Egyptian Journal of Veterinary Sciences

https://ejvs.journals.ekb.eg/

Effects of Oral Administration of Omeprazole and Quercetin on Inflammatory and Histopathological Alterations of Ketoprofen in Rats

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Abstract

KETOPROFEN (KP) is a nonsteroidal anti-inflammatory drug (NSAID) that treats musculoskeletal injuries, osteoarthritis, and acute gouty arthritis. However, its use has been linked to certain detrimental effects on stomach, liver, and renal function. This study looked into how omeprazole and quercetin could help rats overcome the negative effects of KP. For this aim, 32 male rats were divided equally into four groups: Group I consisted of negative control rats. Rats were treated with ketoprofen in Group II (50 mg/kg b. wt.), omeprazole in Group III (20 mg/kg b. wt.), and quercetin in Group IV (50 mg/kg b. wt.). The study assessed TNF-α and IL-10 levels, as well as histological alterations in the stomach, liver, and kidney. Omeprazole plus quercetin treatment significantly ($P< 0.05$) reduced TNF-α and IL-10 production in the stomach, liver, and kidneys. Omeprazole and quercetin are likely to greatly improve the histopathological changes caused by KP. As a result, during the ketoprofen treatment course in rats, it is strongly advised to take either omeprazole or quercetin, or even both together.

Keywords: Ketoprofen, omeprazole, quercetin, histopathology, inflammation, rats.

Introduction

Inflammatory diseases can be effectively treated with the use of nonsteroidal anti-inflammatory medicines (NSAIDs) such ketoprofen [1, 2]. These medications are associated with a decrease in prostaglandins (PGs) due to their nonselective inhibition of the cyclooxygenase enzymes COX 1 and COX 2 [3].

Ketoprofen, a medication containing 2, 3-benzoylphenyl propanoic acid, is useful in the treatment of a variety of musculoskeletal injuries, osteoarthritis, acute gouty arthritis, bursitis, and tendinitis [4, 5]. Although it has many potential benefits, there are also some serious risks associated with using it. For example, it can reduce the production of protective gastric mucosa (PGs), which can lead to ulcers, bleeding, increased intestinal mucosa permeability, and hypermotility of the stomach [6]. A reduction in creatinine clearance, liver damage, and kidney impairment are all possible side effects of ketoprofen [7, 8]. The precise process that causes the side effects associated with using ketoprofen is still not completely known. Some possible causes for these side effects include changes in the hydrophobicity of the intestinal mucosa, an inhibition of PG synthesis—a process essential to many physiological functions—or even the generation of free radicals and reactive oxygen and nitrogen species (ROS and RNS) [9, 10]. Previous studies provided the groundwork for these conclusions.

According to Hisaka [11], quercetin has powerful anti-cancer properties, specifically targeting cells in the liver, breast, ovary, colorectal, and stomach regions. Many different mechanisms have been linked to quercetin's anticancer effects. These include reducing oncogene expression, blocking P-gp channels, suppressing angiogenesis, and modulating signaling pathways [12]. Reason being, inflammatory mediators are released when inflammation occurs, exacerbating the disease profile in specific illnesses like rheumatoid arthritis, ulcers, and similar ailments.

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(Received 19 July 2025, accepted 10 October 2025)
DOI: 10.21608/ejvs.2025.405729.2976

Several investigations have shown that quercetin's anti-inflammatory actions are caused by its ability to inhibit nuclear factor kappa B (IkBa) binding sites, ATP, and proinflammatory cytokines [13]. Another essential property of quercetin is its ability to chelate metal ions, such as Fe2+, Fe3+, Cu2+, and Ni2+. Some of the properties demonstrated for these quercetin metal complexes include actions against allergies, ulcers, infections, cancer, and Alzheimer's disease [14]. Therefore, it is clear that quercetin has several beneficial effects and is used in biomedicine for its pharmacological qualities. However, there are a few drawbacks that make it hard to absorb and make available, including a low bioavailability, a hydrophobic character, poor solubility, and poor permeability. To increase its bioavailability and solubility, quercetin was increasingly complexes with chitosan and biodegradable polymers [15]. We did this to get around the issue.

Quercetin is found in more than twenty distinct plant species. This list includes several species of plants, including Mangifera indica, Emblica of cinalis, Withania somnifera, Santalum album, Cuscuta refexa, Curcuma domestica valenton, and Foeniculum vulgare. Because it has such a wide range of pharmacological effects, quercetin is usually taken as a dietary supplement in the form of capsules or powder. The daily consumption of fruits, vegetables, and tea varied from fifty to eight hundred milligrams across different countries, according to the stated dietary intake levels [16].

This study set out to investigate the ameliorative effects of the oral administration of omeprazole and quercetin on the adverse effects of ketoprofen in rats.

Material and Methods

Chemicals

Ketofan was purchased from Amriya for Pharmaceutical Industries, Alexandria, Egypt. Healsec (capsules) was obtained from Borg chemical company, Egypt. Quercetin was obtained from Sigma Aldrich (St. Louis, MO, USA).

Experimental animals

We used 32 adult male albino rats that seemed to be in good health for our study. They were 10–12 weeks old and weighed 160–180 g b.w.t. A group of rats were sourced from Zagazig University's Animal Breading Unit at the Faculty of Veterinary Medicine. To make sure the animals were comfortable in the lab before the experiments started, we watched them for two weeks. The rats lived in clean metal cages, where they were provided with water constantly and a rodent food.

The rats were divided into four equal groups at random using the following design:

First group: rats used as a control group: Oral gavage with 1 mL of a 0.5% carboxymethyl cellulose (CMC) vehicle was administered to rats for 15 days in a row. Group II: Rats administered ketoprofen: For a duration of 14 days, rats were given 1 milliliter of 0.5% CMC. The rats were administered a single oral dosage of 50 mg/kg body weight of ketoprofen dissolved in 0.5% CMC on the fifteenth day after a 24-hour fast [17]. Rats administered ketoprofen and omeprazole (Group III): For 14 days in a row, rats were orally administered 1 ml of 0.5% CMC. Omeprazole (20 mg/kg b.wt.) was administered to rats on the fifteenth day [18]. After a 24-hour fast, take 50 mg/kg b.wt. of ketoprofen orally one hour before the fast ends, dissolved in 0.5% CMC. Rats given a combination of ketoprofen and quercetin (Group IV): For 14 days, rats were given a single oral dose of quercetin (50 mg/kg b.wt.) dissolved in 0.5% CMC [19]. Following a 24-hour fast, rats were administered quercetin one hour before to taking ketoprofen (50 mg/kg b.wt.) dissolved in 0.5% CMC in a single oral dose on the fifteenth day.

After 15 days of the experiment, the animals were given a combination of ketamine hydrochloride (50 mg/kg b.wt.) and xylazine (5 mg/kg b.wt.) intramuscularly to sedate them after a 24-hour fast. A puncture in the retro-orbital venous plexus was used to collect blood samples. After blood was drawn into anticoagulant-free sterile centrifuge tubes, they were tilted at room temperature to let the blood clot, and then spun at 3000 r.p.m. for 20 minutes to extract clear serums. The animals were subsequently beheaded and their internal organs (kidneys, livers, and stomachs) were swiftly taken for laboratory testing. In order to generate tissue homogenates for the purpose of testing pro- and anti-inflammatory cytokines, the liver, stomach, and one kidney were preserved at -20℃. Prior to histological examination, further sections of the digestive tract, second kidney, liver, and stomach were soaked in 10% neutral buffered formalin.

Evaluation of inflammatory biomarkers

My BioSource, San Diego, USA, supplied the rat ELISA kits. The parameters evaluated were TNF-α (Catalog No. MBS267737) and IL10 (Catalog No. MBS243214). The quantitative estimation of these biomarkers was carried out using the manufacturer's suggested methodology.

Histopathological investigation

All rats were beheaded and necropsied at the scheduled experimental time, and representative liver, kidney, and stomach tissue specimens were collected from five randomly selected animals from each group using the rat and mouse necropsy techniques [20, 21]. The specimens were fixed in 10% neutral buffered formalin for 24 hours, washed in tap water, dehydrated in increasing grades of ethyl alcohol, cleared in Ultra Clear TM clearing agent (Avantor Sciences, PA, USA), infiltrated and blocked-in paraffin wax, sectioned at 4-5 µm thick, and stained with Harris hematoxylin solution and

eosin Y dye [22]. The dyed slides were inspected microscopically, and a full lesion assessment for the observed histological changes was carried out under guidance [23]. The frequencies of histopathological abnormalities were counted in ten non-overlapping microscopic fields (10X for gastric, 40X for hepatic and renal specimens; 100 microscopic fields/organ/group), and the data were given as mean ± SE.

Statistical analysis

The acquired data were reported as mean ± SE. The data were statistically examined and evaluated using one-way analysis of variance (ANOVA). Significant differences between means were determined at p-values < 0.05 [24].

Results

Effects of oral administration of omeprazole and quercetin on inflammatory/ anti-inflammatory status of ketoprofen treated rats

In adult male albino rats, a single oral dose of 50 mg/kg b.wt. of ketoprofen significantly increased the content of TNF-α in stomach tissue (1102.4 ± 39.4 pg/ml) compared to the control group (490 ± 5.5 pg/ml) ($p<0.05$). When rats treated with ketoprofen were also given omeprazole (20 mg/kg b.wt.), the concentration of TNF-α in their stomach tissue was much lower (810 ± 9.5 pg/ml) than in the group that received only ketoprofen ($p<0.05$). When rats treated with ketoprofen were given quercetin (50 mg/kg b.wt.) daily for 15 days, the concentration of TNF-α in their stomach tissue was significantly lower (655 ± 16.7 pg/ml) compared to the group that only received ketoprofen ($p<0.05$). A single dosage of ketoprofen raised the content of IL-10 in the stomach tissue of adult male albino rats (1054.2 ± 82.9 pg/ml) in comparison to the control group (630.2 ± 8.66 pg/ml). Odeprazole reduced the levels of IL-10 in gastric tissue (771.2 ± 24.8 pg/ml) as seen in Table 1.

The hepatic tissue TNF-α levels in the adult male albino rats were considerably higher after a single oral dose of ketoprofen (1002 ± 13.6 pg/ml) when compared to the control group (474 ± 8.7 pg/ml). In comparison to ketoprofen alone, omeprazole and quercetin considerably decreased the amount of TNF-α in liver tissue (811 ± 4.6 pg/ml and 653 ± 21.6 pg/ml, respectively). The hepatic tissue IL-10 concentration was significantly higher in the group treated with oral ketoprofen (941 ± 20.1 pg/ml) compared to the control group (661.2 ± 16.9 pg/ml) ($p<0.05$). In comparison to the group that received only ketoprofen, rats who were given omeprazole orally had significantly lower levels of hepatic tissue IL-10 (554.4 ± 24.1 pg/ml) ($p<0.05$). A significant reduction ($p<0.05$) in hepatic tissue IL-10 level (772 ± 17.47 pg/ml) was observed in the rats treated with ketoprofen and quercetin for 15 days as compared to the animals in the ketoprofen-only group (Table 2).

Compared to the control group, adult male albino rats given a single oral dose of ketoprofen had considerably higher levels of TNF-α in their renal tissue (888.4 ± 18.9 pg/ml) than those in the experimental group (372 ± 14.6 pg/ml). Just like quercetin, which led to a substantial drop (537.2 ± 17.03 pg/ml) compared to the group treated with only ketoprofen, administering omeprazole to rats that had already been given ketoprofen reduced the concentration of tumor necrosis factor-alpha in their renal tissues (691.2 ± 8.35 pg/ml). Compared to the control group, a single dose of ketoprofen considerably raised IL-10 levels in renal tissue (1021.4 ± 28.9 pg/ml). When compared to the group that only took ketoprofen, the concentration of IL-10 in the kidneys was significantly lower in the groups that also took omeprazole and quercetin (655 ± 14.4 pg/ml and 750 ± 23.9 pg/ml, respectively) (Table 3).

Effects of oral administration of omeprazole and quercetin on histopathological alterations of ketoprofen treated rats:

Stomach

Typical histological structures were observed in the control rats' stomach tissue specimens under light microscopic inspection (Fig. 1 A). The ketoprofen-treated rats' gastric mucosae displayed a variety of histological alterations characterizing gastropathy. Primarily, the gastric responses were of an inflammatory, and degenerative nature, and ranged in severity in most specimens from mild to moderate. Notable leukocytic infiltration, minute hemorrhages, and vascular congestions of the laminae propriae and submucosae, accompanied by denudation, erosions, and necrosis of the epithelial cells above the gastric pits and the upper portions of the gastric glands were evident in most specimens (Fig. 1 B). Concurrent treatment with Omeprazole significantly abated the ketoprofen-induced gastropathy as the majority of gastric tissue sections of the Omeprazole+Ketoprofen group exhibited mild lesions represented by desquamation of the gastric tips epithelial cells, with mild submucosal leukocytic infiltrations, and mild vascular congestions (Fig. 1 C). Treatment with quercetin did not rescue the gastric mucosae from the ketoprofen-induced gastropathy, as similar findings to those observed in the ketoprofen-treated group were seen in the majority of the gastric tissue sections of the quercetin+ketoprofen group. The only noteworthy improvement seen in this group was the reduction in the intensity of the gastric inflammatory response (Fig. 1 D). The recorded histopathological alterations in the stomachs of all groups were scored in Table (4).

Liver

The hepatic tissue sections obtained from the control animals showed normal histology (Fig. 2 E). For the ketoprofen-treated rats, there were modest degenerative and circulatory changes including hepatocyte cytoplasmic vacuolations with hydropic or vacuolar degenerations, single-cell necrosis, as well as varying degrees of sinusoidal dilatation and vascular congestion, and portal infiltration with inflammatory cells particularly the mononuclear cells (Fig. 2 F). When compared to the livers of the ketoprofen group, the concurrent omeprazole and ketoprofen treatment did not cause any improvement or deterioration in the liver histology of the omeprazole+ketoprofen group. The hepatopathic alterations included mild portal leukocytic infiltrations, vascular congestions, single-cell necrosis, and hepatocyte vacuolations (Fig. 2 G). Remarkably, it was evident from the hepatic tissue sections of the rats treated with quercetin plus ketoprofen that the quercetin had a significant hepatoprotective effect against the ketoprofen-induced hepatopathy, even though there were still some noticeable histological changes, such as sinusoidal dilatation and microsteatosis (Fig. 2 H). The recorded histopathological alterations in the livers of all groups were scored in Table (4).

Kidneys

The kidneys of the control rats showed normal histology (Fig. 3 I). The rats given ketoprofen showed mild degenerative changes with nearly absence of the inflammatory reactions in their kidneys, as evidenced by tubular epithelial vacuolations, cast formation, and tubular attenuation; however, only a few specimens displayed significant glomerular damage, including glomerular collapse and necrosis (Fig. 3 J). The kidney histology of the Omeprazole+Ketoprofen group worsened by concurrent omeprazole and ketoprofen treatment when compared to the kidneys of the ketoprofen group. Tubular necrosis, noticeable interstitial mononuclear leukocytic infiltrations, and glomerular congestions were the most frequently encountered nephropathic changes in this group (Fig. 3K). The kidney tissue sections of the rats treated with both quercetin and ketoprofen showed that quercetin had a significant nephroprotective effect against ketoprofen-induced nephropathy. There was a significant dimension of the inflammatory response, as well as a notable reduction in the frequencies of the degenerative changes. A few tissue sections still showed few mononuclear cells in the interstitial tissue, vascular congestion, and tubular pyknosis (Fig. 3 L). The recorded histopathological alterations in the kidneys of all groups scored in Table (4).

Discussion

As an NSAID, ketoprofen is recommended for situations involving inflammation, fever, and/or pain. There have been numerous obstacles to the drug's use as a therapeutic compound due to adverse effects, which include peripheral edema and platelet malfunction, headache and drowsiness, skin sensitivity and photosensitization, and gastric ulcer and bleeding caused by cardiovascular, central, dermatological, and gastrointestinal reactions, respectively [25]. The reason of the kidney-related adverse KP changes remains unknown. Given that ketoprofen's inflammatory effects may cause histopathological alterations, this study aimed to characterize them.

The concentrations of TNF- α and IL-10 in stomach tissue were found to be significantly higher ($p<0.05$) in adult male rats that were given a single dosage of ketoprofen (50 mg/kg b.wt.) in comparison to the control group.

An *in vitro* study on the effects of the medicine on specific immune factors in mammary epithelial cells found that KP decreased the rise in mRNA abundance of tumor necrosis factor α (TNF-α), interleukin-8 (IL-8), serum amyloid A (SAA), and cyclooxygenase-2 that was produced by LPS [26].

Furthermore, it has been noted that ketoprofen decreases the synthesis of TNF-α in ewes that were exposed to LPS [27, 28]. It should be noted that postpartum cows suffering from various inflammatory illnesses show an increase in serum TNF-α [29]. This goes against our study, which found that dairy cows treated with ketoprofen had lower levels of TNF-α. This suggests that short-term anti-inflammatory treatment can reduce the inflammatory response in these animals. On the other hand, we found that cows with different inflammatory disorders had higher concentrations of IL-1β [29]. Herath et al. [30] also showed that during the beginning of inflammation, concentrations of proinflammatory cytokines (IL-1α or IL-1β) are higher. The researchers Herath et al. [30] found that the quantities of TNF-α and IL-1 were rising.

According to Ali and Salem [31], the gastric mucosal TNF-α level decreased by 35% and the IL-10 level increased by 44% and 61% when EELMN treatment of gastric ulcers was compared to the ketoprofen-induced gastric ulcer group. Omeprazole reduced gastric mucosal TNF-α levels by 71% and increased IL-10 levels by 78%, indicating that by suppressing the release of proinflammatory cytokines (TNF-α) and enhancing the anti-inflammatory cytokine (IL-10), the gastro-protective effect may be enhanced. Taking omeprazole counteracted the effects of ketoprofen on stomach mucosal myeloperoxidase activity and reactive oxygen species levels, according to the present investigation.

Because of their critical role in excretory function, the kidneys receive approximately 25% of the total cardiac output. They keep homeostasis in check and metabolize and excrete a wide variety of

foreign substances, including pharmaceuticals [32]. How ketoprofen works and the effects it has been detailed in numerous studies. Ketoprofen, like all nonsteroidal anti-inflammatory drugs (NSAIDs), inhibits arachidonic acid (AA) metabolism via the cyclooxygenase (COX) pathway [33].

In this study, the group that was given ketoprofen shows signs of extensive infiltration of inflammatory cells, small amounts of hemorrhage, and the presence of desquamated, dead epithelial cells. After administering ketoprofen to the liver, hepatocellular necrosis, portal mononuclear cell infiltration, and hydropic degeneration were observed. In the kidney, glomerular collapse, glomerular necrosis, tubular attenuation, and tubular vacuolation were observed. Parenchymal degeneration was less common in liver tissues treated with diclofenac for 28 days, according to Tomic et al. [8]. Additionally, coagulation necrosis and perivascular infiltration occurred more frequently in the D28. Additionally, compared to the 7-day group, the 28-day group treated with ketoprofen had a larger frequency of regular findings. The animals were given the same dosage of ketoprofen for five days, and according to Kuczyńska and Nieradko-Iwanicka, [34], we did not find any histological alterations in the kidneys of any of the animals. Histopathologic alterations such as parenchymatous degeneration, coagulation necrosis, and perivascular infiltration were observed in 4.76 percent of livers (n = 18) following 7 days of therapy, according to the study conducted by Tomic et al. [8]. One of the six animals in group 3 showed perivascular infiltration in the liver, according to Kuczyńska and Nieradko-Iwanicka [34]. Tomic et al. [8] found that perivascular infiltration occurs in the liver, and we verified their findings. Even after 5 days of taking ketoprofen, inflammation persisted. The tubules dilated throughout the outer strip of the outer medulla, and the epithelial cells of the PCTs necrosed and sloughed after 70 days of intraperitoneal ketoprofen therapy, according to research by Fadhil and Jebur [35]. The use of nonsteroidal anti-inflammatory medicines (NSAIDs) including oxicams, ketorolac, meloxicam, and piroxicam was associated with an elevated risk of developing chronic kidney disease (CKD), according to Ingrasciotta et al. [36]. Some have hypothesized that acute renal impairments caused by ketorolac use might cause subclinical CKD. The results show that the negative effects of the NSAID KP on the rats in the study are in line with the current knowledge. Acute interstitial nephritis, a dose-independent allergic mechanism involving the nonselective disruption of cyclooxygenases 1- and 2-, can generate systemic NSAID-based kidney damages through acute interstitial nephritis, leading to abrupt renal failure and the reversal of functions in the affected tissues [37]. Nonetheless, as the KP concentration decreased, there was a corresponding decrease in those kidney damages in the rats. Sadek et al. [38] reported that after two weeks of administering Ketoprofen to rats, tissue slices taken from their kidneys revealed substantial nephropathic lesions in both the cortex and medulla. The three main categories of lesions found in the cortex are glomerular, tubular, and interstitial. Our examination revealed the following glomerular lesions: isolation of glomerular atrophy, infiltration of mononuclear cells into the surrounding tissue, thickening of the basement membrane of the glomerulus, increased mesangial matrix, and congestion of the capillary tufts inside the glomerulus. The same kind of glomerular lesions reported previously [39]. Only glomerular hypercellularity and interstitial nephritis observed in goats administered Flunixin meglumine, Ketoprofen, and Phenylbutazone, according to Safarchi et al. [40]. According to Mozaffari et al. [41], the only kidney disease in miniature donkeys caused by KP was interstitial nephritis. According to Sadek et al. [38], histopathological examinations after a 4-week KP treatment showed several glomerular morpho pathological alterations, such as segmental and global glomerulosclerosis, congestion of the capillary glomerular tufts, thickening of the glomerular basement membrane due to expanded mesangial matrix, and a focal segmental glomerular segment that was collapsing.

The findings of Mozaffari and Derakhshanfar [42] may provide more support for these results. They discovered that administering NSAIDs such flunixin meglumine, ketoprofen, and phenylbutazone to fat-tailed sheep had similar effects, including glomerular sclerosis and glomerular hypercellularity. Similar varied changes in renal tubules were observed in rats killed four weeks following the dosage. These changes manifested as vacuolar degeneration, inflammatory cell infiltration into the interstitial space, epithelial cast, hyaline cast formation, and perivascular edema including red blood cells. Other alterations seen in the medulla were dystrophic calcification in certain areas and intraluminal pale eosinophilic proteinaceous debris. Consistent with these findings, Raekallio et al. [43] shown that KP can influence the renal tubules. When a therapeutic dose of ibuprofen was administered to renal tissue, Baisakh et al. [44] also found similar results. Talat et al. [45] observed similar results when studying the effects of ibuprofen on renal tissue; however, their results were accompanied with modest glomerular congestion and no major inflammatory reaction. Several vascular alterations were observed in this investigation after ketoprofen treatment. In their investigations on diclofenac sodium in kidney rats, Owumi and Dim [46] noted comparable results.The major limitation of this study is to compare such effects in both male and female rats. To use the examined chemicals at a wide dose range is another limitation.

Conclusion

This study showed that oral administration of omeprazole and quercetin can significantly improve the inflammatory and histopathological alterations of ketoprofen in rats, possible via reducing the oxidative damage and stress caused by ketoprofen. Therefore, it is highly recommended to use either omeprazole or quercetin or even their combination during the treatment course by ketoprofen in rats.

Acknowledgments

Not applicable.

Funding statement

This study didn't receive any funding support

Declaration of Conflict of Interest

The authors declare that there is no conflict of interest.

Ethical of approval

All procedures, including housing and care, followed the ethical rules established by Zagazig University in Zagazig, Egypt, for the use of experimental animals.

TABLE 1. Effects of oral administration of omeprazole (20 mg/kg b.wt.) and quercetin (50 mg/kg b.wt.) on gastric inflammatory/ anti-inflammatory status of ketoprofen (50 mg/kg b.wt.) treated rats.

Groups	Parameters	
	TNF-α (pg/ml)	IL-10 (pg/ml)
Control	490 ± 5.5^{d}	630.2 ± 8.66^{c}
Ketoprofen	1102.4 ± 39.4^{a}	1054.2 ± 82.9^{a}
Omeprazole +Ketoprofen	810 ± 9.5^{b}	771.2 ± 24.8^{b}
Quercetin +Ketoprofen	655 ± 16.7^{c}	982 ± 38.4^{a}

Mean values for the same parameter carrying different superscripts (a, b, c, d) are significantly different at $p<0.05$.

TABLE 2. Effects of oral administration of omeprazole (20 mg/kg b.wt.) and quercetin (50 mg/kg b.wt.) on hepatic inflammatory/ anti-inflammatory status of ketoprofen (50 mg/kg b.wt.) treated rats.

Groups	Parameters	
	TNF-α (pg/ml)	IL-10 (pg/ml)
Control	474 ± 8.7^{d}	661.2 ± 16.9^{c}
Ketoprofen	1002± 13.6^{a}	941± 20.1^{a}
Omeprazole +Ketoprofen	811 ± 4.6^{b}	554.4 ± 24.1^{d}
Quercetin +Ketoprofen	653 ± 21.6^{c}	772± 17.47^{b}

Mean values for the same parameter carrying different superscripts (a, b, c, d) are significantly different at $p<0.05$.

TABLE 3. Effects of oral administration of omeprazole (20 mg/kg b.wt.) and quercetin (50 mg/kg b.wt.) on renal inflammatory/ anti-inflammatory status of ketoprofen (50 mg/kg b.wt.) treated rats.

Groups	Parameters	
	TNF-α (pg/ml)	IL-10 (pg/ml)
Control	372 ± 14.6^{d}	608.2 ± 16.9^{c}
Ketoprofen	888.4± 18.9^{a}	1021.4± 28.9^{a}
Omeprazole +Ketoprofen	691.2 ± 8.35^{b}	655± 14.4^{c}
Quercetin +Ketoprofen	537.2 ± 17.03^{c}	750± 23.9^{b}

Mean values for the same parameter carrying different superscripts (a, b, c, d) are significantly different at $p<0.05$.

TABLE 4. Microscopic lesion scoring in the gastric, hepatic and renal tissues.

organ	lesion	Control	ketoprofen	omeprazole+ketoprofen	quercetin+ketoprofen
Stomach	Necrosis of the surface epithelium	0 ± 0^{b}	28 ± 7.4^{a}	6 ± 3.05^{b}	24 ± 6.53^{a}
	Epithelial denudation	0 ± 0^{c}	38 ± 6.29^{a}	16 ± 2.67^{b}	30 ± 6.15^{a}
	Mucosal erosion	0 ± 0	6 ± 3.06	0 ± 0	6 ± 3.06
	Bleeding	0 ± 0	6 ± 3.06	2 ± 2	6 ± 3.06
	Vascular congestion	0 ± 0^{c}	18 ± 3.59^{a}	8 ± 3.27^{bc}	14 ± 3.06^{ab}
Liver	Inflammatory cell infiltration	0 ± 0^{b}	26 ± 5.21^{a}	6 ± 3.06^{b}	8 ± 3.27^{b}
	Vacuolar degeneration	0 ± 0	10 ± 4.47	10 ± 4.47	4 ± 2.67
	Hydropic degeneration	0 ± 0^{b}	20 ± 5.96^{a}	18 ± 6.29^{a}	4 ± 2.67^{b}
	Steatosis	0 ± 0	4.2 ± 2.64	4 ± 2.67	2 ± 2
	Single-cell necrosis	0 ± 0	8 ± 3.27	8 ± 3.27	4 ± 2.67
	Vascular congestion	0 ± 0^{b}	12 ± 3.27^{a}	10 ± 3.33^{a}	4 ± 2.67^{ab}
	inflammatory cell infiltration	0 ± 0^{b}	22 ± 6.29^{a}	20 ± 6.67^{a}	6 ± 3.06^{b}
	Sinusoidal dilatation	0 ± 0^{b}	10 ± 3.33^{a}	10 ± 3.33^{a}	6 ± 3.06^{ab}
	Leukocytic infiltration	0 ± 0^{b}	10 ± 3.33^{a}	10 ± 3.33^{a}	4 ± 2.67^{ab}
Kidney	Tubular vacuolation	0 ± 0^{b}	10 ± 3.33^{ab}	18 ± 5.54^{a}	6 ± 3.06^{b}
	Tubular attenuation	0 ± 0^{b}	10 ± 3.33^{a}	12 ± 3.27^{a}	8 ± 3.27^{ab}
	Tubular pyknosis	0 ± 0^{c}	16 ± 4.99^{ab}	28 ± 7.42^{a}	6 ± 3.06^{bc}
	Single-cell necrosis	0 ± 0^{c}	22 ± 6.29^{ab}	32 ± 9.04^{a}	6 ± 3.06^{bc}
	Cast formation	0 ± 0^{b}	12 ± 3.27^{a}	16 ± 2.67^{a}	4 ± 2.67^{b}
	Interstitial congestion	0 ± 0^{b}	10 ± 3.33^{ab}	18 ± 5.54^{a}	4 ± 2.67^{b}
	Glomerular congestion	0 ± 0^{b}	4 ± 2.67^{ab}	8 ± 3.27^{a}	2 ± 2^{ab}
	Glomerular necrosis	0 ± 0^{b}	2 ± 2^{ab}	6 ± 3.06^{a}	0 ± 0^{b}
	Interstitial leukocytic infiltration	0 ± 0^{b}	4 ± 2.67^{b}	14 ± 4.27^{a}	2 ± 2^{b}

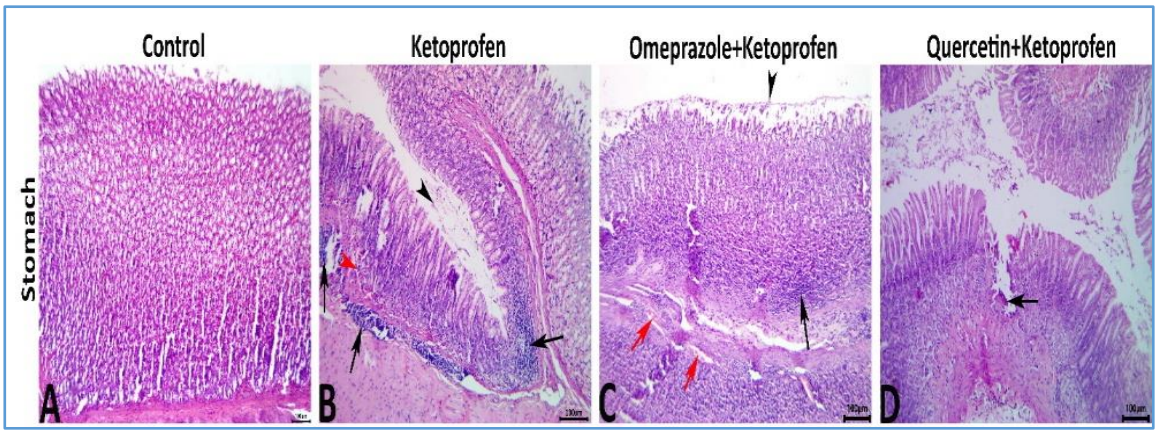

Fig. 1. A-D; Representative photomicrograph of the stomach tissue section stained with hematoxylin and eosin, displaying normal histology in the control group (A). The ketoprofen-treated group exhibits widespread inflammatory cell infiltration (black arrows), minute bleeding (red arrowhead), and desquamated necrotic epithelial cells (black arrowhead) (B). The omeprazole+ketoprofen group manifested a significant reduction in the inflammatory response evidenced by a few numbers of inflammatory cells (black arrow), and mild vascular congestions (red arrows), besides denudation of the epithelial cells above the gastric pits (black arrowhead) (C). The quercetin+ketoprofen group shows gastric erosion with minimal inflammatory response (black arrow) (D). The scale bars are 100 microns.

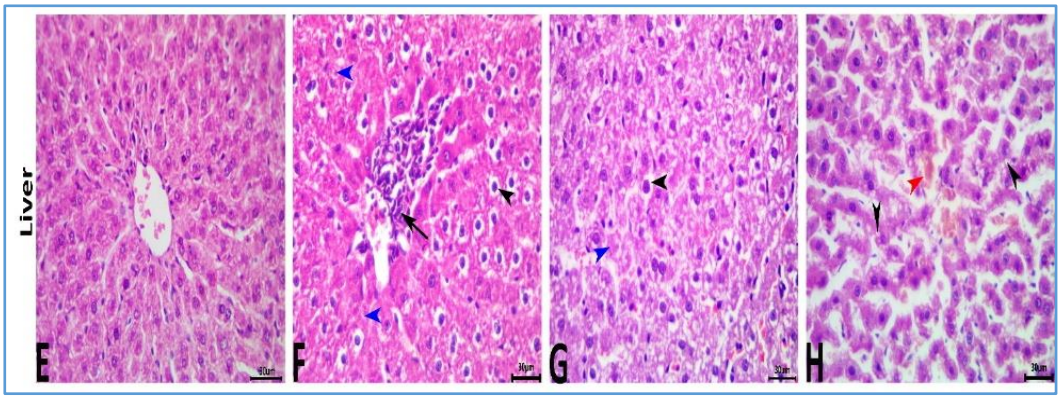

Fig. 2. E-H; Representative photomicrograph of the liver tissue section stained with hematoxylin and eosin, displaying normal histology in the control group (E). The ketoprofen-treated group exhibits portal mononuclear cell infiltration (black arrow), hydropic degeneration (black arrowhead), and single-cell necrosis (blue arrowheads) (F). The omeprazole+ketoprofen group manifested hydropic degeneration (black arrowhead), and single-cell necrosis (blue arrowhead) (G). The quercetin+ketoprofen group shows microsteatosis (black arrowheads), and sinusoidal dilatation (red arrowhead) (H). The scale bars are 30 microns.

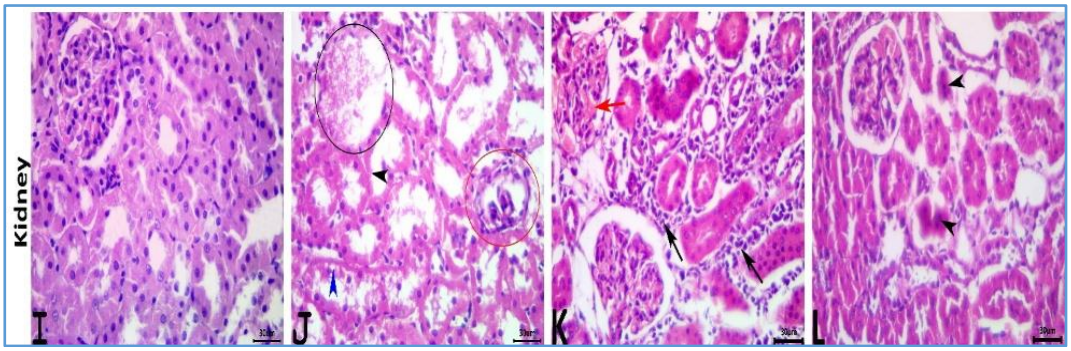

Fig. 3. I-L; Representative photomicrograph of the kidney tissue section stained with hematoxylin and eosin, displaying normal histology in the control group (I). The ketoprofen-treated group exhibits glomerular collapse (red ellipse), glomerular necrosis (black ellipse), tubular attenuation (black arrowhead), and tubular vacuolation (blue arrowhead) (J). The omeprazole+ketoprofen group manifested glomerular congestion (red arrow), and interstitial mononuclear cell infiltration (black arrows) (K). The quercetin+ketoprofen group shows pyknosis of the tubular epithelium (black arrowhead) (L). The scale bars are 30 microns.

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أثر كل من الأوميبرازول والكيرسيتين على التغيرات الالتهابية والتشريحية النسيجية الناجمة عن الكيتوبروفين في الفئران

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الملخص

الكيتوبروفين دواء مضاد للالتهابات غير ستيرويدي يستخدم في علاج إصابات العظام والعضلات والتهاب المفاصل والتهاب المفاصل النقري الحاد. ومع ذلك، ارتبط استخدامه ببعض الآثار الجانبية الضارة على المعدة والكبد والكلى. هدفت هذه الدراسة إلى دراسة تأثير كل من الأوميبرازول والكيرسيتين في الحد من هذه الآثار الجانبية في الفئران. لذلك، تم تقسيم 32 فأرًا ذكورًا إلى أربع مجموعات: المجموعة الأولى (المجموعة الضابطة)، والمجموعة الثانية (مجموعة الكيتوبروفين)، والمجموعة الثالثة (مجموعة الأوميبرازول)، والمجموعة الرابعة (مجموعة الكيرسيتين). تقييم الدراسة مستويات بروتين TNF-α و IL-10، بالإضافة إلى التغيرات التشريحية النسيجية في المعدة والكبد والكلى. أظهرت النتائج أن كل من الأوميبرازول والكيرسيتين قلل بشكل ملحوظ ($P<0.05$) من إنتاج بروتين TNF-α و IL-10 في المعدة والكبد والكلى. ومن المرجح أن يحسن كل من الأوميبرازول والكيرسيتين من التغيرات التشريحية النسيجية التي يسببها الكيتوبروفين. لذلك، يُنصح بتناول الأوميبرازول أو الكيرسيتين أو كليهما معًا أثناء استخدام الكيتوبروفين في الفئران.

الكلمات الدالة: الكيتوبروفين، الأوميبرازول، الكيرسيتين، التشريح النسيجي، الالتهاب، الفئران.