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Dose-dependent protective effects of turmeric ethanolic extract against diclofenac-induced kidney damage: A histopathological study in rats

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ABSTRACT

Background: Non-steroidal anti-inflammatory drugs, particularly diclofenac sodium, are widely prescribed but can cause nephrotoxicity through oxidative stress mechanisms. Turmeric (*Curcuma longa* L.) contains curcumin and other bioactive compounds with potent antioxidant properties that may protect against drug-induced kidney damage.

Objective: To evaluate the dose-dependent effects of turmeric ethanol extract on kidney histopathology in rats with established diclofenac sodium-induced nephrotoxicity.

Methods: Twenty-eight male Sprague Dawley rats were randomly divided into four groups: normal control, diclofenac (10 mg/kg BW for 7 days), and two treatment groups receiving turmeric extract at doses of 100 mg/kg BW and 200 mg/kg BW, respectively. Kidney histopathology was assessed by a blinded pathologist.

Results: The diclofenac control group exhibited severe kidney damage with hydropic degeneration, granular casts, and cellular casts. Treatment with 100 mg/kg BW showed partial, while 200 mg/kg BW demonstrated substantial improvement approaching normal histology with only minimal residual damage.

Conclusion: Turmeric extract demonstrates dose-dependent nephroprotective effects against diclofenac-induced kidney damage, with 200 mg/kg BW providing superior protection, suggesting potential therapeutic applications in mitigating NSAID-induced nephrotoxicity.

Keywords: Diclofenac sodium, nephrotoxicity, turmeric extract, curcumin, histopathology

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed medications worldwide for managing acute and chronic inflammatory conditions [1]. However, their widespread use has raised significant safety concerns, particularly regarding renal complications. Epidemiological data indicate that NSAID use accounts for up to 36% of drug-induced acute kidney injury cases and approximately 7% of all acute kidney injury cases globally [2]. The risk is particularly elevated in vulnerable populations, including elderly patients, individuals with pre-existing renal impairment, and those with comorbidities such as diabetes mellitus, hypertension, or heart failure.

Diclofenac sodium, one of the most commonly prescribed NSAIDs, carries a well-documented risk of nephrotoxicity that may progress from acute kidney injury to chronic kidney disease [3]. The mechanisms underlying diclofenac-induced nephrotoxicity are multifactorial, involving generation of reactive oxygen species that induce oxidative stress and inhibition of prostaglandin synthesis that compromises renal hemodynamics [3,4]. This dual mechanism results in characteristic histopathological changes including tubular epithelial degeneration, cast formation, and interstitial inflammation.

Given the substantial burden of NSAID-induced nephrotoxicity and the continued clinical necessity for these medications, there is an urgent need for safe

and effective nephroprotective strategies. Natural antioxidants have garnered increasing attention as potential protective agents against drug-induced organ toxicity. Curcumin, the principal bioactive component of turmeric (*Curcuma longa* L.), has emerged as one of the most extensively studied natural antioxidants due to its potent free radical scavenging capacity and multi-target therapeutic effects [5]. Curcumin exhibits antioxidant activity through direct neutralization of reactive oxygen species and indirect enhancement of endogenous antioxidant defenses through upregulation of superoxide dismutase, catalase, and glutathione peroxidase [5,6]. Beyond curcumin, turmeric extract contains flavonoids, alkaloids, saponins, tannins, and steroids that may act synergistically to provide comprehensive nephroprotection [7].

Several experimental studies have investigated turmeric's nephroprotective potential with varying results. Ragab et al. (2022) reported complete restoration of normal renal structure in mice treated with curcumin at 100 mg/kg following diclofenac administration, while Owumi and Dim (2019) demonstrated severe renal damage in rats receiving diclofenac at 10 mg/kg for 7 days [8,9]. Thuawaini et al. (2019) and Zhao et al. (2021) reported dose-dependent improvements with turmeric extract at 100 mg/kg and 200 mg/kg, with the higher dose showing superior outcomes including reduced protein casts and epithelial cell swelling [10,11].

Despite accumulating evidence, critical gaps remain in understanding turmeric's therapeutic potential for mitigating NSAID-induced kidney damage. First, comprehensive evaluation of dose-dependent histopathological changes specifically in diclofenac-induced nephrotoxicity is limited. Second, most studies have focused on concurrent administration of turmeric with the nephrotoxic drug (prophylactic approach), while the therapeutic potential when administered after established kidney damage has received less attention. This represents the clinically relevant scenario, as patients typically develop complications after extended NSAID use. Third, more rigorous histopathological assessment using standardized scoring systems is needed to allow objective quantification and reliable comparisons across studies.

Therefore, this study aims to investigate the dose-dependent effects of turmeric ethanol extract at 100 mg/kg and 200 mg/kg BW on kidney histopathology in rats with established diclofenac sodium-induced nephrotoxicity. We employed a therapeutic intervention model in which turmeric extract was administered only after completion of diclofenac exposure and establishment of kidney damage, simulating the clinically relevant scenario of treating existing injury rather than preventing its occurrence. We hypothesize that turmeric extract will exhibit dose-dependent nephroprotective effects, with 200 mg/kg BW providing greater restoration of normal kidney histology compared to 100 mg/kg BW, as evidenced by reduced tubular degeneration, decreased cast formation, and improved overall renal architecture. These findings could have important clinical implications for patients requiring long-term NSAID therapy, particularly those at elevated risk of kidney complications, by potentially establishing turmeric extract as a safe, accessible, and cost-effective adjunctive therapeutic agent for mitigating NSAID-induced nephrotoxicity.

Method

Study design and ethical considerations

This study employed a true experimental laboratory design with a post-test only control group approach. All experimental procedures were approved by the Research Ethics Committee of the Faculty of Livestock, Marine and Fishery, Universitas Nusa Cendana, under approval number 106/1.KT/KEPPKP/VII/2024. All procedures were conducted in accordance with guidelines for the humane treatment of laboratory animals.

Sample size determination

The sample size was determined using the Federer formula, resulting in 6 rats per group, which was then adjusted using drop-out calculations to yield a final sample size of 7 rats per group.

Table 1. Experimental timeline and treatment protocol for each group

Phase	Days	Normal	Diclofenac Control	P1 (100 mg/kg)	P2 (200 mg/kg)
Acclimatization	1–7	Feed + water	Feed + water	Feed + water	Feed + water
Induction	8–14	Feed + water	Diclofenac 10 mg/kg	Diclofenac 10 mg/kg	Diclofenac 10 mg/kg
Baseline	15	—	Euthanasia	—	—
Treatment	15–28	Feed + water	—	Turmeric 100 mg/kg	Turmeric 200 mg/kg
Final	29	Euthanasia	—	Euthanasia	Euthanasia

This sample size provided adequate statistical power while accounting for potential animal loss during the experiment.

Animals and grouping

Twenty-eight male Sprague Dawley rats underwent a 7-day acclimatization period with standard BR-1 feed and distilled water ad libitum under controlled environmental conditions. Animals were then randomly allocated into four groups (n=7 per group):

1. Normal control: Rats receiving only standard feed and water
2. Diclofenac control: Rats receiving diclofenac sodium (10 mg/kg body weight) for 7 days
3. Treatment group 1 (P1): Rats receiving diclofenac sodium for 7 days, followed by 100 mg/kg BW turmeric extract for 14 days
4. Treatment group 2 (P2): Rats receiving diclofenac sodium for 7 days, followed by 200 mg/kg BW turmeric extract for 14 days

Experimental protocol

On days 8-14, the diclofenac and treatment groups received oral administration of diclofenac sodium at 10 mg/kg BW daily to induce nephrotoxicity. On day 15, animals in the diclofenac control were euthanized using ketamine/xylazine anesthesia followed by cervical dislocation to establish baseline kidney damage. On days 15-28, treatment groups 1 and 2 began receiving oral turmeric extract at doses of 100 mg/kg BW and 200 mg/kg BW, respectively, daily for 14 days. On day 29, animals in the normal control and both treatment groups were euthanized. The experimental timeline is summarized in Table 1.

Histopathological examination

Kidney tissues were fixed in 10% neutral buffered formalin for 24 hours, processed through graded alcohols, embedded in paraffin, sectioned at 5 µm thickness, and stained with hematoxylin and eosin (H&E) and evaluated by a pathologist blinded to the experimental groups using the Arsad scoring system, which quantifies renal damage based on glomerular, tubular, and interstitial changes [12].

Results

Normal control group examination

This group received only standard BR-1 feed and distilled water throughout the 28-day study period, demonstrated normal kidney architecture upon histopathological examination. Microscopic evaluation revealed intact glomerular structure with well-defined Bowman's space, normal proximal and distal tubules with preserved brush borders, and absence of pathological changes including cast formation, cellular degeneration, or interstitial abnormalities (Figure 1A). This finding is consistent with research by Rajesham et al. (2021), which also demonstrated normal glomerular and tubular structures in normal control groups [13].

Diclofenac control group examination

This group received diclofenac sodium at a dose of 10 mg/kg body weight for 7 days and was euthanized on day 15 to establish baseline kidney damage induced by diclofenac.

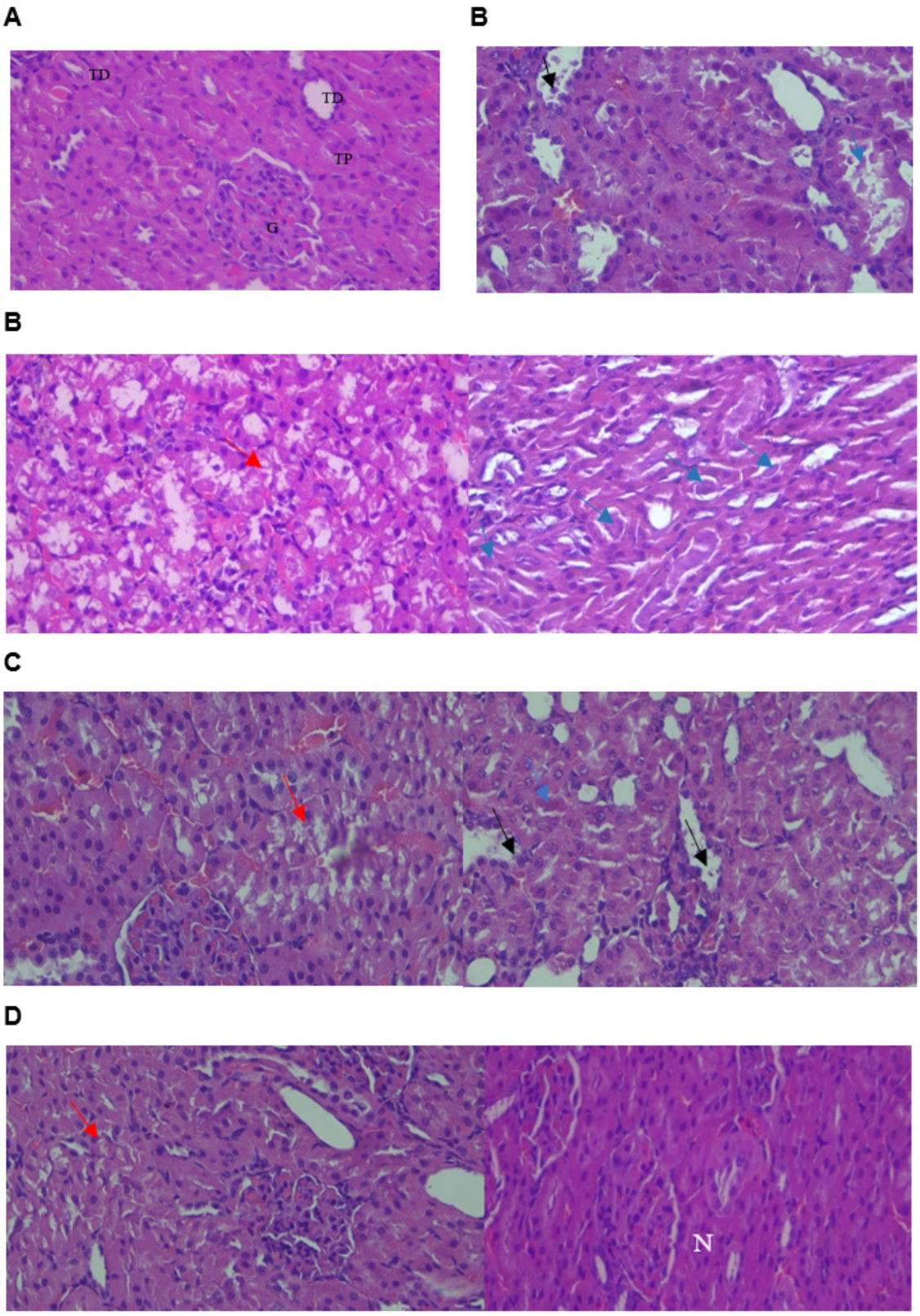

Figure 1. Kidney histopathology of experimental groups (H&E staining, 400× magnification). (A) Normal control group showing intact kidney structure. G = Glomerulus, DT = Distal tubule, PT = Proximal tubule. (B) Diclofenac control (dose 10 mg/kg BW) showing severe pathological changes. Red arrow = Hydropic degeneration, Blue arrow = Granular cast, Black arrow = Cellular cast. (C) Treatment group 1 (turmeric extract 100 mg/kg BW) showing partial improvement with reduced pathological changes. Arrows indicate the same features as in B. (D) Treatment group 2 (turmeric extract 200 mg/kg BW) showing substantial improvement approaching normal histology. Red arrow = Minimal hydropic degeneration, N = Normal structure. Scale bar = 50 µm.

Histopathological examination revealed kidney damage. The kidney damage was characterized by the following pathological features including hydropic degeneration of tubular epithelial cells, granular casts within tubular lumens, and cellular casts (Figure 1B). These findings align with previous studies by Qasim et al. (2022), Mousa et al. (2020), and Mustafa et al. (2019), which reported similar histopathological changes in rat kidneys following diclofenac sodium administration [14–16].

Treatment Group 1 (P1) examination

This group receiving 100 mg/kg BW turmeric extract, demonstrated partial histopathological improvement compared to the diclofenac control. The kidney tissue showed reduced but persistent hydropic degeneration, with tubular epithelial swelling present but less extensive than in the diclofenac control. Granular casts were fewer in number compared to the diclofenac control, and cellular casts were minimal, indicating less severe epithelial damage. Some areas showed restoration toward normal architecture with improved tubular integrity and partial recovery of brush borders in proximal tubules (Figure 1C). However, residual damage markers remained evident throughout the tissue, indicating incomplete recovery at this dose. The improvement occurred but not sufficient to restore completely normal histology, suggesting that while 100 mg/kg BW turmeric extract provides nephroprotection, it offers only moderate therapeutic benefit in the context of established diclofenac-induced damage.

Treatment Group 2 (P2) examination

This group receiving 200 mg/kg BW turmeric extract, exhibited marked histopathological improvement approaching normal kidney architecture. The kidney tissue demonstrated only occasional and mild tubular epithelial swelling observed in scattered areas, representing minimal residual hydropic degeneration. Glomerular structure was well-preserved with intact capillary loops, and most proximal and distal tubules showed normal cellular morphology with intact brush borders. Notably, no granular or cellular casts were observed in the majority of examined fields, indicating successful resolution of tubular dysfunction and epithelial injury (Figure 1D). The overall tissue architecture was substantially restored, with only minimal residual changes visible upon careful examination. This group showed better histopathological outcomes compared to Treatment Group 1, demonstrating the superior nephroprotective effect of the higher dose.

Discussion

This study demonstrates that turmeric extract exerts dose-dependent nephroprotective effects against diclofenac sodium-induced kidney damage in Sprague Dawley rats, with the 200 mg/kg BW dose providing superior protection compared to the 100 mg/kg BW dose. Our histopathological findings reveal that while both doses of turmeric extract reduced kidney damage markers, only the higher dose achieved near-complete restoration of normal renal architecture, suggesting a critical threshold for optimal therapeutic efficacy.

The severe nephrotoxicity observed in the diclofenac control, characterized by extensive hydropic degeneration, granular casts, and cellular casts, confirms the successful establishment of our experimental model. These histopathological changes align with previous studies by Mousa et al. (2020), Mustafa et al. (2019), and Qasim et al. (2022), which reported similar patterns of kidney damage following diclofenac sodium administration at comparable doses [14–16]. The mechanism underlying diclofenac-induced nephrotoxicity involves multiple pathways, including the generation of reactive oxygen species that overwhelm cellular antioxidant defenses, inhibition of prostaglandin synthesis leading to reduced renal blood flow and glomerular filtration rate, and direct cytotoxic effects on tubular epithelial cells [3,4]. The presence of both granular and cellular casts in diclofenac control indicates not only functional impairment but also structural damage with epithelial cell death and desquamation, representing advanced stages of acute tubular injury.

The nephroprotective effects of turmeric extract observed in our study can be attributed primarily to the bioactive compounds present in the extract, with curcumin playing the central role. Curcumin possesses potent antioxidant properties that function through multiple mechanisms, including direct scavenging of reactive oxygen species such as hydrogen peroxide, superoxide anions, and nitric oxide radicals [7]. Additionally, curcumin activates endogenous antioxidant enzymes including superoxide dismutase, catalase, and glutathione peroxidase, thereby enhancing the cellular capacity to neutralize oxidative stress [6]. This dual action of direct free radical scavenging and indirect enhancement of antioxidant defenses explains the substantial protective effects observed in our treatment groups.

Beyond curcumin, phytochemical analysis of our turmeric extract revealed the presence of several other bioactive compounds that contribute synergistically to its nephroprotective properties. Flavonoids present in the extract reduce pathological changes caused by toxic substances through multiple mechanisms, including suppression of oxidative stress-induced cellular damage and inhibition of apoptotic pathways [13]. These compounds have been shown to stabilize cellular membranes and preserve mitochondrial function, thereby preventing the cascade of events leading to cell death. Alkaloids in the extract regulate the expression of Bcl-2 family proteins, particularly the anti-apoptotic Bcl-2 and pro-apoptotic Bax proteins, thereby protecting cells from injury through mitochondrial-mediated pathways [13]. Furthermore, alkaloids suppress the activity of N-acetyl-beta-D-glucosaminidase, a lysosomal enzyme constitutively expressed in proximal renal tubules that serves as a sensitive marker of tubular injury [13]. Tannins present in the extract act as renal vasodilators, potentially improving renal blood flow and glomerular filtration rate, thereby counteracting the hemodynamic alterations induced by diclofenac sodium [17]. Saponins contribute to nephroprotection by inhibiting increases in vascular permeability, thereby preventing inflammation and edema in kidney tissue, and by blocking superoxide formation through interference with hydroperoxide intermediate formation [18]. The steroids present in turmeric extract, particularly plant-derived phytosterols, may contribute to membrane stabilization and possess anti-inflammatory properties that complement the effects of other bioactive compounds [19].

The partial improvement observed in Treatment Group 1 receiving 100 mg/kg turmeric extract represents an important finding that warrants careful consideration. While this dose achieved a with a reduction in pathological features compared to the diclofenac control, it failed to restore completely normal architecture. This outcome differs from findings reported by Ragab et al. (2022), who observed complete restoration of glomerular and tubular structures in mice treated with turmeric extract at the same dose of 100 mg/kg for 14 days following diclofenac sodium administration at 10 mg/kg [8]. Several methodological differences may account for this discrepancy and merit detailed examination.

First, the choice of animal model may influence treatment outcomes, as mice and rats differ in their metabolic rates, drug metabolism pathways, and sensitivity to both toxins and therapeutic agents. Rats generally have lower metabolic rates than mice, which may affect both the extent of diclofenac-induced damage and the therapeutic efficacy of turmeric extract. Second, the route of administration represents a critical variable affecting bioavailability and therapeutic efficacy. Ragab et al. (2022) administered diclofenac sodium intraperitoneally, while our study employed oral gavage. Intraperitoneal administration bypasses first-pass hepatic metabolism and typically results in higher systemic bioavailability compared to oral administration [8]. Conversely, our oral administration of turmeric extract may have resulted in lower bioavailability due to poor aqueous solubility of curcumin, extensive first-pass metabolism, and rapid systemic elimination, all of which are well-documented limitations of curcumin pharmacokinetics [20]. Third, the timing of treatment intervention differs substantially between studies. Ragab et al. (2022) administered turmeric extract concurrently with diclofenac sodium

during the final 14 days of a 21-day treatment period, representing a prophylactic or co-treatment approach [8]. In contrast, our study administered turmeric extract only after the completion of diclofenac administration, representing a therapeutic intervention for established kidney damage. This distinction is clinically important, as prevention of damage may require lower doses than treatment of established injury, where regenerative processes must overcome existing structural and functional deficits.

The substantial improvement observed in P2 receiving 200 mg/kg turmeric extract, with a with a reduction in pathological features and near-complete restoration of normal histology, demonstrates the critical importance of dose optimization in achieving therapeutic efficacy. This finding aligns with the study by Zhao et al. (2021), who demonstrated that curcumin at doses of 100 mg/kg and 200 mg/kg for 7 days exhibited protective effects against kidney damage in rat models exposed to dry-heat environmental conditions, with the 200 mg/kg dose showing superior outcomes including disappearance of protein casts and reduced epithelial cell swelling [11]. Similarly, Thuawaini et al. (2019) reported significant improvements in rats treated with turmeric extract at 200 mg/kg BW for 28 days following rifampicin and isoniazid-induced hepatotoxicity and nephrotoxicity, including reduced severity of kidney lesions, decreased tubular dilatation and inflammation, and normal renal parenchyma with minimal vascular congestion [10]. The consistency of these findings across different models of kidney injury suggests that the 200 mg/kg dose represents a therapeutic threshold at which the concentration of bioactive compounds is sufficient to effectively counteract oxidative stress and promote tissue repair.

The dose-dependent response observed in our study suggests that the relationship between turmeric extract concentration and nephroprotective efficacy follows a predictable pattern within the tested dosage range. The approximate doubling of therapeutic benefit when the dose was doubled from 100 mg/kg to 200 mg/kg indicates a relatively linear dose-response relationship in this range, though it remains unclear whether further dose escalation would yield additional benefits or whether a plateau effect exists at higher doses. From a pharmacological perspective, this dose-dependent pattern may reflect the need for adequate tissue concentrations of curcumin and other bioactive compounds to effectively compete with reactive oxygen species, modulate inflammatory pathways, and support cellular repair mechanisms. The superior efficacy of the 200 mg/kg dose may also relate to the capacity to maintain therapeutic concentrations over extended periods despite the rapid metabolism and elimination of curcumin.

Several important limitations of our study should be acknowledged. First, we did not include biochemical markers of kidney function such as serum creatinine, blood urea nitrogen, and creatinine clearance to correlate with histopathological findings. While histopathology provides valuable information about structural changes, functional markers would offer complementary insights into the physiological impact of the observed damage and the functional recovery achieved with treatment. Future studies should incorporate comprehensive biochemical assessment alongside histopathological examination to provide a more complete picture of kidney health and treatment efficacy. Second, we did not investigate the time course of recovery to determine whether longer treatment periods might result in complete restoration of normal histology, particularly for the 100 mg/kg dose group. It remains possible that extending the treatment duration beyond 14 days could allow for continued tissue repair and further improvement in histopathological morphology. Third, our study did not include comparison with standard nephroprotective treatments such as N-acetylcysteine or vitamin E, which would have provided valuable context for assessing the clinical potential of turmeric extract relative to established therapeutic options. Fourth, we did not measure the actual concentrations of curcumin and other bioactive compounds in kidney tissue, which would help establish pharmacokinetic-pharmacodynamic relationships and guide optimal dosing strategies. Finally, our study focused exclusively on therapeutic intervention

after established diclofenac-induced damage rather than exploring prophylactic administration, which might have revealed different dose requirements or efficacy patterns.

Despite these limitations, our findings provide compelling evidence that turmeric extract, particularly at higher doses, possesses therapeutic potential for mitigating diclofenac sodium-induced kidney damage. The near-complete restoration of normal kidney architecture observed with the 200 mg/kg dose suggests that turmeric extract may offer a viable adjunctive therapy for patients requiring long-term NSAID treatment who are at elevated risk for nephrotoxicity. The dose-dependent nature of the protective effect emphasizes the importance of adequate dosing to achieve optimal therapeutic outcomes and suggests that clinical translation of these findings should prioritize identifying equivalent effective doses in human subjects, taking into account species differences in metabolism and pharmacokinetics.

The clinical implications of our findings extend beyond simple damage mitigation. Given that NSAIDs, including diclofenac sodium, remain among the most widely prescribed medications globally for management of pain and inflammation, strategies to prevent or minimize their adverse effects could have substantial public health impact. Patients with pre-existing kidney disease, elderly individuals, those with diabetes or hypertension, and patients requiring high-dose or prolonged NSAID therapy represent particularly vulnerable populations who might benefit from adjunctive nephroprotective therapy. Turmeric extract, with its established safety profile, widespread availability, and relatively low cost, presents an attractive option for this purpose, particularly in resource-limited settings where access to expensive nephroprotective agents may be limited.

Future research should address several key questions to advance the clinical translation of these findings. First, dose-escalation studies are needed to determine whether doses higher than 200 mg/kg provide additional benefit or whether this dose represents a plateau in efficacy. Second, pharmacokinetic studies measuring tissue concentrations of curcumin and other bioactive compounds would help establish the relationship between systemic exposure and therapeutic effect, guiding optimal dosing strategies. Third, comparative effectiveness studies evaluating turmeric extract against standard nephroprotective treatments would provide essential context for clinical decision-making. Fourth, investigations into optimal timing and duration of treatment, including both prophylactic and therapeutic approaches, would help define the most effective treatment protocols. Fifth, studies examining the potential of enhanced-bioavailability curcumin formulations, such as those incorporating piperine or employing nanoparticle delivery systems, might reveal improved efficacy at lower doses by overcoming the inherent limitations of curcumin pharmacokinetics. Finally, mechanistic studies employing molecular techniques to assess oxidative stress markers, inflammatory cytokines, apoptotic pathways, and antioxidant enzyme activities would provide deeper insights into the mechanisms underlying the nephroprotective effects and potentially identify biomarkers for treatment response.

Conclusion

Our study demonstrates that turmeric extract exerts dose-dependent nephroprotective effects against diclofenac sodium-induced kidney damage, with the 200 mg/kg BW dose providing near-complete restoration of normal kidney architecture. These findings support the potential therapeutic application of turmeric extract as an adjunctive treatment for mitigating NSAID-induced nephrotoxicity, though further research is needed to optimize dosing strategies, establish efficacy in human subjects, and fully elucidate the mechanisms underlying its protective effects.

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Declaration of interest

The authors declare that none of them has any conflict of interest with any private, public, or academic party related to the information contained in this manuscript.

Author contributions

RRA, ALSA, DI, SHEH and TN designed the study. RRA, DI and SHEH collected the data. RRA, DI and TN analyzed the data. RRA, DI and TN drafted the manuscript. ALSA supervised the project. All authors reviewed and approved the final manuscript.

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