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Research Progress of Flavonoids in The Treatment of Diabetic Nephropathy

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Abstract: The advantages of traditional Chinese medicine in the treatment of diabetes mellitus are stable efficacy, fewer adverse reactions, and multi-target effects. Flavonoids, as active ingredients widely distributed in plants, play an important role in the prevention and treatment of diabetes and its complications. During the past few years, domestic and foreign research have founded the application prospect of flavonoids for diabetes mellitus, which offers a new way of researching in this field. This article reviews the research on flavonoids in the treatment of diabetic nephropathy at home and abroad.

Keywords: Flavonoids; Diabetic nephropathy; Research Progress.

1. Introduction

As natural plant compounds, flavonoids have received extensive attention in recent years, and are considered to have the potential to be used in the treatment of diabetic nephropathy due to their antioxidant, anti-inflammatory, anti-fibrotic and other biological activities [1]. This article mainly reviews the existing research results from the two parts of flavonoids and flavonoids in the treatment of diabetic nephropathy.

2. Flavonoids

Flavonoids are a class of natural compounds with a specific structure, a series of compounds derived from the parent nucleus of flavonoids (2-phenylogenone), which are generally widespread in plants. The structure of a compound is a benzene ring and a ring of three atoms on a benzene ring, one or more of which has a hydroxyl group on it [2].

Flavonoids have a variety of biological activities, including antioxidant, anti-inflammatory, antibacterial, anticancer, etc. [3,4] At present, flavonoids have been widely studied and applied in the fields of medicine and health care. They are used to treat a variety of diseases, including cardiovascular disease, cancer, diabetes, inflammatory diseases, and more [5]. Among them, some flavonoids are used as pharmaceutical ingredients to adjuvant the treatment or prevention of these diseases [6].

There are also many scholars who have studied the extraction of flavonoids, such as microwave extraction of flavonoids from grapefruit peel [7] and ultrasonic-assisted extraction of flavonoids from jujubes [8].

3. Role of Flavonoids in The Treatment of Diabetic Nephropathy

(1) Flavonoids have a potent antioxidant capacity and play a key role in the development of diabetes mellitus (DN) against oxidative stress. Oxidative stress is damage to cells and tissues due to an imbalance between the production and elimination of oxygen radicals. RAHIIMADISEH M et al. reported that in DN, oxidative stress cause kidney damage through multiple pathways, such as alteration of the filtration barrier, hemodynamics, and activation of metabolic pathways. Flavonoids contain hydroxyl groups, which can reduce the damage of reactive oxygen species to cells and effectively prevent oxidative stress through a variety of mechanisms, such as interfering with hydrogen atom and single electron transport, metal chelation, and oxidase inhibition [9]. LEOPOLDINI M et al. reported that flavonoids showed significant antioxidant stress effects in different DN models, increasing antioxidant enzyme activity, reducing oxidation levels, reducing urine albumin and MDA contents, and delaying kidney damage. For example, total flavonoids and silymarin in bougainvillea have shown these effects in experiments [10].

(2) Flavonoids have significant anti-inflammatory effects and have potential value in the treatment of diabetic nephropathy (DN). ZOU Jet al. have found that the development of DN is closely related to immune-mediated persistent inflammation, triggering the release of inflammatory mediators such as IL-1β and TNF-α, as well as the infiltration of neutrophils and monocytes, which in turn induces kidney damage. Flavonoids, such as quercetin, rutin, silymarin, and naringin, have been shown to be effective in suppressing inflammatory responses in blood and kidney tissue. In addition, Garbo fruit extract is rich in anthocyanins, which exert anti-inflammatory effects on DN by inhibiting the NF-κB signaling pathway, while regulating the levels of a variety of inflammatory cytokines, such as ICAM-1, VCAM-1, MCP-1, CSF-1, IL-1β, IL-6 and TNF-α. Tanshinone can inhibit the IκB/NF-κB signaling pathway and lower the expression levels of pro-inflammatory cytokines TNF-α, IL-1β and IL-6 in DN rats [11].

(3) Anti-apoptotic effect. HAO H Het al. found that DN is often associated with glomerular hyperfiltration rate, vascular hyperpermeability, abnormal inflammatory factors, and elevated oxidative stress. Flavonoids can attenuate renal apoptosis by modulating multiple signaling pathways, such as inhibition of caspase expression and p38MAPK. Flavonoids can also affect mitochondria-dependent pathways, reduce urine protein production, and delay DN progression [12].

(4) Improve blood sugar and lipid disorders. Hyperglycemia increases lipoprotein glycosylation, resulting in elevated blood lipids. Flavonoids can improve fatty acid oxidation, reduce lipid peroxidation and AGEs deposition,

improve glucose and lipid metabolism, insulin resistance, and alleviate lipid metabolism disorders.

(5) Regulates vasodilation and improves hemodynamic abnormalities. XU L et al. reported that hyperglycemia triggers multiple vasoactive hormone pathways, affecting renal blood flow. Flavonoid compounds increase blood flow velocity, improve vasodilation, reduce glomerular pressure, and contribute to the prevention of DN by promoting vascular smooth muscle relaxation, activating NOS, and inhibiting calcium overload [13].

4. Flavonoids for Diabetic Nephropathy

Several studies have shown that different plant extracts have potential nephroprotective effects and help treat diabetic nephropathy (DN). For example, plant compounds such as rhebalin flavonoids, dihydroflavonoid glycosides of Fern acuminus, flavonoids of mulberry branches, flavonoids of buckwheat, soy isoflavones, total flavonoids of hawthorn leaves, total flavonoids of fern and flavonoids of Eucommia ulmoides have shown significant potential for the treatment of diabetic nephropathy in experimental animal models. They can protect the kidneys from diabetes-induced damage through a variety of mechanisms, such as inhibiting oxidative stress, reducing inflammation, improving kidney function, lowering blood sugar levels, and more. For example, Wang et al. concluded that compared with the model group, the two dose experimental groups of large and medium doses could significantly reduce the blood glucose, urea nitrogen, creatinine, and urine microalbumin levels of model rats, and concluded that flavonoids had a significant nephroprotective effect on rats with diabetic nephropathy [14]. Xiong et al. suggested that Dihydroflavonoid glycosides (CAF) could inhibit renal EMT in rats with diabetic nephropathy (DKD), and the molecular mechanism of its action may be related to the downregulation of β-catenin expression in kidney tissue and the inhibition of GSK-3β (p-GSK-3β) phosphorylation inactivation [15]. Su et al. used the method of intraperitoneal injection of one side ligation kidney + streptozotocin (STZ) to replicate the DN rat model for a controlled study, and the study believed that mulberry flavonoids can reduce blood glucose, improve kidney function, alleviate renal pathological changes in DN rats, and have a protective effect on the kidneys of diabetic nephropathy (DN) rats, and reducing the level of inflammatory factors may be one of the mechanisms [16]. Liu Xiaona found that different doses of buckwheat flavonoids can have a protective effect on rats with diabetic nephropathy by lowering blood glucose, lowering blood lipids, improving renal function, and 24h protein amount, and its protective effect is related to antioxidant effect. The appropriate dose of buckwheat flavonoids for the treatment of diabetic nephropathy rats is 100mg/kg [17]. Zhou Xue found that soybean isoflavones (SI) can effectively alleviate tubular injury, proliferation of glomerular mesangium and basement membrane, and reduce tubular epithelial edema. Compared with the diabetic nephropathy (DN) group, the levels of superoxide dismutase (SOD) and total antioxidant capacity (T-AOC) in the SI group were significantly increased, while the levels of malondialdehyde (MDA) and serum advanced oxidized protein products (AOPPs) were decreased. The serum levels of TNF-α, IL-Iβ and IL-6 were significantly decreased ($P<0.05$). That is to say, soy isoflavones have anti-inflammatory and antioxidant effects, which can effectively protect oxidative stress and inflammatory response in the kidneys of rats with diabetic nephropathy [18]. Xiong Jiajun pointed out that Dihydroflavonoid glycosides of Fern acuminus have inhibitory effects on abnormal proliferation and oxidative damage of renal tubular cells caused by diabetes mellitus under experimental conditions, and can help alleviate some pathological features of diabetic nephropathy, such as collagen deposition, basement membrane thickening, and EMT and fibrosis in the kidney, in animal models [19]. Qin et al. pointed out that the total flavonoids of hawthorn leaves might play a positive part in the progression of diabetic nephropathy by inhibiting oxidative stress, and may improve the damage of oxidative stress to kidney tissue by regulating the p38MAPK signal transduction pathway in diabetic nephropathy [20]. Zhang Junli et al. pointed out that the total flavonoids of Parn fern can reduce the degree of ear swelling caused by xylene in mice, and have a therapeutic effect on diabetic nephropathy model rats, and its mechanism may be related to reducing oxidative stress damage in tissues and reducing the release of inflammatory factor IL-6 [21]. Xu et al. pointed out that flavonoids of Eucommia ulmoides have the effect of reducing fasting blood glucose and improving kidney function in mice with diabetic nephropathy, and its mechanism of action may be related to its ability to improve the oxidative stress state of kidney tissue by regulating the Nrf2/HO-1 signaling pathway [22].

In addition, some studies have also highlighted the potential of the combined application of Chinese and Western medicine in the treatment of DN, which can produce synergistic effects, alleviate adverse reactions, and provide a basis for the development of highly effective and safe drugs for the treatment of diabetic nephropathy in the future (Gu et al., [23]).

5. Summary and Outlook

In summary, the research on flavonoids in the treatment of diabetic nephropathy has achieved rich research results, and scholars at home and abroad have carried out a large number of studies on it, and the research dimensions are diversified, some scholars focus on the research of flavonoids and their extraction processes, and some scholars focus on the multiple mechanisms of action and specific applications of flavonoids in the treatment of diabetic nephropathy (DN). Studies have affirmed the antioxidant stress and enhanced effects of flavonoids in scavenging free radicals, anti-inflammatory, anti-apoptosis, improving blood glucose and lipid disorders, regulating vasodilation and improving hemodynamic abnormalities. In several studies, it has been shown that different types of flavonoids have shown potential benefits in the treatment of DN. For example, flavonoids, dihydroflavonoid glycosides of Pteridophyllum acumina, flavonoids of mulberry branches, flavonoids of buckwheat, soybean isoflavones, total flavonoids of hawthorn leaves, and total flavonoids of Fern have all been shown to have renal protective effects, and are expected to be beneficial supplements for the treatment of DN through different mechanisms to lower blood sugar, improve kidney function, reduce inflammatory responses, and inhibit oxidative stress. However, further clinical researches are needed to confirm these experimental results and determine the best use and dosage of flavonoids in clinical practice.

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