Gut Microbiota and Antidiabetic Drugs: Perspectives of Personalized Treatment in Type 2 Diabetes Mellitus

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Alterations in the composition and function of the gut microbiota have been reported in patients with type 2 diabetes mellitus (T2DM). Emerging studies show that prescribed antidiabetic drugs distort the gut microbiota signature associated with T2DM. Even more importantly, accumulated evidence provides support for the notion that gut microbiota, in turn, mediates the efficacy and safety of antidiabetic drugs. In this review, we highlight the current state-of-the-art knowledge on the crosstalk and interactions between gut microbiota and antidiabetic drugs, including metformin, α-glucosidase inhibitors, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter 2 inhibitors, traditional Chinese medicines and other antidiabetic drugs, as well as address corresponding microbial-based therapeutics, aiming to provide novel preventative strategies and personalized therapeutic targets in T2DM.

Keywords: gut microbiota, antidiabetic drugs, type 2 diabetes mellitus, efficacy and safety, personalized therapeutic targets

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a highly prevalent metabolic disorder characterized by elevated blood glucose levels, primarily caused by insulin secretion disturbance, insulin resistance, or both (Cersosimo et al., 2000). In recent years, gut microbiota, which refers to a complicated assembly of trillions of microbes, is reported to be involved in the pathogenesis and treatment responses of T2DM (Bouter et al., 2017; Koropatkin and Martens, 2017; Vázquez-Baeza et al., 2018). Additionally, emerging evidence has indicated that the gut microbiota affects the pharmacology of antidiabetic drugs, and drug-induced metabolites transform the structure of gut microbiota in turn (Gu et al., 2017; Koropatkin and Martens, 2017).

Gut microbiota is predominated by bacterial phyla Firmicutes and Bacteroidetes, followed by other phyla such as Actinobacteria, Proteobacteria and Verrucomicrobia (Woting and Blaut, 2016).

Abbreviations: T2DM, Type 2 diabetes mellitus; GLP-1, glucagon-like peptide-1; DPP4, dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter 2; TCMs, traditional Chinese medicines; SCFAs, short-chain fatty acids; PPARG, peroxisome proliferative activated receptor; MGAM, maltase-glucoamylase, SI, sucrase-isomaltase; Treg, regulatory T; ILC1, innate lymphoid cell 1; HFD, high fat diet; TLR, Toll-like receptor; AMPs, antimicrobial peptides; DCA, deoxycholic acid; PBAs, primary bile acids; FXR, farnesoid X receptor; GUDCA, glyoursodeoxycholic acid; FMT, fecal microbiota transplantation; PPRG, postprandial glycemic response.
With the growing recognition of gut microbiome as the second human genome, pharmacomicrobiomics has been introduced as the expansion of pharmacogenomics, which facilitates the investigation of the interaction between microbiome variation and drugs response (Doestzada et al., 2018). On the one hand, various studies have shown that antidiabetic drugs can affect the composition and function of gut microbiota (Forslund et al., 2015; Wu et al., 2017). On the other hand, the gut microbiota can influence an individual’s response to a specific drug by altering the drug’s bioactivity, bioavailability or toxicity (Koppel et al., 2017). A recent study showed that two-thirds of 271 tested drugs were subject to gut microbiota metabolism (Zimmermann et al., 2019), in which microbial enzymes transformed them into inactive or even toxic drug metabolites (Spanogiannopoulos et al., 2016). Despite the fact that interaction between gut microbiota and antidiabetic agents is increasingly being understood, the role of gut microbiota in the drug efficacy and safety is not fully clarified.

In the present review, we clarify the interaction between gut microbiota and antidiabetic agents, such as metformin, α-glucosidase inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP4) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, traditional Chinese medicines (TCMs) and other antidiabetic drugs, as well as address the therapeutics based on gut microbiota, aiming to develop personalized treatments and potential individualized preventative and therapeutic strategies.

### INTERACTION BETWEEN GUT MICROBIOTA AND ANTIDIABETIC DRUGS

Lines of evidence have suggested that gut microbiota can not only be influenced by antidiabetic drugs (Table 1), but also in turn affect an individual’s response to those drugs. Furthermore, the interaction between gut microbiota and antidiabetic drugs is complex and bidirectional (Figure 1).

### Antidiabetic Drugs Influencing the Gut Microbiota

Metformin is the most commonly used glucose-lowering drug for the treatment of T2DM, especially T2DM associated with obesity. Previous studies indicated that intravenous administration of metformin did not lower glucose in contrast to oral metformin (Bonora et al., 1984), and the bioactivity of metformin originated in the intestine (Bailey et al., 2008). There is evidence to suggest that metformin changes microbiota composition in not only T2DM patients (Forslund et al., 2015; Wu et al., 2017; Nakajima et al., 2020), but also in healthy people (Bryrup et al., 2019; Ejtahed et al., 2019). Metagenomic analysis of microbiota suggested that metformin influenced antidiabetic effect through short-chain fatty acids (SCFAs) production, as well as potential microbial genes and pathways (Lee and Ko, 2014; Forslund et al., 2015; de la Cuesta-Zuluaga et al., 2017; Wu et al., 2017; Bauer et al., 2018). In addition, increase in the production of SCFAs, especially butyrate and propionate, activated intestinal gluconeogenesis, which improved glycemic control and reduced hepatic glucose production, appetite and body weight (Ejtahed et al., 2016). To elucidate the mechanism by which gut microbiota mediated the antidiabetic effects of metformin, a further study investigated metformin-microbiota interactions and showed that metformin affected pathways with biological functions in species from mucin-degradation bacteria and SCFA production, and related genes in these species encoded metalloproteins or metal transporters (Wu et al., 2017). A systematic review stressed that the changes of gut microbiota were associated with metformin, and T2DM patients receiving metformin showed increases in Enterobacteriales and Akkermansia muciniphila, a mucin-degrading bacteria that has been shown to reverse metabolic disorders (Cao et al., 2020). On the other hand, a randomized trial reported that metformin shifted long-term gut microbiota composition, increasing E. coli and R. torques and decreasing I. bartlettii and R. intestinalis at 6th and 12th month in overweight and obese cancer survivors, respectively (Mueller et al., 2021). Furthermore, in healthy subjects without changes in glycemic control, metformin led to an increased abundance of Escherichia/Shigella spp. and Bilophila wadsworthia, as well as a reduced abundance of Clostridium spp. and Intestinibacter spp. (Bryrup et al., 2019). These results suggest that the changes in microbiota were caused by metformin itself, rather than simply reflecting improved glycemic control.

To figure out the association between diabetes and gut microbiota modified by metformin, Cuesta-Zuluaga et al. performed a retrospective study and found that patients with diabetes taking metformin had higher relative abundance of mucin-degradation Akkermansia muciniphila and several sorts of SCFA-producing microbiota compared with participants without diabetes (de la Cuesta-Zuluaga et al., 2017). Conversely, for diabetic patients not taking metformin, relative abundance was higher in Clostridiales 02d06 and lower in Enterococcus casseliflavus (de la Cuesta-Zuluaga et al., 2017).

α-glucosidase inhibitors, including acarbose, voglibose and miglitol, are the first-line drugs in noninsulin-dependent T2DM characterized by their high efficacy in postponing the digestion of carbohydrates and reducing postprandial hyperglycemia (Montandon and Jornayvaz, 2017), those medications inhibit carbohydrate hydrolysis by binding to human intestinal maltase-glucosaminylase (MGAM) and sucrase-isomaltase (SI), and consequently delay and reduce the absorption of glucose. Furthermore, there is growing evidence that α-glucosidase inhibitors impact microbiota composition. For instance, T2DM patients treated with acarbose showed increased abundance of Bifidobacterium longum and decreased concentration of lipopolysaccharides (Su et al., 2015). Another clinical trial suggested that Butyricoccus, Phascolarctobacterium, and Ruminococcus decreased while Lactobacillus, Faecalibacterium, and Dialister increased in patients with prediabetes after acarbose treatment (Zhang X. et al., 2017). Interestingly, Smith et al. observed that there were notable changes in microbial communities and the concentrations of SCFAs in the mice treated with acarbose compared with those of control mice, and microbial communities and fecal SCFAs increased the lifespan of the...
TABLE 1 | Effect of antidiabetic drugs on gut microbiota in T2DM.

| Antidiabetic drugs | Changes in gut microbiota                                                                 | Mechanisms                                                                 | References                   |
|--------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|-----------------------------|
| Metformin          | Increased Escherichia and lowered Intestinbacter abundance                               | NA                                                                         | Forslund et al., 2015       |
|                    | Increased Escherichia and Bifidobacterium, as well as lowered Intestinbacter abundance   | Affected pathways and regulated genes encoding metalloproteins or metal transporters | Wu et al., 2017             |
|                    | Enriched the abundance of Akkermansia muciniphila and SCFA-producing microbiota          | NA                                                                         | de la Cuesta-Zuluaga et al., 2017 |
|                    | Increased Enterobacteriales and Akkermansia muciniphila                                 | NA                                                                         | Cao et al., 2020            |
|                    | Increased E. coli and R. torques and decreased I. barteltii and R. intestinatus at 6 and 12 months | NA                                                                         | Mueller et al., 2021        |
| α-glucosidase inhibitors | Increased abundance of Bifidobacterium longum and decreased concentration of lipopolysaccharides | NA                                                                         | Su et al., 2015             |
|                    | Increased Lactobacillus, Faecalibacterium, and Dialister and decreased Butyricoccus, Phascolarctobacterium and Ruminococcus | NA                                                                         | Zhang X. et al., 2017       |
|                    | Contributed to the plentitude of Bifidobacterium and Lactobacillus                       | Promoted amino acid pathways                                               | Zhang F. et al., 2019       |
|                    | Decreased the ratio of Firmicutes to Bacteroidetes                                       | Downregulated expression levels of CYP8B1 and HNF4α genes and upregulated PGC1α | Do et al., 2016             |
| GLP-1 receptor agonists | Increased the ratio of Firmicutes-to-Bacteroidetes                                         | NA                                                                         | Wang et al., 2016; Zhao et al., 2018; Changpientier et al., 2021 |
|                    | Elevated SCFA-producing bacteria and Bifidobacterium                                      | Reduced the frequency of Th1 lymphocytes, as well as increased TReg and ILC1 and 3 cells |                                |
| DPP4 inhibitors   | Increased the abundance of Bacteroidetes                                                  | NA                                                                         | Liao et al., 2019           |
|                    | Increased Firmicutes and Tenericutes, as well as decreased Bacteroidetes                  | NA                                                                         | Yan et al., 2016; Zhang G. et al., 2017 |
| SGLT2 inhibitors  | Increased Lactobacillus spp. and propionate production along with decreased Oscillobacter spp. | Restored the expression of AMPs and the depth of the crypts in the ileum  | Olivares et al., 2018       |
|                    | Decreased Firmicutes-to-Bacteroidetes ratio and Oscillospira, as well as increased Akkermansia muciniphila | NA                                                                         | Lee et al., 2018            |
|                    | Increased the relative abundance of Proteobacteria and did not influence the abundance of the Firmicutes-to-Bacteroidetes ratio | NA                                                                         | Yang et al., 2020           |
|                    | Almost did not change                                                                     | NA                                                                         | Du et al., 2018; van Bommel et al., 2020; Yao et al., 2020; Xu et al., 2021 |
| TCMs               | Increased the relative abundance of Bacteroidetes and decreased Proteobacteria            | Attenuated DCA transformation                                               | Zhang Y. et al., 2020       |
|                    | Inhibited Ruminococcus bromii                                                             | Induced ileal gene expression and relieved systemic and local inflammation | Xu et al., 2020             |
|                    | Enriched butyrate-producing bacteria                                                      | NA                                                                         | Chen et al., 2018           |
|                    | Increased SCFAs-producing and anti-inflammatory bacteria                                  | Strengthened gut barrier function and reduced the host inflammatory reaction | Wei et al., 2018; Cao et al., 2019; Su et al., 2020; Chen et al., 2021 |
|                    | Enriched Akkermansia muciniphila and SCFAs level                                          | Up-regulated PBA-FXR-GLP-1 pathway                                         | Zhang F. et al., 2019       |
| Insulin            | Increased the abundance of Fusobacterium                                                 | Up-regulated the genes involved in triglyceride and arachidonic acid metabolism |                                |

T2DM: type 2 diabetes mellitus; NA: not available; SCFA, short-chain fatty acid; AMP, antimicrobial peptide; GLP-1, glucagon-like peptide-1; DPP4, dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter 2; TCMs, traditional Chinese medicines; DCA, deoxycholic acid; PBA, primary bile acid; FXR, farnesoid X receptor.

mice treated with acarbose (Smith et al., 2019). Recently, a study from Chinese population provided that α-glucosidase inhibitors contributed to the plentitude of Bifidobacterium and Lactobacillus, as well as promoted several amino acid pathways (Zhang F. et al., 2019). Also, 12-week voglibose administration decreased the ratio of Firmicutes to Bacteroidetes and improved metabolic profiles including those of blood glucose and lipid metabolism (Do et al., 2016). Therefore, it has been suggested that α-glucosidase inhibitors may have beneficial effects on glycemic control partly through gut microbiota in T2DM.

GLP-1 is an incretin hormone secreted by intestinal endocrine cells (L cells) in response to food ingestion (Drucker and Nauck, 2006). It can enhance glucose-induced insulin from pancreatic β-cells and suppress glucagon secretion; in addition, it also contributes to the inhibition of appetite and gastric emptying (Drucker and Nauck, 2006; Baggio and Drucker, 2014). Numbers of studies have shown that gut microbiota modulates satiety and glucose homeostasis by inducing the secretion of GLP-1 in mice (Tolhurst et al., 2012; Kimura et al., 2013; Vettorazzi et al., 2016; Aoki et al., 2017). Meanwhile, GLP-1 is a key mediator of antidiabetic actions of GLP-1 receptor agonists (Björkman et al., 2006). Therefore, it seems that gut microbiota may orchestrate the effects of GLP-1 and GLP-1 receptor agonists on glucose metabolism.
1 receptor agonists, a new class of antidiabetic drugs, were also reported to affect the intestinal environment and, indeed, changes in the gut microbiota had been linked to GLP-1 receptor agonists (Wang et al., 2016; Zhang et al., 2018; Zhao et al., 2018; Charpentier et al., 2021; Shang et al., 2021). Generally, the Firmicutes to Bacteroides ratio is regarded to be of significant relevance in human gut microbiota composition. Wang et al. demonstrated that liraglutide could modulate the gut microbiota to a more lean-related composition in diabetic mice with normal weight, and they also found a higher Firmicutes-to-Bacteroides ratio after liraglutide treatment (Wang et al., 2016). Inconsistently, another study argued that liraglutide increased...
the *Bacteroides*-to-*Firmicutes* ratio to lower weight significantly regardless of the glycemic status in both simple obese and diabetic obese subjects (Zhao et al., 2018). This discrepancy may be attributed to the different level of hyperglycemia and model systems used. By constructing diabetic animal model, researches showed that administration of GLP-1 receptor agonists profoundly changed the composition of gut microbiota in diabetic male rats (Yuan et al., 2018; Zhang et al., 2018). In particular, several SCFAs-producing bacteria, including *Bacteroides*, *Lachnospiraceae*, and probiotic bacteria, including *Bifidobacterium*, were selectively enhanced in liraglutide-treated diabetic male rats (Zhang et al., 2018). In parallel, liraglutide increased the *Bacteroidetes*-to-*Firmicutes* ratio by reducing the Th1 cell frequency and enhancing certain immune cells, such as regulatory T (Treg) cell, innate lymphoid cell 1 (ILC1) and ILC3, which was linked to the nitrogen or the purine metabolism pathways, thus improving glucose-induced insulin secretion (Charpentier et al., 2021). Crucially, GLP-1 receptor agonists could at least partially restore the balance of gut microbiota (Yuan et al., 2018).

DPP4 inhibitors have been proposed to lower blood glucose primarily through inhibiting the degradation of GLP-1 and are recommended as a first-line hypoglycemic treatment in T2DM by the American Association of Clinical Endocrinologists (Drucker and Nauck, 2006; Handelsman et al., 2015). A previous study proposed the DPP-4-like activity of the gut microbiota as a target of DPP-4 inhibition, which could open new therapeutics uses of DPP4 inhibitors to regulate gut microbiota as a target of DPP-4 inhibition, which could open certain gut microbiota dysbiosis (Olivares et al., 2018b). Liao et al. demonstrated that DDP4 inhibitors improved glucose metabolism by increasing the abundance of *Bacteroidetes*, and substantially reversing the changes in the gut microbiota induced by high fat diet (HFD) (Liao et al., 2019). An investigation into the effect of sitagliptin on gut microbiota indicated that the phyla *Bacteroidetes* decreased, while *Firmicutes* and *Tenericutes* increased; in addition, sitagliptin partially corrected the dysbiosis of microbiota and altered the population of SCFA-producing bacteria in HFD-fed rats with T2DM (Yan et al., 2019). Similarly, another experiment showed that vildagliptin treatment was associated with increased *Bacteroidetes* and decreased *Firmicutes* along with decreased *Firmicutes*/*Bacteroidetes* ratio in the diabetic rats (Zhang Q. et al., 2017). In parallel, vildagliptin was proposed to exert beneficial effects through the modulation of gut microbiota, and was linked with increased *Lactobacilli* spp. and propionate production along with decreased *Oscillibacter* spp. (Olivares et al., 2018a). To explain these changes, Olivares and his colleagues performed these experiments and found that vildagliptin reduced Toll-like receptor (TLR) ligands in caecal content, as well as restored the expression of antimicrobial peptides (AMPs) and the depth of the crypts in the ileum (Olivares et al., 2018a). Furthermore, they also explored that vildagliptin indirectly reduced gene expression of proinflammatory cytokines in liver. These findings demonstrate an important effect of DPP4 inhibitors on the gut microbiota, revealing a potential strategy for improving glucose homeostasis.

SGLT2 inhibitors, a novel class of anti-diabetic substances, are used to achieve the glucose-lowering effect by increasing urinary glucose excretion (Tahran et al., 2013). After 8 weeks of treatment with dapagliflozin, diabetic mice displayed lower arterial stiffness and blood glucose level, and even more importantly, decreased *Firmicutes*-to-*Bacteroidetes* ratio and *Oscillaiospira*, as well as increased *Akklernansia muciniphila* (Lee et al., 2018). Notably, another study demonstrated that dapagliflozin and metformin have similar glucose-lowering effect, but they differentially affected the composition of faecal microbiota in type 2 diabetic rats (Yang et al., 2020). The dapagliflozin group mainly increased the relative abundance of *Proteobacteria* (especially Desulfovibrioaceae) and did not influence the *Firmicutes*-to-*Bacteroidetes* ratio. Conversely, several studies considered that SGLT2 inhibitors had almost no effect on gut bacteria (Du et al., 2018; van Bommel et al., 2020).

Nevertheless, it was essential to emphasize that all the study participants had been treated with metformin, which could have overshadowed the potential effects of dapagliflozin on the gut microbiota (van Bommel et al., 2020). In short, further research is needed to figure out the influence of SGLT2 inhibitors on gut microbiota.

TCMs, generally also known as botanical medicine or phytomedicine, have been shown to effectively reduce blood glucose for many years (Lian et al., 2015; Hu et al., 2016). Although TCMs have significant effects on the treatment of T2DM, the mechanisms underlying the therapeutics effects remain elusive. In recent decades, accumulating evidence confirmed that TCMs could improve T2DM by modulation of gut microbiota (Xu et al., 2015; Nie et al., 2019; Zhang B. et al., 2019; Zheng et al., 2020a; Zheng et al., 2020b). Yao et al. observed that Berberine reduced the blood glucose levels and improved glucose tolerance and serum lipid parameters in type 2 diabetic rats (Yao et al., 2020). Further analysis found that the relative abundance was increased for *Firmicutes* and decreased for *Proteobacteria* and *Verrucomicrobia* after Berberine treatment (Yao et al., 2020). Likewise, after 30 days of administration, *Beresis kansuensis* extract increased the abundance of phyla *Bacteroidetes* and *Akklernansia*, while reduced the abundance of *Proteobacteria* and several harmful bacteria (e.g., *Enterococcus* and *Fusobacterium*), which was related to its antidiabetic effect in T2DM rats (Xu et al., 2021). To investigate the potential microbial-related mechanism underlying the hypoglycemic effect of Berberine, Zhang et al. found that the inhibition of deoxycholic acid (DCA) biotransformation by *Ruminococcus bromii* might be involved in the hypoglycemic effect of Berberine (Zhang Y. et al., 2020). Moreover, a recent study demonstrated that the glucose-lowering effect of Gegen Qinlian Decoction could be attributed to Berberine, and both of them significantly modulated the overall gut microbiota structure and enriched butyrate-producing bacteria, including *Faecalibacterium* and *Roseburia* (Xu et al., 2020). Additionally, two TCM prescriptions, Xiexin Tang and Huang-Lian-Jie-Du Decoction were reported to increase SCFAs-producing and anti-inflammatory bacteria (e.g., *Parabacteroides*, *Blautia*, *Akkermansia*, and *Adlercreutzia*) in T2DM rats (Chen et al., 2020).
α-glucosidase inhibitors, which were not absorbed in the small intestine or not metabolized before excretion, created a chance for unintended cross-interaction with gut microbiota. Previous studies identified that the sequence and structural active sites of human intestinal α-glucosidases (MGAM and SI) and microbial α-glucosidases (from Blaumbia obeum) were highly homologous, and microbial α-glucosidases could process dietary carbohydrates as well as be inhibited by α-glucosidase inhibitors with comparable strengths (Kuriyama et al., 2008; Natori et al., 2011). Thus, the location and any changes of these active sites might affect the access and specificity of these α-glucosidases to α-glucosidase inhibitors (Tan et al., 2018), mediating their therapeutic effect.

GLP-1 resistance has been reported to seriously impair the effect of GLP-1 receptor agonists (Knop et al., 2012). Grasset et al. identified a specific set of ileum bacteria impairing the GLP-1-activated gut brain axis for the control of insulin secretion and gastric emptying, hence inducing GLP-1 resistance (Grasset et al., 2017). Intriguingly, fecal samples from DDP4 inhibitors-treated T2DM patients transferred to HFD-fed mice improved the glucose intolerance of the recipients, suggesting that the altered gut microbiota contributed to hypoglycemic effects of DDP4 inhibitors even in the absence of additional treatments (Liao et al., 2019). In addition, the gut microbiota might improve the therapeutic efficacy and bioavailability of TCMs by affecting their transformation and absorption (Wang et al., 2017).

In addition to the impact on drug efficacy, gut microbiota can also contribute to the side effects of antidiabetic drugs. It is well known that gastrointestinal side effects are reported in up to one-third of patients taking metformin, and these side effects can be attributed to the identified metabolism genes (mainly derived from an increase of E. coli species) and the increase of virulence factors (Forslund et al., 2015). Because of the high homology of the active sites of human α-glucosidases and gut bacterial α-glucosidases, one proposed theory was that α-glucosidase inhibitors could affect the bacterial α-glucosidases in human gut and exert beneficial effects or create adverse gastrointestinal symptoms (Tan et al., 2018).

The Impact of Gut Microbiota on Antidiabetic Drug’s Efficacy and Safety

Although the changes in gut microbiota caused by antidiabetic drugs were not simply reflecting improved glycemic control, the antidiabetic effect and safety of antidiabetic agents depended partly on certain groups of gut microbiota (Table 2). Wu et al. transferred the fecal samples from metformin-treated donors (treated with metformin for 4 months) to germ-free mice and indicated that glucose tolerance was improved mainly through increasing the production of SCFAs or altering plasma bile acid composition, suggesting that increased growth of SCFA-producing bacterial species could potentially contribute to the antidiabetic effect of metformin (Wu et al., 2017). Another study revealed that the level of bile acid glycocholic acid (GUDCA) was increased and Bacteroides fragilis was decreased in newly diagnosed T2DM treated with metformin for 3 days (Sun et al., 2018). Further experiments confirmed that B. fragilis–GUDCA–intestinal FXR axis mediated the glucose-lowering effect of metformin.

NEW INSIGHTS FOR DEVELOPING PERSONALIZED TREATMENTS

Given the interplay between gut microbiota and antidiabetic drugs, there is increasing awareness that altering microbiota can impact metabolic phenotype and provide a rational basis for targeting gut microbiota to develop personalized treatments in T2DM (Aron-Wisnewsky et al., 2019; Ghorbani et al., 2021; Huda et al., 2021). Several new insights including fecal microbiota transplantation (FMT), probiotics or prebiotics, and intermittent-fasting could contribute to the desired drug response and personalized medicine (Table 3 and Figure 2).
(Khoruts and Sadowsky, 2016), which also has attracted increased attention.

In the FMT-treated mice with diabetes, Desulfovibrio and Clostridium cocoides levels were significantly decreased, and the fecal levels of Akkermansia muciniphila were increased (Zhang Y. et al., 2020). Moreover, Akkermansia muciniphila led to increased expression of HDAC3, which remarkably improved glycolipid metabolism. Likewise, glucose tolerance was improved by transfer of fecal samples from patients treated with metformin to germ-free mice (Wu et al., 2017). Metagenomics analysis indicated that metformin promoted functional shifts in gut microbiota of fecal samples, including lipopolysaccharide biosynthesis and SCFA metabolism. Notably, another study investigated the effects of lean donor-FMT versus self-FMT on patients with metabolic syndrome and found that insulin sensitivity was not changed at 18 weeks after self-FMT, but was significantly improved at 6 weeks after lean donor-FMT (Kootte et al., 2017). Moreover, a recent review considered that whether FMT was a future therapeutic option needed further evaluation (Aron-Wisnewsky et al., 2019). Collectively, FMT may be an interesting option to modify certain gut microbiota and a potential target for developing personalized treatments.

**Probiotics**

Probiotics are live microorganisms, which have a beneficial effect on human health when administered in adequate amounts (Hill et al., 2014; Kesika et al., 2019). A number of studies revealed that multi-strain probiotic supplement, including Lactobacillus plantarum HAC01 and Probioglu™, lowered blood glucose and HbA1c levels, as well as improved glucose tolerance by protecting β-cells and restoring the gut microbiota and SCFAs in streptozotocin-induced diabetic rat models with HFD (Hsieh et al., 2021; Lee et al., 2021). Furthermore, a randomized clinical trial performed by Toejing et al. demonstrated that probiotic supplementation L. paracasei HII01 significantly decreased fasting blood glucose level by increasing beneficial bacteria and decreasing pathogenic bacteria, thus suggesting a potential role of this probiotic as an adjuvant treatment in T2DM (Toejing et al., 2021). Another randomized controlled pilot study showed that participants taking metformin in combination with probiotics had higher concentration of plasma butyrate and SCFA-producing bacteria after the 12-week intervention, lower fasting plasma glucose and weaker insulin resistance, which suggested that probiotic might act as an adjunctive to metformin and thus enhanced glucose management at the individual level (Palacios et al., 2020). Consistent with this result, a recent study showed that the probiotic supplementation improved the glycemic parameters in T2DM patients and thus could be recommended as a potential adjuvant treatment alongside medicine for T2DM therapy (Bock et al., 2021). Mechanistically, these probiotics exerted antidiabetic effect and ameliorated the symptom of T2DM, as well as restored gut barrier function via reducing pro-inflammatory cytokines and intestinal permeability, and activating antioxidant enzymes (Sharma et al., 2016; Kim et al., 2018; Wang et al., 2020).

**Dietary Interventions and Prebiotics**

Dietary interventions and prebiotics are the ingredients that beneficially affect the host by selectively promoting the growth and the activity of certain bacterial species (Gibson and Roberfroid, 1995; Wu et al., 2011). Although gut microbiota played an important role in human by interacting with host diet, there was large inter-individual variation in the response to diet (Lampe et al., 2013), and studies displayed that the gut microbial composition could be used to identify those participants who would benefit from dietary interventions or prebiotics (Korpela et al., 2014; Salonen et al., 2014; Kovatcheva-Datchary et al., 2015). A meta-analysis of randomized controlled trials concluded that dietary interventions supplemented with either prebiotics or synbiotics resulted in improvements in glucose homeostasis in patients with T2DM (Mahboobi et al., 2018). Moreover, Yu et al. argued that different dietary supplements might exert synergistic protective effects against T2DM via reducing the blood glucose levels and effectively improving some beneficial bacterium (Yu et al., 2021).

Additionally, prebiotic inulin was conducive to alleviate T2DM by modulating gut microbiota (Li et al., 2019; Birkeland et al., 2020). Further analysis found that dietary inulin increased the relative abundance of Cyanobacteria and Bacteroides, as well as reduced the relative abundance of Ruminiclostridium, Deferrribacteres, and Tenericutes via suppressing inflammation (Li et al., 2019). Noteworthy, a symbiotic mixture of prebiotics and probiotics supplementation could be more beneficial compared to probiotic or probiotic alone (Morshedli et al., 2020). A recent randomized trial also demonstrated that administration of berberine with probiotics improved blood glucose levels compared to the group treated with berberine alone (Zhang Y. et al., 2020). Therefore, there will be a promising
### TABLE 3 | Potential microbial-based therapeutics for developing personalized treatments in T2DM.

| Microbial-based therapeutics | Subjects | Results | References |
|------------------------------|----------|---------|------------|
| **FMT**                     | Mice with diabetes | Increased the fecal levels of *Akkermansia muciniphila*, decreased *Desulfovibrio* and *Clostridium* cocoides levels and lowered fasting blood glucose concentrations | Zhang P.P. et al., 2020 |
|                             | Germ-free mice | Increased SCFAs and bile acid composition, as well as improved glucose tolerance | Wu et al., 2017 |
|                             | Metabolic syndrome patients | Increased fecal acetate or butyrate at 6 weeks | Kootte et al., 2017 |
| **Probiotics**              | (STZ+HFD)-induced T2DM mice | Increased the Akkermansiaceae family and SCFAs, as well as protected β-cells and alleviated hyperglycemia | Lee et al., 2021 |
|                             | (STZ+HFD)-induced T2DM rats | Protected β-cells, stabilized glycemic levels and reduced inflammation | Hsieh et al., 2021 |
|                             | T2DM patients | Increased the level of SCFAs | Toejing et al., 2021 |
|                             | T2DM patients | Decreased fasting plasma glucose and insulin resistance | Palacios et al., 2020 |
| **Dietary interventions and prebiotics** | T2DM patients | Improved lipid metabolism and glucose homeostasis | Mahboobi et al., 2018 |
|                             | T2DM mice | Reduced the blood glucose level and oral glucose tolerance level, as well as increased the level of SCFAs and improved biochemical parameters | Yu et al., 2021 |
|                             | T2DM patients | Increased concentrations of faecal SCFAs with six weeks supplementation of inulin-type fructans | Birkeland et al., 2020 |
|                             | T2DM mice | Reduced abundance of *Deferribacteres* and *Tenericutes*, and suppressed inflammation | Li et al., 2019 |

FMT, fecal microbiota transplantation; STZ, streptozotocin; HFD, high fat diet; T2DM, type 2 diabetes mellitus; SCFA, short-chain fatty acid.

*FIGURE 2* | Potential mechanisms of microbial-based therapeutics for developing personalized treatments in T2DM. There are several relevant mechanisms through which antidiabetic drugs treat T2DM by regulating the gut microbiota. Microbial-based therapeutics, including FMT, probiotics and dietary interventions and prebiotics, could directly target gut microbiota or act as an adjunctive to antidiabetic drugs to restore the balance of several certain dysbiotic gut microbiota, which contributed to reducing pro-inflammatory cytokines, restoring gut barrier function, as well as protecting β cells, therefore improving glycemic control and glucose tolerance. FMT, fecal microbiota transplantation; T2DM, type 2 diabetes mellitus.
synergistic approach in the future involving both diet and probiotics in the personalized prevention and treatment of T2DM. Currently, a prominent study integrated clinical and microbial data and devised machine learning algorithms for postprandial glycemic response (PPGR) prediction (Shilo et al., 2017), which implied that personalized treatments could be customized for individuals in the future.

CONCLUSIONS AND FUTURE PERSPECTIVES

With the bidirectional interaction between gut microbiota and antidiabetic agents is increasingly being understood, targeting gut microbiota can contribute to increasing drug efficacy and safety, and thus enable a personalized medicine approach for the treatment and management of T2DM.

It is noteworthy that pharmacomicrobiomics play an essential role in combing personal microbiome and genetic profiles to better predict individual’s drug response and efficacy at the individual level. Mapping and modeling human microbiome drug metabolism with genome-scale and meta-omics analyses could improve our understanding of the roles of drugs and microbial communities in personalized medicine (Zimmermann et al., 2019; Javdan et al., 2020; Heinken et al., 2021). With the advance of multi-omics in gut microbiota research, microbiota-based personalized treatment is expected to be achieved by integration of multi-omics data with microbiome data in T2DM patients. Excitingly, thanks to current technologies, around 80% of gut microbes are readily available using bacterial culture (Lagier et al., 2016), which helps to mimic the intestinal environment and makes it possible to conduct individual-based drug testing on cultured bacteria, thus developing novel preventative strategies and personalized therapeutic targets.

Finally, applying the abovementioned novel approaches may contribute to a better understanding of the interactions between gut microbiota and antidiabetic drugs in T2DM, ultimately leading to future potential major advances in personalized medicine.

AUTHOR CONTRIBUTIONS

WL, ZL and JZ wrote the original draft. WL and ZL reviewed and edited the draft. BS revised and supervised overall project. All authors read and approved the final version of manuscript. All authors contributed to the article and approved the submitted version.

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