Review of the therapeutic effects of the traditional Chinese medicine yuye decoction on diabetes mellitus and its complications

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Abstract

Ethnopharmacological relevance: Diabetes is a serious metabolic disease which imposes a heavy burden on the society. It may also bring about a variety of complications if the blood glucose level is not well controlled. Yuye Decoction (YYD) is an ancient herbal medicinal formulation of China and has been widely used in Traditional Chinese medicine to treat patients with diabetes for thousands of years. There are seven medicinal herbs in YYD.

Aim of the study: The aim of the present review is to summarize and critically appraise data concerning medicinal plants used in YYD, its main active constituents and signaling pathways mediating its therapeutic effects on diabetes and diabetic complications.

Materials and methods: The search of papers published in the period 2009 to 2019 and recorded in PubMed was conducted using specific search terms.

Results: After screening, 88 studies were included. Among seven medicinal herbs in YYD formulation, six of them exhibited therapeutic effects on diabetes and its complications through different signaling pathways. Most (55.7%) of the studies were animal studies. Type 2 diabetes was studied in most (37.5%) of the research papers and diabetic nephropathy was the most (19.3%) studied diabetic complication. Focus was placed on Astragalus membranaceus (Fisch.) Bge. and Pueraria lobata (Willd.) Ohwi in the largest number of research papers.

Conclusion: YYD exerted a therapeutic effect on diabetes and a preventive effect on diabetic complications.

Abbreviations: ACC: Acetyl CoA Carboxylase; pNF-xB: Activated Phosphorylated Derivative; Acrp30: Adiponectin; (ATP)-binding: Adenosine Triphosphate; AGEs: Advanced Glycation End Products; UA1b: Albuminuria; PGC-1a: Alpha Subunit of Peroxisome Proliferators-Activated Receptor-Gamma Coactivator-1; AMPK: AMP-Activated Protein Kinase; Arg-1: arginase-1; APS: Astragalus polysaccharides; ABCB11: ATP-binding cassette (transporter) B11; Bas: bile acids; BBB: Blood-Brain Barrier; BUN: blood urea nitrogen; BW: Body Weight; CAT: catalase; JNK: Jun N-terminal kinases; CrCl: Collagen Type IV Creatinine Clearance; DCs: Dendritic Cells; DCM: Diabetic cardiomyopathy; DCI: Diabetic Cognitive Impairment; DNP: Diabetic Peripheral Neuropathy; DM: Diabetes (not specific); DN: Diabetic Nephropathy; DO: Diabetic Ophthalmopathy; DR: Diabetic Retinopathy; DVC: Diabetic Vascular Complications; EBPs: Enhancer Binding Protein; eNOS: Endothelial NO Endothelial Nitric Oxide Synthase; ESRD: End Stage Renal Disease; FBG: Fasting Blood Glucose; FABP: Fatty Acid Binding Protein; F/B ratio: Firmicutes to Bacteroidetes Ratio; FN: Fibronectin; FOXO1: Forkhead Box Protein O1; GIN: glutamine; GSH: Glutathione; GIR: Glucose Infusion Rate; GLUT2: Glucose Transporter 2; GLUT4: Glucose Transporter 4; GSH: Glutathione; GPx: Glutathione Peroxidase; HbA1C: Hemoglobin; HGF: Hepatocyte Growth Factor; HMGB1: High Mobility Group Box 1; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; HUVECs: Human Umbilical Vein Endothelial Cells

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Key words: traditional chinese medicine, diabetes, phytochemical, mechanism, medicinal plants

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Cells; HAT: hydroxyacetone; H2O2: Hydrogen Peroxide; IKKβ: IκB kinase β; INOs: Inducible Nitric Oxide Synthase; IGF: Insulin-like Growth Factor-1; IRS: Insulin Receptor Substrate (IRS); IL-1β: Interleukin-1β; IL-6: Interleukin-6; IL-10: Interleukin-10; IR: Insulin Resistance; IRS-1: Insulin Receptor Substrate-1; Ile: Isoleucine; MDA: Malondialdehyde; MnSOD: Manganese Superoxide Dismutase; MEKC: Micellar Electrokinetic Chromatography; MetS: Prediabetes & Metabolic Syndrome; mMVECs: Mouse Vascular Endothelial Cell; NO: nitric oxide; NF-κB: Nuclear-Factor Kappaβ; 2-NBDG: 2-(N-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl)-Amino)-2-Deoxyglucose; PPARα: Peroxisome Proliferators-Activated Receptor α; pIκB: Phospho-Insulin Receptor; P13K: Phosphatidylinositol 3-kinase; NPCs: Primary Mouse Nonparenchymal Cells; PPAR: Proliferator-Activated Receptor γ; PCNA: Proliferating Cell Nuclear Antigen; PUE: Puerarin; ROS: Reactive Oxygen Species; Tregs: Regulatory T cells; sCr: Serum Creatinine; FPG: Serum Fasting Plasma Glucose; SUA: Serum Uric Acid; SOD: Superoxide Dismutase; T1DM: Type 1 Diabetes; T2DM: Type 2 diabetes; UAE: Urinary Albumin Excretion; ACR: Urinary Albumin/Creatinine Ratio; UDP: Uridine Diphosphate; s-VCAM-1: vascular cell adhesion molecule-1; VEGF: Vascular endothelial growth factor; VAT: visceral adipose tissue.

Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycemia due to insulin resistance, absolute insulin deficiency and/or abnormal insulin secretion [1]. According to the WHO, more than 171 million people worldwide suffer from diabetes and the number of diabetic patients keeps escalating [2].

Diabetes may lead to a series of complications such as blindness, stroke, renal failure, nerve damage and limb amputation [3]. Persistent hyperglycemia brings about chronic damage to various tissues in the heart, eyes, kidneys and blood vessels and causes dysfunctions of these organs. These complications, including nephropathy, retinopathy, neuropathy, cardiomyopathy and cognitive impairment, are major causes of morbidity and mortality in diabetic patients. Consequently, diabetes has become a serious social health problem [4]. According to WHO, diabetes is expected to become the 7th leading cause of death in 2030 globally [5].

However, the current treatment of diabetes with western medicine still leaves much to be desired. There is a paucity of information available on effective treatment options for diabetic patients. Thus, the perspective of achieving good long-term metabolic control in diabetes is of central importance. Traditional Chinese medicine has a long history in treating diabetes and is widely popular in China. Many hospitals in China use traditional medicinal plants or a combination of western medicine with Chinese medicine to treat diabetes.

Yuye Decoction (YYD) is an ancient formulation and was first recorded in the book of Chinese medicine “yi-xue zhong-hong canxi lu (醫學衷中參西錄)” written by Zhang XiChun in 1909. It is widely used in Traditional Chinese medicine to treat diabetes. There are seven medicinal herbs that compose YYD, including Dioscorea opposita Thunb. (RD), Astragalus membranaceus (Fisch.) Bge. (AM), Anemarrhena asphodegoids Bge. (RA), Schisandra chinensis (Turcz.) Baill. (SC), Trichosanthes kirilowii Maxim. (TK), Gallus gallus domesticus Brisson (GGD), and Pueraria lobata (Willd.) Ohwi (PL) (Table 1). In traditional Chinese medicine theory, YYD is beneficial to kidney function and improves the amount of body fluid. Thus, it can be used for relieving the symptoms of diabetes mellitus.

However, as medicinal herbs are usually mixed with other herbs and are seldom used alone in traditional Chinese medicine, it is hard to evaluate the effect of individual herbs on treating diabetes and its complications. Therefore, the aim of this review is to provide a comprehensive coverage of the individual herbs of Yuye Decoction regarding their active components and functional mechanisms for treating diabetes and its complications. It also provides an overview for researchers who intend to perform randomized control trials on YYD in the future.

Literature search

The search was done by using the specific search terms listed in Table 2 to gather information in PubMed regarding the use of YYD and its individual components in the treatment of diabetes respectively. After a preliminary search, articles related to YYD and its component herbs and published from 2009 to 2019 were screened. Articles whose topics matched diabetes and its complications were included. The basic information for each article such as country, experimental design (human, animal, cell based, chemical test) and results were extracted. Irrelevant or repeated articles were excluded.

After preliminary screening, clinical trials and mechanistic studies were analyzed respectively. For all human studies, the details of the study were extracted. Mechanistic studies were divided into animal studies, cell-based studies, animals & cell-based studies and chemical tests. These studies were then further grouped into different categories such as diabetes (not specific), insulin and metabolic syndrome; Type 1 diabetes; Type 2 diabetes; diabetic ophthalmopathy; diabetic nephropathy; diabetic retinopathy; diabetic cardiomyopathy; diabetic vascular complications; diabetic peripheral neuropathy; and diabetic cognitive impairment.

### Table 1. Basic information of Yuye decoction

<table>
<thead>
<tr>
<th>Medicinal herbs</th>
<th>family</th>
<th>Full scientific name</th>
<th>Medicinal part</th>
<th>Weight of herbs in ancient medica (qian)/equivalent g</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dioscorea opposita Thunb.</td>
<td>Dioscoreaceae</td>
<td>Dioscorea Opposita Rhizoma</td>
<td>Rhizome</td>
<td>10/30</td>
<td>20</td>
</tr>
<tr>
<td>Astragalus membranaceus (Fisch.) Bge.</td>
<td>Fabaceae</td>
<td>Astragali Membranacei Radix</td>
<td>Root</td>
<td>5/15</td>
<td>10</td>
</tr>
<tr>
<td>Anemarrhena asphodegoids Bge.</td>
<td>Asparagaceae</td>
<td>Anemarrhena Rhizoma</td>
<td>Root</td>
<td>6/18</td>
<td>12</td>
</tr>
<tr>
<td>Schisandra chinensis (Turcz.) Baill.</td>
<td>Schisandraceae</td>
<td>Schisandrae chinensis Fructus (SCF)</td>
<td>Fruit</td>
<td>3/9</td>
<td>6</td>
</tr>
<tr>
<td>Trichosanthes kirilowii Maxim.</td>
<td>Cucurbitaceae</td>
<td>Trichosanthis kirilowii Radix</td>
<td>Root</td>
<td>3/9</td>
<td>6</td>
</tr>
<tr>
<td>Gallus gallus domesticus Brisson</td>
<td>Phasianidae</td>
<td>Galli Gigerii Endothelium Corneum</td>
<td>Conical endothelium</td>
<td>2/6</td>
<td>4</td>
</tr>
<tr>
<td>Pueraria lobata (Willd.) Ohwi</td>
<td>Fabaceae</td>
<td>Puerariae lobatae Radix</td>
<td>Root</td>
<td>1.5/4.5</td>
<td>3</td>
</tr>
</tbody>
</table>
Based on the key word search described in Table 2, 2978 articles were found in the PubMed database. Finally, 88 articles were included in our review after comprehensive screening. All 88 included studies came from Asia. Among them, most (73.8%) of the papers were from China (Tables 3 and 4).

Results

Animal studies: Forty-nine animal studies investigated the effects of YYD on diabetes and its complications (Tables 5-7).

Diabetes (not specific), insulin and metabolic syndrome: Fan et al. showed that a polysaccharide DOTP-80 from *Dioscorea opposita* Thunb. roots had potent hypoglycemic activity [7]. Another study demonstrated that *Discorea batatas* extract could ameliorate insulin resistance in mice which were fed a high-fat diet [8]. In fructose-fed rats, a daily dose of 2 mg/kg astragaloside for 3 weeks improved metabolic syndrome and endothelial dysfunction [9]. In a cohort study, it was found that Huang-qí (*Astragalus membranaceus*) was one of the common Chinese medicines which could reduce the risk of diabetic ketoacidosis in diabetic patients [10].

**Table 2. Strings used in search**

<table>
<thead>
<tr>
<th>Formula or medicinal herbs</th>
<th>Total</th>
<th>Not relevant</th>
<th>Animals studies</th>
<th>Cell-based studies</th>
<th>Chemical studies</th>
<th>Animals &amp; cell-based studies</th>
<th>RCT</th>
<th>Cohort studies</th>
<th>Animals &amp; cohort studies</th>
<th>Included</th>
</tr>
</thead>
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<td>Yuye decoction</td>
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<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
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<td>590</td>
<td>577</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>13</td>
</tr>
<tr>
<td>Astragalus membranaceus</td>
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<td>687</td>
<td>13</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>27</td>
</tr>
<tr>
<td>(Fisch.) Bge.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
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<td>1</td>
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<td>-</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schisandra chinensis (Turcz.)</td>
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<td>756</td>
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<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td>Baill.</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichosanthes kirilowii Maxim.</td>
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<td>167</td>
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<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
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<td>3</td>
</tr>
<tr>
<td>Gallus gallus domesticus Briston</td>
<td>12</td>
<td>12</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Pueraria lobata (Willd.) Ohwi</td>
<td>604</td>
<td>577</td>
<td>17</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Total</td>
<td>2978</td>
<td>88</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>88</td>
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</table>

**Table 3. Results of literature search**

<table>
<thead>
<tr>
<th>Formula or medicinal herbs</th>
<th>Country</th>
<th>Number of papers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yuye decoction</td>
<td>China</td>
<td>62</td>
</tr>
<tr>
<td>Dioscorea opposita Thunb.</td>
<td>South Korea</td>
<td>7</td>
</tr>
<tr>
<td>Astragalus membranaceus</td>
<td>Taiwan</td>
<td>9</td>
</tr>
<tr>
<td>(Fisch.) Bge.</td>
<td>Japan</td>
<td>3</td>
</tr>
<tr>
<td>Anemarrhena asphodeloides</td>
<td>India</td>
<td>5</td>
</tr>
<tr>
<td>Bge.</td>
<td>Hong Kong</td>
<td>2</td>
</tr>
<tr>
<td>Schisandra chinensis (Turcz.)</td>
<td>Gallus gallus domesticus Briston (GGID)</td>
<td>0</td>
</tr>
<tr>
<td>Baill.</td>
<td>Pueraria lobata (Willd.) Ohwi (PL)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 4. Number of papers by countries**

**Table 5. Number of papers related to diabetic or its complications (DM: Diabetes (not specific); T1DM: Type 1 diabetes; T2DM: Type 2 diabetes; DO: Diabetic ophthalmopathy; DN: diabetic nephropathy; DR: diabetic retinopathy; DCM: diabetic cardiomyopathy; DVC: diabetic vascular complications; IR: insulin resistance; DPN: diabetic peripheral neuropathy; MetS: prediabetes & metabolic syndrome; DCI: diabetic cognitive impairment)**

<table>
<thead>
<tr>
<th>Formula or medicinal herbs</th>
<th>DM</th>
<th>T1DM</th>
<th>T2DM</th>
<th>DR</th>
<th>DN</th>
<th>DO</th>
<th>DCM</th>
<th>DVC</th>
<th>IR</th>
<th>DPN</th>
<th>MetS</th>
<th>DCI</th>
<th>Total</th>
</tr>
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<td>-</td>
<td>-</td>
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<td>-</td>
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<td>-</td>
<td>1</td>
</tr>
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<td>3</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>13</td>
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<td>Astragalus membranaceus</td>
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<td>8</td>
<td>2</td>
<td>6</td>
<td>-</td>
<td>4</td>
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<td>-</td>
<td>-</td>
<td>3</td>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td>(Fisch.) Bge.</td>
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<tr>
<td>Anemarrhena asphodeloides</td>
<td>-</td>
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<td>-</td>
<td>2</td>
<td>6</td>
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<tr>
<td>Bge.</td>
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<td></td>
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<td>11</td>
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<tr>
<td>Gallus gallus domesticus Briston</td>
<td>-</td>
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<td>2</td>
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<td>-</td>
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<tr>
<td>Pueraria lobata (Willd.) Ohwi</td>
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<td>2</td>
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<tr>
<td>Total</td>
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<td>3</td>
<td>4</td>
<td>88</td>
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</tbody>
</table>
Table 6. Different studies related to diabetic or its complications

<table>
<thead>
<tr>
<th>Studies Type</th>
<th>DM</th>
<th>T1DM</th>
<th>T2DM</th>
<th>DR</th>
<th>DN</th>
<th>DO</th>
<th>DCM</th>
<th>DVC</th>
<th>IR</th>
<th>DPN</th>
<th>MetS</th>
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<td>-</td>
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<td>2</td>
<td>3</td>
</tr>
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<td>Cell-based studies</td>
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<td>-</td>
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<td>-</td>
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<td>17</td>
<td>2</td>
<td>9</td>
<td>2</td>
<td>3</td>
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<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 7. Applications of herbal TCM and/or monomers in diabetes and its complications

<table>
<thead>
<tr>
<th>Extract</th>
<th>Topic</th>
<th>Duration</th>
<th>Model</th>
<th>Pathways</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIL (Jian, W, et al. 2016)</td>
<td>Diabetic Retinopathy</td>
<td>24 weeks</td>
<td>STZ rats</td>
<td>Through regulating multiple factors involved in the DR pathological pathway.</td>
<td>attenuating the increase in erythrocyte aggregation, plasma viscosity, and acellular vessel and pericyte loss; reversing the hyper-activation of AR, the hyper-expression of VEGF, ICAM-1, and ET-1; reducing the hyper-expression of PEDF and eoculcin in the retinas of STZ-treated rats</td>
</tr>
<tr>
<td>Polysaccharide AERP (Liu, Y, et al. 2019)</td>
<td>Cognitive Dysfunction</td>
<td>10 weeks</td>
<td>db/db mice</td>
<td>Through altering the gut microbiota</td>
<td>Alleviating the hyperglycemia, tissue impairment; inhibiting cognitive impairment; Modulating the composition of metabolites like SCFAs</td>
</tr>
<tr>
<td>Refined-JQ (Q-J-R) (Li-hui Gao, et al. 2014)</td>
<td>Prediabetes</td>
<td>4 months</td>
<td>IFD-C57 mice</td>
<td>Through activating the AMPK signaling pathway</td>
<td>Reducing BW, TC, HOMA-IR; Enhancing the glucose tolerance; Improving insulin response; Activating liver glycogen synthesis; Increasing GHR; Increasing the levels of phosphorylated AMPK and phosphorylated ACC.</td>
</tr>
<tr>
<td>Astragaloside IV (Gu, D, et al. 2013)</td>
<td>Diabetic Nephropathy</td>
<td>8 weeks</td>
<td>STZ rats</td>
<td>Through inhibiting NF-κB mediated inflammatory genes expression</td>
<td>Ameliorating UA1β, renal histopathology and podocyte foot process effacement; decreasing the serum levels of TNF-α, MCP-1 and ICAM-1; decreasing α1-chain type IV collagen mRNA.</td>
</tr>
<tr>
<td>Astragaloside IV (Zhang, N, et al. 2011)</td>
<td>Metabolic Syndrome</td>
<td>3 weeks</td>
<td>fructose-fed rats</td>
<td>Through the NO/cGMP pathway</td>
<td>Reducing blood pressure and TG levels; Improving glucose tolerance and endothelium-dependent vasorelaxation.</td>
</tr>
<tr>
<td>NIL (Ruanzan Zhai, et al. 2019)</td>
<td>Diabetic Nephropathy</td>
<td>12 weeks</td>
<td>STZ rats</td>
<td>Through inhibiting oxidative stress</td>
<td>Uregulating nephrin, α-dystroglycan, Bcl-x; Downregulating inflammation and increase in mean mesangial induced by STZ; Preventing the phosphorylation of eEF2α, PERK and JNK; Inhibiting the expression of GRP78 and ORP150; Inhibiting the TM-induced apoptosis of podocytes, concomitant with decreased CHOP expression and cleaved caspase-3.</td>
</tr>
<tr>
<td>Astragalus polysaccharide (Liu, M, et al.2010)</td>
<td>T2DM</td>
<td>8 weeks</td>
<td>KKaY mice</td>
<td>Through regulating insulin signaling in insulin-resistant skeletal muscle</td>
<td>Ameliorating hyperglycemia and IR; Restoring insulin-induced protein kinase B Ser-473 phosphorylation and glucose transporter 4 translocation in skeletal muscle.</td>
</tr>
<tr>
<td>Astragalus polysaccharide (Chen, W, et al.2009)</td>
<td>Diabetic Cardiomyopathy</td>
<td>10 weeks</td>
<td>STZ hamsters</td>
<td>Through suppressing the local cardiac chymase–Ang II system</td>
<td>Ameliorating myocardial collagen deposition via suppression of chymase-MMP activation; Lowering levels of myocardial collagen type I and ratio of collagen type I/H; Suppressing cardiac MMP-2 and ProMMP-2 activities; Inhibiting heart chymase activation.</td>
</tr>
<tr>
<td>Astragalus polysaccharide (Gu et al.2016)</td>
<td>Diabetic Memory Impairment</td>
<td>8 weeks</td>
<td>STZ rats</td>
<td>Through glucose and lipid metabolism.</td>
<td>Decreasing FPG, HbAlc, and insulin levels; Reversing memory impairment in the diabetic model; Lowering hippocampal MDA concentration.</td>
</tr>
<tr>
<td>NIL (Chen et al. 2017)</td>
<td>T2DM</td>
<td>100 days</td>
<td>STZ rats</td>
<td>Through improving Jccll function and reducing insulin resistance.</td>
<td>Ameliorating impairments in glucose tolerance &amp; insulin release function; Reducing serum levels of IR; Decreasing the expression of NO and MDA; Increasing the expression of SOD and GSHE-px; Restoring the impaired insulin signaling; Uregulating plinR expression, IRS tyrosine phosphorylation, PI3K, GLUT4 expression; Downregulated the serum phosphorylation of IRS.</td>
</tr>
<tr>
<td>Astragalus polysaccharides (Chen et al.2018)</td>
<td>Diabetic Cardiomyopathy</td>
<td>15 weeks</td>
<td>db/db diabetic mice</td>
<td>Through the cardiac PPARα-mediated regulatory pathways.</td>
<td>Improving the myocyte TG accumulation &amp; cardiac dysfunction; Normalizing energy metabolic derangements in diabetic hearts; Repressing the activation of PPARα target genes involved in myocardial fatty acid uptake and oxidation in diabetic hearts; Reversing PPARα-mediated suppression of genes involved in glucose utilization of diabetic hearts.</td>
</tr>
</tbody>
</table>
Wan JH (2020) Review of the therapeutic effects of the traditional Chinese medicine yuye decoction on diabetes mellitus and its complications

### Trichosanthes kirilowii

**Trichosanthes kirilowii lectin (Yandong et al. 2019)**
- **Diabetic Nephropathy**
  - 8 weeks
  - STZ rat
  - Through inhibiting Notch signaling
  - Attenuating STZ induced damages in renal function and structure; Increasing TNF-α & NO production; Suppressing IL-10 & Arg-1 production; Inhibiting induced inflammation by STZ; Blocking the polarization of macrophage into M1 type; Suppressing expression of Notch1, NCKD1, Hes1.

### Schisandra chinesis (Turcz.) Baill.

**NIL (Hong et al. 2018)**
- **T2DM**
  - 10 weeks
  - db/db mice
  - Through suppressing lipid synthesis, oxidative stress, inflammation.
  - Decreasing plasma and hepatic TG & TC concentrations; Downregulating Hepatic expressions for fatty acid & TC synthesis; Upregulating beta-oxidation & TC export. Improving glucose tolerance; Increasing expression levels of antioxidant enzymes; Decreasing inflammatory cytokines, oxidative stress, leptin, insulin levels.

**Acidic polysaccharide (Du et al., 2019)**
- **T2DM**
  - 8 weeks
  - STZ rats
  - Through protecting against β-cells apoptosis.
  - Decreasing FBG, TG, TC, LDL-C, MDA levels; Increasing insulin, HDL-C levels and SOD activity; Improving the pathological changes in pancreatic islet; Inhibiting the up-regulation of phosphorylated JNK, BAX and Cleaved Caspase-3 proteins; Increasing Bel-2 protein expression.

**Ethanol extracts (Zhang et al. 2012)**
- **Diabetic Nephropathy**
  - 9 weeks
  - STZ rats
  - Through inhibiting the epithelial to mesenchymal transdifferentiation.
  - Lessening degree of fibrosis; Lowering the expressions of FN, α-SMA and PAI-1; Inhibiting the endothelial-myofibroblast transition

**Schisandrae chinensis oil (An et al 2015)**
- **T2DM**
  - 8 weeks
  - STZ rats
  - Through improving pancreatic β-cell function
  - Decreasing FBG, TC, TG levels, pancreatic MDA; Increasing SOD & CAT activities; Enhancing protein expression of Bel-2, PDX-1, GLUT-2, GCK; Upregulating expression of anti-apoptotic genes; Increasing expression of glucose metabolism; Delaying islet cell apoptosis.

**Schisandra chinensis fruit extract (Zhang et al. 2012)**
- **diabetic nephropathy**
  - 7 weeks
  - STZ rats
  - Through preserving podocyte integrity by suppressing EMT.
  - Decreasing UAE & ACR; Attenuating glomerulosclerosis and protected against podocyte loss and integrity of the slit diaphragm; Preventing the EMT of podocytes.

**A water-soluble polysaccharide (Niu et al 2017)**
- **T2DM**
  - 28 days
  - STZ rats
  - Through antioxidant effect
  - Scavenging effect on superoxide anion free radical, hydroxyl radical, DPPH free radical; Increasing body weight; Improving the glucose tolerance; Reducing FBG; Elevating levels of FINS and value of ISI; Reducing the MDA content; Increasing GSHPx, CAT, SOD activities.

### Dioscorea opposita Thunb

**Yam dioscorin, dipeptide NW (Wu et al. 2018)**
- **T2DM**
  - 135-day
  - C57BL/6J mice
  - Through impaired glucose tolerance controls
  - Lowering TC & low-density lipoprotein; Lowering TG contents; Reducing total visceral lipid contents; Lowering blood glucose levels.

**Diosgenin (Sato et al., 2014)**
- **T1DM**
  - 2 days
  - STZ rats
  - Through activating the muscular GLUT4 signaling pathway
  - Increasing Serum DHEA level; Decreasing blood glucose level; Increasing GLUT4 translocation and Akt & PKC phosphorylation; Correlations were observed between blood glucose level, GLUT4 translocation level and muscular sex steroid hormone level 150 min after the administrations.

**NIL (Zhi-Hong et al. 2014)**
- **T2DM**
  - 8 weeks
  - STZ rats
  - Through inhibiting polyl pathway
  - Decreasing blood glucose, insulin levels, adipose tissue weight; Improving glucose tolerance; Lowering plasma TG, TC, liver TG levels; Inhibiting the activity of AR; Restoring adiponectin expression in serum.

**Allantoin (Go, H. K. et al 2015)**
- **T1DM**
  - 31 days
  - STZ rats
  - Through modulating oxidative stress
  - Decreasing blood glucose; Decreasing HA/Ac; TC, low-density lipoprotein; Increasing insulin, GLP-1, C-peptide; Ameliorating antioxidant stress; Decreasing MDA; Increasing SOD; Reducing GSH

**DOTP-80 (Fan, Y., et al. 2015)**
- **Diabetes**
  - 18 days
  - alloxan-induced mice
  - Through preventing oxidative damage of pancreatic β-cell.
  - Stimulating an increase in glucose disposal; Had strong hypoglycemic activity; Increasing the levels of antioxidant enzymes (SOD) activity

**Ethanol extract (Cheng, Q. et al. 2015)**
- **T2DM**
  - 10 weeks
  - CD-1 (ICR) mice
  - Through improving glucose and lipid metabolism.
  - Improving glucose intolerance & normalize lipid profile; Increasing peripheral and hepatic insulin sensitivity; Decreasing serum free fatty acid level; Enhancing hepatic gluokinasie activity & glycogen content; Improving serum antioxidant activity; Decreasing fatty deposits in the liver of mice.

**Allantoin (Niu, C. S. et al. 2010)**
- **T1DM**
  - 3 days
  - STZ rats
  - Through increasing β-endorphin secretion from the adrenal gland.
  - Decreasing plasma glucose levels in a dose related manner; Enhancing β-endorphin release from the isolated adrenal medulla of STZ diabetic rat in a dose-related manner; Increasing radioactive glucose uptake in isolated skeletal muscle; Increasing GLUT4 mRNA & protein levels in muscle, Reversing HFD-induced elevations in plasma glucose & insulin levels, HOMA-IR and oral glucose tolerance test values; Up-regulating the level of p-akt protein; Down-regulating the levels of p-ERK and p-S6K1 proteins in the adipose tissues; Reversing the HFD-induced decrease in the plasma membrane GLUT4 level; Improving glucose metabolism.

**DB extract (Kim, S. et al. 2012)**
- **Early-stage obesity-induced insulin resistance**
  - 7 weeks
  - HFD mice
  - Through activating the insulin signaling cascade leading to GLUT4 translocation
  - Reversing HFD-induced elevations in plasma glucose & insulin levels, HOMA-IR and oral glucose tolerance test values; Up-regulating the level of p-akt protein; Down-regulating the levels of p-ERK and p-S6K1 proteins in the adipose tissues; Reversing the HFD-induced decrease in the plasma membrane GLUT4 level; Improving glucose metabolism.
Dioscorea opposita
Thunb polysaccharide-zinc (Zhang, Y. et al. 2018)

Sarsasapogenin
(Yao-Wu Liu, et al. 2018)

Ethanol extract
(Xuan Li, et al. 2013)

Total saponins from
Rhizoma Anemarrhenae
(Liu, Y. W, et al. 2012)

PTV-2 extract
(Tripathi, V. B, et al. 2017)

Puerarin
(Wu, K, et al. 2013)

PTY-2r
(Rashmi, S, et al. 2018)

PTV-2r
(Shukla, R, et al. 2017)

Puerarin

NIL
(Gao, K, et al. 2018)

Flos Puerariae Extract
(Yu, W, et al. 2014)

PTV-2(Shivani Srivastava, et al. 2018)

NIL (Wang, W, et al. 2018)

PTY-2r (Shukla, R, et al. 2018)

Puerariae flos extract
(KUBO, Koshi, et al. 2012)

<table>
<thead>
<tr>
<th>Medicine/Medication</th>
<th>Disease/Condition</th>
<th>Time</th>
<th>Animals</th>
<th>Mechanism/Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2DM</td>
<td>42 days</td>
<td>STZ rats</td>
<td>Through ameliorating lipid levels and oxidative stress.</td>
<td></td>
</tr>
<tr>
<td>Rhizoma Anemarrhenae</td>
<td>9 weeks</td>
<td>STZ rats</td>
<td>Through inhibiting NLRP3 inflammasome activation and AGEs-RAGE interaction.</td>
<td></td>
</tr>
<tr>
<td>Sarsasapogenin</td>
<td>Diabetic nephropathy</td>
<td>12 weeks</td>
<td>STZ rats</td>
<td>Through Inhibiting AGE accumulation, polyol pathway activation and ROS overproduction.</td>
</tr>
<tr>
<td>Total saponins from Rhizoma Anemarrhenae</td>
<td>Diabetes-associated cognitive decline</td>
<td>7 weeks</td>
<td>STZ rats</td>
<td>Through a sum of reduction of Aβ accumulation and inflammation in brain.</td>
</tr>
<tr>
<td>PTV-2 extract</td>
<td>Diabetic Nephropathy</td>
<td>20 days</td>
<td>STZ rats</td>
<td>Through degrading the ECM accumulated in kidney tissue.</td>
</tr>
<tr>
<td>Puerarin</td>
<td>T1DM</td>
<td>14 days</td>
<td>STZ rats</td>
<td>Through elevating insulin expression and maintaining metabolic homeostasis.</td>
</tr>
<tr>
<td>PTV-2r</td>
<td>Diabetic Nephropathy</td>
<td>20 days</td>
<td>STZ rats</td>
<td>Through suppressing oxidative stress and apoptosis.</td>
</tr>
<tr>
<td>PTV-2r</td>
<td>Diabetic Nephropathy</td>
<td>20 days</td>
<td>STZ rats</td>
<td>Through inhibiting the expression of HIF-1α and VEGF.</td>
</tr>
<tr>
<td>Puerarin</td>
<td>T2DM</td>
<td>4 weeks</td>
<td>STZ rats</td>
<td>Through preventing the accumulation of intramyocellular lipids.</td>
</tr>
<tr>
<td>NIL</td>
<td>T2DM</td>
<td>8 weeks</td>
<td>STZ rats</td>
<td>Through altering features of the metabolite profiles and the gut microbiota.</td>
</tr>
<tr>
<td>Flos Puerariae Extract</td>
<td>Diabetic Cardiomyopathy</td>
<td>10 weeks</td>
<td>STZ rats</td>
<td>Through inhibiting JNK and P38 MAPK signaling pathway.</td>
</tr>
<tr>
<td>NIL (Wang, W, et al. 2018)</td>
<td>T2DM</td>
<td>8 weeks</td>
<td>STZ rats</td>
<td>Through the tight correlation between BAs and glucose-lipid metabolism status.</td>
</tr>
<tr>
<td>Puerariae flos extract (KUBO, Koshi, et al. 2012)</td>
<td>T2DM</td>
<td>8 weeks</td>
<td>TSOD mice</td>
<td>Through promoting catabolization/excretion of cholesterol in the liver.</td>
</tr>
</tbody>
</table>

Decreasing the glucose and insulin levels; Reducing MDA contents; Increasing SOD and T-AOC activities significantly in liver; Decreasing the levels of TCHO, TG and LDL-C in serum; Increasing HDL-C level.

Ameliorating renal dysfunction; Decreasing UA,1b, kidney weight index, SUA, FN, Col IV levels. Decreasing IL-18, NLRP3, activated caspase 1 levels, AGEs, RAGE levels in the renal cortex of diabetic rats.

Increasing activities of SOD and GSH-Px in serum; Decreasing MDA, AGE levels in serum and sorbitol concentration in the lens in ERA-treated DO rats; Decreasing E/P ratio; Alleviating pathological changes of lens & retina; Ameliorating subnormal growth of pericytes induced by high glucose.

Reducing glycemia; Increasing serum insulin concentration; Improving dyslipidemia; Alleviating the STZ-lesioned pancreas tissue; Up-regulating intrapancreatic protein levels of IRS-1 & IGF-1; Increasing endogenous mRNA levels of skeletal muscle insulin receptor (InsR) and PPARα.

Raising the activity of antioxidant enzymes; Suppressing oxidative stress and apoptosis; Preventing urinary albumin excretion in a dose-dependent manner.

Decreasing Blood glucose, urine protein, sCr, UA1b levels; Increasing Cr(C); Decreasing glomerular tubular necrosis; Decreasing basement membrane thickening and less ECM deposition; Reducing Mmp-9 activity and expression.

Decreasing expression of HIF-1α & VEGF; Decreasing Blood glucose, urine protein, sCr, and urea level; Decreasing the expression of HIF-1α & VEGF; Increasing the expression of nephrin in a dose-dependent manner.

Allievated dyslipidemia; Decreased the accumulation of intramyocellular lipids by upregulating the expression of a range of genes involved in mitochondrial biogenesis, oxidative phosphorylation, detoxification of ROS, oxidation of fatty acids in the muscle of diabetic rats; Decreasing the traffic of fatty acid translocase/CD36 to the plasma membrane to reduce the uptake of fatty acids by myocytes.

Modulating blood glycemic level; Enriching Bacteroidetes; Acting through TP53, AKT1, PPARa proteins.

Normalizing glucose and weight profile; Preserving myocardial structure; Reducing apoptotic cardiac cell death; Reversing elevated markers of oxidative stress; Increasing the plasma level of GLP-1, GIP, pancreatic expressions of GLP-1R, GIP-R, Bcl2, and insulin.

Enhancing the size and number of islet cells along with the plasma level of GLP-1, GIP, pancreatic expressions of GLP-1R, GIP-R, Bcl2, and insulin.

Decreasing the expression of variation in NF-κB expression and maintaining metabolic homoeostasis.

Decreasing glycemia; Increasing serum insulin concentration; Improving dyslipidemia; Alleviating the STZ-lesioned pancreas tissue; Up-regulating intrapancreatic protein levels of IRS-1 & IGF-1; Increasing endogenous mRNA levels of skeletal muscle insulin receptor (InsR) and PPARα.

Decreasing the expression of variation in NF-κB expression and maintaining metabolic homoeostasis.

Decreasing the expression of iNOS and inflammatory cytokines; Decreasing Blood glucose, urine protein, sCr, and urea level; Decreasing the expression of HIF-1α & VEGF; Increasing the expression of nephrin in a dose-dependent manner.

Decreasing the levels of TCHO, TG and LDL-C in serum; Decreasing FBG; increasing the body weight. |
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| Puerarin (ZHANG, Duohen, et al. 2019) | Diabetic Cataract | 12 weeks | STZ rats | Through inhibiting the nr2/ho-1 signaling pathway. | Reducing blood glucose levels and the incidence of cataract in STZ-induced diabetic rats; Reducing oxidative stress; Restoring the levels of MDA & GSH, Gpx; Decreasing the expression levels of retinal VEGF & il-1β; Increasing the mrna expression levels of nr2 and ho-1. |
| Puerarin (GUO, Bao-Qiang, et al. 2018) | Diabetic Cardiomyopathy | 4 weeks | STZ rats | Through upregulating VEGFA/Ang-1 and suppressing apoptosis. | Reducing the myocardial infarct area; Increasing left ventricular developed pressure in diabetic rats with myocardial I/R; Reducing oxidative stress, inflammation, NF-κB protein expression; Activating the protein expression levels of VEGFA and Ang-1; Increasing NO production, phosphorylated eNOS protein expression and caspase-3 activity. |
| Puerarin (XU, Xiaohui, et al. 2016) | Diabetic Nephropathy | 8 weeks | STZ rats | Through attenuating SIRT1/FOXO1 pathway for renal protection. | Ameliorating FBG, BUN, Scr, 24-hour urine protein levels; Down-regulating IL-6, TNF-α, ROS in kidney; Increasing the activities of MnSOD and CAT; Improving kidney tissue damage; Up-regulating SIRT1, FOXO1, PGC-1α expressions; Down-regulating the protein expression of NF-kB. |
| RPF (CHEN, Zhengye, et al. 2017) | Diabetic Nephropathy | 9 weeks | STZ rats | Through inhibiting the PI3K/AKT pathway in the kidney. | Decreasing blood glucose; Ameliorating Glomerular mesangial matrix expansion, renal capsule contraction, renal tubular epithelial cell edema; Reducing protein levels of PI3K, AKT, α-SMA, collagen IV. |
| NIL (ZHAO, Jindong, et al. 2019) | T2DM | 8 weeks | Gotokakizaki rats | Through improving glucose & lipid levels and modulating the gut microbiota. | Reducing the FBG gain and a shift in the structure of the gut microbiota; Decreasing weight, Fbg level, TC; Decreasing gut microbiota, Bacteroidetes, F/B ratio, Allobaculum, Desulfovibrionaceae; Enriching Lactobacillus. |
| Puerarin (DONG, Songtao, et al. 2018) | T2DM | 28 days | STZ rats | Through upregulating uridine diphosphate (UDP)-glucuronosyltransferase activity. | Altering the pharmacokinetics of puerarin by the metabolic changes in diabetes; Upregulating UDP-glucuronosyltransferase activity; Enhancing puerarin clearance; Altering the hepatic and intestinal gene and protein expressions of Ugt1al1 and Ugt1a7. |

**Cell-based studies**

<table>
<thead>
<tr>
<th>Astragalus membranaceus (Fisch.) Bunge</th>
<th>Extract</th>
<th>Topic</th>
<th>Model</th>
<th>Pathways</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astragaloside IV (Chen, X, et al. 2019)</td>
<td>Diabetic Nephropathy</td>
<td>Renal tubular epithelial cells (HK-2)</td>
<td>Through blocking the mTORC1/p70S6K signaling pathway.</td>
<td>Reducing EMT features in HK-2 cells; Inhibiting mTORC1/p70S6K pathway activation; Downregulating expression of snail &amp; twist; Reducing secretion of FN and Col IV.</td>
<td></td>
</tr>
<tr>
<td>Astragalus polysaccharide (Ruixin Zhang, et al. 2018)</td>
<td>T2DM</td>
<td>3T3-L1 preadipocytes</td>
<td>Through activating AMPK.</td>
<td>Increasing prediabetes proliferation in a dose dependent manner; Increasing PCNA content; Enhancing intracellular lipid accumulation and mRNA expression of PPAR γ, CCAAT/EBPs α, FABP ; Increasing 2-NBDG uptake; Elevating both mRNA and protein content of Glut4; Enhancing tyrosine phosphorylation of IRS 1 and phosphor-Akt content; Increasing phosphorylated AMPK content in the APS treated cells.</td>
<td></td>
</tr>
<tr>
<td>Astragalin (Ke, M, et al. 2012)</td>
<td>Diabetic Retinopathy</td>
<td>Müller cells</td>
<td>Through antioxidiant activity</td>
<td>Decreasing the overexpression of VEGF in Müller cells; Alleviating the effects caused by high glucose; Alleviating endoplasmic reticulum stress.</td>
<td></td>
</tr>
<tr>
<td>Astragalus polysaccharide (Sun, S, et al. 2017)</td>
<td>Diabetic Cardiomyopathy</td>
<td>H9C2 cell</td>
<td>Through inhibiting expression of proapoptotic proteins of extrinsic and intrinsic pathways.</td>
<td>Inhibiting high glucose-induced H9c2 cell apoptosis; Decreasing the expressions of caspases and the release of cytochrome C from mitochondria to cytoplasm; Modulating the ratio of Bcl-2 to Bax in mitochondria.</td>
<td></td>
</tr>
<tr>
<td>Schisandra chinensis (Trucz.) Baill</td>
<td>SCPP11</td>
<td>buffalo rat liver cells (BRL cells)</td>
<td>Through up-regulating the expression of GLUT-4.</td>
<td>Improving the glucose consumption in BRL cells; Increasing the protein expression of Akt, p-AMPK, GLUT-4 in BRL cells; Enhancing the mRNA expression levels of IRS-1, PI3K, Akt, GLUT-4, AMPK, PPAR-a in BRL cells.</td>
<td></td>
</tr>
<tr>
<td>Dioscorea opposita Thunb</td>
<td>T2DM</td>
<td>FL83B cells</td>
<td>Through inhibiting insulin resistance via the activation of JNK.</td>
<td>Increasing glucose uptake &amp; GLUT2 expression of insulin-resistant cells; Stimulating IRS tyrosyl phosphorylation; Increasing p-Akt level to alleviate insulin resistance; Attenuating JNK and IB caused by TNF-α induction; Elevating the levels of p-IRS-Tyr and p-Akt to improve insulin sensitivity in the TNF-R-induced FL83B cells.</td>
<td></td>
</tr>
<tr>
<td>Anemarrhena asphodeloides Bge</td>
<td>T2DM</td>
<td>FL83B cells</td>
<td>Through up-regulating IRS/ AKT and JNK pathways as well as inhibiting TNF and p38 pathways.</td>
<td>Promoting H9c2 cell viability &amp; cell proliferation; Stimulating GM-CSF, CNF1, I-NGF, Suppressing TIP3 expression; Stimulating three interleukin subclases IL-1, IL-6; Down-regulating expression of pro-inflammatory factors TNF- α and IFN- γ; Up-regulating anti-apoptosis related genes Cdkn2c and Ppp3ca, several cardiovascular disease suppressors, anti-inflammatory mediators; Down-regulating pro-apoptotic related genes Caspase and Trnf- α</td>
<td></td>
</tr>
</tbody>
</table>
**Animal studies and Cell-based studies**

<table>
<thead>
<tr>
<th>Extract</th>
<th>Topic</th>
<th>Duration</th>
<th>Model</th>
<th>Pathways</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>The saponins of <em>A. membranaceus</em> (Quan Liu, et al. 2017)</td>
<td>The saponins of <em>A. membranaceus</em> (Quan Liu, et al. 2017)</td>
<td>T2DM 10 weeks</td>
<td>KK/Ay mice/L6 myotubes</td>
<td>Through the insulin-dependent PI3K-akt signaling pathway.</td>
<td>Decreasing fasting insulin levels; Improving the plasma lipid profiles; Increasing activity of SOD; Decreasing MDA &amp; ROS levels; Elevating the insulin-stimulated glucose uptake with upregulated phosphorylation of AKT.</td>
</tr>
<tr>
<td><em>Astragalus polysaccharides</em> (Chen, W, et al. 2015)</td>
<td><em>Astragalus polysaccharides</em> (Chen, W, et al. 2015)</td>
<td>T2DM 16 weeks</td>
<td>MHC-PPARα transgenic male mice/H9c2 cells</td>
<td>Through down-regulating the cardiac PPARα-mediated regulatory pathways.</td>
<td>Preventing myocardial triglyceride accumulation &amp; cardiac dysfunction; Reducing free fatty acids utilization; Increasing glucose uptake; Decreasing the content of IL-6 and TNF-α and the expressions of VCAM-1, ICAM-1, TLR4, nuclear NF-κB p65.</td>
</tr>
<tr>
<td>NIL (Hui, C, et al. 2017)</td>
<td>NIL (Hui, C, et al. 2017)</td>
<td>T2DM 8 weeks</td>
<td>ob/ob mice/ T cells</td>
<td>Through improving abnormal immune and metabolic homeostasis.</td>
<td>Normalizing glucose and insulin level; Increasing the expression of Acrp30; Diminishing fat accumulation &amp; lipogenesis; Promoting glucose uptake; Decreasing Ile, adenosine, TC; Increasing Glu levels in liver and VAT of ob/ob mice; Promoting the shift of pro-inflammatory to anti-inflammatory cytokines; Suppressing T lymphocytes proliferation; Enhancing Tregs differentiation; Inhibiting DCs maturation; Attenuating DCs-stimulated T cells proliferation and secretion of IL-12p70 cytokine from DCs; Promoting the interaction of DCs with Tregs.</td>
</tr>
<tr>
<td><em>Trichosanthes kirilowii</em> Maxim.</td>
<td><em>Trichosanthes kirilowii</em> Maxim.</td>
<td>T2DM 8 weeks</td>
<td>STZ rat/ HK-2 cells</td>
<td>Through inhibiting the LOX1/NFκB/caspase-9 signaling pathway.</td>
<td>Increasing the viability of HG-treated HK-2 cells; Inhibiting cell apoptosis; Attenuating STZ-induced histopathological damage &amp; the inflammatory response in rat kidney tissues; Inhibiting the phosphorylation of IKKβ and NF-κB inhibitor protein (IκBα); Reducing the nuclear translocation of NF-κB (p65); Mobilizing the binding of p65 to the CASP9 gene in HG-treated HK-2 cells; Increasing transcription of the CASP9 gene; Inhibiting lactic acidosis activity in cells co-transfected with p65 and a wild-type caspase-9 construct instead of mutated caspase-9 constructs.</td>
</tr>
<tr>
<td><em>Schisandra chinensis</em> (Trucz.) Baill.</td>
<td><em>Schisandra chinensis</em> (Trucz.) Baill.</td>
<td>T2DM 6 weeks</td>
<td>HFD obese mice/ C2C12 myotubes</td>
<td>Through activating AMPK.</td>
<td>Enhancing the phosphorylation of AMPK/ACC, Akt; Promoting glucose uptake in C2C12 myotubes; Increasing the expression of mitochondria biogenesis &amp; fatty acid oxidation genes in C2C12 myotubes; Decreasing levels of fasting blood glucose &amp; insulin; Improving glucose tolerance; Rescuing decreased phosphorylation of AMPK and Akt; Stimulating expression of mitochondria biogenesis genes in skeletal muscle of HFD mice.</td>
</tr>
<tr>
<td>Water extracts of schisandra chinensis</td>
<td>Water extracts of schisandra chinensis</td>
<td>T2DM 8 weeks</td>
<td>Px rats/ NCI-H716 cells</td>
<td>Through enhancing insulinotropic actions.</td>
<td>Improving glucose tolerance in an oral glucose tolerance test in Px rats; Increased cell mass by hyperplasia; Elevating IRS2 and PDX-1 expression in the islets.</td>
</tr>
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### Chemical studies

<table>
<thead>
<tr>
<th>Astragalus membranaceus (Fisch.) Bunge</th>
<th>Ref erence</th>
<th>Extract</th>
<th>Topic</th>
<th>Pathways</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Astragalosides</strong> (Motomura, K, et al. 2009)</td>
<td><strong>Diabetic Nephropathy</strong></td>
<td>Through inhibiting AGEs</td>
<td>Inhibiting the formation of both CML and pentosidine; Astragaloside V had the strongest inhibitory effect among all if the isolated compounds.</td>
<td></td>
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</tr>
<tr>
<td><strong>NIL (Liu, J, et al. 2014)</strong></td>
<td><strong>Diabetes</strong></td>
<td>Through the temperature-correlated mobility scale</td>
<td>Achieving the optimization of the system conditions for the MEKC separations in the temperature-correlated mobility scale by correcting for viscosity changes; Monitoring the influence of the temperature operating in a more distinct way.</td>
<td></td>
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</tr>
<tr>
<td><strong>NIL (Yin-Shiou Lin, et al. 2016)</strong></td>
<td><strong>T2DM</strong></td>
<td>Through DPP-IV inhibitions.</td>
<td>Lowering the area under the curve (AUCO−120) of blood glucose and DPP-IV activity; Elevating the AUCO−120 of blood insulin.</td>
<td></td>
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<tr>
<td><strong>Mangiferin</strong> (Aishaa Lin, et al. 2019)</td>
<td><strong>T2DM</strong></td>
<td>Through establishing a rapid, reliable, sensitive LC/MS-MS method</td>
<td>The tissue distribution study results showed that mangiferin displayed rapid and wide distribution in plasma and tissues and it could not cross the BBB.</td>
<td></td>
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<tr>
<td><strong>Pueraria Lobata extracts</strong> (DENG, Wenji, et al. 2019)</td>
<td><strong>Diabetes</strong></td>
<td>Through alleviating the oxidative stress &amp; improving the pancreatic function.</td>
<td>Producing significant hypoglycemic effects; Providing outstanding intestinal permeability and transepithelial transport aptness</td>
<td></td>
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It was suggested that acute administration of diosgenin, a compound of *Dioscorea*, could reduce hyperglycemia with increased muscular steroidogenesis in type 1 diabetes rats [12]. Allantoin, another active constituent in *Dioscorea batatas* (Wild.) could promote insulin expression and ameliorate metabolic functions in streptozotocin (STZ)-induced diabetic mice [15]. Another study revealed that the aqueous extract of *Astragalus membranaceus* (Fisch.) Bunge had a therapeutic effect on T2D rats by decreasing fasting plasma glucose, postprandial glucose, and body mass index [26]. It was shown that *Dioscorea komatsutana* could improve pancreatic β-cell function by enhancing the antioxidant potential of the pancreas [23].

**Type 2 diabetes (T2D):** Type 2 diabetes is the most common type of diabetes. It is characterized by insulin resistance in which the human body cannot fully respond to insulin. As insulin cannot exert its action properly, the blood glucose level keeps rising. Finally, the pancreas will be exhausted, and hyperglycemia will result [17].

Chen *et al.* showed that Jia-Wei-Jiao-Tai-Wan (JWJTW), which contains *Astragalus membranaceus*, could ameliorate T2D by improving β cell function and reducing insulin resistance in diabetic rats [18]. *Astragalus polysaccharide (APS)* is an important bioactive component of *Astragalus membranaceus*. It was reported that APS could regulate part of the insulin signaling in insulin-resistant skeletal muscle in KKAY mice [19].

Hong *et al.* stated that *Schisandra chinensis* fruit-supplemented Korean rice cookie called dasik (RCD) had lipid-lowering and antiadipic effects [20]. It was found that an acidic polysaccharide from *Schisandra chinensis* had a therapeutic effect on T2D rats by regulating apoptosis-related protein expression to alleviate the injury from oxidative stress [21]. A water-soluble polysaccharide (SSPW1) from *Schisandra chinensis* had antioxidant activities and anti-diabetic effect on T2D rats [22]. Another study disclosed that *Schisandra chinensis* oil could improve pancreatic β-cell function by enhancing the antioxidant potential of the pancreas [23].

Wu *et al.* demonstrated that, after treatment of C57BL/6 mice on a high-fat diet with yam dioscorin for 135 days, weight gain was reduced, and impaired glucose tolerance was improved [24]. A daily dose of 8.02 g/kg of a functional formula diet including Rhizoma Dioscorea, for 10 weeks improved insulin sensitivity, hepatic glucokinase activity and antioxidant activity [25]. *Carassius auratus* Complex Formula, which also contains Rhizoma Dioscorea, inhibited the polyol pathway in T2D rats [26]. It was shown that *D. opposita* Thunb polysaccharide-zinc inclusion complex could reduce blood glucose and insulin levels in T2D rats [27].
Kubo et al. reported that *Puerariae flos* extract alleviated metabolic diseases in western diet-loaded and spontaneously obese mice representing an animal model of type 2 diabetes [28]. Puerarin (PUE) is a natural isoflavonoid isolated from the root of *Pueraria lobata*. Previous research had shown that PUE promoted fatty acid oxidation by increasing mitochondrial oxidative capacity and biogenesis in skeletal muscle of diabetic rats [29]. More recent studies confirmed that upregulation of UDP-glucuronosyltransferases 1a1 and 1a7 are involved in altered PUE pharmacokinetics in T2D rats [30]. Qijian mixture, a new traditional Chinese medicine (TCM) formula containing *Pueraria lobata* could alleviate T2D by altering metabolite profiles and gut microbiota [31]. Ge-Gen-Jiao-Tai-Wan (GGJTW) formula, which is composed of *Pueraria montana* var. lobata (Willd.), showed a hypoglycemic effect via the tight correlation between BAAs and glucose-lipid metabolism status [32]. It was suggested that another Chinese Herbal Formula called Shenzhu Tiaopi Granule elicited metabolic improvement in T2D rats by modulating the gut microbiota [33].

**Diabetic nephropathy:** Diabetic nephropathy (DN) is one of the major complications of diabetes and is the major leading cause of end stage renal disease (ESRD). It is a progressive disease characterized by rising urinary albumin excretion and declining renal functions [34].

Astragaloside IV (AS-IV) is derived from *Astragalus membranaceus*, a widely used herbal medicine in China. Wang et al. showed that AS-IV attenuated proteinuria in STZ rats by inhibiting endoplasmic reticulum stress [35]. Another study found that AS-IV ameliorated renal injury in STZ rats by inhibiting NF-xB -mediated inflammatory genes expression [36]. According to Wang et al., AS-IV administered to diabetic mice at a dose of 40 mg/kg daily for 10 weeks could delay the renal fibrosis process by influencing the TGF-β/SMADs signaling pathway and down-regulating TGF-β1, SMAD2/3 and α-SMA expression [37]. It was suggested that a novel renoprotective compound, which is composed of *Astragalus membranaceus* and *Panax notoginseng*, could synergistically protect against podocyte injury in STZ-induced diabetic rats [38].

It was shown that *Trichosanthes kirilowii* lectin ameliorated STZ-induced kidney injury via modulating the balance between M1/M2 phenotype macrophage [39]. Zhang et al. observed that *Schisandra chinensis* fruit extract attenuated albuminuria and protected podocyte integrity in STZ-induced diabetic rats [40]. Another investigation revealed that an ethanol extract from *Fructus Schisandrae chinensis* prevented renal interstitial fibrosis [41].

Sarsasapogenin is a major sapogenin from rhizomes of *Anemarrhena asphodeloides* Bunge. It was shown that it could markedly ameliorate DN in rats via inhibiting NLRP3 inflammasome activation and AGEs–RAGE interaction [42].

PTY-2 is an active fraction of tubers from *Pueraria tuberosa*. According to Yamini et al., it could attenuate diabetic nephropathy by upregulating matrix metalloproteinase-9 expression in the kidneys of diabetic rats [43]. In another study by Shukla et al., PTY-2 exerted antioxidant and antiapoptotic effects on DN. Later, the same group discovered that PTY-2 alleviated the kidney damage induced by chronic hyperglycemia and delayed the development of DN by suppressing the expression of HIF-1α and VEGF, thereby restoring the expression of nephrin [44]. It was also found that PTY-2 inhibited iNOS and IL-6 through suppressing the PKC-α and NF-xB pathway in treating DN [45]. Another study suggested that PUE protected against DN by attenuating oxidative stress [46]. A Radix Puerariae and Fructus Craeagi mixture could inhibit DN via decreasing of AKT/Pi3K [47].

**Diabetic retinopathy:** Diabetic retinopathy induced by diabetes involves the retinal capillaries, arterioles and venules. It is accompanied by leakage or occlusion of the small vessels [48].

Jian et al. found that Fufang Xueshuantong capsules, which contain *Astragalus membranaceus*, could attenuate STZ-induced retinal lesions in rats [49].

**Diabetic ophthalmopathy:** Diabetic ophthalmopathy is a disease induced by diabetes. It impairs patients’ eyesight and even causes blindness [50].

It was shown that *Anemarrhena asphodeloides* rhizomes could counteract diabetic ophthalmopathy progression in STZ-induced diabetic rats [51]. Zhang et al. showed that PUE could prevent cataract development and progression in diabetic rats through the Nrf2/HO-1 signaling pathway [52].

**Diabetic cardiomyopathy:** Diabetic cardiomyopathy (DCM) is a diabetes-related complication characterized by left ventricular (LV) hypertrophy, myocardial fibrosis, compromised myocardial function and is a leading cause of morbidity and mortality [53].

The study by Chen et al. revealed that *Astragalus* polysaccharides inhibited DCM in hamsters by suppressing heart chymase activation [54]. It was also demonstrated that *Astragalus* polysaccharides improved PPRAA-mediated lipotoxicity in DCM [55]. Yu et al. showed that Flos Puerariae Extract could prevent myocardial apoptosis by attenuating oxidative stress in STZ-Induced diabetic mice [56]. Recently, Guo et al. suggested that PUE reduced ischemia/reperfusion-induced myocardial injury in diabetic rats through upregulating vascular endothelial growth factor A/angiotsin-1 and suppressing apoptosis [57].

**Diabetic cognitive impairment:** Diabetic and insulin resistance affect the central nervous system as well as the development of cognitive and memory impairments which diminish the quality of life of diabetic patients [58].

*Astragalus* polysaccharides (APS) are active constituents of *Astragalus membranaceus*. Research finding by Liu et al. demonstrated that APS could improve cognitive dysfunction by altering the gut microbiota in diabetic mice [59]. Dun et al. also found that APS could improve memory in rats with STZ-induced diabetes. This was associated with its effects on glucose and lipid metabolism, antioxidative activity and insulin resistance [60]. In addition, Liu et al. showed that total saponins from Rhizoma Anemarrhena alleviated diabetes-associated cognitive decline in rats via reduction of amyloid-beta in the brain [61].

**Cell-based studies:** Twelve cell-based studies investigated the effects on diabetes and its complications (Table 7).

**Diabetes (not specific), insulin and metabolic syndrome:** Allantoin is an active principle of the yam. Allantoin could activate I_{gR} to enhance glucose uptake into cells. Hence it may be a new target for antidiabetic therapy [62]. Kakkalide is the predominant isoflavone extracted from the flowers of *Pueraria lobata*. Zhang et al. demonstrated that Kakkalide inhibited reactive oxygen species (ROS)-associated inflammation and ameliorated insulin-resistant endothelial dysfunction due to effects on insulin receptor substrate 1 (IRS-1) function [63].

Type 2 diabetes: It was shown that *Astragalus* polysaccharide improved insulin sensitivity via AMPK activation in STZ-L1 adipocytes [64]. The *Schisandra* polysaccharide also increased glucose consumption by up-regulating the expression of GLUT-4 in buffalo rat liver cells in...
the study of Jin et al. [65]. It was reported that Dioscorea polysaccharide manifested inhibitory effects on TNF-α-induced insulin resistance in mouse FL83B cells [66].

**Diabetic retinopathy:** Ke et al. showed that astragalin extracted from Astragalus membranaceus, attenuated the overexpression of VEGF in Müller cells and alleviated the effects caused by a high glucose level [67].

**Diabetic nephropathy:** Chen et al. suggested that Astragaloside IV ameliorated high glucose-induced renal tubular epithelial-mesenchymal transition by blocking mTORC1/p70S6K signaling in HK-2 cells [68].

**Diabetic cardiomyopathy:** Astragalus polysaccharides could attenuate DCM by inhibiting the extrinsic and intrinsic apoptotic pathways in high glucose stimulated H9c2 cells [69]. Another study revealed that PUE inhibited high glucose-induced Nlrp3 inflammasome formation and activation by ROS-dependent oxidative pathway [70]. Besides, Danshen–Gegen decoction, which contains Pueraria lobata, had been proven to display a proliferative effect on rat cardiac myoblasts H9c2 via MAPK and insulin pathways [71].

**Diabetic peripheral neuropathy:** Diabetic peripheral neuropathy, which is one of the most debilitating complications of diabetes, is characterized by axonal degeneration, demyelination, and atrophy [72]. Xue et al. suggested that PUE may protect Schwann cells against glucose fluctuation-induced cell injury by inhibiting apoptosis and oxidative stress [73].

**Diabetic cognitive impairment:** It was showed that sarsasapogenin (Sar), an active component purified from Rhizoma Anemarrhenae, suppressed Aβ overproduction induced by a high glucose level in HT-22 cells [74].

**Animal studies & cell-based studies:**

**Diabetes (not specific), insulin and metabolic syndrome:** Astragaloside IV improved vascular endothelial dysfunction by inhibiting the TLR4/NF-kB signaling pathway in vivo and in vitro [75].

According to Huang et al., puerarin attenuated endothelial insulin resistance by inhibiting the inflammatory response in an IKKβ/IRS-1-dependent manner [76].

**T2DM:** It was reported that APS could potentially activate hepatic insulin signaling in vivo and in vitro [77]. Another study revealed that APS could alleviate glucose toxicity and restore glucose homeostasis in diabetic states by activating AMPK [78]. A Chinese herbal medicine preparation JQ-R, which contains Astragalus membranaceus, manifested anti-diabetic effects in vivo and in vitro [79]. Another decoction called Danggulliuhuang (DGLHD) exerted anti-insulin resistance and antisteatotic effects by improving abnormal immune and metabolic homeostasis [80].

Gomisin N (GN) is a lignan derived from Schisandra chinensis. Jung et al. showed that GN exerted anti-hyperglycemic effects by AMPK activation [81]. Another study suggested that GN protected against hepatic cannabinoid type 1 receptor-induced insulin resistance and gluconeogenesis [82]. In Huang-Lian-Jie-Du-Tang supplemented with Schisandra chinensis and Polygonatum odoratum Druce, glucose tolerance was improved by potentiating insulinotropic actions in islets [83]. In the study of Han et al., Rhizoma Anemarrhenae extract ameliorated hyperglycemia and insulin resistance through activating AMP-activated protein kinase in vivo as well as in vitro [84]. The antidiabetic potential of Pueraria lobata root extract through promoting insulin signaling and inhibiting PTP1B was demonstrated by Sun et al. [85]. Besides, PUE acted on the skeletal muscle to improve insulin sensitivity in diabetic rats involving μ-opioid receptor [86]. In a multi-herbal extract including Pueraria lobata, Yeo et al. showed that PUE had therapeutic effects for treating type 2 diabetes in both cells and animal models [87].

**Diabetic nephropathy:** Trichosanthes kirilowii lectin alleviated DN by inhibiting the LOX1/NF-kB /caspase-9 signaling pathway both in vivo and in vitro [88].

**Diabetic cardiomyopathy**

A recent study by Chen et al. showed that APS repressed myocardial lipotoxicity in a PPARα-dependent manner in vitro and in vivo [89] Shengmai san, which includes Schisandra chinensis, was shown to alleviate diabetic cardiomyopathy by improving mitochondrial lipid metabolic disorder [90].

**Diabetic vascular complications:** The vascular complications of diabetes are the most serious manifestations of the disease. Dispo85E is the extract of rhizomes from Dioscorea alata L. It could enhance the clearance of advanced glycation end products (AGEs) through hepatocyte growth factor (HGF)-induced autophagic-lysosomal pathway for treating diabetic vascular complications [91]. Another study suggested that an aqueous extract of the pair of herbs Salvia miltiorrhiza Bunge-Radix Puerariae ameliorated diabetic vascular injury by inhibiting oxidative stress in STZ-induced diabetic rats [92].

**Chemical studies**

**Diabetes (not specific), insulin and metabolic syndrome:** A study by Liu et al. revealed a successful application of temperature-correlated mobility theory for separating the main lignans from Schisandra chinensis Fructus and its prescription Yuye Decoction in MEKC [93]. Jinqi Jiangtang Tablet, which is a traditional Chinese anti-diabetic formula containing Astragalus membranaceus, was demonstrated to scavenge free radicals and inhibit α-glucosidase, aldose reductase, α-amylase and lipase for treating diabetes [94]. Another study suggested that selenium-layered nanoparticles used for oral delivery of mulberry leaf and Pueraria lobata extracts expressed a better antihyperglycemic activity [95].

**T2DM:** Lin et al. conducted a tissue distribution study of mangiferin after intrastracmic administration of the mangiferin monomer, Rhizoma Anemarrhenae, and Rhizoma Anemarrhenae-Phellodendron decoctions in normal or type 2 diabetic rats by LC-MS/MS respectively. Results showed a lower mangiferin distribution in pancreas and intestine of diabetic rats administered with the same dose of the herb pair than that in normal rats [96]. Lin et al. reported that synthetic peptide derived from hydrolys of yam dicoserin in silico exhibited dipetidyl peptidase-IV inhibitory activity and improvements in oral glucose tolerance in normal mice [97].

**Diabetic nephropathy:** A study by Motomura et al. suggested that astragalosides isolated from Astragalus Radix inhibited the formation of advanced glycation end products and astragaloside V had the strongest inhibitory effect. Thus, it could be used to treat diabetic nephropathy [98].

**Human studies**

**Randomized clinical trials (RCT):** There was only one RCT in 88 included studies. This RCT study included 43 newly diagnosed type
2 diabetic patients, who had not used any antidiabetic drugs prior to the study. Then, they were randomly assigned into TCM and placebo groups. TCM mixture contains *Astragalus membranaceus*. Results showed that TCM mixture could ameliorate insulin resistance in type 2 diabetes, so it is safe and effective for diabetic patients [99].

**Case-control study design:** A study by Lien *et al.* retrieved records of samples from the registry for catastrophic illness patients in the National Health Insurance Research Database (NHIRD). Patients with T1DM in 2000–2011 were designated as cases (TCM users) and controls (non-TCM users) based on a frequency (1:4) matched case-control design. TCM treatment for patients with T1DM were then analyzed. The incidence of diabetic ketoacidosis and the annual costs of emergency visits and hospitalizations were also evaluated for all causes. Results showed that TCM may have a substantial positive impact on the management of T1DM [100].

A retrospective cohort study and an animal study: Lo *et al.* conducted a retrospective cohort study to analyze the usage of Chinese herbs in patients with type 2 diabetes in Taiwan and showed that *Trichosanthes kirilowii* Maxim. (TK) was the most frequently used Chinese medicinal herb. An animal study showed that TK protein enhanced the clearance of glucose in a dose-dependent manner [101].

**Discussion**

**Composition:** According to the ancient medical literature "yixue zhongzhong canxi lu", the composition of YYD is 30 g (*Dioscorea opposite* Thunb.); 15 g (*Astragalus membranaceus* (Fisch.) Bge.); 18 g (*Amelarrhena asphodoides* Bge.); 9 g (*Schisandra chinensis* (Turcz.) Baill.); 9 g (*Trichosanthes kirilowii* Maxim.); 6 g (*Gallus gallus domesticus* Brisson); and 4.5 g (*Pueraria lobata* (Willd.) Ohwi). The weight ratio of the herbs is 20:10:12:6:6:4:3.

**Dosage:** In animals’ studies, the dose of herbs or formula administered ranged between 0.5 mg/kg and 12.15 g/kg per day. In RCT, the dose of formula administered was 9 mg/day. In all human, animal and cell studies, the dosage employed was not mentioned in only 4 out of 82 papers. The dose used was stated explicitly in 95.1% of the papers.

**Duration:** In all human and animal studies, 3 out of 70 papers did not mention the duration of the study. 95.7% of the papers stated the duration clearly. In animal studies, the duration of treatment ranged from 2 days to 100 days. In RCT, the duration of treatment 1 was 3 months.

**Toxicity:** No study indicated the toxicity of medicinal herbs or formulas. No toxicity in human trials has been reported.

**The quality of studies:** All human, animal and cell studies stated the ratio of the individual herbs if a formula was used. All studies stated the origin, the extraction method and the composition of each constituent herb. However, some studies did not provide the name of pharmaceutical companies and the batch number of the concentrated tablets used in the experiments. There was only one RCT among all the studies examined. The follow-up study details were not stated in this randomized clinical trial. The method of randomization and the placebo detail were not stated clearly. There should be more well-designed RCT in the future in order to provide more and stronger evidence.

**The statistics of YYD:** There are seven medicinal herbs in YYD. There were research papers on all the herbs except *Gallus gallus domesticus* Brisson. Among them, the largest number of research papers (30.7%) were about *Astragalus membranaceus* (Fisch.) Bge. and *Pueraria lobata* (Willd.) Ohwi. T2DM was studied most (37.5%) of the research papers while DN was the most (19.3%) studied diabetic complication (Table 5).

Most, 49 out of 88 (55.7%) of the papers, reported animal studies. About 20.5% papers were animal & cell-based papers (Table 6). It is encouraging to do so as *in vivo* and *in vitro* studies gave more comprehensive insight on the signaling pathways involved. The protective effects against several diabetic complications are more impressive in *in vivo* and *in vitro* models.

**Conclusion and future perspectives**

The various medicinal herbs in YYD exhibit their antidiabetic activities through different signaling pathways which are illustrated in Figure 1. In compound level all medicinal herbs in YYD, except...
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Gallicus gallus domesticus Brisson because no research was done on it, can treat diabetes and its complications through different mechanisms. The chemical structures of some important compounds of different medicinal herbs in YYD are illustrated in Figure 2. Thus, YYD has strong evidences to treat diabetes and its complications. Since YYD and its components are devoid of toxic or allergic effects, in combination with western medicine they may serve as an alternative for mitigating diabetic complications. However, further investigations are necessitated before translation into clinical practice. Our review suggests that YYD and its herbs can improve diabetes and its complications through a diversity of signaling pathways. It may offer a new therapeutic avenue to treat diabetes and its complications. Besides, compelling evidence from well-designed RCT is needed in the future.

Conflict of interests

The authors have no conflict of interests to declare

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Authors’ contributions

Kalin YB ZHANG and Sydney CW TANG conceived and designed the study; Jack H W AN drafted manuscript; KH LAM, TH SONG, PS HO, Leanne L LEUNG, TL FONG, NC LAU, CH WONG and YY HUANG revised manuscript and check conferences. ZJ ZHANG and YG SHI supervised in the theory of Chinese medicine. George PH LEUNG, YG SHI, Calvin KF LEE, H WAN, TB NG and JF Wang reviewed and edited the manuscript. All authors read and approved the manuscript.

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