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Review

Modulating the gut microbiota: a multi-target mechanism of traditional Chinese medicine for type 2 diabetes management

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is fundamentally linked to gut microbiota dysbiosis, a condition that triggers a cascade of pathophysiological changes including aberrant host-microbe co-metabolism, compromised intestinal barrier integrity, and chronic low-grade inflammation, which collectively drive insulin resistance. While conventional therapies have limitations, traditional Chinese medicine (TCM) presents a promising therapeutic strategy. This review comprehensively elucidates the pathophysiological link between gut dysbiosis and T2DM. It then systematically summarizes the multi-target mechanisms by which TCM exerts its therapeutic effects, including: remodeling the gut microbial ecosystem; reprogramming host-microbe co-metabolism of short-chain fatty acids (SCFAs), bile acids (BAs), and branched-chain amino acids (BCAAs); reinforcing the intestinal barrier to mitigate metabolic endotoxemia; and modulating key signaling pathways involved in inflammation and immunity, etc. Key clinical evidence is also summarized. Furthermore, the review critically evaluates the preclinical and clinical evidence supporting these mechanisms, highlighting both therapeutic potential and current challenges, such as the need for standardization. Finally, current limitations and future prospects are considered, proposing a path forward for integrating microbiota-targeted TCM therapies into the modern, evidence-based management of T2DM.

1. Introduction

Diabetes mellitus (DM) includes a set of metabolic disorders that are defined by persistent hyperglycemia, which can be caused by insufficient production of insulin or lowered insulin sensitivity [1]. This condition acts as one of the most significant issues of global health, imposing huge physical and psychological burdens on people with the disease and remaining as the major cause of death in various countries. The most common form of diabetes is type 2 diabetes mellitus (T2DM), which accounts for over 95% of all cases of diabetes and is one of the most severe problems in health care. The world-wide prevalence of diabetes was estimated to be about 537 million adults aged 20–79 in 2021. It is predicted that this number will increase to 643 million in 2030 and continue to grow to 783 million in 2045. World wide diabetes prevalence rate is projected to increase at a rate of 10.5% in 2021 to 11.3% in 2030 and finally to 12.2% in 2045. Similarly, it is projected that adjusted to age demographics the prevalence will increase from 9.8% to 11.2% within the same period [2]. The core pathological mechanisms of T2DM involve insulin resistance and glucose metabolic dysfunction. These are frequently accompanied by additional metabolic disturbances like chronic systemic low-grade inflammation and lipid metabolism disorder.

One of the most important contributions of gut microbiota (GM) towards T2DM pathogenesis and progression has gained more interest over recent years. The GM is an intricate community of bacteria, archaea, fungi, viruses, and protozoa [3]. Its dysbiosis leads to metabolic derangements such as obesity and insulin resistance [4]. In a healthy state, the gut microbiota maintains host homeostasis by regulating metabolic and immune functions [5]. Yet, T2DM upsets this fine balance with impairment of the intestinal barrier, increased proliferation of opportunistic pathogens and aggravation of chronic low-grade inflammation that worsens the insulin resistance and glucose metabolic dysfunction [6]. Studies suggest that GM can become a new target in preventing and treating T2DM [7, 8], and restoring its balance is considered a key strategy for improving diabetes management.

The use of traditional Chinese medicine (TCM) in treating diabetes has been observed since over 2000 years ago and current studies have continued to investigate its effectiveness [9-11]. Numerous TCM herbs have been reported to exhibit hypoglycemic, insulin-sensitizing, and antioxidant properties [12, 13], indicating some benefits of metabolic regulation. More recent reports have shown that TCM can have anti-diabetic actions in part by altering the gut microbiota [14], which provides a plausible mechanistic basis of its traditional uses.

Consequently, the aim of this paper is to review in a systematic way the available clinical and experimental literature regarding the role of modulating gut microbiota as a component of TCM in diabetes treatment, clarifying the underlying mechanisms and identifying possible ways of implementing TCM into the conventional medicine approach to diabetes care. To criticize the current pre-clinical and clinical support of these mechanisms emphasizing both its strengths as well as, more importantly, its

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weaknesses; to determine the key conceptual and methodological issues in the discipline and suggest what should be prioritized in future research so that they can facilitate the translation of TCM between the bench and the bedside.

2. The relationship between T2DM and the gut microbiota

2.1. Metabolite-mediated host-microbiota interactions

2.1.1. Short-chain fatty acids (SCFAs)

The short-chain fatty acids (SCFAs) butyrate, propionate, and acetate are important metabolites which are made by gut bacteria during the breakdown of dietary fiber. They are involved in the regulation of glucose metabolism. Studies have shown that the overall SCFA concentration is lower in T2DM patients than in controls [15]. Further, butyrate and propionate concentrations were negatively correlated with blood glucose in T2DM patients [16]. Research indicates that SCFAs stimulate glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) secretion *via* activation of FFAR2/3 (free fatty acid receptors) in intestinal L-cells [17], which promote insulin sensitivity (IS) and prevent glucagon release. In particular, FFAR2 has stronger affinity towards acetate and propionate, whereas FFAR3 is more sensitive to propionate and butyrate. A randomized controlled study also confirmed that dietary fibre increased the diversity and population of SCFA-producing microbes and increased GLP-1 synthesis and reduced HbA1c levels [18]. Epigenetic regulators such as histone deacetylases (HDACs) perform essential roles in regulating pancreatic β-cell activity, insulin secretion and glucose homeostasis in individuals with diabetes mellitus (DM) [19]. Butyrate, as an HDAC inhibitor, is part of the epigenetic regulation and can improve β-cell function and glucose homeostasis [20-22]. Propionate has positive regulatory actions on β-cell activity at physiological concentrations and cellular studies have confirmed its direct participation in increasing glucose-dependent insulin release and preservation of β-cell integrity through anti-apoptotic mechanisms [23]. Moreover, acetate reduces adipose tissue and hepatic lipid build up by inducing the expression of hepatic peroxisome proliferator-activated receptor α (PPARα) and other fatty acid oxidation enzymes [24]. Even more so, There is a strong dependence of the integrity of the intestinal barrier on short-chain fatty acids, especially butyrate, which plays one of the most important roles in this respect (see Section 2.2) and suppresses local and systemic inflammation (see Section 2.3). Hence, the decrease in SCFAs is not only a loss of metabolic signals, but an important point of imbalance in the whole intestinal balance, which affects many pathways.

2.1.2. Dysregulated branched-chain amino acid (BCAA) metabolism

Branched-chain amino acids (BCAAs), which consist of leucine, isoleucine, and valine, are nutritionally essential amino acids that require exogenous dietary supply because there are no host biosynthetic pathways. Gut microbiota represents the main location of their metabolic conversion. Among these, *Prevotella copri* and *Bacteroides vulgatus* appear to stand out as the critical microbial species that enable the relationship between branched-chain amino acid synthesis and reduced insulin sensitivity (IR) [25]. BCAAs are also regarded as key biomarkers for T2DM and IR [26]. The statistical analysis confirmed the association between increased intake of BCAAs and increased risk of T2DM [27]. There is evidence that branched-chain amino acids have the ability to contribute to the development of insulin resistance and T2DM with a dual-mechanism method. One mechanistic pathway is the long-term stimulation of mTORC1 signaling cascades where leucine acts as the major trigger at high BCAA levels, leading to the phosphorylation of insulin receptor substrate, which disrupts the process of insulin signal transmission and could lead to insulin resistance. The second mechanism is that BCAA metabolic dysfunction can lead to the accumulation of toxic metabolites especially branched-chain alpha ketoacids. They are toxic byproducts that could damage cells, especially pancreatic β-cells, eventually leading to the onset of IR [28]. It's noteworthy that the dysregulation of BCAA metabolism may interact with SCFA production; for instance, some BCAA-producing bacteria might have a competitive or altered symbiotic relationship with SCFA-producing bacteria. Accordingly, manipulating the BCAA signaling pathway and metabolism of gut microbiota may be a useful strategy to manage IR and T2DM [29, 30].

2.1.3. Bile acid (BA) metabolism and nuclear receptor signaling interactions

Bile acids (BAs) undergo enterohepatic circulation, which constitutes an essential biological pathway for maintaining metabolic balance through the regulation of glucose and lipid processes. In this circulation, the gut microbiota serves as a chemical transformer, transforming primary BAs into secondary BAs. Such BAs coordinate a wide array of metabolic regulatory pathways by interacting with the nuclear transcription factor FXR and the G-protein-coupled receptor TGR5 [31]. The FXR-BA complex induces the expression and release of fibroblast growth factor 19 (FGF19), which creates a negative feedback loop inhibiting the genes encoding cholesterol 7α-hydroxylase (*CYP7A1*) and cytochrome P450 12α-hydroxylase B1 (*CYP8B1*). It is an effective control mechanism to regulate BA synthesis through inhibition of *CYP7A1* [32]. Bile acids are able to stimulate FXR receptors in pancreatic β-cells resulting in the mediation of *E2F3* and *ADCY8* in these cells, which promotes cell proliferation of β-cells and insulin secretion [33, 34]. Activation of the G protein-coupled BAs receptor (TGR5) by BA facilitates GLP-1 secretion from enteroendocrine L-cells [35, 36]. Besides their participation in GLP-1 regulation, activation of TGR5 leads to increased energy consumption in brown fat and muscle tissue due to induction of type 2 iodothyronine deiodinase, a thyroid hormone-activating enzyme, by cAMP [32]. Patients with T2DM have BA profile abnormalities [37], such abnormalities may be related to increased *CYP8B1* mRNA expression in the liver [38]. In the intestinal milieu, the gut microbiota modulates bile acid metabolism through the reduction of tauro-β-muricholic acid (T-β-MCA) levels, a natural FXR antagonist [39]. Conversely, BAs can improve the gut microbiota, playing a significant role in shaping gut microbial ecology [40]. It is important to note that disordered BA metabolism is a multifaceted crossroads that links hepatic metabolism, gut microbiota, energy balance, barrier function, and inflammatory responses. The imbalance in this system has significant implications on the overall pathological condition of T2DM.

2.2. Intestinal permeability

Intestinal barrier integrity maintenance is highly important in supporting the metabolic equilibrium. Increased intestinal permeability (IP) is a common finding in patients with T2DM, facilitating higher levels of microbial products in the gastrointestinal tract especially lipopolysaccharide (LPS) entering the bloodstream, resulting in metabolic endotoxemia and chronic systemic low-grade inflammation. The core mechanism involves the underexpression of epithelial tight junction proteins (TJPs), such as ZO-1 and OCCLUDIN, in addition to the decrease in adhesion protein levels. Studies of mouse models have shown that probiotic bacteria *Bacteroides vulgatus* and *Bacteroides dorei* significantly enhance the expression of tight junction genes in colonic tissue, reduce IP levels, prevent the production of LPS and ameliorating metabolic endotoxemia [41]. Meanwhile, *Akkermansia muciniphila* interacts with the host's TLR2 receptor *via* its outer membrane

protein Amuc_1100, thereby activating the AMPK signaling pathway and promoting TJP expression [42]. Its secreted extracellular vesicles (AmEVs) also increase the level of OCCLUDIN expression, decreasing IP [43]. Additionally, *Roseburia hominis* from the *Firmicutes phylum* can upregulate genes associated with barrier function and innate/mucosal immunity, promoting mucosal T-cell expansion and differentiation [44]. Furthermore, SCFAs (especially, butyrate) maintain the integrity of the intestinal barrier (IB) by increasing mucin production and upregulating expression of TJPs (OCCLUDINs, CLAUDINs, and junctional adhesion molecules) [45]. This confirms the pivotal nature of the gut microbiota in the maintenance of barrier function.

2.3. Chronic inflammation and immune imbalance

T2DM essentially is a chronic subclinical inflammatory disease associated with increased activation of pro-inflammatory immune cells (i.e., M1 macrophages, Th1 cells, Th17 cells), decreased anti-inflammatory cellular reactions (e.g., M2 macrophages, Treg cells), and increased levels of pro-inflammatory mediators (TNF-α, IL-6, IL-1β) [46]. These inflammatory factors directly inhibit insulin signaling pathways and cause IR and β-cell injury: TNF-α intensifies the progression of IR by inducing the inhibitory phosphorylation of insulin receptor substrate (IRS) protein [47, 48], increasing ceramide production [49], stimulating lipolysis of adipocytes [50], as well as suppressing PPARγ activity [51]. IL-6 prevents insulin receptor and insulin receptor substrate-1 (IRS-1) phosphorylation by triggering the expression of suppressor of cytokine signaling 3 (SOCS-3), an inhibitor of insulin signal transduction, which leads to insulin resistance (IR) [52]. Not only does IL-1β lead to a decrease in insulin secretion, causing glucose intolerance, but it also inhibits insulin signaling in peripheral tissues (like adipose tissue) and thus promotes the development of IR even faster, which contributes to the rapid advancement of T2DM [53].

Intestinal dysbiosis and increased IP are the critical starting points that cause this chronic inflammation, as was mentioned before (see Section 2.2). Studies have shown that high-fat diet (HFD) has a role in causing gut microbiota disruption which facilitates *Enterobacteriaceae* growth and increased LPS production. The leakage of LPS into the bloodstream induces metabolic endotoxemia, which subsequently activates the TLR4/NF-κB pathway to elicit macrophage migration and inflammatory cytokine secretion [54]. Furthermore, LPS may directly cause pancreatic β-cell apoptosis through the IFN-β/Xaf1 pathway, which increases the severity of the glucose metabolic disorders [55].

Metabolites produced by probiotics have anti-inflammatory properties due to their ability to act on various elements of inflammatory cascades. Butyrate is a good example of this process because it can inhibit the NF-κB signaling pathway and maintain the stability of IκBα and also inhibit HDAC activity to inhibit the synthesis of inflammatory cytokines [56, 57]. Short-chain fatty acids are examples of microbial metabolites that play an important role in regulation of adaptive immunity by influencing the T-cell lineage commitment, especially in the maintenance of the homeostasis of pro-inflammatory Th17 and immunoregulatory Treg cells. This cell equilibrium is essential in the regulation of metabolic reactions controlling the use of glucose and lipids [58].

2.4. Oxidative stress and mitochondrial dysfunction

One of the important pathological features of T2DM is oxidative stress that occurs due to the combination of excessive reactive oxygen species (ROS) synthesis and ineffective antioxidant protective systems. Elevated blood glucose for a prolonged period leads to the accumulation of reactive oxygen species through three main processes, namely glucose auto-oxidation, deposition of advanced glycation end-products, and mitochondrial electron transport failure, all of which disrupt cell homeostasis and contribute to insulin resistance and pancreatic β-cell injury [59]. In addition to damaging cells directly, excessive reactive oxygen species activate important stress-activated protein kinase pathways, such as NF-κB, c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK), and p38 mitogen-activated protein kinase cascades, creating a chain reaction of hyperglycemia-oxidative stress-inflammation. The gut microbiota also regulates mitochondrial functional homeostasis by various regulatory mechanisms. Sulfate-reducing bacteria of the intestine may generate hydrogen sulfide (H_2S). Large amounts of H_2S are able to inhibit the activities of mitochondrial respiratory chain complexes leading to malfunction of the electron transport chain (ETC) and energy metabolism imbalance, which in turn stimulates the creation of ROS and causes mitochondrial structure and function damage. On the other hand, proper amounts of H_2S may enhance mitochondrial biogenesis and functionality [60]. Additionally, the gut microbiota regulate mitochondrial functional integrity and oxidative stress regulation by producing essential metabolites such as short-chain fatty acids, indole-3-propionic acid, secondary bile acids (ursodeoxycholic acid and tauroursodeoxycholic acid), trimethylamine N-oxide, and δ-valerobetaine [61]. Thus, imbalance of gut microbiome enhances oxidative stress and damage to mitochondria in two ways: lowered synthesis of protective metabolites and increased synthesis of harmful chemicals, which eventually worsen insulin resistance and pancreatic β-cell dysfunction.

2.5. Gut-brain axis

The gut-brain axis (GBA) is a complex signaling network involved in the facilitation of bidirectional communication between the enteric and central nervous systems (CNS) that plays a critical part in regulating energy intake and glucose homeostatic control [62]. In this network, the gut microbiota acts as a major mediator of gut-brain communication. Gut microbiota and metabolites (e.g., SCFAs, BAs, LPS) have been shown to affect the workings of this axis in several ways. As one of the specialized neuroendocrine components of the intestinal epithelium, enteroendocrine cells (EECs) act as metabolic sentinels with the ability to respond to changes in the luminal environment through the secretion of important gut peptides such as GLP-1, cholecystokinin, gastric inhibitory polypeptide, and peptide YY, which regulate metabolic responses [63], These gut-derived hormones function as direct endocrine modulators of pancreatic β-cell activity, facilitating insulin secretion *via* targeted hormonal signaling mechanisms. Beyond direct endocrine effects, these gut hormones activate vagal sensory fibers *via* local paracrine interactions, transmitting metabolic signals to brainstem and hypothalamic nuclei, specifically the nucleus tractus solitarius and hypothalamus, which coordinate appetite suppression, energy expenditure, and glycemic control [64–67]. The gut microbiota generates a diverse range of metabolites, which directly or indirectly impact gut-brain signaling. An example of such influence is how the gut microbiota has been shown to directly regulate the expression of nutrient receptors on enteroendocrine cells and their peptide hormone secretion as well as induce serotonin synthesis in enterochromaffin cells, which subsequently controls enteric nervous system responses and activation of vagal afferents. Metabolites of BA modulate gut-brain communication by regulating TGR5 receptor expression and subsequent enteroendocrine peptide release whereas those of SCFA have a dual action by altering EEC nutrient sensing receptor expression and peptide hormone production as well as stimulating the vagal afferent directly. LPS is opposing due to its negative effect on vagal afferent responsiveness and enteric nervous system signaling [68]. Signalling in the MGBA is often impaired in T2DM. Such impairment does not only affect glucose

homeostasis, but might also be related to cognitive dysfunction and mood disorders caused by T2DM. This indicates that gut microbiota dysbiosis has an effect on T2DM that goes beyond the conventional metabolic sphere, and can impact the nervous system.

2.6. Circadian rhythm

The circadian biological rhythms of the host organism and its gut microbiome interact reciprocally and regulate each other, having an effect on mechanisms important to support metabolic homeostasis [69]. The composition and activity of the gut microbiota are subject to a distinct circadian rhythmicity. Nevertheless, this microbial rhythmicity tends to be much reduced or sometimes absent in T2DM patients. Reitmeier et al. [70] conducted a large cohort study, revealing a loss of gut microbiota rhythmicity in T2DM patients. The absence of oscillations in 13 specific taxa, such as *Bifidobacterium longum* and *Faecalibacterium prausnitzii*, was identified as a potential predictive biomarker for the disease. Such a result indicates that a dysregulated gut microbiota rhythm may be an early sign of T2DM. Moreover, the research also showed that a high-fat diet could interfere with the diurnal dynamics of both the structure and activities of the gut microbiota [71]. Disruption of the circadian rhythm (e.g., shift work, irregular meal timing) is a risk factor of T2DM. This disruption can exacerbate IR by damaging the intestinal barrier, changing the composition of gut microbiota, causing inflammation, and directly impacting the expression of clock genes found in the host (e.g., *Clock*, *Bmal1*) [72]. An animal model study has shown that mice with intestine-specific *Bmal1* knockout show a lack of gut microbiota rhythmicity, which leads to disorganization of SCFA and BA metabolism and eventually triggers a metabolic syndrome phenotype [73]. Moreover, gut microbiota metabolites also lead to the enhancement of host circadian rhythms. It has been shown that SCFAs can control the circadian rhythms of intestinal epithelial cells *via* a HDAC inhibition-dependent pathway [74]. Mice treated with oral unconjugated bile acids evidenced significant changes in circadian rhythm-related gene expression in ileum, colon, and liver, especially influencing the hepatic circadian control components of D-box binding protein and core clock genes *Per2*, *Per3*, and *Cry2*, and thus regulating the host circadian behavior and metabolism patterns [75]. Disruption of the gut microbiota rhythmicity and disruption of the host circadian rhythm can create a vicious circle in T2DM, working together to promote the induction and advancement of metabolic disorders. A schematic summary of the six mechanisms described above is provided in Fig. 1.

2.7. Gut-cardiovascular axis

The development of T2DM involves the integration of the gut and cardiovascular systems into a complicated web of influence. The microorganisms found in the gut and their metabolites have a direct effect on cardiovascular health *via* various mechanisms within this network, which is further aggravated greatly by the existence of T2DM [76].

Trimethylamine N-oxide (TMAO) is an important compound that connects the gut microbiota to cardiovascular disease. The first step in the pathway of its production involves decomposition of dietary sources such as choline and carnitine by gut bacteria to form trimethylamine (TMA). TMA is subsequently oxidized in the liver by flavin-containing monooxygenase 3 (FMO3) [77]. Plasma TMAO levels are significantly increased in patients with T2DM and have been found to be highly correlated with the likelihood of coronary heart disease and serious adverse cardiovascular events. Its pathogenic effects are mainly: (1) Foam cell formation: it enhances scavenger receptors (i.e., CD36, SR-A1) on the surface of macrophages, increasing the rate of lipid uptake and hence promoting foam cell formation and the development of atherosclerotic plaques [78-80]. (2) Enhancing platelet hyperreactivity and thrombosis risk: it enhances the sensitivity of the platelets to ADP and the Ca^{2+} influx through the stimulation of the exogenous Ca^{2+} influx by amplifying the P2Y receptor-mediated Ca^{2+} signaling. This then goes on to activate the αIIbβ3 integrin through the CalDAG-GEFI→Rap1 pathway, eventually leading to platelet aggregation and thrombosis [81-83]. (3) Inducing inflammation and endothelial dysfunction: it initiates mitochondrial and intracellular ROS build-up (e.g., by blocking SIRT3-SOD2) and results in lysosomal-cathepsin B leakage which initiates the TXNIP-dependent NLRP3 inflammasome with upregulation of the NF-κB signaling pathway. This results in the release of inflammatory mediators like IL-1β/IL-18. At the same time, it suppresses the production of eNOS/NO and upregulates the expression of adhesion molecules (e.g., VCAM-1), finally leading to endothelial inflammation and loss of diastolic function [84-86]. (4) Interfering with cholesterol metabolism: it stimulates the hepatic FXR-SHP nuclear receptor axis and the intestinal FGF15/FGF19 signal that reduces the transcription of *CYP7A1*. This prevents the transformation of cholesterol into bile acids and creates metabolic disorders and impairs cholesterol clearance [87, 88].

The SCFAs (e.g., butyrate, propionate) have their effects on various signaling pathways by stimulating G protein-coupled receptors GPR41 and GPR43 in endothelial cells. One aspect of this is the ability of GPR41/43 to control the expression of angiotensin-converting enzyme 2 (ACE2) and hence the homeostasis of the gut-vascular axis. On the other hand, SCFAs increase vascular endothelial diastolic capability, increase nitric oxide (NO) production and suppress the secretion of inflammatory mediators *via* receptor-mediated processes. All these actions contribute to restoring vascular endothelial activity, decreasing blood pressure and alleviating vascular inflammation, and therefore play a protective role in cardiovascular health [89, 90]. Nevertheless, in those with T2DM, the number of useful bacteria that generate SCFAs is decreased. This reduces the protective mechanism and causes a higher cardiovascular risk.

Once endotoxins (lipopolysaccharide, LPS) have entered the bloodstream either by crossing the intestinal barrier or by other mechanisms, they interact with pattern recognition receptors such as TLR4. This triggers signaling pathways such as NF-κB and IKKβ, leading to an upregulated systemic inflammatory response, indicated by a significant increase in inflammatory factors like IL-

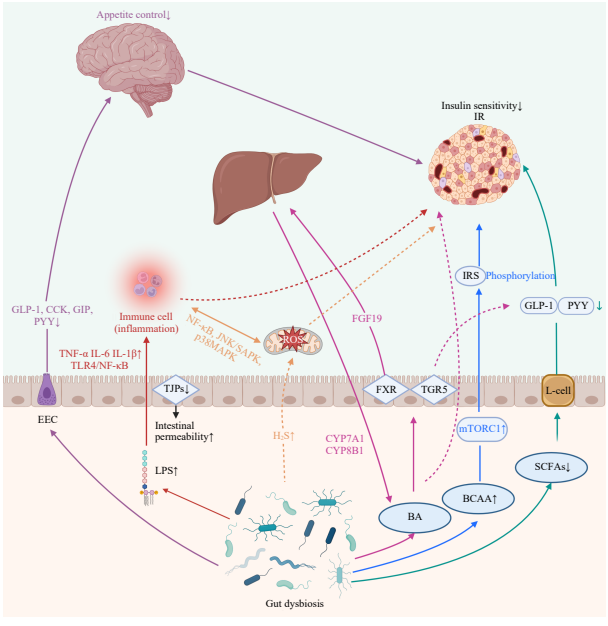

Fig. 1 Mechanisms by which gut microbiota influence T2DM (created in https://BioRender.com).

6, TNF-α, MCP-1, and CRP [91]. These inflammatory factors are not only disruptive to the insulin signaling pathway (e.g., by blocking IRS-1 or increasing SOCS protein levels), but also have direct effects on the vascular endothelium. They promote the upregulation of cell adhesion molecules (VCAM-1, ICAM-1, E-selectin, etc.), downregulate eNOS expression or activity, inhibit NO synthesis, and may even promote endothelial cell apoptosis, thus contributing to the pathogenesis of atherosclerosis [92, 93]. Moreover, metabolites of aromatic amino acids produced by gut microbiota, including phenylacetic acid, p-cresol and its sulfate ester, and phenylacetylglutamine, tend to be accumulated abnormally in conditions of diabetes and insulin resistance. These small molecules may stimulate vascular wall remodeling and hardening through the activation and proliferation of vascular smooth muscle cells, reactive oxygen species generation, and pro-inflammatory signals. At the same time, they can also stimulate platelet reactivity and inflammatory mediator release, which will speed up the development of atherosclerosis and greatly increase a risk of cardiovascular complications [94, 95].

Given the central regulatory role of the gut microbiota in lipid metabolism, bile acid homeostasis, and even systemic inflammation, intervention measures targeting this "gut–cardiovascular axis", such as precise supplementation with probiotics or dietary adjustments, offer highly promising new strategies for the prevention and treatment of cardiovascular complications in type 2 diabetes. A schematic illustration of the above mechanism is provided in Fig. 2.

The dysbiosis of the gut microbiota in T2DM represents a multifaceted and interconnected imbalance within a complex network. The abnormalities in metabolites, the intestinal barrier breakdown, chronic inflammation, oxidative stress, the breakdown of the gut-brain axis communication, and disorganisation of the circadian rhythms are not separate phenomena. The factors rather participate in a reciprocal regulatory relationship and in mutual causation, which together form the underlying gut microenvironmental pathophysiological basis of the onset and development of T2DM. Comprehensive understanding of this multifaceted network is critical for formulating precision therapeutic approaches.

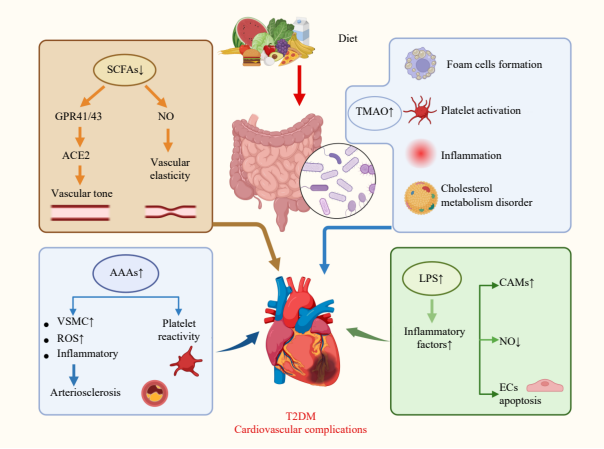

Fig. 2 Gut-cardiovascular axis in type 2 diabetes (created in https://BioRender.com).

3. The traditional Chinese medicine framework for T2DM: from theory to application

3.1. T2DM classification and treatment in traditional Chinese medicine

T2DM is classified as Xiaoke (wasting-thirst syndrome) in TCM. The main pathophysiology is based on the concept of "spleen deficiency with dampness obstruction" as the underlying cause and "Yin deficiency with internal heat" as the manifestation, which is a classic pattern of "deficiency in the root and excess in the manifestation" [96, 97]. T2DM is a systemic metabolic disease that is accompanied by malfunction of many organ systems such as spleen, stomach, liver and kidneys. The therapeutic approach emphasizes multi-target and multi-level comprehensive regulation, primarily encompassing strengthening the spleen and supplementing Qi, nourishing Yin and clearing heat, soothing the liver and regulating Qi, and promoting blood circulation to remove stasis. These therapeutic concepts are intended to reestablish organ function balance, optimize glucose and lipid metabolism, increase insulin sensitivity, and eventually control glycemia with organ protection and avoidance of complications [98, 99].

In the early stage of T2DM, the primary manifestation is "Yin deficiency with internal heat", where treatment focuses on herbs like *Trichosanthes kirilowii*, *Coptis chinensis*, and *Anemarrhena asphodeloides* that clear heat, drain fire, nourish Yin and moisten dryness. At the middle stage, when Qi-Yin deficiency is combined with phlegm-dampness obstruction, *Panax ginseng*, *Ophiopogon japonicus*, *Pinellia ternata*, and *Alisma plantago-aquatica* are added to complement Qi, nourish Yin, reinforce the spleen, and transform dampness. In the final stage, which is associated with Yin-Yang deficiency with blood stasis obstruction, the following herbs are chosen: *Rehmannia glutinosa*, *Cornus officinalis*, *Salvia miltiorrhiza*, and *Ligusticum sinense* to nourish Yin and Yang, promote blood flow and remove stasis. This multi-stage, syndrome-differentiated comprehensive strategy integrates the essence of traditional classical formulations with modern pathological understanding, providing a solid theoretical foundation and practical guidance for the holistic management of T2DM [100].

3.2. The important role of plant components and their traditional uses in T2DM treatment

According to the theory of TCM, there are many medicinal plants with curative properties that have been widely used to treat and prevent T2DM and its complications because of their special therapeutic benefits. These botanical sources provide a critical foundation for modern drug discovery. The derived active compounds generally exhibit favorable safety profiles, high tolerability, and multi-target regulatory properties. Traditional medicinal plants such as *Coptis chinensis*, *Panax ginseng*, *Astragalus mongholicus*, and *Lycium chinense* have been shown to have significant effects on glucose metabolism by a variety of mechanisms, including anti-inflammatory activity and antioxidant effects, increased insulin sensitivity, protection of pancreatic β-cells, and inhibition of hepatic gluconeogenesis. The main active ingredient of *Coptis chinensis*, berberine, has had successful results in the therapy of diabetes mellitus and the water extract of *Coptis chinensis* has reduced serum glucose level in diabetic mice. Recent studies in pharmacology indicate that the various bioactive compounds present in these plants drive these synergistic therapeutic effects. Table 1 details the major chemical constituents and traditional T2DM applications of these essential herbs.

4. Intervention strategies in TCM

4.1. Gut microbiota remodeling

4.1.1. Improving gut microbiota and promoting SCFA production

Different TCM herbs and their active ingredients have been found to have the capability to remodel the gut microbiota. In a GK rat model experiment, berberine (BBR) administration

Table 1 The major chemical components of the aforementioned plants and their traditional applications in T2DM treatment.

Medicinal plant	Active compounds	Traditional uses in TCM	Mechanism of action in treating T2DM	Ref.
Coptis chinensis	Berberine	Clearing heat and drying dampness, purging fire and detoxifying toxins	Anti-inflammatory, anti-oxidative stress, promotes GLP-1 secretion, activation of the PPARγ-FGF21-GLUT2 signalling pathway	101, 102
Astragalus mongholicus	Astragaloside IV, astragalus polysaccharides	Tonifying Qi and nourishing blood, inducing diuresis and reducing edema, regulating blood sugar	Promoting the PI3K/AKT/AMPK signalling pathway, anti-inflammatory, protection of pancreatic β cell function	103, 104
Panax ginseng	Ginsenosides	Tonifying primordial Qi, tonifying the spleen and benefiting the lung, promoting body fluid production and relieving thirst	Activation of AMPK and PI3K/Akt, inhibition of FOXO1/SREBP/NF-κB/NLRP3, improvement of glucose and lipid metabolism, protecting β cells	105
Cinnamomum cassia	Cinnamaldehyde, cinnamyl polyphenols	Tonify fire and support Yang, guide fire back to the source, dispelling cold and relieving pain	Regulation of glucose metabolism, regulation of lipid metabolism, antioxidant and anti-inflammatory mechanisms	106
Crataegus pinnatifida	Hawthorn polyphenols	Strengthen the spleen and promote digestion, eliminate turbidity and reduce lipids	Enhances insulin signaling (SIRT1/AMPK, PI3K/AKT), inhibits NF-κB-mediated inflammation, regulates lipids and LPS, protects vascular and hepatic tissues	107
Mulberry leaf	Quercetin, kaempferol, 1-deoxynojirimycin (DNJ)	Disperse wind-heat, clear the lung and moisten dryness, clear the liver and improve vision	Inhibits sugar absorption, activation of PI3K/Akt and AMPK pathways, anti-inflammatory and anti-oxidative stress	108, 109
Lycium chinense	*Lycium barbarum* polysaccharide	Nourish the liver and kidney, replenish essence and improve eyesight, tonify deficiency and nourish Yin	Activates PI3K/AKT and AMPK pathways, enhances GLUT4 expression and glucose uptake, anti-inflammatory and anti-oxidative stress, regulates TCA cycle and lipid metabolism, modulates gut microbiota	110
Rehmannia glutinosa	Catalpol	Nourish Yin and tonify the kidney, tonify essence and blood, clear heat and cool the blood	Activation of PI3K/AKT pathway, reduction of oxidative stress, inhibition of NOX4, improvement in pancreatic β-cell function, regulation of lipid metabolism	111, 112
Pueraria lobata	Puerarin	Relieves the muscles and clears fever, generates body fluids and alleviates thirst, raises Yang and stops diarrhea	Activates PI3K/AKT and AMPK pathways, inhibits NF-κB, oxidative stress, protects β-cells, improves glucose and lipid metabolism, modulates gut microbiota	113
Dendrobium officinale	*Dendrobium* polysaccharides	Nourishes Yin and moistens the lungs, tonifies the kidneys and replenishes essence, benefits the stomach and generates body fluids	Activates PPAR-RXR signaling pathway, reduces hepatic lipid accumulation, improves lipid metabolism (TC, TG, LDL-C), inhibits fatty acid synthesis (LXR-α, PPAR-γ, SREBP-1c)	114

drastically changed the gut microbiome, with significant decrease in the representation of *Bacteroidetes* and its ratio to *Firmicutes* (B/F) and reduced abundance of *Muribaculaceae* and increased *Allobaculum* population, culminating in the increase in GLP-1 production and the improvement of glycemic control [115]. BBR therapy in *db/db* mice induced the growth of SCFA-producing genera (*Butyricimonas*, *Coprococcus*, *Ruminococcus*) and beneficial commensals (*Lactobacillus*, Akkermansia), and inhibited opportunistic pathogens (*Prevotella*, *Proteus*). Such a positive change in the microbiota was accompanied by SCFA production which was reflected in the rise of fecal SCFA concentration, and metabolic changes such as loss of weight, appetite suppression, normalization of glucose levels, and reduction in HbA1c [116]. A number of studies have established that astragalus polysaccharide (APS), one of the main active ingredients in *Astragalus membranaceus*, can alter the gut microbiota composition by lowering B/F ratios, increasing SCFA-producing bacteria (*Oscillospira*, *Akkermansia*, *Coprococcus*, *Faecalibaculum*), and probiotic populations (*Lactobacillus*, *Bifidobacterium*) and reducing pathogenic species (*Prevotella*, *E. coli*). Such a therapeutic microbiota restructuring contributed to higher SCFA production in gut and serum and increased GLP-1 levels and lower blood sugar [117-119]. In addition, it has been reported that astragaloside (AS) is an additional important active substance of *Astragalus membranaceus* that effectively controls gut microbiota structure and microbial diversity in T2DM mice, with a significant increase in *Muribaculaceae* and *Alloprevotella* and butyrate concentrations with hypoglycemic effects [120, 121].

The optimization of the microbial community structure has directly resulted in the enhancement of the profile of beneficial metabolites especially the promotion of SCFAs (and specifically butyrate and propionate) production. As discussed previously (see Sections 2.1.1, 2.2, 2.3), the restoration of SCFA levels is not limited to enhancing blood glucose *via* the GLP-1 pathway but more importantly can sustain and heal the intestinal epithelium, repair the intestinal barrier and exert anti-inflammatory actions and hence prevent the pathological process of T2DM at various stages. This exemplifies the TCM approach of achieving overall therapeutic effects by regulating the "microbiota-metabolite" axis.

4.1.2. Branched-chain amino acids (BCAAs) metabolism regulation

Other than the previously mentioned effects, it has been shown by research that berberine can help to significantly increase the BCAA degradation in the liver as well as adipose tissue by activating the branched-chain alpha-keto acid dehydrogenase complex. Simultaneously, BBR specifically controls the breakdown of BCAAs through inhibition of the branched-chain ketoacid dehydrogenase kinase (BCKDK), which leads to decreased phosphorylation of the branched-chain ketoacid dehydrogenase E1α subunit (BCKDHA) [122]. A study has established that konjac glucomannan is able to reduce the abundance of BCAA biosynthesis-related genes in the gut microbiota and thus enhance the level of BCAA metabolism in the host [123]. Another study demonstrated that the *Sargassum fusiforme* alginate (SF-Alg) can drastically lower BCAA colon levels in T2DM mice. This could be related to SF-Alg increasing the populations of *Bacteroides* species and there was a strong negative association between BCAA concentrations and the presence of *Bacteroides* [124]. With the reduction of the excessively high circulating BCAA levels or enhancement of their metabolism, TCM may alleviate the over-activation of the mTORC1 pathway and the accumulation of toxic metabolites, thus, alleviating insulin resistance and having hypoglycemic action.

4.1.3. Bile acid (BA) metabolism regulation

Different studies have revealed that some fundamental TCM components increase insulin sensitivity and glucose balance through the modulation of bile acid metabolic networks in the gut. As an illustration, it was found that water extract of *Scutellaria baicalensis* (WESB) had a positive effect on the composition of important gut microbiota communities, increased the levels of

specific secondary bile acids in both fecal and serum samples. This may be attributed to the activation of hepatic *CYP7A1* and the suppression of FXR expression in the intestine [125]. Subsequent deeper studies have found that water extract of *Scutellaria baicalensis* (WESB), total flavonoids of *Scutellaria baicalensis* (TFSB), and baicalin can all enhance bile acid and glycolipid metabolism by suppressing the excessive expression of *CYP7A1* in type 2 diabetic mouse models. On this list, TFSB also significantly reduces the excessive expression of FXR in the ileum [126]. Additionally, classical TCM prescriptions, exemplified by modified Gegen Qinlian Decoction, exert comprehensive therapeutic effects in T2DM mouse models through gut microbiota restructuring, bile acid metabolism optimization, TGR5/cAMP/PKA/CREB pathway activation, and subsequent GLP-1 secretory enhancement [127]. The effects of Jiangtang Sanhuang (JTSH) Pill, a standardized TCM preparation, exerts antidiabetic effects *via* gut microbiome restructuring, leading to unconjugated bile acid enrichment and subsequent upregulation of intestinal FXR/FGF15 and TGR5/GLP-1 regulatory pathways [128]. Moreover, Jingangteng Capsule treatment promoted gut microbiota composition and diversity in diabetic rats, as well as enhanced hepatic FXR expression and altered FXR-mediated bile acid metabolism, specifically the levels of tauro-β-muricholic acid and taurocholic acid. This combined regulation successfully corrected diabetic dyslipidemia and suppressed hepatic lipid accumulation and inflammation pathways significantly [129].

Optimizing BA signaling, TCM can do more than enhance hepatic glucose and lipid metabolism and increase GLP-1 secretion, but may also indirectly affect gut microbiota structure and intestinal integrity. Such all-encompassing control of the "microbiota-BA-host signaling" axis is an important representation of the overall metabolic improvement effects of TCM.

4.2. Intestinal barrier repair

According to a recent study, TCM has special benefits in the restoration of the intestinal barrier. There are more than 25 TCM-derived compounds found effective in increasing the synthesis of tight junction proteins in intestinal epithelial cells. As an example, it was found that puerarin increased the expression of the tight junction proteins (ZO-1, OCCLUDIN, CLAUDIN-1) and E-CADHERIN, which is an indicator of the enhanced physical barrier of the intestinal epithelium. Moreover, stimulation of Paneth cells by puerarin to secrete lysozyme and TGF-β was reported to improve intestinal antimicrobial abilities and immune regulation, and promote proliferation of intestinal stem cells, which supports the self-repair of the intestinal epithelium [130]. Three experimental models of IBD showed that schisandrin C promoted significant recovery of intestinal barrier integrity and reduction of intestinal leakage by upregulation of tight junction proteins (ZO-1, OCCLUDIN), downregulation of IL-1β-induced MLCK/p-MLC, and downregulation of NF-κB and p38MAPK pro-inflammatory signaling [131]. Treating SDD-afflicted pregnant mice with *Atractylodes macrocephala* (Baizhu) improved the integrity of tight junctions by upregulating the expression of genes and proteins associated with the tight junction integrity, namely, OCCLUDIN, CLAUDIN-1, and ZO-1, in the colonic tissues and downregulating the expression of CLAUDIN-2, leading to better functioning of the intestinal barrier [132]. Likewise, baicalein can be used to improve the integrity of the tight junctions in intestines by upregulating the expression of ZO-1 and CLAUDIN-1, thus reducing the permeability of intestines [133]. Moreover, Baochi Pill is one of the TCM formulations that increase intestinal barrier integrity through upregulation of tight junction proteins (ZO-1, ZO-3, CLAUDIN-3, and E-CADHERIN) and promotion of beneficial bacteria comprising *Bifidobacterium* and *Desulfovibrio* and inhibition of pathogenic bacteria comprising *Bacteroides* [134]. Furthermore, the Fufang Zhenzhu Tiaozhi Formula polysaccharides (FTZPs) have been found to raise the levels of SCFA in diabetic mice. They successfully upregulated the mRNA expression of critical tight junction proteins (including ZO-1, OCCLUDIN, and CLAUDIN-4) in the intestinal tissues, while concurrently preventing diabetes-induced disruption of gut microbiota homeostasis [135].

Not only does TCM restore physical integrity of the gut by reinforcing the intestinal barrier, but it also significantly reduces the possibility of endotoxins such as LPS gaining access to the systemic circulation at the source. It effectively halts the critical pathological cascade of "leaky guts-endotoxin enters blood-inflammation" (see Section 2.3). This step is integrated with regulating gut microbiota and promoting useful metabolites (such as butyrate) to maintain intestinal homeostasis.

4.3. Anti-inflammation and immune homeostasis reconstruction

4.3.1. Inhibition of inflammatory pathways

The dysbiosis of the gut microbiota leads to the production of LPS and other endotoxins which initiate the inflammatory cascade *via* the activation of toll-like receptor 4 (TLR4). Bioactive compounds of TCM show strong inhibitory activity against the inflammatory process. Research has shown that licorice extract is able to significantly decrease nuclear factor-κB (NF-κB) expression, TLR4 expression and TNF-α expression in colon tissues of diabetic mice and thus reduces inflammatory reactions [136]. Fructus Mori polysaccharide (FMP) has strong clinical benefits in type 2 diabetic mice due to inhibition of TLR4/MyD88/NF-κB signaling activation, which decreases the level of intestinal inflammation and oxidative stress as well as alleviates the related metabolic disorders such as hyperglycemia, insulin resistance, hyperlipidemia, endotoxemia and systemic inflammation [137]. Treatment of type 2 diabetic mice with *Dendrobium officinale* polysaccharides (DOP) enhanced the integrity of the intestinal barrier and prevented the leakage of lipopolysaccharides and subsequently suppressed the LPS/TLR4/TRIF/NF-κB inflammatory pathway. This mechanism reduced intestinal inflammation and oxidative stress and improved glucose-lipid metabolic dysfunction and minimized systemic inflammatory responses [138]. Similarly, administration of *Cordyceps sinensis* polysaccharide (AEPSa) helps in restoring the homeostasis of gut microbiota in T2DM mice and at the same time inhibits the inflammatory signaling of TLR4/NF-κB and increases the integrity of intestinal epithelium by enhancing the expression of tight junction proteins. These combined mechanisms all ameliorate diabetic pathophysiology [139]. Moreover, the compound TCM formula Baihu Renshen Tang has been confirmed to regulate the gut microbiota composition in T2DM rats and at the same time inhibit the inflammatory cascades of TLR4/NF-κB as well as restore the intestinal barrier function, which results in considerable improvement of the type 2 diabetic pathology [140]. These three actions directly against inflammation, along with the decreased permeability of the intestinal wall (see Section 3.2) and the decreased source of LPS (see Section 3.1.1) by controlling the gut microbiota, form a multilayered approach of TCM to control inflammation associated with T2DM.

4.3.2. Regulation of immune cell balance

Recent research indicates that TCM can bring about systemic therapeutic advantages in diabetes due to the immune homeostasis regulation by microbiota, namely, the rebalancing of essential T cell populations, such as Th1/Th2 and Treg/Th17 populations. For instance, treatment with ginsenoside Rg1 produces therapeutic immunomodulation in both colitic and obese mice using microbiota-mediated mechanisms. The compound also strongly inhibits inflammatory T cell subsets such as Th1, Th17

and memory T cells (central and effector memory) and stimulates naive T cells and Th2 responses, which leads to better immune balance and less inflammatory burden [141]. The total glucosides of paeony (TGP) exert strong immunomodulatory activity by inhibiting $CD4^+$ T cell polarization into Th1 and Th17 phenotypes by inhibiting the expression of certain transcription factors (T-bet and RORγt), leading to decreased pro-inflammatory cytokine production (IFN-γ and IL-17) [142]. Hawthorn extract has a bidirectional regulatory effect in autoimmune imbalance regulation. It downregulates RORγt, a key transcription factor of proinflammatory Th17 cells, and upregulates Foxp3, a characteristic transcription factor of inhibitory Treg cells. This intervention leads to increased levels of IL-10, an anti-inflammatory cytokine, and significant decreases in levels of pro-inflammatory cytokines, such as IL-17, IL-6, and TNF-α [143]. Studies on inulin give a mechanistic perspective related to TCM polysaccharide components. Inulin treatment in the EAE mouse model significantly suppressed the circulating pro-inflammatory cytokines (IL-17, IL-6, TNF-α) and it was found that this inhibition of Th17 cells was dependent on gut microbiota composition and metabolites regulation [144]. Furthermore, *Dendrobium officinale* National Herbal Drink (NHD) successfully restores Th17/Treg balances among $CD4^+$ T cells by manipulating gut microbiota, increasing SCFA production and activating GPR41/43-ERK1/2 pathways in experimental models [145]. Modulating immune cell differentiation and function is crucial for correcting the state of immune imbalance in T2DM and thus essentially controls chronic inflammation.

4.4. Anti-oxidative stress and mitochondrial protection

TCM, by improving the gut microbiota to alleviate oxidative stress, is considered a promising strategy for treating diabetes. As an illustration, studies on T2DM mouse models have indicated that both inulin and oligofructose can increase the diversity and abundance of the gut microorganisms and greatly relieve the different symptoms of metabolic diseases. In particular, oligofructose was found to act more positively on the abnormality of colonic glucose metabolism, reduce fat cell hypertrophy, lower liver mass, and restore histological alterations compared to inulin which was found to be more effective in reducing the oxidative stress level [146]. Likewise, APS has also shown dual therapeutic efficacy in the model of diabetic nephropathy (DN) due to the enrichment of healthy gut microbiota composition and inhibition of oxidative stress as well as inflammatory processes. The changes were brought about by increased expression of the main antioxidant genes and proteins (Nrf-2, GCLC, NQO1, HO-1), causing the increase of gut microbiota-mediated antioxidant enzyme activity (GSH, GSH-Px, SOD) and decrease in lipid peroxidation biomarkers (MDA) [147]. Mulberry fruit polysaccharides altered the structure of gut microbiota in *db/db* mice and increased cellular antioxidant capacity through increased SOD, GSH-Px and CAT activities, lowering the burden of oxidative stress [148]. Researchers have already established that the TCM formula Chaihu Shugan Powder could be used to effectively restructure gut microbiota population and alleviate the mitochondrial oxidative stress (OS) of gastric tissue in rats with functional dyspepsia (FD) thus exhibiting an anti-oxidative stress effect [149]. Additionally, AS-IV, SF-Alg, FMP, DOP and Baihu Renshen Decoction mentioned earlier have been shown to inhibit the effects of oxidative stress [120, 124, 137, 138, 140]. Although exact molecular mechanisms whereby TCM directly enhances mitochondrial functionality by regulating gut microbiota remain to be elucidated, its anti-oxidative effects alone are enough to counteract mitochondrial injury and further preserve cellular functioning. With the anti-inflammatory property of TCM, it is hypothesized that TCM may offer new therapeutic avenues for improving energy metabolic disorders in T2DM by blocking the vicious cycle of "oxidative stress-mitochondrial damage-inflammation."

4.5. Regulation of gut-brain axis signaling

According to recent studies, active components of TCM and herbal formulas have the potential to relieve diabetes-related pathological conditions through the regulation of the microbiota-gut-brain axis. Empirical evidence indicates that this mechanism plays an important role in diabetes prevention and management. As an example, in a mouse model of T2DM, total flavonoids of *Astragalus membranaceus* (TFA) had a significant role in improving brain function by modulating the gut-brain axis. TFA achieved this by initiating the proliferation of beneficial gut microbiota, which in turn restored the integrity of the blood-brain barrier, maintained hippocampal synaptic activity, as well as decreased fasting glucose and food intake [150]. The extract of Pueraria Thomsonii Radix (PTR) was found to be significantly effective in lowering the F/B ratio in the *db/db* mouse model. Mechanistically, PTR activates the gut-brain axis, resulting in the elevation of intestinal gamma-aminobutyric acid (GABA) levels, reducing the hypothalamus-pituitary-adrenal (HPA) axis activity, and hence reducing serum cortisol and increasing glucose metabolism [151]. White hyacinth bean polysaccharide (WHBP) regulates the activity of HPA axis by restoring the intestinal barrier function and stimulating the SCFA biosynthesis in T2DM rats. This intervention significantly prevented excessive production of CRH, ACTH, and corticosterone and thus improved glycemic control [152]. Sinomenine regulated the microbiota of T2DM rats by reducing intestinal barrier permeability and integrity. It also prevented NLRP3-induced neuronal ferroptosis, hippocampal pathological damage in diabetic rats, and thus, relieved cognitive dysfunction [153]. Treatment with Jiangtang Sanhao Formula (JTSHF) in T2DM mice has a significant impact on the gut microbiota composition and its associated metabolite profiles. The formula enhances colonic G protein-coupled receptor expression (GPR41/GPR43), raises POMC levels, and inhibits hypothalamic AgRP and NPY expression. Both up-regulation of serum GLP-1 and reduction of ghrelin are involved in improving glucose and lipid homeostasis through hypothalamic feeding centre regulation [154]. These findings indicate that TCM does not merely affect the peripheral metabolic organs, but also affects the central regulation of appetite, energy metabolism, and even cognitive functions through the mediation of the complex gut-brain communication network. This is a very clear representation of the therapeutic philosophy of TCM known as the "holistic concept".

4.6. Circadian rhythm synchronization interventions

According to recent studies, TCM has been shown to treat T2DM by regulating the circadian rhythms. On the one hand, TCM can alter the composition of the intestinal microbiota and restore SCFA and bile acid metabolism to control circadian rhythms, as discussed earlier. On the other hand, TCM has the ability to control the circadian rhythms *via* different paths. Research shows that *Lycium barbarum* polysaccharides (LBPs) increase the expression of the *Clock* and *Bmal1* genes in diabetic rats, and in turn, promote the improvement of the diurnal glucose profiles and the responsiveness of insulin [155]. Modified Suanzaoren Decoction (MSZRD) alleviated circadian rhythm disorder in insomniac mice by significantly suppressing the serum orexin-A level and hypothalamic *OX2R* mRNA expression. These changes then affected the balance of the hypothalamic-pituitary-adrenal (HPA) axis and the secretion of neurotransmitters related to it [156]. In *APP/PS1* Alzheimer mice, Guben Jiannao Ye (GBJNY) improved cognitive function and circadian rhythm by PI3K/Akt/mTOR pathway regulation and clock gene expression (*Per1*, *Per2*, *Clock*, *Cry1*, *Cry2* and *Bmal1*) [157]. Thus, TCM has the potential of amelior-

ating circadian rhythm disorders in T2DM by regulating the gut microbiota and its metabolites, as well as directly altering the expression of circadian clock genes. The mechanisms that have been identified are not only helpful in the recovery of blood glucose and insulin sensitivity, but are also beneficial in the treatment of T2DM associated sleep disorders and cognitive impairment. TCM, with its double mechanism of action, i.e., the microbiota-metabolite pathway and direct intervention in host biological clock mechanisms, can be used as a therapeutic option to resynchronize the disturbed circadian rhythms in T2DM patients, which is of great importance when restoring the general metabolic homeostasis.

4.7. Amelioration of cardiovascular complications

New findings indicate that multiple active ingredients and herbal preparations of TCM are able to reduce cardiocerebrovascular conditions through regulation of the gut microbiota and offer new opportunities in cardiovascular disease treatment in diabetes.

As an example, it has been established that BBR can simultaneously inhibit microbial choline trimethylamine-lyase (CutC) and host flavin-containing monooxygenase (FMO). This double block successfully eliminates the two-stage biotransformation of dietary choline into the pro-atherogenic metabolite trimethylamine N-oxide (TMAO). The effectiveness of this mechanism was verified in a 4-month study, in which oral BBR treatment of 21 atherosclerotic patients resulted in a 3.2% average decrease in plaque score as well as significant reductions in both fecal and plasma TMAO levels [158]. In a murine model of L-carnitine-induced atherosclerosis, supplementation with ginger essential oil (GEO) and its component, citral, not only lessened the formation of atherosclerotic plaque but also significantly improved a set of metabolic indices, including lipid profiles, glycemic control, insulin resistance, inflammation, and plasma TMAO concentrations [159]. Similarly, allicin administration to ApoE^{-}/$^{-}$ mice significantly decreased aortic lesions and serum concentration of TMAO. Its clinical significance was supported in a human experiment where one week of raw garlic juice intake reduced TMAO levels in high-TMAO producers and increased their microbial diversity of the gut. Mechanistically, allicin was found to directly inhibit the production of TMA and its precursors by microbes thus preventing formation of TMAO at the site of origin [160]. The salvianolic acid A (SalA) treatment in Zucker diabetic fatty rat models not only increased the richness and diversity of the gut microbiota and homeostasis of core microbial populations but also restored the impaired intestinal epithelial barrier. This barrier function reinforcement was able to reduce the translocation of the lipopolysaccharide (LPS) into systemic circulation, thus reducing the subsequent systemic inflammatory response (e.g., TNF-α, IL-6). Taken together, all these effects contributed to the improvement of insulin resistance, hepatic steatosis, and dyslipidemia [161]. There is also encouraging evidence on herbal formulas. Qingxin Jieyu Granules (QXJYG) were discovered to reconfigure the dysbiotic gut microbiota and the resulting bile acid (BA) metabolic signature in mice with diet-induced atherosclerosis. In particular, QXJYG helped synthesize BAs using cholesterol through up-regulation of the main hepatic enzyme CYP7A1 and simultaneous inhibition of the intestinal negative feedback signal driven by FGF15. This mechanism increased the rate of cholesterol catabolism and excretion, which resulted in the improvement of dyslipidemia and delayed the development of atherosclerosis [162]. Moreover, Buzang Tongluo Formula (BZTLF) was found to alleviate diabetic lower-limb ischemia based on two mechanisms. In an animal model, BZTLF was not only capable of restoring blood flow and capillary density in the ischemic limb, partly by regulation of vascular endothelial growth factor (VEGF) signaling pathway, but also of changing the gut microbiota. This remodeling was marked by the significant enrichment of beneficial genera, such as *Akkermansia* and *Bifidobacterium*, and the repression of a number of pathogenic bacteria. More importantly, correlation analysis demonstrated that the above changes in the gut microbiota were significantly related to the enhancement in the VEGF signaling pathway and the metabolic indicators [163].

To sum up, these results highlight the immense potential role of TCM in a multi-target therapeutic approach. These interventions have cardioprotective effects as a result of various, interrelated mechanisms by which the gut microbiota is modulated, such as the inhibition of harmful metabolites, the strengthening of the intestinal barrier, and the reprogramming of host metabolism. The effects of TCM interventions on key gut microbiota-related metabolites and physiological outcomes in T2DM are summarized in Table 2, and the corresponding intervention strategies through the gut microbiota are illustrated in Fig. 3.

5. Clinical efficacy: evidence from TCM interventions on glycemic improvement and gut microbiota regulation

5.1. Macro-level evidence overview from systematic reviews and meta-analyses

The effectiveness of TCM treatments in T2DM has been assessed and discussed in multiple systematic reviews and meta-analyses. In one critical analysis, a combination of five randomized controlled trials (RCTs) established that TCM interventions were able to significantly improve HbA1c, fasting and postprandial blood glucose, insulin resistance, and β-cell function in patients, and found an increased population of *Bacteroides* [164]. Another meta-analysis (12 RCTs) on traditional Chinese herbal formulas (CHF) plus metformin also showed that the combination therapy was more effective when compared to metformin monotherapy in enhancing glycemic control and it was more effective in optimizing the composition of gut microbiota including increasing *Bifidobacterium*, *Lactobacillus*, and *Bacteroides* and decreasing potentially harmful bacteria [165]. All this high-level evidence demonstrates the clinical efficacy of TCM and its relation to gut microbiota modulation.

5.2. Clinical studies on key traditional Chinese medicine monomers and formulas

A multi-center, double-blind RCT also examined the outcomes of BBR alone, *Bifidobacterium* alone, the combination, and a placebo (n = 297). It was found that the BBR alone group and the combination group achieved statistically significant reduction in FPG and PPG. Importantly, the combination group was the only one in which there was a statistically significant decrease in HbA1c levels and it can be assumed that *Bifidobacterium* might improve the long-term glycemic control of BBR. Moreover, BBR (alone or combined with other substances) exerted much more regulatory influence on the gut microbiome than *Bifidobacterium* or placebo alone, thus reconfirming the ability of BBR to change the gut microbiome and implying that combined probiotic treatments can have synergistic effects [166].

Two well-conducted, double-blind RCTs (120 and 187 subjects, respectively) of the classic formula GQD gave very strong evidence [167, 168]. GQD has been proven to be effective not just in reducing HbA1c, FPG, and PPG in T2DM patients (one study even showed a dose-effect relationship), but its underlying mechanism is likely to be the presence of a large amount of the critical butyrate-producing bacterium, *Faecalibacterium*. But more importantly, the study revealed a strong association between the level of the bacterium and better glycemic control and lower ser-

Table 2 Summary of the effects of TCM interventions on key gut microbiota-related metabolites and physiological effects in T2DM.

Metabolite/effect	Change after TCM intervention	Main physiological role	Relevant regulatory mechanisms by TCM	Representative TCM examples	Ref.
SCFAs (butyrate, propionate, acetate, total SCFAs)	Increased	Energy source; intestinal barrier; anti-inflam.; GLP-1/PYY↑; β-cell↑; epigenetics; glucose/lipid metab.	Gut microbiota: F/B ratio↓; SCFA bacteria↑ (*Butyricimonas*, *Coprococcus*, *Ruminococcus*)	BBR; APS; AS-IV; FTZPs	116-121
BCAAs (leucine, isoleucine, valine)	Decreased	IRS phosphorylation (mTORC1 activation); by-product toxicity	BCAA regulation: BCKDC activity↑, BCKDHA/BCKDK phosph.↓; microbiota BCAA synthesis↓; *Bacteroides* influence	BBR; konjac glucomannan; SF-Alg	122-124
Bile acids (BAs)	Metabolic profile optimization/signaling regulated	Glucose/lipid metab. (FXR, TGR5); FGF19/FGF15↑; GLP-1↑; gut microbiota	BA conversion regulation; altered BA profiles; hepatic synthesis (*CYP7A1*); FXR/TGR5 signaling	WESB/TFSB/baicalin; Modified GQD; JTSH pill; JGT capsule	125-129
Lipopolyscharide (LPS) translocation/levels	Reduced translocation/levels	Endotoxemia; inflammation; insulin resistance; β-cell damage	Barrier repair; TJPs↑; LPS translocation↓; Gram-negative bacteria↓; LPS-TLR4 inhibition	Puerarin; schisandrin C; *Atractylodes macrocephala*; baicalein; Baochi Pill; FTZPs	130-135
Inflammatory response	Alleviated/inhibited	Insulin resistance↑; insulin sensitivity↓; β-cell damage; glucolipid metabolism effects	Multi-pathway anti-inflammatory: LPS↓; SCFAs↑; microbiota balance; barrier repair; TLR4/NF-κB inhibition; immune regulation (macrophages, Treg/Th17)	Inhibition of inflammatory signalling pathways: licorice extract; FMP; DOP; AEPSa; Baihu Renshen Decoction. Regulating immune cells: ginsenoside Rg1; TGP; hawthorn extract; inulin; NHD	136-145
Oxidative stress	Reduced	ROS↑→cell/tissue damage→insulin resistance, β-cell dysfunction, T2DM complications	Direct ROS scavenging; antioxidant enzymes (SOD, GSH-Px, CAT)↑; inflammation↓; mitochondrial function↑; microbiota modulation	Inulin; APS; mulberry fruit polysaccharide; Chaihu Shugan Powder; AS-IV; SF-Alg; FMP; DOP; Baihu Renshen Decoction	146-149
Gut-brain axis	Improved signaling	Appetite/energy regulation; mood/stress/cognitive control; insulin secretion/sensitivity (GLP-1, PYY)	Neurotransmitter regulation (GABA, 5-HT); vagus nerve (SCFAs); gut peptides (GLP-1, PYY); HPA axis modulation	TFA; PTR; WHBP; sinomenine; JTSHF	150-154
Circadian rhythms	Synchronized/rhythm restored	Metabolic/hormonal/behavioral rhythms; energy balance; glucose homeostasis	Restores microbiota diurnal rhythms; regulates host clock genes (*Clock*, *Bmal1*) *via* metabolites (SCFAs, BAs)	LBPs; MSZRD; GBJNY	155-157
Gut and cardiovascular system	Improved	Harmful: TMAO, LPS, AAAs metabolites→athero sclerosis, inflammation, thrombosis. Protective: SCFAs→vasculo protection, anti-inflammation	Gut microbiota remodeling; reduce the production of TMAO; intestinal barrier repair; BA synthesis regulation; VEGF pathway modulation	Berberine; GEO/Citral; allicin; SalA; QXJYG; BZTLF	158-163

APS, *Astragalus* polysaccharide; AS-IV, astragaloside IV; FTZPs, Fufang Zhenzhu Tiaozhi Formula polysaccharides; SF-Alg, *Sargassum fusiforme* alginate; WESB, water extract of *Scutellaria baicalensis*; TFSB, total flavonoids of *Scutellaria baicalensis*; GQD, Gegen Qinlian Decoction; JTSH, Jiangtang Sanhuang; JGT, Jingangteng; FMP, Fructus Mori polysaccharide; DOP, *Dendrobium officinale* polysaccharides; AEPSa, *Cordyceps sinensis* polysaccharide; TGP, total glucosides of paeony; NHD, National Herbal Drink; TFA, total flavonoids of *Astragalus membranaceus*; PTR, Pueraria Thomsonii Radix; WHBP, white hyacinth bean polysaccharide; JTSHF, Jiangtang Sanhao Formula; LBPs, *Lycium barbarum* polysaccharides; MSZRD, Modified Suanzaoren Decoction; GBJNY, Guben Jiannao Ye; GEO, ginger essential oil; SalA, salvianolic acid A; QXJYG, Qingxin Jieyu Granules; BZTLF, Buzang Tongluo Formula.

um inflammation, which gives a clear explanation based on the microbiome why GQD works.

An RCT (n = 38) on CP extract [169] showed that CP was comparable to glipizide in improving glycemic indicators such as HbA1c, but more significantly improved blood lipids (TG, HDL-c) and blood pressure (DBP) without affecting liver and kidney function. Mechanistic exploration revealed that CP treatment was accompanied by an increase in the abundance of key beneficial gut bacteria like *Faecalibacterium* and *Akkermansia*, as well as changes in beneficial metabolites (e.g., SCFAs and unconjugated BAs), suggesting that it broadly improves T2DM-related metabolic disorders by regulating the gut microbiota through multiple pathways.

5.3. Integrated traditional Chinese and Western medicine treatment

In addition to the aforementioned studies on single TCM herbs or formulas, combining TCM with conventional Western medicine (CWM) is a common clinical practice, and its efficacy has also been supported by network meta-analyses. A network meta-analysis, which was a synthesis of RCTs in the last ten years [170], found that some TCM preparations (Shenqi Jiangtang Granules, Jinlida Granules) plus conventional Western medicines (sulfonylureas, metformin, insulin) significantly reduced FBG and 2hPG and boosted clinical total effectiveness, and was thus better than the use of a conventional Western medicine alone. This study also ranked different TCM combination regimens in order of their efficacy on different outcome indicators, providing a guide to individualized clinical medication. It is consistent with the findings of the preceding meta-analysis of CHF + metformin [165], collectively emphasizing the advantages of integrated traditional Chinese and Western medicine in T2DM treatment.

5.4. Comprehensive review of clinical evidence and future perspectives

To sum up, an ever-growing amount of clinical evidence, especially that found in high-quality RCTs and systematic reviews, provides strong support to the fact that TCM can improve T2DM through regulation of the gut microbiota. But this sphere has its own issues: it is necessary to conduct more large-scale and long-term studies using RCT methodology with high quality design; efforts must be made to resolve the issue of standardization of Chinese medicines (in particular, compound formulas); multi-omics technology is required to better understand individualized microbiota-mediated processes; the evaluation of long-term safety and effects on other significant outcomes, such as inflammation, should be strengthened. These challenges will play an important role in encouraging a larger presence of TCM in the precision prevention and treatment of T2DM. The clinical evidence of TCM in T2DM management and gut microbiota modulation is summarized in Table 3.

6. Conclusion

TCM has demonstrated great therapeutic prospects in the context of T2DM by means of gut microbiota-mediated mechanisms. As this review shows, there is a strong indication that TCM measures can be used to remodel the intestinal microbiome ecosystem, leading to the increased synthesis of useful metabolites, the recovery of intestinal barrier function, and the correction of

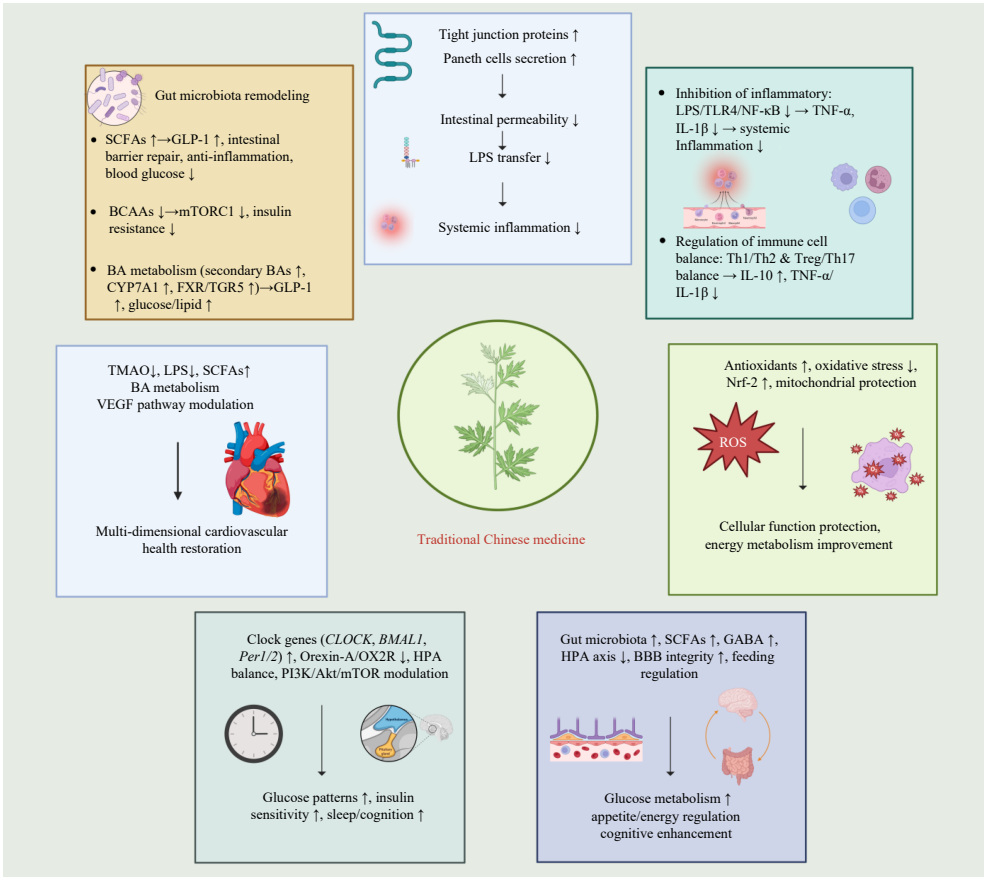

Fig. 3 Intervention strategies of traditional chinese medicine in type 2 diabetes mellitus through gut microbiota (created in https://BioRender.com).

Table 3 Clinical evidence of TCM in T2DM management and gut microbiota modulation.

Evidence type/study design	Intervention(s)	Key T2DM clinical outcomes improved	Gut microbiota & mechanistic insights	Ref.
Systematic review & meta-analysis (5 RCTs)	General TCM interventions	HbA1c (−0.69%), FPG (−0.87 mmol·L^{-1}), 2hPG (−0.83 mmol·L^{-1}), HOMA-IR (−0.99), HOMA-β (0.54)	*Bacteroides*↑0.87%; microbiota changes; diversity↑; inflammation unclear	164
Meta-analysis (12 RCTs) based on systematic review	Traditional Chinese herbal formulas (CHF) + metformin (*vs* metformin monotherapy)	HbA1c (−1.49); FPG (−0.83); 2hPG (−1.58); FINS (−1.54); HOMA-IR (−0.64)	Microbiota optimization: beneficial bacteria↑ (*Bifidobacterium*, *Lactobacillus*, *Bacteroides*); harmful bacteria↓ (*Enterobacteriaceae*, *Enterococcus*, *Yeast*)	165
Multi-center, double-blind, parallel-control-led RCT (n = 297 ITT analysis)	Berberine (Be), bifidobacterium (Bi), berberine + bifidobacterium (BB), placebo	FPG: Be/BB↓ 0.50–0.55 mmol·L^{-1}; 2hPG: Be/BB↓; HbA1c: BB↓ 0.23%; TC: Be/BB↓; LDL-C: BB↓; HDL-C: Be/Bi/BB↑	Microbiota changes: gene richness↓, *Roseburia*↓, *Blautia/Ruminococcus*↑ (Be/BB); *Actinobacteria*↑ (Bi); *Proteobacteria*↑ (Be)	166
RCT (n = 120)	Gegen Qinlian Decoction (GQD) *vs* placebo (PLB)	HbA1c↓ 0.52%; FPG/2hPBG↓; weight/BMI↓; LDL-C↓; systemic inflammation↓; coagulation markers↓	Microbiota changes: diversity↓, *Faecalibacterium*↑, *Romboutsia/Coprococcus*↓; serum SCFAs/MCFAs↑	167
Double-blinded, placebo-controlled RCT (n = 187) with dose-dependent arms	Gegen Qinlian Decoction (GQD) high dose (HD), moderate dose (MD), low dose (LD), placebo	FBG: HD/MD: −1.46/−1.09 *vs* placebo/LD: −0.16/−0.24 mmol·L^{-1}; HbA1c: HD/MD: −0.88%/−0.75% *vs* placebo/LD: −0.35%/−0.36%; HOMA-β↑ (HD); ORM↓ (HD)	Microbiota: dose-dependent gut changes; 47 GQD-enriched phylotypes (17 negatively correlated with FBG, 9 with HbA1c); *F. prausnitzii* enrichment correlated with improved glucose metrics	168
Open-label, randomized controlled trial (n = 38)	*Cyclocarya paliurus* leaves extracts (CP) *vs* glipizide (G group)	CP effects: improved HbA1c, FBG, 2hPBG, OGTT AUC (*vs* glipizide); better TG, HDL-c, DBP than glipizide	Microbiota/metabolites: *Faecalibacterium*, *Akkermansia*↑; *Prevotella* 9↓; SCFAs↑, unconjugated BAs↑; beneficial bacteria negatively correlated with T2DM markers	169
Network meta-analysis & traditional meta-analysis of RCTs	Various TCMs + CWM (e.g., Shenqi Jiangtang Granule + sulfonylurea/metformin; Jinlida Granule + insulin) *vs* CWM alone	Glycemic: significant FBG (−2.17) & 2hPG (−1.94) reductions; efficacy: OR = 1.73 for clinical improvement; safe profile	Not reported	170

metabolic dysfunction. The multi-target nature of TCM compounds—ranging from single bioactive molecules to complex polyherbal formulations—offers a promising complement to conventional antidiabetic therapies.

However, several critical knowledge gaps impede clinical translation. The mechanistic basis for TCM's therapeutic effects remains incompletely understood, with current evidence predominantly correlative rather than causative. The inability to distinguish between direct pharmacological actions and microbiota-mediated effects represents a fundamental conceptual challenge. Furthermore, methodological limitations including over-reliance on animal models, inadequate standardization of herbal prepara-

tions, and superficial microbiome characterization restrict the reproducibility and clinical relevance of existing findings.

The next wave of studies should focus on mechanistic research using germ-free animals and sophisticated *in vitro* models to establish a causal relationship between changes in microbiota and therapeutic results. Rigorous chemical standardization of TCM preparations, coupled with comprehensive pharmacokinetic profiling of bioactive compounds and their microbial metabolites, is essential for reproducible research. More importantly, large scale, longitudinal clinical studies adopting multi-omic strategies are urgently required to confirm preclinical results and formulate personalized treatment plans depending on personal microbiome fingerprints.

An effective implementation of TCM in evidence-based diabetes management will necessitate dealing with such methodological issues and maintaining the general holistic nature of traditional herbal medicine. These attempts can be expected to release new treatment options that make use of the complex host-microbiome-drug interactions to achieve better results in metabolic health.

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Declaration of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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