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REVIEW ARTICLE

Evaluating Gut Microbiota Modification as a Next-Generation Therapy for Obesity and Diabetes

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Abstract: The human body is a complex ecosystem that thrives on symbiosis. It is estimated that around 10^14 commensal microorganisms inhabit the human body, with the gut microbiota being one of the most diverse and complex populations of bacteria. This community is thought to comprise over a thousand different species that play a crucial role in the development of critical human diseases such as cancer, obesity, diabetes, mental depression, hypertension, and others. The gut microbiota has been identified as one of the most recent contributors to these metabolic disorders. With the emergence of inexpensive and high-performance sequence technology, our understanding of the function of the intestinal microbiome in host metabolism regulation and the development of (cardio) metabolic diseases has increased significantly. The symbiotic relationship between the gut microbiota and the host is essential for properly developing the human metabolic system. However, if this balance is disrupted by various factors such as infection, diet, exercise, sleep patterns, or exposure to antibiotics, it can lead to the development of various diseases in the body, including obesity and diabetes type 1 and 2. While many approaches and medications have been developed globally to treat these diseases, none have proven to be entirely effective, and many show side effects. Therefore, scientists believe that treating the gut microbiota using tried-and-true methods is the best option for combating obesity and diabetes. In this study, we aim to identify several feasible ways and prospects for gut microbiota therapy that can shape a new format for the treatment of obesity and diabetes.

Keywords: Gut-microbiota, obesity, diabetes, intestine, treatment, microbiology, bacteriology.

1. INTRODUCTION

The microbiota ecosystem comprises various types of bacteria that interact symbiotically with the human body. The composition of intestinal bacteria is influenced by physiological factors such as age and dietary habits, and it contains at least 10^11 to 10^12 prokaryotes per gram of feces. The number of microbes in the gut lumen is ten times more than the number of eukaryotic cells in the entire organism. Furthermore, the microbial content of the human genome, known as the intestinal microbiome, is 100 times higher [1]. Recent research has focused on the role of gut bacteria in human metabolism, health, and immunity. Dysbiosis, a microbiome alteration, has been linked to numerous diseases, including obesity and diabetes, both directly and indirectly [2].

Obesity is a condition caused by several factors, and it is characterized by excessive fat accumulation in the body. In the past decade, numerous studies have pointed to the role of gut microbiota in the pathogenesis of obesity and associated metabolic diseases. The gut microbiome plays a significant role in controlling fat storage [3]. Substances produced by gut bacteria may enter the bloodstream, leading to obesity-related issues by increasing tissue inflammation and insulin resistance. Obese individuals have lower metabolic energy consumption than healthy individuals because of a decreased gut bacteria variety [4]. Diabetes is characterized by insulin deficiency resulting from reduced insulin sensitivity and the loss of the islet structure and function of the pancreas. The microbiota, which is referred to as the body's second genome, has been linked to diabetes in recent studies. Imbalances in the microbiota have been suggested to affect energy

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metabolism and the inflammatory immune response, leading to diabetes [5].

Currently, no effective treatment for obesity and type 2 diabetes exists. Changing the gut microbiota is considered the primary approach for dealing with these two diseases, with the aim of shaping a new format for treatment. In this review paper, we provide insights into evidence associated with reducing obesity and diabetes development in humans. We also discuss possible approaches for treating the gut microbiome to shape a new format for treating obesity and diabetes.

2. THE GUT MICROBIOTA

2.1. Nature and Composition of Gut Microbiota

It is now known that fetuses are not entirely sterile in the uterus as previously believed, and a small amount of placental bacterial translocation can result in a basic microbiome before birth [6]. Upon delivery, bacteria from the mother and the surrounding environment quickly colonize the infant's gut. The composition of this microbiota is influenced by several factors such as mode of birth, antibiotic use, breastfeeding, or formula feeding, and hygiene of the surroundings [7]. In adulthood, the gut microbiota remains relatively stable with minor fluctuations around a core of steady colonizers. Changes in gut physiology and nutrition may lead to alterations in the microbiota composition at an older age [8]. The human GI tract is estimated to contain about 1014 microorganisms, which is ten times more than the entire human body. The gut microbiota comprises 500-1000 bacterial species per individual (Fig. **1**) [9]. Over 70 divisions have been identified in the biosphere (Table **1**), including 13 archeal ones. The adult human gut is dominated by the firmicutes (gram-positive), the bacteroidetes (gram-negative), and the actinobacteria (gram-positive), which make up over 90% of all bacteria, while the archaea domain is dominated by the Euryarchaeota [4].

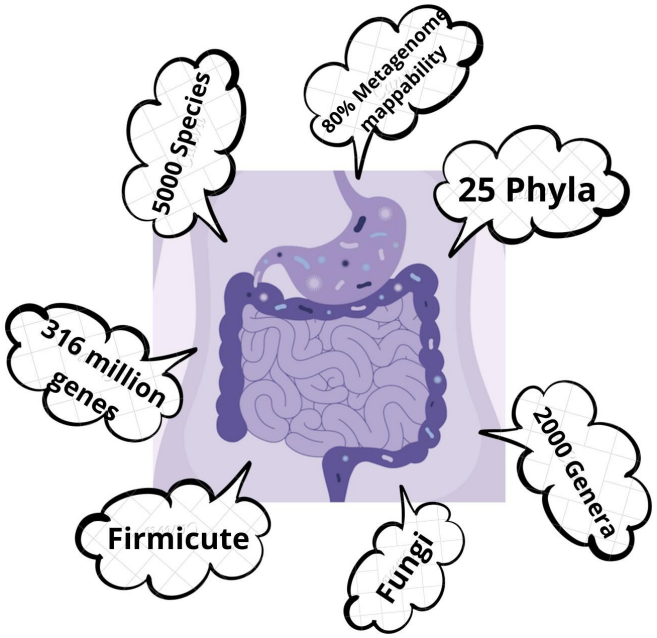

Fig. (1). Composition of gut microbiota in human body.

2.2. Role of Gut Microbiota in the Human Body

Microbes can enter the body through various physiological factors such as dietary habits, age, etc. A gram of sample can contain at least 10^11 to 10^12 procaryotes with a very high concentration [10]. In recent years, there has been a surge in research on human gut microorganisms, which are of significant importance in the host's metabolism, health, and immunity [11]. Researchers have utilized this intestinal microbiota to modulate the intestine for various diseases. The primary factor in changing the composition of the human gut microbiota is dietary behavior. Short-term changes in only dietary profile can alter intestinal flora. For instance, people who consume food high in animal fat had increased levels of bacteroidetes within 24 hours, and this trend continued over ten days [12].

2.3. Evidence of the Relationship between Gut Microbiota and Obesity

The earliest proof of the function of the gut microbiota in host adiposity was studies conducted using non-germin (GF) animals, *i.e*., animals without bacteria and reared in sterilized isolators. In 1983, Wostmann and colleagues (who had their microbiota) noticed that the GF rats needed 30% more calories to maintain their weight than conventional rats with a microbiota [13]. In recent years, there have been numerous published and discovered articles that have made bacteria a significant component in the development of metabolic diseases. Mice with a mutation in the leptin gene and genetically fat have been documented to have distinct microbiota compared to mice with a non-leptin gene mutation with a significant increase in Firmicutes and a corresponding decrease in the two major phyla in the gut microbiota, firmicutes, and bacteroidetes. A similar trend has been observed in humans [14]. The majority of research in this paper has focused on the Firmicutes-Bacteroidetes microbiome and its association with obesity, with a decrease in inflammatory status and an increased ability to harvest dietary energy across borders in obese individuals [15]. However, recent studies have shown that the decline in Bacteroidetes, Verrucomicrobia, and Faecalibacterium prausnitzii species may reflect an increased fraction of the phyla Actinobacteria and Firmicutes (Table **2**) [16].

3. EVIDENCE OF THE RELATIONSHIP BETWEEN GUT MICROBIOTA AND DIABETES

Studies on T2D microbiota suggest that changes in the microbiota may contribute to the development of T2D. The alterations in the abundance of specific bacteria, such as Bacteroides Prevotella group, Eubacterium rectale, Roseburia darts, R. inulinivorans, Clostridiales spp., and Lactobacillus species, have been observed in T2D patients [17, 18]. Furthermore, the frequency of Proteobacteria, which includes bacteria that produce surface components such as LPS and flagella leading to low-grade inflammation, has also been found to increase in T2D patients. Opportunistic infections such as Bacteroides caccae, C. hathewayi, C. ramosum, C. symbiosum, and Escherichia coli have also been reported in T2D patients [19]. Interestingly, antibiotic treatment in BBDP mice has been found to lower the likelihood of T1D development [20]. The 'metabolic infection' concept suggests

Table 1. Prokaryotes and eukaryotes diversity in human gut microbes.

Prokaryotes		Eukaryotes	
Phyla	**Family**	**Phyla**	**Family**
Actinobact eria	Bogoriellaceae, Brevibacteriace ae, Dermacoccaceae, Dermatophilaceae, Dietziaceae, Geodermatophilace ae, Nocardioidaceae, Promicromon osporaceae, Propioni-bacteriace ae, Streptomycetaceae	Fungi	Candida albicans, Candida famata, Candida glabrata, Candida guilliermondii, Candidkefyr, Candida krusei, Candida lambica, Candida lusitaniae,Candida norvo-gensis,Candida parapsilosis, Candida pararugosa
Bacteroidet es	Flavobacteriaceae, Porphyromonadaceae, Prevotellace-ae, Rikenellaceae,Sphingobacteriac eae	Helminths	Ancylostoma duedonale, Necator americanus, Strongyloi-des stercorali
Firmicutes	Carnobacteriaceae, Catabacteriaceae, Christensenellace-ae, Clostridiaceae,Clostridiales, Enterococca-ceae,Erysipelotrich aceae Eubacteriaceae, Lachnospiraceae	Protozoa	Endolimax nana, Entamoeba coli, Entamoeba dispar
Proteobact eria	Desulfovibrionaceae, Enterobacteriaceae, Francisellace-ae, Halomonadaceae,Helicobacter aceae, Legionellace-ae, Methylobacteriaceae, Moraxellaceae, Neisseria-ceae,Oxalobacteracea e, Pasteurellaceae, Pseudomona-daceae, Rhizobiaceae,Rhodobacteracea e, Sali-nisphaeraceae, Shewanellaceae, Sphingomonadaceae,Succinivib rionaceae	-	-

Table 2. Gut microbial population and obesity.

Subject of Study	Comparison Subject	Methods	Community	Finding	References
-	25 overweight *vs* 7 obese vs 24 normal weight	FISH	*Bifidobacteria Lactobacilli Clostridia Staphylococcus aureus*	Lower number of "Bifidobacte-ria". Higher number of S. aureus predict Obese popula-tion.	[71]
-	15 Obese vs. 13 normal weight	qPCR	*Bacteroidetes Bifidobacterium Lactobacillus acidophilus E. rectale F. prausntzi*	No major changes in "Bacteroides and Bifidobacterium" Significant increase of Firmicutes species in obese subjects.	[72]
Human children	3,26,52 weeks age of children (138 subjects)	Culture	*Bacteroides fragilis Bifidobac-terium Lactobacillus Entero-bacteriace a Staphylococcus Clostridium*	High intestinal Bacteroides fragilis and low Staphylococcus concen-trations in infants between the age of 3 weeks and 1 year are associ-ated with ahigher risk of obesity later in life.	[73]
-	91 normal, 62 over-weight, 22 obese	qPCR	*Bacteroidetes Firmicutes*	Bacteroidetes level reduced in obese group but no changes in Firmicutes level.	[75]
-	Obese *vs* Lean	qPCR	*Bacteroides Bifidobacterium Clostridium Staphylococcus Lactobacillus*	The concentration of Firmicutes is increased and Bacteroidetes con-centration decreased in obese children.	[74]
-	12 obese *vs* 2 normal	16S rRNA sequencing	*Bacteroidetes Firmicutes*	Significantly reduction of Bacteroidetes	[76]

(Table 2) Contd…

Subject of Study	Comparison Subject	Methods	Community	Finding	References
Human adults	3 normal weight *vs.* 3 obese *vs.* 3 post-gastric bypass	16S Pyrosequencin g qPCR	Firmicutes Bacteroidetes Proteobacteria Actinobacteria Fusobacteria Verrucomicrobia	Slightly higher number of Bacteroidetes in obese subjects. Significantly higher level of Methanobacteriale s in obese subjects	[77]
-	20 normal weight *vs.* 20 obese *vs.* 9 anorexic	qPCR	Lactobacillus M. smithii Bacteroidetes Firmicutes	Significantly reduction of Bacteroidetes level in obese individuals in compared to healthy individuals. Firmicutes levels are similar in those three categories. Lactobacillus is higher and M. smithii increase in anorexic subjects.	[78]
-	35 overnight *vs.* 33 obese	-	Firmicutes Bacteroidetes Bifidobacteria	Increased level of Bacteroidetes in obese subjects and decreased level of Firmicutes. Decrease in Bifidobacteria and Methanobrevibact er spp. in obese subjects.	[79]
-	5 lean *vs.* 5 normal *vs.* 5 obese *vs.* 5 surgically treated	qPCR	Bacteroidetes Firmicutes	Bacteroides occupy aSignificant place among obese people	[80]
Human adolescent s	1 obese *vs.* 1 lean	qPCR	Bacteroidetes Firmicutes Proteobacteria	Lower level of Bacteroidete and higher level of Firmicutes spp in obese people	[81]
Pregnant women	18 overweight *vs.* 36 normal weight pregnant women	FCM-FISH qPCR	Bacteroides Bifidobacteria Staphylococcus aureus	High concentration of Bacteroides group and S.aureus in the obese pregnant women individuals.	[82]
	16 obese *vs.* 34 normal weight pregnant women	qPCR	Bifidobacterium Lactobacilli Bacteroidetes Escherichia coli Staphilococcus	Bifidobacterium and Bacteroides numbers are significantly reduced in obese pregnant women. Increase the number of Staphilococcus and E. coli in overweight women.	[83]
Human twins	31 monozygoti c twin *vs.* 23 dizygotic twin pairs	16S pyrosequencin g V2 and V6 variable region	Bacteroidetes Firmicutes Proteobacteria Actinobacteria	Level of Bacteroidetes in Obese significantly decrease and increase level of Actinobacteria.	[84]
	20 twin pairs of obese, normal weight	qPCR DGGE	Eubacterium rectale group Clostridium leptum group Lactobacillus Bacteroides spp	The abundance and variety of the bacterial group do not differ among the normal weight and obese. In particular Bacteroidetes spp and Bifidobacterio modulated with diet.	[85]

that the endotoxin produced by bacteria could play a crucial part in the development of insulin resistance in T2D. The functional capability of the T2D intestinal profile has been connected to enhanced sugar membrane transfer, oxidative stress responses, amino acid branched chain transport, sulphate reduced, and decreased butyrate production. Moreover, >3% of the gut microbial genes varied from the T2D patients, indicating the involvement of microbiota in T2D [21]. The alterations in the microbiome makeup are a feature of T2D, and targeting the microbiota could be a logical goal for insulin resistance treatment. Nonetheless, the process behind these alterations to a T2D human microbiome signature remains unknown, and further research is required to understand the exact mechanisms underlying the relationship between the microbiota and T2D.

4. GUT MICROBIOTA ALTERATION TREATMENT ON OBESITY AND DIABETES

There is a lot of scope for shaping Obesity and Diabetes by altering the intestinal microbiome (Fig. **2**). One approach is through the use of probiotics or prebiotics to selectively

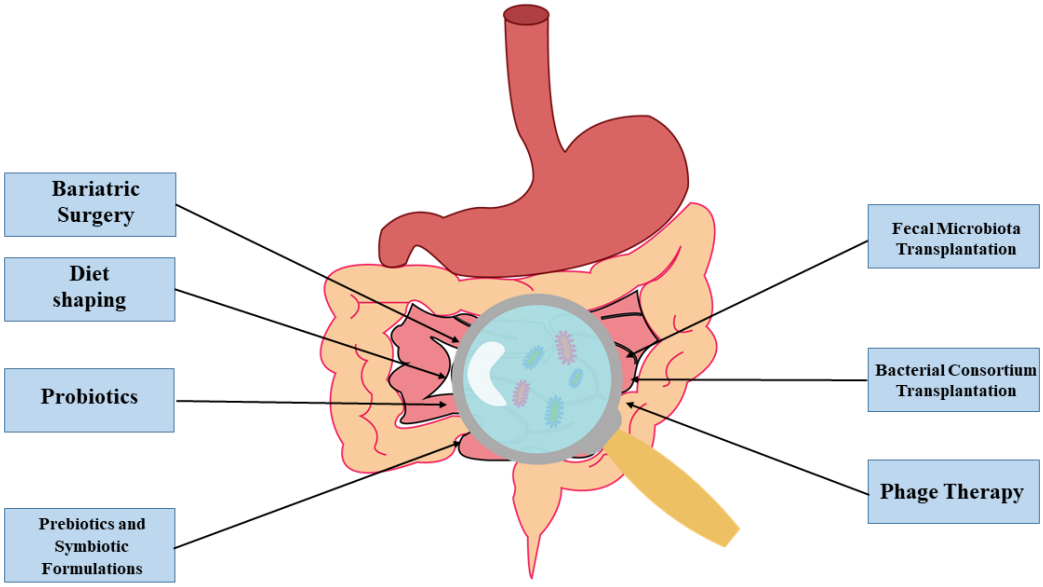

Fig. (2). Different treatments for treating Obesity and Diabetes by changing Gut microbiota. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

modify the composition and activity of the gut microbiota. Another approach is fecal microbiota transplantation (FMT), which involves transferring fecal material from a healthy donor into the gut of a recipient with the goal of restoring a more diverse and balanced gut microbiota. Additionally, more research is needed to fully understand the mechanisms involved and to develop safe and effective interventions for these conditions.

4.1. Diet Shaping the Gut Microbiota

Before discussing the role of gut microbiota in the development of obesity and related metabolic diseases, it is essential to review some published work that defines food as the primary factor contributing to gut microbial composition [22, 23]. Indeed, dietary variables have significant effects on the intestinal flora of animals and humans, leading to the rapid development of appealing mechanisms to prevent or relieve illnesses caused by an altered microbial composition through health benefit adjustments to gut microbiota composition through nutritional changes. Dietary patterns are associated with various gut bacterial combinations, sometimes called enterotypes [24]. One crucial component of diet and exercise is recognized as an essential outcome as the importance of microbial diversity decreases even under overweight and obese circumstances [25]. The type of fat in the diet is also a highly inflammatory and gut-microbiotopic determinant. Diets rich in saturated fat (lard) are linked with enhanced inflammation and metabolic illness of white adipose tissue (WAT), while diets that include polyunsaturated fatty acids (fish oil) may promote a lean and metabolically healthy phenotype [26]. In mice, the levels of Taxa in the Lactobacillus and Akkermansia genera have grown when fed fish oil (explained later), while Bilophila-related taxa have increased in mice fed lard [27]. Bilophila Wadsworth has been found to aggravate colitis in genetically sensitive rats [28]. In conjunction with exercise, Clarke et al. demonstrated that the importance of findings illustrates the relevance of dietary variety and protein consumption in forming the gut microbiome. The protein used in the studies was positively connected to high microbial diversity (22 distinct phyla), and significantly higher Akkermansia was associated with a low body mass index for athletes [29]. The results show how vital dietary macronutrients are and how the gut microbiota composition is favorably shaped. The new multi-taxon Insertion Sequencing (INSeq) technique, which analyzes the genetic variables that allow members of the gut microbial population to grow inside this niche, has produced fascinating findings [30]. At the compositional level, the abundance alterations in two of the most prevalent phyla, namely Firmicutes and Bacteroidetes (including >90% of known phylogenetic groups), are related to obesity [14]. Although some studies show that, concerning average weight reduction and human weight loss, the share of Bacteroidetes in the obese phenotype rose, these findings are not uniform, and the ratio of Bacteroidetes to Firmicutes is, a composite biomarker [31].

Diet is an easy-to-modify component and an appealing treatment strategy for intestinal microbiota modulation. Several functional foods are now being offered. However, it is impossible to provide a diet that fits all subjects. Technologies for metabolic profiling give genuine support for functional food enhancement. The significant interpersonal variability suggests that a more customized strategy, combined with tailored functional meals, is the way forward. Microbiota drugs should be used to cure good dysbiosis. Metabolic profiling can help the creation of functional meals. This can begin with the food ingredient and finding biomarkers to detect consumed food [32]. Randomized, dietary treatments for the form of human gut microbiota were documented clinically. Results show that fiber and vegetable energy-restricted diets ensure microbial intestinal alterations and provide health benefits [32]. Therefore, it is suggested to consume a wide variety of dietary resources and adjust their metabolism according to environmental and nutritional changes [33].

4.2. Bariatric Surgery

Bariatric surgery is considered the last option for treating morbid obesity and related problems, such as type 2 diabetes, and is preferred over other weight-reduction therapies [34]. Significant changes in the GI tract, such as reduced carbon intake, decreased gastric drainage, and alterations in the generation of gastric acid and bile acid, are induced by bariatric procedures, which have significant impacts on the gut microbiome's composition. Tremaroli et al. found that there are similar reactions in the gut microbiome composition for two different bariatric surgical procedures: vertical sleeve gastrectomy (VSG) without intestinal diversion and Roux-en-Y gastric bypass (RYGB) with intestinal diversion [35]. However, a recent meta-analysis has shown that human studies on gut microbial changes following bariatric surgery vary widely [36]. The long-term positive effects of bariatric surgery on weight loss, diabetes remission, and cardiovascular risk are hypothesized to be a result of altered microbiome composition and microbial metabolic output, such as the synthesis of metabolites [37].

4.3. Probiotics

The International Scientific Association for Probiotics has redefined probiotics as "living micro-organisms which, when supplied in adequate numbers, provide the host with a health benefit," and they are known to have many different effects [38]. Probiotics can be used as therapeutic agents to prevent dysbiosis in patients who are exposed to predisposing circumstances, such as long-term antibiotic therapy, severe physical or mental stress, chronic disorders, and more [39]. Immunological advantages of probiotics include increased synthesis of immunoglobulin, modification of cytokine profiles, and induction of hypo-success to dietary antigens, such as the activation of local macrophages. Nonimmunological advantages include digestion, competition with possible nutrients and bowel adhesion pathogens, pH changes, and synthesizing bacteriocins [40]. The probiotics currently utilized include lactic acid bacteria, bifidobacteria, enterococci, yeast boulardii Saccharomyces, milk propionibacteria, Bacillus spp., and the Escherichia coli gram-negative Nissle strain discovered in 1917 [41]. Lactobacilli, for example, are recognized as an inflammatory modulator and an immune system booster and are suggested for use in inflammatory illnesses, diarrhea prevention, enteric diseases, and pediatric patients to prevent or cure newborn colic.

Probiotics of the next generation are Akkermansia muciniphila and members of the Clostridium IV, XIVa, and XVIII clusters. To be considered next-generation probiotics, they must contain strains that belong to large intestinal microbiota groups, be safe and potentially useful. Akkermansia muciniphila is a strict anaerobe of the phylum Verrucomicrobia that degrades mucins and is associated with a better state of metabolism. In patients with fat metabolism, diabetes, and other metabolic diseases, Akkermansia muciniphila is substantially reduced in obesity [42-44]. Another new probiotic applicant is CECT 7771 bacteroid uniforms, which was shown to improve lipid profile, leptin, and glucose, and enhance TNF-α production following oral treatment in fat dietary mice [45].

4.4. Prebiotics and Symbiotic Formulations

The theory underlying the use of prebiotics was first introduced in 1995. According to the World Gastroenterology Organization Global Guidelines, prebiotics are non-digestible compounds that the human host can utilize and selectively stimulate the growth and metabolic activity of a limited number of beneficial indigenous bacteria, such as bifidobacteria and lactic acid bacteria [25, 46]. Prebiotics are believed to provide specific nutrients for the growth of indigenous probiotic bacteria. Prebiotics are mainly nutritional substances added to food as enrichment factors, mostly non-starch polysaccharides, and oligosaccharides. However, inulin supplementation has been shown to regulate metabolic and inflammatory endotoxemia in women with type 2 diabetes [27]. These compounds are often used in synbiotic preparations that include probiotic microorganisms to promote rapid intestinal development. Fructooligosaccharides (FOS) may pass through the digestive lumen undigested and unabsorbed, reaching the ascending colon intact, where they are preferentially metabolized by the resident probiotic component of the microbiota. Their digestion results in a significant decrease in pH, creating unfavorable conditions for the growth of harmful bacteria such as Clostridium. Without medical guidance, consumers may lack the technical expertise to choose the appropriate FOS. Finally, postbiotics are bioactive microbial metabolites from thermally killed microorganisms that have a beneficial effect on human health through their interactions with the immune system and anti-inflammatory properties [47].

4.5. Fecal Microbiota Transplantation

The use of excrement for medical purposes is not a new discovery. Suspension of feces was used to treat foodborne illnesses in China as early as the 4th century, and during the Second World War, German troops utilized fresh camel dung, following Bedouin ideas, to treat bacterial dysentery in Africa [48]. In 1958, an American doctor named Ben Eiseman treated four patients with pseudomembranous fecal microbiota (FMT) colitis. The first effective treatment of FMT infection with Clostridium difficile (CDI) occurred in 1983. While the techniques mentioned above are generally equivalent to conventional therapies, FMT mimics organ transplantation by replacing the microbiota organ. FMT has become an antibiotic-resistant treatment for Clostridium difficile diarrhea [29, 30]. Microbiological studies have shown that the recipient's microbiota composition quickly changes after FMT and is comparable to that of a healthy donor, with these changes lasting for at least 24 weeks. The success of FMT in managing CDIs has led to its application in many pathological areas of FMT centers, including CD, UC, and IBS, and has spurred research into its potential [49]. Given the remarkable effectiveness of fecal transplantation in treating C. difficile diarrhea, we may assume that long-term treatment-related dysbiosis, and dysbiosis that is not responsive to single probiotic treatments, demand an unmatched microbial ecology. However, rigorous FMT research, such as precise experiments with control groups and cohort studies, is necessary to prove its long-term efficacy and safety [50].

4.6. Bacterial Consortium Transplantation

BCT may be used to modulate gut ecology. Recent research has shown that BCT and FMT can both achieve complete recovery from microbial community dysbiosis induced by antibiotics in mice, suggesting similar effects of BCT and FMT [51]. An artificial bacterial mix, RePOOPulate, consisting of 33 pure intestinal bacteria strains obtained from a healthy donor, has been used for BCT. These bacteria include Intestinal acidaminococcus, Ovatoid bacterioids, Adolescent bifidobacterium (2 strains), longum bifidobacterium (two strains), Product of Blueberry, the cocleat of the clostridium, Dorea longicatena Collinsella Aerofaciens (two strains), Chechnya coli, Desmolans eubacterium, ventriosum eubacterium, eubacterium limosum, eubacterium rectale (four strains), Faecalibacterium Prausnitzii, Faecalibacterium prausnitzii Lactobacillus casei, Lactobacillus casei, Lactobaicillus casei, Lachnospira pectinoschiza Distasonic parabacteroids, Raoulle sp., sp. Roseburia faecalis, Roseburia intestinalis, and Roseburia intestinalis. Additionally, recurrent CDI has been treated with Ruminococcus torques (2 strains), Ruminococcus obeum (2 strains), and Mitis of Streptococcus [52].

These bacterial groups are well-developed, reproducible, and may be standardized or modified according to various dysbiosis levels and kinds, including the proportions of each bacteria in BCT. Patient safety may be improved, as bacteria combinations can be controlled for the pathogenic presence of the germ. Thus, BCT may be an effective and safer alternative to FMT [52].

4.7. Phage Therapy

Phages are viruses that infect bacteria and makeup 90% of human viromes, significantly influencing microbial populations. Phages can be used as an alternative to antibiotics for antibacterial purposes or for mitigating microbial communities. They have significant medicinal potential, and genetically modified phages can be used for biosynthesis, nutritional degradation, and as carriers of genes in the gut microbiota [53]. Given the abundance of phages in our microbial ecology, the risks associated with their use for treatment appear to be minimal. Bacteriophages have been recognized as anti-infectious agents for several decades, with established treatment regimens in Eastern Europe and Russia since the early 20th century [54]. However, these studies did not meet the criteria accepted by the global medical research community, and new research is required in combination with changes to the existing EU regulatory framework, which currently limits phage treatment [55]. Phage suspensions can be produced for local or systemic treatment, and phages particularly multiply exponentially after injection.

Although the use of phages as antibacterial drugs has been a long-standing practice in Eastern Europe, important data and research on phages as antibacterial drugs must be approved by the FDA and the EMA [56].

4.8. Predatory Bacteria

Predation is just one of the many ways bacteria interact with each other. Bacteria that engage in hunting, killing, and eating macromolecules for nutrition are appropriately called predators [57]. Typically, predatory bacteria are smaller than their targets, which enables them to penetrate the prey, kill them, and multiply from within. Interestingly, predatory bacteria have developed unique predatory behaviors, including frequent epibiotic predation, a method that does not involve intracellular replication [58]. Given the potential future use of predatory bacteria, it is essential to consider the millions of years since other bacterial players have developed predation mechanisms. Experimental studies have demonstrated that the introduction of predators into an ecosystem can stimulate the development of numerous protective features in prey species. However, many of these processes can also contribute to virulence, thereby increasing the pathogenicity and virulence of environmental colonizing microorganisms, which could be a selection factor [59]. The use of predatory bacteria could be a viable option for cases where Gram-negative intestinal mucosae are over-colonized, such as in patients with inflammatory bowel disease or celiac disease.

5. PHARMACEUTICAL AGENTS THAT IMPACT MICROBIOTA FOR TREATING T2D

While intentional targeting of the microbiota for T2D is in its early research stages, numerous medications taken for a long time have been shown to influence the gut microbiota in ways that can contribute to their effectiveness. Metformin (dimethylbiguanide), a widely used therapy for T2D, particularly T2D linked with obesity, was discovered in 1922 based on research of the herb Galega officinalis (Goat's rue) to reduce blood glucose. The mechanism of metformin action is not fully understood, but it may involve inhibiting mitochondrial activity through respiratory chain complex I or dehydrogenase glycerophosphate; activating AMP-activated protein kinase (AMPK); or improving glucagon-like peptide-1 (GLP-1) and cyclic adenosine monophosphate (cAMP). Furthermore, the gut microbiota plays a critical role in mediating the glycemic control capacity of metformin. In contrast to oral metformin, the lack of intravenous metformin controls hyperglycemia and indicates the gut as an essential location of metformin activity [60]. Evidence that the overall impact of metformin-induced alterations on the microbiota is beneficial is that microbiota transfer from metformin-treated mice has been shown to improve metabolism, demonstrating that changes in the microbiota play a part in its positive effects [61].

The alpha-glucosidase inhibitor acarbose reduces postprandial blood glucose levels by preventing the breakdown of carbohydrates into simpler sugars and delaying their absorption into the bloodstream from the intestines. However, the effects of microbiota composition have also recently been assessed for acarbose. Galactomannan, pectin, capsaicin, and red pitaya betatianine all altered the percentage of Firmicutes to Bacteroidetes. Following body weight management, the overall abundance of Allobaculum, Turicibacter, Anaerostipes, Blautia, Lactobacillus, Butyricimonas, and Desulfovibrio was decreased after intervention, as opposed to alterations in gut microbial composition [62, 63]. In reaction to herbal extracts, changes in intestinal microbiota include increasing microbial diversity, reducing the ratio between Firmicutes and Bacteroidetes, and increasing the abundance of anti-inflammatory bacteria such as Bifidobacterium, Lactobacillus, Akkermansia, and Faecalibacterium,

while reducing pathogenic bacteria such as E. coli and Enterococcus [64].

6. PHARMACEUTICAL AGENTS THAT IMPACT MICROBIOTA FOR TREATING OBESITY

With the progress of gene sequencing technologies, recent research has focused more on the effect of metformin on intestinal microbiota. Using the keywords "Metformin AND Gut Microbiota," we searched PubMed and selected all the papers that clearly showed metformin's influence on the makeup of gut microbiota in obesity [65]. Metformin is a member of the thiazolidinedione class that has hypoglycemic effects believed to be the result of increase activity of the proliferator-activated nuclear receptor peroxisome (PPAR-μ). This stimulation leads to a decrease in insulin resistance and gluconeogenesis, which in turn reduces obesity [66]. For instance, intestinal microbiota in proton pump inhibitor (PPI) users has shown an increased abundance of upper gastrointestinal streptococcal bacteria with enhanced production of fatty acids. On the other hand, metformin users had a higher propensity for Escherichia coli infections. Studies have linked eight distinct pharmacological categories with increased mechanisms of antibiotic resistance: oral antiandrogen contraceptives, beta-sympathomimetic inhalers, laxatives, metformin, other oral antidiabetics, PPIs, anti-inflammatory non-steroidal medicines, and triptans [67].

7. LIMITATIONS AND RISKS OF MICROBIOME-MEDIATED THERAPIES

While this review focuses on the progress and potential benefits of existing microbiome metabolism research, it is important to acknowledge several scientific limitations and potential dangers. Over the past few years, various approaches have been taken to develop treatments for microbiota-related diseases [68]. However, personalized medications may not be effective for everyone due to factors such as an individual's genetics, diet, drugs, and endogenous microbiota. These factors can significantly impact the effectiveness of medical treatments, making them ineffective or even harmful. For example, faecal microbiota transplants (FMTs) have shown promise in treating Clostridium difficile infection, but anecdotal accounts and a single case study have reported increased weight gain from overweight donors due to FMT, reflecting pre-clinical results. Additionally, a transplant from a mentally inadequate donor has been theorized to have the same phenotype. Although bacterial treatments that have undergone extensive pre-clinical and clinical studies are unlikely to convey such harmful characteristics, it is clear that microbiome treatments like FMT will require significant regulation to decrease safety risks and ensure the overall health of the host system [69, 70].

CONCLUSION

A host of research has demonstrated remarkable relationships between the gut microbiota and intestinal microbial metabolites in developing Obesity and Diabetes by using next-generation sequenzation methods. However, a few research investigations have demonstrated intestinal bacteria's mechanistic or causative significance in human metabolic development. As earlier mentioned, factors such as ethnicity, genetics, diet, and medication use can also influence the composition and function of the gut microbiome, making it a complex system to study. Nevertheless, developing strategies to alter the gut microbiome for therapeutic purposes has shown promising results in animal studies and early clinical trials. Probiotics, prebiotics, and fecal microbiota transplantation are some of the approaches being investigated to modulate the gut microbiome in the context of obesity and diabetes. That's why focusing on the gut microbiome for treating these diseases is the radical point at this moment. Microbiome treatment will be one of the best approaches to treating uncontrollable diseases without any side effects in the future. Our depicted techniques for treating gut microbiome to treat the alarming diseases of obesity and Diabetes are more noble and reliable than any other techniques. As more research is conducted in this field, microbiome-based therapies may become an increasingly important component of disease management and prevention in the future.

AUTHORS' CONTRIBUTION

MIH, SRA, and MSA designed the study. MIH, SRA, MOF, SIM, SI, and MSA analyzed and interpreted the data. MIH, SRA, and MSA prepared the manuscript. IHC and MMA reviewed the manuscript. All authors approved the final version of the manuscript.

LIST OF ABBREVIATIONS

FMTs = Faecal Microbiota Transplants

WAT = White Adipose Tissue

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

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