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REVIEW

# New Insights of Anti-Hyperglycemic Agents and Traditional Chinese Medicine on Gut Microbiota in Type 2 Diabetes

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**Abstract:** Type 2 diabetes mellitus (T2DM) is a widespread metabolic disease characterized by chronic hyperglycemia. Human microbiota, which is regarded as a "hidden organ", plays an important role in the initiation and development of T2DM. In addition, anti-hyperglycemic agents and traditional Chinese medicine may affect the composition of gut microbiota and consequently improve glucose metabolism. However, the relationship between gut microbiota, T2DM and anti-hyperglycemic agents or traditional Chinese medicine is poorly understood. In this review, we summarized pre-clinical and clinical studies to elucidate the possible underlying mechanism. Some anti-hyperglycemic agents and traditional Chinese medicine may partly exert hypoglycemic effects by altering the gut microbiota composition in ways that reduce metabolic endotoxemia, maintain the integrity of intestinal mucosal barrier, promote the production of short-chain fatty acids (SCFAs), decrease trimethylamine-N-oxide (TMAO) and regulate bile acid metabolism. In conclusion, gut microbiota may provide some new therapeutic targets for treatment of patients with diabetes mellitus.

**Keywords:** gut microbiota, anti-hyperglycemic agents, traditional Chinese medicine, type 2 diabetes mellitus

## Introduction

Diabetes mellitus (DM), which is contributed to genetic and/or environmental factors, is the most prevalent metabolic disease worldwide characterized by chronic hyperglycemia. Type 2 diabetes mellitus (T2DM), which results from insulin resistance and/or impaired insulin secretion, accounts for more than 90% of patients with DM. Long-term hyperglycemia can result in detrimental micro- and macrovascular complications, involving many organs and systems, especially kidneys, nervous system, eyes and blood vessel.[1]

Tens of trillions of microorganisms indigenously colonize the gastrointestinal tract immediately after birth, collectively termed as gut microbiota. Gut microbiota is a highly complex and dynamic microbial ecosystem and may be regarded as a "hidden organ". Human microbiota, which is considered as a metabolic organ, can perform diverse physiological functions to maintain homeostasis in health.[2] It is estimated that the number of microbial genes approximately exceeds 100-fold higher than that of human genome. The gut microbiota, also considered as the "second genome" of the host, provides humans with additional biological and metabolic functions that cannot be performed by the host.[3] The composition of

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the gut microbiota is influenced by several variables including diet, sex, age, lifestyle, environment, geographical location and genetic background.[4] The gut microbiota is dominated by four phyla: Firmicutes (Gram-positive, 60–65%), Bacteroidetes (Gram-negative, 20–25%), Proteobacteria (Gram-negative, 5–10%), Actinobacteria (Gram-positive, 3%).[5] Growing evidences suggest that the perturbation of normal intestinal microbiota composition, also termed as dysbiosis, may break the homeostasis and result in a variety of common metabolic diseases, including diabetes and diabetic complications.[6,7]

Over the last few decades, a myriad of original research indicates that there is an association between gut microbiota and T2DM. In previous years, some reviews published have reported the interaction between anti-hyperglycemic agents and gut microbiota.[8,9] The association between human microbiome and traditional Chinese medicine on healthcare and cancer treatment has gained attention in recent years,[10,11] but reviews on the association between antidiabetic effect of the traditional Chinese medicine and gut microbiota are insufficient. Accordingly, we summarized the latest literatures and explored the potential mechanisms of how anti-hyperglycemic agents and traditional Chinese medicine influenced the gut microbiota, which might provide some new therapeutic targets of T2DM.

## Gut Microbiota and T2DM

Increasing clinical and animal researches have revealed the important role of gut microbiota dysbiosis in the initiation and development of T2DM.[7,12] Given that hyperglycemia also affect bacterial composition,[13,14] the gut microbiota and diabetes have a reciprocally regulatory relationship.[15]

### Metabolic Endotoxemia

Several studies have determined that the gut microbiota dysbiosis leads to insulin resistance and T2DM through several mechanisms including lipopolysaccharide (LPS)-mediated metabolic endotoxemia (Figure 1A). LPS, which is a major component of the outer membrane of the Gram-negative bacteria, contributes to development of low-grade chronic inflammation known as metabolic endotoxemia.[16] High-fat diet (HFD) may increase LPS-enriched intestinal microbiota and consequently elevate the plasma concentration of LPS.[17] In the intestinal tract, LPS triggers the dysfunction of intestinal barrier and increases gut permeability. Excessive LPS enters the blood and translocates across the damaged intestinal barrier, leading to the low-grade inflammatory injury of intestinal epithelium.[18] A great deal of researches have determined that the low-grade inflammation is associated with insulin resistance and T2DM.[19] A typical LPS molecule is composed of three different constituents: a highly variable O-antigen constituted of repeating oligosaccharide units, a core oligosaccharide and lipid A.[20] Lipid A is one of the core structures of bacterial LPS and is responsible for much of LPS's toxicity. Lipid A, which is an amphipathic glycolipid domain, triggers strong immune and inflammatory responses by tightly binding to Toll-like receptors (TLRs).[21] Most TLRs coordinate a series of proinflammatory signaling cascades through the Myeloid differentiation primary response 88 (MyD88)-dependent pathway.[22–24] The activated MyD88 then stimulates the pro-inflammatory cytokines expression and secretion to induce the low-grade inflammatory, such as IL-1 receptor-associated kinase (IRAK), TNF receptor-associated factor (TRAF6), transforming growth factor B-associated kinase 1 (TAK1), Monocyte Chemoattractant Protein-1 (MCP-1), TNF-α and JNK and IKK complexes. JNK and IKK complexes, which can induce serine phosphorylation of insulin receptor substrate (IRS), inhibit insulin signaling and result in insulin resistance.[25]

### Gut Permeability

An amount of investigation shows that the intestinal mucosal barrier, which can prevent bacteria and toxins from reaching the circulation, plays an important role in maintaining intestinal homeostasis. The intestinal mucosal barrier is composed of the intestinal epithelium cells (IECs), the tight junction proteins between IECs and their protective mucous layer.[26] Under the influence of HFD, inflammatory stimulation and other factors, the intestinal barrier would be destroyed and the intestinal mucosa permeability would be enhanced, which in turn increases excessive inflammatory cytokine and metabolic endotoxemia.[27] Thereby, the disruption of the intestinal barrier or the imbalance of gut microbiota would aggravate the progress of diabetes and its complications.[28] Intestinal permeability is usually regulated by tight junction proteins, such as zonula occludens-1 (ZO-1), occludin, and claudin-1. Recently, prebiotic or exogenous glucagon-like peptide-2 (GLP-2) treatment significantly improves tight junctions and reduces gut permeability by increasing intestinal GLP-2 production in obese and diabetic mice.[29,30] GLP-2 is a 33-amino acid peptide derived from proteolytic cleavage of proglucagon in enteroendocrine L cells. Moreover, blockade of endocannabinoid (eCB)

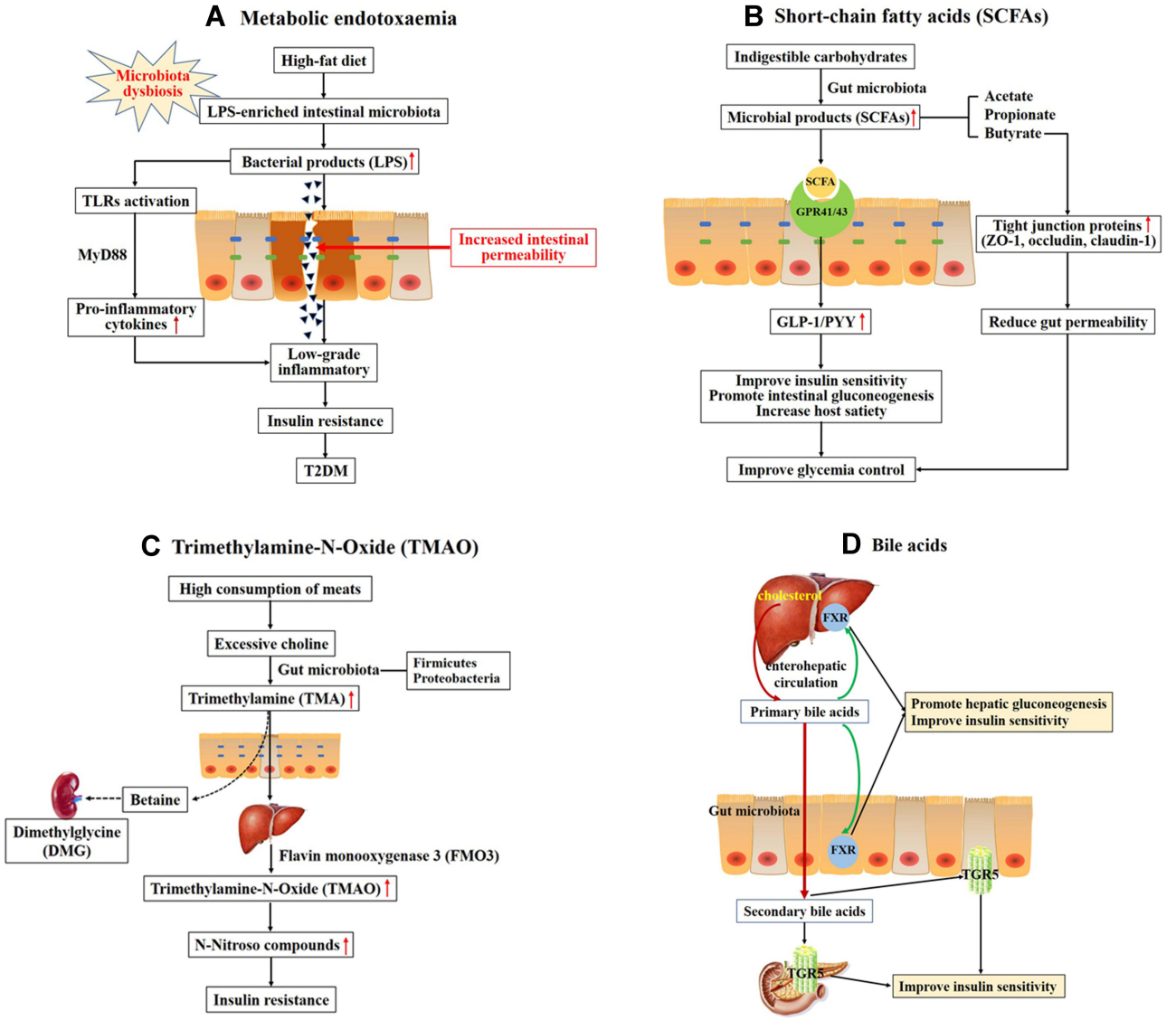


**Figure 1** Overall scheme showing the potential mechanisms linking gut microbiota and the development of T2DM. (**A**) High-fat diet increases LPS-enriched intestinal microbiota, resulting in elevating the concentration of LPS. Excessive LPS triggers the dysfunction of intestinal barrier and increases intestinal permeability, then leading to the low-grade inflammatory through binding and activating Toll-like receptors (TLRs). Chronic low-grade inflammation is associated with insulin resistance and type 2 diabetes. (**B**) Indigestible carbohydrates were hydrolyzed and fermented to produce short-chain fatty acids (SCFAs), such as acetate, propionate and butyrate. SCFAs activate G-protein coupled receptors 41 and 43 (GPR41/43) to stimulate production of glucagon-like peptide-1 (GLP-1) and the intestinal peptide YY (PYY), which improve insulin secretion and promote intestinal gluconeogenesis. (**C**) High consumption of meats leads to produce excessive choline. Choline is metabolized to produce trimethylamine (TMA) by gut microbiota, primarily the *Firmicutes* and *Proteobacteria* phyla. TMA readily passes the intestinal wall to form trimethylamine-N-Oxide (TMAO). TMAO promotes insulin resistance through forming N-Nitroso compounds. Choline may escape microbial degradation and converted into betaine and further metabolites (eg, dimethylglycine (DMG)) which have detrimental osmotic effects by mammalian mitochondrial pathways in kidney. (**D**) Primary bile acids are synthesized from cholesterol in hepatocytes. Secondary bile acids are derived from primary bile acids, mainly by the biosynthetic capabilities of few gut microbes. The primary BAs can regulate hepatic glucose metabolism and insulin sensitivity through activating the nuclear farnesoid X receptors (FXR) in liver and intestine. Secondary bile acids can stimulate GLP-1 secretion from L-cells in the intestine to improve insulin sensitivity through binding to G-protein-coupled bile acid receptor 1 (TGR5) in enteroendocrine cells and pancreatic β-cells.

system could improve the gut barrier and reduce metabolic endotoxemia through increasing tight junction proteins.[31]

## Short-Chain Fatty Acids (SCFAs)

Gut microbiota is able to hydrolyze and ferment the indigestible carbohydrates to yield important microbial products, such as SCFAs, trimethylamine N-oxide (TMAO), amino acids and bile acids (BAs).[32] These metabolites, particularly SCFAs, are involved in the regulation of glucose and energy metabolism (Figure 1B). SCFAs, such as acetate, propionate and butyrate, have considerable effects on regulating pancreatic β cell proliferation, insulin biosynthesis,[33] maintaining gut epithelial barrier function,[34] anti-inflammatory functions and so on. The

principal receptors of gut microbiota-derived SCFAs are G-protein coupled receptors 43 and 41 (GPR43/41), which are expressed in the islets of Langerhans, enteroendocrine and intestinal epithelial cells.[33] Activation of G protein-coupled receptors by SCFAs stimulates the production of glucagon-like peptide-1 (GLP-1) and the intestinal peptide YY (PYY).[35] GLP-1 and PYY are both secreted from the enteroendocrine L-cells, predominantly distributed in the ileum and colon.[36] GLP-1 regulates glucose, lipid and energy metabolism by binding to GLP-1 receptor, including stimulating glucose-dependent insulin secretion from pancreatic β cells, reducing glucagon secretion from pancreatic α cells,[37] inhibiting the production of lipid proteins,[38] slowing down gastric emptying,[39] increasing energy expenditure and losing body weight.[40] PYY participates in suppressing appetite and slowing gastric emptying.[41] Butyrate, the main energy source of the colonic epithelium cell, can protect intestinal barrier through increasing tight junction protein expression (such as ZO-1 and occludin) and reducing intestinal permeability.[42]

## Trimethylamine-N-Oxide (TMAO)

High consumption of meats contributes to undesirable health outcomes through the choline/carnitine-TMAO-pathway (Figure 1C). Choline, which is a water-soluble nutrient, is essential for a wide range of biological activities. Evidences suggest that gut microbiota can convert beneficial dietary choline into the production that are detrimental to human health.[43] Choline is metabolized to produce a precursor trimethylamine (TMA) by gut microbiota, primarily the *Firmicutes* and *Proteobacteria* phyla.[44] TMA is a gas that readily passes the intestinal wall. After being absorbed, TMA is oxidized to form TMAO by flavin monooxygenase 3 (FMO3) in live.[45] Choline may escape microbial degradation and be converted into betaine and further metabolites (eg, dimethylglycine (DMG)) which have detrimental osmotic effects by mammalian mitochondrial pathways in kidney.[46] High circulating level of TMAO can promote insulin resistance by forming N-Nitroso compounds and is a potent novel risk factor of T2DM.[47] In addition, elevated circulating TMAO level independently predicts an increased risk of cardiovascular disease in clinical study.[48–50] A study showed that TMAO could inhibit hepatic bile acid synthesis via activating the nuclear farnesoid X receptors (FXR) and small heterodimer partner (SHP) to accelerate aortic lesion formation in apoE$^{-/-}$ mice.[51] Another study showed that TMAO induced oxidative stress, inflammation and endothelial dysfunction via activating ROS-TXNIP-NLRP3 inflammasome in human umbilical vein endothelial cells, which was involved in development of atherosclerosis.[52] Furthermore, another study suggested that TMAO may induce synaptic plasticity deficits by promoting endoplasmic reticulum stress-mediated PERK signaling pathway.[53] TMAO may be identified a potential new therapeutic target for diabetes and other metabolic disorders.

## Bile Acids (BAs)

BAs, as one of the gut microbiota producing metabolites, also participate in lipid and glucose metabolism and are directly or indirectly related to insulin resistance (Figure 1D).[54] Cumulative data demonstrate that manipulation of BAs via regulating the composition of gut microbiota could help glycemic control and prevent metabolic memory for early-onset T2DM subjects.[55] Primary bile acids (eg, chenodeoxycholic acid (CDCA) and cholic acid (CA)) are synthesized from cholesterol in hepatocytes and stored in the gallbladder. After a meal, bile acids are excreted into the duodenum to facilitate the absorption of dietary lipids. After they complete their job, most bile acids (more than 95%) are efficiently reabsorbed in terminal ileum and recirculated to the liver via enterohepatic circulation. The remaining 5% are excreted via feces.[56] Secondary bile acids (eg, deoxycholic acid (DCA), lithocholic acid (LCA), and ursodeoxycholic acid (UDCA)) are derived from primary bile acids, mainly by the biosynthesis of few gut microbes. Both primary bile acids and their respective secondary bile acids act as key pleiotropic signaling mediators in glucose metabolism through activating FXR and/or the membrane Takeda G-protein-coupled receptor 5 (TGR5).[57] FXR is abundantly expressed in liver and intestine.[58] The relative binding affinity of primary and secondary bile acids to FXR is variable (CDCA > DCA > LCA > CA > UDCA).[59,60] TGR5 is highly expressed in liver, gastrointestinal tract, immune cells, gallbladder and pancreas.[61] Like FXR, its relative binding affinity to primary and secondary bile acids varies substantially (LCA > DCA > CDCA > CA > UDCA).[59] Changes of FXR and/or TGR5 regulate the expression of GLP-1 and PYY, hepatic gluconeogenesis, glycogen synthesis and energy expenditure. FXR deficiency increases the secretion of GLP-1 to improve glucose metabolism.[60] Activation of TGR5 potently stimulates GLP-1[62] and PYY[63] secretion.

## Impact of Anti-Hyperglycemic Agents on the Gut Microbiome Composition

Owing to the importance of gut microbiome in T2DM, we discuss the interaction between gut microbiome and anti-hyperglycemic agents and how do they take effect.

### Metformin

Metformin has been the first-line medication for T2DM more than 60 years worldwide. Metformin can effectively control hyperglycemia through decreasing hepatic gluconeogenesis, reducing hepatic glucose output, and increasing glucose uptake and utilization in muscle cells and adipocytes.[64] Metformin is usually administered through orally. The oral bioavailability is about 30–60%, and up to 30% of an ingested dose is eliminated through the feces.[65] As a result, multiple evidences suggest that the anti-diabetic effect of metformin is at least partly mediated by gut microbiota.[66] In a study of HFD-induced obese mice, when treated with metformin, the abundance of *Akkermansia muciniphila* (12.44%±5.26%) and *Clostridium cocleatum* (0.10% ±0.09%) was significantly increased in the mice.[67] An exploratory longitudinal study in healthy volunteers of Latvian was performed to observe the short-term effects of metformin on the gut microbiome.[68] Participants were treated with metformin 850 mg twice daily for 7 days. After metformin administration, the inner diversity of gut microbiota was significantly reduced. Meanwhile, the families *Peptostreptococcaceae* (M24h vs M7d = 0.72% vs 0.18%) and *Clostridiaceae_1* (M24h vs M7d = 0.49% vs 0.10%) and four genera within these families were significantly decreased. In another study in healthy young Danish men, the participants were given metformin up to 1 g twice daily.[69] The abundance of *Intestinibacter* spp. and *Clostridium* spp. was reduced, while the abundance of *Escherichia/Shigella* spp. and *Bilophila wadsworthia* was increased. After discontinuation of metformin, these changes were reversed. This study also demonstrated that the relative abundance at baseline of 12 bacterial genera could predict the risk of gastrointestinal adverse effects of metformin.

The effects of metformin in newly diagnosed T2DM patients were different from healthy individuals.[70] The alpha diversity of microbiota was reduced after metformin treatment, but not in T2DM. At the species level, the abundance of *Clostridium bartlettii* and *Barnesiella intestinihominis* was reduced, while the abundance of *Parabacteroides distasonis* and *Oscillibacter* was increased. Baseline gut microbiome composition predicted the different efficacy of metformin therapy (changes in HbA1c level) and the incidence of side effects. Another study of patients with T2DM in Japan, the ratio of *Firmicutes/ Bacteroidetes* was significantly decreased (before: 2.72±1.45; after four weeks: 2.26±1.09; $p$ = 0.04) after four weeks of metformin treatment.[71] The decrease of the genus *Parabacteroides* was associated with abdominal pain (r = −0.56, $p$ = 0.008). The decrease of *Parabacteroides* (r = −0.53, $p$ = 0.01) and *Bifidobacterium* (r = −0.56, $p$ = 0.008) might be a predictor of abdominal pain and reflux.

Accumulating evidences suggested that metformin improved glucose homeostasis by several underlying mechanism in diabetes. A study in Colombian found that metformin helped ameliorating hyperglycemia and was positively associated with the abundance of SCFA-producing bacteria, including *Akkermansia muciniphila, Butyrivibrio, Bifidobacterium bifidum, Megasphaera*, and an operational taxonomic unit of *Prevotella*.[72] In db/db mice, metformin treatment had been shown to inhibit bacterial TMA production and decrease TMAO availability.[73] The effect of metformin on glucose metabolism was also linked to bile acid metabolism.[74] In the individuals with newly diagnosed T2DM, metformin treatment could decrease *Bacteroides fragilis* and increase the bile acid glycoursodeoxycholic acid (GUDCA) via inhibiting intestinal FXR signaling, thereby improving glucose metabolism.[75] However, the gut microbiota composition after metformin treatment may differ from these results due to different species, individuals and experimental design.

All above, we concluded that metformin exerted the glucose-lowering effect at least partly through affecting microbiome composition, and an individual's tolerance or intolerance to metformin may also be influenced by the baseline composition of gut microbiome.[65] Firstly, Forslund et al found that the increased abundance of *Escherichia* was consistent with well-known gastrointestinal side effects of metformin treatment.[76] Secondly, in healthy volunteers of Latvian, an increased initial presence of gut opportunistic pathogen *Escherichia-Shigella* spp. before metformin administration was associated with the severity of gastrointestinal side effects.[68] Lastly, another study in healthy young Danish men also indicated that the relative abundance at baseline of 12 bacterial genera might be a determinant for predicting gastrointestinal adverse effects following metformin intake.[69]

## α-Glucosidase Inhibitor

The α-glucosidase inhibitors, including acarbose, voglibose and miglitol, are commonly used oral hypoglycemic agents in Asian, since their diet contains high content of carbohydrates. Under normal condition, the carbohydrates are digested and absorbed in the small intestine. The administration of α-glucosidase inhibitors specifically inhibite the α-glucosidase in the brush border of the small intestine, resulting in a delay of the absorption of carbohydrates in the small intestine and reduction of postprandial glucose concentration.[77] When passing through the colon, the undigested carbohydrates are fermented by gut bacteria, and the microbial ecosystem changes to some degree.[78] There are diverse influences on the abundance of gut microbiota after different glycosidase inhibitors.[79]

In mice fed with either a high-starch or high-fiber diet, acarbose treatment changed gut community, including an increase of the *Bacteroidaceae* and *Bifidobacteriaceae* and a decrease of the *Verrucomicrobiaceae* (such as *Akkermansia muciniphila*) and the *Bacteroidales* S24-7, but not irreversibly.[80] These changes resulted in an increase of beneficial SCFA, especially butyrate. A recent human study of prediabetic patients also found that acarbose increased the abundance of SCFA-producing taxa, such as *Faecalibacterium, Prevotella*, and *Lactobacillus*.[81] Acarbose treatment maybe increased median lifespan through increasing fecal SCFA concentrations in mice.[78] In another cohort of Chinese patients with T2DM, the *Bifidobacterium longum* (8.49±1.00 vs 7.92 ±1.18 lgcopies/g, $P$=0.005) and *Enterococcus faecalis* (6.61±1.27 vs 8.08±1.20 lgcopies/g, $P$=0.001) were significantly increased after 4 weeks of acarbose treatment.[82] These changes of gut microbiota were negatively correlated with inflammatory cytokines, including LPS, PAI-1 and MCP-1. Acarbose treatment also altered the composition of gut microbiome and bile acid profiles, resulting in the improvement of glucose metabolism.[83]

## Thiazolidinediones (TZDs)

Thiazolidinediones (TZDs), also termed as selective peroxisome proliferator-activated receptor-γ (PPAR)-γ agonists, are potent oral insulin sensitizers used for T2DM treatment.[84] This class of drugs once fell into disuse because of serious side effects. Thiazolidinediones reduce hepatic glucose production and increase peripheral utilization of glucose and lipid metabolism by increasing the transactivation activity of PPARs, resulting in improved glycemic control.[85] PPAR-γ is predominantly expressed at high levels in adipose tissue, and is also abundantly expressed in colonic epithelial cells.[86] Thiazolidinediones may influence gut microbiota.

In diabetic db/db mice, rosiglitazone treatment significantly improved insulin sensitivity and glucose homeostasis without altering gut bacterial composition.[87] A global gene expression analysis in rosiglitazone-treated db/db mice showed substantial changes in colon and ileum, with no change in duodenum. Rosiglitazone treatment stimulated fatty acid metabolism by regulating the gene markers of intestinal fatty uptake, transport and disposal in the colon and ileum. The genes involved in gluconeogenesis were upregulated in colon, while the genes involved in glycolysis were downregulated in cecum and ileal. These effects were consistent with the fact that PPAR-γ being abundantly expressed in colonic epithelial cells.[87] Another study found that *Danshensu Bingpian Zhi* (DBZ), a unique PPAR-γ partial agonist, prevented HFD-induced obesity and insulin resistance through modulating gut microbiota dysbiosis.[88] DBZ treatment restored intestinal barrier integrity and reversed gut dysbiosis by increasing the ratio of Bacteroidetes to Firmicutes, the relative abundance of Akkermansia, and reducing the level of HFD-induced pernicious bacteria (such as Helicobacter marmotae, Odoribacter, and Anaerotruncus). DBZ was effective for metabolic syndrome without side effects, which is a promising approach novel therapeutic agent for metabolic diseases. The gut microbiota composition of girls with polycystic ovary syndrome (PCOS) was different from those in healthy controls, including a reduction of alpha diversity, a reduction of *Prevotellaceae, Prevotella* and *Senegalimassilia* and an increase of *Bacillales Family XI*.[89] Spironolactone-pioglitazone-metformin (SPIOMET) treatment normalized the abundance of *Family XI*.

## Glucagon-Like Peptide-1 (GLP-1) Receptor Agonist and Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

GLP-1, an incretin hormone secreted by enteroendocrine L cells in the distal ileum and colon, can stimulate glucose-dependent insulin secretion and suppress glucagon secretion.[90] GLP-1 is degraded within 2~3 mins in the circulation via enzymatic inactivation by DPP-4.[90] At present, various GLP-1 receptor agonists (GLP-1RAs) and DPP-4 inhibitors (DPP-4i) have been developed and widely used in T2DM treatment.[91] GLP-1RAs include

the short-acting compounds (exenatide and lixisenatide) and the long-acting compounds (liraglutide, dulaglutide, albiglutide). The short-acting GLP-1RAs, which are resistant to the cleavage by DPP4, primarily lower postprandial blood glucose level through substantial retardation of gastric emptying. While the long-acting GLP-1RAs, binding to plasma albumin, have a stronger effect on fasting glucose level through their insulinotropic and glucagonostatic actions.[92] Besides the glucose-lowering effect, GLP-1 can inhibit appetite and delay gastric emptying to reduce food intake. Therefore, GLP-1RAs are also recognized as a promising anti-obesity agent in simple obesity and diabetic obesity. However, recent studies indicated that GLP-1 had more beneficial effect on weight loss and glucose metabolism by modulating gut microbial composition than that by restricting food intake alone.[93–95] A study provided evidence that in both simple obese and diabetic obese rats, liraglutide, as a GLP-1 analog, was able to attenuate blood glucose levels and suppress body weight gain via changing the structure of gut microbiota, including decreasing microflora community richness and diversity, increasing *Bacteroidetes* and decreasing *Firmicutes* phyla, decreasing the obesity-related phylotypes and increasing the lean-related phylotypes.[93] Liraglutide effectively prevented the development of diabetes in rats through elevating SCFA-producing bacteria, including *Bacteroides, Lachnospiraceae*, and *probiotic bacteria, Bifidobacterium*.[94] In patients with T2DM, liraglutide could reduce gut microbial alpha diversity and alter gut microbiota composition, including increasing *Firmicutes* and *Bacteroidetes* and reducing *Ruminococcus (Firmicutes)* and *Actinomyces (Actinobacteria)*.[95] Another study confirmed liraglutide was also associated with attenuating nonalcoholic fatty liver disease (NAFLD) through changing the structure of gut microbiota.[96,97] Liraglutide could reduce the genus of *Proteobacteria* and increase the genus of *Akkermansia muciniphila* in HFD-fed mice.[97] A recent research found that GLP-1/GLP-2 co-agonists, GUB09-145, had more effect on reducing food intake and improving glucose tolerance than GLP-1 receptor agonist.[98] The biological actions of GLP-1 and GLP-2 receptor signaling on caloric intake and glucose metabolism in diet-induced obese mice were associated with gut bacterial compositional changes.[99]

DPP4i exerts glucose-lowering effect through inhibiting DPP4 activity and raising the plasma level of native GLP-1.[100] In T2DM patients, treatment with sitagliptin, a DPP-4i, obviously increased the abundance of *Bacteroidetes*, especially the production of succinate.[101] In this study, fecal microbiota transplantation (FMT) was further performed in germ-free mice to confirm the effect of sitagliptin on gut microbiota. These results indicated that the hypoglycemic effect of DPP-4i was at least partially mediated by the alterations of gut microbiota. An animal study found that sitagliptin treatment exerted beneficial effects on gut microbiota, especially increasing SCFA-producing bacteria, *Blautia, Roseburia*, and *Clostridium*, and probiotics *Lactobacillus, Bifidobacterium*.[102] Another study in Western diet-fed mice, vildagliptin exerted beneficial effects by modulating of gut microbiota and increasing the amount of propionate, thus ameliorating gastrointestinal health. But there were no differences in total amount of SCFA, acetate or butyrate.[103]

## Sodium Glucose Co-Transporter 2 Inhibitors (SGLT2i)

Sodium glucose co-transporter 2 (SGLT2) is expressed in the renal proximal tubule and accounts for reabsorbing approximately 90% of filtered glucose, whereas sodium glucose co-transporter 1 (SGLT1) is predominantly expressed in the small intestine mucosa and accounts for transporting glucose into intestinal enterocytes.[104] SGLT2 inhibitors are oral anti-hyperglycemic medications for T2DM treatment, which can effectively improve glycemic control by blocking glucose reabsorption in the renal proximal tubule and increasing urinary glucose excretion.[105] Even though the affinity to SGLT2 of SGLT2 inhibitors is significantly greater than SGLT1, SGLT2 inhibitors also have some affinity for SGLT1. Considering this, SGLT2 inhibitors potentially influence gut microbiota composition through reducing intestinal glucose uptake.[106] Thus far, there are a few researches about the effects of SGLT2 inhibitors or SGLT1/2 dual inhibitors on gut microbiome composition, but the results are controversial. Early study found that dapagliflozin, a SGLT2 inhibitor, improved vascular dysfunction concomitantly subtly altering microbiota diversity in T2DM db/db mice.[107] Dapagliflozin treatment could increase the abundance of beneficial bacterial species *Akkermansia muciniphila* and reduce *Firmicutes/Bacteroidetes*.[107] However, whether these alterations of microbiota conclusively mediate the improvement on vascular function need to be further studied. Further preclinical studies about the effect of SGLT2 inhibitors on type 1 diabetes mellitus

(T1DM) are currently underway. After dapagliflozin or empagliflozin treatment, the intermediate metabolite of gut metabolism known as succinate was significantly reduced in type 1 diabetic mice with diabetic retinopathy.[108] Succinate was reported to promote the angiogenic factor VEGF expression in retinal ganglion cells and was shown to be a pathogenic factor in diabetic retinopathy.[109] Another study in patients with T2DM, dapagliflozin treatment as add-on to metformin therapy had no effect on gut microbiome composition.[110] The dosages of metformin were equal among intervention participants, but the effects of metformin on microbiome composition were very potent. Maybe metformin overshadowed the potential effect of dapagliflozin on microbiome composition. Unlike people, mice are cohousing animals. Then, it also may be a confounding factor. Above all, the effect of SGLT2 inhibitors on microbiome composition was slight. Potent SGLT1/2 dual inhibitor, which can reduce glucose uptake and increase urinary glucose excretion, was more powerful than SGLT2 inhibitor in lowering blood glucose.[111] However, SGLT1/2 inhibitor alone did not alter gut microbiota composition in mice. If increasing glucose by high sucrose diet, SGLT1/2 inhibitor would alter the relative abundance of certain phyla to a certain extent.[112]

## Traditional Chinese Medicine

Traditional Chinese medicine, which had recorded knowledge for more than 2000 years, could significantly improve glucose control and clinical indices through different molecular mechanisms, including simulating insulin secretion, enhancing insulin sensitivity and protecting β-cells.[113] Accumulating evidences recently confirmed that traditional Chinese medicine alleviated diabetes at least partly by modulating the structure of the gut microbiota.[114]

Recently, studies indicated that polysaccharides from natural resources exerted beneficial effect on glucose metabolism. Polysaccharides, as macromolecular carbohydrates, are indigestible and fermentative in the intestinal tract after oral administration. So, polysaccharides would regulate gut microflora composition to alleviate diabetes. *Holothuria leucospilota*, as an edible tropical sea cucumber species, could improve glucose metabolism by regulating the structure of the gut microbiota on diabetic GK rats, including increasing the abundance of beneficial bacteria (such as *Bacteroidetes, TM7, Cyanobacteria* and *Tenericutes*) and SCFA-producing species of gut microbiota (such as *Clostridium, Turicibacter, Allobaculum* and *Ruminococcus*) and decreasing the conditional pathogenic bacteria (such as *Anaerobiospirillum, Collinsella* and *Treponema*).[115] Pumpkin polysaccharide also could enrich key species of *Bacteroidetes, Prevotella, Deltaproteobacteria, Oscillospira, Veillonellaceae, Phascolarctobacterium, Sutterella* and *Bilophila*, leading to an increase of SCFA production in diabetic rats.[116] *Sargassum fusiforme* fucoidan treatment alleviated streptozotocin-induced hyperglycemia in mice by increasing the relative abundances of SCFAs-producing bacteria, such as *Bilophila, Oscillibacter, Mucispirillum*, especially *Alloprevotella*.[117] Mulberry fruit polysaccharides could efficiently alleviate hyperglycemia, dyslipidemia and oxidative stress partly by modulating gut microbiota.[118] Mulberry fruit polysaccharides strongly increased the abundance of *Akkermansia*, resulting in the reduce of insulin resistance.[118] In diabetic mice, polysaccharides from adlay seed increased the abundance of *Lactobacillus* spp. and *Lactobacillus fermentum* in diabetic mice, which may be associated with their beneficial role in T2DM. Furthermore, polysaccharides from adlay seed significantly increased the concentration of GLP-1 and reduced anti-amyloid beta (Aβ1–42) protein.[119] Furthermore, long-term polysaccharides intake also have preventive and therapeutic effect on obesity[120] and TMAO-induced cardiac dysfunction[121] by targeting gut microbiota. In HFD-induced obese rats, a mixture of lentinan and *Flos Lonicera* polysaccharide (LF) could reduce TMAO in the urine, suggesting that LF could have a potential role in reducing the risk of atherosclerosis.[120] Ganoderma lucidum spore (GS) polysaccharides could alleviate TMAO-induced cardiac dysfunction in rats by targeting gut microbiota, such as increasing the abundance of *Firmicutes* and *Proteobacteria* and reducing the abundance of *Actinobacteria* and *Tenericutes*.[121] The flavonoids in *Scutellaria baicalensis* and the alkaloids in *Coptis chinensis* are a classic herbal pair for ameliorating diabetes and various intestinal diseases by inhibiting inflammation and modulating gut microbiota. Zhang et al initially found that *Scutellaria–coptis* exhibited the effect of relieving insulin resistant by regulating intestinal flora and inhibiting inflammatory reaction.[122] Moreover, it was demonstrated that *Scutellaria–coptis* obviously improved metabolic disorders by increasing SCFAs-producing bacteria and decreasing secondary BAs-producing bacteria.[123] Furthermore, the hypoglycaemic effects of *Scutellaria-Coptis* were involved in regulating gut microbiota and alleviating intestinal mucosal barrier damage.[124] *Scutellaria-Coptis* significantly inhibited some potential enteropathogenic bacteria and LPS-producing bacteria, such as *Proteobacteria, Enterobacteriaceae, Enterobacter, Escherichia-Shigella*, and *Enterococcus*, and

**Table 1** The Interaction Between Anti-Hyperglycemic Agents, Traditional Chinese Medicine and Specific Gut Microbiota Composition Changes

| Glucose-Lowering Agent | Treatment | Research Subjects | The Change of Gut Microbiota | | References |
|---|---|---|---|---|---|
| | | | Increased Abundance | Decreased Abundance | |
| Metformin | 300 mg/kg every day for 10 weeks | Mouse model of HFD-induced obesity | Akkermansia muciniphila; Clostridium cocleatum | | [67] |
| | 850 mg twice daily for 7 days | Healthy volunteers of Latvian | | The families *Peptostreptococcaceae* and *Clostridiaceae_1* | [68] |
| | 1 g twice daily for 6 weeks | Healthy young Danish men | *Escherichia/Shigella* spp. and *Bilophila wadsworthia* | *Intestinibacter* spp. and *Clostridium* spp. | [69] |
| | 850 mg twice daily for 7 days | Newly diagnosed T2DM patients | *Parabacteroides distasonis* and *Oscillibacter* | *Clostridium bartlettii* and *Barnesiella intestinihominis* | [70] |
| | 500 mg per day for 2 weeks and then 1000 mg per day for 2 weeks | Japanese patients with T2DM | | The ratio of *Firmicutes/ Bacteroidetes; Parabacteroides* and *Bifidobacterium* | [71] |
| | | Colombian adults with or without diabetes | The abundance of SCFA-producing bacteria, including *Akkermansia muciniphila, Butyrivibrio, Bifidobacterium bifidum, Megasphaera*, and an operational taxonomic unit of *Prevotella.* | | [72] |
| Acarbose | 25 mg/kg or 400 mg/kg for 2 weeks | In mice fed either a high-starch or high-fiber diet | *Bacteroidaceae* and *Bifidobacteriaceae* | The *Verrucomicrobiaceae* (such as *Akkermansia muciniphila*) and the *Bacteroidales* S24-7 | [80] |
| | 50 mg once daily on days 1–3, 50 mg twice daily on days 4–7, 50 mg three times daily for 4 weeks | Prediabetic patients | The abundance of SCFA-producing taxa, such as *Faecalibacterium, Prevotella*, and *Lactobacillus* | | [81] |
| | 150 mg/day for 4 weeks | Chinese patients with T2DM | *Bifidobacterium longum* and *Enterococcus faecalis* | | [82] |
| Danshensu Bingpian Zhi (DBZ) | 50 mg/kg or 100 mg/kg for 10 weeks | HFD-fed mice | Bacteroidetes/Firmicutes ratio; the relative abundance of Akkermansia | Helicobacter marmotae, Odoribacter, Anaerotruncus | [88] |
| Liraglutide | 400 μg/kg/day for 12 weeks | Both simple obese and diabetic obese rats | *Bacteroidetes* phyla; the lean-related phylotypes | *Firmicutes* phyla; the obesity-related phylotypes | [93] |
| | 0.2 mg/kg/day or 0.4 mg/kg/day for 12 weeks | Diabetic rat model | SCFA-producing bacteria (*Bacteroides, Lachnospiraceae, probiotic bacteria, Bifidobacterium*) | | [94] |
| | 1.2 mg once daily for 4 months | Patients with T2DM | *Firmicutes* and *Bacteroidetes* | *Ruminococcus (Firmicutes)* and *Actinomyces (Actinobacteria)* | [95] |
| | 200 μg/kg twice daily for 15 days | HFD induced obese mice and the genetically obese mice, ob/ob mice | The genus of *Akkermansia muciniphila* | The genus of *Proteobacteria* | [97] |

(*Continued*)

**Table 1** (Continued).

| Glucose-Lowering Agent | Treatment | Research Subjects | The Change of Gut Microbiota | | References |
|---|---|---|---|---|---|
| | | | Increased Abundance | Decreased Abundance | |
| Sitagliptin | 100 mg/d for 2 months | T2DM patients | The abundance of *Bacteroidetes*; the production of succinate. | | [101] |
| | 10 mg/kg once a day for 12 weeks | A streptozotocin treated high fat/ high carbohydrate fed rat model | The abundance of Firmicutes and Tenericutes; SCFA-producing bacteria, *Blautia, Roseburia*, and *Clostridium*, and probiotics *Lactobacillus, Bifidobacterium* | The abundance of Bacteroidetes | [102] |
| Dapagliflozin | 60 mg dapagliflozin/kg diet; 0.006%) for 8 weeks. | Diabetic mice | The abundance of *Akkermansia muciniphila* | *Firmicutes/Bacteroidetes* | [107] |
| *Holothuria leucospilota* | 100 mg/kg or 200 mg/kg for 4 weeks | Diabetic GK rats | The abundance *Bacteroidetes, TM7, Cyanobacteria* and *Tenericutes*; SCFA-producing species (*Clostridium, Turicibacter, Allobaculum* and *Ruminococcus*) | *Anaerobiospirillum, Collinsella, Treponema* | [115] |
| Pumpkin polysaccharide | 1000 mg/kg once daily for 4 weeks | Diabetic rats | *Bacteroidetes, Prevotella, Deltaproteobacteria, Oscillospira, Veillonellaceae, Phascolarctobacterium, Sutterella* and *Bilophila* | | [116] |
| *Sargassum fusiforme* fucoidan | 100 mg/kg for 6 weeks | STZ-induced diabetic mouse model | The abundances of SCFAs-producing bacteria, such as *Bilophila, Oscillibacter, Mucispirillum*, especially *Alloprevotella* | | [117] |
| Mulberry fruit polysaccharides | 200 mg/kg or 500 mg/kg or 800 mg/kg for 8 weeks | Diabetic db/db mice | The abundance of *Akkermansia* | | [118] |
| Polysaccharides from adlay seed | 24 mg/kg/day for 4 weeks | Diabetic mice | The abundance of *Lactobacillus* spp. and *Lactobacillus fermentum* | | [119] |
| *Scutellaria–coptis* | 6.3 g/kg for 1 month | Diabetic rats | The SCFAs-producing bacteria such as *Bacteroidales S24-7 group_norank, [Eubacterium] nodatum group, Parasutterella, Prevotellaceae UCG-001, Ruminiclostridium*, and *Ruminiclostridium 9* | Secondary bile acid-producing bacteria such as *Escherichia-Shigella* | [123] |
| | 8.4 or 4.2 or 2.1g/kg/day for 12 weeks | Diabetic rats | The abundances of butyrate-producing bacteria, such as *Lachnospiraceae* and *Prevotellaceae* | LPS-producing bacteria, such as *Proteobacteria, Enterobacteriaceae, Enterobacter, Escherichia-Shigella*, and *Enterococcus* | [124] |
| Berberine | 0.5g/L for 14 weeks | HFD-induced atherosclerosis | The abundance of *Akkermansia spp.* | | [129] |
| | 100 mg/kg for 8 weeks | HFD-fed rats | SCFA-producing bacteria (*Blautia* and *Allobaculum*) | | [134] |

increased the abundances of butyrate-producing bacteria, such as *Lachnospiraceae* and *Prevotellaceae*.[124] The change of gut microbiota resulted in alleviating intestinal mucosa barrier damage by preventing the leakage of LPS and increasing the intestinal tight junction proteins claudin-1, occluding and ZO-1 in diabetic rats.[124] Their anti-inflammation effect of *Scutellaria–coptis* was involved in TLR signalling pathway,[122] TLR-4/TRIF and TNFR-1/NF-$\kappa$B signaling pathways.[124] In a clinical study, the T2DM patients who had already been prescribed metformin and were allotted to additional *Scutellaria baicalensis*, significantly reduced the TNF-α expression and influenced gut microbiota, especially *Lactobacillus* and *Akkermansia*.[125] Furthermore, both in vivo and in vitro experiments indicated that nobiletin effectively

prevented TMAO-stimulated vascular inflammation via inhibiting NF-κB/MAPK signaling pathways.[126]

Berberine, an isoquinoline alkaloid extracted from Chinese traditional herb Coptis chinensis, was used to treat bacterial diarrhea in China for thousands of years.[127] Berberine has poor oral bioavailability and leads to changes in the intestinal bacterial composition. Berberine exerts multiple beneficial effect against metabolic disease by modulating gut microbiota.[128] Berberine significantly increased the abundance of *Akkermansia spp*., resulting in alleviating HFD-induced atherosclerosis.[129] Furthermore, berberine could inhibit TMA/TMAO production by modulating gut microbiota composition.[130] The anti-atherosclerotic effect of berberine may be partly attributed to the reduction of TMAO production.[131] Berberine may be a better modulator to inhibit the development of atherosclerotic plaque. Recently, a large number of researches have demonstrated that berberine exhibited clinically beneficial effect in alleviating T2DM and could be possibly developed into a promising anti-diabetes candidate.[132,133] Berberine administration enriched SCFA-producing bacteria, including *Blautia* and *Allobaculum*, and elevated fecal SCFA concentrations in HFD-fed rats, which may help to alleviate inflammation.[134] Another study indicated that berberine inhibited LPS-induced TLR4/TNF-α activation.[135] These findings suggested that berberine prevented insulin resistance at least partially attributable to structural modulation of the gut microbiota. Berberine could reduce TLR-4, NF-kB and TNF-a expression, increase GLP-2 secretion and improve intestinal permeability by regulating gut microbiota in impaired glucose tolerance (IGT) rats, which may slow the progression of prediabetes to T2DM in ZDF rats.[136] Berberine compounds could increase microbiome mediated deoxycholic acid (DCA) production and upregulate colonic TGR5 expression and GLP secretion in *db/db* mice, which improved hyperglycemia.[137] In China, a clinical trial in newly diagnosed T2DM patients found that the hypoglycaemic effect of berberine was associated with the inhibition of DCA biotransformation by *Ruminococcus bromii* and the reduction of the microbial production of secondary BA.[138]

## Conclusion and Future Perspectives

So far, increasing researches have demonstrated that the alteration of gut microbiota composition and function played pivotal roles in the pathogenesis and treatment of T2DM. While animal and human studies in this field are limited in size. In this review, we summarized the effects of antihyperglycemic agents and traditional Chinese medicine on gut microbiota dysbiosis (summarized in Table 1). The potential gut-targeting glucose-lowering treatment strategies are now emerging, so further longitudinal and interventional studies in preclinical and clinical are needed to fully elucidate the potential mechanism of gut microbiota in T2DM and its potential use in the prevention and treatment of T2DM. We expect in-depth studies providing the basis for the development of novel antidiabetic drugs that target gut microbiota in the future. In conclusion, the modulation of gut microbiota is increasingly regarded as promising targets to improve glucose metabolism and treat T2DM. The development of novel drug presumably requires long and painstaking work with no scope for shortcuts.

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## Disclosure

The authors declare no conflicts of interest.

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