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REVIEW

Developments in the study of Chinese herbal medicine's assessment index and action mechanism for diabetes mellitus

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Abstract

In traditional Chinese medicine (TCM), based on various pathogenic symptoms and the 'golden chamber' medical text, *Huangdi Neijing*, diabetes mellitus falls under the category 'collateral disease'. TCM, with its wealth of experience, has been treating diabetes for over two millennia. Different antidiabetic Chinese herbal medicines reduce blood sugar, with their effective ingredients exerting unique advantages. As well as a glucose lowering effect, TCM also regulates bodily functions to prevent diabetes associated complications, with reduced side effects compared to western synthetic drugs. Chinese herbal medicine is usually composed of polysaccharides, saponins, alkaloids, flavonoids, and terpenoids. These active ingredients reduce blood sugar via various mechanism of actions that include boosting endogenous insulin secretion, enhancing insulin sensitivity and adjusting key enzyme activity and scavenging free radicals. These actions regulate glycolipid metabolism in the body, eventually achieving the goal of normalizing blood glucose. Using different animal models, a number of molecular markers are available for the detection of diabetes induction and the molecular pathology of the disease is becoming clearer. Nonetheless, there is a dearth of scientific data about the pharmacology, dose-effect relationship, and structure–activity relationship of TCM and its constituents. Further research into the efficacy, toxicity and mode of action of TCM, using different metabolic and molecular markers, is key to developing novel TCM antidiabetic formulations.

KEYWORDS
animal model, Chinese herbal medicine, diabetes mellitus, evaluation index, mechanism of action

1 | INTRODUCTION

The endocrine disorder diabetes mellitus (DM) is a global phenomenon, with a significant effect on human health.[1] The International Diabetes Federation (IDF) reported that 537 million people between the ages of 20 and 79 years were affected in 2021 and they predicted that this number will reach 643 million by 2030.[2] The typical clinical symptoms of DM include, in TCM terms, 'three enhances with one reduction', i.e., significantly enhanced thirst, urination, and appetite with significant weight loss. Diabetes is characterized by hyperglycemia, hyperinsulinemia, insulin resistance with elevated oxidative stress and inflammation (Figure 1). It impairs carbohydrate, fat and protein metabolism thus causing various degrees of micro- and macro-vascular deterioration in core organs of the body. Reports have suggested that diabetes is positively correlated with neuropathological disorders, cardiomyopathy, nephropathy, gastrointestinal or genitourinary tract complications and non-healing wounds. Diabetes with progressive end organ complications further worsens the quality of life and is ranked 9th among the top causes of mortality in the world. It is also a huge economic burden. The IDF reported that in 2021 966 billion USD was spent to treat diabetes and related complications.

Antidiabetic therapies in western medicine include metformin, sulfonylureas, glitazone, and DPP-IV inhibitors, among others. Beside their beneficial effects they also have several side effects including hypoglycemia, gastrointestinal distress, liver and kidney dysfunction.[3] Considering these disadvantages, researchers are seeking novel antidiabetic formulations with better efficiency and less toxicity. Natural products have proved to be a good source of novel antidiabetic compounds. Traditional Chinese Medicine, with its long history, is one of the possibilities for providing new antidiabetic formulations with long-lasting effects and fewer adverse reactions that can delay diabetes or its related complications.

Different animal models provide a way of investigating specific aspects of the pathophysiology of diabetes such as hyperglycemia and insulin insufficiency or resistance, and their association with end organ complications, as well as elucidating the antidiabetic effects of antidiabetic drugs. Use of such models has led to the exploration of the therapeutic potential of TCM agents in treating diabetes, and laid the foundation for the efficient utilization, patenting, and manufacture of TCM antidiabetic formulations. In this review, we have investigated the different diabetes model available and highlighted the therapeutic potential of TCM compared to western medicine.

2 | ANIMAL EXPERIMENTAL MODELS OF DM

2.1 | Type I diabetes model in rodents

This model is also known as pancreatic islet injury hyperglycemia model in rodents. It is induced chemically, spontaneously and by genetic modification, resulting in the destruction of the insulin-secreting pancreatic β cells, which leaves the rodent in a chronic state of hyperglycemia through lack of enough insulin to reduce blood glucose. Type I diabetes is manifested by frequent urination, increased thirst, hunger, and weight loss. Different type I diabetes models induced chemically, via genetic manipulation and phenotypically are listed in Table 1.

2.2 | Type II diabetes model in rodents

This model is also referred as the insulin resistance or glucose/lipid metabolism disorder model. It creates an endocrine disorder, usually induced by a high fat and high sugar diet with or without low doses of streptozotocin (STZ). Type II diabetes is characterized by β-cell dysfunction and insulin resistance (IR). Its primary symptoms include increased appetite and thirst, weariness, impaired vision, frequent urination, and weight loss. The different methods used to induce type II diabetes in rats via diet, chemical intervention, or genetic modification are listed in Table 2.[4]

2.3 | Other animal models

Zebrafish can serve as an ideal model to study diabetes pathophysiology or the antidiabetic effects of novel formulations owing to their small body size, large spawning capacity, short growth cycle, and simple mode of adult reproduction.[5] Zebrafish share 87% genetic

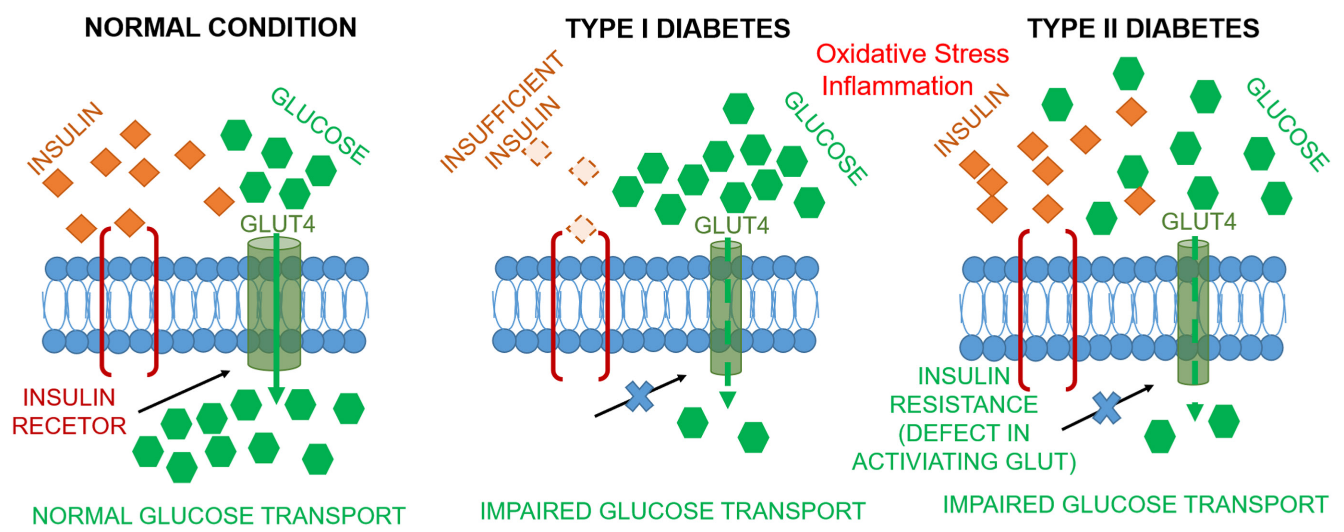

FIGURE 1 Causes of type I and type II diabetes.

TABLE 1 Diabetic model of islet damage in rodents.

Induction mechanism	Model	Induction mechanism	Model
Chemical induction	Streptozocin (single injection 150–200 mg/kg or injections 50 mg/kg for 5 days)	Genetic induction	Akita mouse
	Alloxan (single injection 100–200 mg/kg)	Spontaneous autoimmunity	NOD mouse
Virus induction	Coxsackie B virus		BB mouse
	Cerebral myocarditis virus		LEW.1NR1/ztm-iddm rat
	Kilham rat virus		Lewis-IDDM rat
	LCMV insulin promoter		KDP rat

TABLE 2 Insulin resistance glucose\lipid metabolism disorder model in rodents.

Induction mechanism		Model	Induction mechanism	Model
Induction type	Drug induction	Streptozocin(15–30 mg/kg)	Transgenic type	GK/IRS-1 double knockout
		Intravenous BCG vaccine		INS knockout
		Dexamethasone		Lipoproteinase Knockout
		Monosodiumglutamate		SH2-B knockout
		Milrinone		CAV3 knockout
		Intravenous lipid compounds		IGF-1 knockout
	Food induction	High Fat Diet Feeding		Gck / Hnf4a / Abcc8 knockout
		High sugar feeding		PD-1 gene overexpression
		High-fat high-sugar mixed feeding	Genetic type	KK-Ay, db/db, ob/ob, NSY mice
	Diet plus medication induction	High-fat diet + Streptozocin		ZDF, OLETF rats
		High-fat diet + Alloxan		GK, NOZ rats
	Surgical induction	Pancreatectomy		Zuker obese rats
		Streptozocin + Pancreatectomy		Wistar obese rats

homology with humans.[5] They also feature some key mechanisms for the regulation of glucose metabolism that are similar to other mammals, thus making them a good candidate model for studying diabetes.[6] The type I diabetes model in zebrafish can be induced by surgical removal of the pancreas, chemically inducing β-cell apoptosis, or using transgenic techniques.[7] In contrast, type II diabetes is induced via environmental factors, gene modification or a high fat, high glucose diet.[8,9]

Non-human primates due to their closer genetic similarity can better mimic the pathophysiology of human diabetes mellitus. Animal models of spontaneous diabetes in non-human primates include squirrel monkeys (*Saimiri sciureus*), crab-eating monkeys (*Macaca fascicularis*),[10] rhesus monkeys (*M. mulatta*),[11] Sulawesi monkeys (*M. nigra*), tree shrews (*Tupaia belangeri*),[12] baboons (*Papio hamadryas*), chimpanzees (*Pan troglodytes*), Taiwan macaques (*M. cyclopis*), and gray baboons (*Mandrillus leucophaeus*).[13] Type I diabetes in non-human primate is induced by STZ[14] with or without pancreatectomy,[15] while type II diabetes is induced by a high energy diet with STZ.[16] Transgenic macaques can be obtained commercially and can be especially useful as their genome has been sequenced.[17]

3 | EVALUATION INDEX

3.1 | Human clinical evaluation indexes

The main indicators of human clinical diabetes include fasting glucose and 2-hour postprandial glucose,[18] insulin sensitivity, intestinal diabetic markers and related peptides, glycated protein, glycated hemoglobin (HbA1c),[19] hemorheological parameters (plasma viscosity, low shear whole blood viscosity, sedimentation rate and red blood cell deposition),[20] glycated serum protein, 1,5-anhydroglucitol (1,5-AG), total cholesterol, and triglycerides[21] (see Table 3).

3.2 | Animal model evaluation indexes

The general indicators used to evaluate the antidiabetic effect of novel formulations in islet injury or insulin resistance models include fasting blood glucose, postprandial hyperglycemia, serum biochemical indicators, insulin level, and others.[22] Physical parameters include polydipsia, polyphagia, polyuria, and

TABLE 3 Characteristics of diabetic evaluation indexes.

Indicators	Description	Advantages	Disadvantages
Fasting blood sugar	After 8 hours of fasting, blood glucose levels were tested	Easy to measure Allows rapid assessment of insulin secretion Important for diabetes screening	Highly influenced by diet, fasting status required Not suitable for evaluation of hypoglycemia
Postprandial blood glucose	Tested 2 h after eating and drinking to determine blood glucose levels.	Helps assess insulin resistance and insulin secretion capacity Important for postprandial glucose control in diabetic patients	Requires standardized pre-meal diet Not easy to compare results at different time points
Glycated hemoglobin	Reflects the average level of glucose in red blood cells and is usually measured once in 3–4 months	Represents the average blood sugar levels during a three-to-four-month period. Can predict the risk of diabetic complications	Requires regular testing Interfered by factors such as anemia
Glucose tolerance test	Measured 2 h after ingesting 75 g of glucose orally on an empty stomach to determine blood glucose concentration	Can detect underlying diabetes Helps assess insulin secretion function	Requires large oral doses of glucose Long testing time
Hemorheological parameters	It mainly reflects the changes in blood fluidity, stagnation and blood viscosity caused by changes in blood composition	Can predict the risk of diabetic complications	Highly influenced by diet, fasting status required
Random blood glucose	Measure blood glucose concentration at any time	Easy to measure Allows rapid assessment of blood glucose levels	Highly influenced by diet Cannot assess insulin secretion
Lipid metabolism abnormalities	Abnormalities in lipid metabolism are usually associated with diabetes and include indicators such as HDL-C, LDL-C, and TC.	Assess cardiovascular risk in diabetic patients Can help to understand insulin resistance	Affected by factors such as diet and exercise Not suitable for all diabetic patients
Inflammatory Factors	Testing for inflammation-related indicators can help to understand the health status of diabetic patients	Can assess the degree of inflammation in diabetic patients Can help understand the risk of diabetes complications	Affected by factors such as diet and exercise Not suitable for all diabetic patients
Oxidative stress	Can result in high levels of oxidative stress because of things like hyperglycemia, which raises the risk of complications from diabetes.	Can assess the degree of oxidative stress in diabetic patients Can help understand the risk of diabetic complications	The testing procedure is complicated and necessitates the use of specialist equipment and abilities. Not suitable for all diabetic patients
Intestinal flora	The intestinal flora may be altered due to factors such as diet structure, which increases the risk of diabetic complications.	Can help to understand the intestinal microecology of diabetic patients Can predict the risk of diabetic complications	Complex test method, requires specialized equipment and skills Additional research support is needed
Metabolomics	Can reflect the various chemical reactions that occur when the body status of diabetic patients changes, providing a novel means of diagnosis and treatment of diabetes.	Highly sensitive Non-invasive Comprehensive	Sample processing issues Complex data processing Expensive equipment costs

weight loss. Diabetes is a metabolic disorder so, the evaluation of serum biochemical markers such as total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), blood creatinine (CR), blood urea nitrogen (BUN), alanine aminotransferase (Alt), aspartate aminotransferase (AST) is of fundamental importance. Pathological biopsies from pancreatic and other organs involved are performed to observe tissue destruction. Fasting serum insulin levels, serum insulin levels, insulin sensitivity index, glucose tolerance are also other important markers to evaluate diabetes progression. Diabetes is characterized by significant elevated oxidative stress and inflammation, thus the level of related indicators such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), reactive oxygen species (ROS), interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ)[23] is worth monitoring. The modulation of gut microflora can also be an effective evaluation marker for an antidiabetic therapy (Table 3).[24]

3.3 | In vitro experiments evaluation indexes

There are two major methods for evaluating in vitro antidiabetic models, enzyme and cellular assays, so the evaluation index varies with the assay used. The enzymatic approach usually evaluates the inhibition of α-amylase and α-glucosidase in the presence of antidiabetic compounds,[25] and can be done using a molecular docking approach or an enzyme inhibition assay. This method has the limitation that it fails to predict activity in the whole-animal environment, and so lacks any clinical and safety evaluations, but it is a robust preliminary method for screening a library of compounds and formulations for antidiabetic activity.

Researchers usually replicate enzyme inhibition data in cellular models before testing them in in vivo models. In cellular models, the biological effects of the active material are tested, and they are widely used as active assessment systems. The main evaluation indicators include oxidative stress, lipid metabolism, followed by gene or protein expression of key enzymes in glucose and lipid metabolism (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), reactive oxygen species (ROS),[26] DPPH radical scavenging capacity, ABTS+ radical scavenging capacity, and hydroxyl radical scavenging capacity[27]), glucose metabolism (glucose kinase (GK),[28] glucose-6-phosphatase (G6Pase),[29] pyruvate kinase (PK), hexokinase (HK),[25] protein tyrosine phosphatase 1B (PTP-1B),[30] etc.), relevant signaling pathways (PI3K/Akt,[31] MAPK,[32] cAMP-PKA,[33] AMPK signaling pathways,[34]) etc. (Table 3).

These indicators can be used to evaluate the antidiabetic efficacy of TCM in various in vitro, pre-clinical and clinical studies.

4 | TRADITIONAL CHINESE MEDICINES AS ANTIDIABETIC AGENTS

4.1 | Glucose lowering effect of herbal and Chinese medicinal compounds

TCM herbal formulations and single compounds significantly alleviate the pathophysiology and evaluation indexes of diabetes. These initial findings form the basis of future continuous improvement in TCM formulations and exploration of new glucose lowering TCMs by focusing on different pathogenic mechanisms of diabetes. The main categories of herbs for lowering blood sugar are tonic, heat-clearing and blood-activating, mainly including *Astragali Radix*,[35] *Cinnamomi Cortex*,[36] *Ginseng Radix*,[37] *Lycii Fructus*,[38] *Salviae Miltiorrhizae Radix et Rhizoma*,[39] *Rehmanniae Radix*,[40] Corn Stigma,[41] *Anemarrhenae Rhizoma*,[42] *Angelicae Sinensis Radix*,[43] *Puerariae Lobatae Radix*,[44] *Coptidis Rhizoma*,[45] *Dioscoreae Rhizoma*,[46] *Polygonati Odorati Rhizoma*,[47] *Poria*,[48] *Cuscuta europaea*,[49] *Atractylodis Rhizoma*,[50] *Atractylodis Macrocephalae Rhizoma*,[51] *Agrimoniae Herba*,[52] *Xanthii Fructus*,[53] *Alismatis Rhizoma*,[54] *Platycodonis Radix*,[55] *Polygonati Rhizoma*,[56] *Morus alba* L.,[57] *Momordica charantia* L.,[58] etc.

Usually, TCM formulations are multidirectional and multitargeted, which makes them more effective than chemically synthesized drugs. At present, the Pharmacopeia of the People's Republic of China and the Ministerial Standards includes more than a dozen glucose lowering Chinese patent medicines, including Xiaoke Ling tablets, Thirsty Lening tablets, Jinqi Jiangtang tablets, Yuye Xiaoke granules, Yangyin Jiangtang tablets, Jiangtang A tablets, Jiangtang Shu capsules, Xiaoke Jiangtang tablets, Jiangtang capsules, Xiaoke Jiangtang capsules, Xiaoke pills, etc.[59] Zhenqi antidiabetic capsules are internationally recognized and are mainly refined from *Ginseng Radix*, *Astragalus membranaceus*, *Polygonati Rhizoma*, pearl, and other rare Chinese medicinal herbs. A meta-analysis of treatments for diabetic nephrotoxicity comparing conventional western medicine treatment groups with patients receiving western medicine in conjugation with Bushen Huoxue decoction showed that Bushen Huoxue decoction has certain advantages in lowering blood sugar, regulating blood lipid and reversing renal function when given in combination with western treatments compared to western medicine alone.[60]

At present, many simulation experiments with different blood glucose indicators, conducted in a variety of models, have provided many diabetes assessment indicators, which form the basic evaluation indexes for research on the hypoglycemic effects of TCM. Diabetes often causes complications in multiple tissues and organs that seriously endanger life and health and require long-term medication and dietary attention. The pathogenesis of diabetes mellitus is very complex, and the pathogenesis of different types of diabetes mellitus is also clinically different. Diabetes is often caused by a variety of factors, and its pathogenesis is composed of multiple syndromes. Therefore, continuing studies aimed at discovering the pathogenesis of diabetes mellitus and related evaluation indicators are needed to improve the evaluation index system for glucose reduction by TCM.

4.2 | Traditional Chinese medicine active ingredients and their antidiabetic efficacy

There are many active ingredients of TCM with proven glucose lowering effects, including polysaccharides, saponins, alkaloids, flavonoids and terpenoids. The glucose lowering effects of these constituents are multifactorial but are broadly of four types: (1) to inhibit of pancreatic β cell apoptosis or repair β cells to restore insulin production; (2) to enhance insulin sensitivity toward target cells; (3) to maintain the key enzyme activity (α amylase, α glycosidase enzymes) to enhance sugar metabolism and avoid reabsorption; (4) to scavenge free radicals, enhance antioxidant capacity and prevent lipid peroxidation. (Table 4).

TABLE 4 Diabetic active ingredients and mechanism of action of Chinese medicines.

Active ingredients	Chinese medicine	Action mechanism	Mechanism	Reference
Polysaccharides	Ginseng	Fasting blood glucose ↓, MDA ↓, insulin ↑, SOD activity ↑, liver glycogen content ↑	(1, 4)	[61]
		G6P activity ↓, hepatic glycogen synthase activity ↓, G6PD activity ↑, PFK activity ↑	(3)	[62]
	Lycii Fructus	HbA1c, GSP, insulin level, TC, TG, LDL-C ↓; HDL-C ↑; GLP-1, PYY, GPR41, GPR43 expression ↑, GSK-3β and PEPCK expression ↓, activation of InsR/PI3K/AKT signaling pathway	(2, 4)	[63]
	Vigna umbellata	Body weight ↓, fasting blood glucose ↓, TG↓, HDL-C↑; Expression of INSR, IRS-1, PI3K, AKT, and GLUT-2 ↑ activates the PI3K/AKT signaling pathway	(2, 4)	[64]
	Astragali Radix	Body weight, fasting glucose, TC, TG, LDL-C ↓, HDL-C ↑, antioxidant enzyme activity ↑, MDA ↓	(2)	[35]
	Ophiopogonis Radix	Expression of PI3K, AKT, InsR, PPARγ ↑; expression of PTP-1B at mRNA level and protein level ↓	(2, 3)	[65]
		Lowering blood sugar levels, increasing insulin levels, repairing islet destruction and damage to pancreatic beta cells	(1)	[66]
	Morus alba L.	Inhibited apoptosis, improved insulin secretion capacity of pancreatic β-cells, and increased mRNA and protein expression of PDX-1 and its downstream targets GLUT2 and GCK in pancreatic islet cells of diabetic rats.	(1, 3)	[67]
Saponins	Fructus Momordicae	FBG ↓, serum insulin ↑, mRNA levels of G6Pase and PEPCK ↑, fat oxidation-related genes ↑, activation of AMPK signaling pathway	(2, 3)	[68]
	Ginseng	IRS-1/PI3K/AKT insulin signaling pathway ↑, glucose uptake ↑; MAPK signaling pathway ↓, insulin resistance ↓	(2)	[69]
	Sanchi	Blood glucose and serum insulin levels ↓, mRNA expression of p-PI3K, p-AKT, IRS1 and GLUT4 ↑, IRS1-PI3K-AKT signaling pathway ↑	(1)	[70]
	Melandryum viscidulum	mRNA expression of Glut4, IRS-1, Akt and PI3K ↑, mRNA expression of Moat1, Lipc, Lpcat4 and Smpd4 ↓, PI3K-AKT signaling pathway ↑	(1)	[71]
	Corni Fructus	IL-2, TNF-α and CRP ↑, MDA ↓, SOD activity ↑, mRNA expression of p-PI3K, p-AKT, IRS1 and GLUT4 ↑, IRS1-PI3K-AKT signaling pathway ↑	(2, 4)	[72]
	Lily	Stimulation of glucose depletion in the liver with ↑ PPARγ expression induces GLUT4 translocation to the cell surface	(2)	[73]
Alkaloids	*Morus alba* L.	Activation of insulin receptor pathway and TGF-β/Smads signaling pathway to improve insulin resistance and oxidative stress-induced hyperglycemia	(2)	[74]
	Coptidis Rhizoma	GLP-1 ↑; glucagonogen mRNA expression ↑	(2, 3)	[75]
	Tinosporae Radix	Blocking K-ATP channels to stimulate insulin secretion	(1)	[76]
Flavonoids	*Polygonati Odorati Rhizoma*	Fasting blood glucose ↓, insulin ↑, α-amylase activity ↓	(1, 3)	[77]
	India Madder Root	Scavenging of free radicals, SOD and catalase expression ↓, phosphorylation of IKK ↓	(4)	[78]
	Chinese Angelica	α-amylase and ACAT activities ↓, TC and TG levels ↓	(3, 4)	[79]
	Liquorice root	FBG ↓, SOD ↑, MDA ↓	(4)	[80]
	Ginkgo biloba Linn	α-amylase and α-glucosidase activities↓	(3)	[81]
	Tangerine Peel	GK mRNA level ↑, PCK and G6P mRNA expression ↓, GLUT2 protein expression ↓, GLUT4 and PGC-1 expression ↑	(3)	[82]

TABLE 4 (Continued)

Active ingredients	Chinese medicine	Action mechanism	Mechanism	Reference
Terpenoids	*Cyclocarya paliurus*	Regulation of insulin resistance pathway, PI3K-Akt signaling pathway, HIF-1 signaling pathway, PPAR signaling pathway	(2, 4)	[83]
	Forsythiae Fructus	Scavenging free radicals, protecting and repairing pancreatic beta cells	(1)	[84]
	Polygoni Multiflori Radix	Improvement of insulin resistance, insulin sensitivity↑	(2)	[85]
	Dan-Shen Root	α-Glucosidase and α-amylase activities↓	(3)	[86]
	Croton Tiglium	Glucose uptake ↑, alleviating insulin resistance	(2)	[87]
	Gynostemma pentaphyllum	2-NBDG uptake ↑, GLUT4 translocation, AMPK and ACC signaling pathways ↑	(2, 3)	[88]

Note: ↑cytokine or pathway upregulation; ↓cytokine or pathway downregulation.

In recent years, great progress has been made in understanding the mechanism of action of TCMs as glucose lowering agents. Many Chinese medicinal herbs have been found to be active in controling diabetes and its associated complications.[89,90] The molecular mechanisms behind the antidiabetic effect of active TCM components have been studied. Comparative analyses show that the antidiabetic mechanisms of different TCMs are different; even the same active ingredient exerts its effect differently in different formulations.[61,62] So there is a compelling need to evaluate scientifically the mechanism of action of the active ingredients in different formulations to identify the most appropriate one in the formulation.

5 | SAFETY OF TRADITIONAL CHINESE MEDICINE IN DIABETES TREATMENT AND COMPARISON WITH WESTERN MEDICINE

In western medicine, diabetes is mainly treated by diabetes education, medical nutrition therapy, exercise therapy, drug therapy and blood glucose monitoring. Drugs for the treatment of diabetes mainly include oral drugs and injectable preparations. Among them, the classic drugs include metformin, sulfonylureas, and thiazolidinediones, and the new drugs include GLP-1 RA, DPP-4i, and SGLT-2i, which have different and rapid mechanisms of action, but also have different side effects[91] (Table 5).

Compared with western medicine, TCM mostly regulates the disease based on its cause thus helping the body to gradually improve, reducing the disease burden and reducing toxicity. Studies have shown that the overall effectiveness of Huangqi Xiaoji Huazhou decoction treatment in delaying the progression of diabetes is higher than in control patients, with fewer adverse reactions, thus making it an effective, safe and reliable candidate for antidiabetic therapy.[92] Similarly, in comparison to metformin, Jinlida granules can effectively improve blood glucose indicators with much lower adverse effects.[93] Moreover, TCM in combination with western medicine enhances the therapeutic efficacy of western medicine by reducing adverse effects. A literature survey showed that Danshen dripping pills in combination with western medicine significantly ameliorated diabetes related retinopathy compared to groups using western medicine alone. The treatment significantly normalized blood sugar and lipid profiles, with significantly reduced adverse effects among diabetic individuals.[94] The chance of contracting diabetes and its related end organ complications is higher in the elderly population. A strictly controlled dosage of Yiben Huoxue decoction, a traditional Chinese medicine, ensures normal glucose metabolism.[95] TCM alone or in combination can therefore be a serious intervention for the treatment of diabetes and its associated complications.

6 | CONCLUSIONS AND PROSPECTS

The many varieties of TCM active ingredients with glucose lowering effects have unique advantages in the treatment of diabetes. They not only lower blood glucose, but also regulate human functions, prevent and treat complications, and avoid the toxic side-effects of chemical synthetic drugs that lower blood glucose. With advancements in the development of biological models, the pathophysiology and molecular mechanisms of diabetes are becoming clearer over time. It is now important to take advantage of these advances to further elaborate the pharmacological relevance and molecular mechanisms of traditional and new antidiabetic TCM formulations. Scientific data from further clinical trials of TCM formulations in the treatment of diabetes will help to develop more targeted Chinese herbs and Chinese medicine compound for diabetes treatment. More research into the mechanisms of the various active ingredients of TCM formulations used to treat diabetes and its associated end organ complications is key to developing novel formulations. Preclinical studies using in vitro approaches to test the efficacy and toxicity of TCM formulations will aid the patenting of TCM formulations for treating diabetes and associated complications. Many natural products have both dietary and medicinal value. Chinese herbs provide another option for research into antidiabetic formulations, with a huge global potential market. In summary, the diabetic models described in this review can be used to evaluate TCM alone or in combination with western medicine to control the global problem of diabetes.

TABLE 5 Classification and side effects of western medicine treatment of diabetes.

Drug type	Ensample	Target organ	Mode of action	Side effect
Insulin and insulin analogue	Insulin, Lispro, Aspart, Glulisine, Glargine, Aspart30	Liver Adipose Tissue Skeletal muscle	Mimics normal insulin secretion	Hypoglycemic response Allergic reaction
Biguanide	Metformin	Muscle Liver Intestine	Enhance glucose uptake and absorption Enhanced GLP-1 Decrease gluconeogenesis	Abdominal Discomfort Metallic taste Nausea Diarrhea Lowered eGFR Vitamin B_{12} Deficiency
Sulfonylureas	DiaBeta、Amaryl	Pancreas	Enhance Insulin Secretion	Weight Gain Dizziness
Thiazolidinedione (TDZs)	Avandia, Actos	Pancreas Muscle Adipose Tissue	Enhance glucose uptake Enhance Insulin Sensitivity	Weight gain Edema The risk of fracture is increased Increased risk of heart problems Bladder cancer
Glinide	Repaglinide, Nateglinide	β cell	Triggers the release of insulin from the pancreas	Blood sugar levels drop too low Weight gain Rash Nausea Vomiting
Dipeptidyl peptidase 4 inhibitor (DPP-4i)	Onglyza, Januvia, Tradjenta, Nesina	Pancreas Intestine	Reduced glucagon secretion Enhancing insulin secretion Enhance GLP-1	Dizziness Acute pancreatitis Hepatic dysfunction Severe arthralgia Urinary Tract Infection Skin reaction
α-Glucosidase inhibitors	Glyset, Acarbose	Intestinal tract	Slows the body's ability to break down starches and some sugars	Flatulence Stomach pain Diarrhea
Sodium-dependent glucose transporters 2 inhibitor (SGLT-2i)	Invokana, Farxiga, Jardiance, Steglatro	Kidney	Enhanced glucose secretion	Vulvogavinal candidiasis Urinary tract infections Hypotension Fatal urosepsis Diabetic ketoacidosis Pyelonephritis
Bile acid sequestrants	Chlestyramine, Colestipo	Gallbladder	Lower cholesterol	Flatulence Constipation Dyspepsia The blood fat level increased
Glucagon-like peptide-1 receptor agonist (GLP-1 RA)	Trulicity, Byetta, Adlyxin, Victoza	Pancreas Intestine	Reduced glucagon secretion Enhancing insulin secretion Gastric emptying	Pancreatitis Nausea Vomiting Gallbladder disease Renal injury
5- Aminolevulinic Acid (5-ALA)		Pancreas	Enhance insulin scretion	Diarrhea Menstrual Pain Headache

AUTHOR CONTRIBUTIONS

XL: Formal analysis, Writing-Review & Editing; HZ: Formal analysis, Data Curation; TA: Formal analysis; FW: Data Curation, Supervision and funding support; BF:Data Curation, Supervision, Paper revision and funding support; QW: Data Curation, Supervision, Paper revision and funding support.

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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.

ETHICS STATEMENT

Not applicable.

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