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Research progress on hypoglycemic active components in natural products

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Abstract: Diabetes is one of the most challenging health problems worldwide. Commonly used anti-diabetic drugs include insulin, Pramlintide, GLP-1 receptor agonists and oral hypoglycemic. Due to the limitation of these anti-diabetic drugs related to potency, stability and cell toxicity, new drugs isolated from natural materials have been served for alternative and safe anti-diabetic medications in the most recent decade. In this manuscript, pharmacological reaction and molecular mechanism of hypoglycemic active components in natural products were discussed in detail.

Key words: Diabetes; natural product; anti-diabetic drug; hypoglycemic active components.

1. Introduction

Diabetes mellitus, commonly known as diabetes, is a complex endocrine disease. Following neoplasm and car-diovascular 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 polyneuropathy (1). In diabetes treatment, blood sugar control is signifi-cant 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 inter-national 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 ef-fects were observed in diabetes-free rats. Promoting insu-lin 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 dia-betes rats in 7 days with discontinuous dosage. PCS treat-ment 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 hypoglyce-mic mechanism (3).

In statistical analysis there are almost 50 types of plant polysaccharides possess blood sugar lowering activity, such as Ginseng polysaccharide, Ch.Wolfberry poly-saccharide, Astragalus polysaccharide and Ganoderma lu-cidum polysaccharide. The main hypoglycemic mecha-nisms are promoting insulin secretion, enhancing the glucose utilization by peripheral tissues and target organ, increasing the insulin sensitivity, preventing lipid peroxi-dation 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) Bio-logical 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 treat-ment, ultrasonic treatment and microwave radiation were also used.

Oligosaccharide

With the treatment of *Rehmannia glutinosa oligo-saccharide* (ROS) (100 mg/kg for 15 days, i.p.) in al-loxan-induced diabetic rats, significant decrease in blood glucose levels and hepatic glucose-6-phosphatase activity as well as increase in hepatic glycogen content were ob-served. 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 mecha-nism of ROS on glucose metabolism was adrenal de-pendent 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-in-duced diabetes rats within two weeks after ig administra-tion at low/high dose, which showed the same hypoglyce-mic ability as metformin hydrochloride. At the same time hemoglobin and leucocyte content increased pronounce-dly 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 immuno-competence and oxygen-carrying ability of diabetic pa-tients and helped prevent arteriosclerosis.

Lu et al. (11) observed the effect of one fraction of akonjac oligosaccharides, KOS-A,on streptozoto-cin(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 af-fected 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 in-sulin 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 sti-mulating 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 in-creases 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 *Ampelopsisgrosse-dentata(Hand-Mazz)'s W.T. Wang* which contains myrice-tin and ampelopsin. 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, hastening the repair of injured pancrea-tic 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 mul-berry 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 inhibi-ting the activity of disaccharidase (17).

Recent researches show that plant flavonoids could prevent diabetes and its complication effectively in va-rying ways. Due to the complexity of flavonoids *in vivo*, majority of their mechanism is still in research phase.

The methods of extracting flavonoids include mi-crowave extraction, organic solvent extraction, super critical extraction, enzyme-assisted extraction and ultra-sound-assisted extraction.

2.3 Saponin

Saponin is the major effective ingredient of many im-portant Chinese herbs, including Panaxginseng, Rastraga-li, Panaxnotoginseng, Glycyrrhizauralensis, Rhizoma Anemarrhenae (18). Some type of saponin also showed strong activity to lower the blood sugar level. For instance, saponin of *Litchi*0.2g/kg was able to improve the condi-tion 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 tole-rance test. Saponin caused reductions of the total choles-terol, triglyceride, low-density lipoprotein cholesterol and malondialdehyde content and suppression of *aspartate aminotransferase*(AST), *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 sen-ticosus 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 glycogenoly-sis, 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 re-crystallization, ultrasonic extraction, alumina column chromatographic, macroreticular resin, supercritical car-bon dioxide extraction, microwave-assisted extraction, membrane technique and water extraction were used (23). Sovova, H et al. (24) show that the ratio of dioscin ex-tracted from dioscorea panthaica 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 ex-periments, 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 ex-perimental condition.

2.4 Alkaloids

Alkaloids have physiological activities like antibac-terium, antitumor, antiarrhythmia, hyperglycemia and gastric mucosa protection. T Li-Qin (26) observed a po-sitive effect of *berberine* in lowering blood sugar and blood lipid levels in Sprague-Dawley rats models of dia-betic 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 signifi-cant reduction in the blood sugar levels by modulating the target cells specificity expressed by *Peroxisome prolifera-tor-activated receptors* (PPARsγ).

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 sca-venging 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) ob-served the effect of*berberine*onHepG_2 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 wa-ter/sour water extraction, alcoholic solvent extraction, impregnation, percolation, decoction and reflux method.
Whereas the new ways to extract alkaloids include mi-crowave-assisted extraction, ultrasound-assisted extrac-tion, supercritical fluid extraction, double water phases extraction, chromatography, resin absorbing, molecular imprinting and molecular distillation technology (32).

2.5 Other natural products with hypoglycemic activi-ties

Terpenoid

Lactucin-8-*O*-methylacrylate can be isolated by chlo-roform 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 lactu-cin-8-*O*-methylacrylate the maximal hypoglycemic ac-tivity (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 *Gin-seng 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-induceddiabetic rats. Be-sides, GPP could enhance liver glycogen breakdown with adrenaline. The main hypoglycemic mechanism is en-hancing the activities of the succinate dehydrogenase and cytochrome oxidase to accelerate the sugar oxidation in addition of promoting the glycogenolysis and inhibiting synthesis of lactic acid (34).

Glycoprotein

Urtica Pilulifera Seed Lectins (UPSL)(100mg/kg) showed a significant regulative effect on blood sugar le-vels 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-in-duced 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-diabe-tic 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 sensiti-zing effects of CLA were relative to activation of PPARγat least in part. It was predicted that the antidiabetes mecha-nism of CLA is similar to thiazolidinedione, an antidiabe-tic medicine (37-40).

Sulfuric compounds

Salacia reticulata WIGHT's roots and stems have been widely used for the treatment of diabetes in the Ayurve-dic system of Indian traditional medicine. With the bioas-say-guided separation using α-glucosidase inhibitory acti-vities, 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 in-hibitor.

Allicin(70mg/kg) showed obvious hypoglycemic ef-fects 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 nor-mal and alloxan-induced diabetic rats when administered at 2.5 to 25 mg/kg in doses, and exhibited a dose-dependent response. According to the results from experi-ment, 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-octadecylpyrrole-2-carboxaldehyde, from *Mycale myti-lorum.* They did the research on the toxicity and antidiabe-tic activity of 5-octadecylpyrrole-2-carboxaldehyde.

It showed that there was significant reduction in blood glucose levels observed at a dose of 30mg/kg body in nor-mal and alloxan diabetic rats, which was found to be equi-valent to 30μg/kg in dose of glibenclamide administered orally.

The compound also produced significant hypoglyce-mic 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 see-med to produce antidiabetic activity by pancreatic or ex-trapancreatic mechanisms. The LD50of 5-octadecylpyr-role-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 5 mg/kg. Additionally, the compound increased serum insulin levels and liver gly-cogen content in normal rats. The liver glycogen level in-crease 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 hysiological function. It could especially inhibit gastrointestinal disease and main-tain 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 impro-vement.

3. Conclusion

Along with cardiovascular and cancer diseases, dia-betes are listed as the top 3 life-threatening diseases glo-bally. 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, saporrin, glycoprotein, alkaloids et al. Besides lowering blood su-gar level, various functions were identified for these na-tural materials. For instance, it has been shown that sapo-nin, isolated from rhizomes of furostanol protoneodioscin, performs high anti-tumor activities against leukemia, co-lon cancer, prostate cancer, breast cancer (48,49). Steroi-dal saponin of Trillium tschonoskii could reverse multi-drug resistance of hepatocellular carcinoma and signifi-cantly increase chemosensitations 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 cli-nical 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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