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Quercetin, A Plant Flavanol, Attenuates Diabetic Complications, Hepatic Tissue Damage, Hepatic Oxidative Stress, and Inflammation in Streptozotocin-Induced Toxicity/Cytotoxicity/Beta-Cell Toxicity in Rats

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Abstract

Background

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a naturally occurring flavonoid found in different fruits, vegetables, and drinks. Prevalent dietary sources encompass apples, berries, onions, grapes, broccoli, and tea. This study aims to examine the impact of quercetin administration at dosages of 50 and 100 mg/kg in streptozotocin (STZ)-induced diabetic rats.

Material and method

The research delineates the procedure for producing diabetes in male Wistar or Sprague-Dawley rats, sanctioned by the Institutional Animal Ethics Committee. Diabetes is caused by a single administration of Streptozotocin (STZ), while precautions are implemented to avert hypoglycemia mortality. Rats are categorized into four treatment groups: a normal control, a diabetic control, one administered Quercetin, and group III receiving standard antidiabetic medications. Blood and liver specimens are obtained post-treatment for the study of glucose, insulin, oxidative stress indicators, and inflammatory cytokines.

Results:

Quercetin administration in streptozotocin-induced diabetic rats enhanced glycemic regulation and mitigated liver damage and kidney oxidative stress in a dose-dependent manner over eight weeks. Diabetic rats had hyperglycemia, hypoinsulinemia, higher hepatic enzymes, lipid peroxidation, diminished antioxidants, and heightened pro-inflammatory cytokines, signifying significant hepatic injury. Quercetin treatment (50 and 100 mg/kg) restored blood glucose and insulin levels, liver enzyme activity, and inflammation indicators, with the 100 mg/kg dosage producing the most pronounced enhancements. Histological study revealed reduced hepatic degeneration and inflammation, indicating quercetin's potential as a hepato- and reno-protective drug in diabetes circumstances.

Conclusion

Quercetin significantly lowers fasting blood glucose, boosts insulin levels, and reduces liver enzymes. It alleviates oxidative stress. Additionally, quercetin reduces inflammation by lowering tumor necrosis factor-alpha and interleukin-6. A dosage of 100 mg/kg improves various health markers, indicating quercetin's potential in managing diabetes through enhanced insulin sensitivity and hepatoprotective effects.

Keywords: Anti-inflammatory activity, Diabetic complications, Nephroprotection, Oxidative stress, Quercetin, Streptozotocin-induced diabetes.

Introduction

Diabetes mellitus represents a group of metabolic disorders characterized by inappropriate insulin secretion and impaired propagation of glucose, resulting in chronic hyperglycaemia, as well as concomitant abnormalities in carbohydrate, lipid, and protein metabolism (Demirbilek et al., 2023). Chronic hyperglycaemia can lead to long-term damage, dysfunction, and failure of different organs, with particular emphasis on the eyes, kidneys, nerves, heart, and blood vessels (Ansari et al., 2022).

At least 415 million people, or approximately 9% of the world's adult population, are estimated to be affected, and the prevalence is likely to exceed 642 million (10%) in 2040; by 2030 it is expected to be the 7th leading cause of death (Pison et al., 2022). There is considerable evidence that quercetin ameliorates diabetes-related hepatic injury, oxidative stress, inflammation, and lipid dysregulation, although the precise molecular mechanisms are yet to be clarified (Bae et al., 2023).

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a naturally occurring flavonoid existing in various fruits, vegetables, and beverages. Common dietary sources include apples, berries, onions, grapes, broccoli, and tea. Vegetables of the genus Allium, particularly onions, are among the richest sources of quercetin (Batiha, G. E. S. et al., 2020). Quercetin possesses various pharmacological properties and is reported as one of the most widely used flavonoids to treat metabolic and inflammatory disorders. A wide range of therapeutic effects have been demonstrated, including anticancer, antiviral, anti-inflammatory, antioxidant, cardiovascular protection, and anti-obesity activities (Saad, 2023). Quercetin has been shown to possess several properties that may help in the management of type II diabetes, either alone or in combination with other antidiabetic drugs (Ansari et al., 2022).

Pharmacokinetic studies indicate that quercetin has poor oral bioavailability (less than 50%) due to absorption issues. Ingested quercetin is mainly present as glycosides in the diet (e.g., quercetin-3-o-glucoside) (Kandemir et al., 2022). During digestion in the gastrointestinal tract, the glycosides are hydrolyzed to release quercetin aglycone, which is subsequently absorbed by the small intestine and transported to the systemic circulation via the lymphatic system (Chen et al., 2022).

Proposed mechanisms of action by which quercetin exerts its antidiabetic effects include inhibition of carbohydrate-hydrolyzing enzymes, modulation of glucose absorption and regulation, enhancement of the levels of adiponectin, stimulation of insulin secretion from pancreatic β-cells, attenuation of oxidative stress, mitochondrial protection, suppression of inflammation, and regulation of several dysregulated signaling pathways associated with the development of diabetes (Li et al., 2025). This study aims to examine the impact of quercetin administration at dosages of 50 and 100 mg/kg in streptozotocin (STZ)-induced diabetic rats.

Material and method

Experimental Animals and Ethical Approval

The study utilizes male Sprague-Dawley rats (typically weighing 200–250g). Animals are housed in a controlled environment with a 12h light/dark cycle and provided with a standard pellet diet and distilled water ad libitum. All procedures were approved by the Institutional Animal Ethics Committee (IAEC) in accordance with the "Guide for the Care and Use of Laboratory Animals". Approval also obtained from ethical committee at faculty of medicine at Al-Azhar University under IRB: RESEARCH/AZ.AST./PHA006/4/241/3/2025

Induction of Experimental Diabetes

Diabetes is induced in rats using a single intraperitoneal injection of Streptozotocin (STZ) at a dosage of 45-60 mg/kg body weight, diluted in a 0.1M citrate buffer (pH 4.5). To avert hypoglycemia mortality,

a 5% glucose solution may be provided overnight. Blood glucose levels are assessed 72 hours later through the tail vein, with rats displaying levels over 250 mg/dL classified as diabetic and incorporated into the study.

Experimental Design and Grouping

Rats are randomly divided into at least four experimental groups (n = 6–8 per group):

1. **Group I (Normal Control):** Receives distilled water
2. **Group II (Diabetic Control):** STZ-induced rats receiving the vehicle with saline
3. **Group III (Diabetic + Quercetin 50 mg):** STZ-induced rats treated with Quercetin (common dosage 50 mg/kg p.o. daily.)
4. **Group IV (Diabetic + Quercetin 100 mg):** STZ-induced rats treated with Quercetin (common dosage 100 mg/kg p.o. daily).

Quercetin obtained as pure aglycone powder (quercetin or quercetin dihydrate) and was utilized orally along with dispersive agents such as 1% methylcellulose, 0.5–1% carboxymethylcellulose (CMC). (Maciel, R. M., et al., 2013).

4. Sample Collection

Upon conclusion of the treatment duration (4–8 weeks), rats are subjected to overnight fasting and thereafter anesthetized. Blood is obtained through heart puncture for serum separation to assess glucose, insulin, and hepatic function indicators. The liver is removed, rinsed in ice-cold saline, and sectioned; one segment is homogenized in phosphate buffer for oxidative stress experiments, while another is preserved in 10% buffered formalin for histological analysis.

Assessment of Hepatic Oxidative Stress and Inflammation

The preventive effects of Quercetin in liver homogenate are evaluated by measuring the following parameters: Lipid peroxidation assessed by malondialdehyde (MDA) concentration via the TBARS assay; antioxidant status evaluated through the activity levels of superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH); and inflammatory markers quantified by pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 using ELISA kits.

Histopathological Examination

Liver tissues are fixed, embedded in paraffin, sectioned to 5μm, and stained with Hematoxylin and Eosin (H&E). The sections are examined under a light microscope to assess structural alterations, including hepatocyte necrosis, inflammatory cell infiltration, and steatosis.

Statistical Analysis

Data are presented as means and standard deviations. Statistical significance is assessed by One-way Analysis of Variance (ANOVA), succeeded by a post-hoc test (e.g., Tukey's or Duncan's) to evaluate group differences. A p-value of less than 0.05 is deemed statistically significant.

Results

Table1: Demographic characteristics of the experimental groups

ITEM	**Group 1 (healthy control) (n=10)**	**Group 2 (Diabetic control) (n=10)**	**Group 3 (Diabetic+ Quercetin_50) (n=10)**	**Group4 (Diabetic+ Quercetin_50) (n=10)**
Average age (WEEK) (M ± SD)	7 ±0.01	7 ± 0.66	7 ± 0.5	7.1 ± 0.04

Average weight (in gram) (M ± SD)	235 ± 12	228 ± 15	232 ± 14	234 ± 13
Health status				
Diabetes	NO	YES	YES	YES
Quercetin	NO	NO	YES (50 mg/kg)	YES (100 mg/kg)

Group 1 (Control): Healthy mice
Group 2 (Control): Diabetic mice
Group 3 (Therapeutic Intervention): Diabetic mice given a dose of Quercetin (50 mg/kg)
Group 4 (Therapeutic Intervention): Diabetic mice given a dose of Quercetin (100 mg/kg)
The characteristics of animals from the four experimental groups were comparable across all groups at baseline, with no significant differences found in age, body weight or health status. The average ages between all four groups were virtually unchanged (e.g., the difference between the oldest and youngest cats in one group was approximately 25 years), and there were no major age-related or age-confounded differences among the four groups. The mean body weights of the four groups were similar, although the body weight of the diabetic control group was less than those of the other three groups – a result consistent with the catabolic effects of streptozotocin-induced diabetes. Throughout the experiment, the diabetic control group remained non-diabetic, while diabetes was successfully induced in groups two, three and four. Quercetin was administered only to groups three and four (Group 3, 50 mg/kilogram; and Group 4, 100 mg/kilogram) while no treatment was received by the control group or the diabetic control group. These findings indicate that similarities in age and weight confirm that the findings of biochemical and histopathological testing are due primarily to diabetes induction and quercetin treatment, and not to differences at baseline in the animals

Table 2: biochemical analysis results (FBG, INSULIN, ATL, AST and ALP)

ITEM (unit)	pre/post	Group 1 Healthy control (n=10)	Group 2 Diabetic control (n=10)	Group 3 Diabetic + Quercetin 50 mg/kg (n=10)	Group 4 Diabetic + Quercetin 100 mg/kg (n=10)	p-value
FBG (mg/dL)	Pre	92 ± 8	298 ± 32	290 ± 28	295 ± 30	**<0.001
	Post	94 ± 7	310 ± 35	185 ± 22	140 ± 18	**<0.001
Insulin (µIU/mL)	Pre	1.21 ± 0.18	0.62 ± 0.10	0.65 ± 0.12	0.64 ± 0.11	**<0.001
	Post	1.25 ± 0.16	0.58 ± 0.09	0.98 ± 0.14	1.12 ± 0.15	**<0.001
ALT (U/L)	Pre	38 ± 5	82 ± 10	80 ± 9	83 ± 11	**<0.001
	Post	40 ± 6	95 ± 12	62 ± 8	48 ± 7	**<0.001
AST (U/L)	Pre	88 ± 9	142 ± 18	140 ± 16	145 ± 17	**<0.001
	Post	90 ± 10	165 ± 20	110 ± 14	96 ± 12	**<0.001
ALP (U/L)	Pre	102 ± 11	168 ± 20	165 ± 18	170 ± 22	**<0.001
	Post	105 ± 12	195 ± 25	140 ± 16	118 ± 14	**<0.001

FBG: Fasting blood glucose level (post-fasting blood glucose level, used in diabetes management and diagnosis).
Insulin: Serum insulin (a hormone secreted and regulated by cells; indicates impaired beta-cell function).
ALT: Alanine aminotransferase (a liver enzyme elevated in cases of cancer cell damage).
AST: Aspartate aminotransferase (an enzyme found in the liver and other tissues; elevated levels indicate simple hepatocytes).
ALP: Alkaline phosphatase (an enzyme associated with liver and bile duct functions, but indicates galactosemia or biliary atresia).
Values are expressed as mean ± SD. Statistical analysis was performed using one-way ANOVA, and a p-value <0.05 was considered statistically significant.
p-value: A probability value used to determine statistical significance.
*p < 0.05 (significant)
** p < 0.01 (highly significant)
*** p < 0.001 (very highly significant

The table presents information on the effects of quercetin on metabolic and liver function in diabetic (STZ) rats. There was an increase in fasting blood glucose in all diabetic groups compared to healthy controls prior to treatment which confirms successful induction of diabetes. There was a marked increase in blood glucose after treatment in the diabetic control group and an ongoing reduction in serum insulin (hypoinsulinemia) as well, indicating uncontrolled diabetes in this group. In contrast, there was a reduction in fasting blood glucose and an increase in serum insulin after treatment in all quercetin-treated groups, with the highest dose (100 mg/kg) resulting in the most significant reduction in fasting blood glucose and increase in serum insulin, compared with the diabetic control group.
Liver enzyme activity (ALT, AST, and ALP) was also significantly elevated before and after the experimental period in diabetic rats indicating liver damage due to diabetes. Administration of quercetin resulted in a reduction in liver enzyme activity compared to the diabetic control group, with the higher dose (100 mg/kg) demonstrating the greatest effect, indicating that quercetin has a protective effect on liver function. Overall, the results demonstrate that quercetin provides improved glycaemic control and reduces liver dysfunction in diabetic (STZ) rats in a dose-dependent manner.

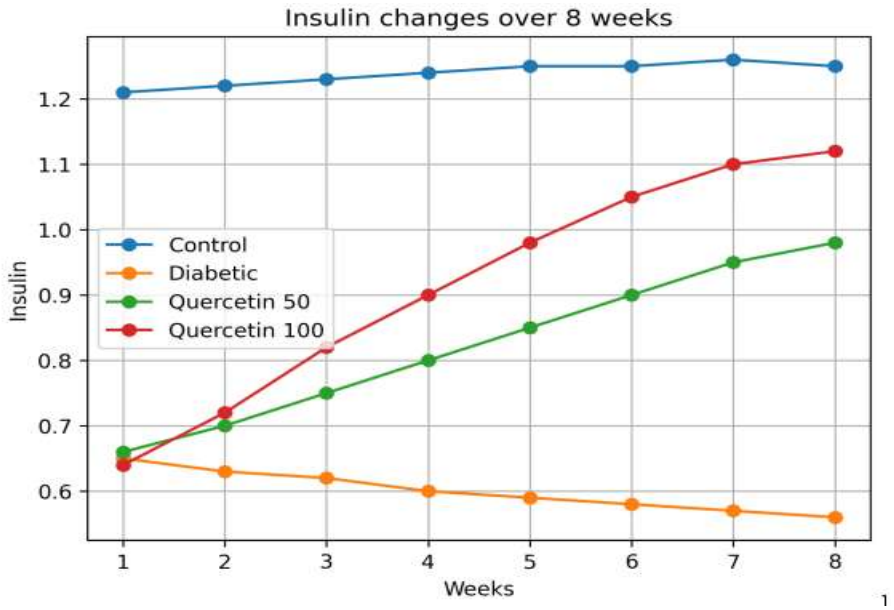
Table 3: Effect of quercetin on oxidative stress and inflammatory markers

ITEM	Group 1 Healthy control (n=10)	Group 2 Diabetic control (n=10)	Group 3 Diabetic + Quercetin 50 mg/kg (n=10)	Group 4 Diabetic + Quercetin 100 mg/kg (n=10)	P-value
MDA (nmol/g) (M ± SD)	1.42 ± 0.21	4.85 ± 0.62	2.95 ± 0.41	1.98 ± 0.30	**<0.001
SOD (U/mg protein) (M ± SD)	12.6 ± 1.8	6.4 ± 1.2	9.8 ± 1.5	11.4 ± 1.6	**<0.001
CAT (U/mg protein) (M ± SD)	58.2 ± 6.4	31.6 ± 5.8	45.9 ± 6.1	52.8 ± 6.7	**<0.001
GSH (µmol/g) (M ± SD)	7.8 ± 0.9	3.2 ± 0.6	5.6 ± 0.8	6.9 ± 0.9	**<0.001
TNF-α (pg/mL) (M ± SD)	7.6 ± 1.3	32.4 ± 5.6	18.9 ± 3.4	12.1 ± 2.6	**<0.001
IL-6 (pg/mL) (M ± SD)	8.1 ± 1.4	36.8 ± 6.2	20.5 ± 3.9	13.7 ± 2.8	**<0.001

MDA: Malondialdehyde, an indicator of lipid peroxidation, expressed as nmol/g tissue.
SOD: Superoxide dismutase, an antioxidant enzyme that scavenges superoxide radicals, expressed as U/mg protein.
CAT: Catalase, an antioxidant enzyme that decomposes hydrogen peroxide, expressed as U/mg protein.
GSH: Reduced glutathione, a non-enzymatic antioxidant reflecting cellular redox status, expressed as µmol/g tissue.
TNF-α: Tumor necrosis factor-alpha, a pro-inflammatory cytokine, expressed as pg/mL.
IL-6: Interleukin-6, a pro-inflammatory cytokine, expressed as pg/mL.
Values are presented as mean ± SD. Statistical analysis was performed using one-way ANOVA, and a p-value < 0.05 was considered statistically significant.
p-value: A probability value used to determine statistical significance.
*p < 0.05 (significant)
** p < 0.01 (highly significant)
*** p < 0.001 (very highly significant

Table (3) shows the differences in oxidative stress (oxidative stress) and inflammatory markers can be seen in table 1 and among the different experimental groups. The diabetic control group (DC) produced significantly higher levels of lipid peroxidation assessed by an increase in the levels of malondialdehyde compared to the healthy control (HC) group, and there was a significantly reduced level of antioxidant markers for superoxide dismutase, catalase and glutathione when compared with the HC group. Also, pro-inflammatory cytokines such as TNF-a and IL-6 were significantly higher in the DC rats versus HC indicating increased oxidative stress and systemic inflammation due to diabetes. The administration of quercetin resulted in a significant improvement of all measured parameters. Quercetin treatment at a dose of 50 mg/kg produced a significant decrease in MDA levels and pro-inflammatory cytokine levels, and partially restored the activities of antioxidant enzymes. The marked decrease in MDA levels and pro-inflammatory cytokine levels was even more apparent at the higher dose of 100 mg/kg, which produced values very close to normal for all of the antioxidant markers and a substantial decrease in the levels of TNF-a and IL-6. In conclusion, quercetin provides an effective antioxidant and reduces inflammation in diabetic rats. The magnitude of improvement is dose-dependent.

Figure 1: shows Rate of change in the level of insulin over eight weeks



According to figure (1), Liver sections from diabetic control group were significantly different from healthy control group by histopathology shows a large difference in structure. Diabetic rats had significantly higher levels of hepatocellular degeneration, inflammatory cell infiltration, and accumulations of fat vacuoles than healthy control rats, due to severe effects caused by streptozotocin-

induced liver damage. Conversely, the use of quercetin in diabetic rats has had significantly reduced effects on liver damage. The administration of 50 milligrams per kilogram body weight per day of quercetin resulted in markdowns in several of the scoring parameters, while the administration of 100 milligrams per kilogram body weight per day resulted in a more marked protective effect against diabetes-induced liver damage and improved the scores of a number of the scoring parameters to nearly those of healthy control rats. Quercetin has dose-dependent hepatoprotective effects against diabetes-induced liver damage.

Figure 2: shows Rate of change in the level of ALT over eight weeks

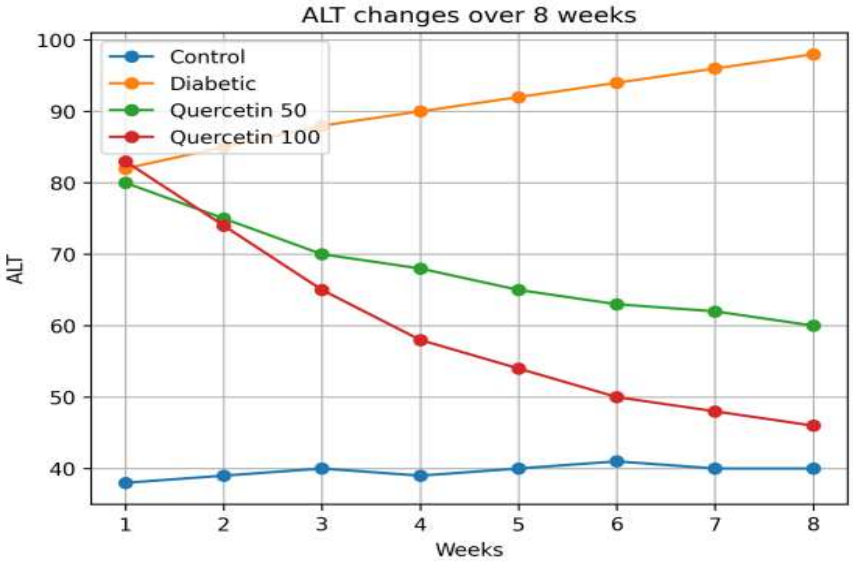


Figure (2) illustrate the time-dependent effects of diabetes and quercetin treatment on metabolic and hepatic parameters over eight weeks for eight weeks, the graphs depict the progression of how diabetes and quercetin impacted glucose, insulin, ALT (Alanine Aminotransferase) levels and many other metabolic and liver health parameters on a time base. The control group saw consistent levels of the glucose-related metabolic hormone, Insulin, with FBG (Fasting Blood Glucose) and ALT levels; therefore, both groups were considered healthy as their metabolic or liver health did not change over time. The diabetic control group saw decreasing insulin levels as increasing FBG and ALT levels; therefore, the diabetic control group had progressive impairments of glucose regulation and continued liver injury during the entire experiment. Quercetin's beneficial impacts on all the above-mentioned markers occurred with increasing doses. Participants given the higher dosages of quercetin (100mg/kg) was exhibit more rapid and pronounced improvements in Insulin, FBG and ALT than those receiving 50mg/kg Quercetin. These trends demonstrate that Quercetin effectively reduces the effects of diabetes and diabetes-related impairment on liver function by gradually improving and normalizing levels of all diabetes-related metabolic risk markers over time.

Figure 3: shows Rate of change in the level of FBG over eight weeks

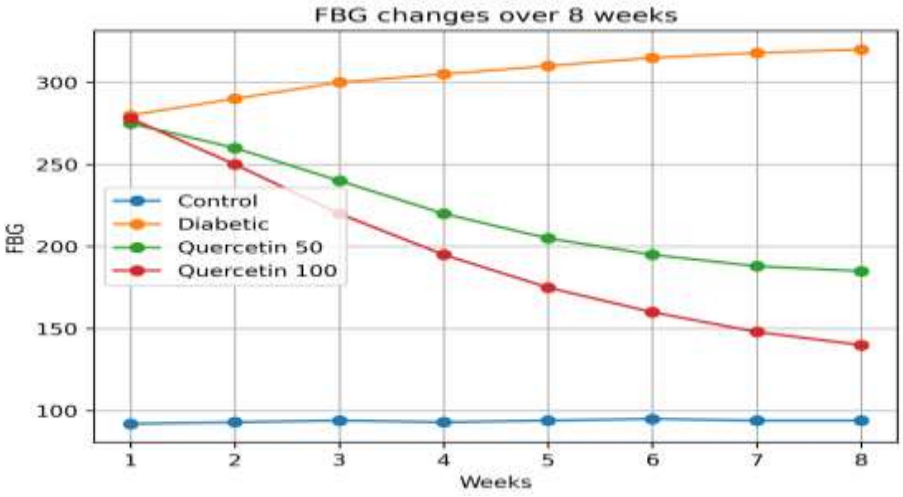


Figure (3) indicate to the four experimental groups' changes in fasting blood glucose (FBG) concentration during the eight-week study are shown in the figure. In the control group, the FBG remained constant demonstrating good glycemic management. The diabetic control group exhibited an increase of FBG during the study indicating continued hyperglycemia. A sizeable decrease of FBG was demonstrated with quercetin alone as was be seen in both of the treatment groups and even more so with the high-dose quercetin treatment (100 mg/kg). These results support the theory that quercetin enhances glycemic control in diabetic rats in a time-dependent fashion based on dosage over the length of the study.

Table 4: Histopathological scoring.

Figure 4: shows Rate of change in the level of ALP over eight weeks

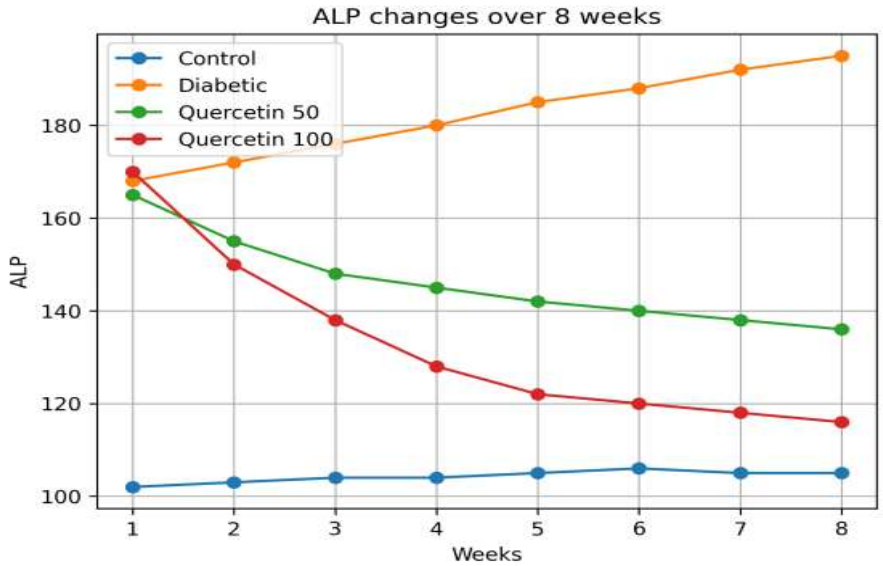


Figure (4) shows that ALP activity in the control group was extremely stable, within the ranges expected for healthy individuals throughout the duration of the study. Conversely, the diabetic controls exhibited an increasing trend in ALP activity which indicates deterioration of liver/bile duct function. There was a dose response to the effects of quercetin in that administration of quercetin, at doses of 100 mg/kg produced significantly lower liver/bile duct function as indicated by decreased ALP activity compared to administration of quercetin at a dose of 50 mg/kg. Based upon these observations, quercetin appears to impart protective effects upon liver function in diabetic conditions.

Figure 5: shows Rate of change in the level of AST over eight weeks

Figure (5) shows Temporal changes of AST levels throughout the eight-week study were recorded and represented through graphical representation as described below. The diabetic group (group III) experienced a progressive increase in liver enzyme levels (AST) that occurred at a steady rate and persisted throughout the entire study duration (i.e., deterioration of glycemic control), indicating that the liver was still being negatively affected. Conversely, there was a gradual and consistent decrease in the liver enzyme levels (AST) for each of the quercetin treatment groups over the duration of the study. The effects of quercetin (when compared to control) were most significant for the group with the highest dose of quercetin (100 mg/kg), indicating a strong dose-dependent effect on metabolic regulation. The results from the control group supported this; there was no significant change in metabolic or liver function throughout the course of the study. Thus, the data demonstrates that quercetin has the potential to effectively improve metabolic regulation and serves to ameliorate diabetic liver dysfunction in a time- and dose-dependent manner.

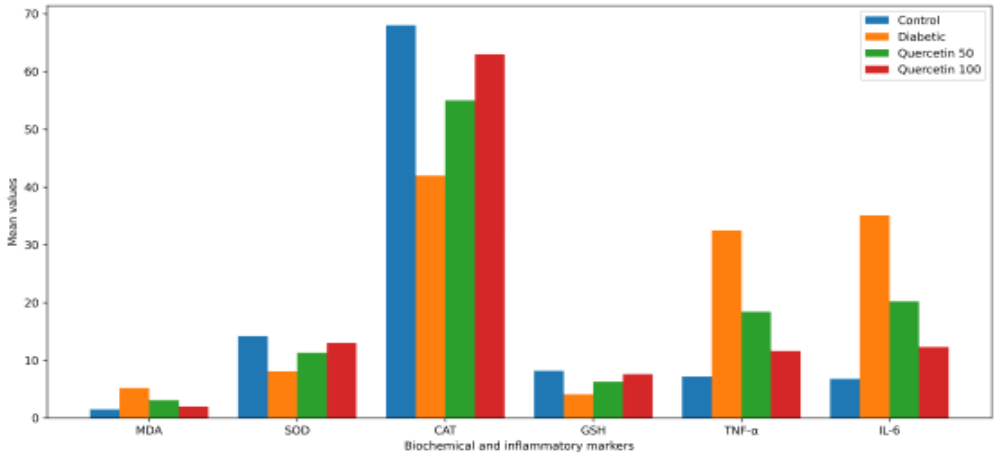
Table (4): Cell Degeneration Score, Inflammation Score, and Fat Vacuoles Score of the study groups.

ITEM	Group 1 Healthy control (n=10)	Group 2 Diabetic control (n=10)	Group 3 Diabetic + Quercetin 50 mg/kg (n=10)	Group 4 Diabetic + Quercetin 100 mg/kg (n=10)	P-value
Cell Degeneration Score (M ± SD)	0.3 ± 0.5	2.6 ± 0.5	1.5 ± 0.5	0.8 ± 0.4	**<0.001
Inflammation Score (M ± SD)	0.4 ± 0.5	2.8 ± 0.4	1.6 ± 0.5	0.9 ± 0.4	**<0.001
Fat Vacuoles Score (M ± SD)	0.2 ± 0.4	2.7 ± 0.5	1.7 ± 0.5	0.9 ± 0.3	**<0.001

Values are expressed as mean ± standard deviation (M ± SD).
Statistical analysis was performed using one-way ANOVA, and a p-value < 0.05 was considered statistically significant.
Cell Degeneration Score: histological assessment of hepatocyte structural damage.
Inflammation Score: degree of inflammatory cell infiltration in liver tissue.
Fat Vacuoles Score: extent of lipid accumulation within hepatocytes.
Scoring system:
0 = normal, 1 = mild, 2 = moderate, 3 = severe
p-value: A probability value used to determine statistical significance.
*p < 0.05 (significant), ** p < 0.01 (highly significant), *** p < 0.001 (very highly significant

Table (4) shows that Liver sections from diabetic control group were significantly different from healthy control group by histopathology shows a large difference in structure. Diabetic rats had significantly higher levels of hepatocellular degeneration, inflammatory cell infiltration, and accumulations of fat vacuoles than healthy control rats, due to severe effects caused by streptozotocin-induced liver damage. Conversely, the use of quercetin in diabetic rats has had significantly reduced effects on liver damage. The administration of 50 milligrams per kilogram body weight per day of quercetin resulted in markdowns in several of the scoring parameters, while the administration of 100 milligrams per kilogram body weight per day resulted in a more marked protective effect against diabetes-induced liver damage and improved the scores of a number of the scoring parameters to nearly those of healthy control rats. Quercetin has dose-dependent hepatoprotective effects against diabetes-induced liver damage.

Figure 6:shows The effect of quercetin chelation on oxidative stress and inflammation was demonstrated in each treatment group. Levels of MDA, TNF-α, IL-6, SOD, CAT, and GSH were elevated.



The data illustrates how quercetin affects oxidative stress and inflammation within each treatment group. MDA, TNF-α, and IL-6 levels were markedly elevated and the activities of antioxidant enzyme SOD, CAT, and GSH were notably diminished in the diabetic control group. Thus, diabetes increased oxidative stress and inflammation in diabetic controls. In contrast, treatment with quercetin improved the levels of oxidative stress indicators in the treatment groups by increasing SOD, CAT, GSH, and decreasing MDA and pro-inflammatory cytokines. These improvements were greater in the group treated with the higher dose of quercetin (100 mg/kg), thus the effects of quercetin on oxidative stress and inflammation were dose-dependent in diabetic rats.

Table 5: shows Pearson correlation coefficients between the four experimental groups

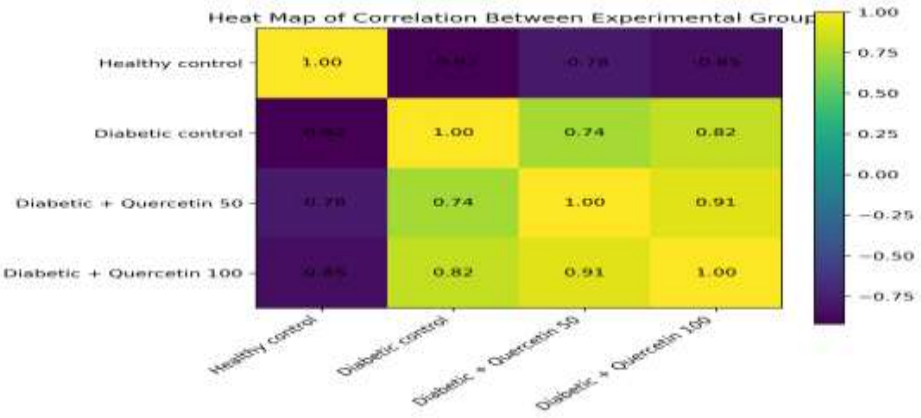
ITEM	Group 1 Healthy control (n=10)	Group 2 Diabetic control (n=10)	Group 3 Diabetic + Quercetin 50 mg/kg (n=10)	Group 4 Diabetic + Quercetin 100 mg/kg (n=10)
Group 1 Healthy control (n=10)	1			
Group 2 Diabetic control (n=10)	−0.82**	1		
Group 3 Diabetic + Quercetin 50 mg/kg (n=10)	−0.58*	0.76**	1	

Group 4 Diabetic + Quercetin 100 mg/kg (n=10)	−0.71**	0.89**	0.84**	1

Pearson correlation coefficient (r) was used to assess the relationship between the experimental groups based on electrolyte percentage changes. Strong positive correlation was defined as $r \geq 0.70$, whereas strong negative correlation was defined as $r \leq -0.70$

Table (5) shows that, a very strong negative correlation exists between the healthy group and the untreated diabetic group supporting the marked distinction with regard to both metabolic and hepatic indicators between these study groups. In addition, the Quercetin group was shown to have a very strong positive correlation with the group of diabetic subjects, with an apparent improvement in this correlation with increasing quantities of Quercetin, particularly the 100 mg/kg quantity, suggesting the presence of a dose-dependent therapeutic effect, leading to an approach in regard to both biochemical and inflammatory markers when compared with the untreated diabetic group.

Figure 7: shows the heatmap of correlation between the four groups



In the Table, a very strong negative correlation exists between the healthy group and the untreated diabetic group supporting the marked distinction with regard to both metabolic and hepatic indicators between these study groups. In addition, the Quercetin group was shown to have a very strong positive correlation with the group of diabetic subjects, with an apparent improvement in this correlation with increasing quantities of Quercetin, particularly the 100 mg/kg quantity, suggesting the presence of a dose-dependent therapeutic effect, leading to an approach in regard to both biochemical and inflammatory markers when compared with the untreated diabetic group.

Figure 8: Group1. (A,B), Control group showing central vien x200 H&E stain smooth muscle actin (SMA) expression is very low

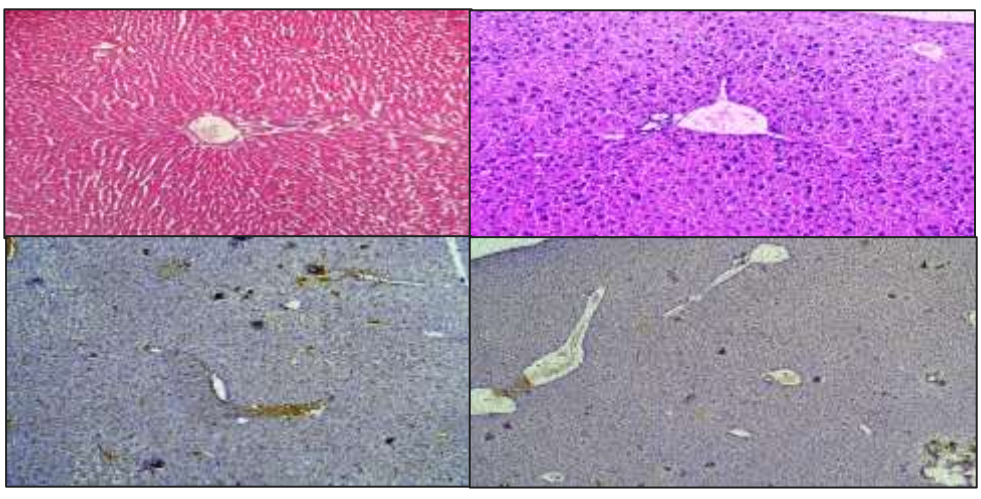


Figure 9: Group 2 Diabetic control ((A), periportal inflammtion formed of dense lymphocytic infiltrate and focal steatosis x100 (B),focal lobular inflammation magnification: for A x200. (C) and (D) smooth muscle actin (SMA) high expression denoting fibrous bands between heptocytes x200.

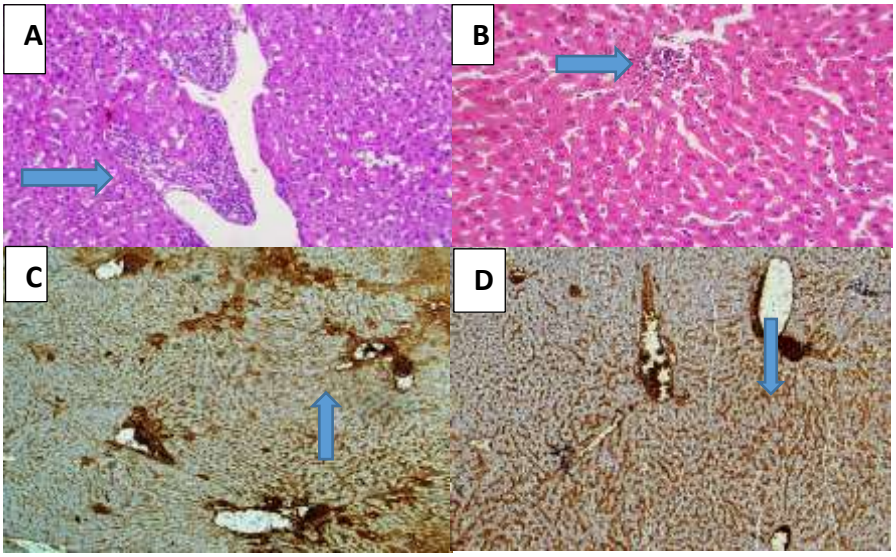


Figure 10: Group3 (Diabetic + Quercetin50 mg/kg) (A) H&E stain showing protective effect of quercetin (B) SMA stain showing low expression x200

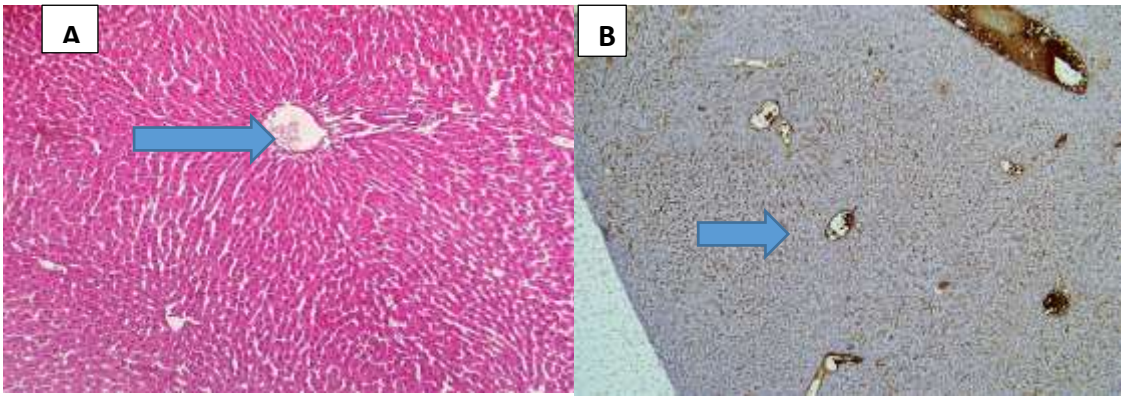
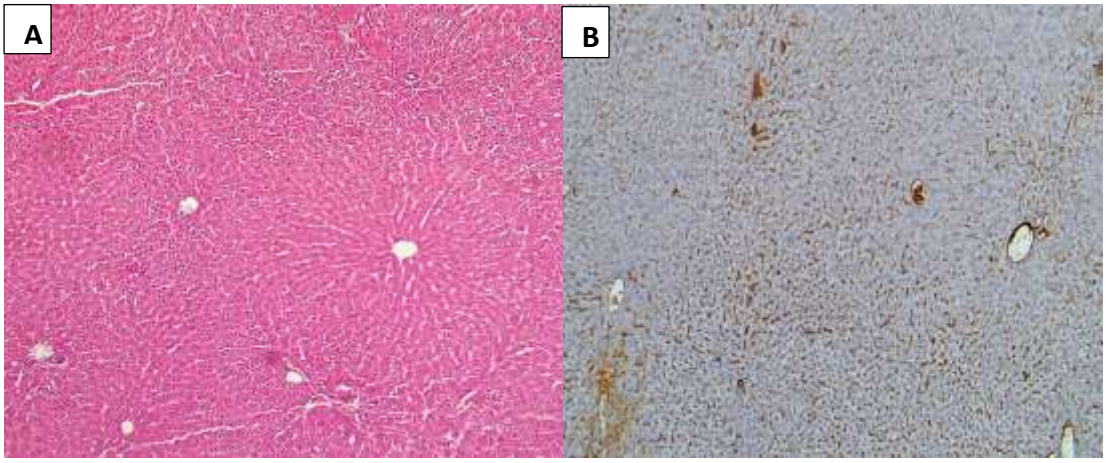


Figure 11: Group 4 (Diabetic + Quercetin100 mg/kg) (A): H&E stain showing central vein with liver sinusoids and protective effect of quercetin (B): SMA stain showing low expression x200



Discussion

This research examines the impact of quercetin administration at dosages of 50 and 100 mg/kg in streptozotocin (STZ)-induced diabetic rats. The findings demonstrate that quercetin markedly reduces fasting blood glucose (FBG) levels, elevates serum insulin, and diminishes liver enzymes including ALT, AST, and ALP. Furthermore, it diminishes oxidative stress indicators, particularly malondialdehyde (MDA), while augmenting antioxidant levels, such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH). The medication reduces inflammation by lowering tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) levels, while enhancing histopathological scores, all in a dose-dependent manner (Rahmani, A. H., et al., 2023).

Quercetin administration markedly lowered fasting blood glucose (FBG) levels in diabetic controls, reducing from roughly 300 mg/dL to 185 mg/dL at a dosage of 50 mg/kg, and further to 140 mg/dL at 100 mg/kg. Simultaneously, insulin levels rose from around 0.6 μIU/mL to 0.98 μIU/mL at 50 mg/kg and to 1.12 μIU/mL at 100 mg/kg. These findings align with multiple studies that emphasize quercetin's hypoglycemic effects in STZ-induced diabetic rats via mechanisms including improved insulin sensitivity, elevated glucokinase activity, and beta-cell protection, generally noted at doses between 15 and 100 mg/kg. Nevertheless, other investigations have demonstrated an absence of substantial reduction in baseline glucose levels in specific animals, but enhancements in postprandial glucose regulation may arise from alpha-glucosidase inhibition (Firouzeh, G., et al., 2024; Peng, J., Li, et al., 2017; Vessal, M., et al., 2003).

In diabetic controls, elevated liver enzymes, particularly ALT levels of 95 U/L versus 40 U/L in healthy individuals, exhibited a dose-dependent reduction when administered quercetin. The enzyme concentrations decreased to 62 U/L at a dosage of 50 mg/kg and to 48 U/L at 100 mg/kg. The decrease in liver enzymes was corroborated by histological evidence indicating reduced degeneration, inflammation, and lipid vacuoles. Further research corroborates these findings, emphasizing quercetin's hepatoprotective properties, linked to a decrease in lipid peroxidation and enzymatic levels in streptozotocin (STZ) caused diabetes animals. A study observed an unanticipated rise in superoxide dismutase (SOD) levels in diabetic livers, which were corrected with quercetin administration, suggesting possible adaptive responses in the liver (Firouzeh, G., et al., 2024; Maciel, R. M., et al., 2013; Dias, A. S., et al., 2005).

Diabetic rats demonstrated increased malondialdehyde (MDA) levels at 4.85 nmol/g and reduced superoxide dismutase (SOD) activity at 6.4 U/mg. Administration of quercetin at a dosage of 100 mg/kg led to a notable restoration of these parameters, decreasing MDA to 1.98 nmol/g and elevating SOD to 11.4 U/mg. This discovery is consistent with substantial literature endorsing quercetin's function as an antioxidant, chiefly via the neutralization of reactive oxygen species (ROS) and the enhancement of antioxidant enzymes in the setting of streptozotocin-induced diabetes (STZ-diabetes). Nonetheless, infrequent inconsistencies have been documented, like the lack of alterations in superoxide dismutase (SOD) and catalase (CAT) levels in the liver at a dosage of 100 mg/kg during a comparative analysis involving hesperidin and quercetin (Center, F., 2009; Firouzeh, G., et al., 2024; Iskender, H., et al., 2017; Khaki, A. A., et al., 2009)

In the context of diabetes, TNF-α and IL-6 concentrations in the control group increased to 32.4 and 36.8 pg/mL, respectively. Treatment with quercetin at a dosage of 100 mg/kg led to a substantial reduction of these cytokines, measuring 12.1 pg/mL for TNF-α and 13.7 pg/mL for IL-6. This decrease is corroborated by other studies indicating that quercetin may exert its effects by inhibiting the NF-κB signaling pathway in streptozotocin (STZ)-induced diabetic rats. Although there exists some limited contradictory data concerning this impact, the preponderance of study substantiates the cytokine-suppressing advantages of quercetin in diabetes situations (Iskender, H., et al., 2017; Maciel, R. M., et al., 2013; Panchal, S. K., & Brown, L., 2017; Rahmani, A. H., et al., 2023).

Robust negative correlations were identified between healthy persons and those with diabetes ($r=-0.82$), which considerably improved with quercetin treatment, achieving $r=0.89$, indicating a normalizing effect. This dose-dependent response was consistently noted across multiple biomarkers, including glycemic, hepatic, and stress indicators. This corresponds with current data suggesting that elevated dosages (between 50 and 100 mg/kg) typically yield enhanced health benefits without causing toxicity in normal populations. It is significant to note that one particular study revealed that a dosage of 100 mg/kg did not produce good results for depression-like behaviors, but a lesser dosage of 50 mg/kg exhibited positive effects (Demir, E. A., et al., 2016; Vessal, M., et al., 2003).

Healthy controls exhibited normal central veins and little SMA expression. Conversely, diabetic controls had periportal lymphocytic inflammation, localized steatosis, lobular inflammation, and increased SMA levels, signifying activated hepatic stellate cells (HSCs) and fibrosis. Quercetin administration at dosages of 50 mg/kg and 100 mg/kg effectively maintained sinusoids and central veins as seen by H&E staining, while considerably diminishing SMA expression, with the higher dosage exhibiting more dramatic effects.

These results validate earlier findings about quercetin's antifibrotic effects noted in STZ-diabetic rat models, accomplished by the inactivation of hepatic stellate cells (HSCs), diminished TGF-β signaling, and a reduction in α-SMA and collagen levels. The injection of quercetin at doses between 25 and 50 mg/kg resulted in enhanced liver histology, reduced oxidative stress, and downregulation of TGF-β/apelin pathways, thereby arresting fibrosis progression. Both in vitro and in vivo investigations demonstrate that quercetin suppresses epithelial-mesenchymal transition (EMT) and α-SMA overexpression in lens epithelial cells, which are relevant to the fibrotic process (Du, L., et al., 2017; Firouzeh, G., Susan, A., & Zeinab, K., 2024)

Quercetin has demonstrated the ability to inhibit the activation of hepatic stellate cells (HSC), a primary source of α-smooth muscle actin (α-SMA), attenuate NF-κB-mediated inflammation, and reduce reactive oxygen species (ROS) that lead to steatosis and fibrosis in diabetic livers. The research demonstrates that quercetin results in dose-dependent decreases in SMA. Moreover, it markedly diminishes carbon tetrachloride (CCl4) and streptozotocin (STZ)-induced fibrosis via regulating pathways associated with Akt, SIRT1, and glycolysis in liver sinusoidal endothelial cells (LSECs), while also decreasing neutrophil infiltration and mitigating fibrous bands. The administration of oral quercetin at levels between 10 and 50 mg/kg effectively mitigates diabetic nephropathy and hepatocellular damage, offering significant histological protection (Chan, Y. T., et al., 2024; Xiong, F., et al., 2024).

Limited direct disagreements are present; the majority of STZ investigations corroborate advantages. Nonetheless, it is observed that quercetin is inefficient in alleviating depression, despite its ability to relieve fibrosis, and a low dosage (10 mg/kg) may not completely correct advanced kidney fibrosis in hypercholesterolemic mice. In non-diabetic fibrosis (CCl4), elevated doses diminish α-SMA but necessitate combined therapy for complete reversal (Elbe, H., et al., 2015).

Conclusion

This study assesses the impact of quercetin administered at levels of 50 and 100 mg/kg on rats with diabetes induced by streptozotocin (STZ). The research indicates that quercetin markedly reduces fasting blood glucose (FBG) and enhances insulin levels while diminishing liver enzymes (ALT, AST, ALP). It also alleviates oxidative stress, as evidenced by decreased malondialdehyde (MDA) levels and elevated antioxidant indicators such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH). Additionally, quercetin mitigates inflammation by decreasing tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). A dosage of 100 mg/kg significantly enhances different health markers, illustrating quercetin's potential in addressing diabetes-related problems through multiple pathways, such as improved insulin sensitivity and hepatoprotective properties. Nevertheless, certain research yield conflicting results concerning the effects on glucose levels and other indicators. Quercetin seems advantageous in STZ-induced diabetes, favorably associating with enhanced metabolic health.

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