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Review article

Mechanisms of antidiabetic effects of flavonoid rutin

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ABSTRACT

Several lines of evidence suggest that flavonoids that originated from vegetables and medicinal plants have beneficial effects on diabetes by improving glycemic control, lipid profile, and antioxidant status. Rutin is a flavonoid found in many plants and shows a wide range of biological activities including anti-inflammatory, antioxidant, neuroprotective, nephroprotective, and hepatoprotective effects. In this review, the anti-hyperglycemic property of rutin and its protective effects against the development of diabetic complications are discussed. Proposed mechanisms for the antihyperglycemic effect of rutin include a decrease of carbohydrates absorption from the small intestine, inhibition of tissue gluconeogenesis, an increase of tissue glucose uptake, stimulation of insulin secretion from beta cells, and protecting Langerhans islet against degeneration. Rutin also decreases the formation of sorbitol, reactive oxygen species, advanced glycation end-product precursors, and inflammatory cytokines. These effects are considered to be responsible for the protective effect of rutin against hyperglycemia- and dyslipidemia-induced nephropathy, neuropathy, liver damage, and cardiovascular disorders. Taken together, the results of current experimental studies support the potential of rutin to prevent or treat pathologies associated with diabetes. Well-designed clinical studies are suggested to evaluate advantages and limits of rutin for managing diabetes.

1. Introduction

Diabetes is still one of the major healthcare challenges in the world. It is associated with the increased risk of macrovascular and microvascular abnormalities in various organs such as heart, kidney, retina, and brain [1]. Despite the growing knowledge of the pathophysiology of diabetes, currently available therapeutics only provide the transient antihyperglycemic effect and failed to completely prevent the development of these abnormalities [2,3]. Therefore, search for new antidiabetic agents that can protect the patients against diabetic complications is of great interest.

An increasing line of evidence confirmed that flavonoids originated from vegetables and medicinal plants have beneficial effects on diabetes by improving glycemic control, lipid profile, and antioxidant status [4]. Rutin (vitamin P) is a bioflavonoid (Fig. 1) that is found in many plants particularly *Fagopyrum esculentum*, *Ruta graveolens*, and *Sophora japonica* [5]. A wide range of biological effects including anti-inflammatory, antioxidant, neuroprotective, nephroprotective, and hepatoprotective activities has been reported for this flavonoid [6–10]. In this review, results of experimental studies evaluating the antihyperglycemic property of rutin have been summarized. Also, the mechanisms involved in the antihyperglycemic effect of rutin and in its protective activity against diabetic complications are discussed.

2. Method of literature search

A literature search was performed in the databases Google scholar, Pubmed/Medline, and Scopus from inception to August 2017 using the key terms *rutin*, *flavonoids, diabetes, glucose, lipids*. The references of all papers were checked for cross-references that had not been found in databases search.

3. Effects of rutin on blood glucose and lipids

A summary of experimental studies evaluating antihyperglycemic and hypolipidemic properties of rutin are shown in Table 1. These studies reported antihyperglycemic effect for a wide range of doses of rutin (5–100 mg/kg) and for different routes of administration (oral or intraperitoneal injection). In streptozotocin (STZ) model of type 1 diabetic rats, oral administration of 50 or 100 mg/kg of rutin significantly decreased fasting blood glucose (FBG) and HbA1c levels [11–18]. The antihyperglycemic effect was also observed after intraperitoneal injection of rutin at a dose of 50 mg/kg [19–21]. There are contradictory reports on the effects of doses less than 50 mg/kg of rutin on FBG level in type 1 diabetic animals. While several studies reported that dose of 5–40 mg/kg of rutin reduced FBG level, two studies showed that dose of 10–25 mg/kg had no significant antihyperglycemic effect [20,22–27]. In an animal model of type 2

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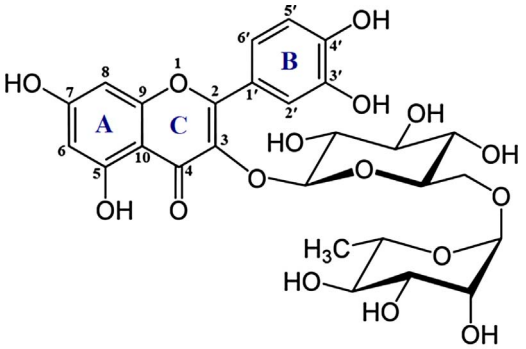

Fig. 1. Chemical structure of flavonoid rutin. The phenolic rings are shown with letters A, B and C.

diabetes, rutin decreased both FBG and non-fasting blood glucose at doses of 5–100 mg/kg [28–30]. Niture et al. [11] reported that the effects of rutin (50 and 100 mg/kg) on FBG and glycosylated hemoglobin were comparable to pioglitazone, a peroxisome proliferator-activated receptor agonist. Jadhav and Puchchakayala [28] observed that among rutin, boswellic acid, ellagic acid, and quercetin, rutin was the most active flavonoid in improving glucose tolerance, reducing FBG, and serum lipids. They found that rutin (100 mg/kg), comparable to glibenclamide (10 mg/kg), decreases plasma glucose both in diabetic and normoglycemic rats [28]. On the other hand, Srinivasan et al. [31] reported that the reducing effect of rutin on blood glucose was only observed in diabetic but not in normal animals. In addition to improving hyperglycemia in established diabetic animals, it has been shown that rutin is able to reduce the development of hyperglycemia (prevalence of diabetes). Srinivasan et al. [31] reported that chronic administration of rutin (200 mg/kg) reduced (30–40%) the prevalence of diabetes in STZ-treated mice.

Many diabetic patients have the elevated levels of triglyceride and low-density lipoprotein (LDL) as well as the reduced level of high-density lipoprotein (HDL). In spite of treatment with statins, fibrates, and other hypolipidemic drugs, a large number of patients do not reach the LDL baseline of < 70 mg/dL [32]. Beneficial effects of medicinal plants and phytochemicals on lipid profile have been confirmed by clinical trials [33–35]. In terms of rutin, several studies reported that it decreases serum level of triglyceride, LDL, and very low-density lipoprotein (VLDL) in experimental models of diabetes [11,14,19,22,28,36]. Also, rutin was able to increase the level of serum HDL in diabetic rats [11,14,19,36]. Current data regarding the effect of rutin on total cholesterol (TC) are conflicting. A number of studies reported a significant decrease in TC level following administration of 50 or 100 mg/kg of rutin to diabetic rats [11,19,28,36]. Ahmed et al. [36] demonstrated that rutin inhibited intestinal cholesterol absorption in a dose-dependent manner. However, other investigators indicated that rutin had no effect on serum TC of diabetic rats. [14,22].

There has not been any well-designed clinical trial employing randomization, placebo control, and double-blind protocol for evaluating antidiabetic effects of rutin. In a non-controlled clinical study, Sattanathan et al. [37] administrated rutin tablets (500 mg) for 60 days to 30 diabetic patients. Rutin supplementation significantly decreased FBG and serum LDL level of patients. Although rutin could also increase the level of HDL, however, it failed to decrease triglyceride, TC, and VLDL, and even a moderate increase in the level of triglyceride and VLDL was observed [37]. Therefore, well-designed clinical studies are suggested to evaluate advantages and limits of rutin for managing diabetic dyslipidemia.

4. Antihyperglycemic mechanisms of rutin

Proposed mechanisms for the antihyperglycemic effect of rutin are shown in Fig. 2. It has been shown that rutin reduced glucose absorption from the small intestine by inhibition of α-glucosidases and α-amylase involved in the digestion of carbohydrates [28,36,38,39]. The inhibitory effect of rutin on maltase and glucoamylase activities was less than acarbose, while it showed higher isomaltase inhibitory effect than acarbose [39]. The inhibition of intestinal glucose absorption prevents the sharp rise in the postprandial blood glucose level. The decrease in blood glucose also can be achieved by stimulating the secretion of insulin from beta cells and increasing glucose uptake by tissues. In isolated rat pancreatic islets, rutin was shown to significantly increase the secretion of insulin [36,40]. In rat beta cells, rutin increased the glucose-induced insulin secretion and preserved glucose sensing ability in high glucose condition [41]. Rutin also showed insulin-mimetic role in rat soleus and diaphragm muscles [36,42]. It stimulated glucose transport into muscle through activating the synthesis and translocation of the transporter GLUT-4 [42]. Like insulin signaling pathway, phosphoinositide 3-kinase (PI3K), protein kinase C, and mitogen-activated protein kinase (MAPK) are involved in the intracellular transduction of rutin, leading to a stimulatory effect on tissue glucose uptake [42,43]. Rutin also increases expression of PPARγ, which thereby improves insulin resistance and glucose uptake in skeletal muscle and adipose tissue [36].

Increased rate of gluconeogenesis is believed to be one of the main causes of hyperglycemia in diabetic patients [44]. Insulin inhibits hepatic glucose output predominantly by inhibiting the gene expression of the key gluconeogenic enzymes glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) [45]. Ahmed et al. [36] demonstrated that rutin (50 mg/kg) reduced the activities of liver G6Pase and glycogen phosphorylase. Similarly, Prince and Kamalakkannan [12] showed that treatment with rutin (100 mg/kg) decreased the activity of G6Pase in the liver (31%) and kidney (37%) of diabetic rats. Also, rutin reduced the activity of fructose-1,6-bisphosphatase, another main gluconeogenic enzyme, in the liver (32%), kidney (25%), and muscle (31%). On the other hand, in all these tissues, rutin increased the activity of hexokinase, an enzyme catalyzing glycolysis pathway (reverse of gluconeogenesis) [12,36].

It has been reported that antidiabetic effect of some phytochemicals is mediated through inhibiting beta cell degeneration [46]. Histopathological studies in animal models of diabetes showed that rutin improves the histoarchitecture of Langerhans islets. Treatment of STZ-induced diabetic rats with 50 mg/kg and 100 mg/kg of rutin prevented the pancreas against shrinkage in size and number of the islets [11,12]. Also, it has been shown that rutin suppressed the glucolipotoxicity in rat pancreatic beta cells through activating insulin receptor substrate 2 and AMP-activated protein kinase signaling [41].

5. Effects of rutin on diabetic complications

5.1. Mechanisms of diabetic complications and possible protective effects of rutin

Chronic hyperglycemia and dyslipidemia are associated with several changes in intracellular metabolic pathways which lead to tissue damage and developing diabetic complications. The most known intracellular changes include excessive generation of intracellular reactive oxygen/nitrogen species (ROS/RNS), increase of advanced glycation end-product (AGE) precursors, sorbitol accumulation, rise in the level of diacyl glycerol, decrease of glyceraldehyde-3 phosphate dehydrogenase (GAPDH) activity, and increase of hexosamine pathway activity [47]. Fig. 3 shows protective effects of rutin against hyperglycemia- and dyslipidemia-induced changes in intracellular metabolic pathways.

Excessive generation of AGE precursors results in glycation of