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Protective Effect of Apple Peel-Derived Quercetin Derivatives Against Indomethacin-Induced Gastric Ulcer in Wistar Rats

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Abstract

Gastric ulcer is a gastrointestinal disorder caused due to use of non-steroidal anti-inflammatory drugs (NSAIDs), which break the gastric mucosa and promote oxidative stress and inflammation. The current work was evaluated the gastroprotective effect of quercetin (QUE) derivatives, quercetin-piperazine (Q7) and pentabenzylated quercetin (Q8), against indomethacin (IND)-induced gastric ulcer in Wistar rats. Gastric ulcers were induced by oral given of IND, and the protective effects of QUE derivatives were assessed through various biochemical and physiological parameters. The ulcer index, gastric secretion markers (total acid output, pepsin activity & mucin content), gastric volume and pH, antioxidant markers, nitrite levels, and inflammatory cytokines were evaluated to determine the degree of gastric mucosal damage & protective effects of the treatments. IND administration significantly elevated ulcer index, gastric acid secretion, pepsin activity, gastric volume, lipid peroxidation, and inflammatory cytokines while reducing mucin content, gastric pH, antioxidant enzyme levels (SOD, CAT, and GSH), and gastric nitrite levels. Treatment with QUE derivatives significantly improved these parameters, indicating strong gastroprotective activity. The compounds reduced ulcer severity, restored antioxidant enzyme activities, improved mucosal defense, and reduced inflammatory responses in gastric tissues. Among the tested treatments, Q8 confirmed the most pronounced protective effect, particularly in reducing oxidative stress and enhancing mucosal protection. Overall, the findings confirm that QUE derivatives possess significant gastroprotective effect and may serve as potential therapeutic candidates for the management of IND-induced gastric ulcers through antioxidant and anti-inflammatory mechanisms.

Keywords: *Gastric ulcer; Quercetin derivatives; Indomethacin; Inflammation; Mucosal protection.*

INTRODUCTION

Gastric ulcer is the common gastrointestinal disorders globally that characterized by gastric mucosal damage with irregular aggressive & defensive factors. Aggressive factors like gastric acid, pepsin, reactive oxygen species (ROS), and inflammatory mediators can overcome protective factors such as mucus secretion, bicarbonate production, prostaglandins, and adequate mucosal blood flow. Recent studies highlight that disruption of this balance leads to inflammation, mucosal erosion, and eventually ulcer formation in the stomach (Lanas & Chan, 2022; Malfertheiner et al., 2023). NSAIDs are the main causes of gastric ulceration due to their extensive use in the control of pain and inflammatory disorders. Among these drugs, IND is commonly used in experimental pharmacology because of its strong ulcerogenic effect and its ability to reliably induce gastric ulcers in laboratory animals. The primary mechanism of IND-induced ulceration includes inhibition of cyclooxygenase (COX) enzymes, which decreases prostaglandin synthesis and subsequently decreases gastric mucus and bicarbonate secretion while increasing gastric acidity and mucosal vulnerability (Sostres et al., 2023; Wallace & Blackler, 2024).

In addition to prostaglandin suppression, IND-induced gastric injury is closely linked with oxidative stress and inflammatory responses. Experimental studies shown that IND increases lipid peroxidation and stimulates the release of TNF-α and interleukins (ILs). Furthermore, activation of NF-κB contributes to inflammatory cell infiltration and apoptosis of gastric epithelial cells, ultimately leading to mucosal damage and ulcer formation (Tariq et al., 2023; Ansari et al., 2024).

Although several anti-ulcer drugs like proton pump inhibitors (PPIs), H_2-antagonists, and antacids are available and effective in suppressing gastric acid secretion, chronic use of these medications has been linked with certain adverse effects and the reappearance of ulcers. Thus, there is increasing interest in identifying safer and more effective therapeutic alternatives. In recent years, natural products and their synthetic derivatives have increased considerable attention as potential gastroprotective agents due to their antioxidant, anti-inflammatory, and cytoprotective action (Scarpignato et al., 2023; Li et al., 2024).

Among natural compounds, polyphenolic flavonoids have been widely explored for their therapeutic potential in gastrointestinal disorders. QUE is a flavonoid present in fruits and vegetables such as apples, onions, and berries. It has antioxidant, anti-inflammatory, antimicrobial, anticancer, and gastroprotective effects. Recent experimental studies have reported that QUE can protect gastric mucosa against NSAID-induced ulceration by reducing oxidative stress, enhancing antioxidant enzyme activities, and suppressing inflammatory mediators (Batiha et al., 2023; Zhang et al., 2024). Despite its promising pharmacological activities, the clinical application of QUE is limited by its relatively low bioavailability and rapid metabolic degradation in the body. To overcome these limitations, researchers have discovered the synthesis of various QUE derivatives with improved physicochemical and pharmacological properties. Structural modification of QUE can improve its stability, lipophilicity, and biological activity, thereby improving its therapeutic potential (Tang et al., 2023; Xie & Wei, 2025). Among these strategies, the incorporation of piperazine moieties into flavonoid structures has involved significant attention in medicinal chemistry because piperazine groups can enhance drug solubility, pharmacokinetic behavior, and receptor interactions. Similarly, benzylation of phenolic hydroxyl groups is commonly used to adapt the lipophilicity and biological activity of flavonoid molecules, potentially leading to improved pharmacological performance (Verma et al., 2023; Chen et al., 2024).

Based on these considerations, the present study examines two structurally modified QUE derivatives: a quercetin-piperazine derivative (Q7), 5,7-Dihydroxy-2-{4-hydroxy-3-[3-(4-methyl-piperazin-1-yl)-propoxy]-phenyl}-chromen-4-one, and a pentabenzylated quercetin analogue (Q8), 3,5,7,3′,4′-Pentakis(benzyloxy)-2-phenyl-4H-chromen-4-one**.** These derivatives were intended to enhance the pharmacological profile of the parent compound QUE. However, their gastroprotective potential against NSAID-induced gastric ulceration has not yet been extensively examined. Therefore, the present work aims to assess the gastroprotective effects of Q7 and Q8 in an IND-induced gastric ulcer model in Wistar rats and to explore their potential antioxidant and anti-inflammatory mechanisms in protecting gastric mucosa.

Materials and Methods

Chemicals and Reagents

IND and QUE were bought from Sigma Aldrich through certified pharmaceutical supplier. The synthesized compounds Q7 and Q8 were prepared and purified in the laboratory following standard synthetic manual procedure. Other chemicals were acquired from Sigma-Aldrich and Merck.

Synthesis of Quercetin Derivatives

QUE derivatives i.e., Q7 and Q8 were synthesized using standard organic synthesis protocols. Q7 was obtained via alkylation of QUE followed by substitution with 4-methylpiperazine, while Q8 was prepared through benzylation of hydroxyl groups of QUE. Their synthesis has been described in our first research paper that communicated to a journal and is currently under review. The synthesized compounds were purified by column chromatography and established by appropriate analytical techniques. These compounds were subsequently used for *in vivo* studies.

Experimental Animals

Wistar rats (150–200 g) were got from the Animal House Facility of RV Northland Institute. Before starting the experiment, the animals were permissible to acclimatize for one week. They were set aside in clean cages with standard conditions, such as temperature of 23 ± 2°C, humidity of 55–65% & 12-hr light/dark cycle. The animals were given with a standard pellet diet and water ad libitum throughout the study. All experimental were conducted according to CPCSEA guidelines, and the study protocol was permitted by the committee i.e., IAEC.

Experimental Design

Five groups were taken with equal number of rats (n = 6). The study was intended to evaluate the gastroprotective effects of QUE and its derivatives against IND-induced gastric ulcer.

- **Group I (Normal Control):** Given distilled water orally.

- **Group II (Ulcer Control):** Given single oral dose of IND (30 mg/kg) after overnight fasting to induce gastric ulcer and did not receive any treatment.
- **Group III (Standard Treatment):** Ulcerated rats were treated with QUE (50 mg/kg, orally) once daily for 21 days.
- **Group IV (Test Treatment – Q7):** Ulcerated rats were treated with Q7 (50 mg/kg, orally) once daily for 21 days.
- **Group V (Test Treatment – Q8):** Ulcerated rats were treated with pentabenzylated Q8 (50 mg/kg, orally) once daily for 21 days.

Treatment with the standard drug and test compounds began 4 hours after IND administration and continued once daily for 21 consecutive days. All treatments were administered orally using an oral gavage.

Evaluation of anti-ulcer activity

Induction of gastric ulcer

Anti-ulcer activity was evaluated using the IND-induced ulcer model in Wistar rats. On last day of treatment, the animals were fasted overnight before ulcer induction. Gastric ulceration was induced by administering a single oral dose of IND (30 mg/kg). IND causes gastric mucosal damage mainly through inhibition of prostaglandin synthesis and induction of oxidative stress (Sostres et al., 2023; Wallace & Blackler, 2024).

Experimental timeline of the study

The experimental study was taken for 21 days. During this period, animals in the treatment groups received QUE or its derivatives (Q7 and Q8) orally once daily. On the final day of the experiment, the animals were fasted overnight and gastric ulcer was induced by administering a single dose of IND (30 mg/kg, p.o.). Four hours after IND administration, the animals were sacrificed, and the stomach tissues were collected for macroscopic examination, ulcer index determination, histopathological analysis, and biochemical antioxidant evaluation (Sostres et al., 2023).

Collection of stomach samples

After 4 hours of IND, the animals were anesthetized and sacrificed. The abdomen was opened carefully, and the stomach was removed and tied at both ends to prevent leakage of gastric contents. The excised stomachs were then opened and gently rinsed with saline (OECD, 2022; Bancroft & Gamble, 2019).

Macroscopic examination of gastric lesions

The inner surface of the gastric mucosa was examined carefully using a magnifying lens to observe the presence of ulcer lesions, hemorrhagic streaks, or mucosal damage. The number and severity of ulcers in each stomach were recorded. The ulcer index was intended to determine the severity of gastric ulceration in each experimental group (Szabo & Hollander, 2019).

Ulcer scoring and ulcer index determination

The severity of gastric lesions was assessed by investigative the inner gastric mucosa under a magnifying lens. The gastric ulcers were scored based on the number and severity of lesions observed on the stomach surface.

Ulcer scoring criteria

Gastric lesions were scored on a scale of 0–5: 0 (normal), 1 (redness), 2 (spot ulcers), 3 (hemorrhagic streaks), 4 (deep ulcers), and 5 (perforation). The ulcer index (UI) was calculated based on the mean severity and number of ulcers in each group (Szabo & Hollander, 2019).

Ulcer index formula

Ulcer Index (UI) was calculated to measure the severity of gastric lesions using the formula:

$$U1 = \frac{UN + US + UP}{10}$$

Where:

- UN = Average number of ulcers / animals
- US = Average severity score
- UP = % of animals with ulcers

Percentage of ulcer inhibition (Batiha et al., 2023).

The protective effect of the treatments was further determined by calculating the percentage inhibition of ulcer formation using formula:

$$Ulcer\ inhibition\ (\%) = \frac{UI_{control} - UI_{Treated}}{UI_{control}} x100$$

Where:

UI control represents the ulcer index of the ulcer control group.
UI treated represents the ulcer index of the treated group.

Measurement of gastric juice parameters
After sacrificing the animals, the stomachs were carefully detached and the gastric contents were obtained into clean centrifuge tubes. The collected gastric juice was centrifuged at 3000 rpm for 10 minutes to remove solid particles and debris. The clear supernatant was used for the estimation of gastric juice volume, pH, and total acidity. The volume of gastric juice was measured using a graduated cylinder. The pH of the gastric juice was assessed using a calibrated digital pH meter. For the determination of total acidity, 1 mL of gastric juice was mixed with distilled water (9 mL) and titrated against 0.01 N NaOH using phenolphthalein until a faint pink color persisted. The total acidity was denoted as mEq/L of gastric juice (Sodhi & Singh, 2021).

Determination of antioxidant parameters
To evaluate the role of oxidative stress in gastric ulceration, antioxidant parameters were estimated from gastric tissue homogenates. A portion of the stomach tissue was washed with ice-cold saline and homogenized in phosphate buffer (pH 7.4) using a tissue homogenizer. The homogenate was then centrifuged for 15 minutes, and the supernatant was collected.

Estimation of Malondialdehyde (MDA)
Lipid peroxidation in gastric tissues was assessed by measuring MDA levels using the TBARS method. The formation of a pink-colored complex was measured at 532 nm. Increased MDA levels indicate higher lipid peroxidation and oxidative stress in gastric tissues (Ohkawa et al., 1979).

Estimation of superoxide dismutase (SOD)
SOD activity was based on its ability to inhibit the autoxidation of epinephrine. The absorbance was measured at 480 nm using a spectrophotometer. SOD activity reflects the antioxidant defense capacity of the tissue against superoxide radicals (Marklund and
Marklund, 1974).

Estimation of catalase (CAT)
CAT activity was measured by determining the decomposition rate of H_2O_2. The reduction in O.D. was recorded at 240 nm, and its activity was given in units / mg protein (Claiborne, 1985).

Estimation of reduced glutathione (GSH)
GSH levels were determined using Ellman's reagent (DTNB), which produces a yellow-colored complex measured at 412 nm (Sedlak and Lindsay, 1968).

Statistical analysis
Results are expressed as mean ± SEM. Statistical analysis was conducted using one-way ANOVA followed by post hoc test, with $p < 0.05$ considered significant.

RESULTS

Effect of quercetin derivatives on ulcer index
The ulcer control group displayed a significant upsurge in ulcer index compared with the normal control group. Treatment with QUE and its derivatives significantly reduced the ulcer index, indicating their gastroprotective activity against IND-induced gastric ulcers. Among the treated groups, the pentabenzylated QUE derivative (Q8) showed the greatest protective effect (Table 1).

Table 1: Effect of QUE derivatives on ulcer index

Group	Treatment	Ulcer Index
NC	Normal Control	**0.5 ± 0.1**
IND	Ulcer Control (IND 30 mg/kg)	**14.2 ± 1.3**$^{###}$
QUE + IND	Standard Treatment (QUE 50 mg/kg, p.o.)	**7.9 ± 0.9****
Q7 + IND	Test Treatment – Q7 (QUE-piperazine derivative 50 mg/kg, p.o.)	**6.3 ± 0.8****
Q8 + IND	Test Treatment – Q8 (Pentabenzylated QUE derivative 50 mg/kg, p.o.)	**5.7 ± 0.7*****

Data are given as mean ± SEM (n = 6) by applying one way ANOVA with Tukey's test.

Effect of quercetin derivatives on gastric secretion parameters
IND administration significantly increased total acid output and pepsin activity while decreasing mucin content compared with the normal control group. Treatment with QUE and its derivatives (Q7 and Q8) significantly decreased gastric acid secretion and pepsin activity and restored mucin levels, indicating their protective effect on gastric mucosa. Among the

treated groups, Q8 showed the greatest improvement in mucin content and reduction in acid secretion (Table 2).

Table 2: Effect of QUE derivatives on gastric secretion parameters

Groups	Total Acid Output (mEq/3h)	Pepsin Activity (µg/ml tyrosine)	Mucin Content (mg % hexose)
NC	46.9 ± 3.0	118.7 ± 8.6	93.5 ± 4.8
IND	82.6 ± 6.9###	188.4 ± 8.3###	40.8 ± 1.7###
QUE + IND	71.2 ± 5.8*	174.6 ± 7.1*	67.9 ± 2.6**
Q7 + IND	69.5 ± 5.3**	170.8 ± 6.4**	76.2 ± 3.1**
Q8 + IND	66.8 ± 4.9***	166.5 ± 5.8***	82.7 ± 3.4***

Data are given as mean mean ± SEM (n = 6) by applying one way ANOVA with Tukey's test.

Effect of quercetin derivatives on gastric volume and pH

The normal control (NC) group showed a low gastric volume (2.05 ± 0.12 mL) and a higher pH (6.32 ± 0.16), indicating normal gastric conditions. In contrast, the IND-treated (IND) group exhibited a marked increase in gastric volume (8.10 ± 0.15 mL) and a sharp decrease in pH (2.38 ± 0.07), confirming successful induction of gastric ulceration. Treatment with QUE (QUE + IND) significantly improved these parameters, reducing the gastric volume to 2.28 ± 0.18 mL and increasing the pH to 5.42 ± 0.29, suggesting strong gastroprotective activity. The Q7 + IND group also showed improvement, with gastric volume decreasing to 5.41 ± 0.11 mL and pH rising to 4.05 ± 0.19, indicating moderate protection. Similarly, the Q8 + IND group demonstrated a noticeable protective effect, with gastric volume reduced to 4.58 ± 0.20 mL and pH increased to 4.74 ± 0.14. Overall, all treatments improved gastric conditions compared to the ulcer control, with QUE showing the most pronounced effect (Table 3).

Table 3: Effect of QUE derivatives on gastric volume and pH

Group	Treatment	Gastric Volume (mL)	pH
NC	Normal control	2.05 ± 0.12	6.32 ± 0.16
IND	IND control	8.10 ± 0.15###	2.38 ± 0.07###
QUE + IND	Quercetin + IND	5.41 ± 0.11*	5.42 ± 0.29*
Q7 + IND	Compound Q7 + IND	4.58 ± 0.20**	4.05 ± 0.19***
Q8 + IND	Compound Q8 + IND	2.28 ± 0.18***	4.74 ± 0.14***

Data are given as mean mean ± SEM (n = 6) by applying one way ANOVA with Tukey's test.

Effect of quercetin derivatives on antioxidant parameters in gastric tissue

IND administration caused a significant upsurge in MDA levels and a decrease in SOD, CAT, and GSH compared with the control group, indicating enhanced oxidative stress in gastric tissues. Treatment with QUE and its derivatives significantly reduced MDA levels and restored antioxidant enzyme activities. Among the treated groups, Q8 exhibited the most pronounced antioxidant effect, suggesting stronger protection against oxidative damage in the gastric mucosa (Figure 1).

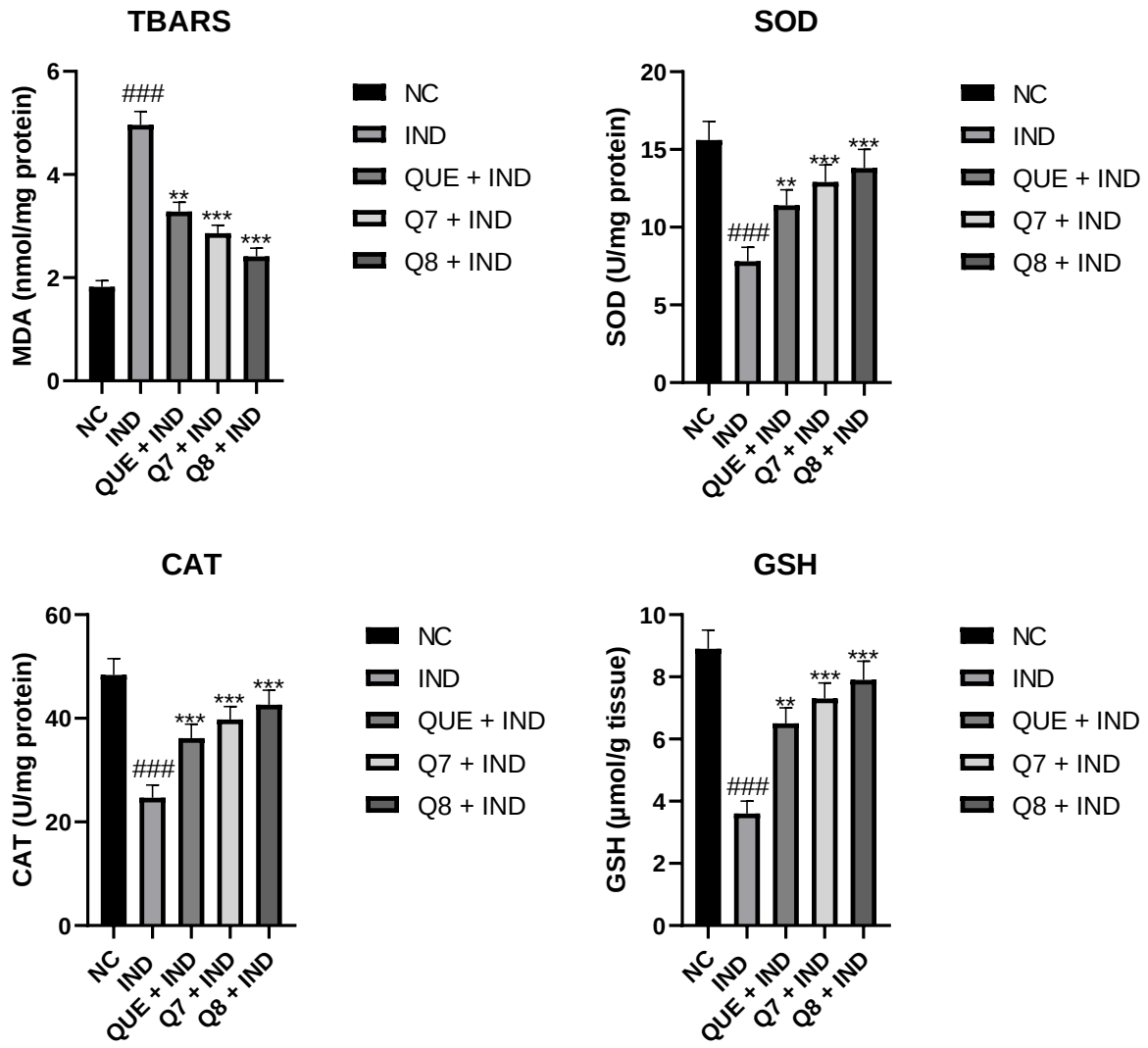

Figure 1: IND increased MDA and reduced SOD, CAT, and GSH, while QUE derivatives reversed these effects, with Q8 most effective. Data are mean ± SEM (n = 6); multiple comparisons applied.

Effect of quercetin derivatives on total gastric nitrite levels

IND administration significantly reduced gastric nitrite levels compared with the control group. Treatment with QUE and its derivatives significantly restored nitrite levels, indicating improvement in gastric mucosal defense. Among the treated groups, Q7 showed the highest restoration of gastric nitrite levels, suggesting better protective activity against IND-induced gastric damage (Table 4).

Table 4: Effect of QUE derivatives on total gastric nitrite levels

Groups	Total Gastric Nitrite (nmol/g wet tissue)
NC	168.5 ± 12.4
IND	82.7 ± 7.6[a]
QUE + IND	118.9 ± 9.8[ab]
Q7 + IND	152.6 ± 11.1[b]
Q8 + IND	94.3 ± 8.5[a]

Data are given as mean mean ± SEM (n = 6) by applying one way ANOVA with Tukey's test.

Effect of quercetin derivatives on inflammatory markers in gastric tissue

IND administration significantly increased the levels of inflammatory markers IL-6 and TNF-α in the ulcer control group compared with the normal control group, indicating a strong inflammatory response in gastric tissue. Treatment with

QUE and its derivatives significantly reduced the levels of both cytokines compared with the IND group. Among the treated groups, Q7 + IND showed the greatest reduction in IL-6 and TNF-α, followed by Q8 + IND and QUE + IND, demonstrating notable anti-inflammatory activity. These findings suggest that QUE derivatives effectively suppress inflammatory responses and contribute to the protection of gastric mucosa against IND-induced gastric damage.

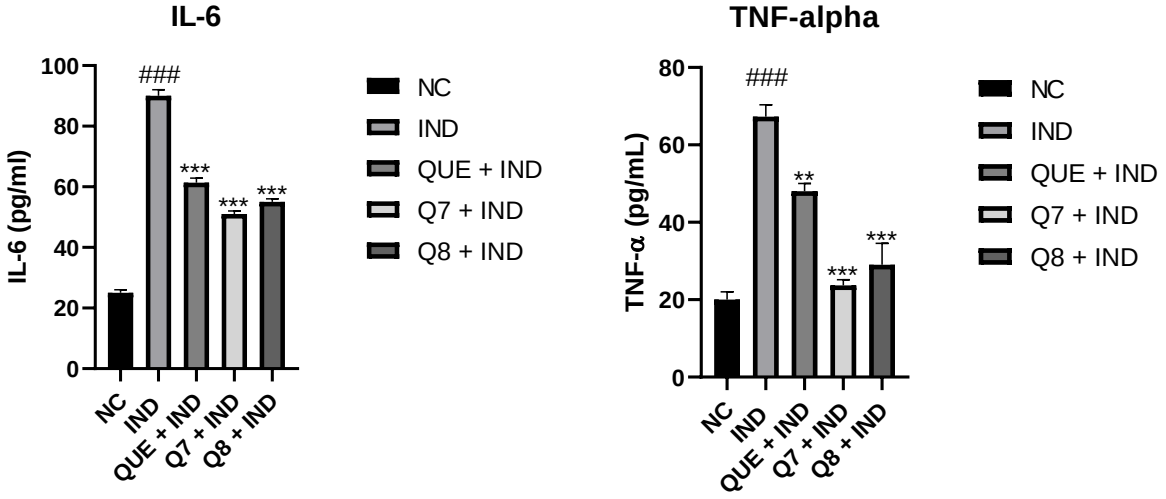

Figure 2. IND elevated IL-6 and TNF-α levels, while QUE derivatives reduced these markers, with Q7 + IND showing the strongest anti-inflammatory result. Data are mean ± SEM (n = 6); multiple comparisons applied.

DISCUSSION

The present study evaluated the gastroprotective potential of QUE and its derivatives (Q7 and Q8) against IND-induced gastric ulceration in Wistar rats. IND is widely used to induce experimental gastric ulcers because it disrupts gastric mucosal defense by inhibiting prostaglandin synthesis and increasing oxidative stress and inflammation in gastric tissues. The findings of the present investigation demonstrated that treatment with QUE and its derivatives significantly attenuated gastric mucosal damage, suggesting their protective role against NSAID-induced gastric injury.

The ulcer index is an important parameter used to evaluate the severity of gastric mucosal damage. In the present study, IND administration significantly increased the ulcer index compared with the normal control group, confirming successful induction of gastric ulceration. However, treatment with QUE and its derivatives markedly reduced the ulcer index, indicating their gastroprotective effect. Among the treated groups, the pentabenzylated QUE derivative (Q8) produced the greatest reduction in ulcer severity. This protective effect may be attributed to the antioxidant and anti-inflammatory properties of flavonoids, which help preserve gastric mucosal integrity and reduce tissue injury. Similar findings have been reported in previous studies demonstrating that QUE and related flavonoids can significantly reduce ulcer formation by protecting the gastric mucosa from oxidative and inflammatory damage (Batiha et al., 2023; Zhang et al., 2024).

Gastric secretion parameters such as total acid output, pepsin activity, and mucin content play a crucial role in maintaining gastric mucosal homeostasis. In the present study, IND administration significantly increased gastric acid secretion and pepsin activity while reducing mucin levels. These findings are consistent with earlier reports indicating that NSAIDs impair gastric mucosal defense by suppressing prostaglandin production, thereby reducing mucus and bicarbonate secretion while increasing acid-mediated injury (Sostres et al., 2023). Treatment with QUE and its derivatives significantly reduced acid output and pepsin activity while restoring mucin levels. Among the derivatives, Q8 demonstrated the most pronounced improvement in mucin content and suppression of gastric acid secretion, suggesting enhanced protective effects on the gastric mucosal barrier.

Gastric volume and pH are additional important indicators of gastric secretory function and ulcer development. In the present study, IND administration caused a marked increase in gastric volume along with a significant decrease in pH, reflecting excessive acid secretion and gastric mucosal damage. Treatment with QUE significantly reduced gastric volume and restored gastric pH toward normal values, indicating strong gastroprotective activity. Similarly, the derivatives Q7 and Q8 improved these parameters, although to varying degrees. The improvement in gastric pH and reduction in gastric volume may be associated with the ability of flavonoids to inhibit gastric acid secretion and enhance

mucosal defense mechanisms. Previous studies have also reported that QUE can protect gastric tissues by regulating acid secretion and strengthening the gastric mucosal barrier (Li et al., 2024).

Oxidative stress is considered one of the key mechanisms involved in NSAID-induced gastric mucosal injury. IND is known to promote the generation of ROS, which leads to lipid peroxidation & antioxidant enzymes depletion. In the present study, IND significantly increased malondialdehyde (MDA) levels while reducing the activities of antioxidant enzymes, indicating enhanced oxidative stress in gastric tissues. Treatment with QUE and its derivatives significantly reduced MDA levels and restored antioxidant enzyme activities. Among the treated groups, Q8 exhibited the most pronounced antioxidant effect. These outcomes are reliable with prior research indicating that QUE possesses strong antioxidant properties and can enhance endogenous antioxidant defenses, thereby protecting gastric tissues from oxidative damage (Tang et al., 2023; Batiha et al., 2023).

Nitric oxide (NO), measured indirectly through gastric nitrite levels, plays a vital role in keeping gastric mucosal integrity by regulating mucosal blood flow, mucus secretion, and epithelial cell protection. In this, IND administration significantly declined gastric nitrite levels compared with the control group, indicating impairment of mucosal defense mechanisms. Treatment with QUE and its derivatives significantly restored nitrite levels, suggesting improved mucosal protection. Interestingly, among the treated groups, Q7 showed the highest restoration of gastric nitrite levels. This finding suggests that the piperazine-substituted derivative may enhance nitric oxide-mediated protective pathways in the gastric mucosa. Similar studies have reported that flavonoids can modulate nitric oxide pathways and improve mucosal defense against gastric injury (Scarpignato et al., 2023).

Inflammation is contributing to the pathogenesis of gastric ulcers. Cytokines TNF-α and IL-6 play a major role in mediating gastric mucosal damage by promoting inflammatory cell infiltration and epithelial injury. In the present study, IND administration significantly elevated TNF-α and IL-6 levels in gastric tissues, indicating an inflammatory response. Treatment with QUE and its derivatives significantly reduced the levels of these inflammatory markers, suggesting their anti-inflammatory potential. The reduction of pro-inflammatory cytokines may be attributed to the ability of QUE derivatives to inhibit NF-κB. Similar findings have been reported that flavonoids can suppress inflammatory cytokine production and reduce gastric mucosal inflammation (Chen et al., 2024; Ansari et al., 2024).

Overall, the findings of the present study indicate that QUE and its derivatives exert significant gastroprotective effects against IND-induced gastric ulcers through multiple mechanisms. These include reduction of gastric acid secretion, enhancement of mucosal defense, restoration of antioxidant enzyme activities, modulation of nitric oxide levels, and suppression of inflammatory cytokines. Among the tested compounds, the pentabenzylated QUE derivative (Q8) showed the most pronounced protective effect, while the piperazine derivative (Q7) demonstrated notable improvement in gastric nitrite levels. These results suggest that structural modification of QUE may enhance its therapeutic potential as a gastroprotective agent.

CONCLUSION

In conclusion, the present study demonstrates that QUE and its derivatives exhibit significant gastroprotective effects against IND-induced gastric ulcers in Wistar rats. Treatment with these compounds reduced ulcer severity, improved gastric secretion parameters, and restored gastric volume and pH toward normal levels. Additionally, QUE derivatives enhanced antioxidant defense by reducing lipid peroxidation and increasing the activities of endogenous antioxidant enzymes (SOD, CAT & GSH). Furthermore, the treatments restored gastric nitrite levels and suppressed inflammatory cytokines, indicating their ability to modulate oxidative stress and inflammatory responses involved in gastric mucosal damage. Among the tested compounds, the pentabenzylated QUE derivative (Q8) showed the most pronounced gastroprotective activity, while Q7 also demonstrated notable protective effects. Overall, these findings suggest that structural modification of quercetin may enhance its therapeutic potential and support the progress of novel flavonoid-based agents for the management of gastric ulcers.

Conflicts of interest

There are no conflicts of interest declared by the authors.

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