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ORIGINAL RESEARCH ARTICLE

THE EFFECTS OF QUERCETIN ON THE HEPATIC TISSUE AND FUNCTION ENZYMES IN STREPTOZOTOCIN (STZ)-NICOTINAMIDE INDUCED DIABETIC RATS

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Conflict of interest: None declared

Abstract

Background: Quercetin is a naturally occurring flavonoid that has been a nutritional supplement and is beneficial against a variety of diseases.

Aim: This study was aimed at investigating the effects of quercetin on hepatic tissue in a streptozotocin – nicotinamide diabetic rats.

Materials and Methods: 40 Wistar rats were used and were divided into 8 groups: (i): Control group(C), (ii) Diabetic group(D), (iii)Quercetin only group(20mg), (iv)Quercetin only group(50mg), (v)Diabetic treated quercetin group(20mg), (vi)Diabetic treated quercetin group(50mg), (vii) Metformin only group and (viii) Diabetic treated metformin group. After 8 weeks of oral administration, the Wistar rats were sacrificed and the liver was removed and fixed into formalin. The liver was processed and stained in Hematoxylin and Eosin.

Results: Results showed that Quercetin significantly increased ($P< 0.05$) in the Glutathione peroxidase (GPx), Glutathione (GSH), and decreased in the Alanine aminotransferase (ALT), Malondialdehyde (MDA), Aspartate transferase (AST), Alkaline Phosphatase (ALP) and Gamma- glutamyl transferase (GGT). Normal liver morphology was seen in the control group as there was normal liver size, intactness of the central vein and portal triad. In the diabetic group, hepatocellular vesicular vacuolization and local fibrotic areas were seen among the hepatocytes as compared to the control group.

Conclusion: These results showed that quercetin antagonizes the toxic effects of streptozotocin and improved the antioxidant and integrity of the liver and will prevent liver damage associated with diabetes.

Key words: Quercetin, liver function, diabetes, antioxidants, streptozotocin, glucose

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INTRODUCTION

Diabetes is a group of metabolic diseases characterized by elevated levels of glucose in blood (hyperglycemia), resulting from insufficiency in insulin production, insulin action, or both[1]. Diabetes, the most common serious metabolic disorder and one of the five leading causes of death worldwide, is characterized by persistent hyperglycemia[2]. Currently, 171 million people are affected with diabetes and the number is expected to rise to 366 million by 2030[3]. This disease is caused by a decrease or deficiency in insulin secretion and increased cellular resistance coincident with the induction of oxidative stress. Therefore, controlling blood glucose level is essential for preventing diabetic complications and improving the health of patients with diabetes[4]. Streptozotocin (STZ) is widely used to induce insulin dependent diabetes mellitus in experimental animals because of its toxic effects on islet beta cells induced diabetes in rats represents well-established diabetic animal models[5]. STZ exposure has been reported to increase the damage in various tissues, reactive oxygen species, and reactive nitrogen species production, lipid peroxidation, protein carbonylation and hydroxyproline. Elevated blood glucose levels cause increased oxidative stress, which contributes to the development and progression of diabetes-associated complications[5]. The diabetogenic action of STZ is the direct result of irreversible damage to the pancreatic beta cells resulting in degranulation and loss of capacity to secrete insulin[6]. Quercetin (3, 3', 4', 5',7 pentahydroxy flavone) belongs to the family of flavonoids, a large class of naturally occurring, low molecular weight plant metabolites[7]. It is found in many foods, including vegetables, tea, fruits and wine. Quercetin is an effective inhibitor of lipoxygenases. It also exhibits a broad range of pharmacological activities such as anti-inflammatory, anti-oxidant, anti-tumor, immunomodulatory, anti-ulcer and vasodilator effects[8]. It also prevents the oxidation of low density lipoproteins in vitro[9]. Quercetin also works as peroxyl radical scavenger[10]. Quercetin is a polyphenolic flavonoid compound[11]. It is abundantly present in kales, onions, berries, apples, red grapes, broccoli, and cherries, as well as tea and red wine. Modern studies have shown that quercetin prevents various diseases, such as osteoporosis, some forms of cancer, tumors, and lung and cardiovascular diseases[12]. The antioxidant effects of quercetin play a significant role in the prevention and treatment of such diseases. Moreover, owing to its high solubility and bioavailability, quercetin may also exhibit strong antioxidant activity after forming a complex or combining to form some novel preparations used for human health care.

Quercetin (QR), which is a derivative of plants, and has been shown in vitro as well as in a few animal models to have several potential anti-inflammatory as well as anti-carcinogenic applications[13]. Quercetin can modulate carbohydrate and lipid metabolism; attenuate hyperglycemia, dyslipidemia, and insulin resistance; improve adipose tissue metabolism; and alleviate oxidative stress and stress-sensitive signaling pathways and inflammatory processes[14]. Quercetin is known to possess both mast cell stabilizing and gastrointestinal cytoprotective activity. A study demonstrates that quercetin has a direct regulatory effect on basic functional properties of immune cells which may be mediated by the extracellular regulated kinase 2 (Erk2). Quercetin affects immunity and inflammation by acting mainly on leukocytes and targeting many intracellular signaling kinases and phosphatases, enzymes and membrane proteins are often crucial for a cellular specific function[2]. The antioxidant activity of quercetin is mainly manifested through its effect on glutathione (GSH), enzymatic activity, signal transduction pathways, and reactive oxygen species (ROS) caused by environmental and toxicological factors. Quercetin shows a strong antioxidant activity by maintaining oxidative balance[15]. Quercetin modulates carbohydrate and lipid metabolism; attenuate hyperglycemia, dyslipidemia, and insulin resistance; improve adipose tissue metabolism; and alleviate oxidative stress and stress-

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sensitive signaling pathways and inflammatory processes[13].

MATERIALS AND METHOD

Ethical Approval: All experiments were approved and conducted in the Department of Anatomy, College of Health Science, University of Ilorin, Nigeria. The rules and regulations governing animal handling were strictly adhered to by the University Of Ilorin and the experiment conducted in accordance with the ethical committee guidelines.

Experimental Animals: 40 male wistar rats were used for this experiment. The rats had free access to a standard rat pellet diet and kept in standard cages at room temperature. Clean drinking water was provided and a proper hygienic environment maintained. All animals were acclimatized in the Animal House of Faculty of Basic Medical Sciences for two weeks.

Experimental Design: The animals were divided into eight (8) groups:

Group 1 was the control group which received 1 ml of normal saline,

Group 2 the diabetic group which was induced with STZ (65mg/kg),

Group 3 quercetin (20 mg/kg), received 1ml of quercetin

Group 4: quercetin (50 mg/kg)), received 0.2-0.4ml of quercetin

Group 5: diabetic + quercetin (20 mg/kg), received 0.5ml of quercetin

Group 6: diabetic + quercetin (50 mg/kg), received 0.5ml of quercetin

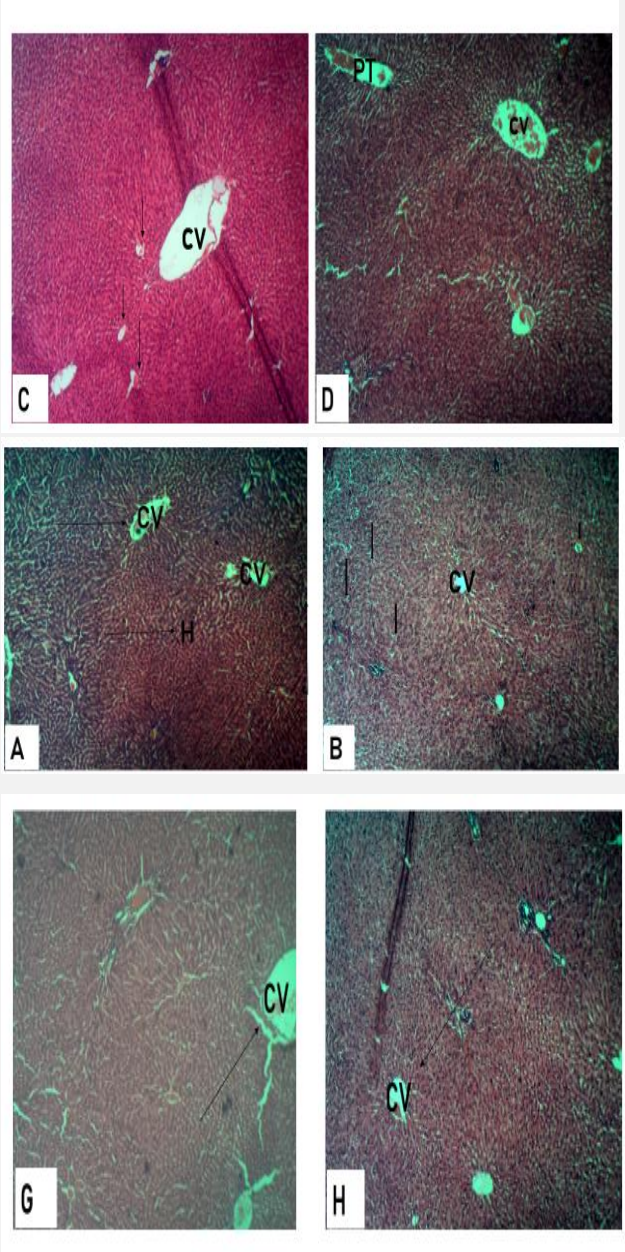
Group 7: Metformin (50 mg/kg), received 0.5ml of metformin

Group 8: diabetic + metformin (50 mg/kg) received 0.5ml of metformin

The route of administration was oral but that of streptozotocin was intraperitoneal and the duration of administration was eight weeks. At the end of 8 weeks of experimentation, the rats were sacrificed using cervical dislocation under anesthesia and liver tissue samples were removed for histological and biochemical examinations. The liver tissue was fixed in formalin for histopathological examination.

RESULTS AND OBSERVATION

Histological observation



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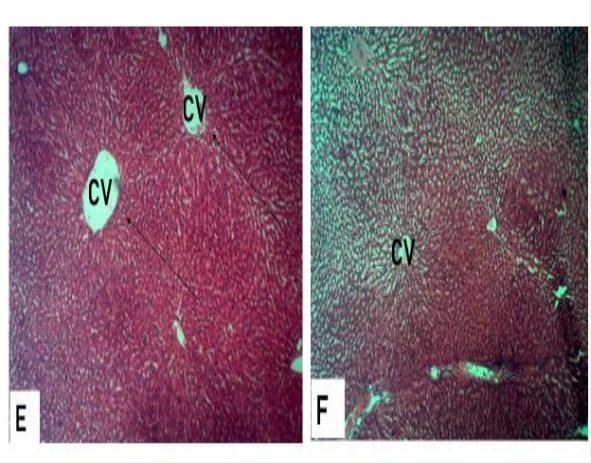


Figure showing the photomicrograph of the liver across all experimental animals showing (x200) Magnification

KEY: A- Control group, B- Diabetic group, C- Quercetin low dose(25mg), D- Quercetin high dose(50mg), E-(DM+QC)Diabetic treated group with quercetin(20mg), F-(DM+QC)Diabetic treated group with quercetin(50mg), G-(ME) Metformin(50 mg/kg), H-(DM+ME)Diabetic treated with metformin.Normal liver morphology was seen in the control group A, C and D as there was normal liver size, intactness of the central vein and portal triad.In the diabetic group(B), hepatocellular vesicular vacuolization and local fibrotic areas were seen among the hepatocytes.In the quercetin treated diabetic group E and F, less vesicular vacuolization and local fibrosis are seen.

Statistical Analysis

All quantitative data were analyzed using GraphPad® (version 6) software and presented as mean±SEM to show statistical significance between each group using the analysis of variance (ANOVA). Results are expressed as mean ± SEM (standard). Statistical differences between control and other groups were determined by ($p<0.05$) taken to imply statistical significance.

Table 1 Appendix 1: Biochemical analysis of experimental animals across the table.

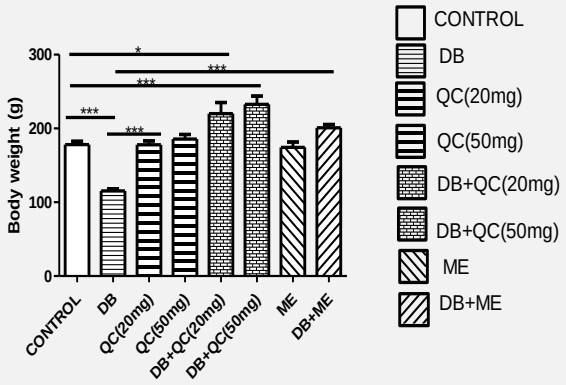
error of mean (mean ±SEM). Statistical differences between control and different groups: $^{*}(P<0.05)$, $^{**}(P<0.01)$, $^{***}(P< 0.001)$. Statistical difference between diabetic group and different groups:$^{\#}(P<0.05)$,$^{\#\#}(P<0.01)$, $^{\#\#\#}(P<0.001)$. Statistical difference between quercetin low dose and different groups: $^{a}(P<0.05)$, $^{aa}(P< 0.01)$, $^{aaa}(P< 0.001)$. Statistical difference between quercetin high dose and different groups: $^{b}(P<0.05)$,$^{bb}(P<0.01)$, $^{bbb}(P<0.001)$. Statistical difference between diabetic+ quercetin low dose and different groups: $^{\beta}(P<0.05)$, $^{\beta\beta}(P<0.01)$, $^{\beta\beta\beta}(P<0.001)$. Statistical difference between diabetic+ quercetin high dose and different groups: $^{\lambda}(P<0.05)$, $^{\lambda\lambda}(P<0.01)$, $^{\lambda\lambda\lambda}(P<0.001)$. Statistical difference between metformin and different group $^{X}(P<0.05)$, $^{XX}(P<0.01)$, $^{XXX}(P<0.001)$.

KEYS: Control= 1 ml of normal saline, Diabetes= 65 mg/kg of STZ, Q= Quercetin 20 mg/kg & 50 mg/kg, DM+ Q= diabetic treated group with quercetin 20 mg/kg &50mg/kg, Met=Metformin 50 mg/kg, DM+Met= diabetic treated group with metformin 50 mg/kg.

BODY WEIGHT:

Quercetin improves body weight induced by streptozotocin

The body weights of the animals were taken on the first day of the administration and the day of sacrifice. The weight gain was estimated as the difference between the initial weight of the animal and the final weight.



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Fig1: Body weights of all diabetic animals were significantly decreased when compared with those of control animals (P<.0.001 and P<.0.05, respectively)

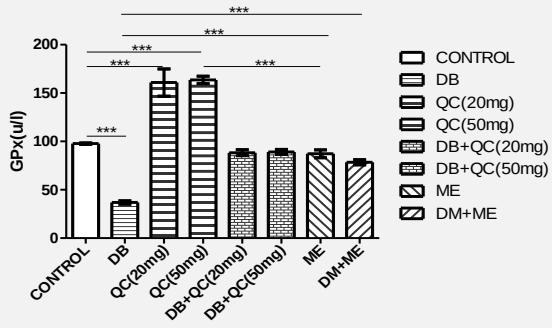


Fig 2: Graphical representation of Glutathione peroxidase levels in animals across all groups. *P<0.05, **P<0.01, ***P<0.001; (n=8)

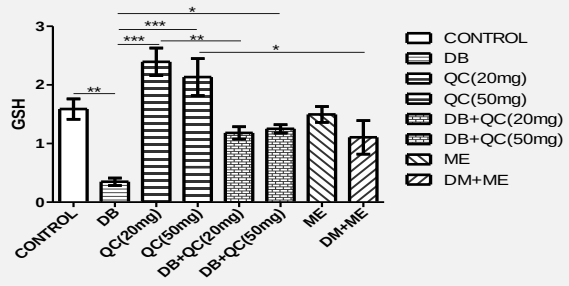


Fig 3: Graphical representation of Glutathione (GSH) levels in animals across all groups. *P<0.05, **P<0.01, ***P<0.001; (n=8)

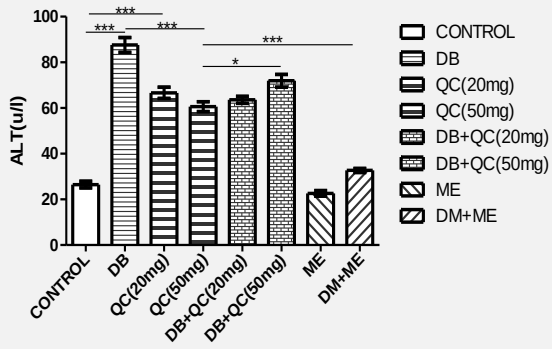


Fig 4: Graphical representation of Alanine Aminotransferase (ALT) levels in animals across all groups. *P<0.05, **P<0.01, ***P<0.001; (n=8)

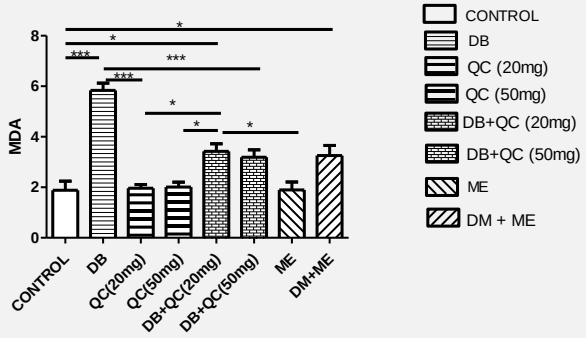


Fig 5: Graphical representation of Malondialdehyde (MDA) levels in animals across all groups. . *P<0.05, **P<0.01, ***P<0.001; (n=8)

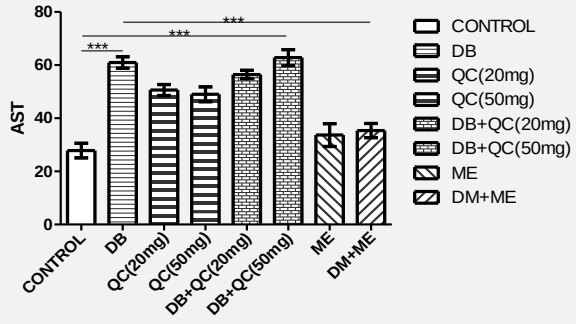


Fig 6: Graphical representation of Aspartate transferase (AST) across all groups. . *P<0.05, **P<0.01, ***P<0.001; (n=8)

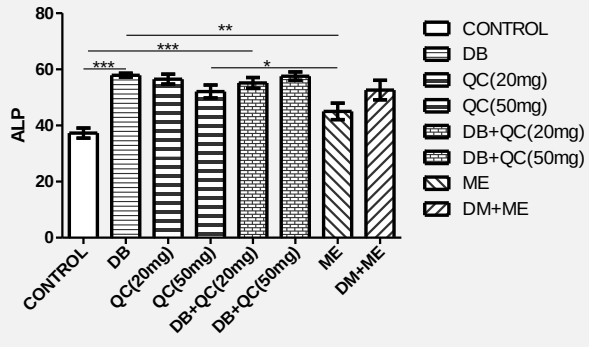


Fig 7: Graphical representation of Alkaline Phosphatase(ALP) across all groups. *P<0.05, **P<0.01, ***P<0.001

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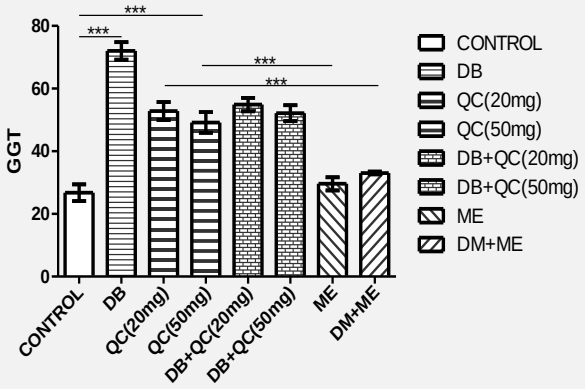


Fig 8: Graphical representation of Gamma- glutamyl transferase (GGT) across all groups. . *P<0.05, **P<0.01, ***P<0.001; (n=8)

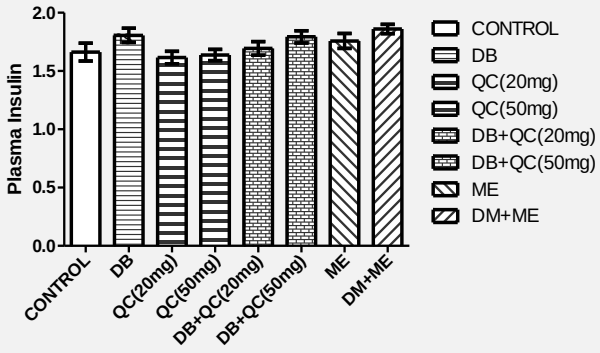


Fig 9: Graphical representation of Plasma Insulin across all groups. *P<0.05, **P<0.01, ***P<0.001; (n=8)

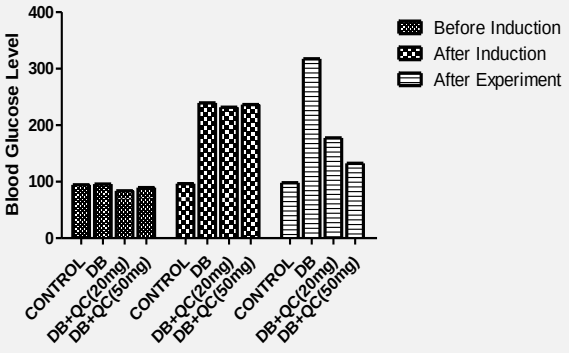


Fig 10: Graphical representation of Plasma Glucose across all groups. . *P<0.05, **P<0.01, ***P<0.001; (n=8)

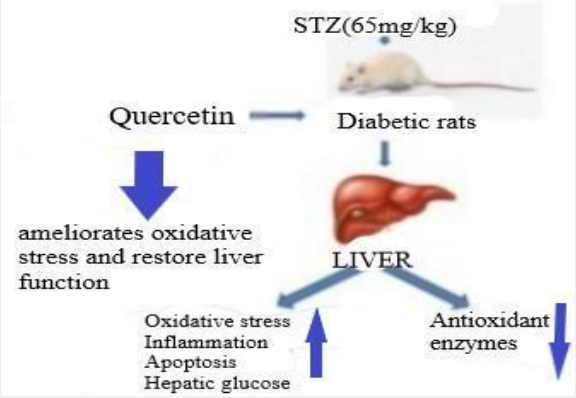


Fig 11: Schematic diagram showing the pathway of quercetin ameliorating diabetic liver function

The study demonstrated the effect of Quercetin on the hepatic tissue associated with STZ-nicotinamide induced diabetic rats. Data from this study show that ALT, ALP and AST activities are elevated in diabetic rats, whereas administration of Quercetin resulted in a decrease in ALT, ALP and AST activities. Treatment with Quercetin markedly improves ALT and AST activities in the liver of rats with STZ-induced diabetes. Under normal physiological conditions, blood glucose levels are tightly regulated by the secretion of insulin by specialized cells in pancreas Langerhans's islets[2]. High blood glucose promotes insulin release from the α-cells of the islets. Insulin stimulates the uptake of glucose from the blood by different tissues such as muscle, kidney and adipose, promotes the storage of glucose in the liver as glycogen, and inhibits lipolysis in adipose tissue[11]. The resulting depletion of blood glucose by the action of insulin in turn promotes the secretion of glucagon from the α-cells in the pancreatic islets, which stimulates glycolysis in the liver and release of glucose back into the blood[16]. Streptozotocin (STZ) demonstrates the diabetogenic effect of stimulating the production of reactive oxygen radicals in pancreatic β cells. In this study, the QR treatment of STZ-induced rats results in alterations in the metabolism of glucose with subsequent reduction in plasma glucose levels[11]. The decrease in increased serum glucose levels is in agreement with the results of other studies[2]. The actual antidiabetic prospective associated with flavonoids are usually large as a result

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of their modulatory effects on blood sugar transporter by enhancing insulin secretion, reducing apoptosis and promoting proliferation of pancreatic β-cells, reducing insulin resistance, inflammation and oxidative stress in muscle[17]. Antioxidants react with and stabilize free radicals and can prevent the damage caused by free radicals. Generally antioxidants are reducing agents which are found both intracellular and extracellular and have the ability to react with ROS and free radicals, this action delaying or preventing the oxidative stress[18]. There was a downregulation of GSH and GPx expression in diabetic group leading to a lower activity level of the GSH and GPx, an antioxidant enzyme in liver tissue. Co-administration of quercetin in diabetic rats reduces oxidative damage effectively in a rat model. MDA is a marker for lipid peroxidation use for the evaluation of liver injury in experimental and human studies[5]. In this study, liver MDA levels decreased after administration of quercetin, whereas MDA levels in the liver of untreated diabetic group were higher. This is due to its protective role against lipid peroxidation[5]. All these results suggested that QR improved the diabetes-induced lipid peroxidation in the liver. QR administration substantially reduced hepatocellular injury. In this study, the quercetin treatment of STZ-induced rats results in alterations in the metabolism of glucose with subsequent reduction in plasma glucose levels. The Quercetin treatment protect liver cells from free radical damage with its antioxidant effect. The Quercetin treatment of STZ-induced rats results in alterations in the metabolism of glucose with subsequent reduction in plasma glucose levels. The decrease in increased serum glucose levels is in agreement with the results of other studies[19]. Hepatocellular damage causes the release of ALT and AST into circulation. Activities of these enzymes are used as an indicator of hepatocyte damage[4]. Data from this study show that ALT and AST activities are elevated in diabetic rats, whereas administration of QR resulted in a decrease in ALT and AST activities. The most common substance used in inducing diabetes was streptozotocin which is taken up by pancreatic β-cells via glucose transporter (GLUT2). The main cause of STZ-induced beta-cell death is alkylation of DNA by the nitrosourea moiety of this compound[20]. Treatment with QR markedly improves ALT and AST activities in the liver of rats with STZ-induced diabetes. The QR treatment may protect liver cells from free radical damage with its antioxidant effect. Normal liver morphology was seen in the control group (A), the quercetin low and high dose (C) and D as there was normal liver size, intactness of the central vein and portal triad. In the diabetic group (B), hepatocellular vesicular vacuolization and local fibrotic areas were seen among the hepatocytes. In the quercetin treated diabetic group E and F, less vesicular vacuolization and local fibrosis are seen. The liver sections of quercetin treated group showed normal polygonal cells around the portal canal and sinusoid showed a layer of fenestrated endothelial cells. GSH-Px, an enzyme dependent on the micronutrient selenium, plays a critical role in the reduction of lipid and hydrogen peroxides. GSH-Px activity was decreased in the liver tissue in this study. Hydrogen peroxide is detoxified by GSH-Px, and so the reduced activity of GSH-Px can be due to its depletion or inhibition as a result of increased production of hydrogen peroxides. Administration of Quercetin caused significant increase in the GSH-Px activity compared with that of untreated diabetic rats[5].

It also showed that the treatment with QR increased the activities of enzymatic antioxidants in diabetic liver[21]. Theirs and our study demonstrated that bioflavonoids have an antioxidant effect in STZ-induced experimental diabetes. This study has demonstrated that the administration of Quercetin to diabetic rats lead to alterations in the oxidant and antioxidant status, and may prevent liver damage associated with diabetes. The results obtained from this study show that quercetin treatment significantly reduces the progression of STZ-induced hyperglycemia and oxidative stress in rats[14]. The results are also supported by morphological improvements in liver tissue.[22] found that the oxidative stress markers (MDA, GPx and GSH levels) were effectively normalized by treatments with QR

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compared with those in diabetic controls, strongly suggesting protective effects of QR in pancreatic β cells. Consequently, Quercetin is more effective than other bioflavonoids in terms of struggling against the oxidative stress[5].

CONCLUSION

The results obtained from this study shows that quercetin treatment significantly reduces the progression of STZ-induced hyperglycemia and oxidative stress in rats. This study demonstrated that the administration of quercetin antagonizes the toxic effects of streptozotocin and improves the antioxidant and integrity of the liver thereby prevent liver damage associated with diabetes.

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Appendix 1

Group	Control	DM	Q(20mg)	Q(50mg)	DM+Q(20mg)	DM+Q(50mg)	Metformin	DM+Metformin
AST	27.81±2.72	61±2.2***^{b}	50.64±2.05	49.04±2.8^{x}	56.45±1.58	63±3.0***	33.68±4.31	35.38±2.66###
ALP	37.29±1.81	58±0.7***	56.52±1.78	52.12±2.3	55.16±1.95	57.59±1.48	45.±2.91^{xxb}	52.62±2.49
ALT	26.50±1.44	67.±3.3***	66.6±2.45###	60.60±2.2$^{\lambda}$	63.58±1.5	71.92±2.8^{b}	22.63±1.23	33.76±0.86^{b}
GSH	1.588±0.18	0.4±0.1**	2.39±0.24###	2.13±0.3###	1.181±0.10^{a}	1.250±0.07#	1.497±0.14	1.11±0.28
GPx	97.63±0.77	38±1.7***	173±2.70***	164±3.7***	88.28±3.07	89.07±2.67	87±4.17***	78.5±2.69***
MDA	1.881±0.36	5.8±0.4***	1.97±0.14###$^{\beta}$	2.011±0.2$^{\beta}$	3.42±0.30^{b}	2.99±0.25	1.90±0.31$^{\beta}$	3.30±0.40*
GGT	26.76±2.70	72.±2.8***	52.82±2.85	49.±3.3***	54.92±2.14	52.20±2.53	29.6±2.1^{bbb}	33.06±0.45

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