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Gut microbiota as a key player in type 2 diabetes: Current perspectives

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a pressing global health issue defined by impaired glucose metabolism, insulin resistance, and β-cell dysfunction. Emerging research underscores the involvement of the gut microbiome in the development and progression of T2DM. A comprehensive online search was conducted across PUBMED, SCOPUS, EMBASE, Web of Science, and Google Scholar to identify all original research articles published in India and internationally over the past 5 years on the topic of gut dysbiosis and diabetes. A mini review was carried out based on their findings. Composed of trillions of microorganisms, the gut microbiota influences host metabolism, immunity, and inflammatory responses. Dysbiosis, or imbalance in microbial composition—particularly, an altered Firmicutes/Bacteroidetes ratio—has been linked to metabolic disorders, including T2DM. Studies show that individuals with T2DM exhibit decreased levels of beneficial, fibre-degrading bacteria and increased opportunistic pathogens and mucus-degrading microbes. Antidiabetic drugs such as metformin, acarbose, glucagon-like peptide (GLP)-1 receptor agonists, and dipeptidyl peptidase-4 inhibitors have been shown to modulate the gut microbiome, suggesting a bidirectional relationship between microbiota and therapeutic efficacy. Furthermore, pharmacomicrobiomics—a field examining microbiota-drug interactions—highlights how individual microbial profiles may predict drug response and side effects. Specific bacteria, such as *Enterococcus faecalis*, can even degrade GLP-1, reducing the efficacy of GLP-1-based treatments. Incorporating prebiotics and probiotics into treatment regimens has shown potential in restoring microbial balance, increasing short-chain fatty acid production, and enhancing glucose metabolism. These interventions may support gut barrier integrity, reduce inflammation, and improve insulin sensitivity. This review seeks to examine the intricate connection between gut microbiome and T2DM, insights into the disease mechanisms, and opens avenues for personalized and more effective therapeutic strategies. Targeting the microbiome may revolutionize diabetes management by enabling microbiota-informed treatment approaches to mitigate disease burden.

1. INTRODUCTION

Diabetes, along with its associated comorbidities, represents a major health risk due to its high rates of disability. The onset of diabetes is affected by various factors, including genetics, lifestyle, dietary habits, aging, use of medications, and physical inactivity. Research has highlighted the important contribution of the gut microbiome in the advancement and progression of type 2 diabetes mellitus (T2DM) [1]. As the economy and urbanization progress rapidly, people's sedentary lifestyles and eating habits have contributed to the growing prevalence of chronic metabolic conditions like obesity and diabetes.

The 2025 edition of the International Diabetes Federation (IDF) Atlas reports that 11.1% of adults between the ages of 20 and 79—roughly one in every nine—are living with diabetes. Strikingly, over 40% of them remain unaware of their condition [2]. As of 2024, an estimated 589 million adults are affected by diabetes worldwide. Looking ahead, the IDF projects that the number will rise by 46%, reaching approximately 853 million adults by 2045. By 2050, it's expected that one in eight adults globally will be affected by diabetes. India has approximately 89.8 million adults aged 20 to 79 years living with diabetes, which makes it the second-highest number of cases globally [3].

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The World Health Organization has forecasted that T2DM will rank as the seventh leading cause of death by 2030, highlighting the critical need for improved prevention and treatment approaches [4]. The primary characteristic of T2DM is impaired glucose metabolism, along with disturbances in protein, fat, water, and electrolyte balance. Insulin resistance and β-cell dysfunction are crucial factors in the development of T2DM.

The gut microbiota, often called "the second human genome," is essential in controlling metabolic processes, immune function, and inflammatory responses [5]. Growing evidence indicates that a disruption in the gut microbiome balance is strongly linked to the development and advancement of T2DM. The human gut hosts over 1,000 species of bacteria, with a microbial population 10 times larger than the number of human cells, primarily composed of Bacteroidetes and Firmicutes. These microorganisms typically maintain a symbiotic relationship with the body, but when disrupted, they can contribute to disease [1].

An increasing amount of research highlights the catalytic role of the gut microbiome in giving rise to a range of multifactorial illnesses, including T2DM. Nowadays, there is a significant focus on the gut microbiome and its influence on T2DM. Numerous metagenomic analyses have demonstrated that the structure of the gut microbiome, particularly the Bacteroidetes to Firmicutes ratio, contributes to the onset of T2DM by affecting intestinal permeability, modulating inflammation and immune responses, and altering energy metabolism [4].

Historically, research on T2DM has focused on the metabolism of the host and hormonal activity. However, growing evidence indicates that gut microbiota, consisting of commensals in the enteric tract, also has a notable influence on the development of T2DM. Gut microorganisms break down dietary substances into small molecules that exert hormone-like activity on human cells. The interaction between these microorganism-derived metabolites and host receptors presents a novel potential target for innovative therapies for patients with T2DM [6]. Emerging studies suggest that metabolites produced by gut microbes can influence host fat accumulation, insulin responsiveness, and hormonal balance, all of which contribute to the progression of T2DM. It is crucial to recognize that these metabolites are detected by specialized receptors in the human host, which could serve as promising new targets for therapy [7]. This review focuses on the modifications in gut bacterial profiles among patients diagnosed with T2DM. It also examines how nutritional and pharmaceutical interventions alter the structure and activity of the gut microbiota and, in turn, how gut flora may affect the effectiveness of drugs used in preventing and managing the condition. Gaining a better understanding of these gut microbiota changes could facilitate the development of precision medicine approaches with improved outcomes for diabetes treatment and prevention.

2. METHODS

An extensive review of literature was performed across major databases such as PUBMED, SCOPUS, EMBASE, Cochrane, Web of Science, and Google Scholar, to gather original research articles published over the last 5 years (2019–2024), both from India and globally, focusing on the relationship between gut dysbiosis and diabetes. The articles included both human and animal studies with diverse findings, encompassing positive, negative and null results regardless of statistical significance. The search utilized keywords such as microbiota, diabetes, gut, dysbiosis, and probiotics. Boolean operators (AND/OR) were applied to search combinations like: "gut microbiome AND diabetes," "gut dysbiosis AND Type 2 diabetes mellitus," and "Type 2 diabetes OR insulin resistance AND gut flora." Non peer reviewed articles, editorials, case reports, perspectives, viewpoints, and letters to the editor were excluded from the selection. Articles published before 2020, unless significant and non English articles were also excluded. The collected studies were subsequently reviewed and analysed. Preparation of this manuscript was guided by the Preferred Reporting Items for Systematic reviews and Meta-Analyses framework.

3. RESULTS AND DISCUSSION

3.1 Differences in flora in diabetic and non-diabetic individuals

The gut microbiome composition is shaped by various factors, such as nutrition, gender, age, lifestyle, environment, geography, and genomic makeup. The gut microbiota is primarily composed of four major phyla (Fig. 1): *Firmicutes* (Gram-positive, 60%–65%), *Bacteroidetes* (Gram-negative, 20%–25%), *Proteobacteria* (Gram-negative, 5%–10%), and *Actinobacteria* (Gram-positive, 3%) [8].

Individuals with T2DM show significant gut microbiome imbalances, including an increase in opportunistic pathogens. Healthy people tend to have higher levels of Bifidobacterium, while T2DM patients show elevated *Lactobacillus* [1,9]. In T2DM, there is a lower abundance of advantageous butyrate-producing and fiber-degrading bacteria, such as *Faecalibacterium prausnitzii, Roseburia, and Bacteroides vulgatus* [10]. In contrast, mucus-degrading and Gram-negative bacteria such as *Akkermansia muciniphila* and *Escherichia coli* are more abundant [11,12]. A higher Bacteroidetes to Firmicutes ratio correlates with elevated blood glucose. Overall, gut microbiota composition in T2DM is shaped by disease status, diet, medications, and environmental factors [13].

In the context of diabetes, alterations in microbiome composition are linked to reduced β-cell function, the development of reduced sensitivity to insulin, and a rise in intestinal permeability. This altered permeability contributes to a pro-inflammatory state and endotoxemia, further exacerbating the progression of the disease [9]. Consequently, directing interventions towards the gut microbiota may represent an emerging option for managing type 2 diabetes and its associated complications. Pharmacomicrobiomics, an emerging field in medicine, focuses on studying the drug–microbiome interplay [14]. Drug-induced changes in microbiota are influenced by the drugs' pharmacodynamics and pharmacokinetics, which determine how the drugs impact the microbiome and how, in turn, the microbiome may alter the effectiveness of a drug [14,15].

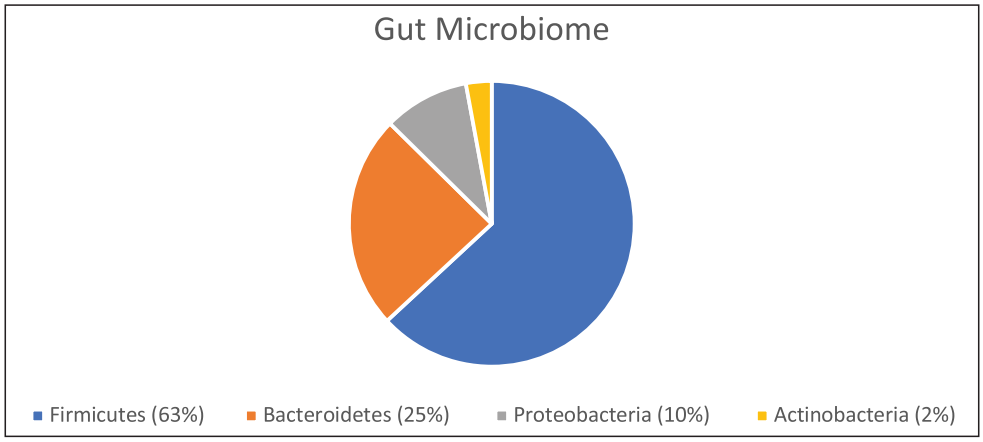

Figure 1. Composition of gut microbiome: Firmicutes – Lactobacillus, Streptococcus, Enterococcus, Ruminococcus; Bacteroidetes – Bacteroides, Prevotella, Porphyromonas; Proteobacteria – Escherichia, Salmonella, Shigella, Klebsiella, Helicobacter; Actinobacteria – Bifidobacterium, Corynebacterium, Mycobacterium, Nocardia.

3.2 Antidiabetic drug-induced changes in gut microbial communities

Relevant studies showing the impact of antidiabetic drugs on gut microbiome have been summarized in Table 1 [16–28].

3.2.1. Metformin

In T2DM patients, metformin uniquely alters the gut microbiota, unlike in healthy individuals, potentially enhancing blood sugar control and insulin sensitivity [29,30]. Treatment with Metformin resulted in the reduction of alpha diversity of the microbiome, a change not observed in healthy individuals [10]. On a species-specific scale, metformin decreased the levels of *Clostridium bartlettii* and *Barnesiella intestinihominis*, while enhancing levels of *Parabacteroides distasonis* and *Oscillibacter* [31]. The gut microbiome profile at baseline was found to predict the efficacy of therapy with Metformin, particularly variations in HbA1c values, as well as the side effects. A study from Japan reported that metformin treatment for four weeks significantly reduced the *Firmicutes* to *Bacteroidetes* ratio. Furthermore, a decrease in *Parabacteroides* was associated with abdominal pain, and reductions in both *Parabacteroides* and *Bifidobacterium* may serve as predictors of abdominal discomfort and acid reflux [16].

Accumulating evidence suggests that metformin improves glucose regulation through different mechanisms in diabetic patients. A research study conducted in Colombia discovered that metformin alleviated hyperglycemia and correlated positively with an increased presence of short-chain fatty acid (SCFA)-producing bacteria such as *Butyrivibrio*, *Bifidobacterium bifidum*, *Megasphaera*, and a specific group within *Prevotella* genus [8,17]. Ejtahed *et al.* [32] observed a reduction in weight in diabetic patients on metformin and subsequently analysed its influence on the gut microbiota composition in non-diabetic obese individuals. Their findings revealed that metformin treatment led to significant weight loss along with notable changes in the microbiome from baseline to post-treatment. Similar findings from other studies indicated an increase in *Proteobacteria* phylum, which includes bacteria such as *Escherichia*, *Pseudomonas*, *Shigella*, and *Yersinia* [18].

3.2.2. Acarbose

Mice that received a diet high in starch or fibres, treatment with acarbose caused alterations in the gut microbiota, resulting in the abundance of *Bacteroidaceae* and *Bifidobacteriaceae* families, and a reduction in *Verrucomicrobiaceae* (like *A. muciniphila*) and *Bacteroidales* S24-7. However, these changes were not irreversible. As a result, there was an elevation in beneficial SCFAs, particularly butyrate [19]. Seven randomized trials in humans involving metformin or acarbose treatment were conducted in obese, pre-diabetic, and diabetic patients. Treatment with metformin or acarbose in pre-diabetes and newly diagnosed diabetic patients was associated with a decrease in the *Bacteroides* genus, along with an increase in both *Bifidobacterium* and *Lactobacillus*. Furthermore, diabetic patients treated with metformin exhibited an increased abundance of several taxa within the *Enterobacteriales* order, as well as *A. muciniphila*. Among the seven studies that reported significant variations in beta-diversity, the taxa that showed increased abundance were associated with enhanced glucose and lipid metabolism [20].

3.2.3. Glucagon-like peptide-1 receptor agonist and dipeptidyl peptidase-4 inhibitors

Diabetic male rats treated with Liraglutide [long-acting glucagon like peptide (GLP)-1 receptor agonist (RA)] showed changes in the gut microbiota; an increase in *Bacteroides* and *Lachnospiraceae*, as well as probiotics like *Bifidobacterium* [10]. These changes could contribute to the therapeutic effects of liraglutide in managing diabetes. Moreover, treatment with liraglutide led to a notable increase in the gut bacterium *A. muciniphila* in both wild-type and diabetic mice [19].

In human studies, liraglutide treatment significantly improved gut microbiota diversity and richness, with notable increases in *Bacteroidetes*, *Proteobacteria*, and *Bacilli* [33]. This included a rise in *Firmicutes* and *Bacteroidetes*, along with a decline in *Ruminococcus* (Firmicutes) and *Actinomyces*

Table 1. Impact of antidiabetic drugs on the gut microbiome.

S. No	Drug class	Drug/dosage regimen	Clinical/preclinical context	Observed microbiome effects	References
1.	Biguanides	Metformin 500 mg/day for 2 weeks followed by 1,000 mg/day for 2 weeks	20 male and 11 female Japanese T2DM patients	↓ *C. bartlettii*, *B. intestinihominis*; ↑ *P. distasonis*, *Oscillibacter* ↓ Firmicutes/Bacteroidetes ratio; ↓ *Parabacteroides*, *Bifidobacterium* associated with abdominal pain/reflux	[16]
		500 mg twice daily	112 participants from Colombia	↑ SCFA-producing bacteria: *A. muciniphila*, *Butyrivibrio*, *B. bifidum*, *Megasphaera*, *Prevotella*	[17]
		500 mg twice daily for 2 months	46 obese, non-diabetic patients; post-weight loss	↑ Proteobacteria (*Escherichia*, *Pseudomonas*, *Shigella*, *Yersinia*)	[18]
2.	Alpha-glucosidase inhibitors	Acarbose (25 and 400 ppm; human-equivalent doses: 15 mg and 240 mg/day)	High-starch/fiber-fed mice	↑ *Bacteroidaceae*, *Bifidobacteriaceae*; ↓ *Verrucomicrobiaceae* (*A. muciniphila*), *Bacteroidales S24-7*; ↑ SCFAs (butyrate)	[19]
			Systematic review of Human studies in obese, prediabetic, and T2DM patients	↓ *Bacteroides*; ↑ *Bifidobacterium*, *Lactobacillus*; ↑ *A. muciniphila*; ↑ *Enterobacteriales*	[20]
		Acarbose 150 or 300 mg/day for 4 weeks	18 Japanese patients with T2DM	↑ *Bifidobacterium, Eubacterium, Megasphaera, and Lactobacillus;* ↓*Bacteroides, Prevotella, Clostridium.*	[23]
3.	GLP-1 RAs	Liraglutide	T2DM patients	↓ Alpha diversity; ↑ *Firmicutes*, *Bacteroidetes*; ↓ *Ruminococcus*, *Actinomyces*	[21]
		Liraglutide 0.2 and 0.4 mg/kg/day (subcutaneous)	Diabetic rats and mice	↑ SCFA producers: *Bacteroides*, *Lachnospiraceae*; ↑ *Bifidobacterium*, *A. muciniphila*	[10]
		Patients currently on (liraglutide or dulaglutide) treatments	52 T2DM patients	↑ *B. dorei, R. inulinivorans, Lachnoclostridium and Butyricicoccus;* ↓ *Prevotella copri, Ruminococcaceae sp., Bacteroidales sp., Eubacterium coprostanoligenes sp.,*	[24]
4.	DPP-4 inhibitors	Sitagliptin 100 mg/day	30 newly diagnosed T2DM patients	↑ *Bacteroidetes*; ↑ succinate production	[21]
		Gemigliptin 50 mg with Metformin 1,000 mg/day	70 Korean patients with T2DM	↑ *Bacteroides;* ↓ *Lactobacillus*, *Ruminococcus torques*, *Streptococcus*	[25]
		Vildagliptin 100 mg/day for 2 months with Metformin	29 T2DM patients	↑ *Bariatricus*, ↑ *Butyricimonas* genera, ↑ *Marinifilaceae* family	[26]
5.	SGLT2 inhibitors	Dapagliflozin 60 mg/kg	24 db/db T2DM mice	↑ *A. muciniphila*; ↓ Firmicutes/Bacteroidetes ratio	[22]
		Empagliflozin 25 mg/kg/day	40 streptozotocin-induced diabetic mice	↓ *Helicobacter* ↑ *Muribaculaceae*; ↑ *Muribaculum*; ↑ *Olsenella and Odoribacter*	[27]
		Empagliflozin 10 mg/day	60 adults with T2DM receiving metformin	↑*Bifidobacterium*; ↑ *Lactobacillus* ↓ *E. coli and Alpha haemolytic Streptococcus*	[28]

(Actinobacteria) [8]. Additionally, in T2DM patients treated with sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, there was a significant rise in *Bacteroidetes*, particularly enhancing the production of succinate [21]. However, a recent trial found that adding liraglutide or sitagliptin to metformin or sulfonylurea therapy failed to induce significant modifications in the gut microbiota alpha or beta diversity [33,34]. Furthermore, a 6-month treatment with a fixed combination of liraglutide and degludec (ultra-long acting basal insulin) had no impact on microbiome biodiversity or community structure in a cohort of very elderly T2DM patients, with a mean age of 82 years [35]. One possible explanation for this lack of change in the microbiome diversity could be that the combination of drugs, such as liraglutide and degludec, masked the effects on the gut microbiota. The interactions between these medications may have counteracted or obscured any potential changes in microbial composition, making it difficult to observe the individual impacts of each drug on the microbiome [10].

3.2.4. Sodium glucose cotransporter 2 Inhibitors

So far, there is limited research on the impact of sodium glucose cotransporter (SGLT) 2 inhibitors or SGLT1/2 dual inhibitors on gut microbial profile, with the findings being somewhat inconsistent. One study demonstrated dapagliflozin, an SGLT2 inhibitor, improved vascular dysfunction while causing subtle changes in the gut microbiome in db/db mice with T2DM [22]. Dapagliflozin was shown to increase good gut bacteria such as *A. muciniphila* and lower the *Firmicutes/Bacteroidetes* ratio, which could have implications for the gut's role in managing metabolic health. Nonetheless, it remains ambiguous whether these variations in the gut microbiome ecosystem directly lead to the improvement in the vascular

function, and this requires further investigation. Another study by Van Bommel *et al.* [36] involving patients with T2DM found that adding dapagliflozin to metformin therapy did not alter the composition of the gut microbiome. It is possible that the metformin's effects may have masked any potential impact of dapagliflozin on the microbiome [36]. In rats with high blood sugar, the SGLT2 inhibitor canagliflozin also impacts intestinal SGLT1, the main carrier for galactose and glucose. This increases the levels of active GLP-1 in the blood and lowers blood sugar spikes after meals [10]. In addition, canagliflozin boosted the production of SCFAs in the cecum and altered the gut bacteria composition. Sotagliflozin and licogliflozin, which inhibit both SGLT1 and SGLT2, demonstrate a greater preference for SGLT1 compared to canagliflozin. This may give them unique benefits in managing high blood sugar, as well as specific safety profiles for the heart and kidneys [10]. Therefore, even though we usually think of SGLT2 inhibitors as working mainly through the kidneys, we should also take a closer look at how they affect the gut microbiome. Furthermore, animal studies examining the effects of SGLT2 inhibitors in managing type 1 diabetes mellitus are ongoing, which may provide more insight into their broader impacts on metabolic and vascular health [8].

3.3. Effect of gut microbiome on antidiabetic drugs' efficacy and safety

It was observed that variations in gut microbiome compositions led to varying responses to GLP-1 RAs in humans [37]. This suggests that the gut microbiome could impact the effectiveness of GLP-1 RAs in managing conditions like T2DM, with certain microbial profiles potentially enhancing or diminishing the therapeutic effects of the drug. In a 12-week study of T2DM patients who were administered GLP-1 RAs (liraglutide or dulaglutide), participants were categorized into GLP-1 RA responders (n = 34) and those who did not respond (n = 18) [37]. Responders experienced reductions in HbA1c and BMI, while non-responders showed no changes in these measures. Beta diversity analysis highlighted notable distinctions in the gut microbiome composition across the groups, with specific bacterial variations, including *Bacteroides dorei* and *Roseburia inulinivorans*, being identified. These findings suggest that the gut flora signature may provide foresight about the effects of GLP-1 RA therapy. Additionally, a 2017 study demonstrated how alterations in gut microbial community could trigger GLP-1 resistance in murine models, further supporting the possible influence of the microbiome on treatment outcomes [38].

Gel-E, an *Enterococcus faecalis*-derived proteolytic enzyme, has been shown to suppress GLP-1 activity by directly cleaving the hormone [39]. This action may impair the beneficial effects of GLP-1, such as improving insulin secretion and glucose metabolism, potentially contributing to reduced efficacy of GLP-1-based therapies in certain individuals. This bacterial behaviour, where *E. faecalis* secretes *Gel-E* to directly cleave GLP-1, could help clarify the variability in efficacy across various classes of antidiabetic drugs. In individuals with a higher abundance of *E. faecalis* or similar bacteria, the cleavage of GLP-1 could diminish the effectiveness of GLP-1 RAs, leading to a reduced response to this class of drugs. This could contribute to differences in treatment outcomes among patients, highlighting the significance of the gut microbial ecosystem in influencing the success of antidiabetic therapies [40]. A conceptual diagram linking gut microbiota, drug effects, and T2DM has been shown in Figure 2.

3.3.1. Prebiotics and probiotics

Prebiotics, when fermented by gut microbiota, can stimulate the production of gut peptides such as GLP-1 and peptide YY, which play important roles in regulating glucose metabolism and appetite [10]. Antidiabetic medications, when combined with prebiotics and other non-digestible dietary components, may help alleviate the impact of chronic conditions like T2DM [41]. Medications like metformin and sulfonylureas may experience increased efficacy through the activity of metabolites derived from the intestinal microbiome. Functional foods like oligofructose and dietary fibre can assist in correcting an imbalanced gut microbiome by increasing microbial diversity. This shift in microbiome composition often resulted in increased beneficial bacteria, including *F. prausnitzii*, *Roseburia* species, and *Bifidobacterium* species [41].

A key outcome is the rise in luminal SCFAs, especially butyrate, which acts as a fuel source for the microbial ecosystem is essential in shaping gut receptor diversity. SCFAs act on G protein-coupled receptors and regulate intestinal motility, inflammation, and immune responses, though the contradictory effects of butyrate on glucose and lipid metabolism—particularly concerning its role in obesity—are still not fully understood [42]. Overall, these beneficial changes contributed to the improvement of intestinal dysbiosis, reduced inflammation, and enhanced gut barrier integrity, all of which helped to alleviate the morbidity associated with T2DM [43]. Administering oligosaccharides alongside pharmacotherapy represents a promising and current treatment modality to help manage T2DM [41].

Probiotics, which are live microorganisms, offer a range of benefits to the host, including strain-specific anti-inflammatory effects in healthy adults. In individuals with metabolic syndrome, a single infusion of *Anaerobutyricum soehngenii*, a duodenal bacterium, has been found to raise plasma levels of secondary bile acids and postprandial GLP-1, leading to enhanced glucose metabolism. This suggests that both prebiotic and probiotic interventions can have a beneficial impact on metabolic health by modulating gut microbiota and influencing metabolic pathways like those involving GLP-1 [44]. Additionally, no negative side effects were observed when *A. soehngenii* was given orally, suggesting it may be a safe probiotic intervention [45]. Additionally, the intake of *Lactobacillus reuteri* has been found to raise GLP-1 and insulin secretion among those with glucose intolerance, demonstrating its possible positive effects on glucose metabolism [46]. Supplementing with VSL#3, a commercial probiotic product that includes eight different strains (such as *Streptococcus thermophilus*, various Bifidobacterium species such as *B. breve, B. infantis, B. longum, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei,* and *Lactobacillus delbrueckii* subsp. *bulgaricus*), for 4 months led to a rise in

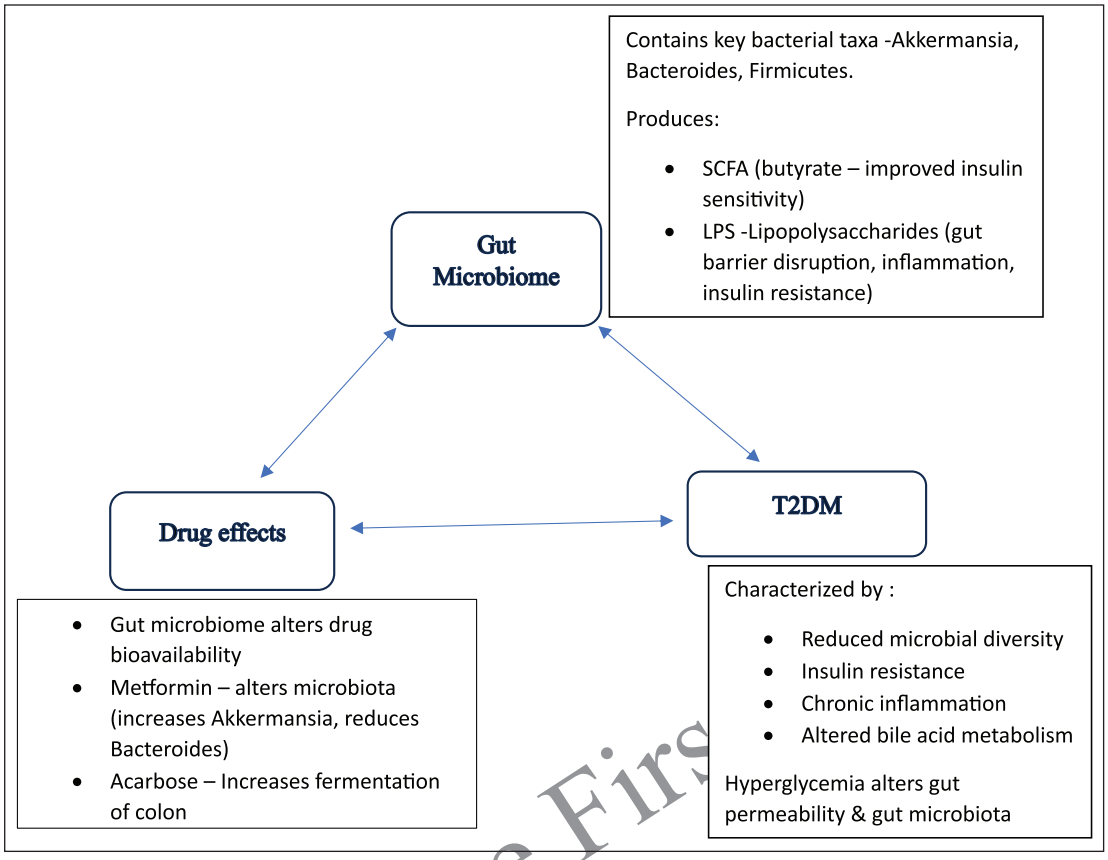

Figure 2. Conceptual diagram linking gut microbiota, drug effects and T2DM.

GLP-1 levels and a reduction in BMI among children having non-alcoholic fatty liver disease (NAFLD) [10]. This suggests that probiotics like VSL#3 may have therapeutic potential in improving metabolic health and addressing conditions like NAFLD.

3.3.2. Exercise

Physical activity is a powerful non-drug strategy for managing diabetes, offering a wide range of health benefits. Research has shown notable differences in the gut microbiota of athletes compared to those with inactive lifestyles. Exercise significantly alters the structure and activity of the gut microbiome, which can influence how overweight individuals with prediabetes respond to physical training [47]. In a study conducted by Torquati *et al.* [48] involving 14 participants, an 8-week exercise program revealed that varying levels of exercise intensity affected the presence and activity of certain gut microbial species among individuals with T2DM who were previously inactive. The intervention led to increases in *Bifidobacterium, Escherichia*, and bacteria that produce butyrate [48].

4. FUTURE DIRECTIONS

Future research is likely to be aimed at personalized, microbiome-based methods. Developments in the areas of metabolomics and metagenomics are likely to help design non-invasive diagnostic devices (using artificial intelligence) that utilize microbial metabolites as biomarkers for insulin resistance. Personalized nutrition based on an individual microbiome profile may offer individualized control of blood sugar levels, and advanced probiotics and genetically engineered microbial treatment have the potential for modulating glucose metabolism and inflammation [49]. Moreover, enhancing faecal microbiota transplantation (FMT) techniques and integrating the correlation between the host genetic profile and the microbiome can uncover new possible therapeutic avenues. FMT can be delivered through a few strategies, such as endoscopy, nasojejunal tube, or enemas. However, donor selection is vital to avoid any disease transmission to the recipient. Recent animal studies have suggested that the normal pattern of insulin secretion was restored after FMT from a normal diet-fed mice to one without gut microbiota [50]. A randomized controlled trial by Vrieze *et al.* [51] involving male patients with T2DM found that FMT over a 6-week period led to enhanced insulin sensitivity and a more diverse gut microbiome. Among the most significant microbial shifts was an increased presence of *Roseburia intestinalis* and *Eubacterium hallii*, both of which are recognized for their role in butyrate production [52]. In a separate study, Ding *et al.* [53] examined the effects of FMT in 17 individuals with T2DM using stool from 20 healthy donors, reporting notable improvements in HbA1c levels and other key metabolic parameters following treatment [54].

Most importantly, the gut microbiome has significant implications for modulating the efficacy of antidiabetic drugs,

such as metformin, highlighting the possibility of designing pharmaceuticals in association with microbiome modulators. The emerging trends emphasize the promise of microbiome-targeted interventions in revolutionizing the prediction, prevention, and control of T2D.

5. LIMITATIONS

Several limitations of this study should be recognized. First, gut microbiota composition varies across different regions of the digestive tract, and the use of diverse sequencing methods can lead to inconsistent findings. Additionally, there are considerable individual and population-level differences, making it difficult to draw broad conclusions. Our knowledge of how microbial functions contribute to T2DM remains incomplete. Furthermore, the scope of this mini-review is constrained by the limited number of studies included, and also, some of the studies yielded mixed results. To advance knowledge in this promising area, more comprehensive systematic reviews and meta-analyses are necessary, as the field holds significant potential for advancing medical research and improving patient outcomes.

6. CONCLUSION

The contribution of the intestinal microbiome in the initiation, progression, and treatment of T2DM is increasingly recognized as a critical area of scientific exploration. Gut dysbiosis, is strongly correlated with T2DM, influencing key factors such as insulin resistance, glucose metabolism and inflammation. As evidence grows, it becomes clear that the intestinal microbial profile can not only influence the onset of T2DM but also impact the efficacy of various antidiabetic therapies, including metformin, GLP-1 RAs, and SGLT2 inhibitors. The emerging field of pharmacomicrobiomics offers exciting potential for personalized treatment strategies that consider individual microbiota profiles to optimize drug responses and mitigate adverse effects. Moreover, prebiotics and probiotics, which modulate the gut microbiome, show promise in enhancing therapeutic outcomes and improving metabolic health in T2DM patients. By leveraging the potential of the gut microbiome, future treatment approaches may shift towards more integrated, microbiome-targeted strategies, offering better management and potential prevention of T2DM and its associated complications. Ultimately, comprehending the gut microbiome's involvement in diabetes can lay the foundation for novel, more effective therapeutic modalities that offer hope for patients battling this growing global health crisis.

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8. AUTHOR'S CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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The authors report no financial or any other conflicts of interest in this work.

11. ETHICAL APPROVAL

This study does not involve experiments on animals or human subjects.

12. DATA AVAILABILITY

Established scholarly databases such as PubMed, Scopus, ScienceDirect, Google Scholar, The Cochrane Library, Web of Science, and/or public domains were accessed by keywords for the findings of this study.

13. PUBLISHER'S NOTE

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14. USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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