Research Article

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Gastroprotective, Hepatoprotective, and Nephroprotective Effects of Combination of Curcumin and Tahini Against the Indomethacin-Induced Gastric and Hepato-Renal Injury in Rats

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Abstract

Gastric ulcer is a common gastrointestinal disorder frequently caused by the use of non-steroidal anti-inflammatory drugs (NSAIDs), such as indomethacin, which can induce gastric mucosal damage, inflammation, and oxidative stress. Although conventional treatments are available, there remains a considerable need for alternative therapies with favorable safety profiles. This study aimed to evaluate the gastroprotective and antioxidant properties of curcumin, tahini, and their combined effects against indomethacin-induced gastric ulcers in rats using biomarkers of oxidative stress, inflammatory mediators, and parameters of liver and kidney function. The rats were divided into six groups and administered curcumin, tahini, or other treatments before ulcer induction with indomethacin. Indomethacin treatment caused acute gastric mucosal injury, increased oxidative stress, as indicated by elevated MDA and reduced SOD, CAT, and GSH levels, altered gastric acid secretion, and impaired liver and kidney function, as demonstrated by increased ALT, AST, urea, and creatinine levels. Curcumin and tahini both showed significant protective effects by reducing oxidative stress and inflammation while improving organ function. Their combination was the most effective treatment, restoring antioxidant and prostaglandin E2 levels to near or above normal values, substantially alleviating gastric mucosal damage, and improving liver and kidney function. This synergistic interaction may be explained by the enhanced bioavailability of curcumin in the lipid-rich medium provided by tahini. The findings suggest that the combination of curcumin and tahini possesses potent gastroprotective and antioxidant properties, making it a promising therapeutic strategy for the prevention and treatment of indomethacin-induced gastric ulcers while providing systemic protection against toxicity.

Keywords: curcumin, tahini, antioxidants, gastroprotective, indomethacin, liver function, kidney function

1. INTRODUCTION

Gastric ulcer is a common gastrointestinal disorder characterized by disruption of gastric mucosal integrity resulting from an imbalance between aggressive and protective mechanisms. It remains a major global health concern because it is associated with substantial morbidity and healthcare costs. Gastric hypersecretion of acid, oxidative stress, inflammation, and compromised blood flow to the mucosa are some of the physiological factors that play a role in the development of gastric ulcers [1].

The use of non-steroidal anti-inflammatory drugs (NSAIDs) is one of the most common causes of gastric ulcers resulting from the intake of medication. Indomethacin is a strong NSAID that is widely applied in animal models to induce gastric ulcers. This effect is mediated by strong inhibition of cyclooxygenase (COX). Inhibition of the synthesis of COX decreases the biosynthesis of prostaglandin, especially prostaglandin E_2 (PGE_2). Prostaglandin plays an essential role in maintaining the integrity of the mucosa, stimulation of mucus and bicarbonate secretion, regulation of blood flow to the mucosa, and stimulation of epithelial cell proliferation [2].

Other than the inhibition of prostaglandin biosynthesis, gastric damage caused by indomethacin results from oxidative stress and inflammation. The excessive production of reactive oxygen species (ROS) in the gastric tissues leads to lipid peroxidation, protein oxidation, and oxidative damage to DNA. Malondialdehyde (MDA) is one of the most common biomarkers of lipid peroxidation, while reduced glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) are essential elements in the body's defense mechanism against ROS [3]. Oxidative stress decreases the efficiency of this defense mechanism and increases mucosal injury. In addition, the inhibition of PGE_2 and stimulation of inflammatory mediators increase gastric epithelial permeability and lead to the formation of ulcers [4].

Despite the effectiveness of conventional drugs such as proton pump inhibitors (PPIs), H_2-receptors antagonists, and cytoprotectors in the treatment of gastric ulcers, their prolonged use results in adverse reactions such as malabsorption of nutrients, vulnerability to infections, and renal toxicity [5]. The need for safer alternatives arises from the above limitations of pharmacological therapies.

Curcumin is the main component of *Curcuma longa*, which is characterized by high antioxidant, anti-inflammatory, and cytoprotective effects. Various experimental studies have shown that curcumin acts as an antioxidant that scavenges free radicals, increases the activity of antioxidant enzymes and modulates inflammatory mediators that cause mucosal injury. Moreover, curcumin increases gastric mucus content and prevents gastric lesions caused by NSAIDs in animal experiments [6].

Tahini is an old type of paste produced from crushed sesame seeds (*Sesamum indicum*) and contains various bioactive compounds such as sesamin, sesamol, and tocopherols. These constituents have antioxidant and anti-inflammatory properties that may prevent tissues from oxidative damage. Many studies have demonstrated the benefits of various foods produced from sesame in decreasing lipid peroxidation, increasing antioxidant defense, and preventing chemical-induced injury of gastrointestinal mucosa [7].

Considering the antioxidant and anti-inflammatory properties of curcumin and tahini, their co-administration might result in synergistic gastroprotection. Combined treatment could provide greater protection against NSAID-induced gastric injury by targeting several pathological mechanisms, including oxidative stress, inflammation, and prostaglandin depletion. Nevertheless, experimental evidence regarding the synergistic effects of curcumin and tahini in an indomethacin-induced gastric ulcer model remains limited [8].

The present study was designed to investigate the gastroprotective and antioxidant effects of curcumin, tahini, and their combination against indomethacin-induced gastric ulcers in rats, with particular emphasis on oxidative stress biomarkers, inflammatory mediators, and liver and kidney function parameters.

2. MATERIALS AND METHODS

Animals and ethical considerations. All experimental procedures were conducted in accordance with the guidelines of the Committee for Research and Animal Ethics of the University of Basrah. Thirty-six male albino Wistar rats weighing $200–250\,\mathrm{g}$ were used. The animals were maintained under standardized laboratory conditions of temperature and humidity and were provided with a standard pelleted diet and water *ad libitum*. Before the experimental procedures, the rats were fasted overnight but allowed free access to water [9].

Chemicals and reagents. Indomethacin was obtained from MEDOCHEMIE Pharmaceutical Co. (Cyprus), and carboxymethyl cellulose (CMC) was obtained from Chem Cruz (China). Curcumin and tahini were obtained locally in Iraq, whereas esomeprazole was supplied by AstraZeneca (Sweden/United Kingdom).

Experimental design and treatments. The animals were randomly divided into six groups of six rats each:

Group A (normal control): Rats received $0.5\,\mathrm{mL}$ of 1% CMC in water as the vehicle.

Group B (negative control): Rats received indomethacin at a dose of $30\,\mathrm{mg\,kg^{-1}}$, suspended in $0.5\,\mathrm{mL}$ of 1% CMC.

Group C (positive control): Rats received esomeprazole at a dose of $20\,\mathrm{mg\,kg^{-1}}$, suspended in $0.5\,\mathrm{mL}$ of 1% CMC.

Group D (curcumin-treated group): Rats received curcumin at a dose of $50\,\mathrm{mg\,kg^{-1}}$, suspended in $0.5\,\mathrm{mL}$ of 1% CMC.

Group E (tahini-treated group): Rats received tahini paste at a dose of $2.5\,\mathrm{mL\,kg^{-1}}$.

Group F (curcumin–tahini-treated group): Rats received curcumin at a dose of $50\,\mathrm{mg\,kg^{-1}}$ in tahini paste at $2.5\,\mathrm{mL\,kg^{-1}}$.

All treatments were administered orally by gavage to fasted animals. Gastric ulceration was induced by the oral administration of indomethacin at a dose of $30\,\mathrm{mg\,kg^{-1}}$, suspended in $0.5\,\mathrm{mL}$ of CMC, one hour after administration of the tested treatments. The normal control group did not receive indomethacin. The treatments and indomethacin were administered once daily for 21 consecutive days, and the animals were provided with their normal diet throughout the study period [10, 15].

At the end of the experimental period, the animals were euthanized by cervical dislocation. Blood samples were immediately collected by cardiac puncture and transferred into gel-containing tubes. The samples were allowed to clot at room temperature and were then centrifuged at $3000 \times g$ for 10 minutes. The resulting serum was carefully separated and stored at $-20\,^{\circ}\mathrm{C}$ until biochemical analysis. Following blood collection, the abdominal cavity was opened, and the stomach was excised, opened along the greater curvature, and examined for gastric mucosal damage.

Assessment of gastric juice acidity. The gastric contents were collected in centrifuge tubes and centrifuged at $4000\,\mathrm{rpm}$ for 10 minutes. The resulting supernatant was collected, and gastric acidity was assessed by titration with $0.1\,\mathrm{mM}$ NaOH [11].

Assessment of oxidative stress and antioxidant biomarkers. Serum levels of malondialdehyde (MDA), reduced glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), and prostaglandin E_2 (PGE_2) were measured using commercially available ELISA and colorimetric assay kits supplied by Elabscience Biotechnology (USA), according to the manufacturer's instructions [12].

Assessment of liver and kidney function. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were measured using commercially available colorimetric assay kits supplied by Elabscience Biotechnology (USA). Serum creatine kinase (CK) activity was assessed using a corresponding commercial colorimetric assay kit. Serum urea levels were measured using a Urea Blood Urea Nitrogen (BUN) Colorimetric Assay Kit based on the urease method. All biochemical parameters were quantified spectrophotometrically according to the manufacturer's protocols [13].

Histopathological examination. Gastric tissue samples were collected, gently cleaned, rinsed with normal saline, and fixed in 10% neutral-buffered formalin. Histological processing was performed for the assessment of the tissue. Sections of the tissue were stained by hematoxylin and eosin (H&E) and examined through the light microscope to assess the damage of gastric mucosa [14].

Statistical analysis. Analysis of statistics was conducted through the use of GraphPad Prism version 8 software (GraphPad Software, San Diego, CA, USA). Results were stated in terms of means $\pm$ SD. The differences between the experimental groups were analyzed by one way ANOVA. Unpaired t-tests were further employed for comparison of treatment groups against indomethacin treated group. Difference was said to be statistically significant at $P < 0.05$ [16].

3. RESULTS AND DISCUSSION

The current experiment examined the gastroprotective, antioxidant, hepatoprotective, and nephroprotective activities of curcumin, tahini (sesame paste), and the combination of the two on the rat in case of indomethacin-induced gastric ulceration. The findings show that administration of indomethacin induced severe gastric mucosal damage with oxidative stress, changed gastric secretion levels, and hepatic and renal dysfunction systematically. Both curcumin and tahini treatment were effective at reducing these changes with the combination therapy showing a greater protective effect

3.1. EFFECT ON GASTRIC ANTIOXIDANT STATUS AND PROSTAGLANDINS E_2 LEVEL

As shown as in Table 1 and Figure 1 (A, B, C, D) and Figure 2, The mechanism of indomethacin-induced gastric trauma is an intricate association with the excessive formation of reactive oxygen species (ROS) and the consequent exhaustion of the endogenous antioxidant defense mechanism. In the present research, redox balance was led to severe disturbance where there was a dramatic decrease of the activity of superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH) in the negative control compared to the normal control group ($p < 0.001$). Specifically, SOD levels were significantly dropped from 1.97 $\pm$ 0.23 mg/mL in normal rats to 1.14 $\pm$ 0.24 mg/mL in the negative control, while CAT levels were significantly decreased from 16.68 $\pm$ 1.65 mg/mL to 4.23 $\pm$ 1.08 mg/mL .This depletion of the antioxidant enzymes was accompanied by a significant increase in malondialdehyde (MDA) levels: 1.10 $\pm$ 0.18 nmol/mL in negative control as compared to the 0.76 $\pm$ 0.11 nmol/mL in normal control, which is evidence of the widespread lipid peroxidation of the

gastric mucosal membranes. These findings are in line with the already known models in which indomethacin causes mitochondrial dysfunction and oxidative damage [17].

Table 1. *Effect of Curcumin, Tahini, and their mixture on oxidative stress in indomethacin-induced gastric ulceration in rats*

Group	GSH (ng/mL)	SOD (ng/ml)	CAT (ng/ml)	MDA (nmol/ml)	PG-E2 (ng/ml)
Normal Control	101.24 ± 4.25	1.97 ± 0.23	16.68 ± 1.65	0.68 ± 0.12	0.76 ± 0.11
Negative Control	52.62 ± 3.64^c	1.14 ± 0.24^c	4.23 ± 1.08^c	1.10 ± 0.18^a	0.34 ± 0.08^c
Positive Control (Esomeprazole)	134.85 ± 7.25^c	1.70 ± 0.16^c	15.56 ± 2.34^c	0.79 ± 0.11^a	0.65 ± 0.14^c
Curcumin	82.65 ± 4.26^c	1.42 ± 0.23^b	12.86 ± 2.72^c	0.92 ± 0.09^a	0.48 ± 0.13^b
Tahini	75.82 ± 3.32^c	1.38 ± 0.11^b	13.26 ± 1.65^c	0.87 ± 0.17^a	0.56 ± 0.19^c
(Curcumin + Tahini) mixture	90.12 ± 4.68^c	1.88 ± 0.26^c	19.42 ± 2.45^c	0.64 ± 0.16^c	0.72 ± 0.16^c

Each value is the Mean ± S.D. for six rats, a < 0.05, b < 0.01, c < 0.001 compared with the normal control. Data was analyzed by using one-way ANOVA followed by a T-test

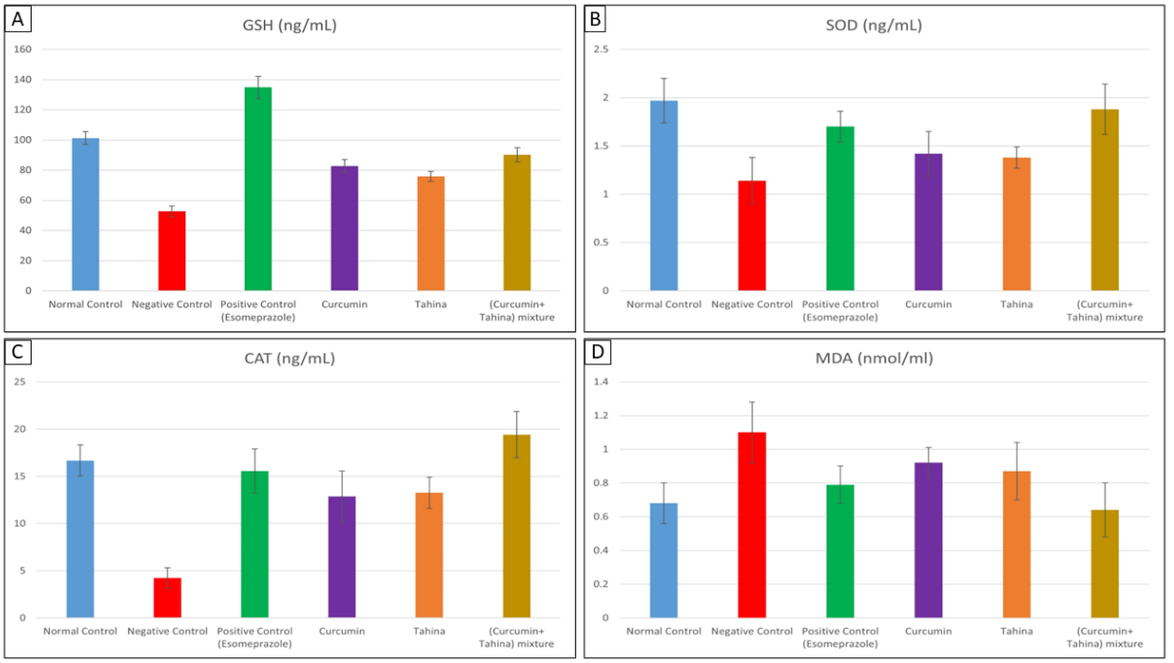

Figure 1. *Effects of Curcumin, Tahini, and their mixture on gastric tissue oxidative stress markers (SOD, MDA, CAT, and GSH) in rats with indomethacin-induced gastric injury*

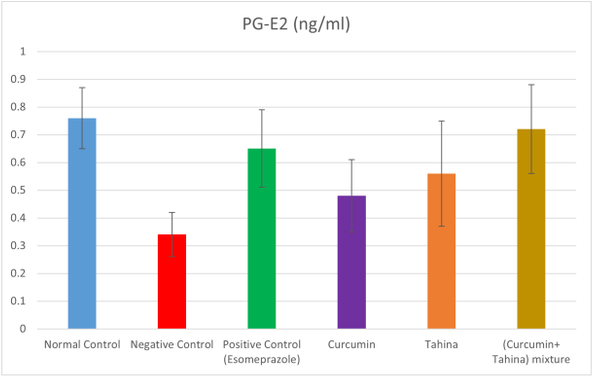

Figure 2. *Effects of Curcumin, Tahini, and their mixture on gastric PGE_2 levels in rats with indomethacin-induced gastric injury*

Curcumin treatment had a significant positive effect on the oxidative status reduction. As compared to the negative control, curcumin-treated rats showed a substantial recovery in SOD (1.42 ± 0.23 mg/mL), CAT (12.86 ± 2.72 mg/mL), and GSH (82.65 ± 4.26 mg/mL) levels ($p < 0.001$). The protective effect of curcumin as a gastroprotective agent is maybe explained by the fact that it activates the Nrf2/ HO-1 signaling pathway. Curcumin enhances the mucosal barrier through the nuclear translocation of Nrf2 to promote the expression of different phase II antioxidant enzymes, neutralizing ROS and stabilizing the mucosal barrier. Furthermore, curcumin significantly restored prostaglandin E_2 ($PG\text{-}E_2$) levels (0.48 ± 0.13 mg/mL) as compared to (0.34 ± 0.08 mg/mL) in negative control, which is crucial for maintaining mucosal blood

flow and stimulating mucus secretion [18].

The contribution of tahini administration also provided significant protection, as SOD (1.38 ± 0.11 mg/ml) and CAT (13.26 ± 1.65 mg/ml) levels were significantly higher than in the negative control group ($p < 0.001$). Tahini contains many sesame lignans, especially sesamin and sesamol; hence, tahini has antioxidant properties. The compounds are proved to be effective radical scavengers and lipid peroxidation inhibitors [19]. Interestingly, tahini-treated rats had more levels of the prostaglandin precursor, which is the increased levels of the fatty acid profile of tahini paste (0.56 ± 0.19 mg/mL) than the curcumin only, which indicated that the fatty acid profile of sesame oil may also have some precursors or protective effects on the production of prostaglandins [20].

The most notable observation was that the combination of curcumin and tahini was more effective than either ingredient alone. This combination restored SOD (1.88 ± 0.26 mg/ml) and CAT (19.42 ± 2.45 mg/ml) levels to levels close to the normal control group. The MDA levels were significantly suppressed into (0.64 ± 0.16 nmol/mL), and PG-E_2 levels reached their highest point (0.72 ± 0.16 mg/mL). This synergistic effect could probably be explained by the improvement in bioavailability of curcumin when it is presented in a lipid-rich medium such as tahini. Curcumin is a hydrophobic substance with low intestinal bioavailability; nevertheless, the structured lipids present in tahini contribute to the micellization and systemic delivery of curcumin [21]. Therefore, it becomes possible for more curcumin to be delivered to the desired tissues, where it combines with the lignans of sesame to form a strong shield against oxidative stress and inflammation [22].

3.2. SECRETION OF GASTRIC ACID AND PH

According to Table 2 and Figure 3 (A, B), hypersecretion and hyperacidity of the gastric acid are characteristic of NSAID-induced gastropathy, thereby causing further damage to the erosions. In our study, the animals of negative control group showed a significant increase in gastric fluid volume (2.5 ± 0.55 mL) as compared with normal control (0.75 ± 0.25 mL) and a sharp decline in pH (1.55 ± 0.35) as compared with normal control (4.5 ± 0.25), indicating a state of severe hyperacidity ($p < 0.001$). This is a very hostile setting to the already deteriorated gastric epithelium.

Table 2. *Effect of Curcumin, Tahini and their mixture on Gastric fluid volume, and pH in the indomethacin-induced gastric ulcerated rats*

Group	Gastric Fluid Volume (ml)	pH
Normal control	0.75 ± 0.25	4.5 ± 0.25
Negative control	2.5 ± 0.55^c	1.55 ± 0.35^c
Positive control (Esomeprazole)	1.25 ± 0.35^b	4.21 ± 0.32^c
Curcumin	1.55 ± 0.20^c	4.15 ± 0.12^c
Tahini	1.75 ± 0.25^c	3.96 ± 0.32^c
(Curcumin + Tahini) mixture	1.0 ± 0.25^c	4.85 ± 0.25^c

Each value is the Mean ± S.D. for six rats, a < 0.05, b < 0.01, c < 0.001 compared with the normal control. Data was analyzed by using one-way ANOVA followed by a T-test.

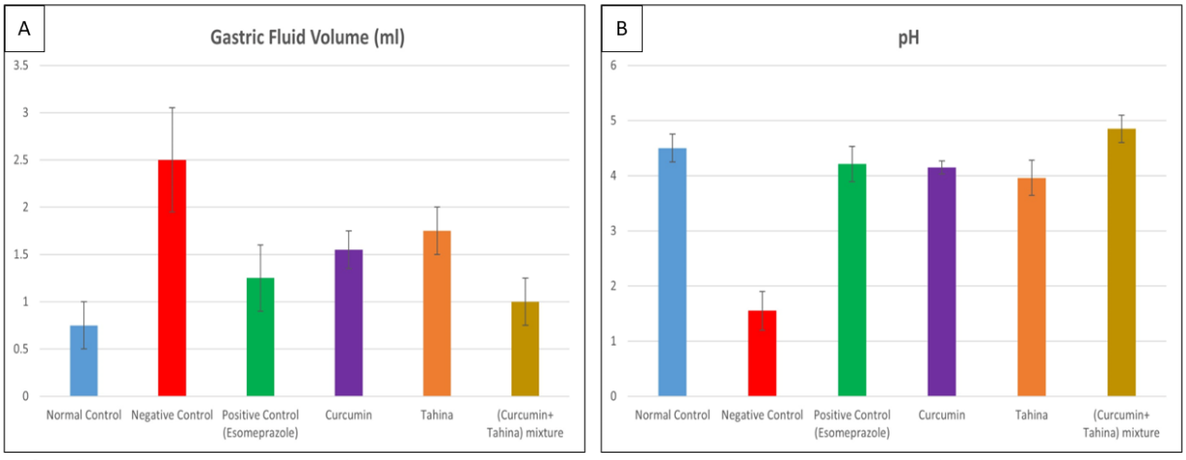

Figure 3. *Effects of curcumin, tahini, and their mixture on gastric pH and gastric fluid volume in rats with indomethacin-induced gastric injury*

The curcumin consumption lowered these secretory alterations considerably ($p < 0.001$) , making the fluid volume reached to 1.55 ± 0.20 mL and pH 4.15 ± 0.12 in comparison with negative control. Even though curcumin is not a direct proton pump inhibitor, its antisecretory activity is mediated by altering the pathways of inflammation and the mucosal barrier, which in turn has an indirect effect on acid production [23]. Tahini exhibited a protective effect as well with gastric

volume of 1.75 + 0.25 mL and pH of 3.96 + 0.32. The presence of a large proportion of unsaturated fatty acids in tahini could give it a protective physical layer on the gastric mucosa protecting against the corrosive action of the hydrochloric acid [24].

The tahini-curcumin mixture showed the strongest antisecretory effect, gastric volume of (1.0 ± 0.25 mL) and a pH of (4.85 ± 0.25), which was significantly greater than the normal control (p< 0.001). This implies that not only is the aggressive factors neutralized, but also an even stronger alkalinity environment is facilitated probably due to the choice of bicarbonate secretion as a result of the higher levels of PG-E_2 [25]. This two-fold effect, which inhibits acid and enhances the mucosal defense, is one of the mechanisms that contribute to the high gastroprotective effect of the mixture.

3.3. HEPATO- AND NEPHROPROTECTIVE EFFECTS

As shown in Table 3, Figure 4 (A, B) and Figure 5 (A, B), it is clear and well known that indomethacin ingestion causes systemic toxicity, particularly its effect on the liver and kidneys due to inhibition of protective prostaglandins and induction of systemic oxidative stress. In the negative control group, we can be observed a significant elevation in serum ALT (56.32 ± 1.48 U/mL), AST (174.2 ± 5.25 U/mL), urea (38.24 ± 2.40 mg/dL), and creatinine (0.72 ± 0.08 mg/dL) compared to the normal control group. These biomarkers reflect hepatocellular membranes leakage and impaired glomerular filtration.

Table 3. *Biochemical marker of liver and renal functions for indomethacin-induced gastric ulcer rats*

Group	Creatinine (mg/dL)	Urea (mg/dL)	ALT (U/mL)	AST (U/mL)
Normal Control	0.62 ± 0.03	21.12 ± 0.48	40.20 ± 1.10	121.16 ± 2.82
Negative Control	0.72 ± 0.08^b	38.24 ± 2.40^b	56.32 ± 1.48^b	174.2 ± 5.25^c
Positive Control (Esomeprazole)	0.68 ± 0.02^a	28.22 ± 1.12^b	28.6 ± 1.46^c	118.36 ± 4.85^c
Curcumin	0.70 ± 0.11	32.20 ± 1.2^b	44.21 ± 2.2^b	132.52 ± 3.4^c
Tahini	0.59 ± 0.02^b	25.42 ± 2.21^b	35.42 ± 2.56^c	130.85 ± 2.82^c
(Curcumin + Tahini) mixture	0.47 ± 0.05^c	28.34 ± 1.2^b	40.52 ± 1.25^b	145.3 ± 3.62^c

Each value is the Mean ± S.D. for six rats, a < 0.05, b < 0.01, c < 0.001 compared with the normal control. Data was analyzed by using one-way ANOVA followed by a T-test.

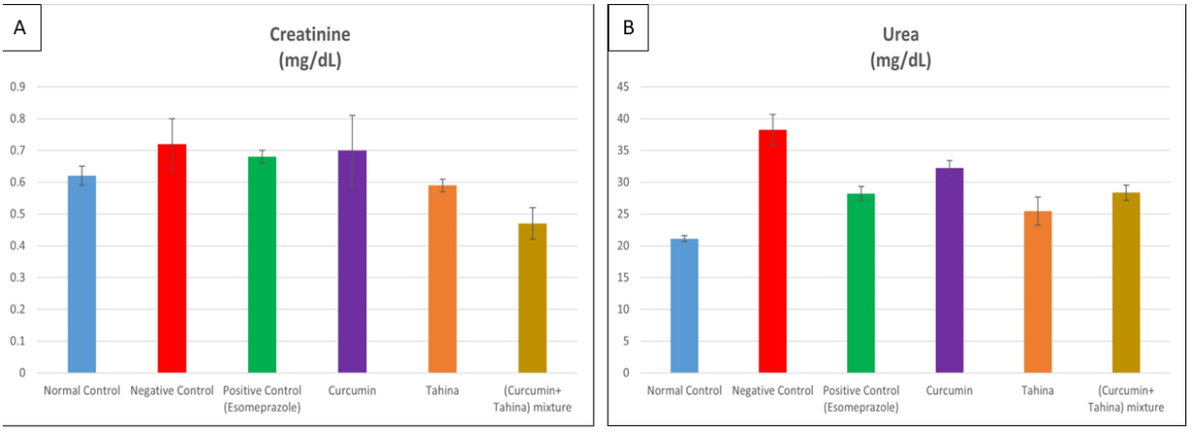

Figure 4. *Serum creatinine and urea levels following experimental treatments in rats with indomethacin-induced gastric injury*

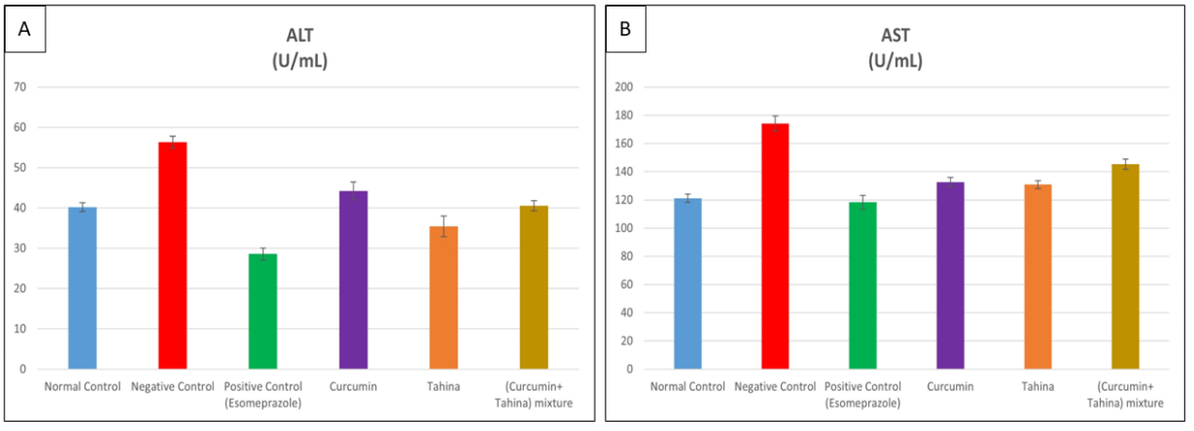

Figure 5. *Serum ALT and AST levels following experimental treatments in rats with indomethacin-induced gastric injury*

The treatment with curcumin was led to significantly decrease these biomarkers (ALT: 44.21 ± 2.2 U/mL, AST: 132.52 ± 3.4 U/mL, urea: 32.20 ± 1.2 mg/dL, creatinine: 0.70 ± 0.11 mg/dL), demonstrating its systemic organ-protective properties. Curcumin's ability to suppress pro-inflammatory cytokines like TNF-α and IL-6, while activating the Nrf2 pathway in hepatic and renal tissues, is well-documented in recent literature [26]. Tahini also contributed to systemic protection, particularly in renal parameters where creatinine levels (0.59 ± 0.02 mg/dL) were lowered significantly more than in the negative control group ($p < 0.01$). Sesame lignans protect from drug-induced hepato and nephrotoxicity through their antioxidant potential and enhancing cellular repair mechanisms [27].

The combination of curcumin with tahini provided the greatest systemic coverage, where the levels of creatinine were reduced to (0.47 ± 0.05 mg/dL) and were substantially lower compared to those in the negative and normal control groups ($p < 0.001$). The concentration of urea (28.34 ± 1.2 mg/dL) and ALT (40.52 ± 1.25 U/mL) was successfully returned back to normal. It is clearly evident in this study of the strong synergism, where the lipid composition of tahini facilitates the systemic delivery of curcumin that effectively neutralizes the reactive oxygen species and stabilizes the cellular membranes in the crucial parts of the body [28]. This broad action defense system implies that the protective effects of the curcumin-tahini complex are not limited only to the gastrointestinally absorbed drugs and acts as a broad-spectrum defense system against the systemic toxicity induced by indomethacin.

3.4. GASTRO HISTOPATHOLOGY

The normal control group (Figure 6A) showed the significantly organized and healthy morphology of the gastric mucosa. The surface epithelium was characterized by regular columnar cells with consistent, basally located, oval nuclei. The gastric pits were elongated and clearly demarcated leading to the formation of organized gastric glands in lamina propria. Parietal and chief cells were present in good condition with normal staining and clearly visible cell borders. Submucosa and muscularis mucosa layers were thin without any signs of pathological conditions such as vascular congestion, edema, or inflammatory cell infiltration. In other words, all these cells that we see demonstrate well-developed cytoprotective mechanisms that ensure the presence of a thick bicarbonate-mucus layer and intact epithelial cells that act as an effective protective barrier from endogenous acid and pepsin [29]. Well-organized layout of the gastric glands enhances their secretory function and ensures the proper supply of blood to the mucosa of the stomach [30].

Such cohort forms the base for healthy tissue. Regarding this, indomethacin administration resulted in severe and significant histopathological damage to gastric mucosa (Figure 6B). Epithelial layer sloughing and ulceration were extensive and all mucosal barrier broke down. There was evident hemorrhage and edema in the lamina propria and submucosa with distortion and displacement of gastric glands. Remaining epithelial cells showed pyknosis and karyorrhexis which is indicative of acute necrotic death. Extensive deep penetration of leukocytes into the tissue, mainly neutrophils, occurred in the penetrated layers whereas the damaged tissue was infiltrated with vascular congestion and fibrin deposition. Such a drastic damage is believed to be caused by massive depletion of cytoprotective prostaglandins with systemic cyclooxygenase inhibition which caused chain reaction of events including reduction of mucosal blood flow and production of reactive oxygen species (ROS). ROS caused lipid peroxidation and cellular integrity damage. [31]. Hemorrhage and edema reflect microvascular injury and an increase in capillary permeability whereas inflammatory infiltration is caused by activation of pro-inflammatory pathways and further augmentation of tissue destruction [32]. This cohort is characterized by the most powerful pathological profile and represents the basis for assessment of gastroprotection.

The restoration of the gastric architecture through esomeprazole administration showed exceptional tissue preservation and restoration which is shown in Figure 6C. Gastric epithelium appeared to be mostly preserved with defined long pits and glands. Epithelial cells were restored to their columnar form with healthy and homogeneous nuclei. Negative control shows absence of mucosal edema and almost complete absence of hemorrhage and inflammatory infiltration. Organization of glands was consistent and the minimal stress of lamina propria. Esomeprazole gastroprotection is based on its effective proton pump blockade, gastric acid secretion inhibition and aggressive activity against the mucosa which contributes to natural tissue regeneration [33]. Furthermore, it can restore smooth mucosal blood flow and promote mucus and bicarbonate secretion which stabilize histological structure and preserves tissue from NSAID-induced necrosis [34]. Tissue preservation in such a cohort was significantly more powerful than in the negative control group and was almost at the normal level and reflects the guidelines for pharmacological gastroprotection.

Curcumin cohort (Figure 6D) revealed normal gastric epithelium with long and short pits and preserved gland. The epithelial network remained intact microscopically. Glandular cells appeared to be healthy, having characteristic features in the form of clear cytoplasm and solid, oval, basally positioned nuclei. No signs of mucosal erosion, hemorrhage or infiltration by large inflammatory cells or major influx of cells were seen. Overall mucosal thickness was preserved in the entirety and connective tissue beneath appeared to be normal. Curcumin's gastroprotection is achieved through interaction of its antioxidant and anti-inflammatory actions. It acts as a strong scavenger of free radicals preventing oxidative damage to cellular membranes and consequently molecular genetic material; thus, curcumin acts not only as a protection mechanism against ulcers but also as one of the key mediators in elimination of biochemical factors responsible

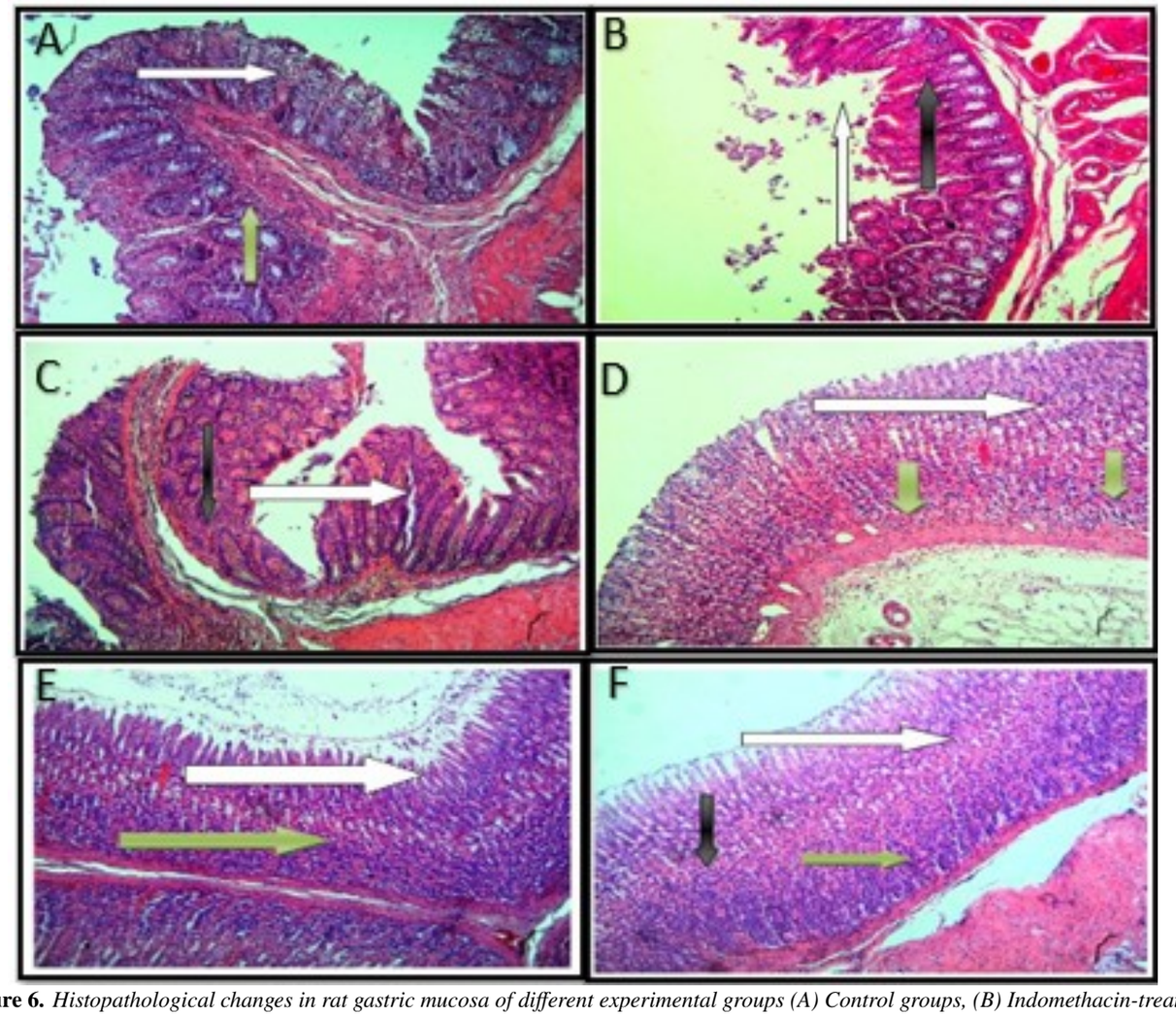

Figure 6. *Histopathological changes in rat gastric mucosa of different experimental groups (A) Control groups, (B) Indomethacin-treated, (C) Esomeprazole-treated, (D) Curcumin-treated, (E) Tahina-treated, and (F) Tahina + Curcumin-treated treated. H&E: 10X.*

for ulcers. It demonstrates an effective antioxidant action by upregulation of endogenous antioxidants and downregulation of proinflammatory transcription factors in the body and thereby curcumin neutralizes biochemical factors causing ulcers [35]. Histologically speaking, it results in overall preservation of gastric pits and glands which maintain structural and functional integrity in the presence of aggressive chemical stressors [36]. Protections from toxins, similar to esomeprazole, are provided by curcumin and thus one of the best examples of an effective natural drug.

Histologically, the tahini cohort (Figure 6E) revealed gastric mucosal architecture to be adequately preserved. Intact epithelial layer with characteristic long pits and smaller glands. Normal cell morphology with normal columnar cells and regular nuclei. Lamina propria were free of great edema or vascular congestion and overall glandular structure was as normal as possible. There were no signs of epithelial sloughing or acute inflammatory infiltration. The sesame lignans and unsaturated fatty acids, acting as vigorous antioxidants, block membrane lipid bilayers and lipid peroxidation and could explain the effective nature of tahini [37]. Moreover, the lipid content of tahini might create a physical barrier, and the fatty acid composition may act as an intermediate for cytoprotective prostaglandin production or counteracting the inhibitory effect of indomethacin on mucosal defense [38].

Tahini as a protector in the body, similar to curcumin and esomeprazole, is indicative of the action of sesame based natural compounds. Group with combined Tahini + Curcumin. Aggregated groups with the combination of tahini + curcumin (Figure 6F) showed the greatest and most active histological preservation of gastric wall. Gastric epithelium revealed the well aligned long pits and healthy short glands. A unique feature was the local vacuolation exhibited in some epithelial cells, and the prominent, healthy nuclei that bore normal chromatin arrangements. Mucosal thickness was completely intact and necrotic/inflammation markers were not present. The submucosa underlying was healthy and well-located and vascularized. Tahini and curcumin were both highly synergistic in retaining gastric mucosa. The lipid structure increased the bioavailability of curcumin through micelles formation which promoted its absorption and penetration into the tissues [39]. This noticeable vacuolation is considered a histological evidence of increased cell intake and metabolism indicating intensive work on the metabolism of lipid-curcumin complexes during the process of cellular

healing and inflammation. Two-fold protection of such an addition of curcumin which works as a potent anti-inflammatory mediator with tahini which protects structurally and biochemically is a strong resistance to the damage of indomethacin [40]. This group had the best recovery rate which brought pharmacological and natural protection closer for the gastric mucosa.

4. CONCLUSION

The current research confirmed that curcumin in combination with tahini and alone revealed good protective activity against indomethacin-induced stomach ulcers in rats. It was clearly shown that combined intake of curcumin and tahini had better gastroprotective effect than alone under the influence of both curcumin and tahini as a co-administration. This combined performance was reflected by a rise in endogenous antioxidant concentrations, decrease of oxidative stress, reduction in inflammation and an overall enhancement in liver and kidney functions as well as gastric mucosal features. Tahini's ability to increase the bioavailability of curcumin and hence facilitate access to the target tissues in higher concentrations explains this potent and effective action. These indications emphasize curcumin-tahini blend for the treatment of gastric ulcers as a natural and effective approach, and the discovery of new therapeutic strategies by using natural curcumin and tahini combination will provide a solid platform for further clinical research in this area.

ETHICAL APPROVAL

The protocol was reviewed and approved by the Animal Ethics Committee. College of Pharmacy, University of Basrah, under approval code EC92, approved these trials in 13 /October/ 2025.

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CONFLICT OF INTEREST

All authors declared no conflict of interest.

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