a transformative period in intestinal microbiome research, emphasizing the critical role of gut microbiota dysbiosis in both intestinal and systemic diseases. FMT has emerged as a groundbreaking therapy, demonstrating the ability to restore microbial balance and revolutionize the treatment of recurrent *Clostridioides difficile* infection (CDI). Beyond CDI, ongoing studies are investigating its therapeutic potential in metabolic, autoimmune, skin diseases, glaucoma and autism spectrum disorder. However, widespread clinical adoption faces key challenges, including variability in donor selection, standardization of safety protocols, and uncertainties surrounding long-term efficacy. Innovations such as multi-donor FMT, synthetic microbiota formulations, and precision microbiome-based therapies offer promising avenues to enhance treatment consistency and scalability. Future research must prioritize patient-specific treatment strategies, deeper insights into host-microbiome interactions, and regulatory frameworks to ensure safety and efficacy. Through well-designed clinical trials and interdisciplinary collaboration, FMT could evolve into a cornerstone of personalized medicine, offering novel and targeted therapeutic options for a broad spectrum of diseases.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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