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Gut microbiota and its metabolites regulate insulin resistance: traditional Chinese medicine insights for T2DM

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The gut microbiota is closely associated with the onset and development of type 2 diabetes mellitus (T2DM), characterized by insulin resistance (IR) and chronic low-grade inflammation. However, despite the widespread use of first-line antidiabetic drugs, IR in diabetes and its complications continue to rise. The gut microbiota and its metabolic products may promote the development of T2DM by exacerbating IR. Therefore, regulating the gut microbiota has become a promising therapeutic strategy, with particular attention given to probiotics, prebiotics, synbiotics, and fecal microbiota transplantation. This review first examines the relationship between gut microbiota and IR in T2DM, summarizing the research progress of microbiota-based therapies in modulating IR. We then delve into how gut microbiota-related metabolic products contribute to IR. Finally, we summarize the research findings on the role of traditional Chinese medicine in regulating the gut microbiota and its metabolic products to improve IR. In conclusion, the gut microbiota and its metabolic products play a crucial role in the pathophysiological process of T2DM by modulating IR, offering new insights into potential therapeutic strategies for T2DM.

KEYWORDS

type 2 diabetes mellitus, gut microbiota, gut microbiota metabolites, insulin resistance, traditional Chinese medicine

1 Introduction

Type 2 Diabetes Mellitus (T2DM) is a metabolic disorder that accounts for 90–95% of diabetes cases and is characterized by insulin resistance (IR) (American Diabetes Association, 2015). It is associated with an increased risk of complications due to factors such as hyperglycemia, IR, low-grade inflammation, and accelerated atherosclerosis (Schlienger, 2013). The Global Burden of Disease (GBD) Study 2021, published by The Lancet, shows that in 2021, there were 529 million people worldwide living with diabetes, of which 96.0% had type 2 diabetes (T2DM). It is projected that by 2025, the prevalence of T2DM will increase from 5.9% in 2021 to 9.5%, affecting more than 1.27 billion people (GBD 2021 Diabetes Collaborators, 2023). Diabetes-related macrovascular diseases and microvascular complications, due to their high incidence, disability, and mortality rates, are significant contributors to the global health burden (Emerging Risk Factors Collaboration et al., 2010; Barrett et al., 2017). IR and chronic inflammation are key factors influencing T2DM treatment. Insulin receptors are widely distributed throughout the body, and insulin signaling primarily occurs in skeletal muscle, liver, and white adipocytes. IR is a pathological condition characterized by reduced insulin response in target tissues (mainly muscle, liver, and adipose

tissue), leading to imbalances in glucose, fat, and protein metabolism (Samuel and Shulman, 2012; Petersen and Shulman, 2018).

The pathogenesis of IR in T2DM involves multiple factors, with genetics, age, gender, diet, environment, and occupation being significant risk factors (Kautzky-Willer et al., 2016; Cole and Florez, 2020; Liu et al., 2023). Recent studies have shown that the gut microbiota is a key factor in developing IR. The gut microbiota regulates signaling pathways that affect energy metabolism through the production of metabolites and interactions with the host's intestinal cells (Lee and Lee, 2020). A reduction in gut bacterial diversity (the number or richness of bacterial species) has been associated with IR, obesity, elevated lipid levels, and increased inflammation (Le Chatelier et al., 2013). Gut microbiota also produces metabolites such as short-chain fatty acids (SCFAs), bile acids (BAs), trimethylamine N-oxide (TMAO), indole derivatives, and lipopolysaccharides (LPS), which participate in insulin signaling and induce the occurrence of T2DM through mechanisms such as IR, bile acid metabolism, lipid metabolic disorders, and endotoxemia (Gurung et al., 2020; Scheithauer et al., 2020; Zhang Y. et al., 2020; Wu et al., 2023). Modulating the gut microbiota and its metabolites can improve the effects of T2DM and underlying mechanisms (Jiang et al., 2024). Probiotics can prevent high-fat-diet (HFD) induced glucose intolerance and hyperglycemia by improving IR (Won et al., 2021). Fecal microbiota transplantation (FMT) has become an effective strategy for treating metabolic diseases, and fecal bacteria from individuals with normal blood glucose levels may represent a promising approach for treating T2DM (Zhang P. P. et al., 2020). Many herbs or their active compounds have therapeutic effects on T2DM by improving the gut microbiota structure, increasing beneficial bacteria and butyrate concentration in the gut, and inhibiting opportunistic pathogens (Xu et al., 2020; Yang X. et al., 2021). Additionally, dietary and exercise interventions can elevate bifidobacteria, improve SCFA levels, lower blood glucose, and enhance insulin sensitivity (Ojo et al., 2020; Zaharieva et al., 2020).

Therefore, investigating the role of the gut microbiota and its metabolites in developing IR could offer new strategies for preventing and treating T2DM. This approach can potentially improve IR and reduce the incidence of related metabolic and cardiovascular complications. In this review, we summarize the impact of the gut microbiota and its metabolites on the pathogenesis of IR and the mechanisms by which traditional Chinese medicine (TCM) regulates gut microbiota and its metabolites to improve IR (Figure 1).

2 The correlation between gut microbiota and insulin resistance

2.1 Mechanisms of gut dysbiosis and insulin resistance

The gut microbiota refers to the microbial community in the gastrointestinal tract, primarily consisting of bacteria, fungi, viruses, and archaea. Studies have shown that the number of gut microbiota is approximately 10 times greater than the number of human cells, with bacteria accounting for more than 90%, mainly including phyla such as Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria (Sender et al., 2016). The composition and diversity of an individual's gut microbiota are influenced by various factors, including diet, lifestyle, genetics, and environmental exposures, collectively shaping the microbial ecosystem. The normal gut microbiota plays a crucial role in metabolism, immune response regulation, and antimicrobial protection (Rinninella et al., 2019; Zhang, 2022). The hallmark of gut dysbiosis is the reduced diversity and abundance of bacteria and fungi, particularly those associated with functional impairments and various pathological conditions (Sun et al., 2019; Zeng et al., 2024). Extensive research has revealed a significant association between changes in the gut microbiota composition and the development of diabetes. Gut microbiota dysbiosis is characteristic of T2DM, with a reduced abundance of butyrate-producing bacteria and increased opportunistic pathogens (Qin et al., 2012). Specifically, the abundance of *Bifidobacterium* is significantly correlated with T2DM. Studies have shown a marked decrease in the total *Bifidobacterium* and *Bifidobacterium adolescentis* in diabetic groups (Xu et al., 2012). Daily supplementation of *Bifidobacterium adolescentis* restores the gut microbiota homeostasis, increases the abundance of SCFA-producing microbes, alleviates inflammation, and lowers blood glucose levels (Moroti et al., 2012; Qian et al., 2022). The presence of *Bifidobacterium, Bacteroides, Faecalibacterium, Akkermansia*, and *Roseburia* is negatively correlated with T2DM, while *Ruminococcus, Fusobacterium*, and *Blautia* show a positive correlation with T2DM (Gurung et al., 2020). Recent research has found that *Alistipes indistinctus* and *Alistipes finegoldii* are linked to IR and insulin sensitivity. These bacteria exhibit distinct carbohydrate metabolism patterns and have been shown to improve IR in mouse models by altering the host's phenotype (Takeuchi et al., 2023). These findings underscore the critical role of microbiota composition in influencing metabolic disorders.

2.2 The role of microbiome therapy in T2DM

The potential for modifying the gut microbiota through dietary interventions to manage T2DM is increasingly recognized. Several beneficial bacterial genera, such as *Allobaculum*, *Bacteroides*, *Blautia*, *Butyricoccus*, and *Phascolarctobacterium*, which are characterized by SCFA production, are associated with the prevention of obesity and IR in HFD-fed rats (Zhang et al., 2012, 2015). Long-term HFD leads to T2DM and disrupts the gut microbiota, with an increase in the relative abundance of *Alistipes* and *Prevotella* and a decrease in the relative abundance of *Butyricimonas*, *Ruminococcus*, and *Bifidobacterium* (Lee et al., 2022; Zhang H. et al., 2024). High-fiber diets improve glucose homeostasis in T2DM by increasing the abundance of *Lactobacillus, Bifidobacterium*, and *Akkermansia* while decreasing the abundance of Desulfovibrio, Klebsiella and other opportunistic pathogens, but it is crucial to evaluate the long-term sustainability and practical applicability of such dietary changes across diverse populations (Chen et al., 2023; Chang et al., 2024). Furthermore, FMT has been used to demonstrate the role of gut microbiota in IR. For example, transferring the fecal microbiota of obese or IR individuals to germ-free mice results in the development of IR, while microbiota from lean, healthy individuals does not (Ridaura et al., 2013). FMT combined with lifestyle interventions or metformin has been shown to improve the gut microbiota in T2DM patients and enhance parameters such as blood lipids, IR, and body mass index (Ng et al., 2022; Wu et al., 2022). While these findings

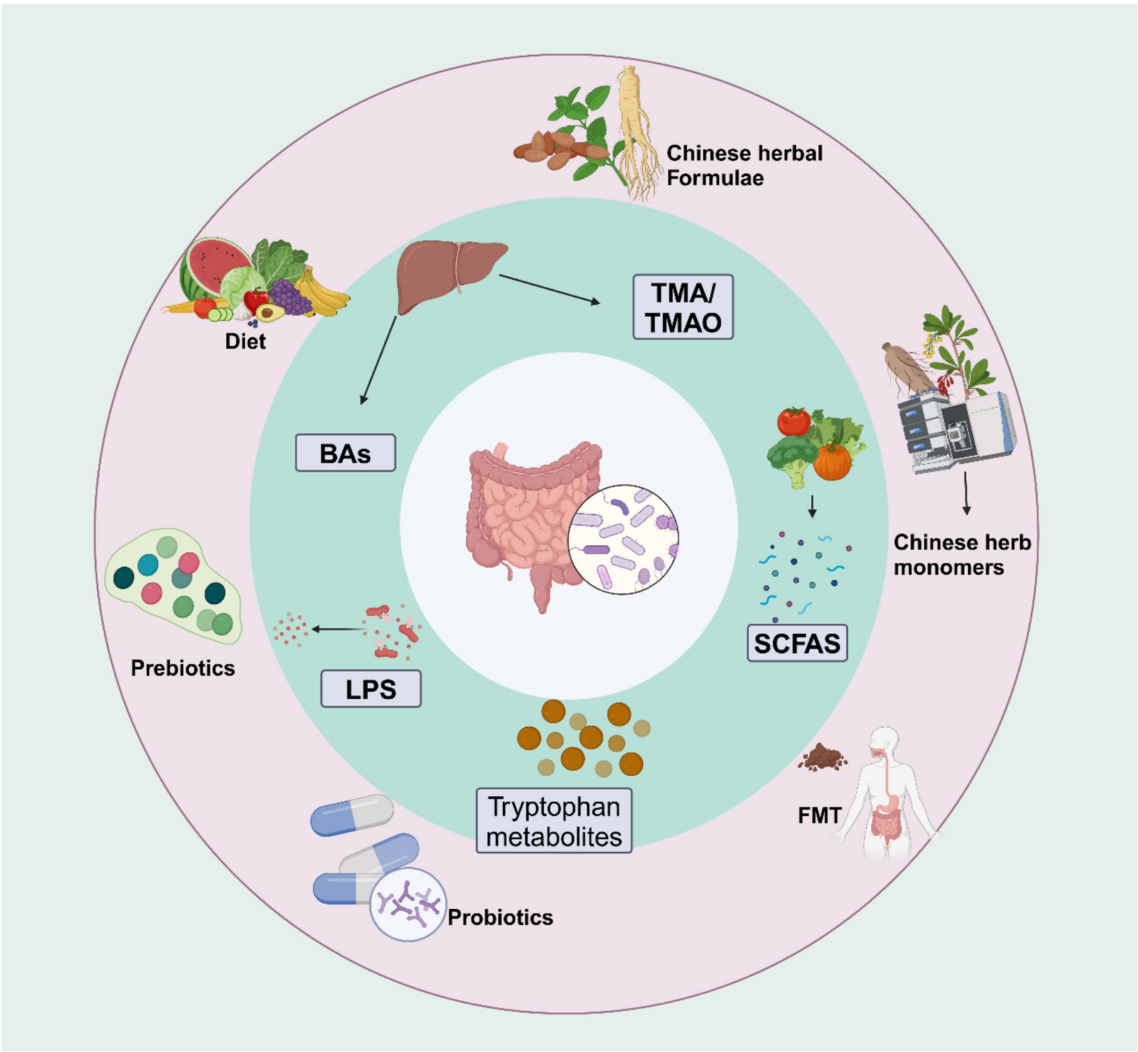

FIGURE 1
Gut microbiota metabolites and their role in improving insulin resistance: Gut microbiota metabolites such as BAs, SCFA, LPS, TMO, and tryptophan metabolites, in combination with different interventions like diet, FMT, prebiotics, probiotics, Chinese herb monomers, and Chinese herbal formulas, can regulate the gut microbiota and its metabolites to improve insulin sensitivity. Created with BioRender.com.

suggest a beneficial role for FMT in restoring microbiota balance and improving metabolic health, the long-term safety and efficacy of FMT require further investigation.

In addition, probiotics also hold promise as a therapeutic tool for T2DM management. *Lactobacillus rhamnosus* downregulates glucose-6-phosphatase expression, reduces fasting blood glucose, and improves glucose tolerance (Farida et al., 2020). *Lactiplantibacillus* and *Lactobacillus plantarum* inhibit intestinal enzymes and increase the concentration of hepatic antioxidant enzymes (Li et al., 2016; Lee et al., 2021; Narang et al., 2024). Several clinical trials have demonstrated that the consumption of probiotics reduces lipids and blood glucose (Tonucci et al., 2017; Hsieh et al., 2018; Mirjalili et al., 2023) and enhances glycemic management by increasing butyrate production to act as an adjunct to metformin (Palacios et al., 2020). However, the overall effectiveness of probiotics in managing T2DM may vary depending on the strain used and the individual's baseline microbiota composition. Considering the patient's unique microbiota profile, personalized approaches may enhance the therapeutic outcomes of probiotic interventions in T2DM management (Xiao et al., 2023). Prebiotics, which selectively promote the growth of beneficial microbes, offer an additional strategy to modulate the gut microbiome and improve insulin resistance. Resistant starch, for example, alters the selective microbiota composition to produce starch-degrading enzymes, promotes the production of gut metabolites, and enhances gut barrier function, thus preventing T2DM and obesity through the gut microbiome (Liu H. et al., 2020). Despite some promising findings, not all prebiotics, such as galacto-oligosaccharides, have significantly improved glucose and lipid metabolism, highlighting the need for more targeted prebiotic interventions (Wan et al., 2023). In conclusion, while modulation of the gut microbiota presents a promising approach for managing T2DM, it is essential to recognize that other factors, including diet, lifestyle, genetics, and environmental exposures, play critical roles in shaping the microbiota and influencing insulin resistance.

3 Gut microbiota metabolites regulate insulin sensitivity

IR is a key factor in the development of metabolic diseases such as T2DM, obesity, and cardiovascular diseases, involving multiple molecular mechanisms, particularly dysfunction of the insulin receptor signaling pathway, abnormalities in insulin receptor substrates (IRS), and chronic low-grade inflammation (Samuel and Shulman, 2012; Petersen and Shulman, 2018). The insulin receptor is a transmembrane receptor that, upon binding with insulin, triggers a series of intracellular signaling events through IRS. It plays a central role in mediating insulin's effects on glucose uptake, metabolism, and cell growth (Goldfine et al., 1973; Kolterman et al., 1981). In IR, insulin receptor signaling is often impaired due to receptor defects, reduced phosphorylation, or functional changes of IRS. These defects result in weakened downstream signaling pathways, crucial for glucose transport and metabolic regulation (Kolterman et al., 1981; Schultze et al., 2012; Kearney et al., 2021). Additionally, chronic low-grade inflammation has become a critical factor in the development of IR (Shoelson et al., 2006; Olefsky and Glass, 2010). Inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) interfere with insulin receptor signaling, further promoting the development of IR by disrupting key metabolic processes (Samokhvalov et al., 2009; Chirivi et al., 2022; Li A. et al., 2022). Understanding these potential mechanisms is crucial for identifying therapeutic targets to alleviate or reverse IR and its associated diseases.

3.1 Regulation of insulin receptor and substrates

3.1.1 SCFAs

SCFAs, key products of gut microbiota metabolism, are the end products of fermenting indigestible food by intestinal microbes, mainly anaerobes in the cecum and colon (Macfarlane and Macfarlane, 2003). Some SCFAs are absorbed by the colon epithelium through H- or sodium-dependent monocarboxylate transporters, providing energy for colon cells (Ruppin et al., 1980). The remaining SCFAs enter circulation via the liver and portal vein, influencing the development of conditions like obesity, IR, and T2DM (Morrison and Preston, 2016). SCFAs significantly affect energy homeostasis by regulating key metabolic tissues, including adipose tissue, skeletal muscle, and the liver (Canfora et al., 2015). Studies have shown that increasing the acetate concentration in the systemic circulation may reduce lipolysis and free fatty acids (FFA) levels, thereby improving insulin sensitivity (Fernandes et al., 2012). Butyrate, as a dietary supplement, increases the phosphorylation of IRS-1 protein at Tyr632 and Akt at Thr308, preventing IR (Gao et al., 2009). meta-analysis found that different SCFA interventions reduced blood glucose in diabetic mice, with butyrate being the most effective intervention (Pham et al., 2024; Zheng et al., 2024). It can also improve AMP-activated protein kinase (AMPK) phosphorylation, increase GLP-1 secretion, and enhance insulin sensitivity (Gonzalez et al., 2019). Propionate and butyrate inhibit lipolysis and *de novo* lipogenesis, suppress acetyl-CoA carboxylase, and increase insulin-stimulated glucose uptake in primary rat adipocytes (Heimann et al., 2014). Clinical trials indicate that oral butyrate supplementation increases insulin sensitivity (Bouter et al., 2018), and long-term intake of acetate and butyrate helps improve glucose metabolism by delaying gastric emptying and intestinal absorption (Wijdeveld et al., 2023). However, some studies have found that acetate, propionate, butyrate, and mixed SCFA do not affect human blood glucose and insulin (Cherta-Murillo et al., 2022). Therefore, further studies are needed to determine the effect of SCFA on glycemic control.

The effects of SCFAs are not limited to directly influencing insulin sensitivity; they also activate specific G protein-coupled receptors (GPCRs), affecting adipocytes, immune cells, and others. Free fatty acid receptors (FFARs) belong to the GPCR family (100), with FFAR2 and FFAR3 being activated by SCFAs. This activation increases the intestinal hormones Peptide YY (PYY) and Glucagon-like peptide-1 (GLP-1), which regulate insulin signaling (Briscoe et al., 2003; Brown et al., 2003). In human and rat colon samples, SCFA receptors FFAR2 and FFAR3 are colocalized with PYY-containing enteroendocrine L cells (Karaki et al., 2008; Tazoe et al., 2009). The absence of FFAR2 and FFAR3 in pancreatic β-cells leads to increased insulin secretion and improved glucose tolerance, while FFAR2 and FFAR3 knockout mice show decreased colon PYY expression and impaired systemic glucose tolerance (Tolhurst et al., 2012; Tang et al., 2015). FFAR2 and FFAR3 mediate SCFA-induced enhancement of GLP-1 secretion. Without FFAR2 and FFAR3, SCFA-triggered GLP-1 secretion is reduced, and glucose tolerance is impaired (Tolhurst et al., 2012). SCFAs inhibit insulin signaling in adipocytes by activating FFAR2, thereby reducing fat accumulation and promoting the metabolism of lipids and glucose in other tissues (Kimura et al., 2013). Propionate and valerate activate FFAR3 to increase insulin-stimulated glucose uptake in adipocytes and skeletal muscle cells (Han et al., 2014).

3.1.2 BAs

In addition to SCFAs, BAs are also considered key factors in regulating insulin sensitivity. BAs exert critical physiological functions in the intestine through microbial metabolic conversion. Primary bile acids are synthesized in the liver. In contrast, the gut microbiota produces secondary bile acids, participating in multiple metabolic processes such as fat digestion and absorption, cholesterol metabolism, and immune regulation (Wahlström et al., 2016; Guzior and Quinn, 2021). IR is positively correlated with hyperbileacidemia in diabetic populations (Sun et al., 2016), and increased total serum BAs are associated with impaired systemic insulin sensitivity, β-cell dysfunction, and elevated glucagon levels in T2DM (Wang X. H. et al., 2020). There is a relationship between elevated BA levels and impaired insulin sensitivity. BAs exert their effects by activating G protein-coupled BA receptor 5 (TGR5) and farnesoid X receptor (FXR). Studies have found that activation of TGR5 in the intestine promotes the transport of BAs, improves glucose metabolism, and enhances lipolysis and energy metabolism (Li et al., 2023). In obese mice lacking TGR5, inflammation in adipose tissue is enhanced, and insulin-stimulated AKT phosphorylation is reduced, leading to decreased insulin responsiveness in adipose tissue and exacerbating IR (Perino et al., 2014). This underscores the critical importance of TGR5 in maintaining metabolic balance.

On the other hand, FXR activation appears to have a somewhat protective effect, with studies indicating that it induces the secretion of fibroblast growth factors in the intestine, which ultimately leads to changes in BA composition. This, in turn, helps reduce obesity and insulin resistance (IR) while encouraging adipose tissue browning

(Fang et al., 2015). After FXR knockout, the expression of inflammatory markers in adipose tissue macrophages and mature adipocytes decreases, protecting mice from high blood glucose and IR induced by HFD (Dehondt et al., 2023). FXR knockout mice show impaired glucose tolerance and reduced insulin sensitivity, suggesting that BA activation of FXR may improve IR by inhibiting hepatic SREBP-1c expression and/or modulating glucose-induced lipogenesis (Lefebvre et al., 2009). In sum, through their receptors TGR5 and FXR, BAs appear to exert a profound influence on glucose homeostasis, fat metabolism, and the broader metabolic landscape. As research advances, novel therapeutic approaches targeting these pathways for treating obesity, diabetes, and insulin resistance may emerge.

3.1.3 TMAO

Another crucial metabolic product is trimethylamine (TMA), primarily produced by the bacterial metabolism of substrates such as phosphatidylcholine, carnitine, and betaine in the colon. TMA is oxidized in the liver by flavin monooxygenase 3 (FMO3) to form trimethylamine N-oxide (TMAO), which is associated with atherosclerosis, cholesterol reverse transport, and glucose and lipid metabolism (Koeth et al., 2013; Zhao Z. H. et al., 2019; Kong et al., 2024). One striking aspect of TMAO is its dynamic regulation of insulin sensitivity. Its levels fluctuate based on diet and an individual's gut microbiome composition. By reducing red meat consumption and increasing plant-based foods, individuals can reduce the production of oxidized TMA and lower the risk of developing T2DM (Heianza et al., 2019; Huang et al., 2024). Higher levels of TMAO are associated with an increased risk of T2DM, possibly through effects on IR, inflammation, or lipid metabolism (Li S. Y. et al., 2022; Huang et al., 2024). The impact of TMAO on β-cell function is particularly alarming. Elevated levels of TMAO have been shown to impair glucose-stimulated insulin secretion, reduce β-cell mass, and worsen glucose tolerance, all of which can contribute to the progression of diabetes (Kong et al., 2024). In this light, TMAO's role in the pathophysiology of diabetes becomes even more evident.

TMAO levels are influenced by FMO3 expression. Increased liver FMO3 activity may reflect hepatic IR, as FMO3 is primarily responsible for converting TMA into TMAO (DiNicolantonio et al., 2019). FMO3 is upregulated in obese/IR male mice, and FMO3 knockdown improves glucose tolerance by reducing endoplasmic reticulum cholesterol, inducing SREBP-2, thereby inhibiting FoxO1 (Miao et al., 2015). Changes in FMO3 activity could be an important mechanism in metabolic diseases, and modulating FMO3 activity may represent a novel strategy for improving these metabolic disorders. In summary, TMAO's role in metabolic regulation is multifaceted, with its production being influenced by diet, microbiome composition, and liver function (Figure 2).

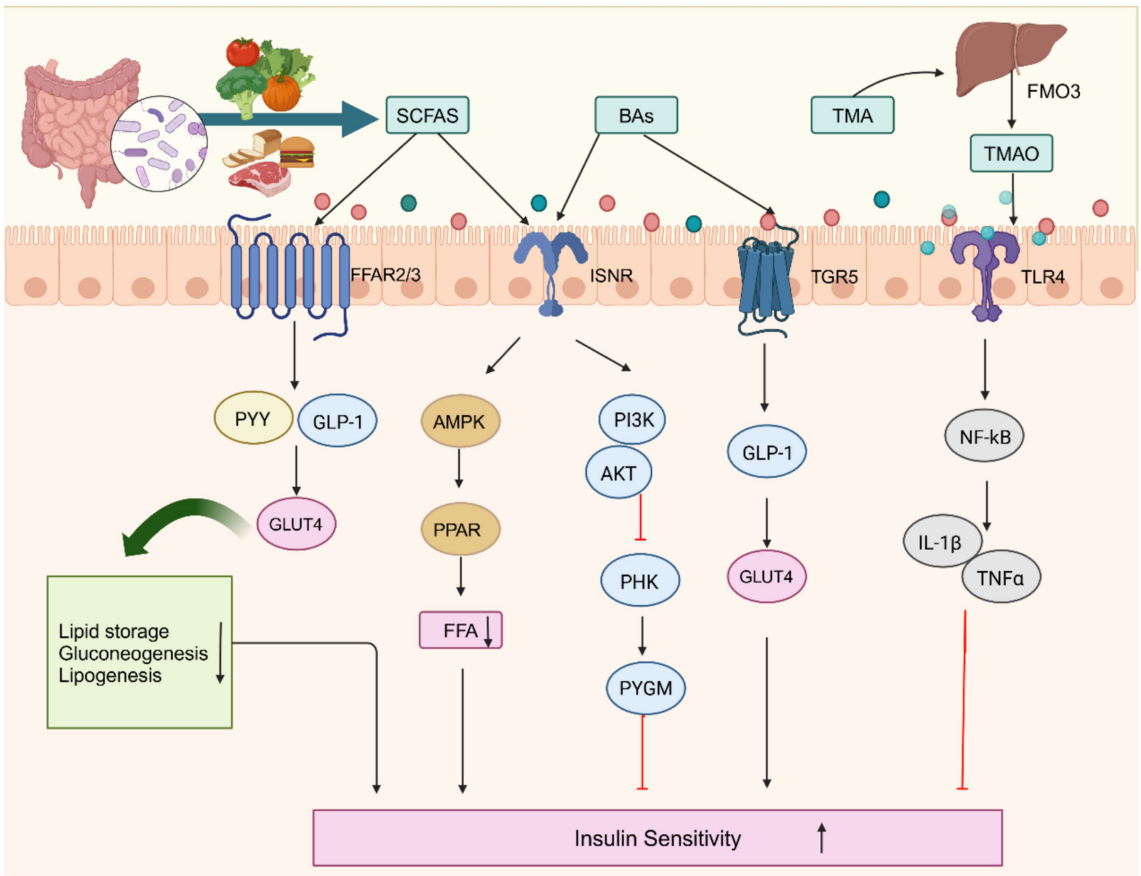

FIGURE 2
Gut microbiota metabolites regulate insulin substrates and receptors to modulate insulin resistance. ISNR, insulin receptor; GLUT4, glucose transporter 4; PHK, Phosphorylase kinase; PYGM, Glycogen phosphorylase; PPAR, peroxisome proliferator-activated; PI3K, phosphatidylinositol 3-hydroxy kinase. Created with BioRender.com.

3.2 Regulation of chronic low-grade inflammation

3.2.1 LPS

LPS is an important component of the cell wall of Gram-negative bacteria and is known to play a significant role in IR and inflammatory responses in T2DM. Studies have shown that plasma LPS levels are positively correlated with markers of IR (Pedro et al., 2018). LPS-induced metabolic endotoxemia can lead to an increase in F4/80-positive cells in adipose tissue and an elevation in inflammatory markers, which in turn increases liver triglyceride content and exacerbates IR and fasting blood glucose levels (Cani et al., 2007). Dysbiosis induced by HFD upregulates LPS concentration, further promoting the release of pro-inflammatory cytokines such as TNF, IL-1, and IL-6, leading to systemic inflammation (Zhu et al., 2020).

LPS activates macrophages in adipose tissue and triggers the Akt–mTOR pathway. Chronic, sustained inflammation activates this pathway, ultimately leading to a decline in insulin sensitivity (Toda et al., 2020). LPS also activates the cAMP/PKA pathway or the MAPK and NF-κB signaling pathways, inhibiting IκB phosphorylation, promoting the release of free fatty acids from adipose tissue, enhancing lipolysis and inflammation, thus aggravating IR (Chung et al., 2006; Hussey et al., 2012; Jung et al., 2018a, 2018b; Chirivi et al., 2022). The end result is a vicious cycle where inflammation and insulin resistance perpetuate one another, further worsening metabolic dysfunction. Furthermore, LPS impairs insulin signaling by directly downregulating the phosphorylation of IRS, phosphoinositide 3-kinase (PI3K), and Akt, thereby reducing the responsiveness of adipocytes to insulin (Samokhvalov et al., 2009; Chirivi et al., 2022). Toll-like receptor 4 (TLR-4) is a key receptor for LPS, and LPS-mediated inflammation induced by saturated fatty acids is associated with IR via TLR-4 (González et al., 2019). Through the TLR-4 signaling pathway, LPS can activate both the MAPK and NF-κB pathways, triggering inflammatory cascades that further promote insulin resistance. Interestingly, inhibiting TLR-4 expression has been shown to improve LPS-induced IR, suggesting that targeting TLR-4 may hold therapeutic potential for managing LPS-related metabolic disorders (Kim et al., 2007; Kawamoto et al., 2008; Hussey et al., 2012). Taken together, this suggests that LPS is a key player in the development of insulin resistance and systemic inflammation, which may provide new therapeutic avenues for the management of T2DM and other metabolic disorders.

3.2.2 Tryptophan metabolites

The gut microbiota plays a crucial role in metabolizing aromatic amino acids into metabolites such as tryptamine, indole, and other derivatives, either directly or through indirect pathways like the kynurenine and serotonin pathways (Dodd et al., 2017). Among these, tryptophan-derived metabolites, including serotonin, tryptamine, and indole, are closely related to IR and the development of T2DM (Alexeev et al., 2018). Studies have shown that tryptophan derivatives such as indole lactate are positively correlated with T2DM, while indole propionate esters are negatively correlated with T2DM (Qi et al., 2022). Additionally, tryptophan metabolites such as 5-hydroxyindole-3-acetic acid (5-HIAA) promote hepatic insulin signaling by directly activating the aryl hydrocarbon receptor (AhR), inhibiting the mTORC1 pathway, and alleviating IR induced by a high-fat diet (Du et al., 2024). Indole-3-pyruvic acid, acting through AhR, downregulates TNF-α in intestinal epithelial cells, further improving insulin sensitivity (Venkatesh et al., 2014, p. 4). Supplementing endogenous AhR ligands, such as tryptophan and indole-3-carbinol, can increase AhR expression in the gut, inhibit the expression of intercellular adhesion molecules and FMO3 in the liver, and reduce plasma levels of IL-6 and TNF-α, thus alleviating inflammation and IR (Liu W. C. et al., 2020). In contrast, AhR deficiency can prevent obesity, hepatic steatosis, IR, and inflammation induced by HFD (Xu et al., 2015). The supply of tryptophan directly affects the synthesis of serotonin (5-HT), and low levels of tryptophan suppress serotonin synthesis, which in turn impacts insulin sensitivity. As a key regulator of IR, prolonged injection of 5-HT can lead to impaired glucose tolerance and IR, indicating that changes in serotonin levels can directly affect the body's ability to effectively use insulin, leading to IR (Liang et al., 1999; Luo et al., 1999). Serotonin triggers inflammation and adipocyte dysfunction through the serotonin reuptake transporter in adipose tissue, serotonin receptor 2B, and tryptophan hydroxylase 1, affecting insulin sensitivity (Chen et al., 2012; Yabut et al., 2020; Choi et al., 2021) (Figure 3).

4 Traditional Chinese medicine regulates gut microbiota and its metabolites to improve insulin resistance

T2DM is associated with dysfunction of the gut microbiota and its metabolites. The current main treatment strategies for T2DM include surgery, pharmacotherapy, exercise therapy, diet, and multifactorial approaches (Magkos et al., 2020; Su et al., 2023). Among these, insulin injection therapy is the most effective method for controlling blood glucose, but insulin injections increase the risk of cardiovascular complications (Home et al., 2014). Currently, first-line hypoglycemic drugs are the primary treatment for T2DM; however, their use is always accompanied by side effects, including weight gain, hypertension, and heart failure (Verbrugge, 2017; Davies et al., 2018). Research has shown that statins reduce blood GLP-1 levels in a microbiota-dependent manner (via the Clostridium bile acid axis), thereby worsening IR (She et al., 2024). TCM compensates for the limitations of first-line hypoglycemic drugs by reducing their side effects. *Lycium barbarum* L. increases the abundance of *Akkermansia muciniphila*, which helps alleviate liver damage by regulating the gut-liver axis (Lu et al., 2023, 2024). Clinical trials have confirmed that metformin and TCM formulas significantly improve blood glucose and lipid levels (Lu et al., 2023, 2024). However, TCM formulas have a more pronounced effect on improving insulin resistance and plasma triglyceride levels, and they have a greater impact on the gut microbiota, particularly increasing the abundance of *Blautia* spp. and *Faecalibacterium* spp., indicating that the gut microbiota is an important target for the treatment of metabolic diseases (Tong et al., 2018; Xu et al., 2022). Therefore, regulating the gut microbiota and its metabolic products to reduce the adverse risks of drug treatments represents a new therapeutic approach for T2DM. TCM's regulation of the gut microbiota shows significant effects in the treatment of T2DM, and the gut microbiota may play a crucial role in the therapeutic effects of TCM (Wang J. et al., 2020).

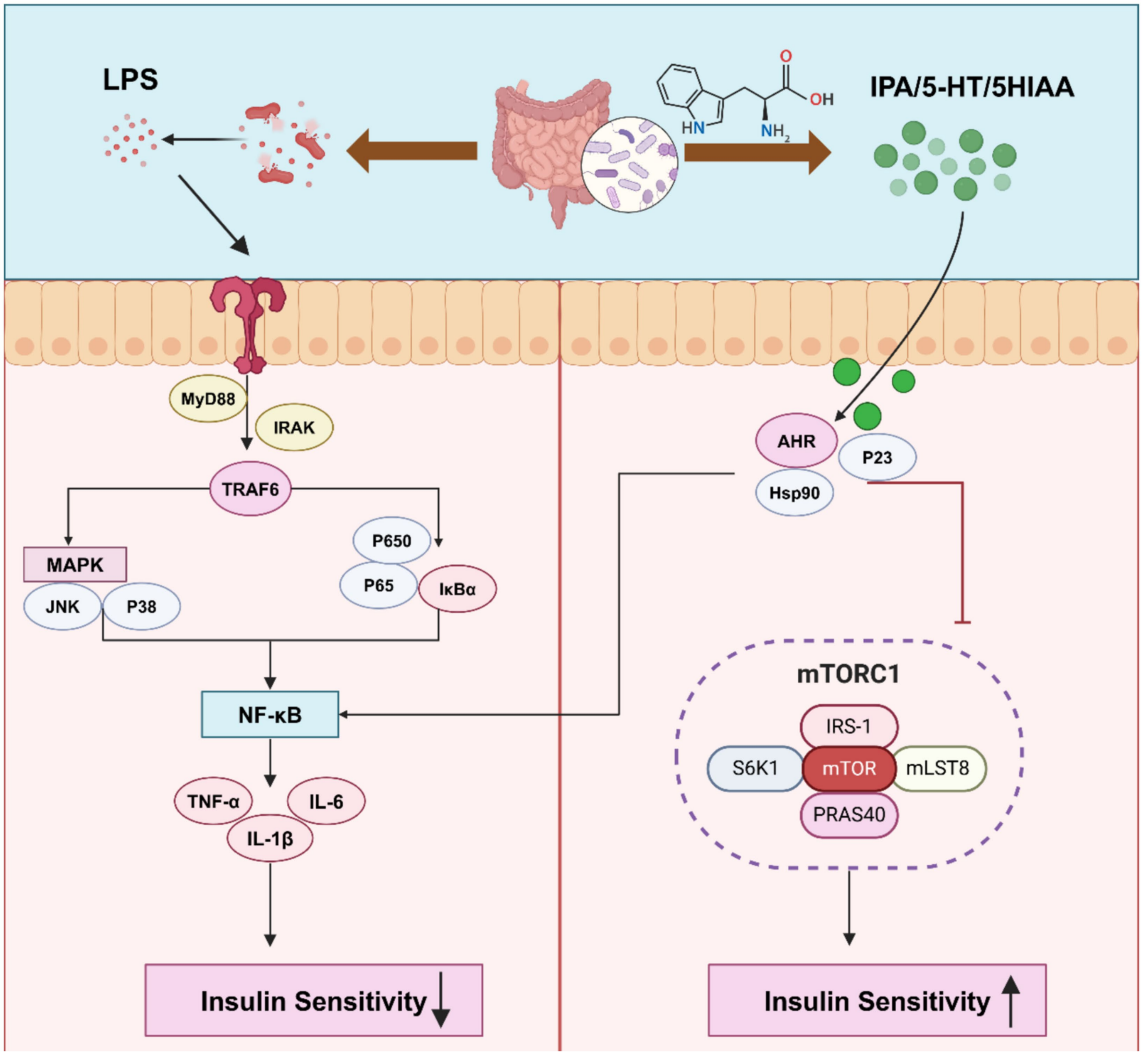

FIGURE 3
Gut microbiota metabolites participate in the regulation of chronic inflammation and insulin resistance. MyD88, myeloid differential protein-88; IRAK, interleukin receptor-associated kinases; TRAF6, tumor necrosis factor receptor-related molecules; Hsp90, heat shock protein 90; S6K1, Ribosomal protein S6 kinase; PRAS40, pras40 monoclonal antibody. Created with BioRender.com.

4.1 Chinese herb monomers

The main components of Chinese herb monomers include polysaccharides, flavonoids, alkaloids, and saponins. These components regulate the abundance of gut microbiota, improve glucose metabolism, and enhance insulin sensitivity, thereby providing auxiliary treatment for diabetes (Luo et al., 2020; Bhambhani et al., 2021; Dias et al., 2021; Zhao et al., 2023). A large number of animal studies have found that TCM monomers, such as Ganoderma lucidum polysaccharides, Cyclocarya paliurus polysaccharides, and licochalcone A, can regulate the abundance of gut microbiota species (increasing *Blautia*, *Bifidobacterium*, and *Parabacteroides*, and decreasing *Aerococcus*, *Ruminococcus*, and *Enterococcus*), reduce blood sugar levels, and improve insulin resistance and glucose tolerance (Chen et al., 2020; Yao et al., 2020; Luo et al., 2023). TCM monomers not only directly regulate changes in the gut microbiota, but also improve insulin resistance by influencing the metabolic products of the gut microbiota. Coix seed polysaccharides, *Lycium barbarum* polysaccharides, and Baicalin regulate the gut microbiota composition, particularly increasing the bacteria that produce SCFAs, thereby improving abnormal glucose and lipid metabolism and showing hypoglycemic effects (Ju et al., 2019; Xia et al., 2021; Yang Y. et al., 2021). Cyclocarya paliurus polysaccharides and Astragalus membranaceus polysaccharides increase SCFA-producing bacteria, promote SCFA production, and upregulate GLP-1 and PYY expression to improve glucose tolerance (Yao et al., 2020; Song et al., 2022). Red ginseng extracts improve glucose metabolism and promote lipolysis, and energy metabolism by activating TGR5 in the gut, significantly alleviating obesity and IR (Li et al., 2023).

Animal studies have found that Baicalin can improve the balance of the gut microbiota, increase the number of bacteria-producing SCFAs, and improve glucose and lipid metabolism (Ju et al., 2019). Baicalein 7-O-glucuronide inhibits FXR-CYP7A1-mediated bile acid signaling in T2DM mice, reducing lipid

accumulation in the liver and bile, thus exerting anti-diabetic effects (Yan et al., 2022). Integrating Mendelian randomization from a genetic perspective identified eight potential targets for Baicalin in the treatment of T2DM. The expression of ANPEP, BECN1, HNF1A, and ST6GAL1 increases the risk of T2DM, while the expression of PGF, RXRA, SREBF1, and USP7 lowers the risk of T2DM (Liang et al., 2024). Ginsenoside Rb1 reverses gut microbiota dysbiosis in diabetic mice, alters the levels of free fatty acids in fecal metabolites (Zhou et al., 2023), increases the abundance of *Akkermansia* spp., significantly elevates long-chain fatty acid content, improves HFD-induced dyslipidemia, and enhances insulin sensitivity (Yang X. et al., 2021; Zou et al., 2022). Clinical trials have found that diabetic patients metabolize Ginsenoside compound K slower than healthy subjects. The differences in the biotransformation ability of Ginsenoside compound K in the gut microbiota of diabetic patients and healthy subjects affect its anti-diabetic efficacy (Huang et al., 2023). The gut microbiota may enhance the efficacy of ginsenosides by influencing their biotransformation and altering the pharmacokinetics of individual ginsenosides (Kim et al., 2020, 2023). In conclusion, TCM monomers can improve insulin resistance by regulating the gut microbiota and its metabolic products (Table 1), while the gut microbiota, in turn, increases the hypoglycemic effect of these monomers by affecting their biotransformation capacity.

4.2 Chinese herbal formulae

Chinese herbal formulas are the primary prescription forms used in TCM clinical applications. Gegen Qinlian Decoction (GQD) is a widely studied anti-hyperglycemic herbal prescription. Animal studies have found that GQD regulates the gut microbiota, improves bile acid metabolism, activates the TRG5/cAMP/PKA/CREB signaling pathway, and stimulates GLP-1 secretion (Liu et al., 2024). It increases the proportion of bacteria that produce SCFAs and possess anti-inflammatory properties while decreasing the proportion of conditionally pathogenic bacteria associated with diabetes phenotypes. These effects regulate the structure of the gut microbiota, lower blood glucose levels, and reduce inflammatory cytokine levels (Tian et al., 2021). Animal experiments suggest that GQD can improve hyperglycemia and protect pancreatic function by regulating the gut microbiota and its metabolic products. Clinical trials have confirmed that, compared to metformin alone, GQD and metformin have a synergistic effect on blood glucose control (Ryuk et al., 2017; Tan et al., 2023). GQD mainly improves type 2 diabetes by increasing the abundance of *Faecalibacterium*, elevating short-chain fatty acid levels, and reducing serum inflammation-related markers, thus alleviating metabolic disorders and inflammation (Gao et al., 2024). Therefore, GQD shows potential efficacy and safety in enhancing glucose and lipid metabolism and alleviating insulin resistance, making it a promising supplementary therapy for T2DM.

Shenzhu tiaopi granule (SZTP) can increase the relative abundance of *Lactobacillus* in the intestines of T2DM rats, reduce the relative abundance of *Allobaculum* and *Desulfovibrionaceae*, improve blood glucose and lipid levels in T2DM rats (Zhao J. et al., 2019), decrease LPS and IL-1β levels, increase the abundance of *Intestinimonas*, reduce the abundance of *Eubacterium coprostanoligenes*, regulate bile acid biosynthesis and cholesterol metabolism, and alleviate hyperglycemia (Zhao and Fang, 2024). Clinical studies have confirmed that SZTP, combined with lifestyle interventions, reduces the conversion rate from impaired glucose tolerance (IGT) to diabetes and increases the conversion rate from IGT to normal blood glucose levels (Fang et al., 2014). JinQi Jiangtang Tablet (JQJT) increases *Akkermansia*, decreases *Desulfovibrio*, increases the concentrations of acetate, propionate, and butyrate, enhances intestinal barrier function, reduces host inflammation, improves insulin resistance in T2DM, regulates gut microbiota, and promotes SCFA production (Cao et al., 2019). Clinical trials have found that after JQJT intervention, the risk of progression from prediabetes to diabetes was 0.58 times lower than in the placebo group, and the likelihood of reaching normal blood glucose levels was 1.41 times higher than in the placebo group. After 12 months of intervention, the percentage of patients with normalized blood glucose was 41.8%, compared to 27.8% in the control group (Wang et al., 2017). Chinese Herbal Formulae Tianqi treatment for 12 months reduced diabetes risk by 32.1%, and no serious adverse events occurred in the trial (Lian et al., 2014). Qinglian Hongqu decoction and JiangTang Sanhuang pill (JTSH) activate the FXR/FGF15 and TGR5/GLP-1 signaling pathways in the gut, reducing lipid accumulation and insulin resistance (Tawulie et al., 2023; Zhang Z. et al., 2024). A retrospective cohort study found that 1-year treatment with JTSH tablets reduced the risk of poor glycemic control by 17.00%. T2DM patients were satisfied with the anti-diabetic effect of JTSH tablets, which significantly lowered blood glucose and insulin resistance and improved pancreatic beta-cell function (Shao et al., 2022). The above animal experiments and clinical trials suggest that Chinese Herbal Formula can significantly reduce the incidence of T2DM in subjects with impaired glucose tolerance, making it an effective intervention for preventing and treating type 2 diabetes (Table 2).

5 Limitations and research prospects of TCM treatment

Specific TCM monomers have progressed in regulating gut microbiota to treat diabetes. For example, baicalin and ginsenosides can improve gut microbiota structure, enhance insulin sensitivity, and regulate glucose and lipid metabolism (Zheng et al., 2019; Sun et al., 2021). However, research has mainly focused on animal experiments and preliminary clinical trials, and clinical translation still faces challenges significantly since the diversity and complexity of gut microecology may vary considerably between humans and animals (Amato, 2016; Cao et al., 2020). The biotransformation capabilities of different TCM monomers and the mechanisms of their metabolites are not yet precise, and further research is needed on the differences in individual responses to gut microbiota, as well as the relationship between drug dosage and effectiveness (Kim et al., 2020; Deng et al., 2024). Although TCM formulas can regulate gut microbiota and improve diabetes symptoms, their molecular mechanisms still require in-depth exploration. In addition, TCM formulas are

TABLE 1 Chinese herb monomers.

Chinese herb monomers	Research subjects	Therapeutic mechanisms and targets	References
Astragalus membranaceus	T2DM mice models	Increases SCFA-producing bacteria, promotes SCFA production, and upregulates GLP-1 and PYY expression to improve glucose tolerance	Song et al. (2022)
Baicalein 7-O-glucuronide	T2DM mice models	Inhibits FXR-CYP7A1-mediated bile acid signaling in T2DM mice, reducing lipid accumulation in the liver and bile, thus exerting anti-diabetic effects	Yan et al. (2022)
Baicalin	T2DM mice models	Increases the number of bacteria producing SCFAs and improves glucose and lipid metabolism	Ju et al. (2019)
Berberine	Zucker diabetic fatty rats	Slows the progression of prediabetes to T2DM by enhancing GLP-2, improving intestinal permeability, and modifying the gut microbiota structure	Wang et al. (2021)
Coix seed polysaccharides	T2DM mice models	Modulates gut microbial composition, especially SCFA-producing bacteria, activates the IGF1/PI3K/AKT signaling pathways, and exhibits hypoglycemic efficacy	Xia et al. (2021)
Cyclocarya paliurus polysaccharides	T2DM rat models	Increase key bacterial species that prevent diabetes, such as *Ruminococcaceae* UCG-005, and improve nutritional metabolism and energy metabolism	Li et al. (2021)
Cyclocarya paliurus polysaccharides	T2DM rat models	Increases the production of SCFAs both *in vivo* and *in vitro*, promotes the production of SCFAs and upregulating SCFA-GLP1/PYY-associated sensory mediators	Yao et al. (2020)
Ganoderma lucidum polysaccharides	T2DM rat models	Reduce the abundance of *Aerococcus*, *Ruminococcus*, *Corynebacterium*, and *Proteus*, while increasing the levels of *Blautia*, *Dehalobacterium*, *Parabacteroides*, and *Bacteroides*. These changes restore amino acid, carbohydrate, inflammation, and nucleotide metabolism to improve glucose metabolism	Chen et al. (2020)
Ginsenoside Rb1	T2DM mice models	Reverses gut microbiota dysbiosis in diabetic mice and alters the levels of free fatty acids in fecal metabolites	Zhou et al. (2023)
Ginsenoside Rb1	Obesity mice models	Increases the abundance of *Akkermansia* spp., significantly elevates long-chain fatty acid content, improves HFD-induced dyslipidemia, and enhances insulin sensitivity	Yang X. et al. (2021) and Zou et al. (2022)
Ginsenoside Ro	Obesity mice models	Promotes GLP-1 secretion and energy expenditure, improving high-fat diet-induced obesity and IR in mice by activating the TGR5 pathway	Jiang et al. (2021)
Licochalcone A	T2DM mice models	Promotes the growth of beneficial bacteria (such as *Bifidobacterium*, *Turicibacter*, *Blautia*, and *Faecococcus*) while inhibiting the growth of harmful bacteria (such as *Enterococcus*, *Dorea*, and *Arachnococcus*) and improves insulin resistance and glucose tolerance	Luo et al. (2023)
Lycium barbarum polysaccharides	Obesity mice models	Improve obesity by modulating the composition of intestinal flora and the metabolism of SCFAs	Yang Y. et al. (2021)
Red ginseng extracts	Obesity mice models	Improve glucose metabolism and promote lipolysis and energy metabolism by activating TGR5 in the gut, significantly alleviating obesity and IR	Li et al. (2023)

complex in composition, and extracting practical components precisely and optimizing dosages and treatment protocols remains a challenge. In the future, it is essential to identify the targets of TCM monomers, optimize biotransformation pathways, explore individualized treatment plans, and conduct large-scale, multi-center, long-term randomized controlled trials to verify efficacy and safety, as well as assess their potential in different diabetes subtypes.

6 Conclusions and future perspectives

In summary, the gut microbiota and its metabolites are crucial in the onset and progression of IR in T2DM. SCFAs, BAs, TMAO, LPS, and indole derivatives significantly regulate glucose metabolism by improving insulin sensitivity, promoting gut hormone secretion, and inhibiting inflammation. TCM formulas and individual herbs, such as *Lycium barbarum*, Ganoderma lucidum, and Baicalin, help improve glucose metabolism and insulin sensitivity by promoting beneficial gut bacteria. Furthermore, TCM monomers, such as polysaccharides, flavonoids, and alkaloids, show the potential to directly influence gut microbiota and metabolic products, highlighting their significant clinical efficacy in managing T2DM. These findings highlight the key role of gut microbial metabolites in IR and contribute to exploring new therapies for metabolic diseases. They help understand how the gut microbiota and its metabolites regulate IR and provide new therapeutic targets for clinical treatment.

Although significant progress has been made in current research, many issues remain unresolved, such as the variability of microbiota among individuals, further clarification of the specific mechanisms, and the feasibility of clinical applications. Future studies should focus on exploring the individual differences in the metabolic effects of different microbiota communities and

TABLE 2 Chinese herbal formulae.

Chinese herbal formulae	Research subjects	Therapeutic mechanisms and targets	References
Baihu Rensheng decoction	T2DM rat models	Increases the relative abundance of *Lactobacillus*, *Blautia*, and *Anaerostipes* in the gut of T2DM rats while decreasing the relative abundance of *Allobaculum*, *Candidatus Saccharimonas*, and *Ruminococcus*. It inhibits TLR4/NF-κB-mediated inflammation and alleviates hyperglycemia and inflammatory responses	Yao et al. (2022)
Gegen Qinlian decoction	T2DM mice models	Regulates the gut microbiota, improves bile acid metabolism, activates the TRG5/cAMP/PKA/CREB signaling pathway, stimulates GLP-1 secretion, and significantly reduces blood glucose levels in T2DM mice, improving oral glucose tolerance	Liu et al. (2024)
Gegen Qinlian decoction	T2DM rat models	Regulates the structure of the gut microbiome by increasing the proportion of SCFA-producing and anti-inflammatory bacteria while decreasing the proportion of conditionally pathogenic bacteria associated with diabetic phenotypes, which helps lower blood glucose and inflammatory cytokine levels	Tian et al. (2021)
Gegen Qinlian decoction	patients with T2DM and T2DM mice models	Improves T2DM by increasing the abundance of *Faecalibacterium*, elevating SCFA levels, and reducing serum inflammation-related markers, thereby alleviating metabolic disorders and inflammatory states	Gao et al. (2024)
JiangTang Sanhuang pill	T2DM rat models	Activate the FXR/FGF15 and TGR5/GLP-1 signaling pathways in the gut, reducing lipid accumulation and insulin resistance	Tawulie et al. (2023)
JiangTang Sanhuang pill	patients with T2DM	Reasonable blood glucose control may positively correlate with the duration of JTSH tablet administration. Patients with T2DM were satisfied with the Anti-diabetic effects of JTSH tablets, which can significantly reduce blood glucose and insulin resistance and improve the function of islet cells	Shao et al. (2022)
JinQi Jiangtang Tablet	T2DM mice models	Increases *Akkermansia*, decreases *Desulfovibrio*, increases the concentrations of acetate, propionate, and butyrate, enhances intestinal barrier function, reduces host inflammation, improves insulin resistance in T2DM, regulates gut microbiota, and promotes SCFA production	Cao et al. (2019)
JinQi Jiangtang Tablet	patients with pre-diabetes	The incidence of diabetes upon treatment completion was 16.5% in the JQJT tablets group compared with 28.9% in the control group. The percentage of patients with normalized blood glucose upon 12-month intervention was 41.8% in the JQJT tablets group compared with 27.8% in the control group	Wang et al. (2017)
PuRenDan	T2DM rat models	Reduces serum lipid metabolism biomarkers and inflammatory factors, regulates the levels of pantothenic acid, 1-methylhistamine, and 1-methylhistidine, participates in the biosynthesis of pantothenic acid and coenzyme A, histidine metabolism, and secondary bile acid biosynthesis, thus improving blood glucose and IR	Ma et al. (2024)
Shenzhu Tiaopi Granule	T2DM rat models	Increase the relative abundance of Lactobacillus in the intestines of T2DM rats, reduce the relative abundance of Allobaculum and Desulfovibrionaceae, and improve blood glucose and lipid levels in T2DM rats	Zhao J. et al. (2019)
ShenZhu TiaoPi Granule	T2DM rat models	Decrease LPS and IL-1β levels, increase the abundance of Intestinimonas, reduce the abundance of *Eubacterium coprostanoligenes*, regulate bile acid biosynthesis and cholesterol metabolism, and alleviate hyperglycemia	Zhao and Fang (2024)
ShenZhu TiaoPi Granule	patients with impaired glucose tolerance	Reduces the conversion rate from impaired glucose tolerance (IGT) to diabetes and increases the conversion rate from IGT to normal blood glucose levels	Fang et al. (2014)
Shengmai San Formula	Obesity mice models	Reduces the abundance of lactobacilli carrying bile salt hydrolase, increases TCA content, promotes M2 macrophage polarization in adipose tissue, and enhances Slit3 release, improving glucose and lipid metabolism	Wang et al. (2024)
Tianqi	patients with impaired glucose tolerance	Reduced diabetes risk by 32.1% and no serious adverse events occurred in the trial	Lian et al. (2014)

conduct clinical trials to assess the clinical application value of microbiota-based therapies in preventing and treating T2DM. Attention should also be given to optimizing the use of TCM in this field and its potential for combination therapy with conventional drugs. These studies offer new approaches to diabetes treatment, primarily through strategies regulating gut microbiota and its metabolites. TCM and related complementary therapies are expected to become effective adjuncts in treating T2DM, improving blood glucose control, and reducing drug side effects.

Author contributions

JL: Conceptualization, Formal analysis, Investigation, Methodology, Software, Writing – original draft. FL: Investigation, Methodology, Supervision, Writing – review & editing. LY: Formal analysis, Methodology, Supervision, Validation, Writing – review & editing, Project administration. SL: Formal analysis, Methodology, Project administration, Supervision, Validation, Writing – review & editing. YD: Funding acquisition, Resources, Supervision, Visualization, Writing – review & editing, Validation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

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