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Quercitrin a bioflavonoid improves the antioxidant status in streptozotocin: induced diabetic rat tissues

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Abstract Quercitrin, a bio flavonoid, was investigated for its antioxidant potential in streptozotocin (STZ)-induced diabetic rats. Rats were induced diabetic by a single intraperitoneal injection of streptozotocin (50 mg/kg). The levels of fasting plasma glucose and insulin were estimated. Lipid peroxidative products and antioxidants were estimated in pancreas, liver, and kidney. Histopathological studies were carried out in these tissues. A significant ($P < 0.05$) increase in the levels of fasting plasma glucose and lipid peroxidative products (thiobarbituric acid reactive substances and lipid hydroperoxides) and a significant ($P < 0.05$) decrease in plasma insulin, enzymic antioxidants (superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase), and nonenzymic antioxidants (reduced glutathione, vitamin C, and E) in diabetic pancreas, liver, and kidney were observed. Oral administration of quercitrin (30 mg/kg) for a period of 30 days significantly ($P < 0.05$) decreased fasting plasma glucose, increased insulin levels, and improved the antioxidant status of diabetic rats by decreasing lipid peroxidative products and increasing enzymic and nonenzymic antioxidants. Normal rats treated with quercitrin (30 mg/kg) showed no significant ($P < 0.05$) effect on any of the parameters studied. Histopathological studies of the pancreas, liver, and kidney showed the protective role of quercitrin. Thus, our study clearly shows that quercitrin has antioxidant effect in STZ-induced experimental diabetes.

Keywords Quercitrin · Streptozotocin · Diabetes mellitus · Lipid peroxidation · Antioxidant

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Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels (World Health Organization [WHO], 2006). According to the WHO projections, the prevalence of diabetes is likely to increase by 35% by the year 2025 [1].

The treatment of diabetes mellitus and its complications in the recent context have focused on the usage of plant extract and their constituents. Much interest has grown in the role and usage of natural antioxidants as a means to prevent oxidative damage in diabetes with high oxidative stress. The WHO had estimated that approximately or equal to 80% of the earth's inhabitants rely on traditional medicine for their primary health care needs, and most of this therapy involves the use of plant extracts as their active components [2].

Streptozotocin was found to generate reactive species (ROS) leading to oxidative stress in the biological system [3]. Oxidative stress is suggested to be a potential contributor to the development of complications in diabetes mellitus. Oxidative stress may result from the overproduction

of precursors to oxygen-free radicals and/or decreased efficiency of antioxidants system [4].

Plants have always been usable sources of drugs, and many currently available drugs are directly or indirectly derived from plants. Many of the oral agents that are presently in use for the treatment of diabetes mellitus suffer from implication in a number of serious and adverse effects [5]. Therefore, it is important to investigate the biologically active components of plants with hypoglycemic actions which include flavonoids, alkaloids, glycosides, polysaccharides, and peptidoglycan [6, 7].

Flavonoids comprise a large group of compounds occurring widely throughout the plant kingdom. Daily flavonoid intake (typically present in onion, apple, grape, wine, herbs, and spices) in the human diet is highly variable, with estimations ranging from 23 mg/day [8] to more than 500 mg/day [9]. Flavonoids exert several biological activities, which are mainly related to their ability to inhibit enzymes and their antioxidant properties, and are able to regulate the immune response [10].

Among flavonoids, quercitrin is the most common flavonoid in nature, and it is mainly present as its glycosylated forms such as quercitrin (5,7,3′,4′-OH, 3-rhamnosylquercetin) [11]. A wide variety of pharmacological activities of quercitrin was reported, that is, anti-inflammatory [12, 13], antidiarrhoeal [14], anti-inociceptive property [15], antileishmanial activity [16], and neuroprotective [17]. However, a majority of studies have been carried out with the aglycone (Quercetin) form and little is known about the biological properties of glycoside forms, due to the lack of commercial standards. Therefore, we undertook the present study to evaluate the role of quercitrin on lipid peroxidation and antioxidant status in diabetic liver, kidney, and pancreas. In addition, the effect of quercitrin on the histopathological alterations of these tissues in normal and diabetic rats was also studied.

Materials and methods

Chemicals

Adenosine triphosphate, magnesium chloride, ammonium molybdate, fructose 1,6-bis phosphate, carboxymethyl cellulose sodium salt, phosphotungstic acid, thiobarbituric acid, 1,1′,3,3′ tetramethoxy propane, butylated hydroxy toluene, xylenol orange, dithionitro bis benzoic acid, ascorbic acid, 2,2′ dipyridyl, p-phenylene diamine hydrochloride, and sodium azide were obtained from SD Fine Chemicals, Mumbai, India.

Quercitrin and streptozotocin were purchased from Sigma Chemical Co., St Louis, MO, USA. All the other chemicals used in the present study were of high analytic grade.

Experimental animals

Male albino Wistar rats (150–180 g) were used in this study. The animals were fed on a standard pellet diet (Pranav Agro Industries, Pune, India) and water ad libitum. The pellet diet consisted of 22.02% crude protein, 4.25% crude oil, 3.02% crude fiber, 7.5% ash, 1.38% sand silica, 0.8% calcium, 0.6% phosphorus, 2.46% glucose, 1.8% vitamins, and 56.17% carbohydrates. It provided a metabolisable energy of 3600 kcal/kg. They were maintained in a controlled environment (12: 12 h light/dark cycle) and temperature (30 ± 2°C). The experiment was carried out according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiment on Animals (CPCSEA), New Delhi, India.

Induction of experimental diabetes

Diabetes was induced in 12 h fasted rats with streptozotocin (50 mg/kg) dissolved in citrate buffer (0.01 M, pH 4.5) intraperitoneally, and the injection volume was 1 ml/rat. Control animals were injected with citrate buffer alone. After 72 h of STZ injection, blood was withdrawn from animals (sinocular puncture) fasted overnight in tubes containing potassium oxalate and sodium fluoride as anticoagulant, and plasma glucose was estimated using a commercial glucose kit (Product No. 72101) provided by Qualigens Diagnostics, Mumbai, India. Rats that had a fasting plasma glucose value of above 13.89 mmol/l (250 mg/dl) were included in the study as diabetic rats.

Experimental design

A pilot study was conducted previously with three doses of quercitrin (10, 20, and 30 mg/kg body weight) to determine the dose dependent effects in STZ-induced diabetic rats. We found that 10, 20, and 30 mg/kg of quercitrin significantly ($P < 0.05$) decreased plasma glucose levels and quercitrin at doses 30 mg/kg was more effective in reducing plasma glucose levels significantly ($P < 0.05$) after 30 days of experimental study. Hence, we chose the dose 30 mg/kg of quercitrin for further studies.

For the present study, the animals were grouped as follows: Group I, normal control; Group II, normal + quercitrin (30 mg/kg); Group III, diabetic control; Group IV, diabetic + quercitrin (30 mg/kg). Quercitrin was suspended in carboxymethyl cellulose (CMC) (0.01 g/ml) and was orally administered to rats (1 ml/rat) using an intragastric tube. Normal control and diabetic control rats received CMC alone (1 ml/rat).

The treatment period was 30 days, and after the last treatment, rats were fasted overnight and sacrificed by cervical decapitation. Blood was collected and plasma was obtained after centrifugation and used for various biochemical estimations. Tissues such as pancreas, liver, and kidney were excised immediately from the animals and stored in ice-cold containers. They were then homogenized with appropriate buffer, centrifuged at low speed (705 g), and the supernatant was collected. Biochemical estimations were carried out using these homogenates.

Biochemical assays

Plasma glucose was estimated using a commercial kit as stated above. Plasma insulin was assayed by an enzyme linked immunosorbent assay (ELISA) method using a commercial kit (Catalog No. SP-401) from United Biotech Inc., Mountain View, CA, USA. Thiobarbituric acid reactive substances (TBARS) and lipid hydroperoxides (HP) were estimated by the methods of Fraga et al. [18] and Jiang et al. [19], respectively. Reduced glutathione (GSH) [20], vitamin C [21], and vitamin E [22] were also estimated in the tissues. Further, the activities of antioxidant enzymes such as superoxide dismutase (SOD) [23], catalase [24], glutathione peroxidase (GPx) [25], and glutathione reductase (GRx) [26] were assayed.

Histopathological studies

For histopathological studies, rats from control and experimental groups were perfused with 10% neutral formalin solution. Pancreas, liver, and kidney were removed immediately from the rats; paraffin sections of 5 μm thickness were made and stained by hematoxylin-eosin (H&E) stain. After staining, the sections were observed under light microscope, and photographs were taken.

Statistical analysis

All the grouped data were analyzed by one way analysis of variance (ANOVA) followed by Duncan's multiple range test (DMRT) using SPSS software package, version 9.05. P-values < 0.05 were considered as significant and included in the study.

Results

The change in body weight of normal and experimental rats

A significant ($P < 0.05$) decrease in the body weight of diabetic control rats was observed when compared with normal control rats. Diabetic rats treated with quercitrin 30 mg/kg showed a significant ($P < 0.05$) increase in body weight when compared with diabetic control rats. Quercitrin of 30 mg/kg did not influence any significant ($P < 0.05$) change in the body weight in normal rats when compared with normal control rats (datas not shown).

Effect of quercitrin on food and water intake

Significantly ($P < 0.05$) higher intake of food and water were observed in diabetic control rats when compared with normal control rats. The food intake was significantly ($P < 0.05$) decreased in diabetic rats treated with quercitrin 30 mg/kg, as well the water intake when compared with diabetic control rats. There was no significant ($P < 0.05$) change in quercitrin-treated normal rats when compared with normal control rats.

Effect of quercitrin on fasting plasma glucose and insulin levels

Fasting plasma glucose levels were significantly ($P < 0.05$) increased, and plasma insulin levels significantly decreased ($P < 0.05$) in diabetic control rats. Diabetic rats when treated with quercitrin significantly ($P < 0.05$) decreased the plasma glucose levels and brought the levels to normal. The plasma insulin levels were significantly ($P < 0.05$) increased in diabetic rats treated with quercitrin (Table 1).

Effect of quercitrin on TBARS and HP

The concentration of TBARS and HP in pancreas, liver, and kidney of normal and diabetic rats is given in Table 2. In diabetic rats, TBARS in liver, kidney, and pancreas increased significantly ($P < 0.05$). A significant ($P < 0.05$) increase of HP was also observed in diabetic liver, kidney, and pancreas. The treatment of diabetic rats with quercitrin

Table 1 Effect of quercitrin on fasting plasma glucose and insulin levels in control and experimental groups of rat

Groups	Plasma glucose (mmol/l)	Plasma insulin (μU/ml)
Normal control	3.93 ± 0.29^{a}	14.92 ± 1.04^{a}
Normal + quercitrin (30 mg/kg)	3.99 ± 0.30^{a}	15.02 ± 1.05^{a}
Diabetic control	22.17 ± 1.62^{b}	7.57 ± 0.22^{b}
Diabetic + quercitrin (30 mg/kg)	7.95 ± 0.60^{a}	12.19 ± 0.48^{c}

Each value is mean ± S.D. for eight rats in each group. Values that have a different *superscript letter* (a, b, c) differ significantly with each other ($P < 0.05$, DMRT)

Table 2 Effect of quercitrin on TBARS and HP in Pancreas, liver, and kidney of normal and diabetic rats

Groups	TBARS (nmol/g wet tissue)			HP (nmol/g wet tissue)		
	Pancreas	Liver	Kidney	Pancreas	Liver	Kidney
Normal control	0.36 ± 0.02^{a}	0.66 ± 0.06^{a}	1.13 ± 0.09^{a}	0.20 ± 0.01^{a}	43.91 ± 3.34^{a}	64.01 ± 4.80^{a}
Normal + quercitrin (30 mg/kg)	0.34 ± 0.02^{a}	0.64 ± 0.06^{a}	1.10 ± 0.08^{a}	0.19 ± 0.01^{a}	43.80 ± 3.32^{a}	63.93 ± 4.85^{a}
Diabetic control	0.71 ± 0.04^{b}	1.59 ± 0.14^{b}	2.34 ± 0.19^{b}	0.37 ± 0.01^{b}	122.02 ± 9.29^{b}	96.02 ± 7.31^{b}
Diabetic + quercitrin (30 mg/kg)	0.44 ± 0.03^{c}	0.90 ± 0.07^{c}	1.50 ± 0.09^{c}	0.24 ± 0.01^{c}	64.01 ± 4.87^{a}	70.01 ± 5.33^{c}

Each value is mean ± S.D. for eight rats in each group. Values that have a different *superscript letter* (a, b, c) differ significantly with each other ($P < 0.05$, DMRT)

Table 3 Effect of quercitrin on GSH in pancreas, liver, and kidney and vitamin C and vitamin E in liver and kidney of normal and diabetic rats

Groups	GSH (mg/100 g tissue)			Vitamin C (μmol/mg tissue)		Vitamin E (μmol/mg tissue)	
	Pancreas	Liver	Kidney	Liver	Kidney	Liver	Kidney
Normal control	19.30 ± 1.23^{a}	35.20 ± 2.41^{a}	23.66 ± 1.88^{a}	1.45 ± 0.10^{a}	$1.16 \pm 0.08_{a}$	0.73 ± 0.06^{a}	0.51 ± 0.04^{a}
Normal + quercitrin (30 mg/kg)	19.36 ± 1.10^{a}	36.70 ± 2.44^{a}	23.74 ± 2.10^{a}	1.51 ± 0.10^{a}	1.19 ± 0.08^{a}	0.75 ± 0.08^{a}	0.53 ± 0.03^{a}
Diabetic control	13.70 ± 0.49^{b}	18.30 ± 1.61^{b}	13.49 ± 0.92^{b}	0.86 ± 0.07^{b}	0.75 ± 0.06^{b}	0.48 ± 0.04^{b}	0.34 ± 0.03^{b}
Diabetic +quercitrin (30 mg/kg)	17.56 ± 1.23^{c}	27.10 ± 2.09^{c}	19.50 ± 1.83^{c}	1.10 ± 0.08^{c}	1.02 ± 0.08^{a}	0.64 ± 0.05^{c}	0.43 ± 0.03^{c}

Each value is mean ± S.D. for eight rats in each group. Values that have a different *superscript letter* (a, b, c) differ significantly with each other ($P < 0.05$, DMRT)

Table 4 Effect of quercitrin on the activities of SOD and catalase in pancreas, liver, and kidney of normal and diabetic rats

Groups	SOD (Units/mg protein)			Catalase (Units/mg protein)		
	Pancreas	Liver	Kidney	Pancreas	Liver	Kidney
Normal control	8.92 ± 0.79^{a}	12.39 ± 0.77^{a}	11.22 ± 0.74^{a}	13.50 ± 1.04^{a}	68.20 ± 6.46^{a}	47.04 ± 2.18^{a}
Normal + quercitrin (30 mg/kg)	8.91 ± 0.52^{a}	12.72 ± 0.60^{a}	11.30 ± 0.69^{a}	$13.66 \pm 0.74^{a}69.15 \pm 6.04^{a}$	47.52 ± 2.00^{a}	
Diabetic control	5.42 ± 0.25^{b}	56.34 ± 0.51^{b}	6.20 ± 0.51^{b}	9.43 ± 0.77^{b}	47.33 ± 4.36^{b}	33.39 ± 2.66^{b}
Diabetic + quercitrin (30 mg/kg)	7.02 ± 0.53^{c}	9.63 ± 0.81^{c}	9.41 ± 0.70^{c}	12.32 ± 0.89^{a}	58.10 ± 5.26^{c}	41.22 ± 3.28^{c}

Each value is mean ± S.D. for eight rats in each group. Values that have a different *superscript letter* (a, b, c) differ significantly with each other ($P < 0.05$, DMRT)

SOD Units: enzyme concentration required to inhibit the OD at 560 nm of chromogen production by 50% in 1 min. *Catalase Units*: μmoles of H_2O_2 consumed/mi

significantly ($P < 0.05$) decreased the concentration of TBARS and HP in these tissues, and the concentration of HP was normalized in the kidney.

Effect of quercitrin on nonenzymic antioxidants

The concentration of nonenzymic antioxidants (GSH, vitamin C, and vitamin E) in liver and kidney of normal and diabetic groups is depicted in Table 3. In the liver of the diabetic rats, the concentration of nonenzymic antioxidants was found to be significantly ($P < 0.05$) decreased. Diabetic kidney also exhibited significantly ($P < 0.05$) low concentration of GSH, vitamin C, and vitamin E. Diabetic rats when treated with quercitrin, led to a significant ($P < 0.05$) increase of the nonenzymic antioxidants in the liver and kidney, and we found that the concentration of vitamin C was normalized in the kidney.

Effect of quercitrin on enzymic antioxidants

In diabetic rats, the activities of SOD and catalase were significantly ($P < 0.05$) decreased in liver, kidney, and pancreas (Table 4). Significantly ($P < 0.05$) decreased activities of GPx and GRx were also observed in these tissues (Table 5). Quercitrin-treated diabetic rats exhibited a significant ($P < 0.05$) increase in the activities of these

Table 5 Effect of quercitrin on the activities of GPx and GRx in pancreas, liver, and kidney of normal and diabetic rats

Groups	GPx (μg of GSH consumed/min/mg protein)			GRx (μmoles of NADPH oxidized/h/mg protein)		
	Pancreas	Liver	Kidney	Pancreas	Liver	Kidney
Normal control	10.05 ± 0.68^{a}	10.21 ± 0.71^{a}	5.35 ± 0.43^{a}	24.60 ± 1.80^{a}	23.00 ± 1.78^{a}	3.28 ± 0.21^{a}
Normal + quercitrin (30 mg/kg)	10.35 ± 0.59^{a}	10.64 ± 0.64^{a}	5.59 ± 0.40^{a}	23.70 ± 1.722^{a}	22.21 ± 1.50^{a}	3.40 ± 0.16^{a}
Diabetic control	6.71 ± 0.62^{b}	5.47 ± 0.51^{b}	3.81 ± 0.32^{b}	17.10 ± 0.91^{b}	17.00 ± 0.76^{b}	2.54 ± 0.18^{b}
Diabetic + quercitrin (30 mg/kg)	9.43 ± 0.44^{c}	8.04 ± 0.61^{c}	4.90 ± 0.30^{c}	23.50 ± 1.68^{c}	21.50 ± 1.51^{c}	2.92 ± 0.23^{c}

Each value is mean ± S.D. for eight rats in each group. Values that have a different *superscript letter* (a, b, c) differ significantly with each other ($P < 0.05$, DMRT)

antioxidant enzymes in the liver, kidney, and pancreas, and the activity of catalase was normalized in the liver.

Effect of quercitrin on the histopathology of pancreas, liver and kidney

The histopathological examination of STZ-induced diabetic pancreas showed the shrinkage of islet cells and the growth of adipose tissues in the pancreas (Fig. 3). Treatment with quercitrin on STZ-induced diabetic rats reduced the changes in the pancreas. (Fig. 4). The histopathological examination of STZ-induced diabetic liver (Fig. 7) showed sinusoidal dilatation and kupffer cell hyperplasia, whereas quercitrin-treated diabetic liver (Fig. 8) showed only mild sinusoidal dilatation. The kidney section of STZ-induced diabetic rat (Fig. 11) showed focal fatty infiltrate, inflammation, and hemorrhage. Quercitrin-treated diabetic kidney (Fig. 12) showed normal glomeruli with normal tubules. No histopathological alterations were observed in pancreas (Fig. 1), liver (Fig. 5), and kidney (Fig. 9) of normal control rats. Normal rats treated with quercitrin also did not exhibit any morphological changes in pancreas (Fig. 2), liver (Fig. 6), and kidney (Fig. 10).

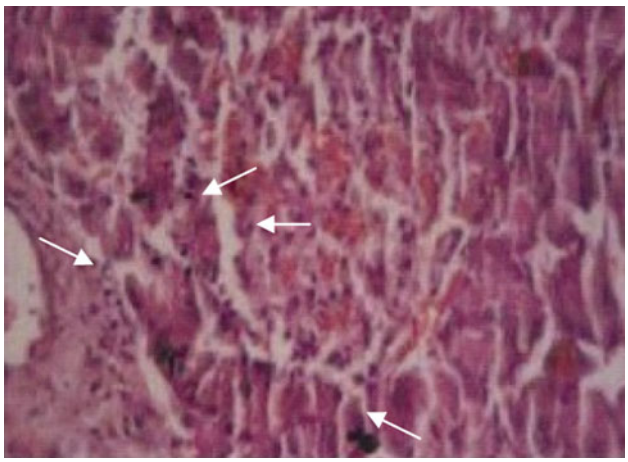

Fig. 1 Normal rat pancreas showing (*arrows*) normal islet cells (H&E ×20)

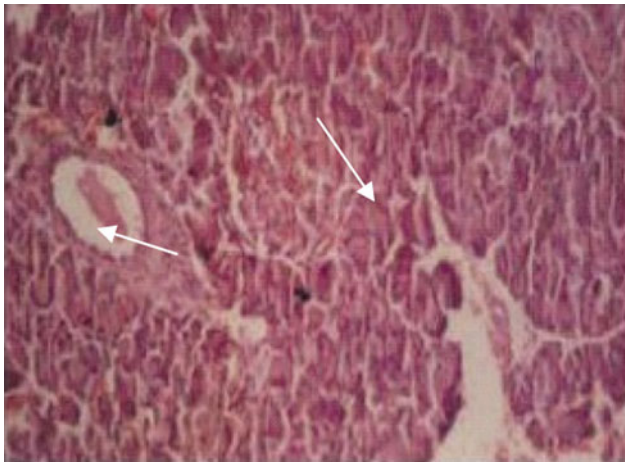

Fig. 2 Normal + quercitrin (30 mg/kg)-treated rat pancreas showing (*arrows*) normal islet cells surrounded by exocrine pancreas (H&E ×20)

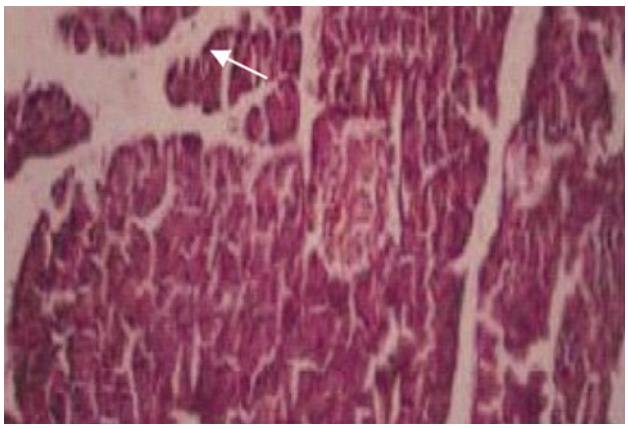

Fig. 3 Diabetic control rats showing (*arrows*) growth of adipose tissue and shrunken islets (H&E ×20)

Discussion

Effect of quercitrin on food and water intake and on body weight

Increased food consumption and decreased body weight were observed in STZ-induced diabetic rats. This shows

polyphagic condition and loss of weight due to excessive break down of tissue proteins. Decreased body weight in diabetic rats could be due to dehydration and catabolism of fats and proteins. Increased catabolic reactions leading to muscle wasting might also be the cause for the reduced weight gain by diabetic rats. Quercitrin administration to diabetic rats decreased food consumption and improved body weight and this could be due to a better control of hyperglycemic state in the diabetic rats. Decreased levels of blood glucose could improve body weight in STZ-induced diabetic rats.

Effect of quercitrin on plasma glucose and insulin

The administration of streptozotocin resulted in increased levels of plasma glucose and decreased levels of insulin.

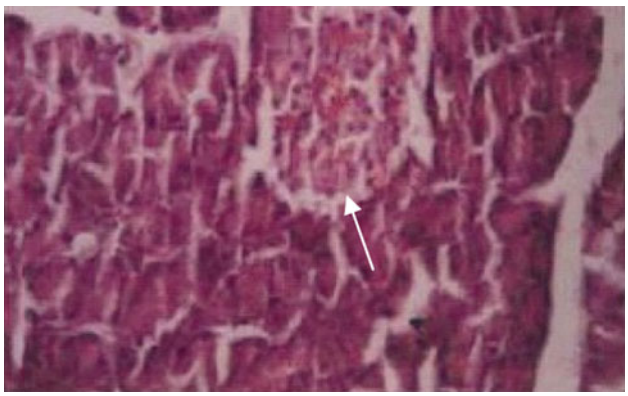

Fig. 4 Diabetic + quercitrin (30 mg/kg)-treated rat pancreas showing expansion of the islets with reduction of the fatty infiltrate (*arrows*) in the surrounding zone (H&E ×20)

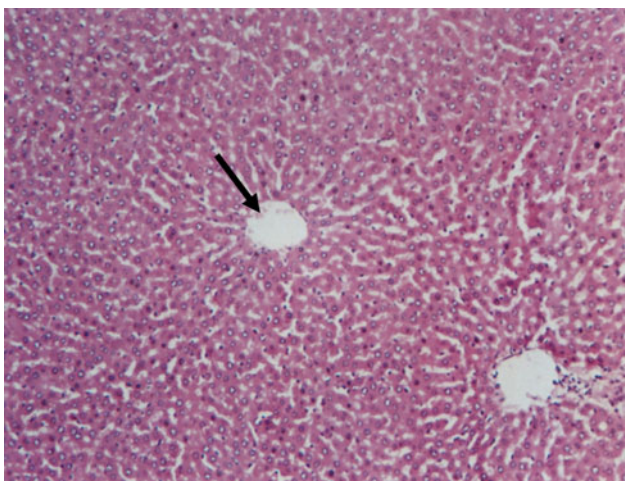

Fig. 5 Normal liver showing central vein (*arrows*) and normal hepatocytes (H&E ×40)

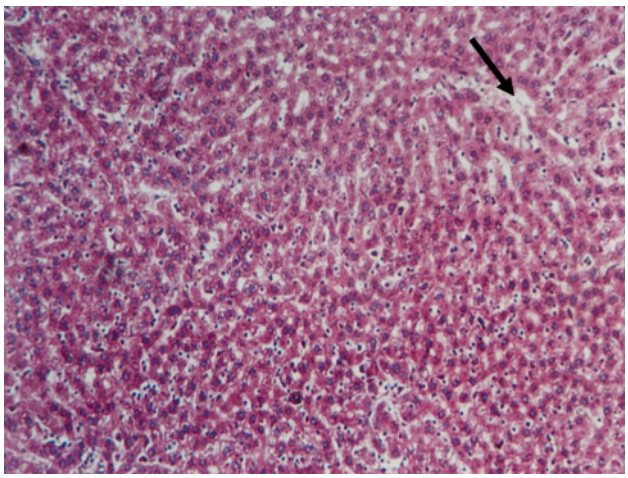

Fig. 6 Normal + quercitrin-treated liver showing (*arrows*) portal triad and normal hepatocyes (H&E ×40)

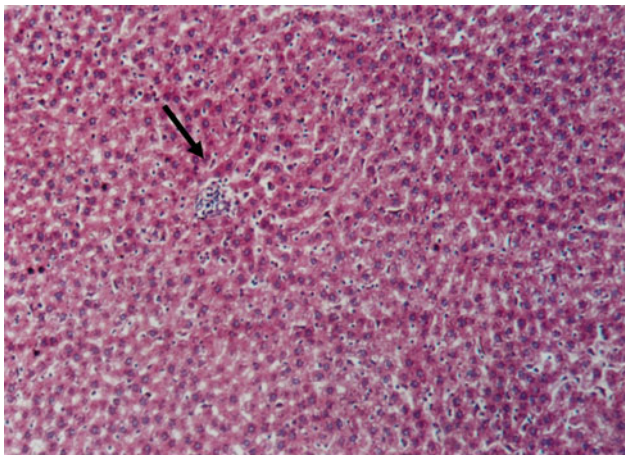

Fig. 7 Diabatic liver showing dilatation of hepatic (*arrows*) sinusoids and kupffercell hyperplasia (H&E ×40)

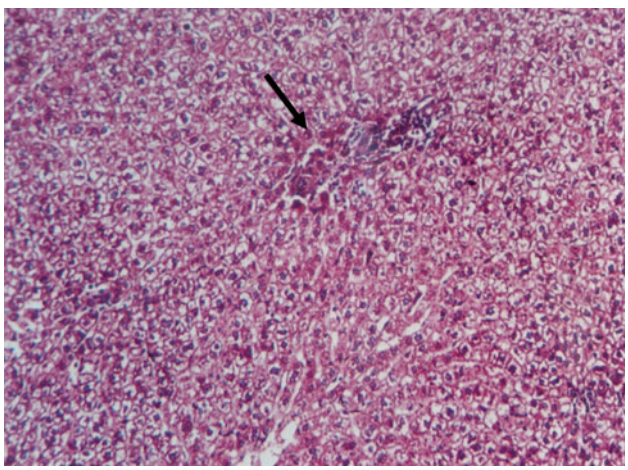

Fig. 8 Diabatic + quercitrin-treated liver (*arrows*) showing mild sinusoidal dilation (H&E ×40)

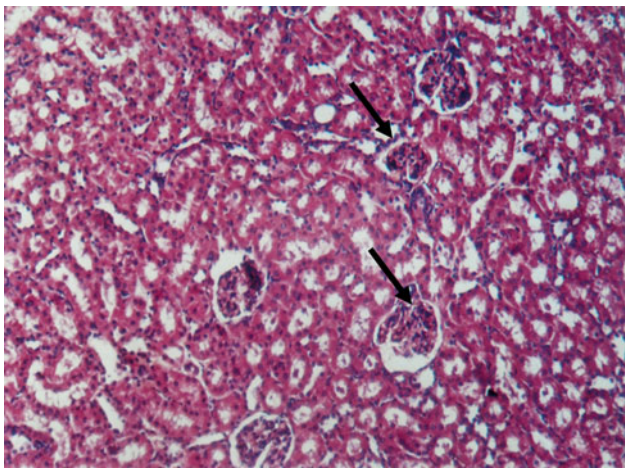

Fig. 9 Normal kidney showing glomeruli (*arrows*) and tubules (H&E ×40)

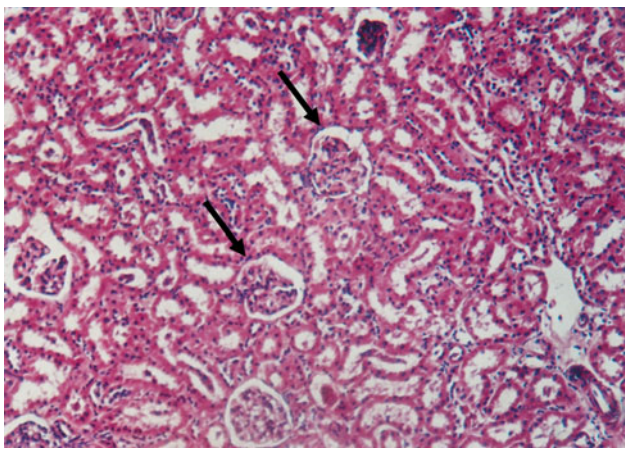

Fig. 10 Normal + quercitrin-treated kidney showing glomeruli (*arrows*) and tubules (H&E ×40)

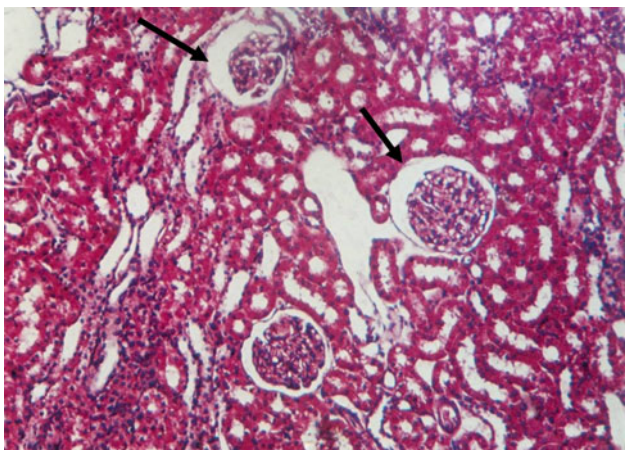

Fig. 11 Diabatic kidney showing increased (*arrows*) and mesangial cell proliferation and cloudy swelling and tubules (H&E ×40)

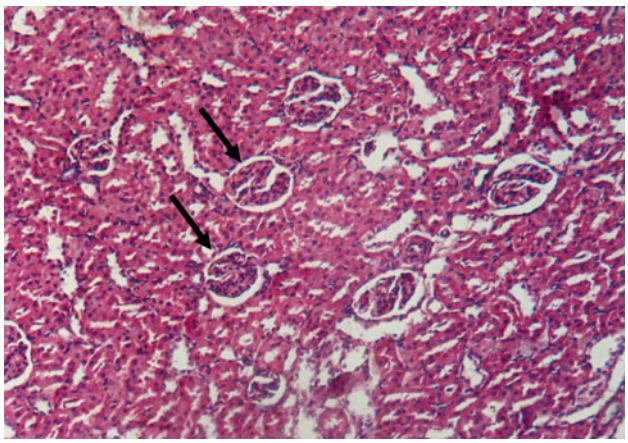

Fig. 12 Diabatic + quercitrin-treated kidney showing normal glomeruli (*arrows*) with normal tubules (H&E ×40)

Treatment with quercitrin decreased plasma glucose and increased insulin levels in diabetic rats. Quercitrin by its ability to scavenge free radicals and to inhibit lipid peroxidation prevents STZ-induced oxidative stress and protects β-cells resulting in increased insulin secretion and decreased plasma glucose levels [24]. Similar results were observed with Quercetin administration in rats with alloxan-induced diabetes promotes the normalization of the level in glycemia [27], Kobori of the National Agriculture and Food Research Organization, Ibaraki, Japan reported that the administration of quercitrin lowers the blood glucose levels and improved the plasma insulin levels in the streptozotocin-induced diabetes mice [28]. In our previous study on quercitrin, we reported that, it increases the glucose utilization and regulates the glucose homeostasis by altering the carbohydrate metabolizing enzymes [29, 30].

Effect of quercitrin on lipid peroxidative products

Lipid peroxidation is a free radical-mediated propagation of oxidative insult to polyunsaturated fatty acids (PUFA) involving several types of free radicals, and termination occurs through enzymatic means or by free radical scavenging by antioxidants [31]. The increased concentration of TBARS and HP were noted in the tissues of diabetic rats. This increase was well mitigated by the treatment of quercitrin. This could be due to the ability of quercitrin to transfer electrons, free radicals, chelate metals catalysts [32], and activate antioxidant enzymes [33]. Reports have shown that quercitrin suppress lipid peroxidation in vitro [34]. In this context, we have reported that quercitrin decreases plasma TBARS and HP in STZ-induced diabetic rats.

Effect of quercitrin on antioxidants

Potential causes of increased oxidative stress in diabetes mellitus include increased production of ROS by NADPH oxidase, decreased antioxidant enzyme activity, and reduced levels of glutathione, α-tocopherol, and ascorbate [35]. SOD combats oxygen toxicity by catalytically reducing superoxide radical anions to hydrogen peroxide, which, if not degraded enzymatically, can be reduced in the presence of transition metals to highly toxic hydroxyl radicals [36]. Catalase catalyzes the transformation of hydrogen peroxide within the cell to harmless products, thereby curtailing the quantity of cellular destruction inflicted by lipid peroxidation byproducts [37]. Diminished activities of SOD and catalase in diabetic tissues might be linked to increased oxidative stress in diabetes accompanied by hyperglycemia [38]. Glutathione provides a first line of defence against ROS, as it can scavenge free radicals and reduce H_2O_2. The decreased concentration of GSH in liver, kidney, and brain might be due to NADPH depletion or GSH consumption in the removal of peroxides [39]. GSH-dependent enzymes provide a second line of defence as they primarily detoxify noxious byproducts generated byROS and also help to prevent propagation of free radicals [40]. GPx serves to detoxify peroxides by reacting them with GSH [41]. Low GPx activity in diabetic tissues might be due to low GSH content, since GSH is a substrate and cofactor of this enzyme [42]. In the process of catalyzing H_2O_2 to water, GPx converts GSH to GSSG, which is reduced to GSH by GRx [36]. The activity of GRx was also decreased in the diabetic tissues in this study. Glutathione may contribute to antioxidant defence by networking with the other major antioxidants such as vitamins E and C. Vitamin E can transfer its phenolic hydrogen to a peroxyl free radical of a peroxidized PUFA, thereby breaking the radical chain reaction and preventing the peroxidation of PUFA in cellular and subcellular membrane phospholipids. As a reducing agent, vitamin C reacts with a vitamin E radical to yield a vitamin C radical while regenerating vitamin E. A vitamin C radical is converted back to vitamin C by GSH [43]. These vitamins also directly scavenge ROS and upregulate the activities of antioxidant enzymes [43]. The treatment with quercitrin increased the activities of enzymic antioxidants and also the concentration of nonenzymic antioxidants in diabetic liver and kidney.

Effect of quercitrin on the histopathology of pancreas, liver and kidney

In our study, histopathological examination of diabetic pancreas showed the shrinkage of islet cells and the growth of adipose tissue in the pancreas. Treatment with quercitrin on STZ-induced diabetic rats reduced the changes in the pancreas. Quercitrin-treated diabetic pancreas showed an increase in the size of the islets and decreased fatty infiltrate around the islets. Quercitrin was able to protect the functional β-cells of the islets by its ability to scavenge free radicals and restore the antioxidant enzyme activities of the pancreas.

Histopathological examination of liver and kidney from diabetic rats revealed morphological changes. Diabetic liver showed dilatation of hepatic sinusoids and also kupffer cell hyperplasia. Similar histopathological changes were reported in the liver of diabetic rats by Evelson et al. [44]. The effect of quercitrin on the histopathological changes of diabetic liver and kidney is also very promising. Quercitrin-treated diabetic liver showed only mild sinusoidal dilatation. The morphological features of diabetic kidney were focal fatty infiltrate and in-flammation. Quercitrin-treated diabetic kidney showed normal glomeruli and normal tubules.

Conclusion

Our study clearly shows that quercitrin improves the antioxidant status in the tissues of diabetic rat. It increases the insulin secretion and improves the antioxidant status as it possesses the structural features of an antioxidant, the ability to sequester metal ions, and by forming metal ion chelates. Morphological assessments also show that the damage caused by streptozotocin to the tissues was also markedly reduced by the administration of quercitrin. In conclusion, quercitrin could be a possible target for the treatment of diabetes mellitus by its protective effect on pancreatic islets.

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