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Systematic Review

Fecal Microbiota Transplantation: A Systematic Review of Therapeutic Potential, Preparation Techniques, and Delivery Methods Across Medical Conditions

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Abstract: Fecal microbiota transplantation (FMT) is revolutionizing the treatment of gastrointestinal disorders by leveraging the gut microbiome in innovative ways. This systematic review evaluates the clinical effectiveness and safety of FMT across various medical conditions, offering insights into its therapeutic potential and limitations. A comprehensive search of PubMed, Web of Science, Scopus, Embase, and ClinicalTrials.gov from January 2000 to December 2023 identified 97 relevant studies on FMT's efficacy, safety, and microbiome changes after eliminating duplicates. FMT has demonstrated high success rates, particularly in treating recurrent and refractory Clostridium difficile infections (CDI), with up to 90% effectiveness, establishing it as a primary treatment for antibiotic-resistant cases. FMT's applications are expanding to inflammatory bowel diseases (IBD), including ulcerative colitis and Crohn's disease, as well as metabolic disorders and neuropsychiatric conditions. Remission rates for IBD range from 37-45%, with outcomes influenced by donor characteristics, stool preparation, and disease subtype. with mild, self-limiting side effects such as transient diarrhea and abdominal cramping. However, rare serious adverse events underscore the need for rigorous donor screening and standardized preparation protocols to mitigate risks. FMT's ability to restore healthy gut flora highlights its promise in both gastrointestinal and systemic disease management. However, further research is essential to establish optimized procedures, standardized guidelines, and long-term safety data to facilitate its integration into mainstream medical practice.

1. Introduction

Fecal microbiota transplantation (FMT) is revolutionizing the treatment of various gastrointestinal diseases via the innovative use of the gut microbiome. This therapy involves the transferring fecal matter from a healthy donor into the patient's digestive system with the goal of re-establishing a balanced and healthy microbiome. The concept, though ancient in origin, has gained modern scientific validation and is transforming medical practices with promising outcomes for patients suffering from conditions that are often resistant to conventional treatments [1]. FMT has shown significant efficacy in treating recurrent and refractory *Clostridium difficile* infection (CDI), a severe and often recurring condition that does not respond well to standard antibiotic therapies. It aids digestion, produces nutrients, matures the intestinal epithelium, and prevents pathogens.

The term "microbiome" refers to the microbiota and the genes making up the microbiota's genomes with a symbiotic, commensal, or pathogenic relationship with the human host. The gut microbiota supports homeostasis through stability and resilience, although it can be disrupted by antibiotic-, probiotic-, prebiotic-, or infection-related events. Therefore, a wide range of health conditions, including obesity, metabolic disorders, neuropsychiatric disorders, autoimmune diseases, and cancers, have implicated dysbiosis. Clinical studies have reported resolution rates of up to 90%, demonstrating the potential of FMT to restore normal microbial homeostasis and break the cycle of recurrent infections [2, 3].

In addition to CDI, FMT is being explored as a treatment for inflammatory bowel diseases (IBD) including ulcerative colitis and Crohn's disease. Meta-analyses have indicated that the success rates are different, with clinical remission achieved approximately in 37-45% of patients. Aspects like the kind of stool, donor traits, and disease subtype are really important for the results, thus, more studies are needed to improve the treatment protocols [4, 5]. Emerging evidence also suggests potential benefits of FMT in treating conditions beyond CDI and IBD, such as metabolic syndrome, hepatic encephalopathy, and antibiotic-resistant infections. Nevertheless, the findings are in their initial stage and thus, the further rigorous studies are necessary to prove them correct and what their side effects are. The therapeutic promise of FMT in these areas is new and would require further research, yet it is a testament to the widespread potential of this therapy [6, 7].

Generally, the safety profile of FMT is positive, with the majority of the reported side effects being mild and self-limiting, i.e. transient diarrhea, abdominal cramping, and bloating. Rarely, the extreme side effects may occur, and hence, the strict selection of donors and adherence to the standardized preparation protocols should be the first step to minimizing the risks. The introduction of standardized procedures is vital for the maintenance of the uniform safety and effectiveness of FMT in the clinical settings [1, 8]. FMT has numerous advantages, however, it also faces many challenges such as lack of standardized protocols on donor selection, stool preparation, and administration routes. Regulations around FMT therapy are still developing with different areas using different guidelines. There is a need for the establishment of transparent and uniform rules for FMT in order to achieve its wide application. In addition, safety data for longer periods is scarce, which means that there is a need for more prolonged studies to observe possible delayed side effects and also to find out the long-term effects of modifying the gut microbiome [9]. The use of FMT as an innovative procedure signifies great progress in dealing with various gastrointestinal disorders, especially CDI and IBD. The method of microbiome restoration in FMT forms a new therapeutic option that transcends standard treatments. FMT, as science moves forward, can be the new approach in facing and tackling problems related to the gut microbiome. Overcoming the present barriers and upholding thorough scientific and regulatory standards will be the key for its eventual incorporation into the mainstream medical practice.

The primary objective of this systematic review is to assess the clinical effectiveness and safety of FMT in the management of various medical disorders. This study is to analyze the therapeutic capabilities of FMT by integrating data from many research sources. The purpose of this study is to produce a detailed analysis that can assist in clinical practice and guide future research endeavors.

2. Methods and Materials

The methodology started by researching on different databases like PubMed, Web of Science, Scopus, Embase, and ClinicalTrials.gov. The aim of conducting research was to discover papers that prove the efficacy, safety, and the working principles of FMT. The search period spanned from January 2000 to December 2023, and the terms used were such as "Fecal Microbiota Transplantation," "Gut Microbiome Therapy," "*Clostridium difficile*," "Inflammatory Bowel Disease," "Metabolic Disorders," and "Dysbiosis." The search phrases were combined using the Boolean operators (AND, OR), and MeSH terms, as well as free-text words, were used. EndNote 20 was utilized for the purpose of managing references and eliminating duplicates. In addition to conducting hand searching, we reviewed the reference lists of relevant articles and contacted associated authors to obtain additional unpublished data and information on ongoing investigations.

The initial search produced a total of 5,532 entries as depicted in figure 1, including 2,643 retrieved from PubMed, 50 from Web of Science, 1,788 from Scopus, 1,044 from Embase, and 7 from ClinicalTrials.gov. Following the elimination of 2,452 duplicate entries (2,431 flagged by EndNote and 21 by Covidence), a total of 3,080 records underwent screening based on their titles and abstracts. A total of 2,827 records were not included. We attempted to obtain 253 complete-text papers, however, 17 were not obtained. An eligibility assessment was performed on a total of 236 research. Out of these, 109 studies were rejected for various reasons. Some of the reasons for exclusion included not reporting primary outcomes (48 studies), lack of control groups or randomization (37 studies), inconclusive results (54 studies). In the final review, a total of 97 studies were included, offering a full analysis of the effectiveness, safety, and mechanisms of FMT.

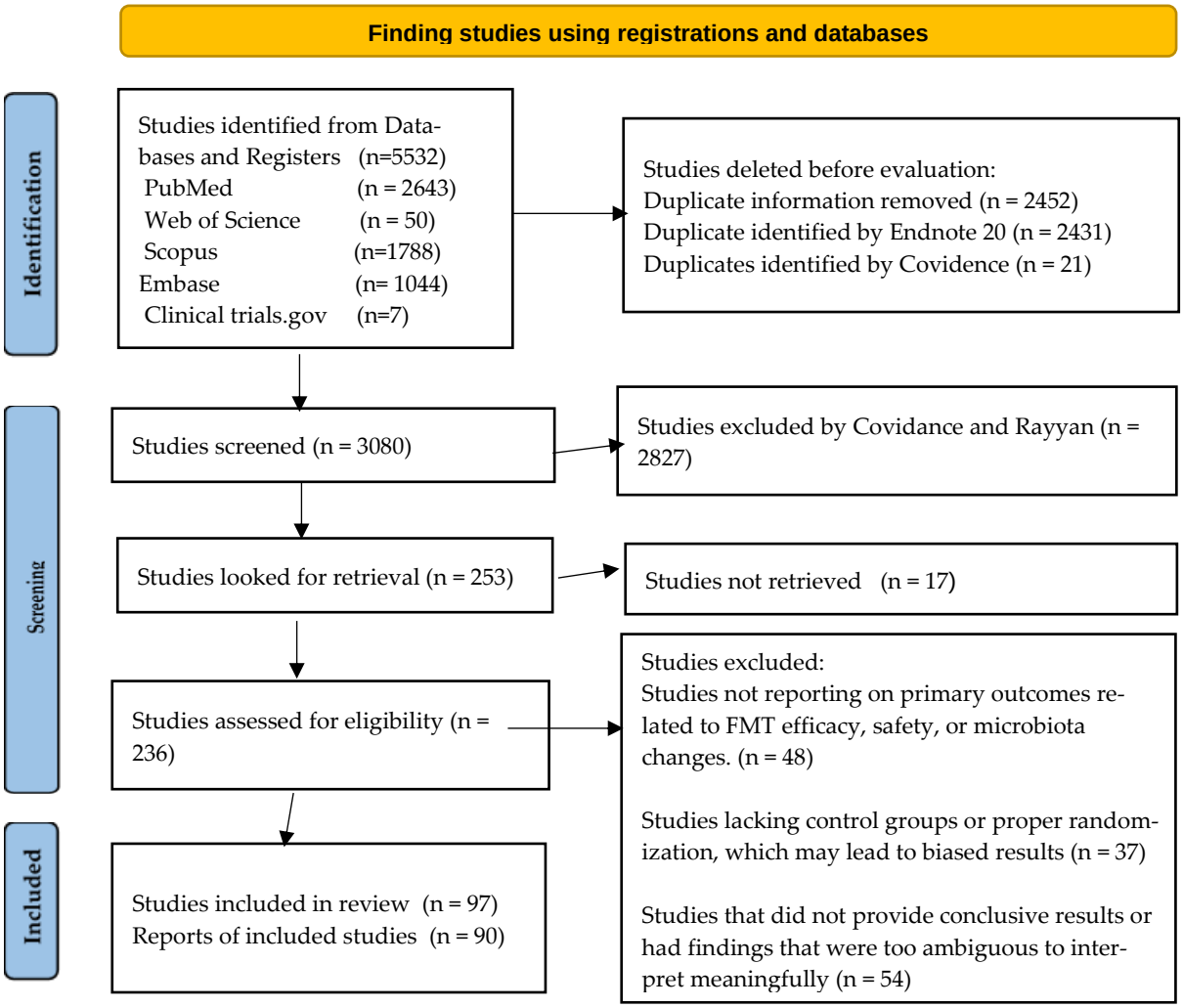

Figure 1: PRISMA flow diagram that provides a concise summary of the search and review technique [10].

3. Mechanism of Action

Fecal Microbiota Transplantation functions through various interrelated pathways that collectively reinstate a robust gut microbiota. The main purpose of FMT is to introduce a varied and well-balanced community of microorganisms into the recipient's digestive system, which then competes successfully against harmful bacteria. The phenomenon of competitive exclusion is most apparent in cases of CDI, when the transplanted microbiota can effectively outcompete and inhibit the growth of *Clostridium difficile* (*C. difficile*), resulting in the remission of symptoms [11]. This is supported by studies showing that after FMT, the recipient's gut becomes more like the donor's microbiota, which is the sign of successful J.A.C. colonization and establishment of a balanced gut microbiota of the recipient [12].

Along with this the other key mechanism of the immune system modulation is also involved. Dysbiosis, or the imbalance of the gut microbiota, can be the cause of the unregulated or a little too much immune response which leads to the chronic inflammation and tissue damage. FMT restores the population of the gut with beneficial organisms which in turn can bring back immune homeostasis and inflammation down. This is especially so in case of disorders like IBD in which FMT has been of help to some patients by reducing the inflammation in the mucosa and thus inducing remission [13]. The rejuvenation of core metabolic functions is another crucial component of FMT's action. The gut microbiota is very important to the metabolism of bile acids, short-chain fatty acids (SCFAs), and some other crucial metabolites. For example, in patients CDI, FMT has been demonstrated to regulate bile acid metabolism, which is critical because bile acids affect the life cycle of *C. difficile*. Prior to FMT, patients with recurrent CDI typically exhibit elevated levels of primary bile acids and reduced levels of secondary bile acids. After FMT, this imbalance is corrected, which is an additional reason why the germination and proliferation of *C. difficile* spores are not stimulated [12]. Furthermore, FMT can augment the output of short-chain fatty acids production (SCFAs), substances that act as anti-inflammatories and which can promote the intestinal barrier function. SCFAs such as butyrate have a dual function: one to be a source of energy for colonocytes and the second to maintain the integrity of the gastrointestinal lining. Therefore, pathogens and toxins cannot translocate into the bloodstream [14]. FMT is also changing the metabolism of the host and can be a systemic effect beyond only the gastrointestinal tract. For instance, the gut microbiome's FMT alteration has been related to the improvement of insulin sensitivity and metabolic profiles in metabolic syndrome patients. This implies that the gut microbiota has the ability to modulate systemic metabolic pathways and thus, can be useful in the treatment of metabolic disorders [15]. The efficacy of FMT in curing different diseases also depends on the donor-receptor compatibility and the diversity of the donor microbiota. Studies have shown that recipients often demonstrate different levels of microbiota transfer success, which can vary according to the individual's microbiome resistance patterns and the strains present in the donor microbiota. This emphasizes the significance of selecting optimal donors and perhaps devising personalized FMT strategies to ensure the best treatment results [16]. These mechanisms work together to address gastrointestinal and systemic disorders. Figure 2 shows FMT treatment and processes.

Step 1: Bowell Preparation is 3-7 days of antibiotics followed by oral polyethylene glycol with an electrolyte purgative to cleanse the bowel.

Step 2- FMT Delivery Methods: The donor stool can be introduced in several ways—nasogastric or mesenteric tube, capsules, dental tube, colonoscopy, and rectal tube.

The potential therapeutic mechanism of FMT is the restitution of microbial diversity. Reduction of pathogen populations and their associated toxins. Improve protection of gut barrier function, reducing inflammation. Immune modulation, which affects both innate and adaptive responses of the immune system, can promote anti-inflammatory pathways and SCFAs. Table 1 provides a comprehensive compilation of the mechanisms by which FMT operates.

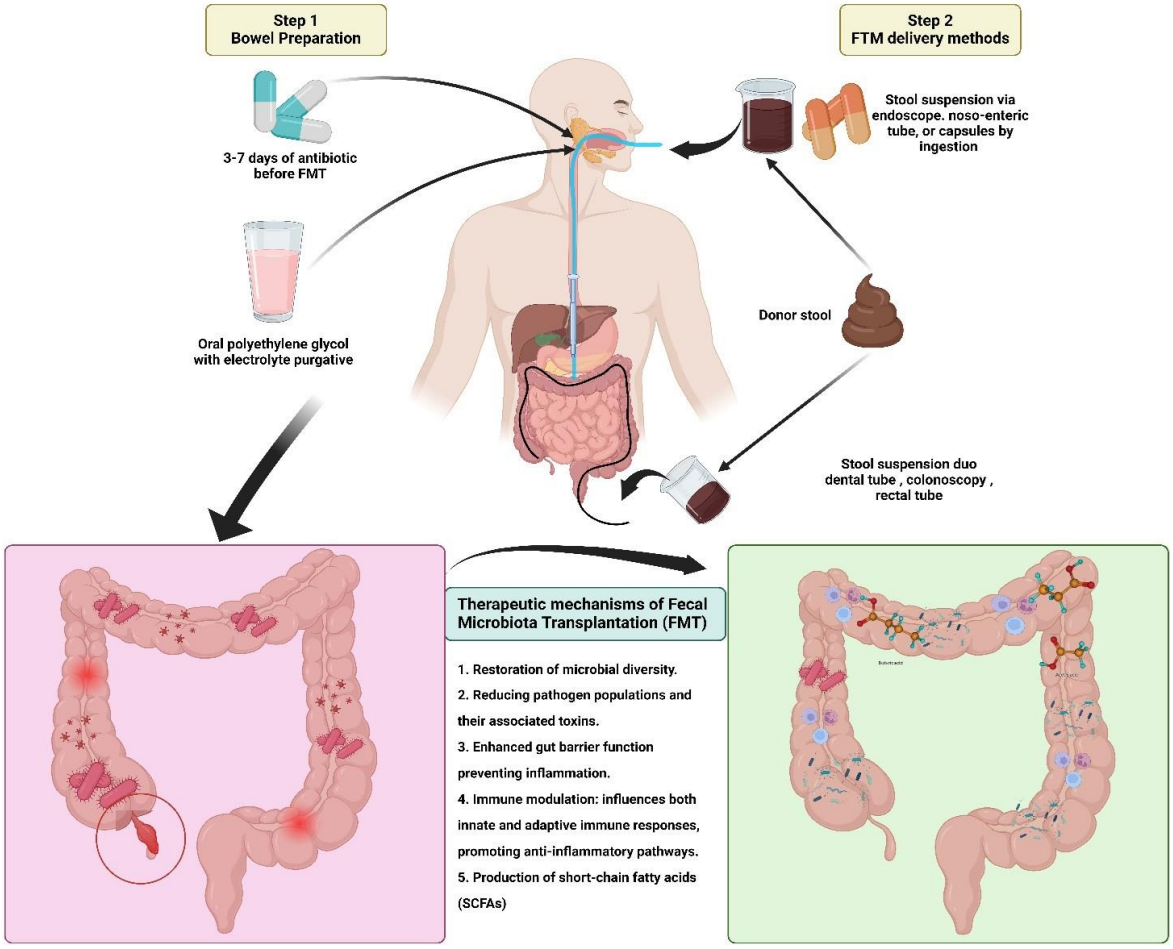

Figure 2: Fecal Microiota Transplantation (FMT).

Table 1: Summary of fecal microbiota transplantation's mechanisms of action.

Mechanism	Animal or Human Model	Type of Delivery	Key Finding	Reference
Modulation of Tumor Immunity	Human (Cancer Patients)	FMT via Enema	FMT enhances the efficacy of immune checkpoint blockers by modulating tumor immunity.	[17]
Restoration of Gut Microbiota	Mouse (Type 2 Diabetes)	Oral Administration	FMT ameliorates hyperlipidemia and hyperglycemia, restoring gut microbiota composition and metabolic pathways.	[18]
Modulation of Immune Response	Human (Recurrent CDI)	FMT via Colonoscopy	FMT modulates immune responses by reducing inflammatory mediators and enhancing regulatory T cells.	[19]
Glycemic Control and Insulin Sensitivity	Human (Type 1 Diabetes)	FMT via Enema	FMT improves glycemic control and modulates autoimmunity, showing potential in managing type 1 diabetes.	[20]
Control of Infectious Diseases	Human (General)	Various Methods	FMT is effective in treating infectious diseases by restoring gut microbiota and reducing pathogen reservoirs.	[21]
Improvement of Liver Function	Human (Liver Cirrhosis)	FMT via Enema	FMT restores gut microbiota, improving liver function and reducing symptoms in liver cirrhosis patients.	[22]
Neurological Improvement	Human (Parkinson's Disease)	Oral Administration	FMT increases gut microbiome diversity, reduces constipation, and improves gut transit and motor symptoms.	[23]
Microbiota Engraftment	Human (IBD and CDI)	Various Methods	Successful FMT requires matching donor and recipient microbiota types for effective engraftment and disease treatment.	[24]

4. Type of Delivery Method in FMT

Fecal Microbiota Transplantation is one of the various delivery methods which involves a healthy donor's stool getting into a patient's gastrointestinal tract to treat dysbiosis-related conditions. One of the frequently used techniques is colonoscopy, which sends the fecal microbiota directly into the colon. Speaking of recurrent CDI, this method is extremely effective because it is directed to the very area that is affected. Scientifically proven, the success rate of colonoscopy FMT in resolving CDI is extremely high, with some reports indicating efficacy rates exceeding 90%[25]. Another method is transendoscopic enteral tubing (TET), which has gained popularity, especially in China. Through TET, one could administer the FMT solution directly into the colon repeatedly, thus, making it suitable for chronic conditions like IBD. This method has evidenced high levels of patient satisfaction and success in keeping disease remission. Besides that, the possibility of administering several doses without having to repeat colonoscopies provides a valuable benefit, thus, minimizing patients' discomfort and the risks related to the procedures [26]. The usage of capsules that are taken orally as medication is increasing in popularity thanks to their capacity to be non-invasive. These capsules are made of lyophilized fecal material which is a product that can be taken by patients without the need for invasive procedures. Research has proved that encapsulated FMT (cFMT) works as effectively as colonoscopic FMT in treating CDI and the additional benefits of patient compliance and ease of use are also provided. This technique has found use in the treatment of other than CDI conditions; however, its efficacy in such cases remains to be investigated [27].

Esophagogastroduodenoscopy (EGD) is another delivery method used for FMT, by which fecal material is delivered directly to the small intestine. This method is particularly helpful for those patients who do not want to put up with the discomfort of colonoscopy or oral capsules. Studies utilizing EGD have shown positive results as well, especially in the case of patients with the small intestinal bacterial overgrowth or those in need of direct intervention in the upper gastrointestinal tract [28].

Yet another innovative approach is the washed microbiota transfer (WMT), which is a procedure whereby the fecal matter used for transplantation is processed to remove the undesired components, thus augmenting the transplant safety and treatment effectiveness. WMT appears to have the fewer adverse events when compared with the traditional FMT, thus it is a treatment option for patients who have a weak immunity system or are receiving several treatments. This approach is gaining momentum for its capacity to standardize and thereby, enhance the quality of the FMT preparations [29]. Each delivery method has its specific indications, advantages, and limitations. Colonoscopy offers direct delivery to the colon but is invasive; TET allows for repeated dosing with less invasiveness; oral capsules are non-invasive and convenient but may be less effective in some cases; EGD targets the small intestine effectively but is also invasive; and WMT enhances safety and consistency of the microbiota transplant.

The choice of method depends on the patient's condition, preference, and the specific clinical scenario, aiming to maximize efficacy while minimizing risks and discomfort [30]. Table 2 shown summarizes type of delivery and used for some diseases. Then, figure 3 shown FMT delivery methods.

Table 2: Types of FMT delivery methods.

Type of Delivery	Used for Diseases	Efficacy Rates Exceeding	Reference
Colonoscopy	CDI, IBD	>90% for CDI	[25]
Transendoscopic Enteral Tubing (TET)	(IBD)	High patient satisfaction, effective in maintaining remission	[26]
Oral Capsules	Recurrent Clostridium difficile infection (CDI), Metabolic Syndrome	Comparable to colonoscopy for CDI, varied for other conditions	[27]
Esophagogastroduodenoscopy (EGD)	Small Intestinal Bacterial Overgrowth, Upper GI conditions	>85% for MDRO decolonization	[28]
Washed Microbiota Transplantation (WMT)	General Dysbiosis, Multiple Conditions	Reduced adverse events, effective in multiple conditions	[29]

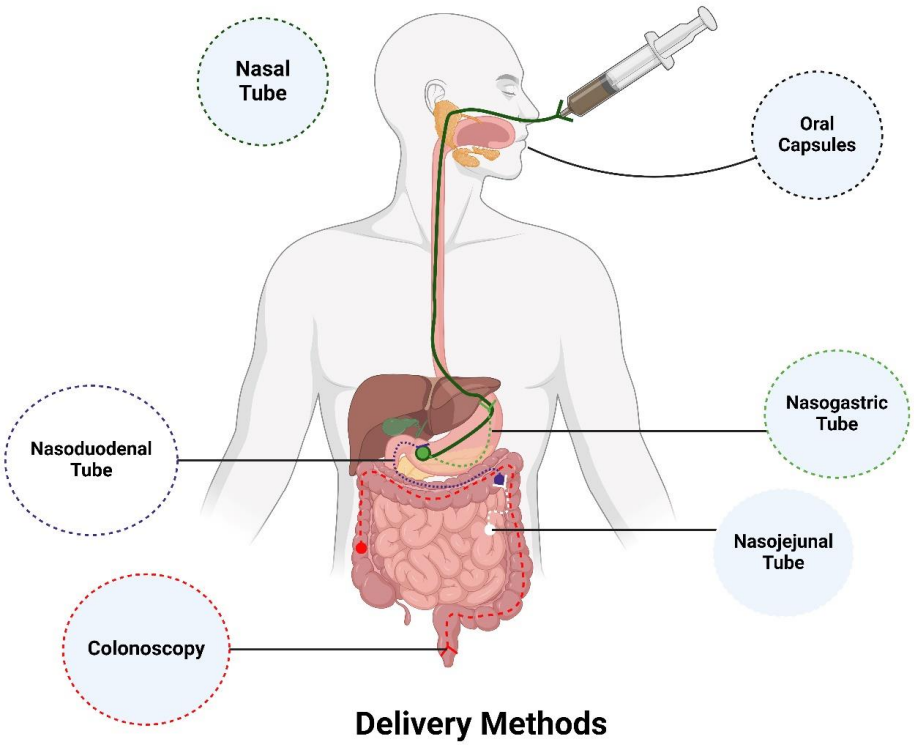

Figure 3: Types of FMT delivery methods.

5. Preparation Method

The preparation methods for FMT vary depending on the delivery method, each with specific steps to ensure the viability and safety of the microbiota being transplanted. For colonoscopy, the process begins with the collection of fresh stool from a screened donor. The stool is then mixed with a saline solution and homogenized. This mixture is filtered to remove large particles, creating a smooth suspension. It is essential to carry out the preparation without any gas exchange in order to ensure the anaerobic bacteria survival. The processed stool is then drawn into syringes for administration during the colonoscopy procedure [31].

In addition, although the first steps of the process, like donor stool screening and saline mixing, are the same for TET, the stool is processed into a flowable solution that can be delivered via a specialized tube. This technique enables the patient to have multiple administrations of FMT. The stool is filtered and then introduced into the colon through the TET, which is left in place for multiple treatments, thus reducing the need for repeated invasive procedures [29]. Moreover, oral capsules involve a more complex preparation process. After donor stool collection and screening, the stool is lyophilized, or freeze-dried, to create a powder. This powder is then encapsulated in gastro-resistant capsules that protect the microbiota from stomach acid. The encapsulation process requires careful control to ensure that the bacteria remain viable until they reach the intestines. These capsules provide a non-invasive alternative for FMT and have shown efficacy similar to colonoscopic administration in treating recurrent CDI [27].

Esophagogastroduodenoscopy is another method but it requires the same preparation steps as colonoscopy this time they are adjusted to deliver the drug to the upper gastrointestinal tract. The stool is collected, mixed with saline, and processed under anaerobic conditions. Through an endoscope, the prepared stool is first inserted into the upper part of the gastrointestinal tract. This technique is advantageous to patients with small intestine bacterial overgrowth or other diseases that affect the upper part of the gastrointestinal tract [28]. At last, WMT is a method with an extra step to improve safety and effectiveness. Firstly, the stool is mixed with saline and homogenized, then subjected to a washing pro-

cess to get rid of impurities and concentrate the beneficial microbes. This method is useful in minimizing the occurrence of adverse events like fever and therefore, is the main reason for the high safety profile of FMT. WMT is a method that helps patients with compromised health as it provides the highest purity of the transplanted microbiota [29]. Figure 4 demonstrates the comparison of the preparation methods that are suitable for different delivery methods.

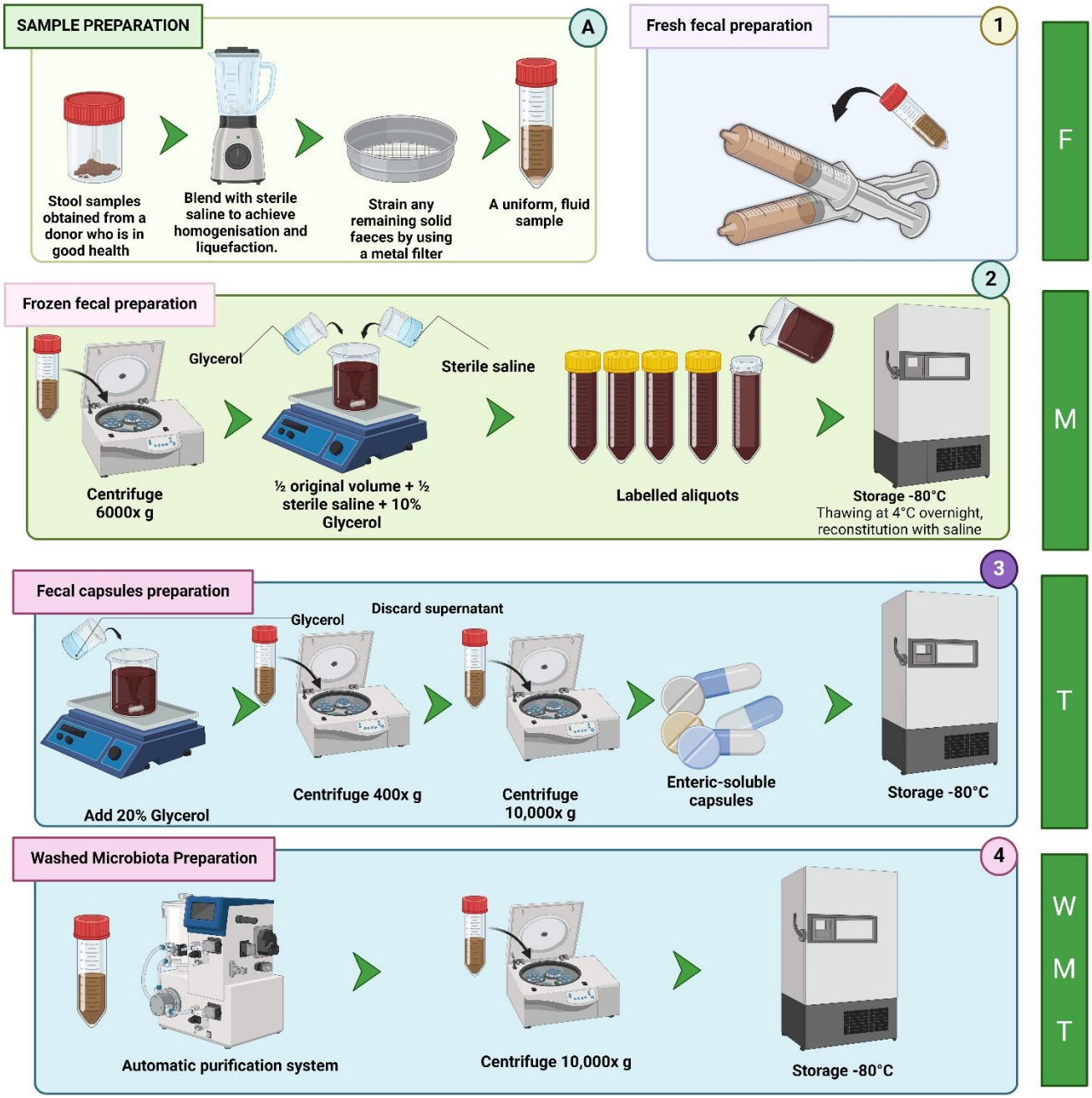

Figure 4: Preparation methods A prepare sample, (1) Fresh fecal preparation, (2) Frozen fecal preparation, (3) Fecal capsules, (4) Washed microiota preparation

6. Application of Transplanting Fecal Microbiota in Human Diseases

FMT restores gut microbial balance and is a viable treatment for many human illnesses. Human health depends on gut microbiota imbalance, which has been linked to several diseases. Figure 5 shows that FMT is widely used in auto-immune inflammatory illnesses, cancer, brain diseases, CVD diseases, liver diseases, obesity and metabolic disorders, gut diseases, and intestinal diseases.

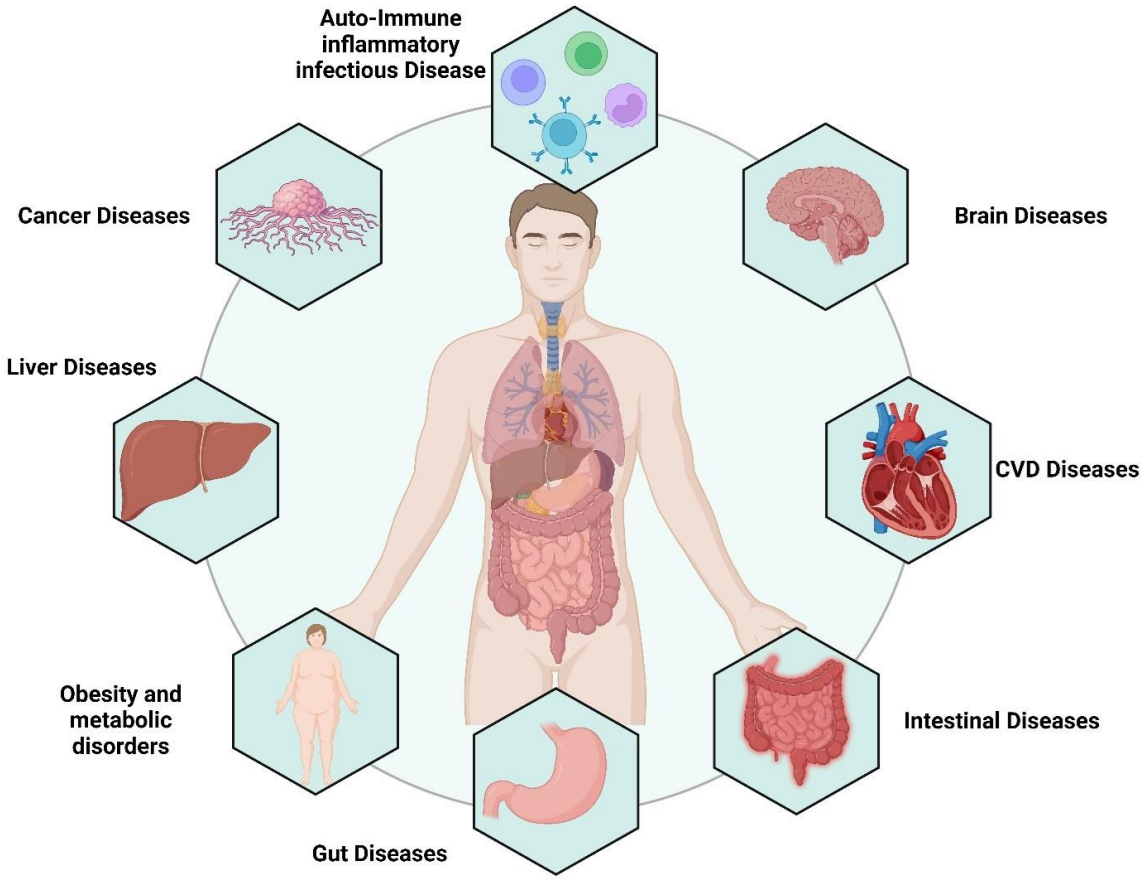

Figure 5: Many diseases can be treated by feces transplants. A diagram representing fecal microiota transplantation clinical trials for various human illnesses.

6.1. I*rritable Bowel Syndrome*

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder with stomach pain and irregular bowel movements. Gut microbiota dysbiosis contributes to the complex cause of irritable bowel syndrome. Fecal microbiota transplantation may help IBS patients restore gut microbiota equilibrium. FMT has shown mixed but promising effects in treating IBS symptoms in many studies. In contrast to IBD, which causes gut wall damage and inflammation, IBS does not. Instead, it causes abdominal bloating, cramps, constipation, and diarrhea. IBS patients have different gut microbiome. In a recent study, Holvoet and colleagues [32] examined patients with refractory IBS who did not improve after three standard treatments.

A single naso-jejunal dose of FMT was given to subjects with major bloating. One year following FMT 56% of patients reported improved IBS symptoms and well-being. The participants' gut microbiomes were more diverse (without particular taxa) than the non-respondents'. This shows that gut microbiome diversity may predict FMT effects [32]. Some clinical trials found better IBS symptoms, microbial profiles, and SCFAs after FMT in IBS patients, but others did not. Halkjaer and colleagues [33] administered the moderate-to-severe IBS patients FMT pills for 12 days. Comparing stool samples before and after FMT showed an improvement in IBS symptoms and gut microbial diversity after three months. It was surprising that six months later, placebo patients reported better symptom relief than FMT patients. This shows that gut microbiome modification may not be enough to treat IBS. Aroniadis and his colleagues [34] recruited people diagnosed with diarrhea-predominant IBS and provided them with over 25 capsules of FMT every day for a period of 3 consecutive days. Each capsule contained approximately 0.50 g of very little processed donor stool.

Nevertheless, there was no notable enhancement in symptoms reported after a duration of three months as compared to the group that received the placebo [34]. Moreover, FMT utilizing feces from

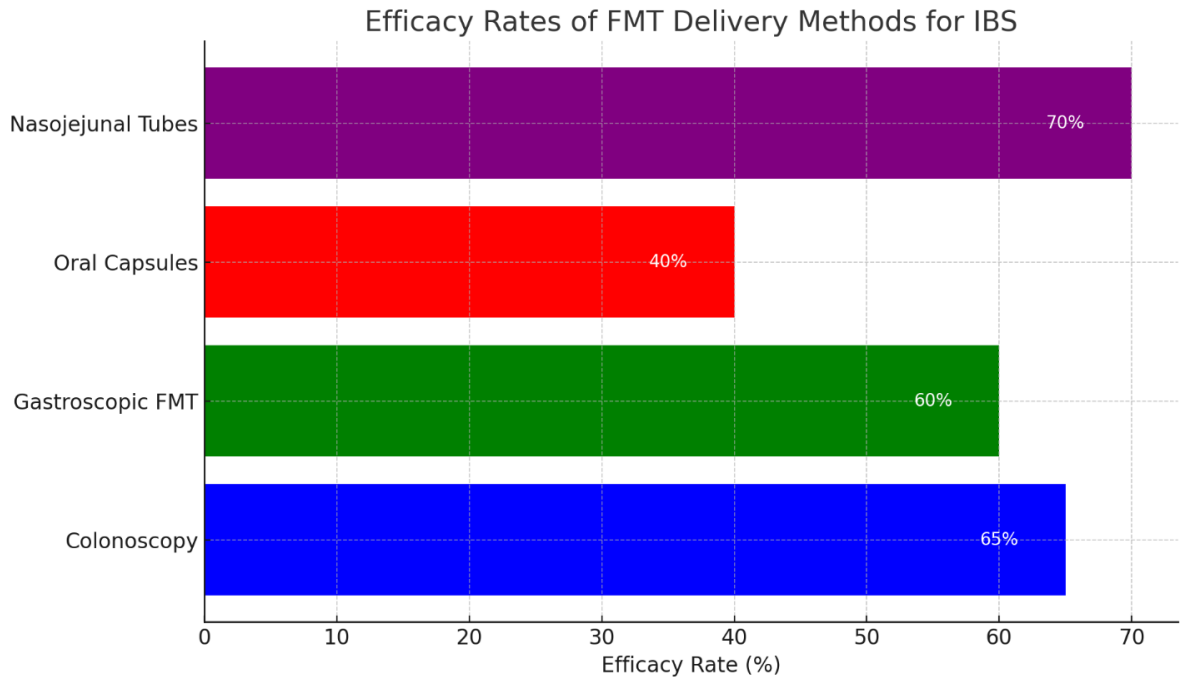

Figure 6: The effectiveness rates of various delivery modalities for FMT in the treatment of Irritable Bowel Syndrome.

a healthy donor (allogenic transplant) or the patients themselves (autologous transplant) was tested in a limited sample of patients by Holster and colleagues. Symptom improvement was similar in the two groups, however the allogeneic group improved relative to baseline [35]. In addition, the research group identified alterations in the interactions between the gut flora and its metabolites. Conversely, a significant randomized, placebo-controlled study showed that FMT has the potential to decrease symptoms of IBS, specifically abdominal bloating. These effects were observed to last for up to one year in certain patients [32]. This study found that patients receiving donor stool reported significant improvements in IBS-related symptoms and quality of life compared to those receiving placebo stool. Further meta-analyses have explored the potential of FMT in IBS treatment, highlighting variations in success rates due to differences in FMT methods and patient factors [36].

For instance, a review of current studies indicated that while gastroscopic FMT appears to be effective, oral capsule FMT might not offer the same level of symptom relief [37]. Long-term follow-up studies suggest that FMT remains an effective and safe treatment for IBS up to one-year post-treatment, with sustained symptom relief and improved quality of life [38]. Despite these positive outcomes, the exact mechanisms by which FMT exerts its effects on IBS remain unclear. There is evidence suggesting that the engraftment of specific anaerobic bacteria may not directly correlate with clinical improvement [39]. The debate over whether FMT is a panacea or placebo for IBS continues, with small studies offering conflicting results and highlighting the need for more rigorous trials [40].

Meta-analyses of randomized controlled trials suggest that FMT can significantly improve IBS symptoms when delivered via invasive routes like colonoscopy or naso-jejunal tubes, compared to oral capsules, which have shown less efficacy [41]. Ultimately, FMT shows potential as a therapeutic method for IBS, specifically for patients who have not experienced positive results from traditional treatments. FMT might be more or less effective depending on the way it is given to the patient and specific patient characteristics. Still, the ever-increasing evidence climbs to its feet and supports the position of FMT to be a treatment for IBS. Current research focuses on improving FMT protocols, comprehending FMT, and ensuring its long-term safety and efficiency. Figure 6 shows the efficacy of five FMT delivery strategies for IBS. This includes colonoscopy, gastroscopic FMT, oral and naso-jejunal tube caps. Table 3 shows recent IBS clinical trials of FMT.

Table 3: Clinical Trials on FMT for Irritable Bowel Syndrome.

Route of Administration	Key Findings	Reference
Oral (Fiber)	Baseline microbiota diversity influences response to fiber intervention in IBS patients.	[42]
Oral (Animal Study)	In a rat model of IBS, probiotic yeast produced from miso reduces visceral hypersensitivity brought on by stress.	[43]
Colonoscopy	FMT significantly relieved IBS symptoms; 65% response in treatment vs. 43% in placebo.	[44]
Oral Capsules	No significant symptom relief with FMT compared to placebo in IBS-D patients.	[34]
Gastroscope	Significant symptom improvement with FMT; higher doses showed better results.	[45]
Nasojejunal	FMT reduced IBS symptoms, particularly abdominal bloating; effects lasted up to one year in some patients.	[32]
Colonoscopy	Long-term changes in gut microbiota and symptom relief post-FMT.	[46]
Gastroscope	FMT led to improved IBS symptoms and quality of life; microbiota changes persisted for up to 28 weeks.	[47]
Colonoscopy	FMT is effective in PI-IBS; significant microbiota changes and symptom relief observed.	[48]
Gastroscope	Long-term efficacy and safety of FMT in IBS patients; sustained symptom relief after one year.	[38]

6.2. Inflammatory Bowel Disease

The treatment of inflammatory bowel diseases (IBDs) including ulcerative colitis and Crohn's disease using fecal microbiota transplantation is novel. Severe abdominal pain, diarrhea, and weight loss can indicate the disease. IBDs's complex cause involves genetic vulnerability, immune system dysregulation, and environmental factors that affect gut flora. FMT injects healthy donor stool into a patient's gut to restore microbial balance, reduce inflammation, and boost clinical activity. FMT has shown mixed but promising effects in treating IBDs symptoms in many studies. The main types of IBDs include ulcerative colitis and Crohn's disease. Crohn's disease affects the mouth, esophagus, stomach, small intestine, large intestine, and anus. However, ulcerative colitis targets the colon and rectum[49, 50].

Typical symptoms of this illness include diarrhea, bleeding from the rectum, abdominal pain, and anemia. The current therapy techniques generally rely on directly targeting the immune response. Dysbiosis, an imbalance in the gut microbiota, is considered a critical factor in the onset of bowel inflammation [51, 52]. Therefore, FMT is seen as a potential therapeutic approach [53]. The initial clinical trials included patients with both major kinds of IBDs, and only a small number of patients experienced clinical remissions that were linked to a high abundance of gut microbiota from the donor [54]. The subsequent clinical trials targeted one IBDs variant. In a pioneering placebo-controlled randomized experiment, Moayyedi and colleagues [55] provided active ulcerative colitis patients a 50 mL retention enema once a week for six weeks, avoiding infectious diarrhea. The trial showed no adverse events following FMT, proving its safety. Additionally, 24% of ulcerative colitis patients remitted.

In a subsequent double-blind, randomized, placebo-controlled study, individuals with active ulcerative colitis underwent treatment with FMT colonoscopic infusion, followed by enemas administered 5 days per week for 8 weeks. The outcome of this treatment approach was a remission rate of 27%, but it also resulted in adverse effects in 78% of the patients. The examination of the ribosomal 16S RNA indicated a consistent and lasting augmentation in microbial variety with FMT. Notably, the presence of the *Fusobacterium spp*. strain was linked to the absence of improvement in ulcerative colitis remission [56].

FMT patients struggled due to the extensive therapy duration in the first two clinical studies. However, the medical staff must devote heavily. A third trial drastically reduced FMT therapy with a nasoduo-denal tube to the study's beginning. The FMT patients' remission rates were not statistically different after three weeks. Results showed that 20.0% of autologous and 30.4% of allogenic FMT patients had good clinical responses. Comparing the two groups revealed no differences. The microbiota profile post-FMT in ulcerative colitis patients correlates with clinical response and microbiota engraftment, making it an essential topic of study. Due to remission rate variations and clinical trial numbers,

this investigation is important [57]. A 5-patient preliminary study addressed this issue. The donor similarity index was 40-50% in 60% of patients after a single colonoscopy-based FMT surgery. Clinical remission was linked to this measure, indicating success. Paramsothy *et al.* [58] compared feces before and after an eight-week intense FMT treatment schedule (five times per week). The researchers found that FMT increased microbial diversity. Remission was associated with a higher abundance of *Eubacterium hallii* and *Roseburia inulivorans* and higher SCFA levels than non-remission.

On the other hand, individuals who did not experience remission had an increase in the presence of *Sutterella wadsworthensis*, *Fusobacterium gonidiaformans* and Escherichia species, as well as elevated levels of lipopolysaccharide. Remarkably, the presence of Bacteroides in the donor stool was linked to a positive response to FMT, while the presence of Streptococcus species was related to a lack of response [58]. Up until now, the clinical trials that have been conducted have focused on adults with ulcerative colitis. However, there is now a growing interest in using FMT techniques for juvenile patients as well. After conducting several trials involving a small number of pediatric patients that produced inconsistent findings [59, 60]. Pai and colleagues conducted the initial randomized clinical trial involving pediatric patients (aged 4 to 17 years) with active ulcerative colitis. At week 6, 92% of the kids in the FMT arm experienced improvement in the juvenile ulcerative colitis activity index, compared to just 50% in the placebo arm. Furthermore, even after one year, 75% of the patients who received the transplant still displayed a clinical response. The clinical result was found to be linked with the bacterial taxa including *Escherichia spp*. and *Alistipes spp*. [61].

On the other hand, the efficacy of FMT also varies depending on whether fresh or frozen stool is used. Studies suggest that fresh stool might be more effective in inducing remission compared to frozen stool, although both forms have been used successfully in clinical practice [62]. Furthermore, the specific strains of bacteria present in the donor stool can significantly impact the outcome, with some strains being more beneficial than others [63]. The power of FMT goes far beyond just getting remission. Through its application, it has been discovered that IBDs patients produce less corticosteroids and other immunosuppressive drugs that would cause drug-related side effects [64]. Moreover, FMT has been associated with the better quality of life and saving on healthcare expenses incurred for the treatment of IBD such as hospital admission and surgery [65].

Despite the fact that FMT in IBDs has shown great potential, it is still fraught with challenges and unanswered questions. The variation in patient response, the optimal frequency of administration, and long-term safety are still the areas which need to be investigated further. Nevertheless, the current evidence prescripts the involvement of FMT in the therapeutic arsenal for IBDs, which may provide a potential path to remission and the patient's improvement outcomes [66].

To sum it up, FMT could be a game-changer in the treatment of IBDs. It could bring the gut microbiota back to the balance, cut down on inflammation, and make the clinical outcomes better. Ongoing research and well-conducted clinical trials are needed for a complete understanding of the mechanisms, the perfection of the protocols, and the establishment of FMT as a standard treatment for IBDs. The figure 7 show efficacy rates of FMT in treating IBDs as reported in various studies. The studies included range from 2018 to 2022 and cover a range of efficacy rates from 57% to 75%, which thus proves the difference in success rates for different trials and methodologies. Study the table 4, in detail, IBDs, the outcomes, route of administration, and the key findings.

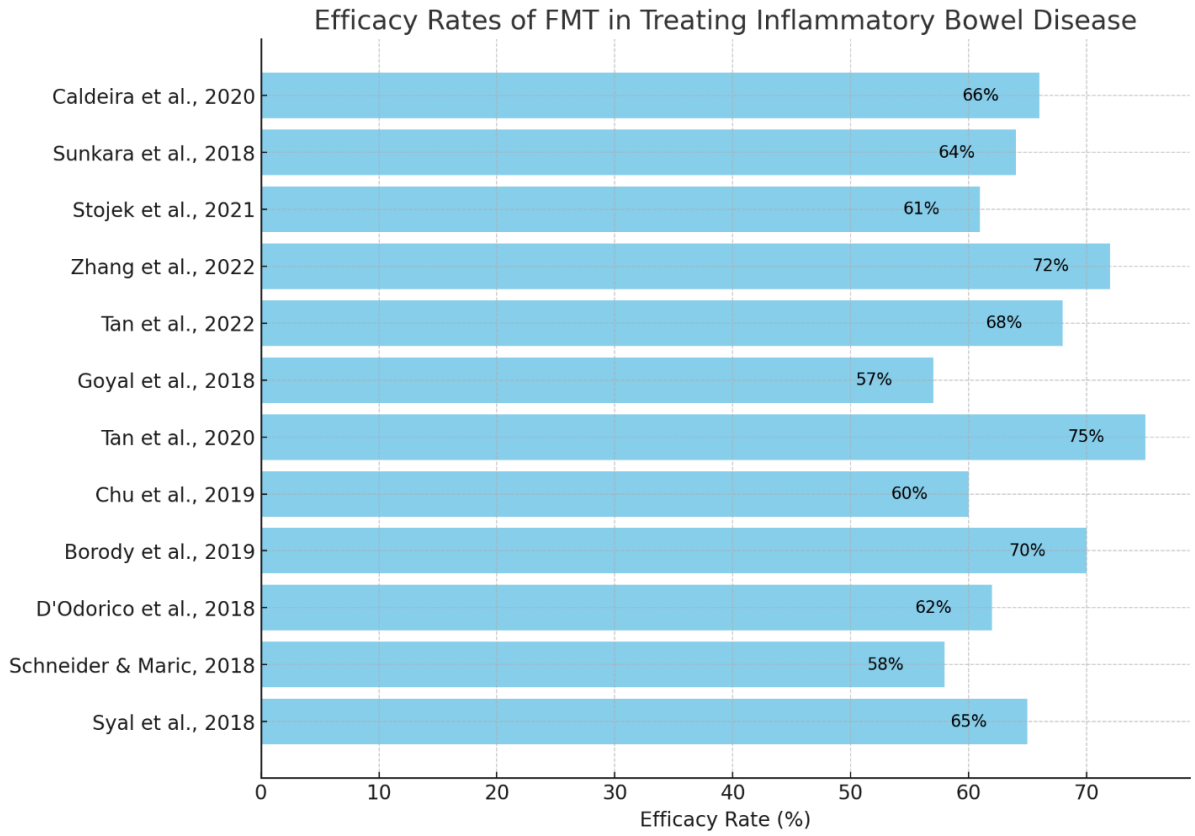

Figure 7: Efficacy rates of FMT in treating inflammatory bowel disease.

Table 4: Summary of outcomes in inflammatory bowel disease treatments.

Route of Administration	Key Findings	Outcome	Ref
Oral	Ganciclovir is effective but has serious adverse effects	High efficacy with serious adverse effects	[67]
Nasogastric tube	FMT showed potential in inducing clinical remission in children	3 out of 8 children achieved clinical remission	[68]
Colonoscopy	Single FMT provides short-term relief but not long-term	Short-term relief, no long-term effect	[69]
Colonoscopy	Multiple FMTs result in short-term remission	Clinical response and remission in over half the patients.	[34]
Gastroscopy or Colonoscopy	No difference in remission or adverse events between gastroscopy and colonoscopy	No difference in clinical remission and adverse events	[70]
Colonoscopy	Single FMT increases gut microbiota diversity and regulatory T-cells	Remission in half the patients, increased gut microbiota diversity, more regulatory T-cells	[71]
Colonoscopy	Higher remission rate with FMT compared to sham transplantation	Higher remission rate with FMT than sham group	[72]

6.3. Autoimmune, Inflammatory, and Infectious Diseases

Fecal microbiota transplantation can treat both inflammatory and autoimmune disorders and the last kind of infectious diseases. Lately, the research has considered this as a potential solution to various ailments and the outcomes seem encouraging. Rheumatic diseases like psoriatic arthritis (PA) are characterized by the autoimmune response and inflammation that cause damage to the joints and organs. PA is linked with microbiota dysbiosis in the gut where the number of beneficial bacteria such as *Coprococcus sp., Akkermansia sp., and Ruminococcus sp*. are low. The findings here imply that using FMT to restore the diversity of the microbiota might lead to new methods of treatment. On the other hand, the very few clinical trials in this field. Kragsnaes [73] carried out a trial among PA patients that showed

no significant symptom improvement after FMT, yet the patients reported to have noticed positive changes in their daily lives. A different group argued that the change in the gut microbiome induced by FMT could, paradoxically, trigger reactive arthritis, thus showing the necessity for more specific clinical trials that will explore FMT's safety and efficacy in various types of inflammatory arthritis in detail. Nevertheless, systemic sclerosis (SSc) is a multi-organ autoimmune disease, which usually has a serious gastrointestinal complication that is caused by the disruption of gut bacteria. Fretheim *et al.* [74] performed a pilot trial using anaerobic cultivated human intestinal microbiota in women with SSc. The intervention, which was carried out using gastroduodenoscopy, turned out to be free from major side effects, and the patient's gastrointestinal symptoms were drastically improved, as the patients reported fewer episodes of bloating and diarrhea.

This study provided initial clinical efficacy for FMT in SSc, although further research with larger cohorts is necessary. Then for the diabetes type 1 diabetes (T1DM) is an autoimmune condition marked by the elimination of beta cells that produce insulin. Considering the gut microbiota's role in T1DM, De Groot *et al.* [75] assessed FMT's efficacy in slowing disease progression in recent-onset T1DM patients. The study found that FMT mitigated the reduction in insulin production and maintained beta cell function, which correlated with alterations in microbiota-derived plasma metabolites. This illustrates FMT's capacity in the modulation of autoimmunity and controlling metabolic functions in T1DM. Atopic dermatitis is a chronic skin condition with links to the gut and skin microbiota dysbiosis. On the other side Huang *et al*. [76] investigated FMT's therapeutic potential in patients with atopic dermatitis and gastrointestinal disorders. The study found that FMT therapy led to significant improvements in both gastrointestinal and dermatological symptoms.

This means microbiota restoration and decline in inflammation could be amenable to FMT as treatment for AD. Furthermore, dysbiosis of gut microbiota is one of the contributing factors of multiple sclerosis, an inflammatory disorder of the central nervous system that affects the brain and spine. Engen *et al.* [77] had a proof-of-principle study where they demonstrated that FMT could be an effective method to increase the population of beneficial bacteria and short-chain fatty acids in the stool, which may alleviate the symptoms of multiple sclerosis. While this study paves the way for the future randomized controlled trials in MS patients, it also opens up the possibility for interventions. Lastly, for Human Immunodeficiency Virus (HIV) and Coronavirus Disease 2019 (COVID-19), the association between HIV infection and gut microbiota dysbiosis that causes chronic inflammation should be noted. Oral FMT capsules were given to HIV patients on antiretroviral therapy in a pilot study by Serrano-Villar *et al.* [78]. The results showed that FMT was safe, it increased the diversity of the gut microbiota, and it decreased the intestinal damage markers.

The results of the research have given a manner for further investigation of FMT use as FMT can treat HIV-induced dysbiosis. Moreover, the COVID-19 pandemic has established the gut's microbiota in determining the severity of the disease and in recovery. Gut microbiota alterations have been discovered in COVID-19 diseased people, developing the pathogens and declining the beneficial bacteria. Wu *et al.* [79] started a clinical trial in which the effectiveness of FMT in curing gut microbiota dysbiosis in COVID-19 patients was studied, the patients were assessed based on gastrointestinal symptoms, disease recovery, and inflammatory response. The outcomes of this trial are being waited to figure out whether FMT is effective in treating gut microbiota alterations caused by COVID-19.

6.4. Cardio-Vascular Diseases

FMT is becoming generally accepted as a strategy to treat cardiovascular diseases (CVD) because it can affect the gut microbiota, which plays a major role in their development. Recent research has demonstrated that FMT improves cardiovascular health through particular processes, which is why its benefits are growing. Gut microbiota dysbiosis is connected to CVD via many routes and metabolites. Witkowski et al. [80] found that gut microbiota-dependent compounds such Trimethylamine N-oxide (TMAO) and phenylacetylglutamine increase cardiovascular risk. The research indicated that these metabolites cause heart disease by binding to host receptors. Metabolic syndrome, a cluster of conditions that increase the risk of heart disease, has been a primary focus of FMT studies. Smits *et al.* [81] conducted a double-blind randomized controlled trial to evaluate the effect of vegan-donor FMT on TMAO

production and vascular inflammation in metabolic syndrome patients. Despite changes in gut microbiota composition, there were no significant functional improvements observed, indicating the complexity of microbiota interactions in metabolic syndrome. FMT has shown potential in modulating gut microbiota to improve cardiometabolic health. Leshem *et al.* [82] reviewed the role of FMT in cardiometabolic syndrome, highlighting its ability to transmit cardiometabolic phenotypes and suggesting its use as a preventive and therapeutic measure.

Similarly, Hanssen *et al.* [83] discussed the impact of FMT on insulin sensitivity and its potential to alter the course of type 1 diabetes, emphasizing the therapeutic promise of microbiota-targeted interventions. In a different investigation, Zhou *et al.* [84] analyzed the cardioprotective impacts of FMT on mice suffering from doxorubicin-induced cardiac toxicity. The results showed that FMT could affect the gut microbiota and the blood metabolites, leading to the lower cardiac injury by Nrf2-mediated mitochondrial regulation. Finally, many clinical trials are conducted to check FMT's effectiveness in cardiovascular diseases. Battipaglia *et al.* [85] reported that FMT was effective in decolonizing multidrug-resistant bacteria in patients undergoing hematopoietic stem cell transplantation, suggesting its potential in managing infections that can exacerbate cardiovascular conditions. Zhang *et al.* further evidenced that FMT was able to augment glucose tolerance and vascular function in the models of obesity-associated vascular dysfunction which is suggestive of its wider application in metabolic and cardiovascular health [86].

6.5. Cancer

FMT has been under scrutiny of late as a state-of-the-art venture in the cure and management of cancer. The gut microbiota has a significant role in the modulation of the patient's response to cancer therapy, thus, leading to the discovery of new ways for the existing treatments such as immunotherapy, chemotherapy, and radiotherapy to become more effective. Recent research has offered promising material on the use of FMT in cancer, signaling its power and complications. One of the most promising areas of FMT application is in the enhancement of the efficiency of immunotherapy. Research has demonstrated that the composition of the gut microbiota has a significant role in determining how patients respond to immune checkpoint inhibitors. Baruch *et al.* [87] conducted a phase one clinical experiment which shown the capability of FMT to stimulate an anti-PD-1 therapeutic response in patients diagnosed with metastatic melanoma. The trial observed a positive clinical response in a limited number of patients, which was associated with heightened activation of CD8+ T cells and a beneficial alteration in the tumor microenvironment. In like manner, Davar *et al.* [88] said that FMT in combination with anti-PD-1 therapy was able to break through the resistance of immunotherapy in patients with melanoma. This research revealed that FMT was responsible for significant modifications in gut microbiota composition, boosting CD8+ T cell activation, and lowering the number of immunosuppressive myeloid cells, which in turn, led to better clinical outcomes in some of the patients.

Colorectal cancer (CRC) is yet another area where FMT has shown potential benefits. According to research by Kaźmierczak-Siedlecka *et al.* [89], one of the relevant causative factors of dysbiosis of gut microbiota is inflammation and tumorigenic pathways through which microbe composition imoacts the carcinogenic process. FMT can replenish the missing healthy gut microbiota that can then regulate the pathways and consequently increase the efficacy of CRC treatments . Additionally, a study by Chen *et al.* [90] in a mouse model of rectal cancer demonstrated that FMT could effectively alter gut microbiota and reduce tumor growth. This preclinical evidence supports the potential of FMT as an adjunct therapy in CRC management. Along with other benefits, the gut microbiota is responsible for patients' responses to chemotherapy and radiotherapy. Wu *et al.* [91] investigated the influence of gut microbiota on the therapeutic responses to these treatments and suggested that FMT could be utilized to optimize treatment efficacy and minimize toxicity. The review has underlined the necessity for further exploration to gain a complete understanding of the mechanisms involved as well as to formulate safe and effective FMT protocols for cancer patients.

Currently, the clinical trials with different cancer research are assessing the efficiency of FMT, such as, the TACITO trial is exploring the potential of FMT to enhance the effectiveness of immune checkpoint inhibitors in renal cell carcinoma patients. The initial study results indicate that transferring

FMT from responders to immune checkpoint inhibitors can considerably increase the effectiveness of the treatment [92]. Nonetheless, the aforementioned encouraging outcomes, the road to commonizing FMT procedures, attaining safety, and deciphering long-term effects remains challenging. In the future, the research should emphasize the selection of suitable donors, the development of appropriate delivery methods, and revealing the interaction between gut microbiota and cancer therapies. Antushevich [93] highlighted that the effectiveness of FMT in different cancer therapies is known, but the long-term effects and safety profiles require more thorough studies to be carried out.

6.6. Obesity and Metabolic Syndrome

Because it changes gut microbiota, FMT has garnered interest as a treatment for obesity and metabolic syndrome. The gut microbiota is crucial for energy metabolism, insulin resistance, and inflammation, which cause obesity and metabolic syndrome. A breakthrough randomized controlled experiment by Machado da Ponte Neto *et al.* [94] examined FMT's effects on metabolic syndrome patients. This study compared 32 female upper gastrointestinal endoscopists who received FMT or saline. FMT patients had significant postprocedural alterations in their microbiota, although clinical indicators did not differ [94]. Zhang *et al.* [86] conducted assessing the impact of FMT on obesity and metabolic syndrome. The research included three randomized placebo-controlled studies and found mixed results regarding metabolic improvements. Although several studies have shown that individuals who received FMT experienced enhanced peripheral insulin sensitivity and reduced HbA1c levels, there were no noticeable variations in fasting plasma glucose or cholesterol indicators when compared to the control group.

In addition, Proença *et al.* [95] conducted a meta-analysis of randomized clinical trials on FMT and obesity/metabolic syndrome. The meta-analysis of six studies with 154 individuals found that FMT lowered HbA1c and raised high-density lipoprotein cholesterol short-term. After 12 weeks of the treatments, obesity measures did not alter, indicating the need for longer trials. In addition, Yu *et al.* [96] used FMT-TRIM double-blind placebo-controlled pilot trial examined the safety and efficacy of oral FMT capsules. The study included 24 obese adults with mild-to-moderate insulin resistance. FMT capsules induced gut microbiota engraftment but did not improve insulin sensitivity or other metabolic parameters compared to placebo. In contrast, Mocanu *et al.* [97] examined the effects of FMT and fiber supplementation in extreme obesity and metabolic syndrome patients. Their randomized experiment found that low-fermentable fiber supplementation with FMT significantly increased insulin sensitivity compared to high-fermentable fiber or FMT alone, suggesting that dietary adjustments may improve FMT outcomes.

Then Allegretti *et al.* [98] conducted a study on obese patients using oral FMT capsules. They observed sustained shifts in microbiomes and reduced stool levels of taurocholic acid among FMT recipients, although no significant changes in body mass index or glucagon-like peptide-1 levels were detected. This shows the complicated relationship between gut flora and metabolism. Finally, Craven *et al.* [99] examined allogenic FMT in obesity-related nonalcoholic fatty liver disease. FMT did not enhance insulin resistance or hepatic fat fraction, although it did lower small intestine permeability in some patients, suggesting gut barrier benefits. Then Guirro *et al.* [100] employed a multiomics approach to study the impact of FMT on diet-induced obesity in rats. They found that FMT reversed microbiota disruptions caused by a high-fat diet, restoring normal metabolic functions and alleviating obesity symptoms.

7. Conclusions and Future Perspectives

Due to its impact on the gut microbiota, FMT has shown promise as a treatment for several disorders. FMT initially proved beneficial in treating recurrent CDI, with success rates nearing 90%, sparking interest in its use in other gastrointestinal disorders like IBD.FMT can restore gut microbial diversity and produce remission in some IBD patients. However, results vary widely. Besides gastrointestinal illnesses, FMT is being studied for autoimmune and inflammatory conditions like rheumatoid arthritis and MS. FMT has been shown to regulate immune responses and relieve symptoms. The diversity in patient outcomes calls for personalised treatment and more research into these effects' causes. FMT also shows potential in treating infectious disorders, especially antibiotic-resistant bacteria. FMT can decolonize multidrug-resistant organisms in immunocompromised patients, improving health and lowering

infection rates. This shows that FMT may work for difficult infections. The promise of FMT in cardiovascular disorders is growing. Modifying gut microbiota using FMT may improve cardiovascular health by changing metabolites and lowering inflammation, according to preliminary research. In metabolic syndrome patients, FMT from vegan donors improved gut microbiota composition but did not improve metabolic parameters. FMT has also been studied for obesity and metabolic syndrome. FMT can enhance insulin sensitivity and gut microbiota in some individuals, but its effects on weight and other metabolic parameters are variable.

More research is needed to improve treatment methods and understand therapy effects. FMT is growing in cancer treatment, especially for immunotherapy. Studies suggest that gut microbiota composition affects immune checkpoint inhibitor responses. FMT has improved responses in metastatic melanoma patients, suggesting it could be used with traditional cancer treatments. Several research and development areas will shape the future of FMT in clinical practice. Large, well-designed randomized controlled studies are needed to prove its efficacy and safety across conditions. For reliable results, FMT processes must be standardized, including donor screening, preparation, and administration. Next-generation sequencing and metabolomics will help us comprehend FMT's processes and therapeutic benefits. Personalized medicine methods that tailor FMT therapies to microbiome profiles and illness features may improve therapeutic effects. Synthetic stool preparations and tailored microbial consortia may offer more regulated and scalable FMT options. Finally, FMT uses the gut microbiome to treat disease, revolutionizing disease management.

Although limitations exist, accumulating evidence supports its use across a variety of disorders. Research, innovation, and clinical validation are needed to properly integrate FMT into mainstream medical practice, improving patient outcomes and understanding the gut microbiome's role in health and illness.

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