Am J Transl Res 2025;17(10):7586-7601
www.ajtr.org /ISSN:1943-8141/AJTR0167628

Review Article

Mechanism of action and research advancements of Qi-tonifying traditional Chinese medicine in the treatment of type 2 diabetic mellitus

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Received July 22, 2025; Accepted September 20, 2025; Epub October 15, 2025; Published October 30, 2025

Abstract: Type 2 diabetes mellitus (T2DM) is a metabolic disorder marked by persistent hyperglycemia, potentially leading to irreversible organ damage and posing significant risks to patients' health and life. The prevailing treatments for T2DM consist of oral medications and insulin injections; nonetheless, they are constrained by numerous adverse reactions, drug resistance, and a singular mechanism of action. Qi-tonifying traditional Chinese medicine (QTTCM) is efficacious in the prevention and treatment of T2DM. Research indicates that QTTCM primarily modulates the PI3K/Akt, Insulin Receptor Substrate 1 (IRS-1)/phosphatidylinositol 3-Kinase(PI3K)/Protein kinase B(Akt), glucose transporter (GLUT) and Activated Protein Kinase (AMPK) pathways to enhance the proliferation of pancreatic islet β-cells, restore their functionality, ameliorate insulin resistance (IR), rectify disturbances in glucose and lipid metabolism, mitigate oxidative stress, and suppress inflammation. Consequently, QTTCM sustains glucose homeostasis in patients with T2DM through multiple pathways and targets, thereby improving the pathological state of slow metabolism, which is advantageous for the prevention and treatment of T2DM. QTTCM exerts a beneficial therapeutic impact on T2DM by sustaining glucose homeostasis and enhancing metabolic rate in T2DM patients via many pathways and targets.

Keywords: Qi-tonifying traditional Chinese medicine, type 2 diabetes mellitus, mechanism of action

Introduction

Diabetes mellitus (DM) is a chronic hyperglycemic condition characterized by inadequate insulin secretion or insulin resistance (IR), along with disrupted metabolism of carbohydrates, lipids, proteins, and other substances [1]. A report published by the IDF in 2025 anticipates that the global population of individuals with diabetes would rise to 853 million by 2050, with 90% diagnosed with type 2 diabetes mellitus (T2DM). This presents a significant risk to human health and the global economy [2]. The prevalent treatments for T2DM mostly include insulin injections, oral pharmacotherapy, physical activity, and nutritional management [3].

Nonetheless, prolonged administration of insulin or diverse hypoglycemic agents may induce a range of adverse effects, including weight gain, hypoglycemia, drug resistance, and gastrointestinal distress [4]. Therefore, the prevention and management of T2DM is of fundamental importance. Traditional Chinese medicine (TCM) has a long history of understanding diabetes and also has substantial advantages in its treatment [5]. The Huangdi Neijing (The Yellow Emperor's Classic of Internal Medicine) states that the etiology of DM is mostly attributed to excessive dry heat, resulting in a deficit of yin fluids. Over time, this impacts qi insufficiency, ultimately resulting in a state characterized by both qi and yin deficiency. The primary clinical signs encompass polydipsia, polyphagia, polyuria, and weight reduction [6]. Contemporary Chinese medicine frequently employs techniques to enhance vitality and replenish yin for the treatment of diabetes. Nourishing yin

https://doi.org/10.62347/HXCH1009

herbs are highly effective in the treatment of diabetes. Refer to the publication of Dai et al. for additional information [7]. In TCM, diabetes is predominantly associated with the lung, spleen, and kidney organs [8]. Qi-tonifying traditional Chinese medicine (QTTCM) mostly affect the lung, spleen, and kidney meridians, aligning with the disease's location. Pharmacological research indicates that tonic herbs are abundant in diverse active compounds and can contribute positively to the prevention and management of T2DM by mechanisms including the reduction of IR, regulation of insulin secretion, inhibition of the inflammatory microenvironment, and mitigation of oxidative stress. This article examines recent advancements in research regarding the application of QTTCM for the prevention and treatment of T2DM. It offers a crucial theoretical foundation for the rational development and clinical application of Chinese herbal medicines in the prevention and treatment of T2DM, while also establishing a basis for clarifying the contemporary scientific implications of the multi-component, multi-pathway, and multi-target mechanisms of these herbal medicines in diabetes management.

The perspective of traditional Chinese medicine on diabetes

TCM possesses a rich history in the comprehension of DM, categorizing it as "xiao ke disease". In the Yuan Dynasty, the physician Zhu Danxi documented in the "Xiaoke Chapter" of his work "Danxi Xinfang": "Upper Xiaoke impacts the lungs, presenting with excessive thirst without appetite, while bowel movements remain normal; middle Xiaoke influences the stomach, marked by excessive thirst and yellowish-red urine; lower Xiaoke affects the kidneys, characterized by cloudy urine resembling grease, a dark complexion, and emaciation". This differentiates upper Xiaoke as impacting the lungs, middle Xiaoke as influencing the stomach, and lower Xiaoke as affecting the kidneys. Certain medical practitioners have put forth the theory of "spleen deficiency leading to consumption", contending that the spleen plays a crucial role in transformation and transportation. The fundamental role of food and drink in the body depends on the movement of spleen qi, which ascends to the head and face while descending to the internal organs and bones to fulfill its nourishing purpose. According to the Suwen, when fluids are ingested, their essence and qi disseminate, rising to the spleen. The spleen's qi disseminates this essence, which subsequently ascends to the lungs, regulates the waterways, and descends to the bladder. The distribution of fluids within the body is essential, and the five zang organs operate in a harmonious manner. When the qi of the zang-fu organs is deficient and fails to transport and transform effectively, it can become stagnant and subsequently transform into heat. This process can harm yin and deplete qi, ultimately resulting in the development of DM [9]. According to the established medical principle of "tonifying deficiency", QTTCM can enhance symptoms in DM patients through mechanisms that include tonifying qi, bolstering the body's defenses, and regulating organ function. Consequently, QTTCM may act as a valuable intervention for the clinical prevention and management of T2DM.

Mechanisms of QTTCM in anti-T2DM

QTTCM exert their anti-T2DM effects through multiple targets and pathways. During our review and synthesis, we found that the pharmacological effects of QTTCM in treating T2DM can be primarily summarized as follows: promoting the proliferation of pancreatic β-cells and restoring their function, improving IR, regulating disorders in glucose and lipid metabolism, alleviating oxidative stress, and suppressing inflammatory responses. However, these factors are not independent of one another; rather, they exhibit significant interactions.

The onset and progression of T2DM are primarily driven by IR, which can accelerate disease progression independently of risk factors such as obesity [10]. In the IR state, peripheral tissues such as muscle, adipose tissue, and liver exhibit reduced insulin sensitivity, leading to persistently elevated blood glucose levels. To maintain glucose homeostasis, pancreatic β-cells compensatorily increase insulin secretion, resulting in hyperinsulinemia. Prolonged hyperglycemia and hyperinsulinemia not only exacerbate IR but also directly damage pancreatic tissue and promote β-cell apoptosis by inducing oxidative stress (manifested as decreased superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activity and elevated oxidative markers

such as Malondialdehyde (MDA) and Nitric Oxide (NO)). This ultimately forms a vicious cycle of "IR-β-cell dysfunction-glucose dysregulation" [10-12]. Notably, the hallmark pathological features of T2DM involve a reduction in β-cell mass and functional decline against a backdrop of IR. The plasticity of insulin secretion - its capacity for dynamic responses to stimuli such as glucose and inflammatory factors - is significantly impaired. β-cell apoptosis represents the key mechanism underlying this functional failure [13, 14]. Concurrently, impaired glucose homeostasis also involves dysregulation across multiple metabolic pathways, including glycogen synthesis, breakdown, and gluconeogenesis. Within this complex pathological network, lipid metabolism abnormalities - such as elevated total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL) levels alongside reduced high-density lipoprotein cholesterol (HDL) - serve as key catalysts. Through lipotoxicity, these abnormalities exacerbate IR and β-cell damage [15]. Chronic low-grade inflammation is mediated by the upregulation of proinflammatory factors such as Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6) and Interleukin-1β (IL-1β), which interfere with insulin signaling and promote IR [16-19]. Oxidative stress forms multiple positive feedback loops with inflammatory responses, lipotoxicity, and hyperglycemia, collectively driving disease progression. Therapeutically, metformin - as a first-line drug for T2DM - inhibits hepatic gluconeogenesis by activating the Activated Protein Kinase (AMPK) signaling pathway, targeting the core pathway of impaired glucose metabolism [20]. This further confirms the intertwined role of the glucose, lipid, inflammation, and oxidative stress network in the mechanisms of T2DM. This report involves a comprehensive discussion based on QTTCM and detailed illustrations are provided (see **Figure 1**).

The preventive and therapeutic effects of QTTCM and its active components on T2DM

QTTCM has the potential to safeguard pancreatic islet cells and restore their functionality, regulate insulin secretion, reduce oxidative stress, and address dysregulation of glucose and lipid metabolism. Additionally, they may inhibit the inflammatory microenvironment and influence the diversity of the gut microbiota, among other benefits. This review outlines the various pathways, targets, and mechanisms through which specific herbs contribute to the prevention and treatment of T2DM. We provide a summary of the preventive and therapeutic effects of commonly used QTTCM, including Astragalus membranaceus, Codonopsis pilosula, Panax ginseng, Panax quinquefolius, Dioscorea opposita, Glycyrrhiza uralensis, Atractylodes macrocephala, Codonopsis lanceolata, and honey, along with their active ingredients and mechanisms of action related to T2DM (See **Table 1**).

Astragalus

Astragalus, a Chinese herbal medicine, is derived from the roots of the leguminous plants Mongolian Astragalus and Podastrum Astragalus. It is known for its ability to strengthen the spleen and replenish the middle, elevate yang and counteract sagging, as well as benefit the protective qi and solidify the exterior [21]. Astragalus primarily comprises astragalus polysaccharides, flavonoid compounds, saponin compounds, and alkaloids [22]. Astragalus has the potential to effectively alleviate IR and restore glucose homeostasis within the body. The liver serves as the central site for glucose synthesis and metabolism, and it is also the primary target organ for the development of IR [23]. Astragalus polysaccharides play a significant role as macromolecules in Astragalus. When combined with berberine, they have the potential to reduce IR in human liver cancer cells (HepG2). The underlying mechanism includes the inhibition of Ca^{2+} activation, downregulation of p-FoxO1^{Ser256} and phosphoenolpyruvate carboxykinase (PEPCK) protein expression, and activation of glucose transporter 2 (GLUT2) proteins, which collectively contribute to the regulation of glycogen synthesis and the alleviation of IR [24]. Astragalus polysaccharides have the potential to enhance metabolic irregularities induced by endoplasmic reticulum stress through the inhibition of glycogen synthase kinase 3β (GSK3β). Additionally, they may improve liver insulin sensitivity and reduce fasting blood glucose (FBG) levels in mice [25]. Gu and other researchers also discovered that it can reduce endoplasmic reticulum stress by inhibiting GSK3β expression, and can modulate the Sirtuin 1 (Sirt1)/Peroxisome Proliferator-Activated Receptor

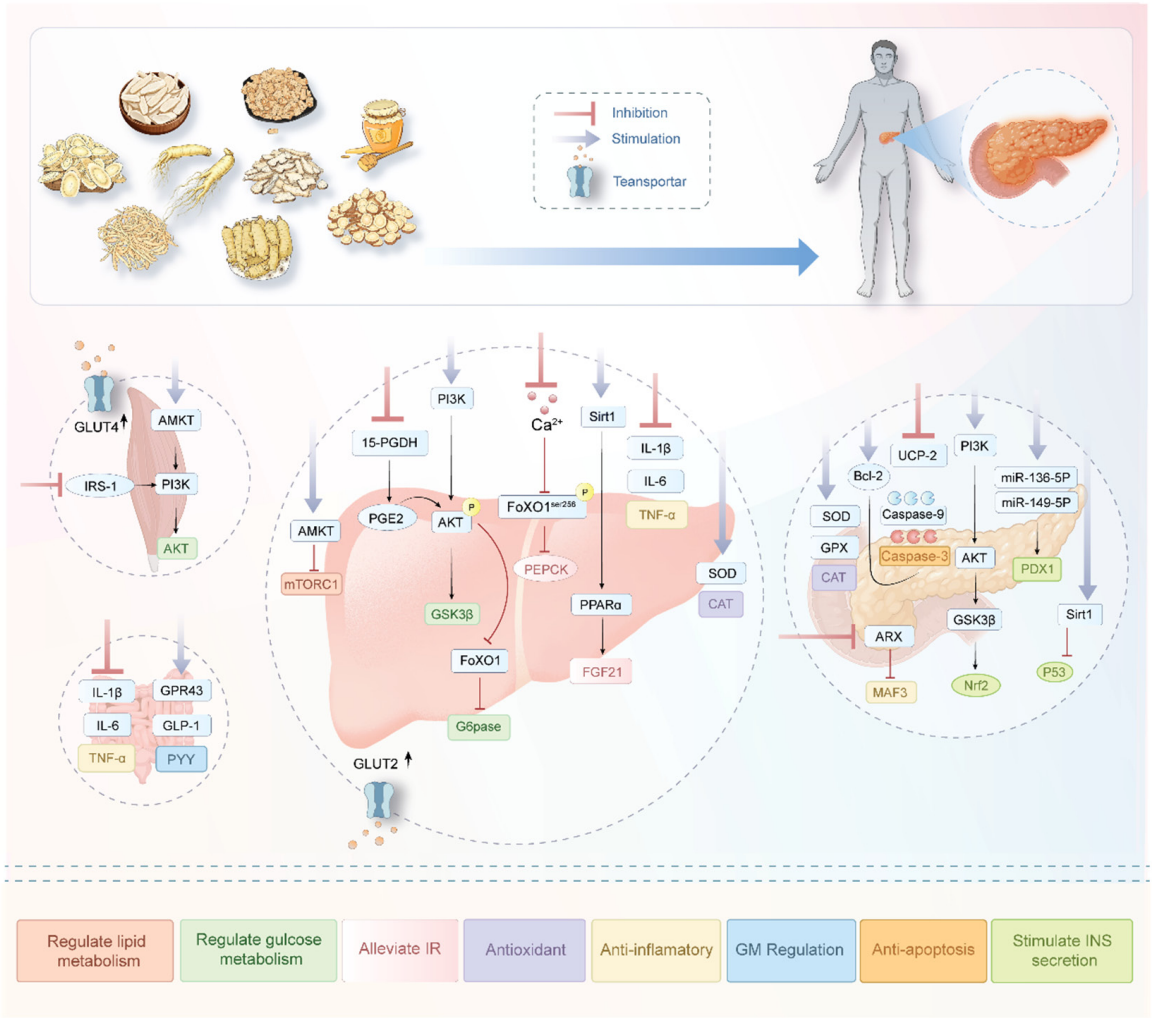

Figure 1. Mechanism of QTTCM in the treatment of T2DM. IR: insulin resistance, INS: insulin, GLUT 2: glucose transporter 2, GLUT 4: glucose transporter 4, AMPK: Activated Protein Kinase, PI3K: Phosphatidylinositol 3-Kinase, Akt: Protein kinase B, IL-1β: Interleukin-1β, IL-6: Interleukin-6, TNF-α: Tumor Necrosis actor-α, GPR43: G Protein-Coupled Receptor 43, GLP-1: Glucagon-Like Peptide-1, PYY: Peptide YY, mTORC1: mechanistic target of rapamycin1, 15-PGDH: 15-Hydroxyprostaglandin Dehydrogenase, PGE2: Prostaglandin E2, GSK3β: Glycogen Synthase Kinase 3 β, FoxO1: Forkhead Box Protein O1,G6Pase: Glucose-6-Phosphatase, PEPCK: phosphoenolpyruvate carboxykinase, SIRT1: Sirtuin 1, PPARα: Peroxisome Proliferator-Activated Receptor α, FGF21: Fibroblast Growth Factor 21, SOD: Superoxide Dismutase, CAT: Catalase, GPx: Glutathione Peroxidase, Bcl-2: B-cell Lymphoma-2, Caspase-9: Cysteine-Aspartic Acid Protease-9, Caspase-3: Cysteine-Aspartic Acid Protease-3, ARX: Aristaless Related Homeobox, MAFB: V-Maf Avian Musculoaponeurotic Fibrosarcoma Oncogene Homolog B, UCP-2: Uncoupling Protein 2, Nrf2: Nuclear Factor Erythroid 2-Related Factor 2, PDX1: pancreatic and duodenal ehomebox 1, p53: Tumor Protein P53.

α(PPARα)/Fibroblast Growth Factor 21 (FGF21) signaling pathway to decrease the acetylation level of hepatocytes and regulate glycolipid metabolism molecules, thereby further alleviating IR [26]. Studies indicate that the expression levels of microRNA (miRNA) play a significant role in the onset and progression of diabetes [27]. Astragalus polysaccharides have the capability to regulate miRNAs, thereby playing a role in the development of T2DM. For instance, enhancing the expression of miR-136-5p and miR-149-5p facilitates insulin secretion from pancreatic β-cells and reduces their apoptosis rate in conditions of high-glucose and high-fat stress, while also increasing the expression of pancreatic and duodenal homebox 1 (PDX1). This contributes to the maintenance of pancreatic cell function homeostasis and mitigates the onset and progression of T2DM [28, 29]. Wei discovered that Astragalus polysaccha-

Table 1. Active constituents and their methods of action in typical QTTCM

Herb	Active Ingredient	Target organ	Anti-diabetic effect	Curative mechanism	Ref.
Milkvetch Root	Astragalus polysaccharide	Liver	Regulates gluconeogenesis, Alleviating IR	Inhibition of Ca^{2+} activation, down-regulation of p-FoxO1Ser256 and PEPCK expression, activation of GLUT2	[24]
Milkvetch Root	Astragalus polysaccharide	Liver	Relief of endoplasmic reticulum stress, Alleviating IR	Regulation of GSK3β expression and activation of SIRT1/PPARα/FGF21 signaling pathway	[25, 26]
Milkvetch Root	Astragalus polysaccharide	Liver	Relief of endoplasmic reticulum stress	Upregulation of miR-203a-3p and inhibition of GRP78	[30]
Milkvetch Root	Astragalus polysaccharide	Pancreas	Promote recovery of pancreatic islet cell function	Activation of miR-136-5p, miR-149-5p and PDX1 expression	[28, 29]
Milkvetch Root	Astragaloside IV	Pancreas	Anti-oxidative stress, Improvement of islet cell function	Regulation of Sirt1/p53 and Akt/GSK3β/Nrf2 pathways	[32]
Milkvetch Root	Astragaloside IV	Pancreas	Inhibition of apoptosis	Regulation of the PI3K/AKT pathway	[34]
Codonopsis Lanceolata	C. lanceolata polysaccharide	Liver	Relieves oxidative stress; Reducing IR	Increased expression of SOD and CAT	[39]
Codonopsis Lanceolata	Codonopsis lanceolata water extract	Liver	Promotes lipid metabolism; Improves IR	Activation of the pAkt/pGSK3β signaling pathway	[40]
Ginseng	Ginsenoside Rg1	Liver	Regulation of glucose metabolism	Activation of Akt, inhibition of FoxO1 and G6Pase expression	[44]
Ginseng	Ginsenoside Rg1	Liver	Regulates glucose metabolism; Inhibition of the inflammatory microenvironment	Activation of PI3K/Akt signaling axis and inhibition of G6Pase, IL-1β, IL-6 and TNF-α expression	[45]
Ginseng	Ginsenoside Rb1	Liver	Regulation of glucose metabolism	Inhibition of 15-PGDH, activation of PGE2, AKT, GSK3β expression	[46]
Ginseng	Ginseng extract	Pancreas	Suppression of the inflammatory microenvironment; restoration of islet cell function	Inhibition of ARX and MAFB expression	[42]
American Ginseng	American Ginseng powder	Liver and Pancreas	Promoting lipid metabolism, Relief of oxidative stress, Suppression of inflammation	Increased SOD, CAT and GSH-Px activities and inhibited IL-1β, IL-6 and TNF-α expression	[55]
American ginseng	Malonyl Ginsenosides	Liver and Muscle	Improvement of glucose-lipid metabolism	Regulation of IRS-1/PI3K/AKT and AMPK/ACC pathways	[56]
American Ginseng	Panax quinquefolius	Pancreas	inhibition of apoptosis	Inhibition of UCP-2, caspase-9 expression, Activation of Bcl-2	[52]
Yam	Yam polysaccharide	Liver and Pancreas	antioxidant stress	Enhanced expression of GSH-Px, SOD and CAT	[63]
Yam	Yam gruel	Intestine	Regulates intestinal flora	Regulates GPR43, GLP-1, PYY activity	[64]
Yam	Yam polysaccharide	Liver and adipose tissue	Promotes lipid metabolism, Alleviates oxidative stress	Increased PK, HK and GSH-Px activities and inhibited MDA content	[65]
Licorice	Licochalcone A	Liver	Promote lipid metabolism	Regulates AMPK and mTORC1 expression	[74]
Glycyrrhiza Glabra	Liquiritigenin	Pancreas	Inhibition of apoptosis, Relief of endoplasmic reticulum stress	Down-regulates the expression of Caspase-3, PARP and enhances Bcl-2 activity; inhibits the expression of PERK, eIF-2α and CHOP	[75, 76]

Glycyrrhiza inflata	Licochalcone E	adipose tissue	Promote lipid metabolism	Regulation of the Akt/PPARγ signaling axis	[72]
Glycyrrhiza Uralensis Root	Glycyrin	adipose tissue	Promote lipid metabolism	Activation of PPAR-γ	[73]
Licorice	Licorice extract	Intestine	Promotes lipid metabolism, Suppresses inflammation	Inhibition of IL-6, TNF-α and IL-12 expression	[77]
Baizhu	Atractylenolide I	Muscle	Promote glucose metabolism	Activation of AMPK/PI3K/Akt signaling pathway and GLUT4 expression	[80]
Pseudostellaria Heterophylla	Novel polysaccharide H-1-2	Muscle and adipose tissue	Promote glycolipid metabolism	Regulation of HIF1α and Sirt1 expression	[83, 84]
Tualang Honey	Tualang honey	Pancreas	Inhibition of oxidative stress	Enhanced SOD and GPx activity	[85, 87]

IR: insulin resistance, PEPCK: phosphoenolpyruvate carboxykinase, GLUT 2: glucose transporter 2, GLUT 4: glucose transporter 4, GSK3β: Glycogen Synthase Kinase 3 β, Sirt1: Sirtuin 1, PPARα: Peroxisome Proliferator-Activated Receptor α, FGF21: Fibroblast Growth Factor 21, GRP78: Glucose-Regulated Protein 78, PDX1: pancreatic and duodenal ehomebox 1, Akt: Protein kinase B, Nrf2: Nuclear Factor Erythroid 2-Related Factor 2, PI3K: Phosphatidylinositol 3-Kinase, SOD: Superoxide Dismutase, CAT: Catalase, FoxO1: Forkhead Box Protein O1, ACC: Acetyl-CoA Carboxylase G6Pase:Glucose-6-Phosphatase, IL-1β: Interleukin-1β, IL-6: Interleukin-6, TNF-α: Tumor Necrosis Factor-α, 15-PGDH: 15-Hydroxyprostaglandin Dehydrogenase, PGE2: Prostaglandin E2, ARX: Aristaless Related Homeobox, MAFB: V-Maf Avian Musculoaponeurotic Fibrosarcoma Oncogene Homolog B, GSH-Px: Glutathione Peroxidase, IRS1: Insulin Receptor Substrate 1, UCP-2: Uncoupling Protein 2, caspase-9: Cysteine-Aspartic Acid Protease 9, Bcl-2: B-cell Lymphoma-2, GPR43: G Protein-Coupled Receptor 43, GLP-1: Glucagon-Like Peptide-1, PYY: Peptide YY, AMPK: Activated Protein Kinase, mTORC1:mechanistic target of rapamycin1, PARP: Poly ADP-ribose polymerase, Caspase-3: Cysteine-Aspartic Acid Protease-3, PERK: Protein Kinase R-like Endoplasmic Reticulum Kinase, eIF-2α: Eukaryotic Initiation Factor 2 α, CHOP: C/EBP-homologous protein, HIF1α: Hypoxia-Inducible Factor 1 α, HK: hexokinase.

rides can enhance miR-203a-3p levels in liver, decrease the expression of glucose-regulated protein 78 (GRP78), mitigate endoplasmic reticulum stress, and slow the advancement of diabetes [30]. Astragaloside IV is a triterpenoid glycoside that belongs to the cycloartane class and can be extracted from the water of Astragalus root. It is known for its antioxidant, anti-inflammatory, and anti-apoptotic properties [31]. Lin et al. demonstrated that astragaloside IV has the capacity to inhibit apoptosis via the Sirt1/Tumor Protein P53 (p53) pathway. Additionally, it regulates the Protein kinase B(Akt)/GSK3β/Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) signaling pathway to counteract oxidative stress, enhances pancreatic cell function, and boosts pancreatic cell enzyme activity [32]. The research conducted by Jiang et al. supports the aforementioned explanation, indicating that astragaloside IV has the capability to reduce the apoptosis rate of pancreatic β-cells through the upregulation of the Phosphatidylinositol 3-Kinase (PI3K)/Akt pathway, which in turn enhances insulin secretion and mitigates functional impairment [33, 34].

Codonopsis

Codonopsis (Codonopsis radix) is the dried root of plants from the Codonopsis genus within the Campanulaceae family. This herbal remedy is recognized in TCM for its dual role as both a food and a medicinal substance. It is noted for its ability to tonify the qi of lung and spleen, as well as to generate body fluids to alleviate thirst [35]. The primary active components identified in Codonopsis pilosula consist of phenylpropanoids, terpenoids, triterpenoid saponins, polyacetylenes, and a range of alkaloids [36]. It performs regulatory functions, including the enhancement of glucose and lipid metabolism, as well as the mitigation of oxidative stress. Su et al. successfully extracted a homogeneous polysaccharide known as CPP-1 from Codonopsis pilosula. Experimental results indicated that the oral administration of CPP-1 effectively prevents obesity, enhances dyslipidemia, mitigates IR, and reduces FBG levels in mice [37]. Liu successfully isolated a neutral polysaccharide designated as CERP1 from the extract of Codonopsis pilosula. CERP1 exhibited significant hypoglycemic activity in both in vitro and in vivo studies. Additionally, it has the potential to mitigate oxidative stress, enhance sugar and lipid metabolism, and boost the activity of glycolytic enzymes, thereby contributing to the management of T2DM through these mechanisms [38]. The moderate intake of Codonopsis polysaccharide GLPS has been shown to enhance the activity of antioxidant enzymes, including SOD and CAT, in diabetic mice. This balance of oxidation-reduction contributes to a reduction in FBG levels, effectively alleviating IR and restoring damaged pancreatic signaling pathways [39]. Weight loss in diabetic rats typically results from heightened urinary glucose loss linked to diminished glucose utilization. The oral administration of Codonopsis pilosula water extract has been shown to counteract this effect without elevating triglyceride levels in the body. Furthermore, Codonopsis pilosula water extract can modulate insulin secretion, enhance pancreatic beta cell function, improve hepatic insulin signaling, and address IR [40].

Chinese ginseng

Chinese ginseng (Panax ginseng C. A. Mey.) is the dried rhizome of a perennial herbaceous plant from the Araliaceae family and Panax genus, often referred to as the “king of herbs”. It is recognized for its ability to significantly replenish vital energy, tonify the spleen and lungs, as well as generate body fluids and nourish the blood. Recent pharmacological research indicates that the primary chemical components consist of ginsenosides, essential oils, various amino acids, and trace elements [41]. The effects include enhancing the inflammatory microenvironment, facilitating glucose and lipid metabolism, increasing the abundance of intestinal flora, and regulating glycogen synthesis and gluconeogenesis to sustain glucose homeostasis. Yin et al. demonstrated that ginseng extract can effectively alleviate symptoms in T2DM mice, such as reducing FBG, improving pancreatic tissue pathology, preserving β-cell number and function, and inhibiting the expression levels of Aristaless-related homologous box (ARX) and V-Maf Avian Musculoaponeurotic Fibrosarcoma Oncogene Homolog B (MAFB), while promoting the conversion of pancreatic α-cells to β-cells. Furthermore, levels of inflammatory factors in T2DM mice were significantly reduced following the administration of ginseng extract [42]. Ginsenosides represent the primary active constituents in the Chinese

herb ginseng, encompassing steroidal ginsenosides, protopanaxadiol, and protopanaxatriol [43]. Ginsenoside Rg1 has the capability to activate Akt and inhibit the translocation of fork head box transcription factor O1 (FoxO1) to the cell nucleus. This action reduces the liver's response to glucagon, inhibits gluconeogenesis, and decreases glucose output. Additionally, Rg1 lowers the expression of glucose-6-phosphatase (G6Pase), further decreasing hepatic glucose output and ultimately contributing to the reduction of blood glucose levels [44]. Rg1 has the capability to inhibit the expression of nuclear factor κB (NF-κB) as well as IL-1β, IL-6, TNF-α, and other inflammatory factors. This action further promotes the PI3K and Akt, thereby activating the PI3K/Akt signaling axis and enhancing the liver's glucose absorption. Additionally, ginsenoside Rg1 can reduce glucose output from the liver by inhibiting the expression of G6Pase in rats, which contributes to the alleviation of inflammation levels and IR in T2DM rats through these mechanisms [45]. Furthermore, another ginsenoside, Rb1, is significant in combating T2DM. The oral administration of Rb1 decreases the activity of 15-hydroxyprostaglandin dehydrogenase (15-PGDH) in the livers of T2DM mice, which in turn activates prostaglandin E2 (PGE2). This activation allows PGE2 to bind to the prostaglandin E2 receptor (EP4), resulting in the phosphorylation and activation of AKT, which subsequently increases the phosphorylation level of GSK3β. The phosphorylation of GSK3β facilitates glycogen synthesis, thereby supporting glucose homeostasis [46].

American ginseng

American ginseng (Panax quinquefolium Linn), commonly referred to as American ginseng or flower ginseng, is the dried rhizome of a perennial herbaceous plant that is part of the ginseng genus within the Araliaceae family. The substance is known for its ability to tonify qi, nourish yin, clear heat, and generate body fluids. Contemporary pharmacological studies have demonstrated that American ginseng comprises a range of active components, such as ginsenosides, polysaccharides, and flavonoids [47]. This substance enhances glucose metabolism, optimizes lipid metabolism, mitigates oxidative stress, and reduces inflammation. Clinical trials indicate that the daily oral intake of 3 g of American ginseng powder significantly lowers postprandial blood glucose levels in patients with T2DM, while having no impact on blood glucose levels in non-diabetic individuals [48, 49]. Mucalo et al. have shown that the long-term use of American ginseng is both safe and reliable for patients with T2DM [50]. Metabolomics has confirmed that the anti-T2DM effect of American ginseng operates through multiple pathways and targets. This includes mechanisms for inhibiting inflammation, ameliorating oxidative stress, addressing lipid metabolism disorders, and enhancing the quality and function of pancreatic islet cells [51]. The aqueous extract of ginseng facilitated insulin secretion from pancreatic β-cells, suppressed the expression of uncoupling protein-2 (UCP-2), reduced the activity of the pro-apoptotic protein Cysteine-Aspartic Acid Protease 9 (caspase-9), and elevated the expression of the anti-apoptotic protein B-cell Lymphoma-2 (Bcl-2), thereby improving the metabolic activity and viability of the cells [52]. Ginseng fruit extract has been shown to effectively reduce blood glucose levels, enhance the secretion of insulin by pancreatic β-cells, and directly eliminate free radicals, demonstrating significant antioxidant properties. This contributes to the improvement of cellular dysfunction caused by oxidative stress [53]. The polysaccharide fraction derived from the fruit extract of Panax quinquefolium demonstrated notable blood glucose-lowering effects in T2DM mice, with these effects remaining significantly sustained for 30 days post-drug withdrawal [54]. The administration of American ginseng powder to T2DM rats resulted in a significant reduction in FBG, TC, TG, LDL, and free fatty acid levels. Additionally, there was an elevation in serum HDL levels, an increase in the activities of SOD, CAT in liver, and GSH-Px, as well as enhanced antioxidant properties. The treatment also led to a reduction in the activities of inflammatory factors IL-1β, IL-6, and TNF-α, alleviating lipid metabolic disorders and oxidative stress, while inhibiting the inflammatory microenvironment to mitigate inflammation. These effects contributed to the alleviation of pancreatic histopathological damage and demonstrated anti-T2DM effects [55]. Malonyl ginsenoside, a natural component of ginsenoside, is commonly present in both fresh and raw American ginseng. Research indicates that malonyl ginsenoside enhances glucose uptake and promotes glucose me-

tabolism through the activation of the Insulin Receptor Substrate 1 (IRS-1)/PI3K/Akt signaling pathway in liver and muscle, leading to a reduction in blood glucose levels. Additionally, it activates the AMPK/Acetyl-CoA Carboxylase (ACC) signaling pathway, which contributes to decreased lipid accumulation [56]. The efficacy of qi replenishing Chinese medicine is noteworthy, and the combination of American ginseng and Astragalus has the potential to enhance the anti-T2DM effect. Zhou et al. confirmed through network pharmacology and molecular docking that the pairing of American ginseng and Astragalus may achieve an anti-T2DM effect by promoting lipolysis and regulating the cGMP-PKG signaling axis as well as the thyroid hormone signaling pathway; however, further experimental validation is required [57].

Yam

Yam (Dioscorea opposita) refers to the dried rhizome of the Dioscorea opposita plant, which is part of the Dioscoreaceae family and is recognized as a traditional medicinal food. This root is characterized by its sweet and flat nature, and it is associated with the spleen, lung, and kidney meridians. Its effects include benefiting Qi, tonifying the spleen, generating fluids, supporting lung health, tonifying the kidneys, and astringing spermatozoa [58]. Pharmacological studies have identified that yam contains significant amounts of yam polysaccharides, resistant starch, diosgenin, and various other active components [59]. This substance exhibits a range of effects, including the reduction of blood glucose levels, enhancement of lipid metabolism, and mitigation of oxidative stress. It is extensively utilized in the management of diabetes and various multimetabolic disorders [60]. Li successfully isolated the novel polysaccharide HSY from yam, demonstrating its efficacy in reducing FBG levels and enhancing insulin sensitivity in T2DM mice [61]. Xu utilized network pharmacology to forecast that the active components in yam, including diosgenin, stigmasterol, cauliflower sterol, and arbutin, which may exhibit significant preventive and therapeutic effects on T2DM. Experimental results corroborated this hypothesis, demonstrating that all aforementioned active ingredients effectively reduced FBG and glycated serum protein levels in model mice [62]. Yam and yam polysaccharides have the potential to enhance lipid metabolism and regulate intestinal flora, contributing to the management of hyperglycemia and hyperlipidemia. Furthermore, yam polysaccharides may promote the expression of antioxidant enzymes such as GSH-Px, CAT, and SOD, thereby mitigating oxidative stress-related damage [63]. Yam porridge is a traditional dietary formulation attributed to Ming Dynasty physician Zhang Xichun, featuring a singular flavor of yam. Research conducted by Lin involved administering yam porridge to T2DM rats, revealing a significant reduction in FBG levels among these subjects. Notably, the glucose-lowering effect observed was comparable to that of the metformin group, with no statistically significant differences. This effect may be linked to the ability of yam to enhance the proliferation of intestinal probiotics in T2DM rats, which subsequently elevates the Ca^{2+} concentration in intestinal cells through the activation of the short-chain fatty acid receptor GPR43 signaling pathway. This process ultimately stimulates the secretion of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), contributing to the regulation of blood glucose levels [64]. Yam polysaccharides notably improve the activities of pyruvate kinase (PK) and hexokinase (HK) in T2DM zebrafish, while also decreasing the levels of TC, TG, and LDL. This leads to an enhancement in glycolipid metabolism and a reduction in tissue glucose content. Furthermore, they increase the activity of GSH-Px and lower the levels of MDA, a product of lipid peroxidation, effectively mitigating tissue damage associated with oxidative stress [65]. An aqueous extract of Yam and its bioactive compound, allantoin, demonstrated a significant reduction in FBG levels in T2DM mice. Furthermore, these components assisted T2DM mice in managing body weight and decreasing water intake, thereby enhancing glucose utilization and lowering urinary glucose levels. Additionally, they contributed to a reduction in TC, TG, and LDL, while also mitigating tissue damage associated with pancreatic hyperplasia and fatty liver [66]. Yam, a traditional food with roots in both culinary and medicinal practices, can be beneficial when incorporated into the diet of patients with T2DM. The judicious inclusion of yam in their meals may help to suppress inflammatory factors, safeguard the intestinal mucosa, and mitigate the onset and progression of T2DM and its associated complications [67]. In elderly

patients with T2DM, incorporating 150 g of Dioscorea porridge into breakfast daily for a duration of 12 consecutive weeks has been shown to significantly lower fasting and postprandial blood glucose levels. This effect may be associated with an increase in the activity of SOD and GSH-Px. Additionally, the consumption of Dioscorea porridge may enhance the ability of elderly patients with T2DM to resist oxidative stress, a key factor in the development of pancreatic cell damage and IR [68].

Liquorice

Liquorice is the dried rhizome of the leguminous plant Uralia glabra, Glycyrrhiza glabra glabra, or Glycyrrhiza distensa [69]. Glycyrrhiza glabra demonstrates the ability to tonify qi and strengthen the spleen, clear heat, remove toxins, and harmonize various medicines. It possesses significant pharmacological activities and is abundant in compounds such as flavonoids, glycyrrhetinic acid, and coumarins. These compounds contribute to the promotion of glucose and lipid metabolism, relief of endoplasmic reticulum stress, alleviation of IR, and regulation of bacterial flora abundance, which is crucial in the management of T2DM [70]. Glycyrrhizic acid derived from Glycyrrhiza glabra demonstrated a significant reduction in FBG levels and serum TC, TG, and LDL cholesterol accumulation, while also enhancing HDL cholesterol. This compound contributes to the improvement of glucose-lipid metabolism disorders, boosts insulin sensitivity, and effectively mitigates the progression of T2DM in murine models of the condition [71]. Licochalcone E is a flavonoid that lowers blood glucose levels and serum triglyceride levels in T2DM mice. This effect may be attributed to a reduction in adipocyte cell size and the stimulation of Akt signaling in adipose tissue, which subsequently activates the expression of peroxisome proliferator-activated receptor (PPARγ) [72]. The oral administration of photofagaric acid glycyrrhizidine to T2DM mice over a period of 4 days resulted in a reduction of blood glucose levels and a decrease in abdominal fat accumulation. This effect may be associated with the activation of PPAR-γ, aligning with findings from prior research [73]. Glycyrrhiza glabra chalcone A is a biologically active chalcone compound derived from Glycyrrhiza glabra. It has demonstrated the ability to improve glucose-lipid metabolism disorders in T2DM mice. This includes inhibiting lipogenesis, accelerating lipolysis, reversing hepatic steatosis, increasing hepatic glycogen synthesis, and decreasing gluconeogenesis. Additionally, it plays a role in maintaining energy homeostasis, potentially through the activation of AMPK and the inhibition of mammalian rapamycin complex 1 (mTORC1) expression, both of which are essential in metabolic processes [74]. Glycyrrhizin demonstrates a significant ability to lower blood glucose levels in Streptozocin (STZ) induced diabetic mice. It notably enhances cell viability, inhibits the activity of cystatinase-3 (Caspase-3) and the repair enzyme Poly ADP-ribose polymerase (PARP), and up-regulates Bcl-2 expression to prevent Palmitic acid (PA) induced apoptosis. Additionally, it reduces the phosphorylation levels of Protein Kinase R-like Endoplasmic Reticulum Kinase (PERK), Eukaryotic Initiation Factor 2 α (eIF-2α) and C/EBP-homologous protein (CHOP) in the cells, alleviates endoplasmic reticulum stress, and provides multifaceted protection to the endoplasmic reticulum in pancreatic β-cells [75, 76]. Licorice extract demonstrated a significant improvement in FBG levels, enhanced IR, and increased insulin sensitivity. Additionally, it led to a notable reduction in TC, TG, and LDL, while increasing HDL in T2DM mice. This extract effectively reversed the disorders associated with glucose and lipid metabolism in these mice. The underlying mechanism may involve a reduction in lipopolysaccharides in the serum of diabetic mice, along with the inhibition of IL-6, TNF-α, and IL-12 expression, which alleviates intestinal inflammation. Furthermore, it enhances the permeability of the intestinal barrier, preventing lipopolysaccharides from entering the bloodstream, and increases the abundance of intestinal flora, thereby exerting anti-T2DM effects through multiple pathways [77].

Additional qi tonic herbs with research prospects

In addition to the aforementioned herbs, there are several qi replenishing herbs that have shown notable effectiveness in the prevention and treatment of T2DM. Including Atractylodes macrocephala, honey, and tai qui ginseng. However, the current literature regarding the mechanisms of action, active ingredients, and clinical applications of these Chinese medi-

cines for T2DM treatment is relatively limited, with relevant studies still in the preliminary phase. Given the constraints of the existing evidence, this study analyzed the aforementioned qi replenishing herbs collectively to systematically evaluate their potential value in the prevention and treatment of T2DM.

Atractylodes macrocephala is the dried rhizome of the plant belonging to the Asteraceae family. It is recognized for its ability to benefit qi, strengthen the spleen, and address dampness while promoting diuresis. Contemporary pharmacological research has identified that Atractylodes macrocephala is primarily composed of active constituents, including volatile oils, lactones, and polysaccharides, which demonstrate properties that inhibit inflammation and mitigate oxidative stress [78]. Atractylenolide I, a principal active component of Atractylodes macrocephala, has been shown to enhance the mental state of T2DM rats, elevate insulin and C-peptide secretion levels, significantly lower fasting glucose, MDA, and cellular iron content, and promote the expression of SOD and GSH-Px. This contributes to the protection of pancreatic islet cell function to a certain degree [79]. Atractylenolide I, when combined with atractylenolide II, activates the AMPK/PI3K/Akt signaling pathway, enhances glucose uptake in myotubular cells, increases the expression of glucose transporter 4 (GLUT4), facilitates its translocation to the plasma membrane, and improves glucose metabolism levels [80]. Network pharmacological studies have indicated that several active ingredients in Atractylodes macrocephala may interact with diabetes-related therapeutic targets; however, their specific mechanisms of action require further experimental validation [81]. Pseudostellariae Radix is the dried tuberous root of Pseudostellariae Radix, associated with the lung and spleen meridians. It is known for its ability to benefit qi and strengthen the spleen, generate fluids, and moisten the lungs. Contemporary pharmacological research indicates that Pseudostellariae Radix contains polysaccharides, volatile oils, saponins, and various alkaloids, contributing to its role in promoting glucose-lipid metabolism, which can aid in the management of DM. Its efficacy in alleviating diabetes is noteworthy [82]. The novel polysaccharide H-1-2, isolated from Panax ginseng, demonstrates the ability to reduce blood glucose levels, enhance IR, and decrease the in vivo accumulation of TC, TG, and LDL. Additionally, it increases HDL levels and significantly improves glucose and lipid metabolism disorders in T2DM rats. In vitro experiments confirm that polysaccharide H-1-2 inhibits the expression of Hypoxia-Inducible Factor 1α (HIF1α), which subsequently activates Sirt1, alleviating cellular hypoxia and promoting glucose absorption and utilization in muscle and fat cells. This process accelerates glucose metabolism and mitigates the progression of T2DM [83, 84]. Honey is a natural substance produced by bees after they collect nectar from plants or their secretions. This process involves combining the nectar with their own secretions and undergoing a series of biological transformations, dehydration, and other processes, ultimately leading to brewing and maturing within the hive. It is rich in active ingredients, including glucoses (approximately 75%), acidic compounds, flavonoids, and various enzymes essential for human health [85]. It is widely believed that honey may not be appropriate for individuals with diabetes due to its elevated glucose content. Nevertheless, findings from a study indicate that the consumption of natural honey by patients with T2DM does not adversely affect blood glucose levels [86]. It is possible that it may yield advantageous effects against T2DM. In studies involving diabetic rats, the use of honey water notably decreased blood glucose levels and improved the activities of SOD and GSH-Px. This indicates that honey water is effective in mitigating oxidative stress and protecting pancreatic cells, likely due to the high antioxidant properties inherent in honey [85, 87]. Fructose is a key component found in honey, facilitating hepatic glucose uptake and promoting glycogen synthesis and storage through the activation of hepatic glucokinase and glycogen synthase. It positively influences the regulation of blood glucose levels, weight management, food consumption, and energy expenditure [88].

Summary and outlook

T2DM is a collection of metabolic disorders primarily marked by persistent hyperglycemia, potentially resulting in irreparable harm to several organs, including the kidneys, eyes, nerves, and microvessels, so significantly jeopardizing patients' quality of life and impacting the social

and medical economy [19]. TCM offers numerous advantages, including notable efficacy, minimal adverse effects, prolonged benefits, and a broad spectrum of targets. In 2017, the Chinese Guidelines for the Prevention and Control of T2DM incorporated TCM treatment, and the mechanisms and clinical significance of QTTCM in the prevention and management of T2DM have garnered heightened interest from the academic community. Substantial advancements have been achieved regarding the function and mechanisms of QTTCM, including Astragalus, Codonopsis, Ginseng, American ginseng, Chinese yam, licorice, Atractylodes macrocephala, Radix et Rhizoma Atractylodis Macrocephala, Radix et Rhizoma Pinelliae, Radix et Rhizoma Ginseng, and honey, in the prevention and management of type T2DM. These herbs enhance pancreatic islet β-cell functionality, mitigate IR, alleviate glucose-lipid metabolic disorders, and inhibit oxidative stress and inflammatory microenvironments, thereby effectively delaying the progression of T2DM.

Despite advancements in the efficacy of QTTCM for treating T2DM, numerous challenges persist. Primarily, the extraction and purification techniques for certain active constituents of qi-tonic Chinese medicines remain underdeveloped, impeding research progress. For instance, malonyl ginsenoside from American ginseng exhibits notable hypoglycemic and insulin-sensitizing properties; however, its isolation proves challenging, leading to a scarcity of related studies that constrains further investigation into its efficacy and mechanisms [89]. Secondly, contemporary research on QTTCM for the treatment of T2DM predominantly focuses on extracts of individual Chinese medicinal herbs or singular components in model organisms or cell cultures. In contrast, TCM treatments primarily utilize water decoctions. Modern investigations have demonstrated that the decoction of TCM soup constitutes not merely a straightforward dissolution of active constituents, but rather a dynamic system characterized by intricate chemical reactions and intermolecular interactions, which subsequently alters the therapeutic efficacy and safety profile of the Chinese medicine [90]. Consequently, a singular extract cannot adequately represent the comprehensive and synergistic effects of Chinese medicine. Subsequent research should concentrate on the principles of Chinese medicine formulation and decoction techniques, thorough analysis of chemical constituents, and detailed clarification of the interactions among active compounds and their therapeutic mechanisms in relation to T2DM.

Moreover, in contrast to contemporary medicine, there is a paucity of clinical studies regarding qi-tonic herbs for the management of T2DM, particularly concerning their integration with advanced technologies such as genetic testing and precision medicine, which remains largely unexplored, thereby hindering the advancement of qi-tonic herbs in the personalized treatment of T2DM. Moreover, the quality of market herbs is inconsistent and may be compromised, as exemplified by honey, which is frequently adulterated with sucrose or synthetic syrup. This not only undermines the reliability of experimental outcomes but may also introduce variability in clinical efficacy. Akhtar administered both natural honey and honey adulterated with saturated sucrose solution to normal and diabetic rabbits, demonstrating that equivalent doses of natural honey did not elevate their blood glucose levels, whereas adulterated honey significantly raised blood glucose in both normal and hyperglycemic rabbits, even at minimal doses [91]. Consequently, stringent regulation of herbal medicine quality is essential for the utilization and investigation of qi-tonic herbs in the prevention and treatment of T2DM.

Our literature review revealed that numerous mechanistic studies have employed bioinformatics tools, including high-performance liquid chromatography-mass spectrometry (HPLC-MS), network pharmacology, molecular docking, 16S sequencing of gut microbiota, and metabolomics analyses for target prediction, significantly enhancing the efficiency and accuracy of the research. Furthermore, for compounds exhibiting low bioavailability or solubility challenges, their stability can be augmented through nanocarrier technology or structural modification. Furthermore, for drugs exhibiting limited bioavailability or challenging solubility in water, their stability may be enhanced using nanocarrier technology or structural alteration [92].

Acknowledgements

This work was funded by the National Natural Science Foundation of China (No. 82174334).

Disclosure of conflict of interest

None.

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