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The Therapeutic Potential of Rutin for Diabetes: An Update

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Abstract: Diabetes and its major risk factor, obesity, have become a world-wide epidemic and cause of suffering for millions of people. There is still no drug of cure for diabetes and the currently available drugs suffer from a number of limitations either due to side effects and/or loss of efficacy during prolonged use. Rutin is one of the most abundant polyphenolic compounds belonging to the flavonoid class. In the present communication, its therapeutic potential for diabetes is critically analysed by reviewing its effect on the various targets of diabetes. The multifunctional nature of rutin including action *via* antioxidant, anti-inflammatory, organoprotection, etc., mechanisms is outlined through review of evidences from *in vitro* and *in vivo* studies.

Keywords: Rutin, diabetes, anti-inflammatory, antioxidant, organ protection, multifunctional compound.

INTRODUCTION

Hyperglycaemia associated to the metabolic disorder, diabetes (diabetes mellitus), results from either deficiency in insulin secretion and/or resistance to insulin. In type-1 diabetes (T1D), the underlying insulin deficiency is caused by autoimmune-mediated destruction of pancreatic β-cells while type-2 diabetes (T2D) mainly results from insulin resistance that may also be associated with impaired insulin secretion and β-cell death. The worldwide diabetics figure is now estimated to be 347 million of which about 90% are of T2D [1]. With the incidence of the disease currently increasing at alarming epidemic proportion, the projected worldwide diabetics case by the year 2030 is about 552 million [2]. It still remains the case that there is no drug of cure for diabetes and the currently available medications have serious drawbacks either due to side effects and/or loss of efficacy during prolonged use. There is therefore a growing urgent need to discover new drugs including those from natural sources that are commonly available in fruits and vegetables and/or those considered relatively safe [3].

Quercetin-3-*O*-rutinoside, commonly known as rutin, is a flavonoid glycoside with a structural composition of a quercetin aglycone and rutinose sugar units (Fig. **1**). Numerous plant serials, leaves, fruits and other parts are known to contain rutin in abundance. Due to the phenolic hydroxyl groups and particularly the catecholic functional moiety, rutin possesses potent antioxidant activity that is often utilized as a reference standard in bioassay studies [4]. Rutin has also shown to display numerous pharmacological activities including anti-inflammatory [5-7], anti-alzheimer's [8, 9], anti-obesity [10], cytotoxicity in cancer cells [11], hepatoprotective [12] and neuroprotective [13-15] effects. Owing to its reputed health benefits, rutin tablets and many other formulations are now widely available to the public as

health supplements. In this communication, the antidiabetic potential of rutin is reviewed through appraisal of recent literature in the field.

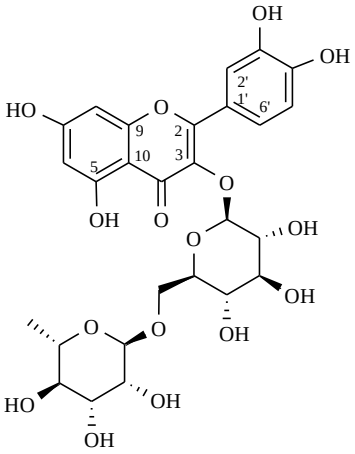

Fig. (1). Structure of Rutin. Notice the rutinose sugar is attached at position-3 of the quercetin flavonoid skeleton through *O*-glycosidic linkage.

EVIDENCE FROM *IN VIVO* STUDIES

Streptozotocin (STZ) is toxic to insulin-secreting pancreatic β cells and hence routinely used as an experimental agent to induce the onset of diabetes in animals. A single dose injection (e.g. intra peritoneal) of 45-100 mg/kg dose of STZ in adult mice or rats results in pancreas swelling leading to degeneration of Langerhans islet β cells coupled with characteristic metabolic abnormalities of diabetes mellitus in 2–4 days. Using this model, the antidiabetic potential of drugs is often assessed by introducing the drugs and measurement of glucose level along with other metabolic parameters. Daily oral administration of 2 and 4 mg/kg of rutin for 15 days in rats have been shown to normalize blood glucose levels and serum biochemical parameters in STZ-induced diabetes [16]. In a seven day trial experiment, Rauter *et al.* [17] have also shown that rutin lowers the blood glucose level of diabetic animals along with improvement in glucose tolerance and protection of the liver and kidneys against STZ-induced damage. Oral administration of a larger dose (100 mg/kg) for 45 days

has also protected the STZ-induced kidney damage as normalisation of the hydroxyproline and collagen content, activity of matrix metalloproteinases and tissue inhibitors of metalloproteinases in the kidney were observed [18]. Similar experiments by others [19-21] not only shown rutin to decrease plasma glucose but also to increase insulin levels along with the restoration of glycogen content and the activities of carbohydrate metabolic enzymes. Expansion of the islets, decreased fatty infiltrate of the islets and glycosylated haemoglobin, increased insulin C-peptide, haemoglobin and protein levels, decreased thiobarbituric acid reactive substances and lipid hydroperoxides, and increased non-enzymic antioxidants were also observed. In a 12 week study using 100 and 300 mg/kg oral doses of rutin, attenuated serum triglycerides and cholesterol levels were also observed [22]. Increased levels of plasma high-density lipoproteins-cholesterol and reduced level of low-density lipoproteins (LDLs) and very low-density lipoproteins-cholesterol coupled with reduced activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase and increased activity of plasma lipoprotein lipase and lecithin:cholesterol acyltransferase were observed. Decreased glycoproteins in plasma, liver and kidney were also reported [19]. Other data have shown similar results where improvement in the lipid profile and augmentation of alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase activities were significantly augmented in serum, liver and heart [23]. The study by Hao et al [24] was also in agreement with these findings as decreased levels of fasting blood glucose, creatinine, blood urea nitrogen, urine protein, the intensity of oxidative stress and Phospho-Smad 7 were observed. Inhibition of the expression of advanced glycation end products (AGEs), collagen IV and laminin, transforming growth factor-β(1), Phospho-Smad 2/3 and connective tissue growth factor was also reported. Furthermore, inhibition of proliferation of mesangial cells and decreased thickness of glomerular basement membrane were observed following treatment by rutin [24]. The rutin-mediated decrease of non-fasting blood glucose and

normoglycaemic effect in the oral glucose tolerance test has also been reported by other authors [25, 26].

EVIDENCE FROM *IN VITRO* STUDIES

Carbohydrate digestion

One of the crucial factors governing the blood level of glucose is carbohydrate intake and inevitably, key carbohydrate digestive enzymes such as α-glucosidase, are major targets for diabetes therapy. A number of flavonoids including the rutin aglycone, quercetin, have shown α-glucosidase inhibitory activity in micro-molar range by their own and also through synergism with others [27]. In some studies using yeast α-glucosidase, however, rutin failed to show activity up to 100 μM [27] while other studies reported activity at higher (millimolar and submillimolar) concentrations [28, 29]. In some enzyme preparations, however, there are also reports where rutin has shown to display potent α-glucosidase inhibitory activity (e.g. IC_{50} ca. 3 μM by Pham *et al.* [30]). Although the *in vitro* studies have not brought up conclusive evidence on the direct carbohydrate digestive enzymes inhibitory activity of rutin, an *in vivo* effect is likely as rutin's hydrolysis product (quercetin) possess enzyme inhibitory activity [27,31].

Glucose transport and storage

One of the most prominent roles of insulin is to stimulate glucose uptake in fat, skeletal muscle and kidney cells *via* expression of the glucose transporter isoform 4 (GLUT4). The induction of GLUT4 translocation by insulin is mediated through activation of the insulin receptor substrates (IRS) and several kinase activities including the phosphatidylinositol 3-kinase (PI3K) and two serine/threonine kinases (Akt and the atypical

protein kinase C zeta/lambda downstream of PI3K [3]. Interestingly, the insulin-dependent GLUT4 translocation in muscle myotubes under diabetes condition has been shown to be improved by rutin *in vitro via* potentiating the insulin receptor kinase activity [25]. Stimulation of glucose uptake in skeletal muscles have also been reported for rutin through mechanisms including increased calcium uptake through voltage-dependent calcium channels as well as mitogen-activated kinase and protein kinase A signalling pathways [32]. These *in vitro* data also revealed rutin's effect on increasing the activity of extracellular calcium and calcium-calmodulin-dependent protein kinase II [32]. Further studies by the same authors also reported the involvement of PI3K, atypical protein kinase C and mitogen-activated protein kinase pathways associated with rutin's effect on increased glucose uptake in isolated muscle cells [33]. In contrast to GLUT4, the absorption of glucose in other sites such as the liver is mediated *via* GLUT2 which is insulin-independent. Likewise, increased glucose uptakes in isolated hepatocytes *in vitro* have been shown to be induced by rutin [34]. Hand in hand with this activity, an effect of rutin in promoting Akt phosphorylation and preventing degradation caused by high-glucose induction in hepatocytes culture were demonstrated [34]. In addition to insulin, the translocation of GLUT4 in skeletal muscles is also modulated by oxidative stress and/or reactive oxygen species (ROS) and shown to be upregulated by rutin [35]. Since stimulation of glucose uptake is a validated antidiabetic mechanism shared by classical drugs like metformin [34], the reported effect for rutin on various cell types is a good indication of its antidiabetic therapeutic potential.

Pancreatic β cells viability and function

In rat pancreatic β cells, Cai and Lin [36] have reported that rutin preserves the insulin secretory machinery and stimulates insulin receptor substrate 2 signalling, possibly through activation of AMP-activated protein kinase signalling, inhibition of lipogenic enzymes

activities and amelioration of mitochondrial function. Through stimulation of Ca(2+) uptake in rat pancreatic islets, rutin can also potentiate insulin secretion both *in vitro* and *in vivo* [32, 33]. Detailed mechanistic study by the same authors have shown that rutin modulates Ca(2+) uptake in pancreatic islets by opening L-type voltage-dependent Ca(2+) channels, and alters intracellular Ca(2+), PLC and PKC signalling pathways. Since the role of ROS in β cell loss has been established beyond any doubt [35, 36], the prominent antioxidant effect of rutin is likely to make it a beneficial therapeutic agent in prolonging the life span of pancreatic β cells. By activating AMPK signalling to inhibit the activities of lipogenic enzymes and ameliorating mitochondrial function, rutin has also shown to suppress glucotoxicity in pancreatic β cells [36]. Partly due to direct scavenging action on free-radicals and chelation of metal ions, rutin also inhibits post-Amadori formation thereby suppressing AGEs in the eye [39], lipoproteins [40] and matrix proteins such as collagens [41].

Lipid metabolism

The association between diabetes and the other major global epidemic, obesity, have been well understood in recent years and current estimates suggest that over 80% of people with T2D are obese while obesity and/or excess lipid accumulation is proven to lead to impairment of insulin function [42]. Rutin has been reported to suppress adipogenesis through inhibition of glycerol-3-phosphate dehydrogenase (GPDH) activity, expression of peroxisome proliferator-activated receptor (PPARγ), CCAAT/enhancer binding protein-α and leptin, and up-regulation of expression of adiponectin at the protein level [43]. As PPARγ is predominantly expressed in adipocytes and acts as an insulin sensitizer, it is a validated target for treating obesity [44]. In hepatocyte cells, rutin has also shown to attenuate lipid accumulation by decreasing lipogenesis and oxidative stress. These effects have also been shown to be coupled with rutin's action to inhibit the transcriptions of HMG-CoA reductase,

glycerol-3-phosphate acyltransferase, fatty acid synthase, and acetyl-coenzyme carboxylase [45]. This means that by inhibiting the rate limiting enzyme for cholesterol (HMG-CoA) and fatty acids synthesis, rutin interferes with fat metabolism. Furthermore, a correlation between the antioxidative effect of rutin and expression of PPAR-α and antioxidative enzymes have been established [45]. All these data suggest that rutin not only offers antidiabetic effect but also has potential to tackle one of its major risk factor, obesity.

EVIDENCE FROM ABSORPTION AND PHARMACOKINETIC STUDIES

Evidence from *in vitro* studies using Caco-2 cells suggested that rutin is transported across the apical membrane by P-glycoprotein and multidrug-resistant proteins 2 and 3 in metabolic enzymes-dependent fashion [46]. The absorption of rutin, though to the lesser extent than quercetin, was also established through *in vivo* experiments using rat small intestine [47]. Using the model of luminally administered rutin in an isolated preparation of luminally and vascularly perfused rat small intestine, Andlauer *et al.* [48] have shown that about 10% of the administered rutin appeared at the vascular side, chiefly as free rutin (5.6%), but also in the form of rutin sulfate (2.5%) and glucuronide (2.0%). While these data suggest that rutin in its intact form can induce pharmacological effects after oral administration, evidence suggests that its aglycones quercetin is readily detected in plasma [49] and hence may serve as the pharmacologically active principle. The antidiabetic activity of quercetin has also been validated through a number of *in vivo* drug-induced experimental diabetes models in rats [50, 51] and *in vitro* systems including insulin-stimulated glucose uptake studies [52]. Hence, the antidiabetic effect of rutin could be orchestrated both through its direct effect and its aglycone metabolite, quercetin.

THE MULTIFUNCTIONAL NATURE OF RUTIN'S ACTION

A growing body of evidence suggests that inflammation is closely correlated with the pathogenesis of diabetes. For example, the two major products of activated macrophages and adipocytes, tumour necrosis factor α and interleukin-6 are implicated with insulin resistance in diabetes [53-55]. The anti-inflammatory activity of rutin both *in vivo* and *in vitro* has been well documented [56] and one expects a beneficial effect for treating inflammatory conditions associated with diabetes. Since rutin has been shown to offer beneficial effects in experimentally-induced nephrotoxicity and renal dysfunction induced by oxonate [57], glucose [58], hexachlorobutadiene [59], ischemia/reperfusion [60], potassium bromide [61], STZ [24], its role in diabetes end-stage diseases such as nephropathy could not be underestimated. The other major pathologies associated with diabetes are those related to the cardiovascular system such as hypertension and heart diseases. Rutin has been shown to exert a vasodilator effect on arteries through the nitric oxide-endothelial nitric oxide synthase activation pathways [62]. The beneficial effect of rutin to the cardiovascular system under high-carbohydrate and high-fat diet-fed rats has also been documented [63].

CONCLUDING REMARKS

Although clinical evidence is required to confirm the true antidiabetic therapeutic potential of rutin, all the available scientific data today suggest that it has beneficial effect for diabetes and associated diseases. Given the pathological role of ROS and associated oxidative stress in diabetes has been well established, some of the beneficial effects of rutin and its metabolites could inevitably be mediated through antioxidant actions. The major advantage of rutin-based drugs would be their multifunctional effects as antioxidant, antidiabetic, antiobesity, anti-inflammatory, organoprotective, and etc agents. The combined effect of rutin at the various targets would allow the regulation of glucose level under diabetes condition and normalisation of major organ dysfunctions.

CONFLICT OF INTEREST

The authors confirm that this article has no conflict of interest.

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ABBREVIATIONS

GLUT	=	Glucose transporter
HMG CoA	=	3-hydroxy-3-methylglutaryl-coenzyme A
PI3K	=	Phosphatidylinositol 3-kinase
PPAR	=	Peroxisome proliferator-activated receptor
ROS	=	Reactive oxygen species
STZ	=	Streptozotocin
T1D	=	type-1 diabetes
T2D	=	type-2 diabetes

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