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Original Research Article

Anti-Inflammatory Effects of Quercetin in a Diabetic Rat Model of Acute Inflammation

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ABSTRACT

Diabetes mellitus is a metabolic disorder characterized by elevated blood glucose levels, often associated with delayed wound healing and heightened inflammatory responses. Quercetin, a flavonoid found in various fruits, vegetables, and grains, possesses notable anti-inflammatory properties. This study evaluated the anti-inflammatory effects of quercetin at doses of 25, 50, and 100 mg/kg in a diabetic rat model with acute local inflammation. Intraperitoneal injection of streptozotocin (60 mg/kg in sterile water) was used to induce diabetes. Diabetes was diagnosed when fasting blood glucose levels were more than 16 mmol/L 24 hours after injection. Two acute inflammation models: carrageenan-induced paw edema and peritoneal vascular permeability were employed. Parameters assessed included paw volume, vascular permeability (Evans Blue dye extravasation), nitric oxide (NO) levels, COX-2 activity, and prostaglandin concentrations. Carrageenan administration induced significant paw edema, peaking at 5 hours post-injection. Quercetin treatment at all tested doses significantly reduced paw edema, with the highest inhibition (67.59%) observed at 100 mg/kg. NO levels were markedly decreased in treatment groups, indicating reduced inflammatory mediators. Prostaglandin levels were elevated in diabetic rats with inflammation but were significantly suppressed by quercetin, especially at 100 mg/kg. Vascular permeability, assessed via Evans Blue extravasation, was also significantly reduced in quercetin-treated groups. No significant differences in COX-2 activity were observed among groups. Quercetin exhibits potent anti-inflammatory effects in diabetic rats, demonstrated by reductions in paw edema, vascular permeability, nitric oxide production, and prostaglandin levels. These findings support quercetin's potential as a therapeutic agent for managing inflammation associated with diabetes.

Keywords: Quercetin, Carrageenan-induced paw edema, Carrageenan-induced peritoneal vascular permeability, Nitric Oxide,Cyclooxygenase, Prostaglandin, Diabetes, Human health

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by elevated blood glucose levels resulting from impaired insulin secretion, insulin action, or both. It is recognized as one of the most prevalent diseases worldwide and poses a significant health burden, with increasing incidence globally and particularly in Malaysia.[1,2] DM is a non-communicable disease that is not transmissible between individuals. The etiology of diabetes involves multiple factors, including genetic predisposition, obesity, physical inactivity, and infections. The disease is primarily classified into two main types: Type 1 and Type 2 diabetes. A hallmark of diabetes is the presence of chronic low-grade inflammation, which contributes to various complications, including delayed wound healing- a major concern among diabetic patients.[3]

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Inflammation is a physiological response initiated by the body in response to injury or infection, characterized by clinical signs such as redness, heat, swelling, pain, and loss of function. It serves as a protective mechanism, involving processes like vasodilation, increased vascular permeability, and leukocyte recruitment.[4] There are two primary forms of inflammation: acute and chronic. Acute inflammation is a rapid and short-term response essential for host defense and tissue repair, involving the release of various inflammatory mediators. Chronic inflammation persists over a longer duration and can lead to tissue damage and various pathologies.[5,6] Although inflammation plays a vital role in immune defense and tissue healing, excessive or prolonged inflammatory responses can result in discomfort and disease. Commonly used anti-inflammatory agents include Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as indomethacin, aspirin, and phenylbutazone, which are readily available over the counter or via prescription. However, long-term use of NSAIDs is associated with adverse effects such as gastrointestinal ulcers and bleeding.[7]

Flavonoids are a diverse group of polyphenolic compounds found abundantly in various plants, including onions, berries, apples, green tea, and olive oil. These phytochemicals can be classified into several subclasses, among which quercetin is a prominent flavonoid with well-documented health benefits.[8] Quercetin can be obtained naturally through diet or supplemented as a nutritional supplement. It exhibits multiple pharmacological properties, notably antioxidant and anti-inflammatory activities, which contribute to its therapeutic potential.[9] Previous studies have demonstrated that flavonoids, including

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quercetin, possess anti-inflammatory effects capable of modulating inflammatory pathways involved in various diseases. However, the specific effects of quercetin on inflammation associated with diabetic wound healing remain to be fully elucidated. Given the similarities between the inflammatory processes in diabetes and acute inflammation, exploring quercetin's therapeutic potential in diabetic inflammation is warranted. Thus, this study evaluated the anti-inflammatory effects of quercetin in a diabetic rat model.

Materials and Methods

Chemicals and Reagents

Quercetin (Cayman Chemical, Ann Arbor, MI, USA) (Figure 1), normal saline (0.9%), carrageenan, Evans Blue Dye, indomethacin, streptozotocin, Griess' reagent, sodium nitrate, COX Activity Assay Kit (Cayman Chemicals), PGE_2ELISA Kit (Cayman Chemicals), chloroform were purchased from Sigma-Aldrich (St. Louis, MO, USA) unless otherwise stated.

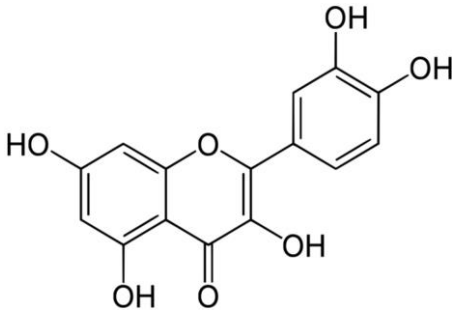

Figure 1: Chemical structure of Quercetin

Animals

A total of 126 male Sprague Dawley rats (200–300 g) were housed in standard conditions (23±2°C, 12h light/dark cycle) with *ad libitum* access to food and water. After a 2-week acclimatization, rats were fasted for 18 hours prior to experiments. Ethical approval was obtained from the Animal Care and Use Committee, University Putra Malaysia (UPM/FPSK/PADS/BR-UUH/00455.

Experimental Design

Rats were divided into two models, each with seven groups (n=6 per group). Group allocations included normal controls, diabetic controls, and treatment groups receiving quercetin (25, 50, 100 mg/kg) or indomethacin (10 mg/kg). Treatments were administered orally 30 min before inflammatory induction.

Induction of Diabetes

Diabetes was induced via a single intraperitoneal injection of streptozotocin (60 mg/kg in sterile water). Fasting blood glucose levels >16 mmol/L, measured 24 hours post-injection, confirmed diabetic status.

Carrageenan-Induced Paw Edema

Rats received treatments 30 min prior to intraplantar injection of 0.1 ml of 10 mg/ml carrageenan in saline.[10] Paw volume was measured hourly over 5 hours using using a digital plethysmometer (UGO Basile 7140). Edema inhibition was calculated as:

$$\%Inhibition = \frac{(C_t - C_0)_{control} - (C_t - C_0)_{treatment}}{(C_t - C_0)_{control}} \times 100$$

Peritoneal Vascular Permeability

One hour post-treatment, rats received 10 mg/kg Evans Blue intravenously, followed by intraperitoneal injection of 0.3 ml of 1% carrageenan. After 3 hours, peritoneal exudates were collected, centrifuged, and Evans Blue concentration measured at 630 nm.[11]

Nitrite Measurement

Post-peritoneal lavage, nitrite levels were assessed using the Griess reaction. Supernatants (50 µl) were mixed with Griess reagent, incubated for 10 min, and absorbance read at 548 nm.

COX Activity Assay

COX activity was quantified using the Cayman COX Activity Assay Kit, following manufacturer instructions. Briefly, samples and standards were prepared in assay buffers with heme and inhibitors, then incubated with substrate at 25°C. Absorbance was measured at 590 nm.

Prostaglandin E_2 (PGE_2) Measurement

A commercial ELISA Kit (Cayman Chemicals) was used to measure PGE_2. Exudates (50 µl) were incubated with specific antibodies and tracers, followed by washing and addition of Ellman's reagent. Absorbance was read at 420 nm.

Statistical analysis

Data are presented as mean ± SEM. Group differences were analyzed by one-way ANOVA (Analysis of Variance) using GraphPad Prism (v10.1). When ANOVA was significant, Tukey's HSD (Honestly Significant Difference) post hoc test was applied. A p value < 0.05 was considered significant.

Results and Discussion

The carrageenan-induced paw edema model is a widely accepted experimental approach for evaluating the anti-inflammatory potential of various compounds due to its reliable induction of localized inflammation without tissue injury.[10,11] This model simulates the sequential release of inflammatory mediators, providing insight into the mechanisms underlying acute inflammation. In the early phase, histamine and serotonin are promptly released from mast cells, initiating vasodilation and vascular permeability changes.[12] As the inflammatory response progresses, mediators such as prostaglandins and nitric oxide become predominant, contributing to sustained edema and increased vascular permeability, particularly evident at approximately the 5th hour post-injection.[12,13]

In this study, following carrageenan injection (Table 1), the mean paw volumes in the inflammation, negative control, and positive control groups were 0.30 ± 0.02 mL, 0.01 ± 0.04 mL, and 0.21 ± 0.02 mL at the first hour, respectively. The treatment groups administered quercetin at doses of 25, 50, and 100 mg/kg exhibited paw volumes of 0.41 ± 0.04, 0.43 ± 0.01, and 0.31 ± 0.05 mL, respectively, at the same time point. Gradually, paw volume increased in both the inflammation and negative control groups, reaching maximums at the fifth hour of 0.68 ± 0.04 mL and 0.71 ± 0.05 mL, respectively. In contrast, the diabetic control group, which did not receive carrageenan, showed no increase in paw volume throughout the experimental period, indicating that diabetes may impair or alter the inflammatory response.

All quercetin-treated groups (25, 50, and 100 mg/kg) demonstrated significant reductions in paw volume compared with the negative control group at the fifth hour, with mean values of 0.31 ± 0.07, 0.32 ± 0.07, and 0.05 ± 0.03 mL, respectively ($p < 0.05$). When compared to the diabetic control group at this time point, the 25 mg/kg and 50 mg/kg quercetin groups showed significant reductions in paw volume ($p < 0.05$), whereas no significant differences were observed between the diabetic group and the positive control or the 100 mg/kg quercetin group. Notably, the positive control and the 100 mg/kg quercetin group showed significant reductions from earlier hours (first, second, and third), indicating early onset of anti-inflammatory activity (Table 1). Dose-dependent effects were evident, with the 100 mg/kg quercetin group showing significantly greater reductions at the third, fourth, and fifth hours compared with the 25 mg/kg and 50 mg/kg groups ($p < 0.05$). No significant difference was observed between the 25 mg/kg and 50 mg/kg groups, suggesting a plateau in efficacy at these doses.

The maximum paw volume in the positive control group was observed at the first hour (0.32 ± 0.07 mL). Similarly, the 50 mg/kg and 100 mg/kg quercetin groups showed an initial increase in paw edema at the first hour, followed by a gradual decrease over time in all but the 50 mg/kg group, where edema reduction began after the third hour.

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Table 1: Effect of quercetin on mean paw edema volume in carrageenan-induced paw edema

Groups	Dose (mg/kg)	Increase paw volume at time (H)					
		0	1	2	3	4	5
Inflammation Control	-	*0.00*	*0.30±0.02^{bx}*	*0.40±0.02^{bx}*	*0.50±0.02^{cx}*	*0.53±0.03^{bx}*	*0.68±0.04^{by}*
Diabetic Control	-	0.00	0.01±0.04^{ax}	0.02±0.02^{ax}	0.15±0.02^{ax}	0.10±0.04^{ax}	0.14±0.04^{ax}
Negative Control	-	0.00	0.21±0.02^{ax}	0.38±0.04^{ay}	0.53±0.03^{by}	0.65±0.03^{cz}	0.71±0.03^{cz}
Positive Control	10	0.00	0.32±0.07^{ax}	0.33±0.05^{ax}	0.25±0.04^{ax}	0.17±0.04^{ax}	0.13±0.07^{ax}
	25	0.00	0.41±0.04^{ax}	0.49±0.06^{ax}	0.42±0.08^{bx}	0.36±0.07^{bx}	0.31±0.07^{bx}
Quercetin	50	0.00	0.43±0.01^{ax}	0.44±0.09^{ax}	0.44±0.10^{bx}	0.35±0.08^{bx}	0.32±0.07^{bx}
	100	0.00	0.31±0.05^{ax}	0.29±0.04^{ax}	0.21±0.05^{ax}	0.10±0.03^{ay}	0.05±0.03^{ay}

Value are mean ± SEM, *n*=6. Edema was determined by subtracting the volume of the negative control paws from that of the treated paw. Positive Control received Indomethacin 10mg/kg.
$^{a-c}$ -mean with different superscript differ significantly ($p<0.05$) between groups.
$^{x-z}$ - mean with different superscript differ significantly ($p<0.05$) in the same group

The 25 mg/kg group achieved its maximum edema at the second hour (0.42 ± 0.08 mL), with subsequent decreases. The percentage inhibition of paw edema at the fifth hour, which was the point of greatest inter-group difference was highest in the 100 mg/kg quercetin group (92.96%), followed by the positive control (81.69%), and was 56.34% and 54.93% for the 25 mg/kg and 50 mg/kg groups, respectively (Table 2).

Previous investigations in normal rats have reported maximum swelling at the 3rd hour, with subsequent decline.[14] In contrast, diabetic rats exhibited a continued increase in paw volume throughout the observation period, indicating that diabetes may exacerbate inflammatory responses or impair resolution mechanisms. The effect of quercetin on vascular permeability was evaluated using Evans blue dye leakage into the peritoneal cavity.[15] The dye leakage in the inflammation, diabetic, positive, and negative control groups was 20.48 ± 1.56, 11.73 ± 1.72, 24.87 ± 1.16, and 12.66 ± 4.18 µg/rat, respectively (Table 3). Treatment groups with quercetin at 25 mg/kg, 50 mg/kg, and 100 mg/kg exhibited dye leakages of 11.63 ± 2.52, 10.94 ± 0.86, and 9.81 ± 0.91 µg/rat, respectively. Compared to the inflammation and negative control groups, the highest dye leakage was in the negative group, while the lowest was in the 100 mg/kg quercetin group, with a significant reduction observed ($p < 0.05$). No significant differences in dye leakage were found between the diabetic group and the quercetin-treated groups ($p > 0.05$), indicating that quercetin effectively stabilizes vascular endothelium, thereby reducing permeability. This supports the premise that quercetin stabilizes vascular endothelium, potentially by modulating mediator release.[16]

Table 2: Percentage inhibition of paw volume at 5th hour of carrageenan injection at the hind paw of diabetic rats

Group	Percentage inhibition(%)
Positive control	81.69
25 mg/kg quercetin	56.34
50 mg/kg quercetin	54.93
100 mg/kg quercetin	92.96

Assessment of cyclooxygenase (COX) activity in Table 4, revealed no significant differences among groups ($p > 0.05$), with the highest total COX activity observed in the negative control (10.92 ± 5.60) and inflammation control (10.04 ± 4.36) groups, and the lowest in the 100 mg/kg quercetin group (2.09 ± 0.52), which was possibly due to variability and assay sensitivity.[17,18] Despite the lack of significant difference, prostaglandin (PGE2) levels in Table 5, showed marked variation; the highest concentrations were in the negative control (193.5 ± 7.79 pg/mL) and inflammation control (156.9 ± 14.90 pg/mL) groups, while the lowest were in the positive control (85.72 ± 17.15 pg/mL) and the 100 mg/kg quercetin group (94.30 ± 12.55 pg/mL). The percentage inhibition of prostaglandin release was highest in the positive control (55.70%) and the 100 mg/kg quercetin group (51.57%), with significant decreases compared to the negative control ($p < 0.05$). The reductions across all quercetin doses suggest suppression of prostaglandin synthesis, aligning with observed decreases in paw edema.[19,20] Interestingly, the prostaglandin levels in diabetic rats were marginally higher than in normal counterparts, consistent with the pro-inflammatory state associated with diabetes.[21] The efficacy of quercetin in lowering prostaglandin levels, although slightly diminished in diabetic rats, indicates its potential to modulate inflammatory pathways compromised by diabetic pathology.

Nitrite levels, indicative of nitric oxide (NO) production,[22] shown in Table 6, were highest in the negative control and lowest in the positive control (indomethacin).[23]

Table 3: Effect of quercetin on mean concentration of peritoneal dye leakages from Carrageenan-induced diabetic rats

Group	Peritoneal Dye Leakage (µg/rat)	Percentage inhibition (%)
Inflammation control	20.48±1.56^{a}	-
Diabetic control	11.73±1.72^{b}	-
Negative control	24.87±1.16^{a}	-
Positive control(indomethacin)	12.66±4.18^{b}	49.10
25 mg/kg quercetin	11.63±2.52^{b}	53.24
50 mg/kg quercetin	10.94±0.86^{b}	56.01
100 mg/kg quercetin	9.81±0.91^{b}	60.55

Value are mean ± SEM, *n*=6
$^{a-b}$ -mean with different superscript differ significantly at $P<0.05$ between groups.

Table 4: Effect of quercetin on mean total COX activity from Carrageenan-induced inflammation in diabetic rats

Group	Total COX activity	Percentage inhibition(%)
Inflammation control	10.04 ± 4.36	-
Diabetic control	7.35 ± 3.05	-
Negative control	10.92 ± 5.60	-
Positive control (indomethacin)	3.43 ± 1.30	68.59
25 mg/kg quercetin	4.47 ± 2.25	59.07
50 mg/kg quercetin	2.92 ± 0.84	73.26
100 mg/kg quercetin	2.09 ± 0.52	80.86

Values are mean ± SEM, *n*=6

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Table 5: Effect of quercetin on mean prostaglandin concentration from Carrageenan-induced inflammation in diabetic rats

Group	PGE2 (pg/ml)	Percentage inhibition (%)
Inflammation control	156.9±14.90[ab]	-
Diabetic control	137.0±19.38[b]	-
Negative control	193.5±7.79[a]	-
Positive control (indomethacin)	85.72±17.15[b]	55.70
25 mg/kg quercetin	116.0±12.62[b]	40.0
50 mg/kg quercetin	110.9±11.38[b]	42.69
100 mg/kg quercetin	94.30±12.55[b]	51.27

Values are mean ± SEM, *n*=6
[a-b] -mean with different superscript differ significantly at P<0.05 between groups.

This inhibitory effect was comparable to that of indomethacin, suggesting that quercetin effectively suppresses both eNOS and iNOS activity during inflammatory responses.[24,25] All quercetin-treated groups exhibited significantly lower nitrite concentrations ($p < 0.05$), with inhibition approaching that of indomethacin at 100 mg/kg, demonstrating quercetin's capacity to suppress NO production (Table 6). The reduction was more pronounced in diabetic rats, implying an enhanced anti-inflammatory effect under diabetic conditions characterized by elevated NO levels. [26,27]

Table 6: Effect of quercetin on mean nitrite concentration from carrageenan-induced inflammation in diabetic rats

Group	Mean concentration of Nitrite (µmol)	Percentage inhibition (%)
Inflammation control	18.55±4.15[b]	-
Diabetic control	14.69±3.93[b]	-
Negative control	31.35±5.44[a]	-
Positive control-indomethacin	8.24±1.74[b]	73.72
25 mg/kg quercetin	10.68±2.09[b]	65.93
50 mg/kg quercetin	9.03±1.19[b]	71.20
100 mg/kg quercetin	8.31±1.16[b]	73.46

Values are mean ± SEM, *n*=6.
[a-b] -comparison of means significantly different at P<0.05 between groups.

In summary, quercetin exerts a multi-faceted anti-inflammatory effect in carrageenan-induced paw edema in diabetic rats. Its actions likely involve inhibition of key mediators such as prostaglandins and nitric oxide, stabilization of vascular endothelium, and reduction of edema and vascular permeability. The dose-dependent efficacy, particularly at 100 mg/kg, which achieved nearly 93% inhibition of edema which was comparable to the positive control and this underscores its therapeutic potential. Importantly, the ability of quercetin to mitigate inflammation exacerbated by diabetic pathology highlights its promise as an anti-inflammatory agent with enhanced efficacy in diabetic conditions. These findings support the potential application of quercetin in managing inflammatory conditions, especially those complicated by diabetes, where inflammatory responses are often amplified. Further studies exploring the molecular mechanisms and clinical relevance of quercetin are warranted to fully elucidate its therapeutic potential.

Conclusion

The methanol extracts of *T. bangwensis* leaf, *T. globiferus*, and *P. incana* flowers have larvicidal potential. Generally, after partitioning, their resulting fractions are more active than the methanol extracts. The *n*-hexane fraction of *T. bangwensis*, the ethyl acetate fraction of *P. incana*, and the aqueous fraction of *T. globiferus* demonstrated the highest activity. Efforts are ongoing to isolate the active compounds of these active fractions.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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