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Original Research Article

Antidiabetic and Cognition-Protective Effects of Quercetin in Streptozotocin-Induced Diabetic Rats: A Comparative Study with Metformin

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Abstract:

Background: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder of rapidly increasing global prevalence that is frequently accompanied by dyslipidemia, weight loss and progressive cognitive decline. Quercetin (QC), a naturally occurring flavonol, has demonstrated anti-hyperglycaemic, antioxidant and neuroprotective properties in preclinical models, but its comparative efficacy against a standard antidiabetic agent on glycemic control, body weight, and cognition and lipid profile together has not been widely characterised. Objective of this study is to evaluate the effect of oral quercetin (25 mg/kg/day) on fasting blood glucose, body weight, cognitive performance and serum lipid profile in streptozotocin (STZ)-induced diabetic Wistar rats, in comparison with metformin (100 mg/kg/day).

Methods: Forty adult male Wistar rats were allocated to five groups (n = 8 each): normal control, diabetic control, diabetic + quercetin, non-diabetic + quercetin, and diabetic + metformin. Diabetes was induced using a high-fat-diet/low-dose-streptozotocin model. Treatments were administered orally for 35 days. Fasting blood glucose and body weight were recorded at baseline and on day 35. Cognitive function was assessed using the Morris water maze (MWM) and passive avoidance tests, and serum lipid profile was estimated at the end of the study. Data were analysed by one-way ANOVA followed by Tukey's post-hoc test.

Results: Baseline parameters were comparable across groups ($p > 0.05$). Diabetic control rats showed persistent hyperglycemia (312.8 ± 26.7 mg/dL), weight loss (214.7 ± 13.2 g), impaired spatial memory (MWM escape latency 39.8 ± 4.8 s) and marked dyslipidemia at day 35. Quercetin significantly reduced fasting blood glucose to 168.4 ± 19.6 mg/dL, preserved body weight (248.9 ± 15.1 g), improved MWM escape latency (23.9 ± 3.5 s) and passive avoidance latency (176.8 ± 20.4 s), and improved all lipid parameters compared with diabetic controls ($p < 0.001$ for all). Metformin produced a marginally greater glucose-lowering effect than quercetin (142.9 ± 17.3 mg/dL, $p = 0.041$ versus quercetin), while cognitive and weight-preserving effects of the two agents were broadly comparable.

Conclusion: Quercetin exerts substantial antidiabetic, weight-preserving, cognition-protective and lipid-modulating effects in STZ-induced diabetic rats, approaching those of metformin, supporting its potential as an adjunct or alternative nutraceutical in the management of diabetes and its cognitive complications.

Keywords: Quercetin; Streptozotocin; Diabetes mellitus; Cognitive dysfunction; Morris water maze; Metformin; Dyslipidemia; Flavonoid.

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Introduction

Diabetes mellitus (DM) is the most common metabolic disorder worldwide, characterised by chronic hyperglycemia arising from inadequate insulin secretion, insulin resistance, or both. According to the American Diabetes Association, DM is broadly classified into type 1 and type 2 forms, with type 2 diabetes mellitus (T2DM) accounting for the vast majority of cases [2]. Global estimates place the burden of the disease at approximately 537 million adults living with diabetes in 2021, a figure projected to rise to 783 million by 2045, reflecting the disease's escalating public-health impact [1]. Beyond hyperglycemia, T2DM is associated with dyslipidemia, unintended

weight change, and an increased risk of microvascular and macrovascular complications, and it has emerged as an independent risk factor for cognitive impairment and dementia, an association now recognised as "diabetic encephalopathy." Flavonoids are polyphenolic compounds ubiquitously distributed in fruits, vegetables, tea and wine, and have long been of interest for their broad pharmacological activity [3]. Quercetin (3,3′,4′,5,7-pentahydroxyflavone; QC) is the most abundant dietary flavonol and possesses potent antioxidant, anti-inflammatory and free-radical-scavenging properties. Mechanistically, quercetin has been shown to stimulate glucose uptake in skeletal muscle through an insulin-independent, mitogen-activated protein kinase (MAPK)-dependent pathway that promotes translocation of glucose transporter-4 (GLUT4) to the plasma membrane, while in the liver it suppresses key gluconeogenic enzymes, thereby lowering hepatic glucose output [4]. Quercetin also crosses the blood–brain barrier and scavenges reactive oxygen species within brain tissue, modulating neuroinflammation without an appreciable toxicological burden [5,6].

A number of experimental studies have demonstrated antidiabetic, antioxidant and nephroprotective effects of quercetin in streptozotocin (STZ)-induced diabetic rodents [12,13,14,15], and quercetin has also been reported to attenuate features of the metabolic syndrome, including dyslipidemia and adipose tissue dysfunction [7].

Separately, quercetin has shown neuroprotective and memory-enhancing effects in models of chemically induced neurotoxicity and chronic stress, improving performance in the Morris water maze and passive avoidance paradigms [9,10,11].

However, comparatively few studies have examined, within a single experimental design, the combined effect of quercetin on glycemic control, body weight, cognitive performance and lipid profile, and fewer still have benchmarked this composite effect against a first-line antidiabetic drug such as metformin. Since quercetin is well tolerated as a dietary supplement and no significant adverse effects have been reported with its use, characterising its potential to simultaneously address hyperglycemia and diabetes-associated cognitive impairment is of considerable translational interest. The present study was therefore designed to evaluate the antidiabetic properties of quercetin, with particular focus on cognition, in a high-fat-diet/low-dose-STZ model of experimental diabetes in male Wistar rats, using metformin as an active comparator.

Objective of this study is to evaluate the effect of oral quercetin (25 mg/kg/day) on fasting blood glucose, body weight, cognitive performance and serum lipid profile in streptozotocin (STZ)-induced diabetic Wistar rats, in comparison with metformin (100 mg/kg/day).

Materials and Methods

Ethical Approval: The study protocol, titled 'Evaluation of Anti-diabetic properties of Quercetin with special focus on cognition in rats', was approved by the Institutional Animal Ethics Committee (IAEC) of Coimbatore Medical College, Coimbatore, in accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines (Registration No. 1806/GO/Re/S/ CPCSEA). All experimental procedures conformed to institutional and national guidelines for the care and use of laboratory animals.

Animals: Ninety-day-old healthy male Wistar rats weighing 220–300 g were procured from a CPCSEA-approved breeder and housed in the central animal house under standard laboratory conditions (temperature 27 ± 2 °C, relative humidity 50–70%, 12-hour light/dark cycle) with free access to standard pellet diet and water ad libitum. Animals were acclimatised for 10 days prior to the commencement of the study.

Induction of experimental diabetes: Type 2 diabetes was induced using a high-fat-diet (HFD)/STZ model. Rats were fed a high-fat diet for 2–4 weeks to induce insulin resistance and glucose intolerance, followed by a single low intraperitoneal dose of streptozotocin (30–35 mg/kg) dissolved in citrate buffer. Blood glucose was measured from the tail vein 72 hours after STZ administration, and animals with fasting glycemia exceeding 250 mg/dL were included as diabetic.

Drugs and chemicals: Quercetin (≥95% purity; molecular formula $C_{15}H_{10}O_7$; molecular weight 302.24 g/mol) was procured from Sisco Research Laboratory and administered orally at a dose of 25 mg/kg/day suspended in distilled water, based on doses previously reported to be neuroprotective and antidiabetic in rodent models [9,10] Metformin was administered orally at 100 mg/kg/day suspended in distilled water. Both drugs were administered once daily for 35 consecutive days.

Experimental design and grouping: Animals were randomly allocated into five groups of eight rats each:

- Group I – Normal control: standard diet, received vehicle for 35 days.
- Group II – Diabetic control: diabetic rats treated with vehicle for 35 days.
- Group III – Diabetic + Quercetin: diabetic rats treated with quercetin (25 mg/kg/day, oral) for 35 days.

- Group IV – Non-diabetic + Quercetin: non-diabetic rats treated with quercetin (25 mg/kg/day, oral) for 35 days.
- Group V – Diabetic + Metformin: diabetic rats treated with metformin (100 mg/kg/day, oral) for 35 days.

Assessment of fasting blood glucose and body weight: Fasting blood glucose was estimated at baseline (day 0) and on day 35 using the glucose oxidase–peroxidase method. Body weight was recorded at baseline and at the end of the treatment period using a calibrated digital balance.

Behavioural assessment of cognitive function: Spatial learning and memory were assessed using the Morris water maze (MWM) test, in which the mean escape latency to locate a hidden platform was recorded across training trials for each group. Long-term retention memory was assessed using the passive avoidance test conducted in a shuttle-box apparatus, with step-through/step-down latency recorded as the outcome measure.

Estimation of serum lipid profile: At the end of the treatment period, blood was withdrawn by cardiac puncture and serum was separated for estimation of total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol using standard enzymatic assay kits, with results expressed in mg/dL.

Statistical analysis: Data are expressed as mean ± standard deviation (SD) for eight animals per group. Differences between groups were analysed using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc multiple comparison test where indicated.

A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software.

Results

Baseline body weight and fasting blood glucose did not differ significantly among the five experimental groups (one-way ANOVA, $p = 0.91$ and $p = 0.88$, respectively), confirming comparability of the groups prior to diabetes induction and treatment (Table 1).

Table 1: Baseline characteristics of experimental animals

Group	Body weight (g)	Fasting blood glucose (mg/dL)
Normal control	246.8 ± 12.5	92.4 ± 8.6
Diabetic control	244.9 ± 10.8	94.8 ± 9.1
Diabetic + quercetin	247.6 ± 11.3	93.6 ± 7.9
Non-diabetic + quercetin	245.2 ± 13.1	91.8 ± 8.3
Diabetic + metformin	246.1 ± 12.0	93.9 ± 8.7

One-way ANOVA: $p = 0.91$ (body weight), $p = 0.88$ (fasting blood glucose). Values are mean ± SD ($n = 8$/group).

Diabetic control rats exhibited persistent and worsening hyperglycemia over the 35-day study period, whereas quercetin treatment produced a marked reduction in fasting blood glucose (Table 2). Metformin produced a slightly greater glucose-lowering effect than quercetin (Tukey post-hoc, $p = 0.041$), although both agents differed significantly from diabetic controls ($p < 0.001$ for each comparison).

Table 2: Effect of quercetin on fasting blood glucose after 35 days

Group	Day 0 (mg/dL)	Day 35 (mg/dL)
Normal control	92.4 ± 8.6	94.7 ± 7.9
Diabetic control	286.5 ± 21.4	312.8 ± 26.7
Diabetic + quercetin	289.2 ± 18.9	168.4 ± 19.6
Non-diabetic + quercetin	91.8 ± 8.3	89.6 ± 7.4
Diabetic + metformin	287.6 ± 20.8	142.9 ± 17.3

One-way ANOVA (Day 35): $p < 0.001$. Tukey post-hoc: diabetic control vs diabetic + quercetin, $p < 0.001$; diabetic control vs diabetic + metformin, $p < 0.001$; diabetic + quercetin vs diabetic + metformin, $p = 0.041$. Induction of diabetes was accompanied by significant weight loss in diabetic control animals by day 35, whereas quercetin treatment prevented this diabetes-induced weight loss and produced a final body weight close to that of the metformin-treated group (Table 3).

Table 3: Effect of quercetin on body weight after 35 days

Group	Initial body weight (g)	Final body weight (g)
Normal control	246.8 ± 12.5	272.6 ± 14.8
Diabetic control	244.9 ± 10.8	214.7 ± 13.2
Diabetic + quercetin	247.6 ± 11.3	248.9 ± 15.1
Non-diabetic + quercetin	245.2 ± 13.1	276.8 ± 13.7
Diabetic + metformin	246.1 ± 12.0	255.4 ± 14.2

One-way ANOVA (Day 35): $p < 0.001$. Values are mean ± SD (n = 8/group).

Diabetes significantly impaired spatial learning and memory, reflected by increased Morris water maze (MWM) escape latency and reduced passive avoidance latency in diabetic control rats. Quercetin treatment markedly improved both measures of cognitive performance relative to diabetic controls, indicating protection against diabetes-associated memory impairment, with effects approaching those seen with metformin (Table 4).

Table 4: Effect of quercetin on cognitive function

Group	MWM escape latency (s)	Passive avoidance latency (s)
Normal control	18.6 ± 2.9	201.4 ± 18.6
Diabetic control	39.8 ± 4.8	98.7 ± 15.2
Diabetic + quercetin	23.9 ± 3.5	176.8 ± 20.4
Non-diabetic + quercetin	17.8 ± 2.4	208.6 ± 16.9
Diabetic + metformin	21.6 ± 3.1	185.2 ± 17.7

One-way ANOVA: MWM, $p < 0.001$; passive avoidance, $p < 0.001$. Lower MWM escape latency and higher passive avoidance latency indicate better cognitive performance. Diabetic control rats developed marked dyslipidemia, with elevated total cholesterol, triglycerides and LDL cholesterol, and reduced HDL cholesterol, relative to normal controls. Quercetin treatment significantly improved all four lipid parameters compared with diabetic controls, indicating a beneficial effect on diabetes-induced lipid abnormalities that paralleled the effect of metformin (Table 5).

Table 5: Effect of quercetin on serum lipid profile (mg/dL)

Parameter	Normal control	Diabetic control	Diabetic + quercetin	Diabetic + metformin
Total cholesterol	86.5 ± 8.4	154.8 ± 12.6	102.7 ± 9.3	96.4 ± 8.7
Triglycerides	72.4 ± 7.8	138.6 ± 14.1	88.9 ± 10.2	82.7 ± 9.5
LDL cholesterol	28.6 ± 4.1	82.5 ± 9.8	46.8 ± 6.3	41.2 ± 5.9
HDL cholesterol	42.8 ± 4.6	26.9 ± 3.8	37.6 ± 4.2	39.4 ± 4.1

One-way ANOVA: $p < 0.001$ for all lipid parameters. Values are mean ± SD (n = 8/group).

Discussion

The present study demonstrates that oral quercetin (25 mg/kg/day) significantly ameliorates hyperglycemia, prevents diabetes-associated weight loss, protects against cognitive impairment, and improves the deranged lipid profile in a high-fat-diet/low-dose-STZ model of experimental diabetes, with effects that were broadly comparable to, though for glycemic control marginally less than, those of metformin.

The glucose-lowering effect of quercetin observed in this study is consistent with earlier reports describing its antihyperglycemic action in STZ-induced diabetic rats [14,15]. Mechanistically, quercetin is believed to stimulate GLUT4-mediated glucose uptake in skeletal muscle through an insulin-independent MAPK pathway, while concurrently suppressing key hepatic gluconeogenic enzymes, thereby lowering both peripheral insulin resistance and hepatic glucose output [4]. This dual mechanism differs from that of metformin, which primarily suppresses hepatic gluconeogenesis and activates AMP-activated protein kinase (AMPK) in the liver and skeletal muscle [16,17]. The slightly greater glucose-lowering efficacy of metformin observed here may reflect its more direct and potent action on hepatic AMPK signalling, whereas quercetin's efficacy is likely to be constrained by its comparatively low oral bioavailability, given the extensive first-pass intestinal and hepatic metabolism to which dietary flavonols are subject [18].

Diabetic control animals in this study exhibited significant weight loss, a well-recognised consequence of the catabolic state induced by insulin deficiency and increased breakdown of structural proteins and fats for energy. Quercetin treatment substantially prevented this weight loss, an effect that has similarly been reported with quercetin in other STZ-diabetic rat models and that likely reflects improved glycemic control together with the antioxidant amelioration of diabetes-associated tissue catabolism [13,14].

The cognitive protection conferred by quercetin, evidenced by improved Morris water maze and passive avoidance performance, corroborates previous work showing that quercetin ameliorates diabetes-induced memory dysfunction in streptozotocin-treated rats [11] and improves hippocampus-dependent spatial learning through the attenuation of oxidative stress and neuroinflammation in models of chemically induced neurotoxicity and chronic stress [9,10]. Chronic hyperglycemia promotes the generation of reactive oxygen species, advanced glycation end-products and neuroinflammatory cytokines within

the hippocampus and cerebral cortex, processes collectively implicated in diabetic encephalopathy. Quercetin's capacity to scavenge free radicals and modulate neuroinflammatory signalling in brain tissue [5,6] provides a plausible mechanistic basis for the improved cognitive performance observed in the quercetin-treated diabetic group in the present study, and these effects were of a magnitude approaching those seen with metformin, which itself is increasingly recognised to have neuroprotective actions independent of its glucose-lowering effect.

With respect to lipid metabolism, quercetin significantly improved total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol relative to diabetic controls.

This finding is consistent with earlier work showing that quercetin lowers plasma cholesterol and triglycerides in STZ-induced diabetic rats [14], and that quercetin, alone or in combination with other polyphenols, attenuates features of the metabolic syndrome through modulation of adipose tissue fatty acid composition and sirtuin expression [7]. The reno- and hepato-protective antioxidant actions of quercetin described in diabetic rodent models [12,13,15,20] may further contribute to the observed metabolic improvements by limiting oxidative damage to lipid-metabolising tissues. Taken together, these findings support the hypothesis that quercetin's antidiabetic, weight-preserving, cognition-protective and lipid-modulating actions are interlinked and substantially mediated by its combined insulin-sensitising and antioxidant properties, distinguishing it from metformin, whose principal action is confined to suppression of hepatic glucose output. The comparability of quercetin's effects to those of a first-line antidiabetic agent, despite quercetin's more modest glucose-lowering potency, is noteworthy given its favourable tolerability profile as a dietary flavonoid.

This study has certain limitations.

The relatively short 35-day treatment duration, use of a single dose of quercetin, and absence of histopathological and biochemical (oxidative stress marker) correlation in the present report constrain mechanistic interpretation.

Additionally, the modest sample size (n = 8/group), while adequate for the primary comparisons performed, limits the precision of effect-size estimation.

Future studies incorporating dose-ranging, histopathological confirmation of pancreatic, hepatic and hippocampal changes, and measurement of oxidative stress and inflammatory biomarkers would strengthen the mechanistic basis of these findings and further clarify quercetin's therapeutic potential in diabetes-associated cognitive dysfunction.

Conclusion

In this high-fat-diet/low-dose-streptozotocin model of experimental diabetes, oral quercetin (25 mg/kg/day) for 35 days significantly reduced fasting blood glucose, prevented diabetes-induced weight loss, improved spatial learning and memory on the Morris water maze and passive avoidance tests, and corrected the deranged serum lipid profile associated with diabetes.

These effects were comparable to those of metformin, a standard first-line antidiabetic agent, for weight, cognitive and lipid parameters, though metformin showed marginally greater efficacy for glycemic control. These findings support further evaluation of quercetin as a well-tolerated adjunctive or alternative therapeutic option for the management of type 2 diabetes mellitus and its associated cognitive complications.

References

1. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.
2. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S13–S27.
3. Brown JP. A review of the genetic effects of naturally occurring flavonoids, anthraquinones and related compounds. Mutat Res. 1980;75(3):243–277.
4. Haddad PS, Eid HM, Nachar A, Thong F, Sweeney G. The molecular basis of the antidiabetic action of quercetin in cultured skeletal muscle cells and hepatocytes. Pharmacogn Mag. 2015;11(41):74–81.
5. Chakraborty S, Stalin S, Das N, Choudhury ST, Ghosh S, Swarnakar S. The use of nano-quercetin to arrest mitochondrial damage and MMP-9 upregulation during prevention of gastric inflammation induced by ethanol in rat. Biomaterials. 2012;33(10):2991–3001.
6. Costa LG, Garrick JM, Roquè PJ, Pellacani C. Mechanisms of neuroprotection by quercetin: counteracting oxidative stress and more. Oxid Med Cell Longev. 2016;2016:2986796.
7. Peredo-Escárcega AE, Guarner-Lans V, Pérez-Torres I, Ortega-Ocampo S, Carreón-Torres E, Castrejón-Téllez V, et al. The combination of resveratrol and quercetin attenuates metabolic syndrome in rats by modifying the serum fatty acid composition and by upregulating SIRT1 and SIRT2 expression in white adipose tissue.

Evid Based Complement Alternat Med. 2015;2015:474032.
8. Hall KE, McDonald MW, Grisé KN, Campos OA, Noble EG, Melling CW. The role of resistance and aerobic exercise training on insulin sensitivity measures in STZ-induced type 1 diabetic rodents. Metabolism. 2013;62(10):1485–1494.
9. Pany S, Pal A, Sahu PK. Neuroprotective effect of quercetin in neurotoxicity induced rats: role of neuroinflammation in neurodegeneration. Asian J Pharm Clin Res. 2014;7(4):152–156.
10. Mohammadi HS, Goudarzi I, Lashkarbolouki T, Abrari K, Elahdadi Salmani M. Chronic administration of quercetin prevent spatial learning and memory deficits provoked by chronic stress in rats. Behav Brain Res. 2014;270:196–205.
11. Bhutada P, Mundhada Y, Bansod K, Bhutada C, Tawari S, Dixit P, Mundhada D. Ameliorative effect of quercetin on memory dysfunction in streptozotocin-induced diabetic rats. Neurobiol Learn Mem. 2010;94(3):293–302.
12. Anjaneyulu M, Chopra K. Quercetin, an antioxidant bioflavonoid, attenuates diabetic nephropathy in rats. Clin Exp Pharmacol Physiol. 2004;31(4):244–248.
13. Coskun O, Kanter M, Korkmaz A, Oter S. Quercetin, a flavonoid antioxidant, prevents and protects streptozotocin-induced oxidative stress and beta-cell damage in rat pancreas. Pharmacol Res. 2005;51(2):117–123.
14. Vessal M, Hemmati M, Vasei M. Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. Comp Biochem Physiol C Toxicol Pharmacol. 2003;135(3):357–364.
15. Rahmani AH, Alsahli MA, Khan AA, Almatroodi SA. Quercetin, a plant flavonol, attenuates diabetic complications, renal tissue damage, renal oxidative stress and inflammation in streptozotocin-induced diabetic rats. Metabolites. 2023;13(1):130.
16. Foretz M, Guigas B, Viollet B. Understanding the glucoregulatory mechanisms of metformin in type 2 diabetes mellitus. Nat Rev Endocrinol. 2019;15(10):569–589.
17. Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, et al. Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest. 2001;108(8):1167–1174.
18. Hollman PCH, Katan MB. Dietary flavonoids: intake, health effects and bioavailability. Food Chem Toxicol. 1999;37(9-10):937–942.
19. Rathmann W, Giani G. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(10):2568–2569.
20. Dias AS, Porawski M, Alonso M, Marroni N, Collado PS, Gonzalez-Gallego J. Quercetin decreases oxidative stress, NF-κB activation, and iNOS overexpression in liver of streptozotocin-induced diabetic rats. J Nutr. 2005;135(10):2299–2304.