

## ORIGINAL ARTICLE

# Potential Protective Effects of Curcumin on Aspirin-Induced Toxicity Kidney in Rats

Batrisyia Balqis Mohd Asri<sup>1</sup>, Elysha Nur Ismail<sup>2</sup>, Reezal Ishak<sup>1\*</sup>

<sup>1</sup> Universiti Kuala Lumpur, Institute of Medical Science Technology, A1-1, Jln TKS-1, Taman Kajang Sentral, 43000 Kajang, Selangor, Malaysia

<sup>2</sup> Department of Biomedical Science, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia

## ABSTRACT

**Introduction:** Aspirin, a widely used nonsteroidal anti-inflammatory drug (NSAID), is known for its benefits in preventing cardiovascular disease (CVD) and offering protective effects against cancer when administered at preventative doses. However, excessive aspirin consumption can lead to hepatotoxicity, nephrotoxicity, and life-threatening complications. Curcumin, a yellow-colored polyphenol derived from turmeric (*Curcuma longa*), possesses various biological properties, including protective effects against drug-induced toxicity. This study aims to evaluate the protective role of curcumin against aspirin-induced nephrotoxicity in rats by assessing kidney function parameters.

**Materials and Methods:** Twelve adult male Sprague Dawley rats were divided into three equal groups: Group I (control), Group II (aspirin 300 mg/kg b.wt/orally), and Group III (aspirin 300 mg/kg b.wt/orally + curcumin 400 mg/kg b.wt/orally). Blood samples were collected for biochemical analysis after 14 and 28 days, and kidney tissues were examined histopathologically. **Results:** After two weeks, no significant changes in serum creatinine and uric acid levels were observed in either the untreated or curcumin-treated aspirin groups. However, after four weeks, the untreated aspirin group exhibited a statistically significant increase in these biomarkers. Histopathological analysis further revealed notable kidney damage, including glomerular tuft retraction and brush border loss. Interestingly, curcumin administration over four weeks led to a dose-dependent reduction in elevated kidney function biomarkers, mitigating aspirin-induced damage. **Conclusion:** The findings suggest that curcumin exerts protective effect against aspirin-induced nephrotoxicity likely due to its antioxidant properties, with significant benefits observed after four weeks of continuous administration.

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**Keywords:** aspirin, curcumin, nephrotoxicity, uric acid, creatinine

## Corresponding Author:

Reezal Ishak, PhD  
Email: reezal@unikl.edu.my  
Tel: +603-8739 5894  
Fax: +603-8739 5895

## INTRODUCTION

Kidney disease has become a major public health concern in recent years. Global deaths attributable to chronic kidney disease have continued to rise, increasing from about 1.2 million in 2015 to over 1.6 million in 2019, reflecting the growing global burden of kidney-related mortality (1, 2). The widespread use of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, for their analgesic and anti-inflammatory properties has further exacerbated the issue (3, 4). Although aspirin is widely available and used by millions of people daily, prolonged administration has been associated with an

increased risk of chronic interstitial nephritis, interstitial fibrosis, and chronic renal dysfunction (5, 6).

Aspirin (acetylsalicylic acid), a widely used NSAID derived from salicylates, is available over the counter in most countries. It possesses analgesic, antipyretic, and anti-inflammatory properties and is well established for its role in preventing cardiovascular disease (CVD) and reducing the risk of colorectal cancer when taken at low preventative doses (7, 8). However, long-term use of aspirin raises concerns, particularly regarding gastrointestinal toxicity and adverse effects on renal function (3).

Recent research suggests that prolonged and excessive use of aspirin can lead to significant retention of creatinine and uric acid, impairing renal filtration mechanisms (9, 10). Aspirin overdose inhibits the synthesis of renal prostaglandins, further compromising

kidney function (3). To counter NSAID-induced toxicity, natural polyphenols and herbal medicines, including curcumin, have been explored for their antioxidant properties and ability to neutralize lipid peroxides (11, 12). Curcumin, a yellow, lipophilic, and water-insoluble compound found in turmeric (*Curcuma longa*), a plant from the Zingiberaceae family, has been widely used in traditional Indian and Chinese medicine for treating various conditions, such as respiratory disorders, sinusitis, rheumatism, ulcers, fever, trauma, diabetes wounds, and skin diseases (13, 14). It has gained significant attention for its potent antioxidant properties and low toxicity in rodents. Curcumin exhibits a broad range of therapeutic effects, including antibacterial, antifungal, antiviral, antimalarial, antitumor, and antigenotoxic activities, as well as chemopreventive and chemotherapeutic properties (15, 16). Additionally, it has been shown to protect against oxidative stress in renal cell lines (17, 18), and demonstrate renoprotective activity in various renal diseases, including nephrotoxicity induced by adriamycin, cisplatin, and paracetamol. Its ability to scavenge free radicals and neutralize lipids contributes to its protective role against drug-induced toxicity, including paracetamol intoxication (19, 20). Therefore, the current study aims to investigate the protective potential of curcumin against aspirin-induced renal damage in rats.

## MATERIALS AND METHODS

### Materials

Turmeric powder (60-80 mesh, locally sourced), 95% ethanol (analytical grade), distilled water, aspirin (pharmaceutical grade), ketamine, xylazine, and 0.9% normal saline were used in the experimental procedures. Laboratory reagents included ethylenediaminetetraacetic acid (EDTA), Jaffe reagent, 10% neutral buffered formalin (NBF), ethanol, xylene, paraffin wax, hematoxylin, and eosin (H&E). All chemicals and reagents employed were of analytical or reagent grade and procured from standard laboratory suppliers.

### Laboratory Animal Model and Experimental Design

This study utilized twelve healthy adult male Sprague Dawley rats, each weighing between 215 and 315 g. The animals were housed in clean metal cages under controlled conditions, provided with a balanced commercial diet, and given ad libitum access to drinking water throughout the experimental period. To ensure acclimatization, the rats were kept in these conditions for 14 days before the experiment commenced. The study was conducted over a one-month period, during which twelve rats were divided into three equal groups based on the treatment they received, with each group consisting of four animals.

Group I, served as the control group and was maintained on a basal ration with water provided ad libitum, without any additional intervention. Group II, was administered

aspirin at a dose of 300 mg/kg body weight, dissolved in 1 mL of distilled water, and given orally via stomach tube on alternate days for a period of 4 weeks. Group III, received a combination treatment of curcumin and aspirin, where curcumin was given at a dose of 400 mg/kg body weight and aspirin at 300 mg/kg body weight. Both substances were administered orally with a 2-hour interval between them, once daily for 4 weeks. This animal study was approved by the Institutional Research Ethic Committee (IREC) at the Institute of Medical Science Technology, Universiti Kuala Lumpur (AEC/MESTECHUNIKL/2023).

### Extraction of curcumin from turmeric powder

Dried rhizomes of *Curcuma longa* (turmeric) were ground into a fine powder and passed through a 60-mesh sieve to ensure uniform particle size. Curcumin was extracted from the turmeric powder using a solvent-based extraction method, a widely employed technique for isolating curcumin (21). Initially, 45 g of turmeric powder was weighted and mixed with 450 mL of 95% ethanol, a solvent commonly preferred for curcumin extraction due to its efficiency (21). The mixture was left to blend for 24 hours, allowing efficient extraction of curcumin from the turmeric powder. After the extraction period, the mixture was filtered using filter paper (No. 3, 110mm, Whatman) to separate the liquid extract, containing curcumin, from the solid residue. The liquid extract was then concentrated using a rotary evaporator (Rotovap IKA RV 10, IKA Germany) at the speed of 100 rpm and 40°C until the solvent is removed (22). The final curcumin extract weighed 9 g and was stored in a suitable container, protected from light, inside a refrigerator maintained at 2-8°C.

### Cardiac puncture for blood collection

After two and four weeks, blood samples were collected via cardiac puncture under anesthesia. Rats were anesthetized using a ketamine-xylazine mixture (2:1 ratio (v/v)), administered into the lower right quadrant of the abdomen. The anesthesia solution consisted of 4.0 mL ketamine, 0.4 mL xylazine, and 0.6 mL of 0.9% saline diluent, with each rat receiving approximately 0.4 mL of the mixture. Blood was aseptically drawn from the heart, specifically from the ventricle, ensuring a slow withdrawal to prevent cardiac collapse. A total of 1 mL of blood was carefully collected into an EDTA tube for subsequent biochemical analysis.

### Biochemical analysis

The blood collected via cardiac puncture was centrifuged at 3000 rpm for 10 minutes to separate the serum (23), which was then used to assess kidney function parameters. Serum uric acid levels were measured using a uric acid reader (EasyTouch GCU, Biotek Technology Inc.), a specialized instrument that quantifies uric acid concentration based on specific biochemical reactions. Simultaneously, serum creatinine levels were determined using the Jaffe colorimetric method at a wavelength of

500-520 nm, in which creatinine reacts with the Jaffe reagent, producing a colour change proportional to its concentration. The absorbance of the resulting complex was measured spectrophotometrically to quantify serum creatinine levels. These analytical techniques provide precise and reliable measurements of serum uric acid and creatinine, offering valuable insights into kidney function and the effects of experimental interventions on these biochemical parameters.

### Tissue sample for histological study

Based on the kidney function parameter results indicating dysfunction, the rats were humanely euthanized for histological examination. Euthanasia was performed using cervical dislocation or decapitation, after which the kidneys were carefully removed for further histological analysis (23). Kidney samples obtained from the rats were bisected along the mid-dorsal plane and immediately fixed in 10% neutral buffered formalin. The tissues were then washed in tap water and dehydrated in ascending grades of alcohol before being cleared in xylene and embedded in paraffin wax. A paraffin embedding centre was used to prepare tissue blocks within the paraffin wax medium. Thin sections, measuring 3-6  $\mu\text{m}$  in thickness, were cut using a rotary microtome. The resulting ribbon was transferred into a floatation bath, where a labelled glass slide was immersed to facilitate the proper mounting of the tissue sections. The mounted sections were air-dried before being stained with Hematoxylin and Eosin (H&E) for morphological evaluation under a light microscope (Olympus CX22, Olympus) (24).

For histological assessment, tubular structure evaluation was conducted using the EGTI (endothelial, glomerular, tubular, and interstitial) scoring system (Table I), while glomerular assessment followed the glomerular scoring

**Table I: The EGTI (endothelial, glomerular, tubular, and interstitial) scoring system**

| Tissue type | Histological condition                                                                    | Score |
|-------------|-------------------------------------------------------------------------------------------|-------|
| Tubular     | No damage                                                                                 | 0     |
|             | Loss of Brush Border (BB) in less than 25% of tubular cells. Integrity of basal membrane. | 1     |
|             | Loss of BB in more than 25% of tubular cells, Thickened basal membrane.                   | 2     |
|             | (Plus) Inflammation, cast formation, necrosis up to 60% of tubular cells.                 | 3     |
|             | (Plus) Necrosis in more than 60% of tubular cells                                         | 4     |

system specifically developed for animal studies on kidney injury (25, 26). The evaluations were conducted as a single-blinded assessment by an investigator unaware of the experimental groups.

### Statistical analysis

The data were expressed as mean  $\pm$  standard deviation (Mean  $\pm$  SD) and analysed using a one-way analysis of variance (ANOVA). Statistical analysis was conducted using SPSS software (version 26). A p-value of less than 0.05 ( $p < 0.05$ ) was considered statistically significant.

## RESULTS

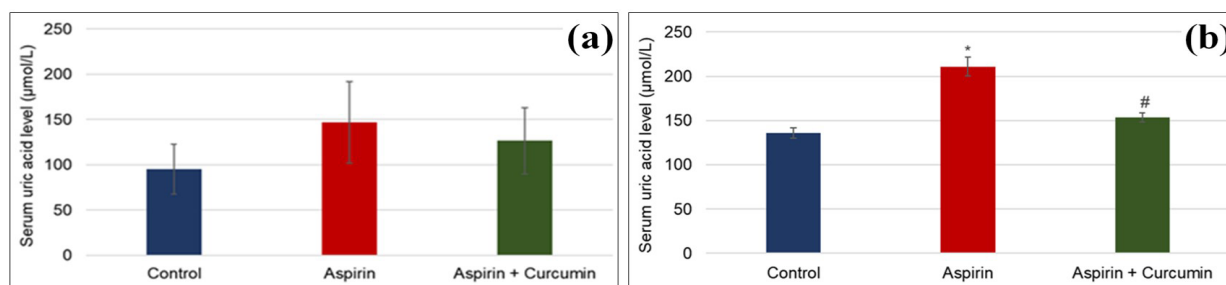
### Effect of aspirin and curcumin on the level of serum uric acid

Fig. 1a illustrates that after two weeks, there were no significant changes in serum uric acid levels in either the aspirin group or the aspirin + curcumin group compared to the control. The mean serum uric acid levels at this time point were similar across the groups: Control ( $95 \pm 54.9 \mu\text{mol/L}$ ), Aspirin ( $146.8 \pm 89.5 \mu\text{mol/L}$ ), and Aspirin + Curcumin ( $126.5 \pm 73.1 \mu\text{mol/L}$ ).

However, as shown in Fig. 1b, a significant increase ( $p < 0.05$ ) in serum uric acid levels was observed in aspirin-intoxicated rats compared to the control group after four weeks. The mean uric acid level in the aspirin group was  $210.8 \pm 21.3 \mu\text{mol/L}$ , whereas the control group had a mean level of  $136 \pm 11.2 \mu\text{mol/L}$ . Notably, curcumin administration at a single dose led to a significant reduction ( $p < 0.05$ ) in serum uric acid levels compared to aspirin-intoxicated rats. The mean uric acid level in the curcumin-treated group was  $153.5 \pm 9.7 \mu\text{mol/L}$ , indicating a protective effect against aspirin-induced elevation of uric acid levels.

### Effect of aspirin and curcumin on the level of serum creatinine

The results in Fig. 2a demonstrates that after two weeks, there were no significant changes in serum creatinine levels in either the aspirin group or the aspirin + curcumin group compared to the control. The mean serum creatinine levels at this time point were similar across the groups: Control ( $47.3 \pm 27.7 \mu\text{mol/L}$ ), Aspirin ( $97.24 \pm 56.6 \mu\text{mol/L}$ ), and Aspirin + Curcumin



**Fig. 1: Mean levels of serum uric acid. (a) After 2 weeks, and (b) after 4 weeks of treatment ( $n = 4$ ). \* Significantly different from control group ( $p < 0.05$ ). # Significantly different from aspirin group ( $p < 0.05$ ).**

( $50.2 \pm 29.3 \mu\text{mol/L}$ ). However, as shown in Fig. 2b, a significant increase ( $p < 0.05$ ) in serum creatinine levels was observed in both the aspirin-intoxicated and aspirin + curcumin groups compared to the control group after four weeks. The mean creatinine level in these groups reached  $123.1 \pm 19.7 \mu\text{mol/L}$ , while the control group had a mean level of  $56.1 \pm 5.4 \mu\text{mol/L}$ . Notably, curcumin administration at a single dose led to a significant reduction ( $p < 0.05$ ) in serum creatinine levels compared to aspirin-intoxicated rats. The mean creatinine level in the curcumin-treated group was  $70.72 \pm 8.1 \mu\text{mol/L}$ , demonstrating a protective effect against aspirin-induced elevations in creatinine levels.

### Effect of aspirin and curcumin on renal histopathological assessment

The group treated with a combination of aspirin and curcumin exhibited notable histopathological

improvements in the glomeruli, including mild expansion of the mesangial matrix and preservation of the tubular brush border, as shown in Fig. 3. These improvements were significant when compared to the aspirin-only group ( $p < 0.05$ ). In contrast, the aspirin group in Fig. 4 displayed significantly greater abnormalities than the control group in Fig. 5 ( $p < 0.05$ ). These abnormalities included abnormal dilation of the capillary lumen, retraction and collapse of the glomerular tuft, and a marked loss of the brush border in tubular structures. However, no significant difference ( $p > 0.05$ ) was observed between the control group and the aspirin + curcumin group in terms of renal histopathological scoring (Fig. 6). The renal histopathological scores (mean  $\pm$  SD) were recorded as; Control group at  $1.3 \pm 0.3$ , Aspirin group at  $5.8 \pm 0.3$ , and Aspirin + Curcumin group at  $3 \pm 0.5$ .

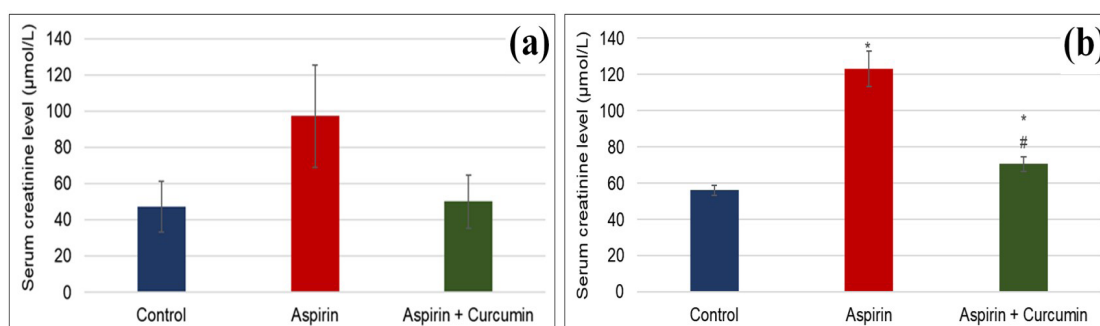


Fig. 2: Mean levels of serum creatinine. (a) After 2 weeks, and (b) after 4 weeks of treatment ( $n = 4$ ). \* Significantly different from the control group ( $p < 0.05$ ). # Significantly different from the aspirin group ( $p < 0.05$ ).

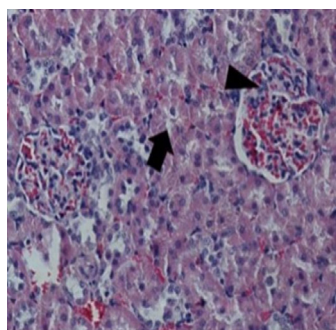


Fig. 3: Rat's kidney from aspirin and curcumin group. The histological features show mild expansion of mesangial matrix for glomeruli (arrowhead) and preservation of brush border for tubular (arrow). H&E staining at 200x magnification.

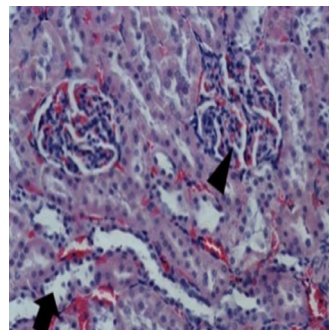


Fig. 4: Rat's kidney of positive control (aspirin) group. The histological features show retraction of the glomerular tuft (arrowhead) and marked a loss of brush border for tubular (arrow). H&E staining at 200x magnification.

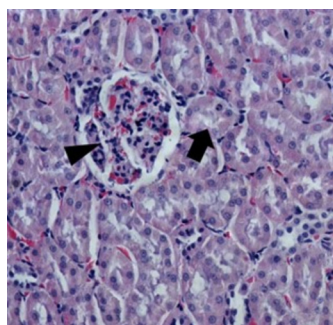


Fig. 5: Rat's kidney of control group. The histological composition shows normal renal glomeruli (arrowhead) and normal tubules (arrow). H&E staining at 200x magnification.

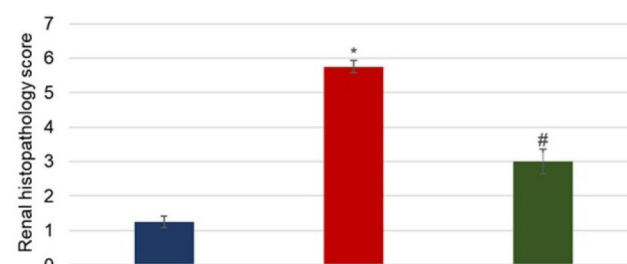


Fig. 6: The kidney histopathological score. Renal histopathological scoring (mean  $\pm$  SD) for control group, aspirin group, and aspirin + curcumin group. \* Significantly different from control group ( $p < 0.05$ ). # Significantly different from aspirin group ( $p < 0.05$ ).

## DISCUSSION

The kidneys play a crucial role in regulating total body fluid volume, composition, and acid-base balance through the actions of their nephron segments, making them vital organs for overall homeostasis (27). Dysfunction in these organs can lead to a wide range of health complications, highlighting the importance of research aimed at understanding the factors that influence renal function. Among these factors, pharmaceutical agents particularly nonsteroidal anti-inflammatory drugs (NSAIDs) have become a significant area of interest. NSAIDs are among the most commonly prescribed therapeutic agents for conditions such as rheumatic diseases, providing analgesic, antipyretic, and anti-inflammatory effects. Aspirin, a widely used NSAID, also serves as an anticoagulant to reduce the risk of thrombotic diseases. However, high-dose or prolonged administration of aspirin has been linked to severe adverse effects, including nephrotoxicity and impaired renal function (28).

To test this hypothesis, the effects of aspirin alone was examined at a dose of 300 mg/kg and a combination of aspirin (300 mg/kg) with curcumin (400 mg/kg). After two weeks of administration, analysis of serum uric acid and creatinine levels (Fig. 1a and 2a) revealed no statistically significant differences between the control group, the aspirin-only group, and the aspirin + curcumin group. However, by the four-week mark, with continued administration of aspirin and curcumin, a significant shift was observed in both serum uric acid and creatinine levels (Fig. 1b and 2b), suggesting a progressive impact of aspirin and the potential protective role of curcumin.

Aspirin irreversibly acetylates Cyclooxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2), suppressing intrarenal synthesis of Prostaglandin E2 (PGE2) and Prostaglandin I2 (PGI2), which are essential for maintaining afferent arteriolar tone, glomerular perfusion, and solute excretion under physiological and stress conditions (29). Diminished prostanoid availability leads to compromised Glomerular Filtration Rate (GFR) and impaired urate clearance, thereby explaining the late-onset hyperuricemia observed in the aspirin-intoxicated rats (30). In parallel, salicylate's mitochondrial uncoupling activity mediated through collapse of the proton gradient and increased oxygen consumption induces ATP depletion in proximal tubular epithelial cells, triggering cytoskeletal disorganization and brush border loss (31). This mechanism aligns with the marked glomerular tuft retraction, capillary dilation, and tubular disruption identified histologically.

Curcumin, a natural polyphenol derived from the rhizome of *Curcuma longa*, is widely recognized for its potent antioxidant properties. It has been shown to protect the kidneys from the harmful effects of NSAID overdose, such as that seen with paracetamol

toxicity (23). It is hypothesized that curcumin, due to its well-documented anti-inflammatory and antioxidant properties, could mitigate the adverse renal effects associated with prolonged aspirin administration. Curcumin's ameliorative effects appear to arise from its capacity to modulate multiple redox- and inflammation-associated pathways implicated in salicylate nephrotoxicity. Curcumin is a well-characterized activator of the Nrf2-ARE axis, inducing transcription of HO-1, NQO1, and glutathione-synthesizing enzymes, thereby enhancing the kidney's antioxidant capacity and mitigating salicylate-driven ROS accumulation (32). Concurrently, curcumin's inhibition of NF- $\kappa$ B activation attenuates downstream expression of TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and iNOS, which are central drivers of mesangial expansion, microvascular dysfunction, and epithelial injury in chemically induced nephropathies (33). The improved histopathological scores observed in the aspirin and curcumin group including the reduction of mesangial alteration and preservation of tubular brush borders are consistent with suppression of NF- $\kappa$ B-dependent inflammatory cascades.

Additionally, curcumin stabilizes mitochondrial integrity by inhibiting the Bax/cytochrome c/caspase-9 apoptotic pathway and preserving mitochondrial membrane potential (34, 35), thereby sustaining ATP-dependent transport processes essential for creatinine handling and tubular viability. The partial normalization of uric acid levels with curcumin treatment further suggests an improvement in renal hemodynamics, potentially mediated through restoration of nitric oxide bioavailability or upregulation of protective prostanoids, as previously reported in other models of nephrotoxicity (36). Collectively, these mechanisms converge to confer substantial renoprotection against aspirin-induced biochemical and structural injury, supporting curcumin's therapeutic potential as a nephroprotective adjunct during chronic salicylate exposure.

In this study, no significant differences in creatinine and uric acid levels were observed among the three groups; control, aspirin, and aspirin with curcumin, after the initial two-week period. The limited duration of this study may have constrained the ability to detect potential changes in kidney function parameters as longer-term assessments are more sensitive (23). Additionally, curcumin has inherently poor bioavailability, meaning it is not readily absorbed by the body. As a result, its therapeutic effects may require several weeks or even months of consistent administration (37). Therefore, both aspirin and curcumin may need prolonged exposure to fully manifest their impact on renal function. The findings presented in Fig. 4 indicate a significant impairment in renal function among rats treated with aspirin, as evidenced by a marked increase in serum creatinine and uric acid levels. Elevated uric acid in the bloodstream, known as hyperuricemia, along with increased serum creatinine, suggests substantial nephron damage, a key

indicator of renal dysfunction (38).

This current results align with previous studies that reported a significant increase in serum urea, uric acid, and creatinine levels in rats administered paracetamol, a drug with therapeutic properties similar to aspirin (39). These findings further reinforce the association between prolonged NSAID use and renal impairment. Histopathological examination of the kidneys, as illustrated in Fig. 4, further supports these findings. The control group exhibited normal renal tissue morphology, whereas rats exposed to aspirin displayed signs of glomerular congestion and necrosis, along with significant degeneration of the brush border in renal tubules. This observed damage may be attributed to the accumulation of salicylic acid, a primary metabolite of aspirin, which, at high concentrations, has been implicated in renal injury. These findings are consistent with the previous report on renal dysfunction that is characterized by glomerular and tubular degeneration following aspirin poisoning or salicylism (20).

The protective role of natural antioxidants found in herbs against oxidative stress has been well-documented. In the present study, the co-administration of aspirin and curcumin exhibited a significant synergistic effect, suggesting an enhanced protective mechanism against nephrotoxicity. This effect was reflected in the substantial reduction of serum uric acid and creatinine levels compared to the aspirin-only group. Previous studies have demonstrated that the co-administration of curcumin with paracetamol, a NSAID with similar properties to aspirin, attenuated renal damage by significantly lowering elevated serum uric acid and creatinine levels induced by a nephrotoxic dose of paracetamol (23).

Moreover, in alignment with the biochemical findings, Fig. 3 illustrates a significant reduction in the mild expansion of the mesangial matrix in glomeruli and the preservation of tubular brush border integrity in rats treated with aspirin and curcumin. These histopathological improvements suggest that curcumin mitigates renal damage. Treatment with curcumin demonstrated that the extracts provides substantial morphological protection against drug-induced nephrotoxicity (40).

In summary, the results in this current study indicate that curcumin exhibits potent protective effects after four weeks of administration. These findings suggest that curcumin may serve as a valuable therapeutic agent for safeguarding kidney tissues against aspirin-induced damage, reinforcing its potential role in renal protection.

## CONCLUSION

In conclusion, this study demonstrates that the co-administration of curcumin with aspirin significantly

reduces uric acid and creatinine levels compared to aspirin alone, highlighting its protective effects on renal function. Additionally, curcumin preserves tubular structures by maintaining the brush border and minimizing glomerular tuft expansion. These findings suggest that curcumin exerts a nephroprotective effect against aspirin-induced renal damage, primarily through its antioxidant properties, with pronounced benefits observed after four weeks of regular administration. This study underscores the importance of evaluating both short-term and long-term impacts on renal function. Future research should explore additional parameters, including serum urea levels, blood urea nitrogen, mineral concentrations, kidney lipid peroxidation, and antioxidant activity, to provide a more comprehensive understanding of renal protection. While acknowledging certain limitations, this study establishes a foundation for further investigations, contributing to the growing knowledge of the complex interactions between pharmaceutical agents and renal health.

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