RESEARCH ARTICLE Indian Journal of Animal Research, Volume 60 Issue 4: 635-643 (April 2026)

Role of Quercetin against the Effect of Piroxicam on the Liver and Kidney in Pregnant Rats

Fawziah Alshabanat[1], Promy Virk[1], Dalia Fouad[1]

10.18805/IJAR.BF-2102

ABSTRACT

Background: Piroxicam (PX) is an NSAID linked to hepato-renal toxicity. This study evaluated quercetin's (QUE) protective role against PX-induced damage in pregnant rats.

Methods: Pregnant rats (n=40) were divided into four groups (13 days): Control, QUE (75 mg/kg), PX (7 mg/kg *i.p.*) and QUE+PX. Hepato-renal toxicity was assessed *via* hematological, biochemical, histopathological, immunohistochemical (caspase-3, TNF-α, IL-6), oxidative stress markers and DNA fragmentation.

Result: PX caused hematological disturbances, elevated liver enzymes (ALT, AST) and kidney markers (creatinine, urea), decreased albumin and tissue damage. Increased MDA and decreased GSH/SOD indicated oxidative stress. Elevated caspase-3, TNF-α and DNA fragmentation confirmed apoptosis. QUE supplementation significantly reversed these alterations. Quercetin effectively ameliorated PX-induced hepato-renal toxicity through its antioxidant and anti-apoptotic properties.

Key words: Anti-oxidant properties, Dna damage, Hepato-renal toxicity, NSAIDS, Oxidative stress, Piroxicam, Pregnant rats, Quercetin.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most prescribed medications worldwide, accounting for approximately 5% of all prescriptions, due to their well-established analgesic, anti-inflammatory and antipyretic properties. Beyond these effects, they may also play a protective role against certain serious conditions, including cardiovascular diseases and cancer (Panchal *et al*., 2023; Ignácio *et al*., 2024; Montinari *et al*., 2019). However, their use is not without risk. Numerous studies have documented adverse effects associated with NSAIDs overdosing, affecting the cardiovascular, gastrointestinal, hepatic and renal systems (Zhang *et al*., 2023; Masubuchi *et al*., 2019). During pregnancy, NSAIDs can cross the placental barrier, potentially impacting both embryonic and neonatal development. The severity of these effects is influenced by the specific drug, dosage, duration of therapy and gestational period (Antonucci *et al*., 2012; Burdan *et al*., 2004). Notably, certain NSAIDs such as piroxicam (PX) are associated with a higher risk profile compared to others like ibuprofen or diclofenac (Plappert *et al*., 2019; Ghlichloo *et al*., 2023).

Piroxicam (PX), a member of the oxicam class, is widely prescribed for various inflammatory conditions, including rheumatoid arthritis, osteoarthritis and post-traumatic inflammation (Sahu, 2016; Abdeen *et al*., 2020). Its primary mechanism involves the non-selective inhibition of cyclooxygenase (COX-1 and COX-2) enzymes, thereby suppressing prostaglandin synthesis (Burdan, 2015). However, the same mechanism contributes to its toxicity profile. Given that the liver is the main site of drug metabolism, it is particularly susceptible to PX-induced injury (Orinya *et al*., 2016; Badawi, 2018). Similarly, the kidney, where prostaglandins play a key role in regulating renal blood flow, is also a target for PX toxicity, especially following acute or chronic exposure (Shaheen *et al*., 2019; Rahmani Del Bakhshayesh *et al*., 2020). Accumulating evidence indicates that oxidative stress is a central mediator of PX-induced hepato-renal damage. This is characterized by lipid peroxidation (LPO), mitochondrial dysfunction, depletion of endogenous antioxidants, DNA oxidation and ultimately apoptosis (Ai-Rufaei *et al*., 2025; Abdeen *et al*., 2019). Therefore, strategies aimed at enhancing the body's antioxidant capacity may represent a viable approach to mitigating PX-induced organ toxicity (Vivek *et al*., 2025).

Quercetin (QUE), a naturally occurring flavonol abundant in fruits and vegetables, has garnered considerable attention for its potent antioxidant, anti-inflammatory and anti-apoptotic properties (Qi *et al*., 2022; Ullah *et al*., 2020; Gungor *et al*., 2025). Its ability to scavenge free radicals and modulate key cellular pathways positions it as a promising candidate for protecting against chemical-induced tissue injury (Yang *et al*., 2020; Khan *et al*., 2025).

[1]Department of Zoology, College of Science, King Saud University, PO Box 22452, Riyadh 11495, Saudi Arabia.

Corresponding Author: Fawziah Alshabanat, Dalia Fouad, Department of Zoology, College of Science, King Saud University, PO Box 22452, Riyadh 11495, Saudi Arabia.
Email: fawziahsaud1122@gmail.com; dibrahim@ksu.edu.sa

How to cite this article: Alshabanat, F., Virk, P. and Fouad, D. (2026). Role of Quercetin against the Effect of Piroxicam on the Liver and Kidney in Pregnant Rats. *Indian Journal of Animal Research.* **60(4):** 635-643. doi: 10.18805/IJAR.BF-2102.

Submitted: 02-01-2026 **Accepted:** 23-03-2026 **Online:** 13-04-2026

The main objective of current research was effect of quercetin in pregnant Wistar rats against piroxicam-induced toxicity in the liver and kidney by ameliorating the oxidative stress, DNA damage and apoptosis.

MATERIALS AND METHODS

Chemicals and reagents

Piroxicam (C15H13N3O4) was purchased from Bruschettini S.R.I. Company (USP, Genoa) and the exposure dose for the experiment was 7 mg/kg according to a previous study by Abdeen *et al.* (2020). Quercetin (>95% purity) was procured from Sigma-Aldrich Chemical Co., Saint Louis, MO, USA, (CAS No: 117-39-5). Assay kits for biochemical analyses were purchased from Cayman Chemical Company (Sieda) and Sigma-Aldrich (Rockwood, United States). The antibodies for caspase-3, TNF-α and IL-6 used for immunohistochemistry were purchased from Thermo Scientific (Waltham, Massachusetts, USA). DNA extraction kits were supplied by Qiagen (Hilden, Germany). All other chemicals used in the experiments were of high-quality analytical grade.

Animals and experimental design

Forty female Wistar rats weighing 180 to 200 grams were procured from the animal house facility at King Saud University in Riyadh, Saudi Arabia. The study was reviewed and approved by the Institutional Review Board (IRB) and ethical consent was provided with reference number (KSU-SE-24-23) through the Ethics Committee at King Saud University. The experimental work was conducted at the animal house of the central lab at King Saud University during the period from January to October 2025. All animals were housed in plastic crates under standard conditions with regular changes in light and dark periods, constant humidity and a temperature between 23 and 28°C. The rats had access to both a commercial pellet meal and tap water ad libitum. After acclimatization, animals were randomly divided into four groups (n=10 each) and treated for 13 consecutive days as follows:

- **Group 1 (Control):** Animals were orally administered normal saline for 13 days.
- **Group 2 (QUE):** Animals were orally administered quercetin (75 mg/kg) dissolved in normal saline for 13 days (Molina *et al.*, 2003).
- **Group 3 (PX):** Animals were injected intraperitoneally (*i.p.*) with piroxicam (7 mg/kg body weight/day) for 13 days.
- **Group 4 (QUE+PX):** Animals were orally administered quercetin (75 mg/kg) and injected intraperitoneally with piroxicam (7 mg/kg body weight/day) for 13 days.

On the 19th day of pregnancy, animals were anesthetized with CO_2 and sacrificed and embryos were extracted from each group (Karampour *et al*., 2014).

Sample collection and preparation

After decapitation, blood was immediately collected from the trunks of the rats. Blood samples were placed in EDTA tubes for hematological testing and in serum separator tubes for biochemical studies. Blood samples were also collected in sterile, closed plain tubes and placed at 25°C to coagulate. All tubes were then cooled and centrifuged for 15 minutes at 4°C at a speed of 3500 rpm. Serum samples were transferred into sterile Eppendorf tubes and frozen at -80°C for further analyses.

Liver and kidney tissues were excised immediately after collection and placed in ice-cold saline. A portion of each tissue was transferred immediately to 10% buffered formaldehyde for histopathological and immunohistochemical investigations. The remaining tissue samples were stored at -80°C for further analysis of oxidative stress markers, antioxidant defense enzymes and DNA damage assays.

Laboratory analyses

Hematological parameters

Hematological parameters, including red blood cells (RBC), hemoglobin (HGB), white blood cells (WBC) and platelets (PLT), were measured using a fully automated hematology analyzer (Beckman Coulter Ac. T 5diff, USA) following standard protocols and manufacturer's instructions (Shuker *et al*., 2022).

Biochemical analysis of Liver and Kidney function

Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, urea and albumin were determined spectrophotometrically using commercial diagnostic kits according to the manufacturer's guidelines (Fouad *et al*., 2019).

Histopathological examination

Liver and kidney specimens, fixed in 10% buffered formaldehyde and embedded in paraffin, were sectioned at 5-6 µm thickness, stained with hematoxylin and eosin (HandE) and examined under a light microscope (Olympus CX23, Japan) for histopathological changes (Abdeen *et al*., 2020).

Immunohistochemical detection of caspase-3, TNF-α and IL-6

Tissue sections were incubated overnight at 4°C with primary monoclonal antibodies against caspase-3, TNF-α and IL-6. Following PBS washing, sections were incubated with HRP-conjugated secondary antibody (1:2500), developed with DAB and counterstained with hematoxylin. Positively stained cells were counted in three fields per sample (Potocnjak, 2016; Abdeen *et al*., 2019).

Oxidative stress markers and antioxidant enzymes

Liver and kidney tissue homogenates (5 mg) were assayed for malondialdehyde (MDA), reduced glutathione (GSH) and superoxide dismutase (SOD) using commercial assay kits following the manufacturer's protocols (Abdeen *et al*., 2020).

DNA fragmentation assay

DNA was extracted from kidney tissue (25 mg) using a Qiagen DNeasy kit according to the manufacturer's instructions. DNA integrity was assessed by 1.5% agarose gel electrophoresis, visualized under UV light at 300 nm and photographed (Shuker *et al*., 2022).

Statistical analysis

One-way ANOVA was performed using SPSS software (version 22). All P-values were analyzed as two-sided and values below 0.05 were regarded as statistically significant. The analysis was complemented with a least significant difference (LSD) post-hoc test to identify specific group differences. Results were expressed as mean ± standard deviation (SD) for continuous data and as percentages for categorical data.

RESULTS AND DISCUSSION

Hematological parameters

When compared to the control group, the PX-treated pregnant rats' hemoglobin (HGB) and red blood cell counts were considerably lower, but their blood platelet (PLT) and white blood cell counts were higher (Fig 1). When compared to the PX group, the treated group (QUE+PX) showed a decrease in WBCs and PLT count, as well as an increase in RBCs and HGB levels. Significant restoration against the hematological alterations was observed on quercetin supplementation. The ameliorative effect of quercetin against xenobiotic-induced hepato-renal dysfunction is well-documented, with recent studies confirming its ability to attenuate hematological and biochemical alterations caused by various toxins (Alanazi *et al*., 2025). This protective effect indicates quercetin's ability to mitigate PX-induced hematotoxicity, aligning with Pasdar *et al*. (2020), who reported that quercetin supplementation improves hematological profile through its antioxidant and immunomodulatory properties.

Liver and kidney function

Biochemical analysis revealed that PX exposure significantly elevated serum ALT, AST, creatinine and urea levels, while reducing albumin concentration (Table 1, 2). These findings indicate substantial hepato-renal dysfunction, corroborating earlier reports by Abdeen *et al*. (2020) and Lina *et al*. (2017), who demonstrated similar patterns of liver enzyme elevation and renal impairment following PX administration. The reduction in albumin may be attributed to impaired hepatic synthetic function secondary to hepatocellular damage. Notably, quercetin supplementation markedly attenuated these alterations, supporting this, dietary quercetin supplementation has been shown to significantly elevate the activity of hepatic enzymes ALT and AST, indicating enhanced protein metabolism and improved physiological function (Raghuvaran *et al*., 2025). This hepatoprotective and nephroprotective effect is consistent with Jia *et al*. (2023), who documented quercetin's ability to modulate liver enzyme activity in hepatocarcinogenesis

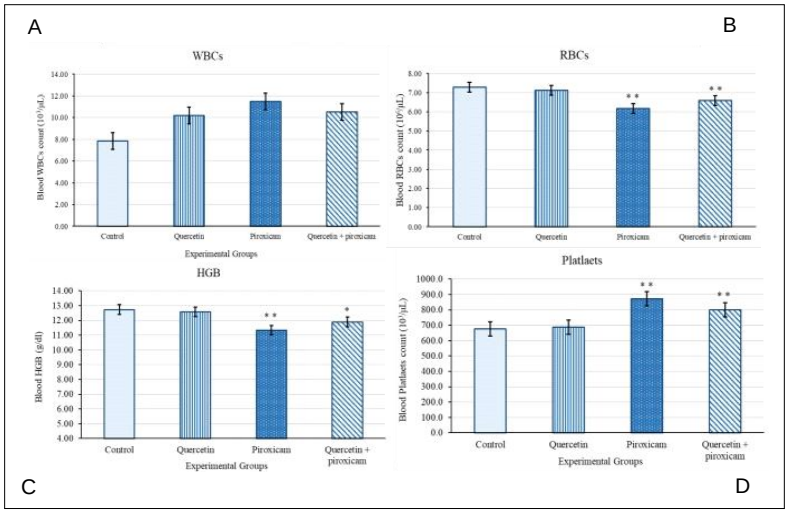


Fig 1: (A) Effects of Quercetin on Piroxicam induces changes in level of WBC count (10^3/µL) in the control and experimental pregnant rats. (B) Effect of Quercetin on piroxicam induces changes in level of RBC count (10^6/µL) in the control and experiment pregnant rats. (C) Effect of Quercetin on piroxicam induces changes in level of hemoglobin (HGB) (g/dL) in the control and experimental pregnant rats. (D) Effect of quercetin on piroxicam induces changes in level of platelet count (10^3/µL) in the control and experimental pregnant rats.

Table 1: Effect of quercetin on piroxicam induced alterations in alanine transaminase (ALT) (U/L) and aspartate aminotransferase (AST) (U/L) in the different pregnant rats.

Group parameter	Control	Quercetin	Piroxicam	Quercetin +Piroxicam
ALT (U/L)	65.00±8.4	75.06±18.75	114.9±10.35**	100.62±18.51**
AST (U/L)	97.2±21.9	117.6±15.8	159.0±17.4**	128.4±17.6*

(*p<0.05, **p<0.01) compared to untreated group (control).

models and with Qi *et al*. (2022), who highlighted its capacity to prevent lipid peroxidation in renal tissues.

Histopathological examination

Histological examination of liver tissues using H and E staining revealed normal hepatocytes and blood sinusoids in the control group (Fig 2A). Similar normal architecture was observed in the quercetin-treated group (Fig 2B). In contrast, liver sections from PX-treated rats showed marked pathological alterations including congested veins with hemorrhage, inflammatory cell infiltration, severe steatosis and edema (Fig 2C). However, the QUE+PX group exhibited notable improvement in liver architecture, with most hepatocytes appearing healthy and only sporadic infiltrative cells observed (Fig 2D). Kidney sections from control and QUE-treated rats showed normal glomeruli and tubules (Fig 3A, 3B). PX exposure resulted in significant renal damage characterized by interstitial hemorrhage, inflammatory cell aggregates and tubular casts (Fig 3C). Meanwhile, QUE+PX treatment markedly improved renal histology, demonstrating enhanced glomerular structure and reduced inflammatory infiltration (Fig 3D).

The histopathological alterations observed in PX-treated rats, including hepatic steatosis, inflammatory infiltration and renal tubular casts, confirm the biochemical evidence of hepato-renal damage and align with previous reports of piroxicam-induced tissue injury (Al-Hamdany *et al*., 2023; Abdeen *et al*., 2020). The marked improvement in both hepatic and renal architecture following quercetin co-administration demonstrates its tissue-protective potential, consistent with Badawi (2018), who reported that antioxidants facilitate tissue repair by neutralizing free radicals and reducing inflammatory cell recruitment. Additionally, the reduction in inflammatory infiltrates and restoration of normal glomerular structure support quercetin's well-documented anti-inflammatory properties (Qi *et al*., 2022; Ullah *et al*., 2020).

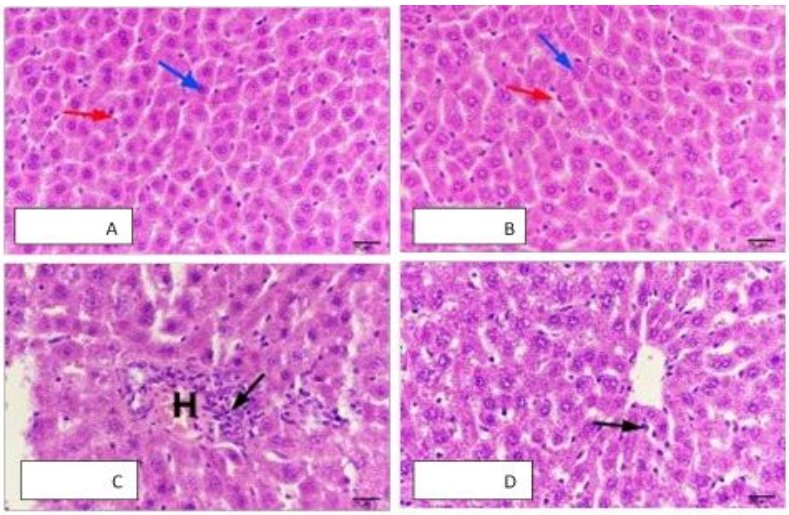
Immunohistochemical investigation

Immunohistochemical analysis demonstrated strong positive expression of caspase-3 and TNF-α in both liver

Table 2: Effect of quercetin on piroxicam induced changes in creatinine (U/L), urea (mg/dl) and albumin (g/dl) in the different pregnant rats.

Group parameter	Control	Quercetin	Piroxicam	Quercetin+Piroxicam
Creatinine (mg/dl)	0.211±0.153	0.218±0.157	0.376±0.326	0.296±0.277
Urea (mg/dl)	60.04±7.76	62.22±8.75	88.40±12.76**	77.80±15.07*
Albumin (g/dl)	2.46±0.23	2.70±0.36	2.15±0.01	2.29±0.17

(*p<0.05, **p<0.01) compared to untreated group (control).



(**A**) Photomicrograph of pregnant rat's liver treated of control liver showing no pathological features, hepatocytes (blue arrow), sinusoids with Kupffer cells (red arrow). (H and E-400X). (**B**) Photomicrograph of pregnant rat's liver treated with QUE revealing no pathological features, hepatocytes (blue arrow), sinusoids with Kupffer cells (red arrow). (H and E-400X). (**C**) Photomicrograph of pregnant rat's liver treated with PX displaying congested vein with hemorrhage (H), aggregation of infiltrative cells (black arrow). (H and E-400X). (**D**)**:** Photomicrograph of pregnant rat's liver treated with QUE+ PX showing improved liver tissue, scattered infiltrative cells (black arrow). (H and E-400X).

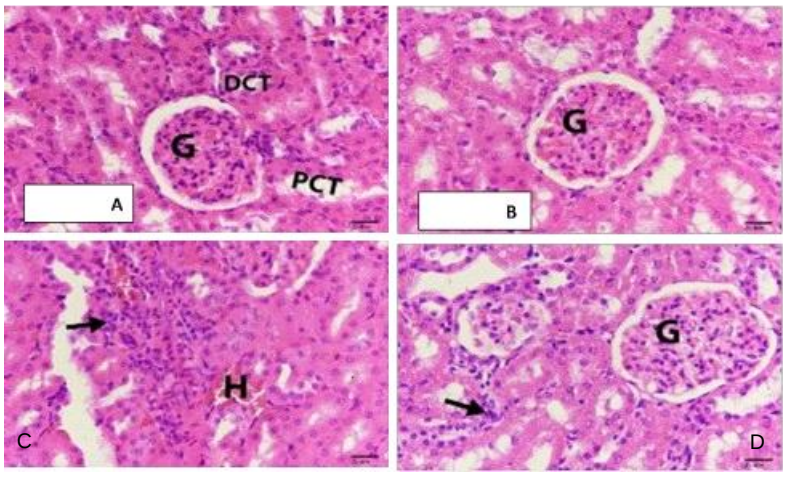
Fig 2: Histological examinations by hematoxylin and eosin staining demonstrating the effect of quercetin (QUE) on piroxicam (PX) induced liver damage in pregnant rats.

and kidney tissues of PX-treated rats, indicating enhanced apoptosis and inflammation (Fig 4-7). These findings align with Abdeen *et al.* (2019), who reported that PX-induced oxidative stress triggers apoptotic pathways through caspase activation. Interestingly, IL-6 expression showed only minimal changes across all groups (Fig 8,9). Quercetin co-treatment markedly reduced caspase-3 and TNF-α expression, confirming its anti-apoptotic and anti-inflammatory properties. The moderate reduction in IL-6 immunoreactivity observed in the QUE+PX group further supports quercetin's modulatory effect on inflammatory mediators (Michala, 2022).

Oxidative stress markers and antioxidant enzymes in liver and kidney tissues.

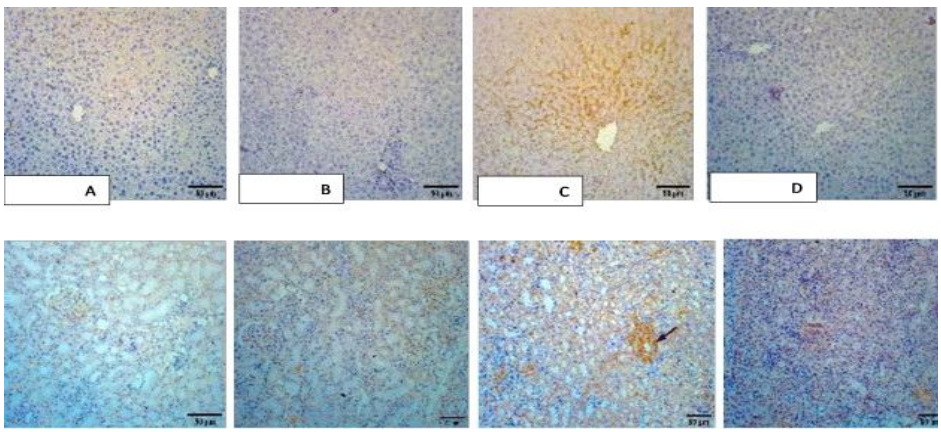
Oxidative stress markers

PX treatment significantly increased hepatic and renal MDA levels, indicative of enhanced lipid peroxidation, while



(A) Photomicrograph of control renal cortex showing no pathological signs, glomerulus (G), proximal convoluted tubules (PCT), distal convoluted tubules (DCT). (H and E-400X). (B) Photomicrograph of renal cortex treated with quercetin showing no pathological signs, glomerulus (G) (H and E-400X). (C) Photomicrograph of renal cortex treated with Piroxicam displaying hemorrhage (H), aggregation of infiltrative cells (black arrow). (H and E-400X). (D) Photomicrograph of renal cortex treated with Quercetin +Piroxicam revealing abundant glomerulus (G), less infiltrative cells (black arrow). (H and E-400X).

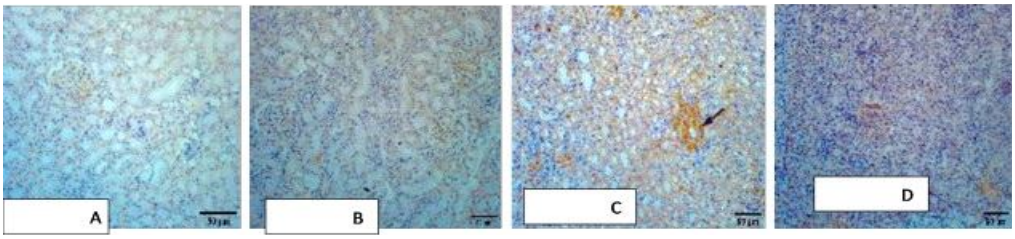
Fig 3: Histological examinations by hematoxylin and eosin staining demonstrating the effect of quercetin (QUE) on piroxicam (PX) induced kidney damage in pregnant rats' Light micrographs of the kidney.



(A) Control and (B) Quercetin groups show no positive expression of activated caspases 3. (C) PX-exposed rat reveals a strong expression of caspase-3. (D) Quercetin + Piroxicam show moderate and mild expression, respectively. The positive activated caspase-3 expression is indicated by the brown color of the hepatic nuclei.

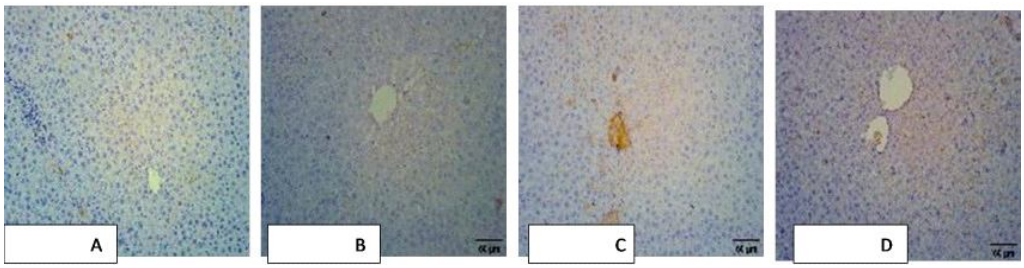
Fig 4: Effects of quercetin on activated caspases-3 expression after piroxicam intoxication in the liver pregnant rats.

concomitantly depleting GSH content and reducing SOD activity (Table 3,4). This redox imbalance confirms the role of oxidative stress in PX-mediated tissue injury, consistent with Ahmed *et al*. (2015) and Chen *et al*. (2023), who demonstrated that NSAIDs-induced mitochondrial dysfunction elevates ROS production and impairs antioxidant defenses.



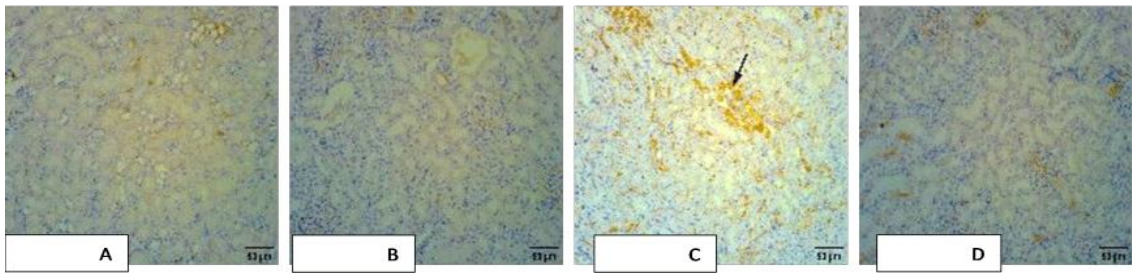
(A) Control and (B) Quercetin groups show no positive expression of activated caspases 3. (C) PX-exposed reveals a strong expression of caspase-3. (D) Quercetin + Piroxicam show moderate and mild expression, respectively. The positive activated caspase-3 expression is indicated by the brown color of renal nuclei.

Fig 5: Effects of quercetin on activated caspases-3 expression after PX intoxication in the kidney of pregnant rats.



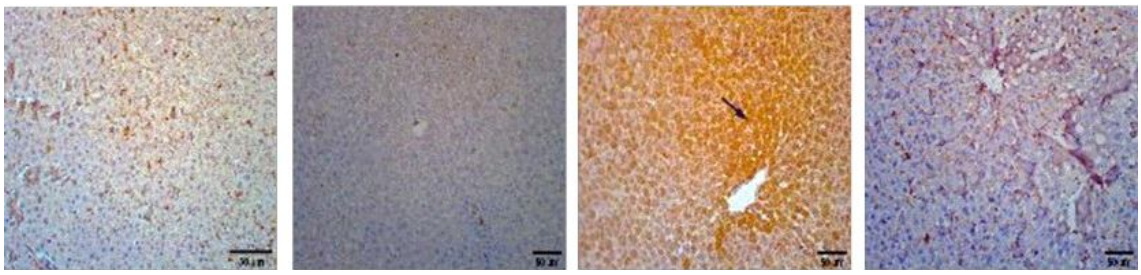
(A) Normal control. (B) Quercetin. (C) Piroxicam. (D) QUE+ PX (,original magnification ×20.

Fig 6: Immunohistochemical staining for TNF-∂ expression in the liver of pregnant rat's section obtained.



(**A**) Normal control. (**B**) Quercetin. (**C**) Piroxicam. (**D**) QUE+ PX (,original magnification ×20.

Fig 7: Immunohistochemical staining for TNF-∂ expression in the kidney of pregnant rat's section obtained.



(A) Normal control in the kidney of pregnant rats. (B)Quercetin. (C)Piroxicam. (D)QUE+PX (,original magnification ×20.

Fig 8: Immunohistochemical staining for IL-6 expression in the liver of pregnant rat's section obtained.

Table 3: Effect of quercetin on piroxicam induced alterations in malondialdehyde (MDA) levels (nmol/g fresh tissue) and reduced glutathione level (GSH) (nmol/g fresh tissue) in liver and kidney in the different pregnant rats.

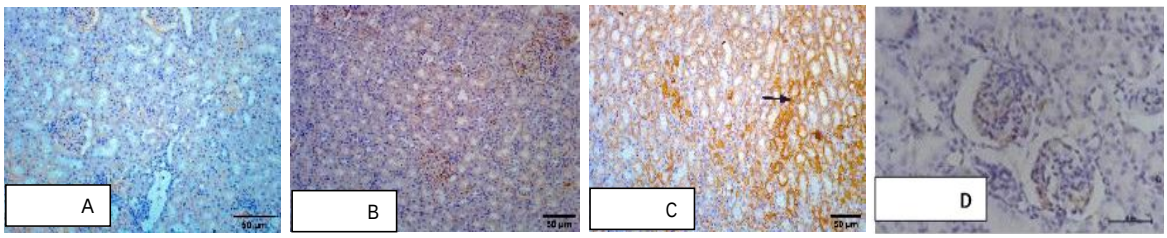
Group parameter	Control	Quercetin	Piroxicam	Quercetin +Piroxicam
Liver				
MDA (nmol/g)	218.2±48.2	286.4±42.7*	506.2±55.6**	394.2±25.7**
GSH (nmol/g)	0.778±0.718	0.894±0.522	0.446±0.590	0.451±0.594
Kidney				
MDA (nmol/g)	126.4±16.1	116.2±13.3	175.8±17.1**	159.8±19.4**
GSH (nmol/g)	1.433±0.904	1.319±0.905	0.712±0.651	0.955±0.593

(*p<0.05, **p<0.01) compared to untreated group (control).

Table 4: Effect of quercetin on piroxicam induced alterations in superoxide dismutase activity (SOD) (U/ml fresh tissue) in liver and kidney in the different pregnant rats.

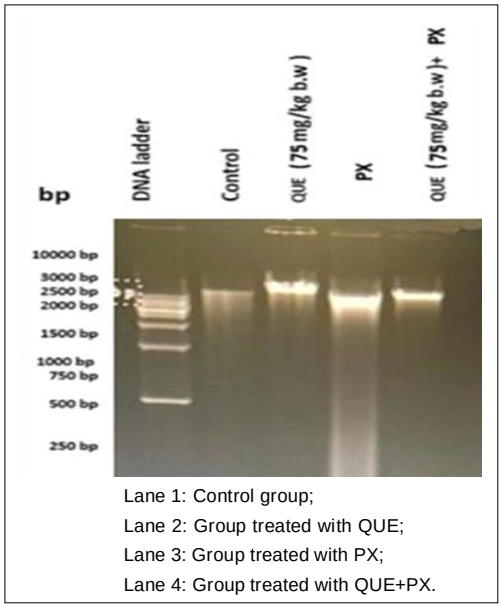
Group parameter	Control	Quercetin	Piroxicam	Quercetin +Piroxicam
Liver				
SOD (U/ml)	1.260±0.828	1.418±0.694	0.798±0.370	1.112±0.397
Kidney				
SOD (U/ml)	2.27±0.68	2.75±0.63	1.56±0.24*	1.67±0.41

(*p<0.05, **p<0.01) compared to untreated group (control).



(A) Normal control. (B) Quercetin. (C) Piroxicam. (D) QUE+ PX (, original magnification ×20.

Fig 9: Immunohistochemical staining for IL-6 expression in the kidney of pregnant rat's section obtained.



Lane 1: Control group;
Lane 2: Group treated with QUE;
Lane 3: Group treated with PX;
Lane 4: Group treated with QUE+PX.

Fig 10: DNA fragmentation in control and experimental in the kidney of pregnant rats.

Quercetin supplementation effectively reversed these changes, restoring antioxidant enzyme activity and reducing lipid peroxidation. The ability of quercetin to scavenge free radicals and enhance endogenous antioxidant capacity has been well-documented (Ullah *et al*., 2020; Yang *et al*., 2020), explaining its protective efficacy in the present study. However, quercetin is known to inhibit key drug-metabolizing enzymes (*e.g.*, CYP3A4) and efflux transporters (*e.g.*, P-gp, MRP2), which may reduce the formation of toxic metabolites and enhance the bioavailability of co-administered drugs (Patel *et al*., 2022).

DNA fragmentation

A major indicator of apoptosis is DNA fragmentation. Agarose gel electrophoresis has been used to investigate the qualitative assessment of the integrity of the altered genomic DNA (Fig 10). While PX treatment caused DNA fragmentation (lanes 3), the DNA isolated from control pregnant rats (lane 1) and QUE-treated animals (lane 2) showed high-quality DNA. QUE+ PX-treated groups (lane 4) showed reduced DNA damage, nevertheless. These findings are consistent with Hosseini *et al*. (2021),

who reported that quercetin protects against DNA damage through its antioxidant activity and ability to modulate apoptotic signaling pathways. The observed reduction in DNA fragmentation following quercetin co-treatment further supports its anti-apoptotic role, complementing the caspase-3 immunohistochemical findings.

CONCLUSION

Taken together, treatment with PX showed detectable changes in blood analysis, serum biochemical parameters, antioxidants and DNA in both the liver and kidney of the animals, as well as noticeable histological alterations. The use of quercetin clearly mitigated the renal and hepatotoxicity. However, quercetin could be incorporated as a dietary supplement only under the approval of a healthcare professional in accordance with the daily recommended dose.

ACKNOWLEDGEMENT

The authors extend their appreciation to the “Ongoing Research Funding Program” (ORF-2026-965), King Saud University, Riyadh, Saudi Arabia.

Disclaimers

The views and conclusions expressed in this article are solely those of the authors and do not necessarily represent the views of their affiliated institutions. The authors are responsible for the accuracy and completeness of the information provided, but do not accept any liability for any direct or indirect losses resulting from the use of this content.

Informed consent

All animal procedures for experiments were approved by the Committee of Experimental Animal care and handling techniques were approved by the University of Animal Care Committee.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article. No funding or sponsorship influenced the design of the study, data collection, analysis, decision to publish, or preparation of the manuscript.

REFERENCES

Abdeen, A., Abdelkader, A., Elgazzar, D., Aboubakr, M., Abdulah, O.A., Shoghy, K., Abdel-Daim, M., El Serehy, H.A., Najda, A. and El-Mleeh, A. (2020). Coenzyme Q10 supplementation mitigates piroxicam-induced oxidative injury and apoptotic pathways in the stomach, liver and kidney. *Biomedicine and Pharmacotherapy*. **130:** 110627.

Abdeen, M. Aboubakr, D. Elgazzar, M. Abdo, A. Abdelkader, S. and Ibrahim, A. (2019). Elkomy rosuvastatin attenuates piroxicam-mediated gastric ulceration and hepato-renal toxicity in rats. *Biomed. Pharmacother.* **110:** 895-905. doi: 10.1016/j.biopha.2018.11.004.

Abdeen, A.O.A., Abou-Zaid, H.A., Abdel-Maksoud, M., Aboubakr, A., Abdelkader, A., Abdelnaby, A.I., Abo-Ahmed, A. El-Mleeh, O., Mostafa, M. and Abdel-Daim, L.(2019). Aleya Cadmium overload modulates piroxicam-regulated oxidative damage and apoptotic pathways. *Environ. Sci. Pollut. Res.* **26:** 25167-25177. doi: 10.1007/s11356-019-05783-x.

Ahmed, W., Zaki, A. and Nabil, T. (2015). Prevention of methotrexate-induced nephrotoxicity by concomitant administration of garlic aqueous extract in rat. *Turk. J. Med. Sci.* **45(3):** 507-516. doi: 10.3906/sag-1408-121.

Ai-Rufaei, I.A., Ali, S.A., Kareem, D.A. and Majeed, M.F. (2025). Single and combined effects of lead and piroxicam on the structural and functional profiles of the liver and kidney. *Polski merkuriusz lekarski: Organ Polskiego Towarzystwa Lekarskiego.* **53(3):** 328-335. http://www.curipms.umlub.pl/.

Alanazi, R., Omer, S., Albasher, G. and Mohammed, O.B. (2025). Hematological and biochemical response to methyl mercury toxicity and the ameliorative effect of quercetin flavonoid in wistar rats. *Indian Journal of Animal Research*. 1-7. doi: 10.18805/IJAR.BF-2005.

Al-Hamdany, M., Al-Tai, F. and Ismail, H.K. (2023). Histological changes induced by piroxicam on the hepatic and renal tissues of mice with and without administration of peppermint oil. *Current Issues in Pharmacy and Medical Sciences.* **36(2):** 123-130.

Antonucci, R., Zaffanello, M., Puxeddu, E., Porcella, A., Cuzzolin, L., Pilloni, M.D. and Fanos, V. (2012). Use of non-steroidal Anti-inflammatory drugs in pregnancy: Impact on the fetus and newborn. *Current Medicinal Chemistry*. **13(4):** 474-490.

Badawi, M.S. (2018). Histological study of the protective role of ginger on piroxicam-induced liver toxicity in mice. *J. Chin. Med. Assoc.* **82:** 11-18. doi: 10.1016/j.jcma.2018.06.00.

Burdan, F. (2004). Developmental toxicity evaluation of ibuprofen and tolmetin administered in triple daily doses to Wistar CRL:(WI) WUBR rats. *Birth defects research. Part B. Developmental and Reproductive Toxicology*. **71(5):** 321-330. doi.org/10.1002/bdrb.20018.

Burdan, F. (2015). Basic principles of pharmacology: NSAIDs mechanism of action and toxicity. *Journal of Pre-Clinical and Clinical Research.* **9(2):** 73-78.

Chen, Y., Li, Q., Wu, S., Xu, H. and Zhang, J. (2023) Mitochondrial dysfunction and oxidative stress in NSAID-induced hepatotoxicity: focus on diclofenac and piroxicam. *Toxicol. Lett.* **379:** 58-67. https://doi.org/10.1016/j.toxlet.2023.01.004.

Fouad, D., Badr, A. and Attia, H. (2019). Hepatoprotective activity of raspberry ketone is mediated *via* inhibition of the NF-κB/TNF-α/caspase axis and mitochondrial apoptosis in chemically induced acute liver injury. *Toxicol Res*. **8:** 663-676.

Ghlichloo, I. and Gerriets,V. (2023). Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). A service of the National Library of Medicine, National Institutes of Health.

Gungor, M.M. and Kurutas, E.E.B. (2025). Effect of quercetin and resveratrol on raftlin and 8-iso prostaglandin F2α levels in renal ischemia-reperfusion injury. *Indian Journal of Animal Research.* doi: 10.18805/IJAR.BF-1850.

Hosseini, A., Razavi, B.M., Banach, M. and Hosseinzadeh, H. (2021). Quercetin and metabolic syndrome: A review. *Phytotherapy Research: PTR*. **35(10):** 5352-5364.

Ignácio, F.S., Garcia, L.V., de Souza, G.G., Amatti, L.Z., de Barros, L.D., Bergfelt, D.R., Camargo, G.S., de Meira, C. and de Almeida, B.F.M. (2024). Hematological and biochemical effects associated with prolonged administration of the NSAID firocoxib in adult healthy horses. *Veterinary Sciences.* **11(6):** 256. doi.org/10.3390/vetsci11060256.

Jia, S., Wang, R., Zhang, D., Guan, Z., Ding, T., Zhang, J. and Zhao, X. (2023). Quercetin modulates the liver metabolic profile in a chronic unpredictable mild stress rat model based on metabolomics technology. *Food and Function.* **14(3).** doi: 10.1039/d2fo03277e.

Karampour, N.S., Arzi, A., Varzi, H.N., Mohammadian, B. and Rezaei, M. (2014). Quercetin preventive effects on theophlline-induced anomalies in rat embryo. *Jundishapur Junrnal Natural Pharmaceutical Products*. **9(3):** 17795-17834.

Khan, N., Kakar, A., Rabbani, I., Naseem, M., Sheikh, I.S., Yaqub, T. and Imran, M. (2025). Quercetin verses metformin, comparative efficacy on the lipid metabolism gene expression in different organs of diabetic wistar rats. *Indian Journal of Animal Research*. 1-8. doi: 10.18805/IJAR.BF-1968.

Lina M.A., Majeed, A. and Abass, K. (2017). Biological effects of different doses of Piroxicam in albino males rats Department of Biology, College of Science, University of Baghdad, Baghdad, Iraq.

Masubuchi,Y., Yamada, S. and Horie, T. (2019). Possible Mechanism of Hepatocyte Injury Induced by Diphenylamine and Its Structurally Related Nonsteroidal Anti-Inflammatory Drugs Laboratory of Biopharmaceutics, Faculty of Pharmaceutical Sciences, Chiba University, Chiba, Japan.

Michala, A and Pritsa, A. (2022). Quercetin: A molecule of great biochemical and clinical value and Its benefical effect on diabetes and cancer. *Diseases*. **60(37):** 31-16.

Molina, M., Sanchez-Reus, I., Iglesias, I. and Benedi, J. (2003). Quercetin, a flavonoid antioxidant, prevents and protects against ethanol-induced oxidative stress in mouse liver. *Biological and Pharmaceutical Bulletin.* **26:** 1398-1402.

Montinari, M., Minelli, S. and Caterina, R. (2019). The first 3500 years of aspirin history from its roots-aconise summary. *Vascular Pharmacology.* **113:** 1-8.

Orinya, O.A., Adenkola, A.Y. and Ogbe, R.J. (2016). Haematological and biochemical studies on the effect of diclofenac sodium on Wistar Rattus norvegicus. *International Journal of Biological and Chemical Sciences.* **10(5):** 2231-2242. doi: 10.4314/ijbcs.v10i5.23

Panchal, N.K. and Sabina, E.P. (2023). Non-steroidal anti-inflammatory drugs (NSAIDs): A current insight into their molecular mechanism eliciting organ toxicities. *Food and Chemical Toxicology.* **172:** 113598.

Pasdar, Y., Oubari, F., Zarif, M.N., Abbasi, M., Pourmahmoudi, A. and Hosseinikia, M. (2020). Effects of quercetin supplementation on hematological parameters in non-alcoholic fatty liver disease: A randomized, double-blind, placebo-controlled pilot study. *Clin. Nutr. Res*. **9(1):** 11-19. doi: 10.7762/cnr.2020.9.1.11. PMID: 32095444; PMCID: PMC7015726.

Patel, H.B., Patel, U.D., Modi, C.M., Ladumor, V.C., Makwana, C.N. and Rao, S.S. (2022). Pharmacokinetics of marbofloxacin following oral administration in piperine, quercetin alone and both in combination pretreated broiler chickens. *Indian Journal of Animal Research*. **56(10):** 1269-1273. doi: 10.18805/IJAR.B-4300.

Plappert, S.F., Liebner, F.W., Konnerth, J. and Nedelec, J.M. (2019). Anisotropic nanocellulose gel-membranes for drug delivery: Tailoring structure and interface by sequential periodate-chlorite oxidation. *Carbohydrate Polymers*. **226:** 115306.

Potocnjak, I. and Domitrovic, R. (2016). Carvacrol attenuates acute kidney injury induced by cisplatin through suppression of ERK and PI3K/Akt activation. *Food Chem. Toxicol*. **98:** 251-261.

Qi, W., Qi, W., Xiong, D. and Long, M. (2022). Quercetin: Its antioxidant mechanism, antibacterial properties and potential application in prevention and control of toxipathy. *Molecules*. **7(19):** 6545. doi: 10.3390/molecules27196545.

Raghuvaran, N., Sahu, N.P., Sardar, P., Varghese, T., Shamna, N., Rani, B., Bhuvaneshwaran, T. and Revathi, A. (2025). Effect of selected nutraceuticals on growth and metabolism of penaeus vannamei juveniles reared in inland saline water. *Indian Journal of Animal Research*. **59(8):** 1355-1362. doi: 10.18805/IJAR.B-5587.

Rahmani Del Bakhshayesh, A., Akbarzadeh, A., Alihemmati, A., Tayefi Nasrabadi, H., Montaseri, A., Davaran, S. and Abedelahi, A. (2020). Preparation and characterization of novel anti-inflammatory biological agents based on piroxicam-loaded poly-ε-caprolactone nano-particles for sustained NSAID delivery. *Drug Delivery*. **27(1):** 269-282.

Sahu, C.R. (2016). Mechanisms involved in toxicity of liver caused by piroxicam in mice and protective effects of leaf extract of Hibiscus *Rosa-sinensis* L. *Clin. Med. Insights Arthritis Musculoskelet. Disord.* **9:** 9-13. doi: 10.4137/CMAMD. S29463.

Shaheen, G., Habib, S.H., Khizar, S.H., Safiullah, S., Malik, M.O., Khan, N. and Tariq, S.A. (2019). Evaluation of hepatotoxic and nephrotoxic effects after 2 weeks treatment of piroxicam sulfonated derivatives in albino rats. *Pakistan Journal of Physiology*. **15(3):** 27-33.

Shuker, E., Farhood, M., Al-Qudaihi, G. and Fouad, D. (2022). Potential effects of boldine on oxidative stress, apoptosis and inflammatory changes induced by the methylprednisolone hepatotoxicity in male wistar rats. *Dose Response*. **20(1):** 1-16.

Ullah, A., Munir, S., Badshah, S.L., Khan, N., Ghani, L., Poulson, B.G., Emwas, A.H. and Jaremko, M. (2020). Important flavonoids and their role as a therapeutic agent. *Molecules*. **25(22):** 5243.

Vivek, H.S., Rajendra, S.V., Harshitha, N., Jyothi, Y. and Jothi, A. (2025). Effect of melatonin in amelioration of piroxicam induced liver and renal oxidative stress in rats. *Int. J. Basic Clin. Pharmacol.* **14:** 375-381.

Yang, D.,Wang, T., Long, M. and Li, P. (2020). Quercetin: Its main pharmacological activity and potential application in clinical medicine. *Oxid. Med. Cell. Longev.* 8825387.

Zhang, J., Li, Q., Kiu, Z. and Zhao, L. (2023). Rapid and sensitive determination of Piroxicam by N-doped carbon dots prepared by plant soot. *Spectrochimica Acta*. **299:** 122833.