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Review article

Mechanisms of antidiabetic effects of flavonoid rutin

Ahmad Ghorbani

Pharmacological Research Center of Medicinal Plants, Mashhad University of Medical Sciences, Mashhad, Iran

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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

E-mail address: ghorbania@mums.ac.ir.

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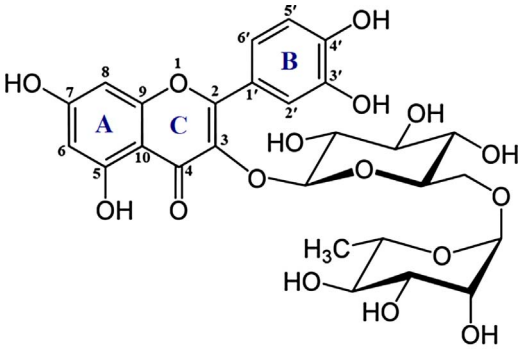

Fig. 1. Chemical structure of flavonoid rutin. The phenolic rings are shown with letters A, B and C.

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

Table 1
Summary of experimental studies evaluated metabolic effects of rutin in diabetes.

No.	Study model	Treatment	Effects	Refs.
1	STZ model of type 1 diabetic rats	Rutin 50 mg/kg (i.p.), once a week for 45 days	↓FBG; ≈Serum insulin; ↓Weight lost; ↓TG; ↓TC; ↓LDL; ↑HDL	[19]
2	STZ and high fat diet-induced diabetic rats	Rutin 50 or 100 mg/kg (oral), daily for 21 days	↓FBG; ↓HbA1c; ↓Weight lost; ↓TG; ↓TC; ↓VLDL; ↑HDL; ↓Histological damage in the pancreas	[11]
3	STZ model of type 1 diabetic rats	Rutin 100 mg/kg (oral), daily for 45 days	↓FBG; ↑Serum insulin; ↓Histological damage in the pancreas	[12,13]
4	STZ model of type 1 diabetic rats	Rutin 8 mg/kg (oral), daily for 12 days	↓FBG; ↓Weight lost; ↓TG; ≈TC	[22]
5	STZ model of type 1 diabetic rats	Rutin 100 mg/kg (oral), daily for 5 weeks	↓FBG; ↑Serum insulin; ≈Weight lost	[16]
6	STZ model of type 1 diabetic rats	Rutin 100 mg/kg (oral), daily for 6 weeks	↓FBG; ↑Serum insulin	[17]
7	STZ model of type 1 diabetic rats	Rutin 100 mg/kg (oral), daily for 45 days	↓FBG; ↑Serum insulin; ↓TG; ≈TC; ↓LDL; ↓VLDL; ↑HDL	[14]
8	STZ model of type 1 diabetic rats	Rutin 100 mg/kg (oral), daily for 5 weeks	↓FBG; ↓Weight lost; ↑Serum insulin	[15]
9	STZ model of type 1 diabetic rats	Rutin 50 mg/kg (oral), daily for 24 weeks	↓FBG; ↓HbA1c; ↓Weight lost	[18]
10	STZ model of type 1 diabetic rats	Rutin 50 mg/kg (i.p.), once a week for 7 weeks	↓FBG; ↑Serum insulin; ↓Weight lost	[21]
11	STZ model of type 1 diabetic rats	Rutin 10–90 mg/kg (oral), daily for 10 weeks	↓FBG	[24]
12	Alloxan combined with fat-induced type 1 diabetes in rats	Rutin 25–100 mg/kg (oral), daily for 6 weeks	↓FBG	[25]
13	STZ model of type 1 diabetic rats	Rutin 40 mg/kg (oral), daily for 28 days	↓FBG	[26]
14	STZ model of type 1 diabetic rats	Rutin 5–50 mg/kg (i.p.), daily for 12 days	↓FBG	[20]
15	Alloxan model of type 1 diabetic rats	Rutin 20 and 40 mg/kg for 57 days	↓FBG	[27]
16	STZ model of type 1 diabetic rats	Rutin 4 mg/kg (i.p.), daily for 7 days	↑Glucose tolerance	[66]
17	STZ model of type 1 diabetic rats	Rutin 100 and 300 mg/kg (oral), daily for 12 weeks	≈FBG; ↓Weight lost; ↓TC; ↓TG	[76]
18	STZ model of type 1 diabetic rats	Diet supplemented with 0.2% rutin-glucose derivative for 30 days	≈FBG; ≈Weight lost; ↓AGE plasma proteins; ↓Glycation of proteins in the muscle and kidney	[53]
19	STZ model of type 1 diabetic rats	Rutin 10 mg/kg (oral), daily for 46 days	≈FBG	[23]
20	STZ-nicotinamide model of type 2 diabetic rats	Rutin 50 mg/kg (oral), daily for 30 days	↓FBG; ↑Glucose tolerance; ↑Serum insulin; ↑Serum C-peptide; ↓Hepatic glycogen content; ↓TG; ↓TC; ↓LDL; ↓VLDL; ↑HDL; ↓Histological damage in the pancreas	[36]
21	STZ-nicotinamide model of type 2 diabetic rats	Rutin 50 or 100 mg/kg (oral), daily for 14 days	↓FBG; ↑Glucose tolerance; ↓TG; ↓TC	[28]
22	STZ model of type 2 diabetic rats	Rutin 5 or 15 mg/kg (oral), daily for 11 days	↓Non-fasting blood glucose	[29]
23	Insulin receptor antagonist-induced hyperglycemic mice	Rutin 25 mg/kg (oral) prior to oral glucose tolerance test	↑Glucose tolerance	[30]

AGE: advanced glycation end-product; FBG: fasting blood glucose; HDL: high-density lipoprotein; i.p.: intraperitoneal injection; LDL: low-density lipoprotein; STZ: streptozotocin; TC: total cholesterol; TG: triglyceride; VLDL: very low-density lipoprotein; ↑: increase; ↓: decrease; ≈: no significant effect.

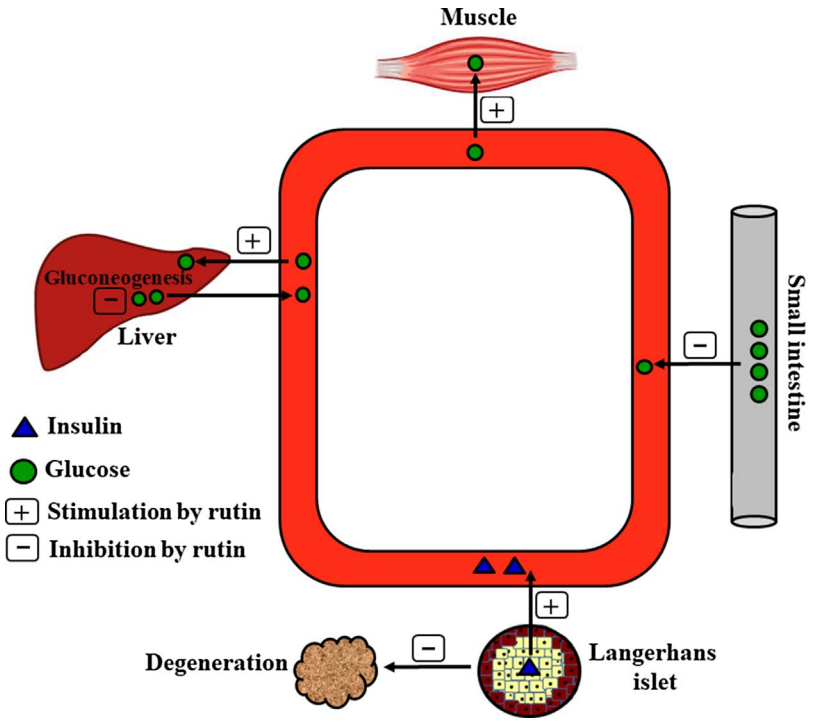

Fig. 2. Schematic overview of the proposed mechanisms for the anti-hyperglycemic effect of rutin. Rutin decreases absorption of carbohydrates from the small intestine, stimulates the secretion of insulin from beta cells, protects Langerhans islet against degeneration, increases glucose uptake by tissues, and inhibits gluconeogenesis in the liver.

intracellular proteins (e.g., proteins involved in the control of gene transcription) and modification of extracellular matrix (ECM) molecules. The AGE precursors also can diffuse out of the cells and modify plasma proteins. These AGE plasma proteins can bind to AGE receptors and thereby trigger the formation of growth factors and inflammatory cytokines, which in turn contribute to vascular pathology [47–49]. Under in vitro conditions, it has been shown that rutin derivatives suppressed the formation of AGE in rat muscle and kidney proteins [50,51]. Akileshwari et al. [52] reported that rutin inhibited the formation of AGE on eye lens proteins. In diabetic rats, a rutin-glucose derivative (dietary G-rutin) could reduce the level of AGE proteins in serum and kidney [53]. Diabetes is associated with the increased content of collagen and hydroxyproline in the extracellular matrix, which because of slow turnover are vulnerable to AGE accumulation. Treatment of diabetic rats with rutin was shown to reduce the content of collagen and hydroxyproline and to increase the activity of matrix

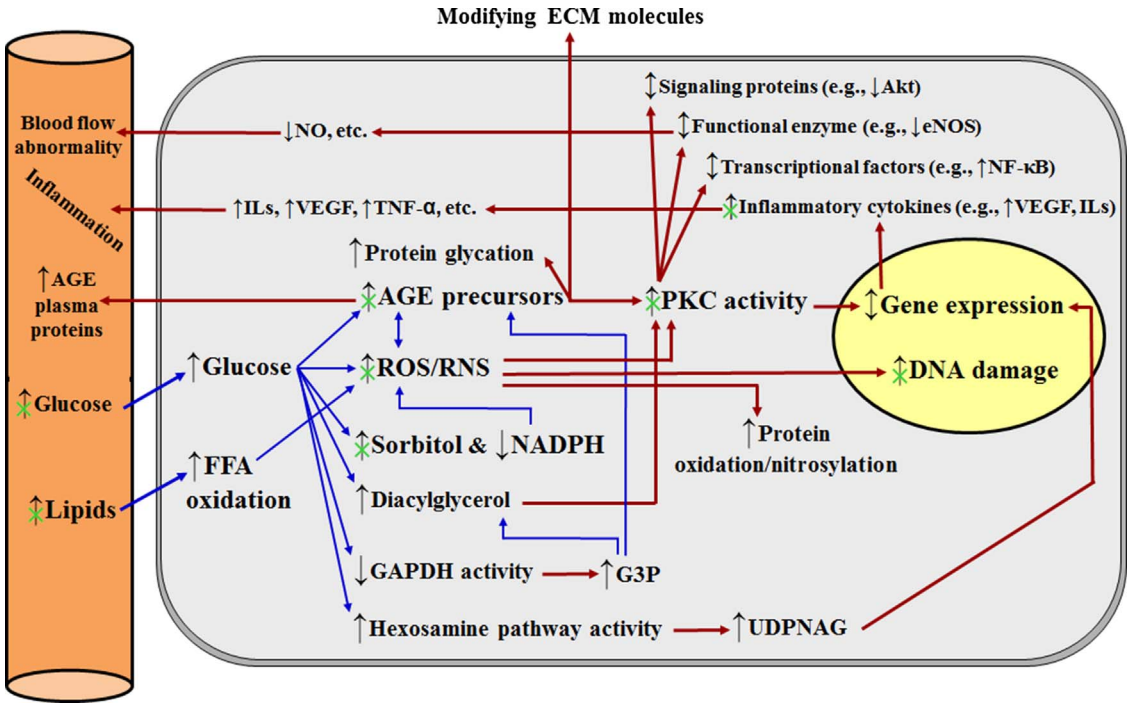

Fig. 3. Schematic overview of the protective mechanisms of rutin against intracellular pathways responsible for diabetic complications. AGE: advanced glycation end-product; eNOS endothelial nitric oxide synthase; FFA: free fatty acid; GAPDH; glyceraldehyde-3 phosphate dehydrogenase; G3P: glyceraldehyde-3-phosphate; ILs: interleukins; NO: nitric oxide; PKC: protein kinase C; ROS/RNS: reactive oxygen/nitrogen species; TNF-α: Tumor necrosis factor-alpha; UDPNAG: uridine diphosphate N-acetyl glucosamine; VEGF: vascular endothelial growth factor; ↑: increase; ↓: decrease; ↕: modulatory effect; ×: inhibitory effect of rutin.

metalloproteinases in the kidney [54].

Hyperglycemia and hyperlipidemia lead to oxidation of intracellular glucose and free fatty acids, which generate excessive ROS/RNS. Also, an increase of intracellular glucose concentration results in increased conversion of glucose to sorbitol (by aldose reductase), with concomitant consumption of NADPH. The decrease of NADPH attenuates regeneration of reduced glutathione, a critical intracellular antioxidant, and therefore increases susceptibility to oxidative stress [47]. Increased production of ROS/RNS disturbs functions of intracellular biomolecules such as proteins, RNA and DNA. In addition, accumulation of ROS and hyperglycemia-induced increase of diacylglycerol activate protein kinase C (PKC), which in turn promotes a variety of metabolic processes in the cytosol and the nucleolus depending on the cell type. For example, in vascular cells, chronic activation of PKC is associated with vascular permeability, ECM expansion, production of inflammatory factors, leukocyte adhesion, changes in vasodilation, and angiogenesis [55]. It has been shown that dietary rutin inhibits aldose reductase and decreases the concentration of sorbitol in erythrocytes under high glucose conditions, indicating the potential of rutin to preserve the intracellular level of NADPH [53,56]. In diabetic animals, administration of rutin improved the antioxidant status in different tissues by increasing non-enzymatic (e.g., reduced glutathione) and enzymatic (e.g., superoxide dismutase and catalase) antioxidants [11,13,22,23]. Rutin like other flavonoids that contain multiple OH substitutions has a considerable effect on scavenging free radicals [7,57]. Analysis of structure-function relationship demonstrates the importance of the B-ring and the 3′-OH and 4′-OH moieties (Fig. 1) in free radicals scavenging effect of rutin [58]. Because of these moieties, rutin has a tendency to give electrons to free radicals, converting them to more stable radical intermediates and inhibiting further free radical reactions [58].

The antioxidant activity of rutin and its inhibitory effect on the AGE formation create the expectation that rutin can interfere with PKC signaling pathways. In fact, several flavonoids such as fisetin, quercetin, and luteolin have been shown to inhibit PKC activity [59]. However, there is still insufficient information on the effect of rutin on this enzyme. Ferriola et al. [60] indicated that rutin had no considerable inhibitory effect on rat brain PKC, while End et al. [61] observed that it inhibited the activity of PKC prepared from the bovine brain. Activation of specific isoforms of PKC as a result of hyperglycemia and hyperlipidemia is one of the responsible elements for the enhanced level of inflammatory cytokines in diabetes [55,62]. It has been shown that treatment of diabetic rats with rutin decreased the level of inflammatory factors (e.g., TNF-α and IL-6) in serum and some tissues including the heart [11,22].

5.2. Complications of diabetes

5.2.1. Effects of rutin on nephropathy

Diabetic nephropathy is a main microvascular complication and represents the major cause of end-stage renal disease. Pathogenetic mechanisms of diabetic nephropathy are complex and involve hyperglycemia-induced metabolic and hemodynamic alterations [63,64]. As mentioned above, hyperglycemia increases AGE formation, induces oxidative stress, stimulates PKC, and enhances the activity of the polyol pathway. Chronic hyperglycemia also results in hemodynamic changes such as shear stress, activation of vasoactive systems, glomerular hyperfiltration, and microalbuminuria [64]. These changes are associated with an increase in the proliferation of mesangial cells, and in the deposition of ECM proteins (e.g., collagen, fibronectin, and laminin), leading to mesangial expansion and glomerular basement membrane thickening [63,64].

Experimental and clinical studies reported that rutin supplementation improves the kidney function of diabetic subjects (Table 2). Hao et al. [24] showed that oral administration of rutin (10–90 mg/kg) for 10 weeks reduced proteinuria and decreased the level of blood urea nitrogen (BUN) and serum creatinine in diabetic rats. Hu et al. [65] showed that 4 weeks treatment with rutin (50 or 100 mg/kg, oral) reduced serum creatinine and BUN concentrations in a rat model of metabolic syndrome. On the other hand, Rauter et al. [66] indicated that intraperitoneal injection of rutin (4 mg/kg, for 7 days) had no effect on serum urea. This might be due to a low dose of rutin, route of administration, and short duration of the study. In a clinical trial of Sattanathan et al. [37] on diabetic patients, rutin supplementation for 60 days significantly decreased the concentrations of serum urea and creatinine, whereas discontinuing the supplementation from 60th day onwards restored the level of these parameters. In agreement with these beneficial effects on the kidney function, experimental studies have shown that rutin decreases oxidative stress, AGE formation, and content of hydroxyproline and collagen in the renal tissue [13,15,24,53,54]. The decrease of oxidative stress was associated with inhibition of lipid peroxidation, reduced level of ROS and oxidized glutathione, increased the level of reduced glutathione and glutathione peroxide, and decreased the activity of superoxide dysmutase in the renal tissue [15]. Also, rutin decreases the level of tissue inhibitors of metalloproteinases and increases the activity of matrix metalloproteinases (MMPs) in the kidney [54]. The MMPs are a family of proteolytic enzymes that play an important role in maintaining the balance between synthesis and degradation of ECM. In diabetes, the expression of MMPs is modulated by increased levels of ROS, AGEs, TGF-β, etc. [67]. The stimulatory effect of rutin on MMPs contributes to decrease of collagen deposition in the ECM of renal tissue [54]. In addition, rutin can suppress the signaling pathway of TGF-β1/Smad, which is known to be involved in the process of ECM accumulation, and thereby prevent renal fibrosis and the mesangial expansion [24]. These findings are consistent with histopathological examinations reporting that rutin improved diabetes-induced histological damage in the kidney [13,24,65].

5.2.2. Effects of rutin on neuropathy

Neuropathy affects more than half of all patients with diabetes and is associated with altered sensory perception (e.g., hyperalgesia, paresthesias, and allodynia), motor neuron dysfunction, and abnormality in autonomic function (e.g., orthostatic hypotension) [47]. Al-Enazi et al. [17] showed that administration of rutin (100 mg/kg) to diabetic rat ameliorated analgesia, hyperalgesia, and motor coordination. Tian et al. [20] reported that treatment of diabetic rats with rutin (25 and 50 mg/kg) inhibited cold allodynia, mechanical hyperalgesia, thermal hyperalgesia, and partially improved nerve conduction velocity. This treatment enhanced the activity of Na^+,K^+-ATPase and reduced the expression of proapoptotic protein caspase-3 in sciatic nerves. Also, rutin was able to reduce pro-inflammatory markers TNF-α, IL-1β, and IL6 in the serum of diabetic rats [17]. In addition, rutin attenuated neuroinflammation (reducing NF-κB, IL-6, and TNF-α) and oxidative stress (reducing ROS generation and lipid peroxidation) in peripheral nerves, which might contribute to its favorable effects on neuropathy [17,20]. Although the structure-activity relationship of rutin to its neuroprotective mechanisms is not fully understood, it appears that the 2,3-double bond and the 4-oxo group in the C ring of rutin are related to its neuroprotective action [68].

5.2.3. Effects of rutin on diabetic liver damage

Diabetes is considered as a risk factor for chronic liver disease and progression of non-alcoholic steatohepatitis to cirrhosis [69]. Patients with diabetes often show a higher incidence of abnormalities in the liver function tests than non-diabetic individuals [70]. Also, it has been reported that diabetic complications (e.g., neuropathy and retinopathy) are associated with the activities of liver enzymes independent of body mass index, alcohol intake, HbA1c and serum lipids [71]. One of the biochemical triggers for diabetic liver damage is oxidative stress, which is characterized by the increased level of free radicals and the reduced activity of antioxidant enzymes (catalase, superoxide dismutase, and glutathione peroxidase) in hepatocytes [72,73].

Table 2
Protective effects of rutin on organs/systems that are highly vulnerable to diabetic damages.

Organ/System	Study model	Treatment	Effects	Refs.
Kidney	STZ model of type 1 diabetic rats	Rutin 100 mg/kg (oral), daily for 45 days	↓Oxidative stress in the renal tissue; ↓Histological damage in the kidney	[13]
	STZ model of type 1 diabetic rats	Rutin 10–90 mg/kg (oral), daily for 10 weeks	↓Proteinury; ↓BUN; ↓Serum creatinine; ↓Oxidative stress in the renal cortex; ↓AGE level in the renal cortex; ↓Histological damage in the kidney	[24]
	STZ model of type 1 diabetic rats	Rutin 100 mg/kg (oral), daily for 45 days	↓Renal hydroxyproline, collagen, and TIMPs content; ↑MMPs activity	[54]
	STZ model of type 1 diabetic rats	Rutin 100 mg/kg (oral), daily for 5 weeks	↓Oxidative stress in the renal tissue	[15]
	STZ model of type 1 diabetic rats	Diet supplemented with 0.2% rutin-glucose derivative for 30 days	↓Oxidative stress in the renal tissue; ↓AGE and glycated proteins in the kidney	[53]
	STZ model of type 1 diabetic rats	Rutin 4 mg/kg (i.p.), daily for 7 days	≈Serum urea	[66]
	fructose-induced metabolic syndrome in rats	Rutin 50 or 100 mg/kg (oral), daily for 4 weeks	↓Serum creatinine; ↓BUN; ↓Serum uric acid; ↓Histological damage in the kidney	[65]
Nervous system	STZ model of type 1 diabetic rats	Rutin 100 mg/kg (oral), daily for 45 days	↓Oxidative stress in the brain; ↓Brain edema	[13]
	STZ model of type 1 diabetic rats	Rutin 5–50 mg/kg (i.p.), daily for 12 days	↓Mechanical and heat hyperalgesia, ↓Cold allodynia; ↑Nerve conduction velocities; ↑Na^+,K^+-ATPase activity and ↓Oxidative stress in sciatic nerve; ↓Neuroinflammation in dorsal root ganglions	[20]
	STZ model of type 1 diabetic rats	Rutin 100 mg/kg (oral), daily for 6 weeks	↑Motor coordination; ↓Serum inflammatory cytokines; ↓Oxidative stress in sciatic nerve	[17]
	STZ model of type 1 diabetic rats	Rutin 5–50 mg/kg (i.p.), daily for 12 days	↓Oxidative stress and apoptosis in the retina; ↑Neurotrophic factors (BDNF and NGF) in the retina	[16]
Liver	STZ and high fat diet-induced diabetic rats	Rutin 50 or 100 mg/kg (oral), daily for 21 days	↓Oxidative stress in the liver	[11]
	STZ model of type 1 diabetic rats	Rutin 50 mg/kg (i.p.), once a week for 45 days	↓ALT, AST, and LDH in the serum and liver	[19]
	STZ model of type 1 diabetic rats	Rutin 100 mg/kg (oral), daily for 45 days	↓Oxidative stress in the liver; ↓Histological damage in the liver	[13]
	Alloxan combined with fat-induced type 1 diabetes in rats	Rutin 25–100 mg/kg (oral), daily for 6 weeks	↓Total bilirubin and ALT in the serum; ↓Histological damage of hepatocytes	[25]
	STZ model of type 1 diabetic rats	Rutin 4 mg/kg (i.p.), daily for 7 days	≈AST; ≈ALT	[66]
	STZ-nicotinamide model of type 2 diabetic rats	Rutin 50 mg/kg (oral), daily for 30 days	↓Oxidative stress in the liver	[36]
Cardiovascular system	STZ model of type 1 diabetic rats	Rutin 50 mg/kg (oral), daily for 24 weeks	↓Oxidative stress in the heart; ↓Expression of TNF-α in the heart; ↓C-reactive protein and brain natriuretic peptide in the heart; ↓Histological damage in the heart	[18]
	STZ model of type 1 diabetic rats	Rutin 8 mg/kg (oral), daily for 12 days	↓Serum CK-MB, LDH and AST; ↓Oxidative stress, inflammation and apoptosis in the heart	[22]
	STZ model of type 1 diabetic rats	Rutin 100 and 300 mg/kg (oral), daily for 12 weeks	Improving echocardiographic parameters (e.g.,↑Ejection fraction); ↓Myocardial fructose; ↓Histological damage in the heart	[76]
	Ischemia-reperfusion-induced myocardial infarction in STZ model of type 1 diabetic rats	Rutin 5 and 10 mg/kg (i.p.), 10 min before reperfusion	↓Oxidative stress in the serum and heart; ↓Myocardial infarct size	[77,78]
	STZ model of type 1 diabetic rats	Rutin 50 mg/kg (i.p.), once a week for 7 weeks	Improving echocardiographic parameters (e.g.,↓Left ventricle hypertrophy); ↑Myocardial intrinsic contractile	[21]
	STZ model of type 1 diabetic rats	Rutin 40 mg/kg (oral), daily for 28 days	↓Myocardial damage; ↓Collagen content and tissue transglutaminase in the heart; ↓AST; ≈CK; ≈CK-MB; ≈LDH	[26]
	STZ model of type 1 diabetic rats	Rutin 50 mg/kg (i.p.), once a week for 45 days	↓ALT, AST, and LDH in the serum and heart	[19]

AGE: advanced glycation end-product; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; BDNF: brain-derived neurotrophic factor; CK: creatine kinase; CK-MB: creatine kinase-MB; i.p.: intraperitoneal injection; LDH: lactate dehydrogenase; MMPs: matrix metalloproteinases; NGF: nerve growth factor; STZ: streptozotocin; TIMPs: tissue inhibitors of metalloproteinase; ↑: increase; ↓: decrease; ≈: no significant effect.

It has been reported that treatment with rutin (50 and 100 mg/kg) could improve the antioxidant status of the liver through increasing the levels of glutathione peroxidase, catalase, and superoxide dismutase [11,13,36]. Also, rutin decreased the levels of liver enzymes in the serum and improved histological injury of hepatocytes [13,19,25]. In experimental studies, the effect of rutin on liver enzymes was seen at doses of 25–100 mg/kg after 7 weeks administration, while a dose of 4 mg/kg was ineffective [19,25,36]. Among rutin, boswellic acid, ellagic acid, and quercetin, rutin was the most effective flavonoid in reducing ALT and AST activities [28]. In the clinical study of Sattanathan et al. [37], rutin supplementation (500 mg, for 60 days) significantly decreased serum alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase in diabetic patients.

5.2.4. Effects of rutin on cardiovascular diseases

Patients with diabetes mellitus have increased the risk of cardiomyopathy, atherosclerosis, and post-myocardial infarction death compared to those without diabetes [74]. Hyperglycemia- and hyperlipidemia-induced oxidative stress activate several pathogenic pathways in cardiomyocytes and vessels through stimulating proatherogenic transcription factors (e.g., forkhead box O), overexpressing the nuclear receptor PPARα, reducing the metabolic capacity of the mitochondrial ATP synthesis, increasing post-translational protein modifications (e.g., phosphorylation of ryanodine receptors and downregulation of Ca^{++}-ATPase transcription), etc. [75].

In several studies, cardioprotective effects of rutin have been demonstrated in animal models of diabetic cardiac injury. Echocardiographic observations showed that rutin improved parameters of systolic and diastolic functions (e.g., improving ejection fraction) and prevents cardiac remodeling (e.g., left ventricle hypertrophy, left ventricle dilation, left atrium dilation, and septal wall thickness) in STZ model of diabetic rats [21,76]. In left ventricular papillary muscles isolated from diabetic rats, rutin improved myocardial intrinsic contractile function [21]. In diabetic rats subjected to ischemia/reperfusion-induced myocardial infarction, rutin (5 and 10 mg/kg) improved ECG parameters (heart rate, and QRS and QT intervals) and significantly diminished the infarct size. These effects were accompanied by enhanced antioxidant enzymes superoxide dismutase and catalase [77,78]. Similarly, in other works, rutin was shown to decrease myocardial necrosis, oxidative stress, and inflammation in the heart of the diabetic rats [18,22,26]. A number of studies indicated that rutin induced better cardioprotection (e.g., reducing myocardial necrosis) compared to quercetin [76,77]. This might be due to a sugar moiety on the chemical structure of rutin, which give rise to better pharmacological activity compared to quercetin [79].

5.2.5. Effects of rutin on other diabetic complications

Recent experimental works suggest the benefits of rutin in the treatment of other complications associated with diabetes such as gastropathy, retinopathy, and sexual abnormalities [16,23,27,80]. In alloxan-induced diabetic rats, rutin improved the decreased gastric emptying and intestinal transit time [27]. In diabetic rat retina, rutin increased intracellular antioxidant glutathione, inhibited lipid peroxidation, decreased the level of proapoptotic protein caspase-3 and enhanced the level of anti-apoptotic protein Bcl-2. Also, rutin treatment showed neurotrophic support as it could increase the levels of nerve growth factor, brain-derived neurotrophic factor [16]. In addition, rutin was shown to scavenge free-radicals and inhibit protein glycation in goat eye lens [52]. Finally, it has been reported that treatment with rutin improved diabetic-induced alterations in sexual behavior and sperm parameters (count, viability, motility) of diabetic rats. It also reduced serum pro-inflammatory markers (IL- 1β, IL- 6, and TNF-α), testicular oxidative stress, and histopathological damage in testicular tissues in these animals [23,80].

6. Conclusion

Results of current studies support the beneficial effects of rutin on glycemic status, lipid profile, and diabetes associated microvascular and macrovascular complications. At least twenty experimental works and one clinical study have shown that rutin improves glycemic status in diabetes. The mechanisms proposed for this effect include inhibition of intestinal carbohydrate absorption, a decrease of gluconeogenesis, an increase of tissue glucose uptake, stimulation of pancreatic insulin secretion, and protecting Langerhans islet against degeneration. Considering the negative relationship between risk of diabetic complications and control of blood glucose and lipids, rutin can be recommended as a dietary supplement for prevention of diabetes complication. Further well-designed clinical studies are suggested to evaluate advantages and limits of rutin for managing diabetes.

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