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REVIEW ARTICLE

The Role of Quercetin in Diabetes Mellitus

Beyza Mendes[1]*, Ayşe Gunes-Bayir[1]

[1]Department of Nutrition and Dietetics, Faculty of Health Sciences, Bezmialem Vakıf University, 34065 Istanbul, Türkiye.

***Corresponding author:** Lecturer Dietetian Beyza Mendes, Department of Nutrition and Dietetics, Faculty of Health Sciences, Bezmialem Vakif University, 34065 Istanbul, Türkiye. E-mail: bmendes@bezmialem.edu.tr, ORCID ID: 0000-0002-4182-1273.

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ABSTRACT

Natural compounds obtained from vegetables, fruits or medicinal plants have been widely used in recent years due to their therapeutic and preventive properties of chronic diseases. Quercetin is a type of flavonoid which was found as plant pigment in most fruits and vegetables. In studies, its various pharmacological activities in hypoglycemia, inflammation, and cancer as well as its protective effects on cardiovascular diseases, Type 2 Diabetes Mellitus (T2DM) and hyperlipidemia have been shown. Quercetin regulates blood glucose due to different metabolic pathways including impaired glucose tolerance in T2DM, stimulation of insulin secretion, and improvement in the insulin resistance. However, there is a need for further clinical studies on diabetes mellitus. In this review, the role of quercetin in diabetes mellitus is discussed in the light of in vitro and in vivo studies.

Keywords: Diabetes mellitus, quercetin, flavonoid, insulin regulation

INTRODUCTION

Diabetes Mellitus (DM) is a disease characterized by the hyperglycemia which is associated with abnormalities in carbohydrate, protein, and lipid metabolism. It is caused by a decrease or deficiency in secretion insulin (1). Diabetes can cause acute and chronic complications such as diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, and diabetic foot (2). Therefore, it is important to keep the blood sugar level in balance to prevent diabetic complications and improve the health of patients (1). A number of complementary and alternative medicine methods been used more and more to effectively to control diabetic complications (3).

Natural compounds obtained from medicinal plants are widely used in the prevention and/or treatment of chronic diseases due to their different properties. Flavonoids are an important phytochemical compound, and have been shown therapeutic effects on metabolic diseases in studies (4). Quercetin is an important flavonoid found in fruits and vegetables. It has various activities such as hypoglycemic, hypolipidemic, protective against cardiovascular and liver diseases, anti-inflammatory, and anti-cancer, as well as beneficial effects on diseases such as T2DM (5). Therefore, quercetin and its derivatives are found mainly in the Western diet, and people can benefit from its protective effects only by taking it through diet or as a food supplement (4). However, some studies have shown that quercetin has a poor aqueous solubility, poor permeability, instability in stomach and intestines, short biological half-life, and extensive first past metabolism in the liver before reaching the systemic circulation (6). Based on poor oral bioavailability of quercetin is low, which can limit its therapeutic application. Nanoformulation is a promising approach to solving problems with the bioavailability of quercetin. Recently, it was reported that quercetin-loaded nanomicelles could improve antidiabetic activity of quercetin (7, 8).

This review was aimed to research the efficacy of quercetin in the treatment and prevention of diabetes mellitus. In this context, quercetin will be described and its effects on human T2DM including metabolic pathways will be discussed according to scientific literature findings.

General knowledge about quercetin

Flavonoids are a super family of phytochemicals and mainly found in the form of glycosides in numerous plants such as edible leafy vegetables, many fruits, onions and tubers, herbs, spices, tea, as well as wine (5, 9). On the other hand, quercetin has a high amount of flavonoid molecules. It is especially used in the treatment of diseases in traditional Chinese Medicine. The main core of quercetin is phenyl benzoyl ketone consisting of 2 benzene rings and connected by an oxygen-containing pyrene ring (10). Dietary quercetin is mostly found in the form of glycosides in which one or more sugar groups are attached to phenolic groups by a glycosidic bond. It combines with glucose, rhamnose, mannose, xylose, and some oligosaccharides (11). The amount of quercetin contained in foods is affected by growing conditions. Although most of the daily flavonoid intake is quercetin, men and elderly individuals consume it at lower levels (5).

Quercetin's Role in Diabetes Mellitus

Regulatory effects on glycemia

Quercetin inhibits α-glucosidase activity by increasing insulin sensitivity, promoting glycogen synthesis. It also helps lower blood sugar by improving insulin resistance (12). In streptozotocin (STZ), alloxan, and STZ-nicotinamide-induced rat models, various doses of quercetin was administered orally. It was found decreased blood glucose, hemoglobin, and glycosylated hemoglobin levels (8). Quercetin can reduce pancreatic islet cell insufficiency of langerhans, and increase insulin secretion by β-cells. It can also prevent the development of diabetes mellitus by reducing oxidative stress (13).

Effect on insulin release from β-cells

Diabetes patients usually have decreased insulin secretion as a result of dysfunction in pancreatic β cells (8). Quercetin stimulates pancreatic β-cell proliferation. It helps to increase insulin sensitivity by improving glucose metabolism and insulin secretion. In addition, studies have been reported that quercetin is an inhibitor of α-glucosidase and α-amylase (14). Also, in a study on quercetin and T2DM, it has been shown to have a protective effect in the development of T2DM (9). Quercetin can induce decreasing pancreatic islet cell of langerhans failure in diabetic patients and promote insulin secretion by β-cells. It can also prevent a reducing oxidative stress in diabetic patients (8). In another study, it was observed that diabetic rats treated with 120 mg/kg/day oral quercetin for 8 weeks significantly decreased plasma volumes, excess plasma insulin and significantly increased insulin during oral glucose tolerance testing. Overweight or obese women consumed 1000 mg of quercetin daily for 12 weeks significantly improved insulin resistance in the quercetin group. However, changes in insulin resistance values were not statistically significant when compared with the placebo group (13).

Enhancement of glucose uptake in tissues and organs

Quercetin stimulates Akt and glucose transporter type 4 receptors in the cell membrane by activating adenosine monophosphate kinase (AMPK) in skeletal muscles (15). Glucose utilization enters the cell via (GLUTs) which the blood glucose level is regulated (8, 15). Antidiabetic effect of quercetin includes stimulation of glucose uptake insulin-dependent mechanism glucose transporters via the mitogen-activated protein kinase (MAPK) Stimulation of the mechanism in skeletal muscles resulted in glucose transporter type 4 (GLUT4) displacement (5). It increases basal glucose uptake through an insulin-independent mechanism involving the activation of adenosine monophosphate-activated protein kinase (AMPK) in skeletal muscle cells. At the same time, AMPK activation leads to the suppression of hepatic gluconeogenesis and the lowering of fasting blood glucose in diabetic patients (16). This role of MAPK differs from its function in the liver, where it decreases glucose production mostly through the down-regulation of essential gluconeogenesis enzymes (5). According to the results of cytological experiments, it was found that quercetin intervention significantly diminish blood glucose levels while GLUT4 expression and glucose uptake of skeletal muscle cells rise by stimulating AMPK (8).

Improvement in insulin resistance

Insulin resistance (IR) is the occurrence of hyperglycemia as a result of decreased glucose uptake and the use of insulin (17). Quercetin protects pancreatic beta cells from oxidative stress and improves insulin secretion by increasing the antioxidant defense status of cells (15). In an experimental study, the hypoglycemic activities of quercetin were investigated in diabetic male Wistar rats. They were fed a high-fat diet for 3 weeks, and were applicated to induce diabetes mellitus 50 μg/kg streptozotocin intraperitoneally. As a result of the study, quercetin increases Sirtuin 1 (SIRT1) protein expression in the duodenal mucosa. It was also found that it activates AMP-dependent protein kinase (AMPK) and decreases glucose production by increasing insulin sensitivity in hepatocytes (8).

Inhibition of α-glucosidase

Quercetin is an inhibitor of α-glucosidase secreted from the pancreas and salivary glands, which is necessary for the digestion of carbohydrates (18, 19). Hyperglycemia occurs after meals due to increased α-glucosidase and α-amylase activities in diabetic patients. Therefore, for the inhibition of α-amylase and α-glucosidases, a diet containing mixed carbohydrates may help lower blood sugar levels (20). As a result of an in vitro study to see the inhibitory activities of quercetin and its glycoside derivatives against α-glucosidases, it was shown that it has a high oxygen radical absorbance capacity (ORAC) value and inhibits α-glucosidase activity (8).

Protective Effects of Quercetin on Diabetes Complications

Several studies on quercetin have shown that it has positive effects in the treatment of diabetic microvascular complications. Diabetic nephropathy (DN) is one of the most important causes of chronic kidney disease and its incidence is increasing all over the world (21). In a DN study, streptozotocin was used to induce diabetes (100 mg/kg/day, 3 days) in male apoE−/− mice (8 weeks old). After 6 weeks, mice were randomized to receive untreated non-diabetic soybean oil or oral quercetin. As a result, this treatment significantly reduced polyuria and significantly normalized glycemia and hypertriglyceridemia (22).

Diabetic retinopathy (DR) is one of the serious complications of DM, causing blindness and visual impairment in adults (23). A work examined the retinal neuroprotective effects of quercetin on streptozotocin-induced retinopathy in rats was found to provide significant protection against diabetes-induced retinal neurodegeneration. Quercetin affects through reduced oxidative stress-mediated damage to proteins and nucleic acids and reduced NF-κB-mediated inflammation. It protects against neuronal damage in the diabetic retina by inhibiting apoptosis of neurons and improving the levels of neurotrophic factors in in vitro and in vivo studies, but it has not been fully elucidated yet (8). Therefore, it may be a suitable therapeutic agent to prevent neurodegeneration in DR. On the other hand, quercetin supplementation given diabetic rats resulted in decreasing oxidative stress due to low glutathione level in the diabetic retina (24).

CONCLUSION

Drugs are used in the treatment of diabetes mellitus, which is one of the most common chronic diseases in the world. In addition to these, compounds of medicinal plants are in great interest. As a result of studies, it has been seen that quercetin has positive effects on diabetes mellitus due to its strong antioxidant property. Especially, it can provide the regulation of insulin secretion, increasing glucose uptake in tissues and organs, improvement in insulin resistance. Quercetin has also protective effects on complications of diabetes mellitus. Further clinical trials are needed by a quercetin supplementation with high bioavailability which is to decide efficient supplement for the complementary therapy and the management of diabetes mellitus.

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