Research progress on hypoglycemic active components in natural products
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1. Introduction

Diabetes mellitus, commonly known as diabetes, is a complex endocrine disease. Following neoplasm and cardio-vascular disease, diabetes is the third leading disease worldwide. It is triggered by hyperglycemia and other metabolic disorders inducing a cause of morbidity. It can also cause some chronic vascular complications such as diabetic nephropathy, retinopathy, and polynepropathy (1). In diabetes treatment, blood sugar control is significant to prevent the above complications. To eliminate the side effects of common diabetes drugs, many studies are done targeting to functional factors in natural materials. This article summarizes some recent domestic and international researches on natural materials which are used as diabetes treatment.

2. Natural materials for diabetes treatment
2.1 Carbohydrate
Polysaccharide
The polysaccharide found in Ophiopogon japonicas shows potential in diabetes treatment. In experiments, 150mg/kg and 300mg/kg of the polysaccharide inhibited the blood glucose level on glucose-induced diabetes, adrenaline-induced diabetes and alloxan-induced diabetes rats. With the same doses, significant hypoglycemic effects were observed in diabetes-free rats. Promoting insulin secretion, inhibiting glucose absorption and utilization, protecting β cells from alloxan or taking actions as well as repair β cells are considered to be its mechanism (2).

Polysaccharides from cultured Cordyceps sinensis (PCS)(600mg/kg) were given to Alloxan-induced diabetes rats in 7 days with discontinuous dosage. PCS treatment causes significant reduction of fasting blood sugar levels, the glycosylated serum protein levels and increase of glucose tolerance. Stimulating insulin resistance to glucose uptake by adipose tissue might be its hypoglycemic mechanism (3).

In statistical analysis there are almost 50 types of plant polysaccharides possess blood sugar lowering activity, such as Ginseng polysaccharide, Ch.Wolfberry polysaccharide, Astragalus polysaccharide and Ganoderma lucidum polysaccharide. The main hypoglycemic mechanisms are promoting insulin secretion, enhancing the glucose utilization by peripheral tissues and target organ, increasing the insulin sensitivity, preventing lipid peroxidation and improving microcirculation et al. (4). Without any known toxic side effect, polysaccharide will possibly become an oral hypoglycemic agent of high efficiency and low toxicity in the future.

Common methods to extract polysaccharide extracts include: a) Solvent extraction (5). Solvent extraction is a usual method to extract polysaccharide. Water is used as a solvent to extract polysaccharide grossly and ethanol with high concentration is used to precipitate subsequently. b) Acid/base extraction (6,7). Some types of polysaccharides were easy to be extracted by diluted acid or base. c) Biological enzyme-assisted extraction (8). In this approach, plant tissues tended to decompose in mild condition and it can accelerate the polysaccharide release and extraction (9). Protease, cellulase and pectinase are commonly used. Additionally, other methods such as ultra-filtration treatment, ultrasonic treatment and microwave radiation were also used.

Oligosaccharide
With the treatment of Rehmannia glutinosa oligosaccharide (ROS) (100 mg/kg for 15 days, i.p) in alloxan-induced diabetic rats, significant decrease in blood glucose levels and hepatic glucose-6-phosphatase activity as well as increase in hepatic glycogen content were observed. Furthermore, ROS raised plasma insulin level and lowered plasma corticosterone levels in alloxan-induced diabetic rats. The results indicated that oligosaccharide of ROS exerted a significant hypoglycemic effect in normal
and alloxan-induced diabetic rats. The regulatory mechanism of ROS on glucose metabolism was adrenal dependent and had a close relation with the neuroendocrine system (10).

Albrecht, S et al. (11) utilized the highly active β-man nanase which is produced by engineering bacterium to hydrolyze konjac glucomannan and they obtained konjac oligosaccharide finally. The hypoglycemic effect and the regulation of blood glucose were observed. Experiment demonstrated that the konjac oligosaccharide lowered the blood sugar levels pronouncedly (P<0.01) in alloxan-induced diabetes rats within two weeks after ig administration at low/high dose, which showed the same hypoglycemic ability as metformin hydrochloride. At the same time hemoglobin and leucocyte content increased pronouncedly while cholesterol content decreased approaching to normal level two weeks after administration. It is worth emphasizing that konjac oligosaccharides could not only reduce the blood glucose, but also improve the immunocompetence and oxygen-carrying ability of diabetic patients and helped prevent arteriosclerosis.

Lu et al. (11) observed the effect of one fraction of akonajon oligosaccharides, KOS-A, on streptozocin(STZ)-induced diabetic rats of isolated islets. At concentrations less than 1.5 mmol/L, KOS-A positively decreased STZ-induced NO level of islets; however, normal NO release for non-STZ-treated islets was not affected within the range. At 15 mmol/L, KOS-A played a contrary role and increased NO level for islets both with and without STZ-treatment. These results indicated that low dosage of KOS-A, with its function on attenuating STZ-induced NO level, didn’t alter normal NO and insulin secretion pathways of isolated islets. Therefore it could normalize the insulin secretion activity and balance the blood glucose.

2.2 Flavonoids

Flavonoids are natural pigments which were widely existed in plants. It can exert hypoglycemic effect by stimulating insulin release, enhancing insulin sensitivity, inhibiting α-glucosidase activity and increase the glucose utilization. Quercetin dose-dependently decreased the plasma glucose levels of STZ-induced diabetic rats pronouncedly, though quercetin had no effect on plasma glucose level of normal animals (12,13) Glucose tolerance tests result of the diabetic animals approached those of normal rats. Plasma cholesterol and triglycerides were reduced while hepatic glucokinase activity was significantly increased (14,15). The regeneration of the pancreatic islets and increases insulin release in streptozocin-induced diabetic rats might be its hypoglycemic mechanism. However, it may cause some disturbances in insulin signaling of the normoglycemic animals (16).

Tengcha flavonoids (TF) are the efficacious ingredients extracted from the stems and leaves of Ampelopsis grosses dentata(Hand-Mazz)’s W.T. Wang which contains myricetin and amelopsin. Blood glucose level in STZ-induced diabetic rats reduced(P<0.05) significantly after large dose administration(0.10g/kg 30 days).The lower doses treatment showed a similar trend. Its mechanism might be reducing pancreatic β cells injury through antioxidation by streptozotocin, fastening the repair of injured pancreatic β cells, enhancing islet secretion function, and thereby relieving hyperglycemic reaction.

Mulberry leaves flavonoids could cause a significant reduction in the blood sugar levels in alloxan-induced diabetes rats. In the experiment, the blood sugar levels of rats decreased from original 18.4mmol/L to 10.2mmol/L(P<0.001). However, it didn’t show any impact on the blood sugar level of normal rats. Inhibition rate of mulberry leaves flavonoids are 68.0% on Sucrase, 47.1% on Maltase,27.8% on lactase, respectively. Mulberry leaves flavonoids elicit hypoglycemic potential in rats by inhibiting the activity of disaccharidase (17). Recent researches show that plant flavonoids could prevent diabetes and its complication effectively in varying ways. Due to the complexity of flavonoids in vivo, majority of their mechanism is still in research phase.

The methods of extracting flavonoids include microwave extraction, organic solvent extraction, supercritical extraction, enzyme-assisted extraction and ultrasound-assisted extraction.

2.3 Saponin

Saponin is the major effective ingredient of many important Chinese herbs, including Panaxginseng, Rastragali, Panaxnotoginseng. Glycyrrhizauralensis, Rhizoma Anemarrhenae (18). Some type of saponin also showed strong activity to lower the blood sugar level. For instance, saponin of Litchi0.2g/kg was able to improve the condition of IGT in rat models with desamethasone-induced insulin resistance and decreased blood glucose/ fasting blood glucose (P<0.05) levels 2h after oral glucose tolerance test. Saponin caused reductions of the total cholesterol, triglyceride, low-density lipoprotein cholesterol and malondialdehyde content and suppression of aspartate aminotransferase(ALT), alanine aminotransferase(ALT) activities and the ratio of AST/ALT in one hand and it could potentiate superoxide the activity of dismutase and thereby enhanced antioxidant capacity on the other (19-21). The hypoglycemic actions of Acanthopanax senticosus saponins (ASS) were obvious in STZ-induced type 2 diabetes rats. ASS could improve hemorheology, it show antagonistic effect on the hyperglycemia caused by epinephrine and exogenous glucose. It is indicated that ASS might have the function of hastening the repairing of injured pancreatic β cells or protecting pancreatic β cells from further injury of STZ, inhibiting hyperglycemia, promoting peripheral organ to intake and utilizing the glucose (22).

Different approaches of extracting saponin, including impregnation, percolating filter method, reflux method, n-butyl alcohol extraction, isopropanol-dissolved recrystallization, ultrasonic extraction, alumina column chromatographic, macrorieticular resin, supercritical carbon dioxide extraction, microwave-assisted extraction, membrane technique and water extraction were used (23). Sovova, H et al. (24) show that the ratio of dioicin extracted from Dioscorea panthica with SFE-CO₂ was 1.5 times higher than by traditional naphtha extraction. He, J et al (25) used water as a solvent to extract naphtha under microwave irradiation conditions. Before the experiments, they made an investigation on the effects of different microwave power, microwave irradiation time, solid-to-liquid ratio, extraction time, extraction times and other factors on extraction, so they could optimize the experimental condition.
2.4 Alkaloids

Alkaloids have physiological activities like antibacterial, antitumor, antiarrhythmia, hyperglycemia and gastric mucosa protection. T Li-Qin (26) observed a positive effect of berberine in lowering blood sugar and blood lipid levels in Sprague-Dawley rats models of diabetic nephropathy and she conjectured that it stimulated the regeneration of pancreatic β cells. T Hui et al. (27) found that the hypoglycemic function of Rhizoma Cop-tidis capsules was superior to metformin. JD Lalau et al. (28) research shows that metformin could cause a significant reduction in the blood sugar levels by modulating the target cells specificity expressed by Peroxisome proliferator-activated receptors (PPARs).

Hypoglycemic mechanisms of alkaloids are as follows. Z Qian, P Xiang-Lan et al. (29) demonstrated alkaloids could improve glucose metabolism, berberine affected carbohydrate consumption directly which resembled the function of insulin. Alkaloids may influence inflammatory factors which were vitally important for insulin resistance. Alkaloids possessed anti-oxidize activity and helped scavenging free radical. Additionally, berberine alleviated the pathological progression of liver and reverted the increased hepatic glycogen and triglyceride to near the control levels. It was also predicted that berberine could prevent cardiovascular complications. Chi et al. (30) observed the effect of berberine on HepG2 cells. The results indicated that berberine reduced the blood sugar levels by increasing the glucose consumption in hepatocytes, which are independent on insulin. Xue, BJ et al. (31) found Cop-tidis decoction for Detoxification possessed the function of reducing sugar and lipid levels. This mechanism might be relevant to increasing insulin sensitivity and promoting its secretion.

The traditional ways to extract alkaloids include water/sour water extraction, alcoholic solvent extraction, impregnation, percolation, decoction and reflux method. Whereas the new ways to extract alkaloids include microwave-assisted extraction, ultrasound-assisted extraction, supercritical fluid extraction, double water phases extraction, chromatography, resin absorbing, molecular imprinting and molecular distillation technology (32).

2.5 Other natural products with hypoglycemic activities

Terpenoid

Lactucin-8-O-methylacrylate can be isolated by chloroform extraction of Parmentiera edulis dried fruits. Identification was based on spectroscopic methods. The compounds isolated from the active fraction were tested for hypoglycemic activity (33). In these experiments the guaianolide was administered intraperitonially at a dose of 50 mg/kg to alloxan diabetic. With the lactucin-8-O-methylacrylate the maximal hypoglycemic activity (57.55% reduction) was observed 4.5 h after the administration of the compound. This effect persisted for longer than 24 h.

Polypeptide

After a single ip or multiple ih administration of Ginseng polypeptide(GPP) at the dose of 50, 100, 200mg/kg respectively, the obvious effect of lowering blood glucose and liver glycogen levels showed up in glucose-induced, epinephrine-induced and alloxan-induced diabetic rats. Besides, GPP could enhance liver glycogen breakdown with adrenaline. The main hypoglycemic mechanism is enhancing the activities of the succinate dehydrogenase and cytochrome oxidase to accelerate the sugar oxidation in addition of promoting the glycolgenolysis and inhibiting synthesis of lactic acid (34).

Glycoprotein

Urtica Pilulifera Seed Lectins (UPSL)(100mg/kg) showed a significant regulative effect on blood sugar levels in STZ-induced diabetic rats(P<0.005) in experiment. Research on islet cells indicated that UPSL processed protective effects against cell damage and lowered blood glucose levels by combining with glucoreceptors while competing with STZ (35).

Stilbene

Stilbene compounds can cause a significant reduction in the blood sugar levels in alloxan-induced and STZ-induced diabetic rats, type 2 diabetic animal models, KK rats in a dose-dependent manner. The hypoglycemic mechanism is as follows: improving interaction efficiency of insulin and insulin sensitivity to liver tissue, decreasing the serum cholesterol and triglyceride levels (36).

 Unsaturated Fatty Acid

Conjugated linoleic acid(CLA) could repair glucose tolerance and improve hyperinsulinemia in the pre-diabetic ZDF rats. Besides, dietary CLA increased steady state levels of aP2 mRNA in adipose tissue of fatty ZDF rats consistent with activation of PPARγ. The insulin sensitizing effects of CLA were relative to activation of PPAR at least in part. It was predicted that the anti-diabetes mechanism of CLA is similar to thiazolidinedione, an anti-diabetic medicine (37-40).

Sulfuric compounds

Salacia reticulata WIGHT’s roots and stems have been widely used for the treatment of diabetes in the Ayurvedic system of Indian traditional medicine. With the bioassay-guided separation using α-glucosidase inhibitory activities, Yoshikawa et al. (41) isolated potent α-glucosidase inhibitors termed salacinol from the water-soluble portion together with several phenolic compounds. The inhibitory effects of salacinolon serum glucose levels in maltose- and sucrose-loaded rats were found to be more potent than that of acarbose, a commercial medicine. Experiments in vitro indicated salacinol was a kind of potent α-glucosidase inhibitor.

Allicin(70mg/kg) showed obvious hypoglycemic effects on alloxan diabetes rats (P<0.01) 15days after they were administered by IG continuously. In addition, it could increase the C-peptide content profoundly. This mechanism was relative to increasing insulin secretion and improved the function of damaged pancreatic β cells (42,43).

Tetrahydropyrane (THP)

Prerez et al. (44) extracted a new tetrahydropyrane, coyolosa, from the Arocomia Mexicana root. The extract showed a significant blood sugar lowering effect on normal and alloxan-induced diabetic rats when administered at 2.5 to 25 mg/kg in doses, and exhibited a dose-de-
ponential response. According to the results from experiment, coyolosa had a more profound improvement for glucose tolerance than tolbutamide. This mechanism may be relative to increasing insulin secretion or promoting the glucose utilization of surrounding tissues.

**Pyrrolic compounds**

Reddy et al.(45) extracted a new pyrrolic compound, 5-octadecylpyrrrole-2-carboxaldehyde, from Mycale mytilorum. They did the research on the toxicity and anti-diabetic activity of 5-octadecylpyrrrole-2-carboxaldehyde.

It showed that there was significant reduction in blood glucose levels observed at a dose of 30mg/kg body in normal and alloxan diabetic rats, which was found to be equivalent to 30μg/kg in dose of glibenclamide administered orally.

The compound also produced significant hypoglycemic activity in alloxan-induced diabetic rats even at lower dose level, i.e. 10mg/kg when compared to matching control and glibenclamide30 μg/kg treated rats. It seemed to produce antidiabetic activity by pancreatic or extrapancreatic mechanisms. The LD₅₀ of 5-octadecylpyrrrole-2-carboxaldehyde was found to be approximately 300mg/kg in those rats.

**Organic acids**

Through hypoglycemic activity-guided fraction Peungvicha et al. (46) isolated the known compound, 4-hydroxybenzoic acid, from Pandanus odorus Ridl. This compound showed a hypoglycemic effect in normal rats after the oral administration of 5mg/kg. Additionally, the compound increased serum insulin levels and liver glycogen content in normal rats. The liver glycogen level increase might be due to insulin stimulating the synthesis of liver glycogen by activating the glycogen synthase.

**Dietary fiber**

Dietary fiber is an indigestible carbohydrate of plant origin, which possesses important physiological function. It could especially inhibit gastrointestinal disease and maintain the health of gastrointestinal tract (47). OL Erukainure et al. (47) showed dietary fiber could decrease the fasting blood glucose and sugar tolerance in alloxan-induced diabetic rats. For diabetic patients, the blood sugar level could decrease by consuming approximately 20g dietary fiber daily, making the condition take a favorable improvement.

**3. Conclusion**

Along with cardiovascular and cancer diseases, diabetes are listed as the top 3 life-threatening diseases globally. Effective clinical medications with higher potency, lower toxicity and reduced cost are urgently needed. In this article, 14 different natural materials that have been proved experimentally or clinically have been discussed, including carbohydrate, flavonoid, polypeptide, saponin, glycoprotein, alkaloids et al. Besides lowering blood sugar level, various functions were identified for these natural materials. For instance, it has been shown that saponin, isolated from rhizomes of furostanol protanoidins, performs high anti-tumor activities against leukemia, colon cancer, prostate cancer, breast cancer (48,49). Steroidal saponin of Trillium tschonoskii could reverse multi-drug resistance of hepatocellular carcinoma and significantly increase chemosensitization of cancer cells (50-52). Another example is the flavonoid has been shown with antioxidant, anti-inflammatory and anti-tumor activities (53-56). Reduced risk of cardiovascular disease for patient treated with dietary flavonoids were also observed in clinical trials (53). Therefore, more biomedical evaluations of these natural compounds deserves to be studied both in vivo and in vitro. Instead of treating diabetic patients with single type of anti-diabetic drug, a combination of traditional drugs and newly identified natural compounds should be applied to each patient according to their own specific condition.

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