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THE EFFECT OF QUERCETIN ON DIABETES COMPLICATIONS

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Abstract

Diabetes is a serious metabolic disorder with a numerous complications and one of the five leading causes of death worldwide. Diabetes, so called "soft killer" is characterized by persistent hyperglycemia associated with carbohydrate, protein, and lipid metabolism abnormalities. However, the currently available diabetic drugs have numerous limitations because of their side effects including hypoglycemia, cell death, and high rates of secondary alterations. Recently, emphasis has been placed on complementary and alternative treatments for diabetes focused on functional food and its bioactive compounds. One of them is quercetin, a powerful antioxidant flavonoid, which posseses various biochemical and physiological effects (anti-diabetic, antioxidant and anti-inflammatory). The aim of this study is a literature review focused on the impact of quercetin on diabetic complications. In vivo and in vitro studies suggest that quercetin is a promising bioactive compound for treatment of this disease, but its efficacy should be confirmed by clinical trials.

Key words: diabetic complications, bioactive compound, quercetin

INTRODUCTION

Diabetes is a chronic metabolic disease which is characterized by persistent hyperglycemia frequently followed by absolute or relative insulin secretion deficiency or insulin resistance (1). The International Diabetes Federation, in its report for 2018, lists a number of 425 million people with diabetes. This number is expected to double by 2030 (2).

In vivo and in vitro studies (3, 4, 5) confirm an association between hyperglycemia and diabetic microvascular complications (diabetic cardiomyopathy, retinopathy, nephropathy, neuropathy, angiopathy, tingling and foot pain - diabetic foot), present in any type of diabetes (6). Throughout last few decades researchers are committed to studies of potential mechanisms for the onset and progression of diabetes, in order to develop effective preventive and therapeutic strategies for pathologic aspects resolution of the disease.

Investigations suggest that some bioactive compounds, such as flavonoids, may influence the potential cellular mechanisms. Quercetinot (Quercetin - QE) is a key member of flavonoids family, extracted from many types of vegetable and fruit, such as: blueberries, radish, onion, apple, seed, etc. In large quantities, it is found in the plant buds of *Flos Sophorae* and *Morus alba*, or a white blackberry, which is a subject of numerous studies due to its medicinal properties. In China, black tea is used for tea preparation (7).

Contemporary studies (8, 9) suggest that QE has anti-diabetic, anti-ulcerous, antioxidant and anti-inflammatory biological effects as well as a cardiovascular protective role. However, the main limitation for this flavonoid is its poor oral bioavailability. In plants it exists in form of hydrophilic glycosides which are difficult to absorb by direct pathway. There are two main forms: glycosides and N glycosides, which are studied through cellular analysis and experimental animal models. Recent years QE is popularized as a natural nutritional therapy for diabetes and its complications (10).

This article is a literature overview (in vitro and in vivo studies) related to therapeutic effects of QE on diabetic complications. Also, the molecular action mechanisms of QE are presented, in order to understand its therapeutic properties, which can be applied in the treatment of diabetic complications.

Potential Action Mechanisms of Quercetin on Diabetic Complications

Long-term hyperglycaemia induces increased risk of macro and microvascular complications. Numerous studies (1,4,11) confirm the positive effect of QE for treatment of various diabetic microvascular complications. The therapeutic attributes of QE can be related to prevention of cellular apoptosis, antioxidant defense, reduction of inflammatory mediators and genetic regulation by various transcription factors modulation. (12).

Quercetin and Diabetic Nephropathy

Diabetic nephropathy (DN) is one of the major microvascular complication of diabetes characterized by high incidence, low detection rate, long duration, high treatment costs and high rates of disability and mortality.

In the early stages of diabetes, blood glucose levels increase but the capacity of kidneys to reabsorb glucose from the renal filtrate is inadequate. The glycose is kicked out into urine and increases the urinary osmotic pressure and volume. Albuminuria, present in the progressive phase of diabetes as the consequence of hyperglycemia and glomerular hyperfiltration leads to thickening of the glomerular basal membrane, expansion of mesangium and glomerular sclerosis (13, 14). In addition, serum lipids, such as total cholesterol (TC), triglycerides (TG), and free fatty acid (FFA) can be increased in uncontrolled type 2 diabetes (15).

Excessive energy input exceeds the capacity of fatt tissue storage, resulting in energy accumulation excess in form of fat (16.17). Renal lipid accumulation and increased oxidative stress can lead to renal dysfunction (16.18).

The longstanding abnormal glycose level is one of the etiological factors of DN development and its transformation into chronic kidney disease. Persistent hyperglycaemia induces renal cellular hypertrophy, proliferation, and renal interstitial fibrosis. Pathological changes include glomerulosclerosis, interstitial fibrosis, and tubular atrophy due to mesangial expansion and thickening of the glomerular basal membranes which can finally lead to renal insufficiency (19). On the other hand, chronic hyperglycemia in diabetes induces non-enzymatic reactions between reducing sugars and free amines of proteins and lipids, thereby accelerating the formation of advanced glycation end products (AGEs) in the glomerulas and renal tubules (20).

Animal experiments show that the kidney structure and function has been revitalized to varying degrees when diabetes was treated with QE. QE can correct the shape of the kidneys, which has previously been altered due to hyperglycemia. Possible mechanisms through which QE postpones renal hypertrophy are: inhibition of protein kinase C (PKC) activity, reduction of

transforming growth factor (TGF-β1) expression and reduction of extracellular matrix formation (21).

Chenet at al. (7) determine that QE alleviates renal pathological changes, postpones DN progression, improves glycolipids metabolism, and reduces the urine protein and 24h kidney ubikvityn in type 2 diabetic mice. Also, these investigators have found that QE can prevent oxidative stress caused by diabetes as well as the damage of deoxyribonucleic acid (DNA), both associated with reduced levels of nitric oxide synthetase (NOS) in the renal tissue (7).

Recent study of Srinivasan and coworkers (8) conducted on mice with type 1diabetes, notifies that QE may reduce blood glucose levels when treated with streptozotycin (STZ). Gembardt and coworkers (22) suggest that the key role in the onset of renal fibrosis and DN has the activation of sphingosin kinase-1(SphK1-S1P) signal induced by hyperglycemia and oxidative stress. However, the involvement of QE in protection of the kidney function and prevention of diabetic renal fibrosis through SphK1-S1P signaling should be a subject of further investigation. The treatment of diabetic nephropathy covers multiple risk factors, and the goal is to prevent the development or disease progression and reduce the risk of cardiovascular disorders (23).

Quercetin and Diabetic Retinopathy

Diabetic retinopathy (DR) is a severe complication of diabetes and one of the main causes of eyesight damage and blindness in adults. There are 150 million people with this diabetic complication worldwide. DR is a result of microvascular complications in the retina, which may progress to vision loss as a result of malnutrition and degeneration of retinal cells (5). The progression of the disease is characterized by capillary occlusion, bleeding, and new blood vessels formation (3). The conducted investigations do not fully explain the pathogenesis of diabetic retinopathy. Effective clinical treatment is lacking (24). The up-to-date DR treatment includes drug therapy, laser photocoagulation, treatment with anti-vascular endothelial growth factor (anti-VEGF), intra-vitreous steroids, and systemic blood sugar control. Oxidative stress, inflammation, neurodegeneration and damaged vascularity of retina are dominant disorders in DR (25).

The therapeutic effects of QE on diabetic retinopathy have been demonstrated in a recent study (26) conducted in adult male STZ-induced CD mice. QE was administered in a dose (150 mg / kg) per day, through gastric perfusion, over a period of 20 weeks. It was found that QE alleviates the degree

of retinopathy by reducing the expressive levels of monocytic hemoattractant protein-1 (MCP-1), matrix metalloproteinase-9 (MMP-9) and vascular endothelial growth factor (VEGF).

In vitro studies on human retina by A.A. Thomas et al (27) demonstrate the role of QE in cellular cell proliferation inhibition induced by high levels of glycosis through reducing the expression of VEGF in endothelial cells.

Kumar at al. (28) evaluate the neuro-retinal protective effects of QE in STZ-induced retinopathy in mice. It has been proven that QE reduces the oxidative stress and inhibits neuronal apoptosis, resulting in effective protection against retinal neurodegeneration caused by diabetes. These authors suggest that QE can be a suitable biological therapeutic agent for diabetic retinopathy by preventing neurodegeneration.

Quercetin and Diabetic Neurodegenerative Diseases

Diabetic neurodegenerative diseases include cognitive and memory deficits, stroke and Parkinson's disease, as a result of changes in the central nervous system. These diseases are caused by chronic hyperglycaemia, oxidative stress, and cholinergic dysfunction. Recently, there has been a growing interest in development of a new plant therapeutic agent for the treatment of diabetic neurodegenerative diseases (29).

Research of Ekimova at al. (30) carried out on experimental animals prove that anti-diabetic, antioxidant and acetylcholine esterase (AChE) inhibitors have beneficial effects on diabetic neurodegenerative disease, particularly on memory damage and cognitive dysfunction (30). Studies on various in vivo models (9.30, 31) confirm the neuro-protective effects of QE. However, the basic mechanisms are not fully illuminated yet.

The team of Sundstromet et al (31) examines the meliorative effect of QE on memory dysfunction in CTC- diabetes induced mice with administration of 5-20 mg / kg QE twice/ daily for a period of 30 days. Treatment with QE prevents fluctuations of blood glucose level and body weight (31).

Researchers Zorrilla-Zubileteet at al. (9) use STZ to induce diabetes and memory damage in male mice. The aim of study is focused on the protective effect of QE by intragastric administration of 2.5, 5 and 10 mg / kg, over 20 days. The metabolism in the brain is changed, with a marked decrease of adenosine triphosphate (ATP) content. QE significantly reduces cerebral blood flow and blood glucose levels, preventing memory loss, and at the same time, it increased the activity of antioxidant enzymes (9).

Quercetin and Other Diabetic Complications

Diabetic cardiomyopathy is a disease characterized by high incidence rate and mortality (1). This form of cardiomyopathy is associated with insulin resistance, changes in mitochondria and endoplasmic reticulum, hyperinsulinemia which results in hypertension and coronary disease (1). The effect of QE on diabetic cardiomyopathy is rarely investigated.

Li at al. (11) in their research determine a decrease of cardiomycytic damage in STZ-induced type II diabetes adult mice, treated with QE (5, 20, and 80 mg / kg / day orally) for 4 weeks, with and without glibenclamide.

Depression is also a severe diabetic complication that is prevalent in diabetics and weakens the regulation of blood glucose (12). The identification and effective treatment of co-morbid depression is treated as a crucial component in the clinical care of diabetics. Anjaneyulu et al. (32) suggest that administration of QE (50 and 100 mg / kg) has an antidepressant effect in STZ-induced diabetic mice (32).

CONSLUSION

Diabetes and the complications it causes is a complex disorder with a high prevalence and severe social and economic repercussions. The inefficiency of current therapeutic agents in the management of long-term complications of diabetes initiates a search for safe and effective approaches. Therapeutic potential of various bioactive compounds, such as quercetin, resveratrol, curcumin and lycopene, attract the attention of researchers. The last decade abounds with studies (in vitro and in vivo) that investigate the effects of quercetin for treatment of diabetes and its complications.

In this article, studies of different experimental designs and doses of quercetin are presented. The data published confirm the anti-diabetic, anti-ulcerous, antioxidant, antiinflammatory and cardiovasculo-protective effects of quercetin.

Animal models provide many useful informations about the bioavailability of quercetin in vivo. Additional carefully designed clinical trials are necessary in order to provide authentic evidence for the potential therapeutic use of bioactive compounds, such as quercetine, in the treatment of diabetes and its complications.

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