RESEARCH ARTICLE

Herbal drugs for the treatment of diabetic nephropathy: Current status and prospects for the application

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Diabetes mellitus being a global epidemic with approximately 40% of the patients resulting in diabetic nephropathy (DN). There is a need for development and further clinical application of the safe natural drugs for the prevention and treatment of DN. Scientific data concerning medicinal plants and their individual active substances with the potential to be used for the treatment of DN have been collected and summarized. The extracts of *Astragalus membranaceus*, *Ginkgo biloba, Silybum marianum* and *Juglans regia*, which were used in several clinical trials, exhibited nephroprotective action, with different mechanisms. Individual active substances, derived from plants, curcumin and breviscapine, applied in clinical trials, possessed positive impact for kidney activity in DN patients.

Key Words: *Diabetes; Diabetic nephropathy; Nephroprotective herbal drugs; Clinical application*

INTRODUCTION

Diabetes mellitus is a metabolic disorder resulting to improper blood sugar regulation. Prevalence of diabetes has reached epidemic proportions in the world. According to the International Diabetes Federation, there were 366 million people with diabetes in 2011, and this is expected to rise to 552 million by 2030. With the global epidemic of diabetes, diabetic nephropathy (DN) has become an important clinical and public health challenge [1].

The kidneys are vital for ridding the body of toxic waste products, and maintaining fluid, mineral and electrolytes at levels compatible with life. Elevated blood glucose can damage the cells and micro blood vessels of the kidney. Advanced kidney damage results in the need for artificial filtration of the blood by dialysis and potentially the need for a kidney transplant [2]. The kidney is an organ that diabetes impairs its function so the increased blood levels of urea and creatinine are indicative of impaired in glomerular filtration, which is due to oxidative stress which has been known to play an important role in the development and progression of DN, and the formation of r*eactive oxygen species* (ROS) is a direct consequence of hyperglycemia [3]. The severity of renal disease in diabetic patients correlates with the levels of blood urea and serum creatinine. Antioxidants can reduce the level of urea and creatinine [4].

Although the precise mechanism of DN is still ambiguous, oxidative stress has been deemed as a central mediator in promoting the progression of nephropathy in patients who have diabetes. Excessive production and generation of ROS induced by sustained hyperglycemia are a crucial contributor underlying the pathogenesis of diabetes associated with macrovascular and microvascular complications including DN [5].

Diabetic nephropathy is a common complication of diabetes and the leading cause of chronic kidney disease in the developed world, accounting for nearly half of all end stage renal disease (ESRD) cases. Approximately 40% of people with diabetes develop DN, manifested as albuminuria and/or decreased glomerular filtration rate [1]. DN is a progressive and irreversible kidney disease that is characterized by initial hyperfiltration, albuminuria, expansion of mesangial matrix, interstitial fibrosis, thickening of basement membranes, and renal cell damage, excessive accumulation of extracellular matrix (ECM), and ultimately leads to nodular glomerulosclerosis and chronic renal failure [6].

Due to an increasing demand of patients for the use of natural products and other herbal drugs with anti-diabetic activity, the general trend nowadays is to apply themwith medicinal purposes in their crude form [7].

Herbal drugs show moderate efficiency and prolonged prescription of an herbal drug is essential for treatment against a chronic disease [2]. These may play a vital role in future in the treatment of diabetes and studies may be carried for determining their mechanism of action and also in the isolation and identification of main principles useful for treating diabetes induced nephropathy.

Numerous natural antioxidants, extracts of medicinal plants were tested in animals' models of DN: ginger (*Zingiber officinale*), green tea (*Camellia sinensis*), guava (*Psidium guajava*), *Rosa laevigata*, garlic (*Allium sativum*), black seed (*Nigella sativa*), *Panax ginseng*, fenugreek (*Trigonella foenum-graecum*), *Rosmarinus officinalis, Ginkgo biloba,* flaxseed (*Linum usitatissimum*), cinnamon (*Cinnamomum zeylanicum*), *Astragalus membranaceus,Silybum marianumetc* [8]. At present, many botanical medicines are applied as complementary therapy for diabetic nephropathy [9].

The objective of the current research is summarization of scientific data related to promising effects of herbal drugs for the treatment of DN, which were demonstrated in clinics.

MATERIALS AND METHODS

A systemic review of scientific data concerning impact of herbal substances for DN, investigated in clinical conditions, in databases (Pubmed, Researchgate, Google Scholar) has been carried out.

RESULTS AND DISCUSSION

Astragalus membranaceus is an important traditional herb used for thousands of years in China and East Asia for kidney disease. Astragalus injection had more therapeutic effect in DN patients including renal protective effect and systemic state improvement (serum albumin level) compared with the control group. Astragalus and its active extracts have been integrated in clinical management of early DN with satisfying safety profiles, partly for its protective effect against oxidative stress as a free radical scavenger. In modern medicine, Astragalus shows significant renal protective effect in DN [10].

Milk thistle's (*Silybum marianum*) effects on the kidney closely mirror the herb's effects on the liver;the application of the plant in nephrology is supported by some intriguing clinical research [11]. The clinical trial [12] found that patients with ESRD had significant thiol deficiency that was directly correlated with significantly diminished T-lymphocyte activation and increased synthesis of TNF-a. Treatment with silymarin restored thiol status to normal within 72 hours *in vivo* and *in vitro*. Similarly, T-cell activation increased and TNF-a release was reduced, showing a normalizing effect on immunoregulatory defects.Peritoneal macrophages treated with silymarin or silybin stabilized cellular thiol status witha resulting improvement of phagocytosis [13].

Silymarin stimulates RNA polymerase I in kidney epithelium, leading to increased protein synthesis and cellular regeneration. Silybin and

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silichristin are believed to be mostly responsible for these effects while silidianin produces little effect. The publication suggests that silymarin may be particularly useful in situations in which renal epithelium is becoming necrotic [11]. Also Dietzmann et al. consider that milk thistle should be used as a renal protectant as well as a liver protectant; the herbal drug should be prescribed to counter the adverse effects of any drug or treatment modality that may damage the kidneys;milk thistle should also be considered for treating patients with acute tubular necrosis or in other situations, in which epithelial-cell loss is occurring, based on the renal regenerative effects of the herb [12].

Turmeric (*Curcuma longa*)has been used for the treatment of diabetes in Ayurvedic and traditional Chinese medicine. Its active component, curcumin, has caught attention as potential treatment for diabetes and its complications primarily because it is a relatively safe and inexpensive drug that reduces glycemia and hyperlipidemia in rodent models of diabetes [13,14]. There are multiple mechanisms by which curcumin may ameliorate renal damage. The compound increases blood urea nitrogen and promotes clearance of creatinine and urea. In addition, curcumin decreases levels of albuminuria and enzymuria. The substance can also restore renal integrity by normalizing glutathione, superoxide dismutase, *etc*. Clinical trials confirmed the effect of curcumin on ESRD and showed that it reduced TGF-β, IL-8, and urinary protein levels.

Breviscapine, a purified flavonoid extract from *Erigeron breviscapus*, possesses a variety of pharmacological functions other than hemodynamic effects, and can serve as an anti-oxidative stress agent and inhibitor of protein kinase C. Breviscapine can inhibit in diabetic rat models podocyte apoptosis by modulating the expression of B-cell lymphoma 2 (Bcl-2) and Bcl-2-associated X protein genes. The meta-analysisquantitatively evaluated the clinical effect of the compound in the treatment of DN patients by integrating the results of 35 randomized clinical trials (RCTs) that investigated the effects of breviscapine on 1,188 patients with DN and 1,132 control subjects. The outcomes demonstrated that the expression levels of serum creatinine and blood urea nitrogen (BUN) were significantly lower in patients treated with breviscapine in comparison with control subjects, suggesting that the drug serves a protective role in the renal system of DNpatients. The substance can reduce urinary protein levels, with a reduction in 24-h urine protein values and the urinary albumin excretion rate; a reduction in urinary protein may contribute towards the renal protective effect of breviscapine in patients with DN [15].

A traditional Chinese medicine*Ginkgo biloba* extract (GbE) has been shown to exhibit numerous pharmacological effects. GbE may reduce the risk of toxicity and preserve the therapeutic effectiveness in clinical trials and it has been used to treat cardiovascular and neurological disorders. Evidence accumulated *in vitro* and *in vivo* shows that GbE may ameliorate hemodynamics, suppress platelet-activating factor, scavenge ROS, relax vascular smooth muscles. Several studies explored the GbE effects and ascertained its protective effects on DN *in vivo*. GbE postpones the ECM accumulation by inhibiting its synthesis and promoting its degradation, and therefore, is a potential drug for the prevention and treatment of DN [16].GbE prevents against apoptosis induced by high glucose in human lens epithelial cells [17]. GbE has been used widely in Chinaas a supplement to improve albuminuria and kidney function during the early stage (characterised by microalbuminuria) of DN. Many *in vitro* and *in vivo* experiments have shown that the extract can reduce relative total superoxide dismutase activity after adjusting for the expression of cytokines in DNpatients [9].

The effectiveness of a GbE for patients with early DN was evaluated [9], considering data of 16 RCTs conducted on adults. It decreased the urinary albumin excretion rate (UAER), fasting blood glucose, serum creatinine, and BUN. GbE was estimated as a valuable medicine which has prospect in treating early DN, especially with high UAER baseline level [6].

In the double-blind, placebo-controlled, parallel-group RCT, the capsules, containing 100 mg *Juglans regia* leaf extract, were administered twice daily for 8 weeksto 50 type 2 diabetic patientsand control group (placebo).The extract did not significantly change the blood glucose and insulin resistance condition. However, in this group, body weight, body mass index, and systolic blood pressure significantly decreased compared with the baseline measurements [18].

CONCLUSION

Medicinal plants and the individual active substances of plant origin which have shown nephroprotective effects in patients with diabetic nephropathy should be recommended for wider clinical application with an objective of the prevention and treatment of diabetes and its possible consequences.

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