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Review Article

Advances in Chinese herbal medicine for the treatment of diabetes

Niannian Wang, Feifei Zhu, Keping Chen

Institute of Life Sciences, Jiangsu University, China

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Abstract: Diabetes is caused by excessive accumulation of glucose in human blood. The disease is hereditary, but can also be affected by the environment. At present, there are many limitations in the development of single-target drug therapy for the treatment of diabetes. Chinese herbal medicine has long been used for diabetes treatment as well as many other diseases in East Asia. Clinical practice has demonstrated the efficacy and multi-target functionality of Chinese herbal medicine in anti-diabetes. This review summarized the use of Chinese herbal medicine, including *Astragalus membranaceus* (Fisch.) Bge, *Helianthus tuberosus* L., *Lycium barbarum* L., *Angelica sinensis* (Oliv.) Diels., *Rehmannia glutinosa* Libosch, stigma maydis, *Salvia miltiorrhiza* Bunge, radix puerariae, *Momordica Charantia* L., *Paeoniae lactiflora* Pall, *Anemarrhena asphodeloides* Bunge and mulberry leaves, for the treatment of diabetes and discussed relevant mechanisms and physiological pathways of the treatment. This work expects to raise people's attention to the potential of Chinese herbal medicine as potent drugs for diabetes treatment, and provides valuable information and ideas for researchers.

Keywords: Diabetes, Chinese herbal medicine, chemical compositions, mechanism

Introduction

Diabetes, characterized by chronic hyperglycemia metabolic disorder, was caused by varieties of genetic and environmental factors. Diabetes was classified into type I diabetes, type II diabetes (>90%), gestational diabetes and other special types of diabetes according to WHO criteria in 1999. Long term suffering from diabetes may cause systemic damage to the body, such as eye, kidney, nerve, cardiovascular, cerebrovascular diseases and other complications [1-7]. In 2015, there are about 415 million diabetes patients in the world. It was projected that the population will increase to 642 million by 2040. The number of diabetes patients in China is about 110 million, ranking first in the world. More shockingly, 1.3 million people die because of diabetes and its complications in China for the year of 2015, of which 40.8% were younger than 60 years old [8]. Visibly, diabetes has become an increasingly serious health problem globally, especially in developing countries. Controlling the occurrence and development of diabetes has been urgent.

Clinically, type II diabetes can be treated with either injection with insulin-like drugs or taking orally with hypoglycemic drugs, such as metformin, biguanides, thiazolidinedione, sulfonylureas, benzoic acid derivatives and inhibitors of α-glucosidase. The therapeutic mechanisms of these hypoglycemic drugs vary considerably. For example, metformin controls blood glucose by reducing the conversion from liver glycogen into glucose and increasing the taking of extra blood glucose by liver, muscle cells and fat cells [9, 10]. Thiazolidinedione reduces blood glucose concentration via enhancing insulin sensitivity [11, 12]. Gliepiride (sulfonylurea), like repaglinide (benzoic acid derivatives), can stimulate pancreatic islets to secrete more insulin, therefore to regulate blood glucose [13]. Inhibitors of α-glucosidases, such as acarbose and voglibose, control postprandial blood glucose through directly reducing absorption of glucose by human digestive tract [14-17]. Development of these anti-diabetes drugs has provided more options for clinical drugs, however, it is commonly found that some patients developed resistance to the drugs or secondary failure after long-term treatment. For instance, pa-

tients taking insulin and sulfonylurea drugs tend to gain weight and suffer from higher risk of hypoglycemia [18, 19]. The digestive tract would act adversely to metformin and α-glucosidase inhibitors [20]. Thiazolidinedione and metformin may lead to edema and increase the burden of the heart and the risk of bone fracture [21, 22]. Therefore, finding preferable hypoglycemic drugs that have little side effect has become an urgent task for medical research workers.

Chinese herbal medicine is not only Chinese wealth but the world's treasure as well. Chinese people cemented the wisdom through constant exploration in the long process of practice. They feed on extracts from mulberry leaves, stigma maydis and *M. Charantia* L. (bitter melon) to lower blood glucose pressure [23-25]. Chinese herbal medicine improves the sensitivity and resistance of insulin and increases its secretion [26, 27]. In addition, herbal medicine stimulates the consumption of glucose by peripheral tissues and target organs [28] and reduces the production of glucose by inhibiting α-glucosidase [29]. The efficacy of Chinese herbal medicine has withstood the test of practice. Many potent chemicals from Chinese herbal medicine have been confirmed for the treatment of diabetes, such as flavonoids [30], alkaloids [31], polysaccharides [32] and saponins [33]. Chinese herbal medicine exerts almost none, if any side effects in patients, therefore is attracting more and more attentions. In this review, we provided a relatively comprehensive discussion on Chinese herbal medicine regarding their main active components and functional mechanisms in the treatment of diabetes.

Main chemical constituents of Chinese herbal medicine in the treatment of diabetes

Polysaccharides

Astragalus polysaccharides: The main components of *Astragalus membranaceus* (Fisch.) Bunge are astragalus polysaccharides, alkaloids, flavonoids, and folic acid. Astragalus polysaccharides (APS), as α-glucosidase inhibitor, is an active constituent for diabetes treatment. The inhibitory activity of APS on α-glucosidase was determined to be 0.28 mg/ml as the semi-inhibitory concentration [34]. APS not only significantly reduces the streptozocin (STZ)-induced blood glucose levels in diabetic rats, but remarkably improves the ultrastructure degradation of pancreatic β-cell. APS distinctly reduced the expression of fibrin adhesion system and inhibited the apoptosis of β-cell during diabetes treatment [35].

Boren J. explored the effects of Astragaloside IV (AS-IV), a polysaccharide from *A. membranaceus*, on the lipolysis and insulin resistance, which refers to decrease in the efficiency of insulin on glucose assimilation and utilization. The body will secrete more insulin, leading to pancreatic dysfunction, which contributes to diabetes in turn. The results showed that TNF-α induced down-regulation of key enzymes in lipogenesis, including lipoprotein lipase (LPL), fatty acid synthase (FAS) and 3-phosphate-acetyltransferase (GPAT), were attenuated by AS-IV [36]. APS also inhibits liver acetylation, thereby improving liver function, regulating glycolipid metabolism and improving insulin resistance [37]. Mao discussed the possible mechanism of APS in reducing blood glucose levels and improving insulin resistance [38]. The results indicated that APS enhanced adaptive capacity of the endoplasmic reticulum and promoted insulin signal by suppressing the expression and activity of protein tyrosine phosphatase 1B [38]. Hepatic glycogen phosphorylase (GP) and glucose-6-phosphatase (G6Pase) also play an important role in regulating blood glucose [39]. Lv studied the regulation mechanisms of *A. membranaceus* Bunge in liver glucose metabolism, and suggested that this herbal medicine may function via inhibiting the activity of GP and G6Pase [39].

Helianthus tuberosus: The main components of Jerusalem artichoke, *Helianthus tuberosus* L. (*H. Tuberosus*) include inulin, protein, pectin, and organic acids. *H. Tuberosus* could reduce the fasting blood glucose level in non-insulin dependent db/db mice model [40]. The inhibitory activity of purple Jerusalem artichoke (PJA) on α-glucosidase depends on the degree of polymerization of fructan [40], and also varied with different microorganisms used in fermentation treatment. The inhibitory activity was 49.34% and 12.45% after fermentation with *Lactobacillus plantarum* and *Bacillus subtilis*, respectively [40]. Though there are plenty research reports on the inhibitory activity of Jerusalem artichoke on α-glucosidase, the specific mechanism is not very clear yet.

Jerusalem artichoke can also reduce the apoptosis of β cells [41]. Jerusalem artichoke improved insulin sensitivity of hepatic probably by enhancing tyrosine phosphorylation of insulin receptor substrate 2 (IRS2, the first insulin signal protein), phosphorylation of Akt (downstream receptor for insulin receptor signal), AMPK (AMP dependent kinase) and acetyl-CoA carboxylase (downstream regulator of AMPK), but attenuating the expression of phosphoenolpyruvate carboxykinase (PEPCK), a key regulator of gluconeogenesis [41].

Lycium barbarum: Chinese wolfberryis the dry mature fruit of *Lycium barbarum* L. The main chemical components of *L. barbarum* are lycium barbarum polysaccharides (LBP). The *in vitro* and *in vivo* experiments showed that LBP-s-1 from *L. barbarum* significantly promoted blood glucose and insulin sensitivity by increasing glucose metabolism, insulin secretion as well as pancreatic cell proliferation [42]. LBP has a remarkable effect on reducing blood glucose at an optimal dose of 40 mg/kg body weight [43]. Although LBP prominently increased the body weight of diabetic rats, total cholesterol (TC) and triglyceride (TG) levels were strikingly decreased. LBP restored abnormal oxidative index near normal levels and protected the liver and kidney tissue from the damage of STZ-induced diabetic rats [44]. Clinical studies indicated that LBP significantly reduced blood glucose in patients with type II diabetes and increased the levels of pro-insulin and high-density lipoprotein (HDL) [45]. The serum levels of inflammatory cytokines, including IL-2, IL-6, TNF-α, IFN-α and the expression activity of nuclear factors kappa B (NF-κB) was inhibited. Furthermore, the activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in serum were enhanced strikingly in response to oxidative stress and inflammatory in STZ-induced diabetic rats [46]. The double reaction results indicated that LBP possesses antidiabetic antioxidant and anti-inflammatory activities.

Angelica polysaccharides: Angelica sinensis (Oliv.) Diels. is commonly used in traditional Chinese herbal medicine for regulating physiological metabolism. The main ingredients of angelica root are aromatic compounds, such as ferulic acid and phthalides, which had protective effects on acute kidney injury induced by cisplatin (CisPt) [47]. Volatile oil extracted from angelica, containing various compounds such as Z-ligustilide, phthalic acid, 6-N-butylcycloheptadiene, executed anti-inflammatory and hepatoprotective functions via inhibiting the secretion of inflammatory promoters such as TNF-α, IL-1β and IL-6, inflammatory mediators such as histamine, 5-hydroxytryptophan and other inflammatory-related enzymes, and boosting the production of anti-inflammatory cytokine IL-10 [48]. Angelica polysaccharides (ASP), a β-D-glucopyranose polysaccharide with an average molecular weight of 72,900 Da, notably enhanced activities of antioxidant enzymes such as SOD and GSH-Px, and removal of lipid peroxidation capacity in CCl_4-induced rat [49]. The potential hepatoprotective features of ASP was demonstrated by the obvious attenuation in serum transaminase, lipid oxidation, reactive oxygen species, pro-inflammatory cytokines and the apoptosis levels of Caspase-3-dependent cells, while strengthening the activities of SOD in mice induced by concanavalin A [50].

Rehmannia polysaccharides: Rehmannia is the roots of *Rehmannia glutinosa* (*R. glutinosa*) Libosch. The main chemical constituents of *R. glutinosa* include iridoid, its glycosides, and organic acids. Meng investigated the effect of *R. glutinosa* aqueous extract on STZ-induced type II diabetic rats. The results manifested that the extract played a role in lowering blood glucose by up-regulating the expression of pro-insulin mRNA and protein, and improving the function of pancreatic β cell in type II diabetic rats [51]. Additionally, rehmannia catalpol had an effect on reducing the levels of blood glucose, TC, TG and increasing serum high-density lipoprotein cholesterol levels in alloxan-induced diabetic mice [52]. The effects of rehmannia glutinosa polysaccharide (RGP) on STZ-induced diabetic nephropathy rats were also discussed. The results suggested that RGP could up-regulate the activity of peroxisome proliferator-activated receptor γ (PPARγ) in skeletal muscle, adipocyte fatty acid-binding protein (aP2), and glucose transporter 4 (Glut-4) mRNA and protein levels to serve certain roles in diabetic nephropathy rats [53]. Fasting blood glucose and fasting insulin in STZ-induced type II diabetic rats were cut down by up-regulating speculatively the expression of IRS2, PI3K, Akt mRNA and protein in PI3K/Akt signal pathway [54].

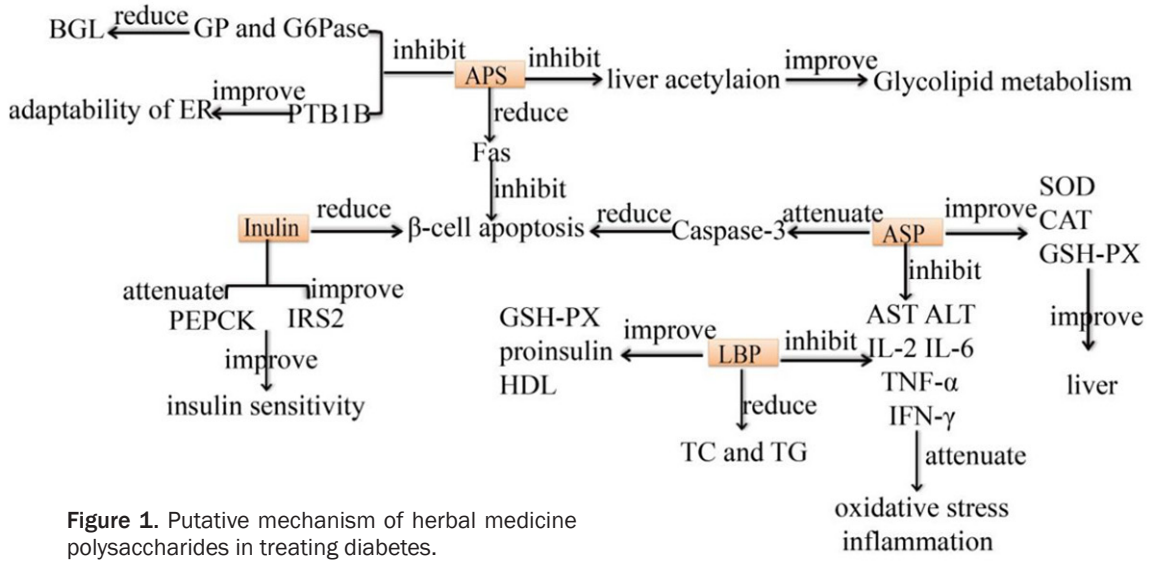

Figure 1. Putative mechanism of herbal medicine polysaccharides in treating diabetes.

Stigma maydis: Stigma maydis, the dry stigma of *Zea mays* L, contains polysaccharides, flavonoids, sterols, alkaloids and other chemical constituents. 3'-methoxyhirsutrin and cyanidin-3-(6''malonylglucoside) isolated from the purple maize kernel, a specie of *Zea mays* L, had an inhibitory effect on PTP1B activity with IC_{50} of 64.04 μM and 54.06 μM, respectively [55]. The polysaccharide extract of stigma maydis [56] dose dependently decreased the blood glucose level of alloxan-induced diabetes rats. Stigma maydis could potentially be employed as an effective medicine to increase the quality and quantity of favorable microbes such as Lactobacillus and Bacteroides, keep the balance of intestinal microbial flora and shoulder the role of weight-gaining. The inhibition rates of stigma maydis on α-amylase and α-glucosidase were 5.89 mg/mL and 0.93 mg/mL, respectively [57]. Cataract induced by diabetic complication could be prevented by taking purple waxy corn seed extract. Interestingly, moderate does of the extract functions via reducing oxidative stress, while high doses may function via inhibiting the activity of aldose reductase [58]. Collectively, the putative mechanisms of herbal medicine polysaccharides in treating diabetes may be summarize in **Figure 1**.

Salvia: Salvia miltiorrhiza (*S. miltiorrhiza*) Bunge has two main types of chemical constituents in the root and stem: the tanshinone compounds such as tanshinone, cryptotanshinone, isotanshinone, and water soluble phenolic compounds such as Danshensu A, Danshensu B, Danshensu C. *In vivo* experiments revealed that polysaccharide SMPW1 parted from *S. miltiorrhiza* Bunge was able to increase the activities of CAT, SOD, GPX and reduce the level of malondialdehyde (MDA) in the serum and liver homogenate, showing prominent antioxidant function [59]. Besides, *S. miltiorrhiza* was capable of repairing liver and kidney damage and retinopathy caused by diabetes [60, 61]. Furthermore, through decreasing plasma endothelin and thromboxane levels and increasing plasma 6-keto-prostaglandin levels, it also could guard against the diabetic vascular complications [62].

Puerarin: Radix puerariae is the dry root of *Pueraria lobata* (Willd.) Ohwi. The main chemical constituents of Radix puerariae are puerarin, daidzin and glycosides. Puerarin, the main active ingredient of puerarin flavonoids, was known as isoflavone glucoside in traditional Chinese herbal medicine [63]. Puerarin had a role in lowering blood sugar. Xu explored the inhibition mechanism of the puerarin on α-glucosidase. The results indicated that puerarin is a reversible competitive inhibitor of α-glucosidase with IC_{50} of 4.32 μM and the inhibitory constant of 0.41 μM. Comparing with acarbose, puerarin could distinctly inhibit the increase of blood glucose in rats. In addition, puerarin has characteristics of improving insulin resistance [64], which may be related to the activation of CAP pathway and the transposition of Glut-4 to the cell membrane [65]. Puerarin also directly acted on pancreatic β cells to protect the function and survival of β cell, and this protective mechanism may be mediated by

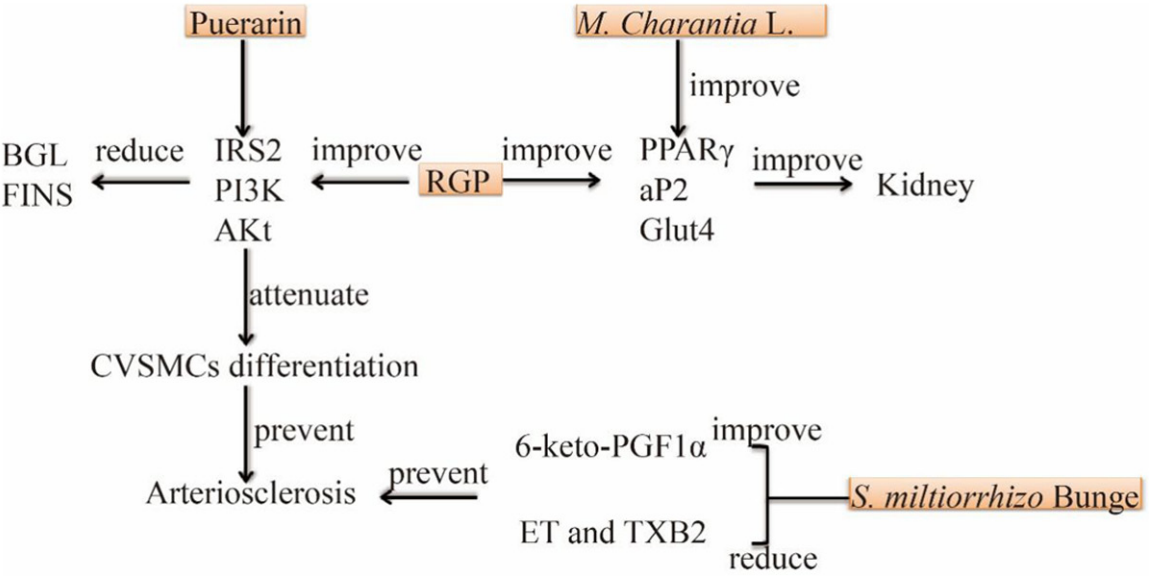

Figure 2. Putative mechanism of *Puerarin, M. charantia L.,* and *S. miltiorrhizo Bunge* in treating diabetic complications.

PI3K/Akt pathway [66].

Cardiovascular disease (CVD) is a complication of type II diabetes. More than 60% of type II diabetic patients die of CVD [67]. As a natural phytoestrogen, puerarin likewise attenuated the differentiation of calcified vascular smooth muscle cells through the ER/PI3K-Akt signal pathway, thereby preventing arterial calcification [68]. The putative mechanism of Puerarin, *M. charantia* L. and *S. miltiorrhizo* Bunge in treating diabetic complications were shown in **Figure 2**.

Bitter gourd: The main hypoglycemic components of *Momordica charantia* L. (bitter gourd) are flavonoids, saponins and polysaccharides. The protein extracts of two varieties of bitter gourd, namely *M.* charantia var. Charantia and *M.* charantia var. Muricata, have an equivalent inhibitory activity on α-amylase and α-glucosidase compared with those of acarbose, with IC_{50} range from 0.26 mg/ml to 0.29 mg/ml [70]. Polysaccharides (MCP) isolated from bitter gourd reduced fasting blood glucose level and bettered glucose tolerance in diabetic mice induced by STZ [71]. Bitter melon aroused the up-regulation of Glut-4, PPARγ and PI3K [72]. Five different saponins were isolated from bitter gourd. Two of them, Momordicin K and Momordicin L, had no inhibitory effect on PTP1B, the main negative regulator protein of insulin signal transduction. However, the rest of the saponins, including Momordicin A, α-spinasteryl-3-O-β-D-glucoside,19(R)-carbonyl-25-dimethoxy-5β-cucurbitane-6,23-diene-3β,25-hydroxy-5-19-epoxy-3-O-β-D-glucopyranoside inhibited PTP1B to a certain extent and the inhibitory rates were 16.4%, 24.0% and 1.3%, respectively [73].

Radix paeoniae rubra: The main active ingredients of radix paeoniae rubra are peony total glycosides, tannins, flavonoids, and volatile oils. The water extract of radix paeoniae rubra had the effect of improving cardiomyopathy in STZ-induced diabetic rats, which may be related with the decrease of GRP78 (a glucose-regulated protein) expression level, the inhibition of the endoplasmic reticulum oxidative stress, and the apoptosis of myocardial [74]. Water extract of radix paeoniae rubra inhibited macrophage infiltration and proliferation to reduce myocardial hypertrophy and fibrosis [74]. Three chemical constituents, paeoniflorin, ethyl palmitate and ethyl linoleate showed potential hepatoprotective activity [75]. Moreover, when the concentration of 1,2,3,4,6-pentachloro-O-behenyl-D-glucopyranose parted from the roots of paeonia lactiflora reached 10 μg/ml, the activity of PTP1B dropped to 30% [76]. In addition, the ethanol extract of radix paeoniae repressed the expression of PEPCK mRNA in *db/db* mice in a

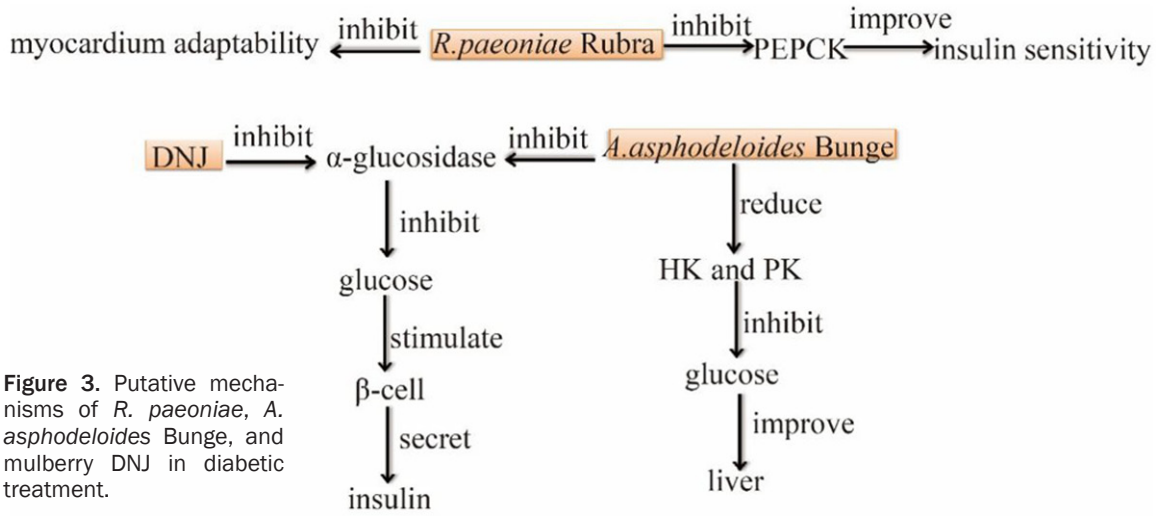

Figure 3. Putative mechanisms of *R. paeoniae*, *A. asphodeloides* Bunge, and mulberry DNJ in diabetic treatment.

dose-dependent manner. It lessened hyperglycemia by enhancing the uptake of peripheral glucose and inhibiting the overproduction of gluconeogenesis [77].

Anemarrhena saponins: Anemarrhena asphodeloides (*A. asphodeloides*) Bunge belonged to Liliaceae. The main composition of *A. asphodeloides* Bunge is saponin. Previous work has shown that anemarrhena saponin at 15 g/L could strikingly inhibit α-glucosidase activity with inhibition rate of 73.09%. It remarkably increased glucose tolerance and reduced postprandial blood glucose in the alloxan impaired mice model, indicating that the hypoglycemic effect of anemarrhena saponins was served by inhibiting the activity of α-glucosidase, gluconeogenesis or glycogenolysis [78]. The water extract of *A. asphodeloides* could promote the utilization of glucose, the activities of hepatic hexokinase and pyruvate kinase to elevate the entry of glucose into hepatocytes and the regulation of glucose metabolism [79].

Morus alba L.: The main components of mulberry (*Morus alba* L.) leaves are polysaccharides, flavonoids and alkaloids. Researchers had experimentally investigated that polysaccharides, flavonoids and alkaloids all had hypoglycemic function with blood glucose decrease rates of 14.42%, 27.33% and 37.55%, respectively, showing alkaloids as the most outstanding hypoglycemic compound in mulberry leaves [80]. As a piperidine alkaloid, 1-deoxynojirimycin (DNJ) is considered a potent α-glucosidase inhibitor [81]. The interaction mechanism between DNJ and the enzyme was elucidated. DNJ competitively bound to α-glucosidase stronger than the affinity of oligosaccharide such as sucrose and maltose, reducing the chances of oligosaccharides from binding with α-glucosidase. DNJ can also promote the absorption of glucose in intestinal brush edge [82, 83]. The dual roles of DNJ helps control postprandial blood glucose and improve diabetes syndromes. By inhibiting glycogen phosphorylation enzyme, DNJ could keep glycogen from breaking into glucose and therefore regulates the balance of fasting blood glucose level [84]. Not surprisingly, the hypoglycemic effect using a combination of DNJ and mulberry polysaccharide was much better than using either of them [85]. Wang reported that total mulberry polysaccharides alleviated sharp weight loss in alloxan-induced diabetic mice and the blood glucose of mice decreased by 56.82% [86]. The putative mechanisms of *R. paeoniae*, *A. asphodeloides* Bunge, and mulberry DNJ in diabetic treatment were shown in **Figure 3**.

Prospect and challenges of Chinese herbal medicine in treating diabetes

The treatment of diabetes is a long and complex process for each patients. A single medication is often difficult to balance all parties, thus two or more Chinese herbal medicine could be combined according to their functional characteristics. In clinic, astragalus, rehmannia and

Table 1. Species classification of 12 traditional Chinese herbal medicines

Spices	Family	Genus	Pictures
Radix puerariae	Leguminosae sp.	*Pueraria*	
Astragalus membranaceus (Fish.) Bunge	Leguminosae sp	*Astragalus*	
Momordica Charantia L.	Cucurbitaceae	*Momordica*	
Helianthus tuberosus L.	Compositae	*Helianthus*	
Rehmannia glutinosa Libosch	Scrophulariaceae	*Rehmannia*	
Radix Paeoniae Rubra	Ranunculaceae	*Paeonia*	
Lycium barbarum L.	Solanaceae	*Lycium*	
Salvia miltiorrhiza Bunge	Labiatae	*Salvia*	
Zea mays L	Gramineae	*Zea*	
Angelica sinensis (Oliv.) Diel	Umbelliferae	*Angelica*	
Anemarrhena asphodeloides Bunge	Liliaceae	*Lycopus*	
Morus alba L	Moraceae	*Morus*	

salvia were compatible for the treatment of type II diabetes. There were no significant differences in fasting plasma glucose, two hours postprandial blood glucose (2hPG) and glycated hemoglobin (HbAIC) between the control (metformin) and experimental groups. After the treatment using these three compounds, FPG, 2hPG and HbAIC were all markedly decreased, indicating satisfying results in treatment of type II diabetes [87]. Water extract mixture of *S. miltiorrhiza.* Bunge and radix paeoniae rubra gave more desirable effect on clearance of negative oxygen radical than that of separate usage [88]. Similarly, astragalus, radix paeoniae rubra and blends of the two could all decrease the level of serum IL-6 and IL-8 in immune liver-injured mice, and the combination of them are better than using any one of them [89]. Liver fibrosis could be prevented by astragalus and paeonia lactiflora extracts (APE) through regulating the TGF-β/Smad signal pathway [90]. In practice, Nao xin tong made from *A. membranaceus* (Fisch.) Bunge *A*, *P. lactiflora* and *A. membranaceus* (Fisch.) Bge. was used as the treatment drug of atherosclerosis and its complications [91].

Though the research of Chinese herbal medicine has made great progress, it is still difficult to make the medicine standardized due to somewhat unclear material basis, wide geo-

graphical distribution and different efficacy with different seasons (species classification of 12 traditional Chinese medicines were shown in **Table 1**). In addition, compound preparation from Chinese herbal medicine is still at its early stage. The hypoglycemic mechanism is also quite superficial for the lack of molecular biological interpretation. Appropriate selection and combination of potent anti-diabetes compounds from various herbal medicines is the key to achieve the modernization and standardization of Chinese herbal medicine.

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Disclosure of conflict of interest

None.

Abbreviations

BGL, blood glucose level; HK, Hexokinase; ER, Endoplasmic reticulum; PK, Pyruvate kinase; AST, Aspartate transaminase; ALT, Alanine transaminase; Fas, fatty acid synthase; aP2, adipocyte fatty acid-binding protein; IRS2, insulin receptor substrate2; PEPCK, phosphoenolpyruvate carboxykinase; ET, Endothelin; TXB2, Thromboxane B2.

Address correspondence to: Keping Chen, Institute of Life Sciences, Jiangsu University, Zhenjiang 212003, Jiangsu, China. Tel: +86-13952871835; E-mail: kpchen@ujs.edu.cn

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