ADVANCES IN PHARMACOLOGICAL EFFECTS OF ASTRAGALOSIDE IV ON DIABETES MELLITUS AND ITS COMPLICATIONS

Dongdong Yu[1], Hui Cao[1], Yuxiang Guan[2,*]
[1]Graduate School of Anhui University of Chinese Medicine, Hefei, PR China - [2]The First Affiliated Hospital of Anhui University of Chinese Medicine, Hefei, PR China

ABSTRACT

Diabetes mellitus is one of metabolic diseases characterized by elevated blood sugar, which has seriously threaten human health. At present, traditional Chinese medicine treatment of diabetes and its complications has the characteristics of multi-target, owning unique advantages in the prevention and treatment of diabetes. Astragaloside is an important active ingredient of astragalus membranaceus. With the analysis of its pharmacological effects, it can improve the function of endothelial cells and neovascularization, promote the increase of neural stem cells, increase the immune function of the body, and also have anti-inflammatory and anti-oxidative effects. Its application in diabetes mellitus can improve pathological damage by regulating blood sugar level, such as diabetic retinopathy and diabetic cardiomyopathy. In this paper, the pharmacological effects of astragaloside IV in the diabetes mellitus treatment and its complications were analyzed in order to provide relevant basis for clinical research.

Keywords: *Astragaloside, diabetes mellitus, complications, pharmacological effects.*

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Introduction

Diabetes mellitus (DM) is the systemic metabolic disease characterized by persistent hyperglycemia. Long-term metabolic disorders can cause disorders and exhaustion of systemic organs such as eyes, kidneys, cardiovascular diseases, nervous system, and also seriously affect the life quality of thousands people around the world[(1)]. Diabetes belongs to the category of "quenching thirst" in traditional Chinese medicine, which has complicated causes. Inadequate innate endowment is an important internal factor causing diabetes. In addition, dietary disorders, mental stimulation, excessive labor and desire can all cause accumulation of heat and develop into diabetes. Its pathogenesis is mainly yin deficiency, jin deficiency and excessive dry heat, which is based on yin deficiency and standard for dryness and heat. In recent years, larges of studies have been carried out on the clinical efficacy and mechanism of astragalus membranaceus and its effective fractions in the prevention and treatment of diabetes mellitus[(2)]. Astragalus membranaceus belongs to leguminous herbs with mild temperature and sweet tasten, which has the functions of replenishing qi and strengthening the surface, antimicrobial, detoxifying, strengthening heart and diuresis. In modern pharmacological research, astragalus membranaceus plays an important role in regulating immunity, anti-virus, diabetes and so on. The main active ingredient of astragaloside is astragaloside, which can improve the function of endothelial cells and neovascularization, promote the increase of neural stem cells, increase the immune function of the body, and also has anti-inflammatory and anti-oxidative effects. Therefore, astragaloside is often used in the treatment of respiratory diseases, cardiovascular and cerebrovascular diseases, diabetes and related complications[(3)]. In this paper, the pharmacological effects of astragaloside IV on diabetes mellitus and its complications has been review for further study astragaloside IV.

Pharmacological action

Hypoglycemic effect

Persistent elevation of blood sugar is one of the important characteristics in diabetes mellitus patients, which causes the decrease of islet beta cell secretion ability. If hyperglycemia is formed in a vicious cycle, diabetic complications will occur. Relevant data show that astragaloside can reduce blood sugar level by inhibiting the activities of blood sugar-6-phosphatase and hepatic glycogen phosphorylase. By animal experiments, some scholars have found that astragaloside can significantly reduce the blood sugar level of diabetic mice model. Chen Tingfang, etc. found that astragaloside 120 mg/kg could significantly reduce blood sugar in mice after 1, 2, 3 and 4 weeks administration[4]. Li Shuang, etc. found that astragaloside (50 mg/kg) could significantly reduce the glycosylated hemoglobin and fasting blood sugar in diabetic mice[5]. Xu Chonghua found that astragaloside can reduce the blood sugar of hyperglycemic mice induced by intraperitoneal injection of adrenaline and alloxan[6].

Hypolipidemic effect

Most patients with diabetes have disorders of lipid metabolism. As insulin is insufficient in vivo, visceral fat sensitivity to lipolysis hormones can be enhanced, thereby increasing the levels of intracellular fat and free fatty acids, promoting the synthesis of more triglycerides in the liver, aggravating insulin resistance and impaired function of islet beta cells. Hyperglycemia and hyperlipidemia can significantly accelerate atherosclerosis, leading to the decline and failure of organ functions. The animal experiments carried by You Liangzhen et al. showed that astragaloside IV could reduce blood lipid by regulating the serum triglyceride levels, low and high density lipoprotein in diabetic mice[7]. Ruo Dan, Zhang Jing and other scholars have shown that astragaloside IV can induce activation of STAT3 phosphorylation stimulated by Tumor Necrosis Factor (TNF-alpha), induce apoptosis of 3T3-L1 adipocytes, and reduce the level of free fatty acids in vivo[8]. The related reason may be that astragaloside can increase the level of key lipid metabolic enzymes such as fatty acid synthase.

Improvement of insulin resistance

Diabetes mellitus patients have suffered different degrees damage from cell receptor defect, and the damaged receptor cannot effectively bind to insulin, inducing insulin resistance. The pathogenesis of diabetes mellitus is closely related to insulin resistance. Insulin resistance is predisposed to the binding of insulin with its receptor, which produces cytokines such as TNF-α, adiponectin, and free fatty acids. Liu Xinhui has shown that astragaloside A can improve insulin resistance by increasing the uptake rate of 2-deoxy-[3H]-D-glucose in adipocyte 3T3-L1 and regulating insulin level under insulin resistance mice model[9]. In addition, Cao Yujing et al. treated human insulin resistance cells with astragaloside, showed that astragaloside could promote the uptake of glucose and glucose transporter protein by human insulin resistance cells, inhibiting the over-activation of IKK/IkBalpha, and improving insulin resistance[10].

Inhibits inflammation

Studies have confirmed that some of the protein factors related to inflammatory response in patients with diabetes can be highly expressed. These factors can not only affect blood glucose concentration, but also regulate insulin secretion, which is closely related to the development of diabetes. Modern clinical studies have shown that astragaloside has significant anti-inflammatory effect. Via increasing the expression of glucocorticoid receptor, it can reduce the adhesion of endothelial cell selectin and vascular cell adhesion molecules induced by lipopolysaccharide. In addition, astragaloside can block TNF-α-mediated expression of vascular cell adhesion molecules and exhibit significant anti-inflammatory activity for pneumonia, asthma, and pancreatitis. By detecting the expression levels of TNF-α, MCP-1 and ICAM-1 in serum and renal tissues of diabetic mice, Guo Weiwen, Li Shuai, and other scholars found that astragaloside can significantly reduce the levels of these factors and improve the development of diabetic nephropathy[11].

Reduce oxidative stress response

Oxidative stress refers to the imbalance between oxidation and anti-oxidation of the body, leading to tissue damage caused by accumulation of ROS and RNS. Related data show that oxidative stress can induce diabetes by reducing the sensitivity of peripheral tissues to insulin (12). In addition, ROS can directly damage islet β cells leading to insulin resistance. By detecting the level of oxidative stress in diabetic mice kidney tissue, Li Zhong, Zhang Peihua and other scholars found that astragaloside can significantly reduce the level of malondialdehyde, increase the activity of superoxide dismutase, and improve the oxidative damage caused by oxidative stress[13].

Astragaloside iv and diabetic complications

Diabetic vascular disease

Diabetic vascular disease is the common chronic complication of diabetes. Traditional Chinese medicine believes the pathological mechanism of diabetic blood vessels is phlegm and blood stasis and obstruction of the meridians. These pathological products can cause stagnation of blood and blood fluids. The collateral self-stabilizing network blood stasis thickens the venous wall, causing the narrowing of the collateral veins, and producing pathological effects to the venous tissue such as erosion and burns, which eventually leads to the damage of the venous wall structure[14]. Modern medical research has found that astragaloside can protect myocardial injury caused by ischemia and hypoxia in diabetic patients, and then protecting the heart. The mechanism of action may be as follow: 1 inhibition of Ca2+/Can signaling pathway to prevent cardiac hypertrophy; 2 inhibition of protein kinase activity tp improve cytoskeletal remodeling; 3 inhibittion TLR4/NF-kB signaling pathway to attenuate cardiomyocyte injury induced by β-adrenergic hypertrophy; 4 inhibiting cell adhesion factor activity to reduce cellular inflammation; 5 lowering density lipoprotein levels to improve endothelial cell function. Li Xianghua and other scholars found that astragaloside can reduce the proliferation of smooth muscle cells, which may be related to the inhibition of apoptosis and cell metabolism by astragaloside[15-17].

Diabetic retinopathy

Diabetes retinopathy is the important microvascular complication in diabetic patients. In developed countries, DR is the leading cause of adult blindness[18]. Oxidative stress, inflammatory cytokines, and polyhydric pathway hyperthyroidism can all induce the occurrence of DR, and retinal neurodegeneration can occur early in DR, which may be related to retinal neurons and glial tissues. Aldose reductase is the key enzyme in the damage of DR polyol pathway, and astragaloside can inhibit the activity of retinal AR and reduce the cells apoptosis rate suffering from RGC, which has been confirmed that it is responsible for apoptosis and inflammatory immunity of DR. Via animal studies, Jiao et al. found that the astragaloside treatment group can significantly increase serum MDA, reduce GSH content, improve retinal oxidative stress in diabetic mice compared with normal mice and function on retinal ganglion cells[19].

Diabetic nephropathy

Diabetic nephropathy is glomerulosclerosis, which is caused by microangiopathy resulted from diabetes mellitus. It is the first disease that causes chronic kidney disease and its pathogenic factors are closely related to heredity, hemodynamics and oxidative stress. It has been proved that astragaloside has the function of dilating renal vessels and protecting renal cells.

The related mechanisms may be as follows:

• Astragaloside can improve renal pathological injury and podocyte injury by up-regulating the expression of Nephrin and Podocin, in addition, astragaloside can also reduce the apoptotic rate by regulating the expression of Bcl-2 protein;

• By inhibiting the activity of p38/MAPK signaling pathway and regulating the expression of renal small hepatocyte growth factor, astragaloside can protect kidney cells.

• Renal tubular lesions and interstitial fibrosis are typical pathological changes of tubular injury in diabetic nephropathy. Wang Yaning and other scholars have found that astragaloside IV can inhibit the production of ROS in mice with renal tubular epithelial cell injury and promote the increase of E-cadherin content[20-22].

Diabetic peripheral neuropathy

Diabetic peripheral neuropathy (DPN) is a common chronic complication of diabetes. It refers to the symptoms similar to peripheral nerve dysfunction in diabetic patients. Traditional Chinese medicine believes that the disease is caused by the accumulation of diabetes deficiency syndrome (Yin and Yang qi and blood deficiency, blood stasis, vein obstruction)[23]. Qi, blood, Yin and Yang deficiency as the source of the disease, phlegm and blood stasis as the surface symptoms, diabetic peripheral neuropathy often occurring in the skin, muscles, veins, liver, kidney, spleen and other organs. It has been proved that astragaloside IV can significantly improve diabetic peripheral neuropathy caused by increased aldose reducing sugar activity, increase the expression of nerve growth factor, promote the proliferation of nerve cells and increase nerve conduction[24]. Wang Chaohui has found that astragaloside A can inhibit TNF-alpha-induced lipolysis of mouse embryonic fibroblasts, thereby delaying the progress of neuropathy[25]. In addition, astragaloside IV can significantly inhibit the expression of cyclooxygenase, which is the mechanism of its anti-inflammatory mechanism.

Diabetic cardiomyopathy

Diabetic cardiomyopathy is a specific cardiomyopathy, whose main characteristics are cardiomyocyte hypertrophy and coronary artery basement membrane thickening. As the complication of diabetes, Chinese medicine believes that its clinical regularity is closely related to the development of diabetes. Diabetes is characterized by long-term qi and yin deficiency and qi deficiency. Meanwhile, qi and yang deficiency syndrome may be caused by the disease, which may lead to various changes such as qi stagnation and turbidity[26]. Relevant data show that astragaloside A can improve myocardial remodeling, anti-ischemia-reperfusion, inhibit myocardial hypertrophy and enhance myocardial contractility. By studying the rat model of diabetes, Wang Shiguang, Xu Yan and other scholars found that astragaloside can significantly improve myocardial tissue damage in rats. The related factors may be related to the up-regulation expression of peroxisome proliferator-activated receptors γ-coenzyme activating factor 1α and related to key regulators of mitochondrial biosynthesis[27]. Via studying the rat cardiomyocyte injury model induced by high glucose, Wang Yazhen, Dai Jihuan and other scholars have found that astragaloside A can significantly reduce the apoptotic rate of cardiomyocyte by activating PI3K/AKT signaling pathway to mediate mitochondrial apoptosis[28]. In addition, astragaloside can significantly reduce the expression of NF-kB, regulate oxidative stress, increase oxidase activity abd reduce inflammatory mediators during inflammation, protecting myocardial cells from diabetes mellitus. In addition, astragaloside can significantly reduce the expression of NF-kB, regulate oxidative stress, increase oxidase activity abd reduce inflammatory mediators during inflammation, protecting myocardial cells from diabetes mellitus.

In summary, astragaloside A has the effect of controlling blood sugar and improving insulin resistance in diabetes mellitus. It may become one of the clinical effective drugs for diabetes in the future. However, the direct target and specific molecular mechanism of astragaloside A in the diabetes mellitus treatment are still unclear. Therefore, the pharmacological effects of astragaloside A should be further studied in clinic.

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Corresponding Author:
Yuxiang Guan
Email: 897213643@qq.com
(China)