

An Overview on Fecal Microbiota Transplantation and it's Therapeutic Applications on Dysbiosis: As Golden Juice

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Abstract

In current scenario, the investigational studies in pathology fields focus on those microbiotas which can produce sever disorders and also terminate the microbiota colonies that cause or which altered and arise with some disease-causing agents. Fecal microbiota transplantation (FMT) may alter the acceptors gut microbiota and maintain the composition in normal range, which helps to give beneficial pharmacological effects in gastrointestinal tract (GIT) related disease as well as, extra-GIT disorders. Alteration in microbiomes have given appropriate clinical perceptions in both gut and oral disorders. FMT re-established miscellaneous bacterial profile to GIT. The study was focused on the evaluation of efficacy of this method to treat various infections arises with *Clostridium difficile* bacteria. From the various studies, it may be hypothesized that the FMT reflects that it has potency to treat the *C. difficile* infections and achieved success rate in between 80 and 100%. Fecal microbiota can be transplant by both either antegrade or retrograde routes. The history of FMT belongs to the 4th century and comes in enforcement in 2013 after approving by the USFDA.

Key words: And its application, *Clostridium difficile* bacteria, fecal microbiota transplantation

INTRODUCTION

There are 100 trillion microorganisms of different species that may exist in the human intestine.^[1] Gastrointestinal tract (GIT) provides environment having large numbers of nutrients to almost 1000 plus of microorganism. The quantity and unpredictability of gut populaces are surprising. The GIT may be expectable to the host, usually 10¹⁴ microbiota, from which a large colony presents in colon and the densities of them can be approaches 10¹¹–10¹² cells/ml, with the genome of the microbiota resists in intestine and can be evaluate to check the presence of microbiota genes in human genome comparatively. From the study, it was found that intestinal microbiota having 100 times more genes than the human genome.^[2] In the gut microbiome the degree of parasitic infection relatively difference, because these include various bacteria, gut microbes with fungi, viruses, and eukaryotes. In every individual having altered composition of intestinal microbiota, due to various research, it can be concluded that the intestinal microbes having vigorous role in human health and

disorders through its participation in metabolic and immune functioning.

Dysbiosis refers to an imbalance in the microbiota in the human biological system. Irritable bowel syndrome, inflammatory bowel disease, chronic fatigue syndrome, obesity, cancer, metabolic disease, and irritable bowel syndrome are all possible causes (IBS).^[3] Now, the microflora has potency to cause many Sevier diseases as such as cardiac metabolic disorder, autoimmune disease, and a group of tumors. It is been mentioned the initial four cases of fecal transplantation for regulation of pseudo-membranous enterocolitis. Chronic diarrhea caused due to alteration in the intestinal microflora.^[4]

Recently, the concern of researchers is increasing in this field, the fecal transplantation uses in chronic intestinal disorders, including colitis, IBS, and *Clostridium difficile* infection

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(CDI). Fecal transplantation had been used form ancient China for treatment of the GI disorder.^[5]

HISTORY OF FECAL MICROBIOTA TRANSPLANTATION (FMT)

The human donor faces use as a therapeutic agent that having efficacy to treatment the disease that comes from China. It is an early tomb in Middle China, called “Fifty-two Treatment Formulae.”^[4,6] On some official paper in 770 BC, regarding the production of fecal material called “golden juice” got, it had shown detoxication. In the 4th century, Ge Hong in the “Handbook of emergency conditions” write about the ingestion of feces of human, chicken, horse, etc., for the variability of the disease.^[7] Song *et al.* reported that the supplement containing fecal preparations are used to cure dysentery and other GI related disorders. Detoxication having medical potency that is used in emergency happenings, elimination of injurious causes in infections, also cure of several GI complications such as diarrhea, vomiting, and also as anti-allergic decoction in chronic anaphylaxis-like emergencies,^[8] several kinds of “fecal medicine” are defined in Table 1. Herb Books and a couple of senior old physicians still favor these applications.^[9] Due to this in current scenario, fecal transplantation is an emerging field in medical sciences.

FMT

Since past 10 years, researcher has increasing interest in the FMT. Fecal microbiota transplantation (FMT), also called stool/fecal transplantation or fecal bacterio therapy, is the fermentation or engraftment of liquescent filtrate feces from a healthy donor into the gut of a receiver to treatment a selected disease.^[10] FMT can be administered through a GIT with the help of endoscopy, a nanosized enteric tubes, and capsules for incorporation. The supposed mechanism of this method is the replacement of microbiota community of gut which recreates the traditional gut function.^[11] The concept behind this is repopulating the gut with a healthy microbiome. Efficient FMT is suggested to treat inflammation of colon cause by CDI, and some other disorders such as chronic inflammation and swelling of intestine, autoimmune disorders, some hypersensitive actions, and obesity.^[12,13] In recurrent CDI (rCDI), various randomized clinical trials can be used to prove the efficacy and safety of FMT. In the second-line treatment, the developed rules can support the applications related to FMT. In the treatment of rCDI, the success rates were approached up to 92%.^[14]

FMT have achieved more success to treat different kinds of ailments so the use of FMT increasing day by day, which growing the demand of fecal material of standard quality.

Table 1: Eleven Chinese medicines fecal compositions

S. No.	Official name/ source animal	Classic medical monograph	Physical properties and taste	Clinical applications
1	Flying dragon/ Pigeon	Bencao Gangmu (Herb Dictionary)	Bitter, warm	Infection
2	Moonlight sand/Bat	Special Bencao (Herb Book)	Bitter, cold	External application, eye infection
3	Moon sand/Rabbit	Original classic	Bitter, cold	External infection
4	Chicken White/ Chicken	Ancient Bencao (Ancient Herb Book)	Bitter, salty, cold	Detoxify, diuretic
5	Silk worm sand/Silk worm	Bencao Gangmu (Herb Dictionary)	Sweet, bitter, warm	diarrhea, rheumatism
6	Golden Juice/ Human Male	Handbook of Emergency Conditions	Slight-bitter, cold	Detoxify, chronic fever
7	Bipolar Pin/Rat	Handbook of Distinguished Clinician	Bitter, salty	Abdominal cramp, high temperature
8	Perfume of Dragon/ Whale	Ancient Bencao (Herb Book) extension	Sweet, sour, warm	Analgesia, diuretic, bronchial spasm
9	Human Yellow/ Human (Male or female)	Special Bencao (Herb Book)	Bitter, salty, cold	Detoxify, chronic infection
10	White clove/ Sparrow	YunnamBencas (Herb Book)	Bitter, warm	G.I. associated disease
11	Penta crease/Small bat	Original Bencao (Herb Book)	Sweat, bitter, warm	External application

DONOR SELECTION

In the present time, the potential donors undertaking severe screening with history collection and some tests such as serological test, fecal test for parasitic infection, bacterial pathogen testing, and virology. These all can reduce the danger of infection or transmission of different kinds of diseases [Figure 1].^[15] There are some differences between organizations, regarding acceptance of the present protocols for the screening of donors [Tables 2 and 3].^[16,17] Donor microbiota containing fecal material may be achieved by two sources: From the donors directed by the patient (identified by the recipients, usually) and universal donors through stool banks.^[18]

Exclusion criteria for potential stool donors

The following criteria were excluded from the study:

- Age: 18 to under 65 years
- Body mass index should be more than 30 kg/m²
- Metabolic disorder
- Modest to chronic undernutrition
- Detail information about antibiotics taken in the past 180 days
- Looseness of the bowels within the past 3–6 month
- Presence of *C. difficile colitis* in past
- Detail account about Immune disorders or medicine used in the treatment of immunosuppressive disease
- History of drug used, current risk factors such as HIV, viral hepatitis, any GIT disorder and major surgeries

Table 2: Required tests performed in laboratories for probable donors to perform FMT

Related Evaluation	Blood sample	Stool or fecal
Bacteria	Treponema	Enteric pathogen culture: <i>Salmonella</i> , <i>Shigella</i> , <i>Campylobacter H. pylori</i> (EIA) VRE
Viruses	Hepatitis A virus IgM Hepatitis surface antigen Anti-hepatitis C virus HIV 1 and 2	Norovirus EIA or PCR Rotavirus EIA
Parasites	Entamoeba histolytica Strongyloides stercoralis	Ovum and parasite Microsporidia Giardia fecal antigen/EIA <i>Cryptosporidium</i> EIA AFB for <i>Isospora</i> and <i>Cyclospora</i>
Others	total blood count Liver function test ESR and CRP	<i>C. difficile</i> test Toxin by Polymerase chain reaction

Where: AFB (acid-fast bacilli), CRP (C-reactive protein), EIA (enzyme immunoassay), ESR (erythrocyte sedimentation rate), IgM (immunoglobulin M), PCR (Polymerase chain reaction), and VRE (vancomycin-resistant Enterococcus), HIV (human immunodeficiency virus).

- Have donor visit in any tropical region in the past 3 month
- Presence of autoimmune or atopic illness
- Presence of severe pain disorder (fibromyalgia and chronic fatigue syndrome)
- Neurological syndrome.

Sometime relatives or any known person of patient-directed donors are not preferred more frequently, because the knowledge of diet and other features has an important role in this process.^[15] On the other hand, the recipient should be careful about the agents which have to transfer, that can be called as universal donors.^[16]

There are some problems which associated with the utilization of patient-directed donor stool-based treatment. It required a huge time to search a donor, screening, and testing of donors, which results delayed treatment, high cost, and scheduling problems.^[17] In addition, the donors feeling can also be pressurized by patient-directed donors at the end. The use of universal donors in FMT has an important role due the most utilized method in our life. Young age healthy volunteers having traditional body mass index can donate the microbiota after compiling the detailed history and physical check-up. Screening tests for serum and pathogens are also necessary for better results.^[18,19] Universal donor method shows various advantages in FMT. The use of fecal material of healthy donor in patient can increase the therapeutic efficacy. The therapeutic efficacy of an infusion and ingestion theoretically increases if the patient uses fecal material of healthy donors. The patients received greater microbial diversity with endoscopic improvement.^[20] There is need of some deep studies which may be helpful to verify the worth of multi-donor FMT.

A study performed a non-inferiority randomized controlled trials (RCT) of FMT, in which they compared the fresh stool with frozen and thawed processed stool to check out the viability of freeze microbes.^[18,21] The clinical resolution rate was obtained 82.9% and 84.9% in the volunteers, which reveals that the frozen fecal material have strong efficacy as same as fresh stool. Utilization of frozen stool from universal donors helps to decrease the cost of recipient, because it required huge time to choose the methods of FMT.^[22]

In current scenario, the various stool banks and open biome have been come in forth, due to the economical and conventional use of fecal material, which may be donated by the donors throughout the world.^[23] There are various strict rules to be followed in the open biome for the implementation of healthy volunteers such as screening, standardization, and development of reliable products.^[24] It is also important to store it in suitable freezing condition and deliver it as soon as possible to 99% of the whole us.

The advantages of stool bank is as follows:

- Power to trace the registered donors and further research on them
- Through FMT a huge data may be obtain from the various sites

Table 3: Examination of mode of implementation for FMT

Approach	For	Dimness
Nasoenteric tube	<ol style="list-style-type: none"> 1. No need of anesthesia 2. Small price 	<ol style="list-style-type: none"> 1. Uneasiness during administration 2. Radiological authorization may be required 3. Risk of nausea and aspiration
Upper endoscopy	<ol style="list-style-type: none"> 1. Reduces the risk of complications arise with colonoscopy in different patients 	<ol style="list-style-type: none"> 1. Weaknesses as same as in the case of nasoenteric tube approach 2. Methodology related risks 3. Drowsiness
Capsule	<ol style="list-style-type: none"> 1. Noninvasive 2. More esthetic appeal 3. Economic and less time consuming 4. Ease for administration 	<ol style="list-style-type: none"> 1. Huge burden of the capsule 2. Risk like nausea and aspiration 3. Price
Colonoscopy	<ol style="list-style-type: none"> 1. Evidence of efficacy for rCDI 2. Suitable for different kinds of diagnosis 	<ol style="list-style-type: none"> 1. Procedure-related risk 2. Need for sedation 3. Technical experts may be required. 4. large amount of money required
Sigmoidoscopy	<ol style="list-style-type: none"> 1. Favored by the acceptor 	<ol style="list-style-type: none"> 1. Procedure-related risk 2. Inability to target at right-place in colon
Retention enema	<ol style="list-style-type: none"> 1. Less expensive 2. Tolerable 3. Tranquilizers may be avoided 4. Repetitive so can be use easily 	<ol style="list-style-type: none"> 1. Tough to retain in some cases 2. Implantation related issues 3. Low efficacy

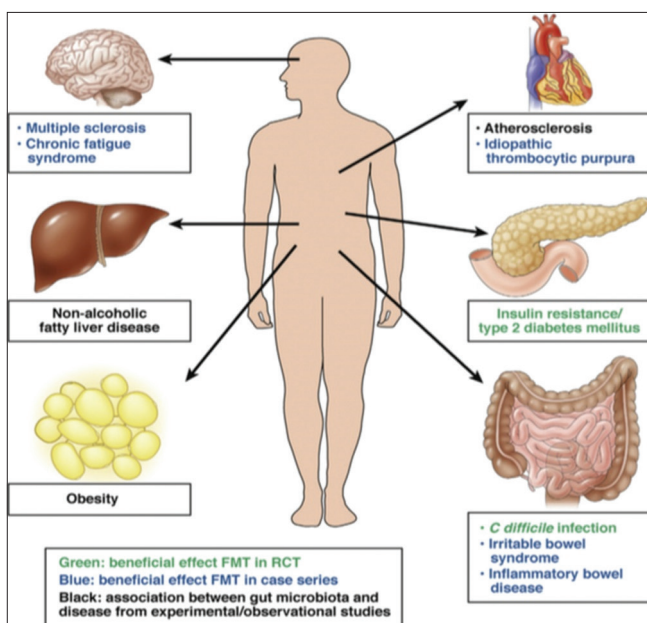


Figure 1: Disorders caused by the alterations in the intestinal microbiota which may be treated by Fecal microbiota transplantation (FMT). The green, blue, and black color specifies ailments for which FMT have more efficacy in randomized controlled trials, in case series studies and disorders that have been associated with disruption of the intestinal microbiota simultaneously

- It predicts Higher safety and efficacy
- The US-FDA having power to give approval to stool bank as like Open Biome, which provides tool for FMT for the curing of rCDI.^[25]

Open Biome bank follows standard and detailed questionnaires for the donor and rescreen donor after 2 months after the submission and before the discharge of stool and sample is store for further study.

Processing of fecal material

After the screening, contributor can donate the new stool within the altered months. This stool is collected in a suitable sack and pass into the microbial science research facilities. After that, the 50–300 g stool dissolve in 50–100 ml of normal saline.^[26] This solution was either blended or mixed by hand to form a slurry. The obtained slurry was filter by passing it from the metal strainer foe 4 h. The slurry transferred into the pipe with colonoscopy/ endoscopy by applying five layers of sterile dressings.^[27]

Hypermellose containers are normally used for the storing the waste microbiota. These containers are corrosively safe. The temperature required for storage of these microbiota capsules is about -80°C (112°F) for half year (6 months) before use [Figure 2].^[28]

Mode of action of FMT

Follow-up plan for fecal microbiota transplant [Figure 3]

Patients having a fruitful FMT ordinarily have a goal of indications inside 2–3 days. Proposals ought to be offered to family members to perception for hints of chronic adverse events (AEs), including however not restricted to elevated temperature,

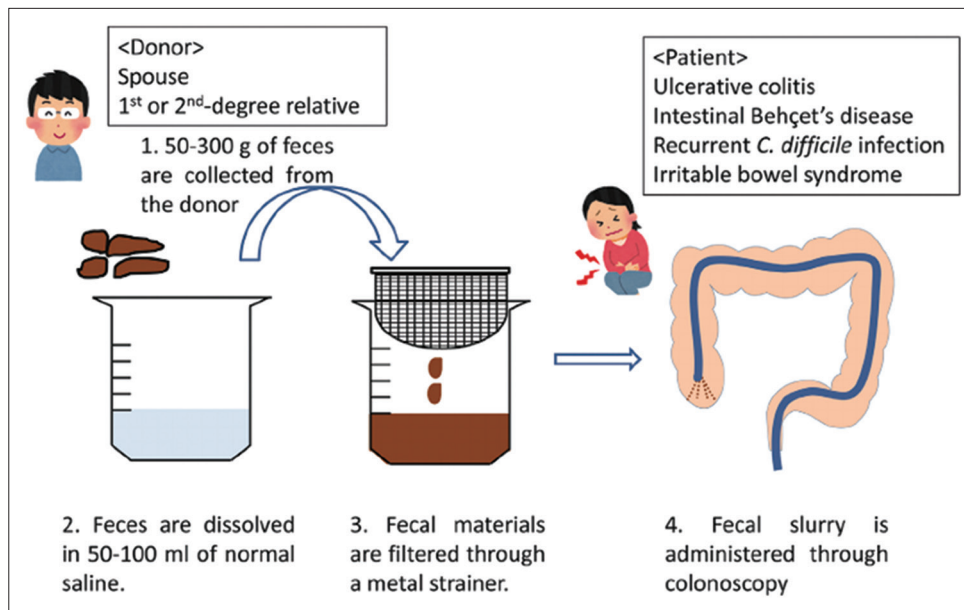


Figure 2: Preparation of fecal material for fecal microbiota transplantation

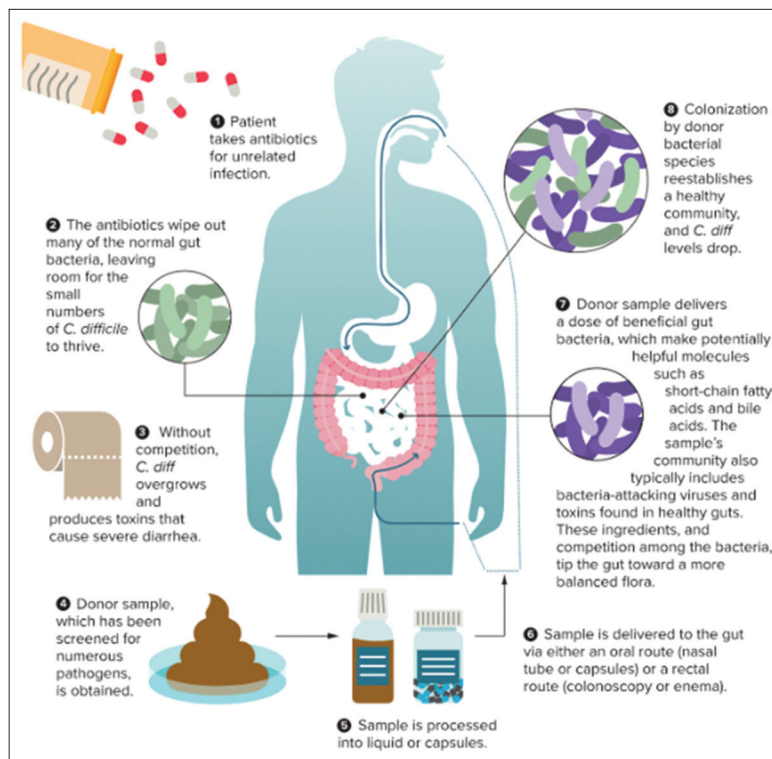


Figure 3: How a fecal microbiota transplant can treat recurring *Clostridium difficile* infections

extreme stomach agony, and spewing.^[29] A subsequent call is proposed inside multi week after the fact the interaction to affirm goal (absence of fluid or diarrheas) and to screen for AEs. In spite of the fact that endorsements shift on definite timetables, FMT is ordinarily pondered viable if indications of CDI do not repeat inside 2–90 days post-strategy.^[30] In the event that pointers return before long the early FMT. This method can be revised. The screening of reused patient and donor required just before repetitive FMT is patient-and site-explicit and ought not

really to settle by the treating supplier/group.^[31] In spite of the fact that there is no proof to help these proposals, the creators suggest the accompanying:

Even though there is no proof to help these proposals, the creators suggest the accompanying: by doctors or medical attendants around various numbers weeks after performing FMT for archiving any AEs and reaction to FMT.^[32] Follow-up plans by a pediatric gastroenterologist inside 2–90 days of

FMT to get clinically fix and any AEs. In asymptomatic patients testing for *C. difficile* does not prefer the following FMT.

An extra subsequent visit in a year after FMT might be measured to survey for possible long-haul AEs. These supplementary effects might be incorporate; however, they were not restricted to, variation in weight, advancement of metabolic illness, and demolishing course of IBD or other basic infection.^[33] Observation of late AEs and long-haul impacts of FMT is significant and another motivation behind the thinking that why the creators suggest execution of FMT in set up focuses, where long-haul checking frameworks and security libraries are set up. Long-haul multicenter follow-up examinations, which are as of now being developed, will assist with clarifying these possible difficulties.^[34,35] Relatives of patient should be directed to contact the provider post-FMT with any potential AEs.

CURRENT APPLICATIONS

Inflammatory bowel disease

FMT for IBD was first revealed in 1989. He performed transplantation of a solid benefactor stool by maintenance purification.^[36] Adverse effect vanished for a very long time after FMT, and dynamic aggravation was not distinguished at follow-up biopsy testing of the colon.

The writing contains a report of some cases and also case series, in which mostly relates to the ulcerative colitis patients. There have been not any randomized, controlled openings of FMT as a treatment for IBD.^[37] In some detailed survey discovered nine articles, which describes 26 patients, in which 18 have ulcerative colitis, six suffered from the Crohn's sickness, and two patients have vague.^[38] They all have received FMT for the boarding of IBD. Results were described for 17 of the 26 patients. Following FMT, 13 of 17 patients (76%) had the option to suspend all IBD meds inside 6 weeks, and at 4 months, all had manifestation decrease or resolution.

IBS

A study distributed the first RCT exploring the impact of FMT in IBS patients. Patients received a benefactor FMT mixture with new or frozen defecation (50–80 g). FMT was conveyed in the cecum by colonoscopy.^[39] They observed significant decline in IBS seriousness score at 90 days post-FMT in 36 patients out of 55, that is, 65% after FMT, contrasted and 43% from 12 patients treated with an autologous FMT (control bunch), $P = 0.049$. In any case, at a year post-FMT, the distinction between bunches was less articulated. Frozen FMT suspensions were not substandard compared to new suspensions.^[40]

HEPATIC ENCEPHALOPATHY

Hyperammonemia can potentiate the neuronal breakdowns and HE in modified gut microbiota. Commensal taxa (Lachnospiraceae, Ruminococcaceae, and Clostridiales XIV) can be used in the treatment of neuronal brokenness and HE.^[41] At present time, the treatment utilized for HE, mainly intensive on the gut microbiota and comprises lactulose or potentially the non-absorbable anti-infection rifaximin. In a study of RCT, take 10 volunteers had a liver disease like cirrhosis.^[42] On the other hand, the repetitive HE was selected and treated with solitary FMT with standard of care, and they all have been got exclusively standard-of-care treatment.

GRAFT-VERSUS-HOST DISEASE

Colonization with multidrug-safe creatures (MDRO) has huge chance to cause the contaminations in weak patients. It is a dangerous medical care which expanding regularly. The various researchers hypothesized that the colonization associated with MDRO can be protected by the FMT.^[43] This outcome was first seen in the defecation of patients who were treated with FMT for rCDI, in which the quantity and quality and variety of antimicrobial barrier diminished.

In some comparative studies, it was found that the extinction of Gram-positive vancomycin-resistant enterococci by FMT have off an impression of being more fruitful when contrasted and Gram-negative MRDOs.^[44] The obtained results can be elaborate by the transfer and production of bacteriocins either in between process or after the FMT and it found more powerful in clearing Gram-positive microorganisms. It's unclear whether carefully selected donors are expected to eliminate MDROs, and more research is needed.

METABOLIC SYNDROME

Metabolic disorder is frequently portrayed as a collection of indications including insulin opposition, dyslipidemia, hypertension, and expanded stomach bigness. Dysbiosis of the gut microbiota in metabolic disorder can arise the pro-inflammatory state and a weakened mucosal functioning, regularly referred to as defective gut condition.^[45] Two different RCTs showed that FMT of lean donor stool expanded glucose margin in heavy Caucasian peoples with some metabolic disorders.^[46] The researcher concluded that there is no profitable impact on clinical boundaries, but the use of microbiota in metabolic disorder might be a likely objective for treatment of these disorders.

AUTISM SPECTRUM DISORDERS

In an open-name concentrate on exploring the impact of FMT on ASD and GI side effects, matured youngsters

(7–16 years old) were treated with a serious FMT routine. Microbiota was inserted either by oral or rectal route.^[47] The observer found significant decay in both GI and neuropsychiatric related side effects, and it can be tolerated by the patients for a long time after receiving the treatment.^[48,49] Microbiota examination revealed that pieces of contributor microbiota were implanted into the beneficiaries.^[50] These results help to find out the further examination related with the treatments which maintain gut microbiota in patients with ASD.

CONCLUSION

Despite being said withinside the literature as a long way back as the 4th century, FMT research remains in its infancy, specifically as regards to its mechanism of effect. A considerable attempt has for the reason that been spent in identifying the different factors which make contributions to FMT success. In a vast sense, excessive variety of the intestine microbiota, specifically withinside the donor, seems to pleasant expect a affected person's reaction to FMT. More specifically, the efficacy of FMT probable depends at the cappotential of the donor to offer the vital taxable to restoring metabolic deficits in recipients that are contributing in the direction of disease. Further, characterization of super donors will probable bring about the improvement of extra delicate FMT formulations to assist standardize remedy and decrease variability in affected person reaction. In parallel, endured optimization of FMT protocols, inclusive of a shift in the direction of capsule-primarily based totally approaches, will assist fight the sturdiness problems related to FMT and create an extra affected person-pleasant opportunity to modern-day disease control schemes.

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