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RESEARCH ARTICLE

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A study on the hepatoprotective effect of turmeric (*Curcuma longa*) extract on the liver histopathology of albino rats induced by sodium diclofenac

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ABSTRACT

Background: Diclofenac sodium, a widely used nonsteroidal anti-inflammatory drug (NSAID), causes significant hepatotoxicity through oxidative stress mechanisms. Turmeric (*Curcuma longa* L.), rich in curcuminoid antioxidants, may offer hepatoprotection.

Objective: To evaluate the hepatoprotective effects of turmeric extract against diclofenac sodium-induced liver injury in rats.

Methods: Twenty-eight male Sprague Dawley rats were randomly divided into four groups (n=7): normal control, negative control (diclofenac sodium 10 mg/kg BW for 7 days), and two treatment groups receiving diclofenac sodium followed by turmeric extract at 100 or 200 mg/kg BW for 14 days. Liver histopathology was assessed using hematoxylin-eosin staining. Data were analyzed descriptively.

Results: Turmeric extract attenuated hepatocellular damage in a dose-dependent manner. The 200 mg/kg BW dose completely prevented necrosis, demonstrating superior hepatoprotection compared to 100 mg/kg BW.

Conclusion: Turmeric extract exerts hepatoprotective effects against diclofenac-induced liver injury through attenuation of histopathological damage.

Keywords: hepatoprotection, hepatotoxicity, NSAID, oxidative stress, turmeric

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed and self-administered medications worldwide, used primarily to treat pain, fever, and inflammatory conditions [1]. Their widespread availability, including over-the-counter formulations, contributes to high rates of unsupervised use [2]. However, chronic or inappropriate NSAID use is associated with significant adverse effects, particularly drug-induced liver injury (DILI), making NSAIDs one of the leading causes of hepatotoxicity globally [3].

In Indonesia, NSAID consumption is particularly prevalent. Household survey data revealed that 19.8% of households (20,516 households) stored NSAIDs, with 65.17% indication for use. Notably, a substantial proportion of these medications were obtained without prescription, indicating widespread self-medication practices [4]. This pattern of unsupervised use increases the risk of hepatotoxicity, as prolonged or excessive NSAID intake can lead to serious liver dysfunction [5].

Diclofenac sodium, one of the most widely used NSAIDs globally, exhibits higher hepatotoxic potential compared to other drugs in its class [6]. The mechanisms underlying diclofenac-induced hepatotoxicity are multifactorial and not fully elucidated [7]. Current evidence indicates that

mitochondrial damage and reactive oxygen species (ROS) generation play central roles in initiating hepatocellular injury. These events trigger lysosomal dysfunction and impair autophagy flux, preventing efficient clearance of damaged mitochondria through mitophagy. The resulting accumulation of dysfunctional mitochondria perpetuates ROS production, creating a cycle of oxidative injury that ultimately causes hepatotoxicity [8]. Experimental studies have confirmed that oral administration of diclofenac sodium at 10 mg/kg BW for 7 days induces significant hepatotoxic effects in rats [9].

Given the clinical burden of NSAID-induced hepatotoxicity, identifying safe and effective hepatoprotective agents is a priority. Herbal medicines containing antioxidants represent a promising therapeutic approach for managing drug-induced liver injury [10]. The World Health Organization (WHO) has endorsed the use of traditional medicine for health maintenance, disease prevention, and treatment, noting that approximately 21,000 medicinal plants are utilized for various medical purposes globally. In Indonesia, the Ministry of Trade has identified 15 biopharmaceutical plants commonly used by the population, including turmeric (*Curcuma longa* L.) [11].

Turmeric has been used traditionally for centuries and is now recognized for its bioactive polyphenolic compounds, particularly curcumin, which exhibits anti-inflammatory, antioxidant, and anticancer properties [12]. Curcumin and related curcuminoids protect cells from oxidative stress and inflammation, key mechanisms in hepatotoxicity, thereby conferring hepatoprotective effects. Phytochemical studies demonstrate that turmeric rhizomes possess the highest antioxidant activity among plant parts, particularly in ethyl acetate extracts [13].

Several experimental studies support turmeric's hepatoprotective potential. Utami et al. (2022) demonstrated that turmeric rhizome extract at 200 mg/kg BW significantly reduced parenchymatous degeneration and necrosis in thioacetamide-induced hepatotoxicity in rats [14]. Similarly, Thuawaini et al. (2019) reported hepatoprotective effects of turmeric aqueous extract at doses of 100 and 200 mg/kg BW administered daily for 4 weeks against rifampicin and isoniazid-induced liver injury [15]. These findings underscore the need for continued research to establish the safety, quality, and therapeutic efficacy of turmeric-based traditional medicines.

Despite growing evidence of turmeric's hepatoprotective properties against various hepatotoxins, its specific effects on diclofenac sodium-induced liver injury remain incompletely characterized. Given diclofenac's widespread use and distinct hepatotoxic mechanisms involving oxidative stress, investigating turmeric extract's potential to mitigate diclofenac-induced hepatotoxicity is clinically relevant. Therefore, this study aimed to evaluate the hepatoprotective effects of turmeric extract on liver histopathology in a rat model of diclofenac sodium-induced hepatotoxicity.

Methods

Study design and ethical approval

This study employed a laboratory experimental design using a true experimental 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 105/1.KT/KEPPKP/VII/2024.

Animals and housing

Male Sprague Dawley rats (*Rattus norvegicus*) were obtained from a certified supplier. Animals were housed under standard laboratory conditions with a 12-hour light/dark cycle. Food (BR-1 standard pellet diet) and water were provided ad libitum throughout the study period.

Sample size determination and grouping

Sample size was calculated using the Federer formula, yielding an initial requirement of six animals per group. To account for potential attrition, the sample size was increased using a dropout formula, resulting in seven animals per group (dropout rate 15%).

Table 1. Experimental timeline and treatment protocol for diclofenac-induced hepatotoxicity study

Phase	Days	Normal control	Negative control	Treatment Group 1	Treatment Group 2
Acclimatization	1-7	Standard diet + water ad libitum	Standard diet + water ad libitum	Standard diet + water ad libitum	Standard diet + water ad libitum
Induction	8-14	Vehicle (distilled water)	Diclofenac sodium (10 mg/kg BW, PO, once daily)	Diclofenac sodium (10 mg/kg BW, PO, once daily)	Diclofenac sodium (10 mg/kg BW, PO, once daily)
Euthanasia (Negative control)	15	—	Euthanized	—	—
Treatment Phase	15-28	Vehicle (distilled water)	—	Turmeric extract (100 mg/kg BW, PO, once daily)	Turmeric extract (200 mg/kg BW, PO, once daily)
Final Euthanasia	29	Euthanized	—	Euthanized	Euthanized

Note: BW = body weight; PO = per os (oral gavage); — = not applicable (group no longer in study or not receiving intervention)

$$n' = \frac{n}{1 - 0.15} = \frac{6}{0.85} \approx 7$$

n' = adjusted sample size; n = initial sample size

A total of 28 rats were randomly allocated into four experimental groups (n = 7 per group): normal control (untreated), negative control (diclofenac sodium only), treatment group 1 (diclofenac sodium + turmeric extract 100 mg/kg BW), and treatment group 2 (diclofenac sodium + turmeric extract 200 mg/kg BW).

Turmeric extract preparation and standardization

Turmeric extract was prepared and standardized according to established protocols. The extract was formulated as a suspension for oral administration.

Experimental protocol

The experimental timeline is summarized in Table 1. Following a 7-day acclimatization period (Days 1-7) during which all animals received standard diet and water, the hepatotoxicity induction phase commenced. On Days 8-14, animals in the negative control and both treatment groups received diclofenac sodium at 10 mg/kg BW via oral gavage once daily. The normal control group received vehicle only (distilled water) throughout the study.

On Day 15, animals in the negative control group were euthanized to assess diclofenac-induced hepatotoxicity. Concurrently, the treatment phase was initiated for treatment groups 1 and 2, which received turmeric extract at doses of 100 mg/kg BW and 200 mg/kg BW, respectively, via oral gavage once daily for 14 days (Days 15-28). The normal control group continued to receive vehicle only. On Day 29, all remaining animals (normal control, treatment group 1, and treatment group 2) were euthanized for sample collection.

Sample collection and processing

Animals were euthanized using cervical dislocation under anesthesia in accordance with institutional animal care guidelines. Following confirmation of death, laparotomy was performed, and liver tissue was immediately excised. Liver samples were rinsed in cold normal saline, blotted dry, and fixed in 10% neutral buffered formalin for 24-48 hours prior to histopathological processing.

Histopathological examination

Fixed liver tissues were processed using standard histological techniques. Briefly, tissues were dehydrated through graded ethanol series, cleared in xylene, and embedded in paraffin wax. Sections of 4-5 µm thickness were cut using a rotary microtome and mounted on glass slides.

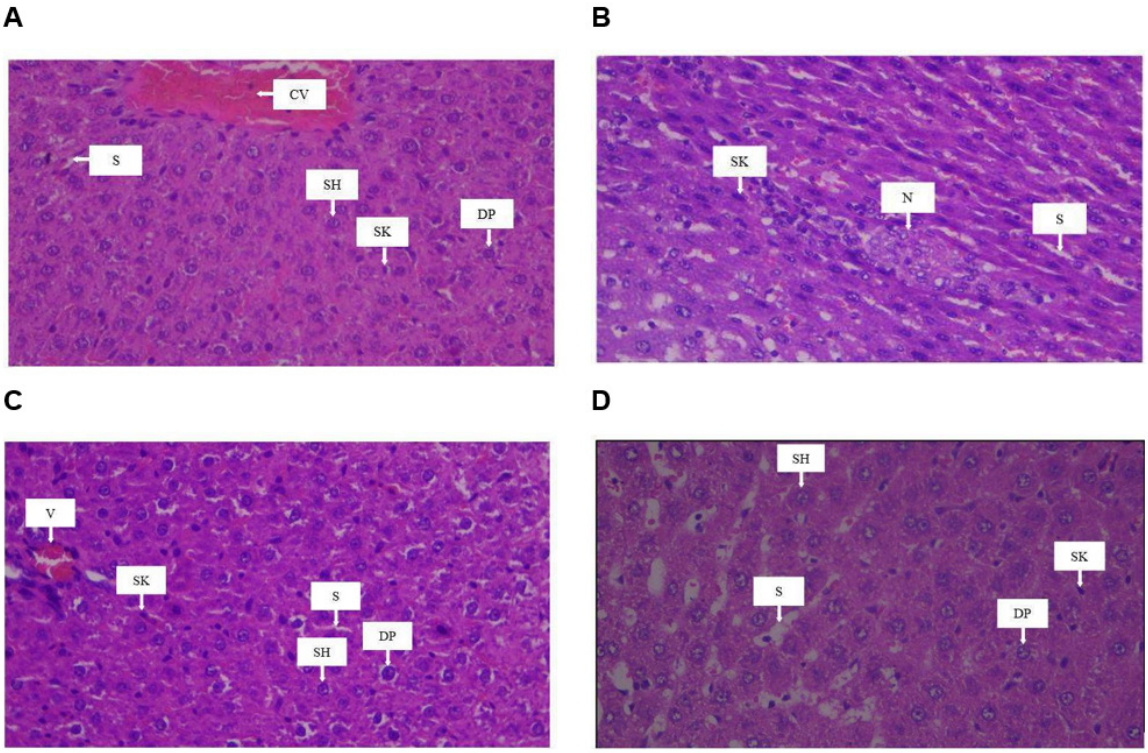

Figure 1. Representative photomicrographs of liver histopathology (H&E staining, 400× magnification): (A) Normal control group showing normal liver architecture; (B) Negative control group showing diclofenac-induced hepatotoxicity; (C) Treatment group 1 receiving diclofenac sodium 10 mg/kg BW plus turmeric extract 100 mg/kg BW; (D) Treatment group 2 receiving diclofenac sodium 10 mg/kg BW plus turmeric extract 200 mg/kg BW. S = sinusoid; SK = Kupffer cells; CV = central vein; SH = normal hepatocytes; DP = parenchymatous degeneration; N = necrosis; V = vein.

Sections were stained with hematoxylin and eosin (H&E) according to standard protocols.

Histopathological evaluation was performed by using light microscopy at 400× magnification. Parameters evaluated included parenchymatous degeneration, hydropic degeneration, necrosis, and inflammatory cell infiltration. For each animal, five randomly selected fields were examined at 400x magnification.

Results

Normal control group

Liver tissue from the normal control group exhibited predominantly normal histological architecture. Hepatocytes displayed characteristic polyhedral morphology with distinct cellular boundaries, well-defined nuclei, and clear sinusoidal spaces. Kupffer cells were visible within the sinusoids. Minimal parenchymatous degeneration was observed in some specimens, characterized by mild cellular swelling and slightly granular cytoplasm, likely representing normal physiological variation [16]. No hydropic degeneration, necrosis, or inflammatory infiltrates were detected.

Negative control group

Animals receiving diclofenac sodium (10 mg/kg BW) for 7 days demonstrated marked hepatocellular injury. Multiple pathological features were observed, including:

1. Parenchymatous degeneration: Hepatocytes exhibited cellular swelling with granular, opaque cytoplasm, indicating impaired cellular metabolism and protein accumulation [17].
2. Hydropic degeneration: Numerous hepatocytes contained small cytoplasmic vacuoles, reflecting disrupted ionic homeostasis and water accumulation [18].
3. Necrosis: Evidence of irreversible cellular injury was present, characterized by karyorrhexis

(nuclear fragmentation) with scattered chromatin fragments and loss of nuclear definition [18].

4. Inflammatory infiltration: Mononuclear inflammatory cells were present in, confirming hepatic inflammation.

These findings confirmed successful induction of diclofenac-mediated hepatotoxicity.

Treatment turmeric extract 100 mg/kg BW

Animals receiving turmeric extract at 100 mg/kg BW following diclofenac exposure showed improved histological features compared to the negative control group. The severity and frequency of parenchymatous degeneration, hydropic degeneration, and necrosis were reduced. However, residual hepatocellular injury was still evident. Specifically, necrotic hepatocytes were observed, indicating incomplete hepatoprotection at this dose level.

Treatment turmeric extract 200 mg/kg BW

The higher dose of turmeric extract (200 mg/kgBW) demonstrated superior hepatoprotective efficacy. Liver histology showed substantial improvement with minimal parenchymatous and hydropic degeneration. Notably, no necrotic hepatocytes were detected in any specimens from this group, contrasting with treatment group 1. Hepatocellular architecture closely resembled that of the normal control group, suggesting near-complete restoration of liver tissue integrity. These findings indicate that 200 mg/kgBW turmeric extract provided more effective protection against diclofenac-induced hepatotoxicity than the lower dose.

Discussion

This study demonstrates that turmeric extract exerts significant dose-dependent hepatoprotective effects against diclofenac sodium-induced liver injury in rats. Notably, the higher dose (200 mg/kg BW) completely prevented necrosis, whereas the lower dose (100 mg/kg BW) showed residual necrotic changes in some specimens.

The largely normal histological appearance in the normal control group confirms that liver damage observed in treated groups resulted from experimental interventions rather than baseline conditions or housing stress. The polyhedral morphology, clear cellular boundaries, and visible nuclei reflect healthy hepatic architecture. Occasional mild parenchymatous degeneration observed in control animals likely represents normal physiological protein accumulation or minor metabolic stress and does not indicate pathological change [16].

Administration of diclofenac sodium (10 mg/kg BW) for 7 days successfully induced hepatotoxicity, consistent with previous studies [9]. The observed pathological triad—parenchymatous degeneration, hydropic degeneration, and necrosis—reflects the progressive nature of diclofenac-induced hepatocellular injury [17,18]. Parenchymatous degeneration, characterized by cellular swelling and granular cytoplasm, indicates impaired intracellular water regulation and protein accumulation. Hydropic degeneration results from failure of ATP-dependent ion pumps in plasma membranes, leading to ionic imbalance and osmotic water influx. The presence of karyorrhexis and nuclear fragmentation confirms irreversible cellular injury and necrosis, while inflammatory cell infiltration indicates activation of innate immune responses [18].

The hepatotoxic mechanism of diclofenac is multifactorial and involves oxidative stress as a central pathogenic pathway [8]. Diclofenac metabolism generates reactive intermediates that damage mitochondria, triggering excessive ROS production. This oxidative cascade impairs lysosomal function and autophagy flux, preventing efficient clearance of damaged mitochondria through mitophagy [8]. Accumulation of dysfunctional mitochondria perpetuates ROS generation, creating a self-amplifying cycle of oxidative injury that ultimately leads to hepatocellular necrosis.

The observed hepatoprotection conferred by turmeric extract can be attributed primarily to its rich curcuminoid content, particularly curcumin, which possesses potent antioxidant and anti-inflammatory properties. Our findings align with previous

research demonstrating hepatoprotective effects of turmeric extract against various hepatotoxins, including rifampicin and isoniazid , thioacetamide, and acetaminophen [14,15,19].

Curcumin functions as an exogenous antioxidant through multiple mechanisms. As a polyphenolic compound, it directly scavenges free radicals by donating hydrogen atoms, thereby neutralizing ROS and terminating lipid peroxidation chain reactions [13]. Additionally, curcumin upregulates endogenous antioxidant systems by inducing glutathione reductase and increasing glutathione production, enhancing cellular capacity to neutralize oxidative stress [14,19]. Curcumin also elevates catalase levels, further augmenting antioxidant defense mechanisms [14]. By stabilizing ROS and preventing oxidative damage to cellular macromolecules, curcumin protects hepatocytes from diclofenac-induced injury.

Beyond its antioxidant properties, curcumin exerts anti-inflammatory effects by suppressing proinflammatory mediators. It inhibits cyclooxygenase-2 (COX-2) expression, thereby reducing prostaglandin synthesis and inflammatory responses. Curcumin also attenuates production of proinflammatory cytokines, including transforming growth factor-beta (TGF-β), which plays a central role in hepatic inflammation and fibrogenesis [14]. Furthermore, curcumin stabilizes cellular membranes and promotes hepatocyte regeneration, facilitating tissue repair following injury [20].

While curcumin represents the predominant bioactive constituent, turmeric extract contains additional secondary metabolites that may contribute synergistically to hepatoprotection, including flavonoids, steroids, alkaloids, tannins, and saponins [21]. The relative contribution of these compounds to the observed hepatoprotective effects warrants further investigation.

The superior efficacy of the 200 mg/kg BW dose compared to 100 mg/kg BW demonstrates a clear dose-response relationship. Complete prevention of necrosis at the higher dose suggests that adequate curcuminoid concentrations are necessary to fully counteract diclofenac-induced oxidative stress. This finding parallels previous studies showing enhanced hepatoprotection with 200 mg/kg BW turmeric or curcumin compared to lower doses [14,20].

Our results corroborate and extend previous findings on turmeric's hepatoprotective properties. Thuawaini et al. (2019) demonstrated significant hepatoprotection with turmeric aqueous extract (100 and 200 mg/kg BW) against rifampicin and isoniazid toxicity over 4 weeks [15]. Similarly, Utami et al. (2022) reported that 200 mg/kg BW turmeric rhizome extract significantly reduced parenchymatous degeneration and necrosis in thioacetamide-induced hepatotoxicity [14]. Our study extends these findings by specifically examining diclofenac-induced injury and demonstrating complete necrosis prevention at the higher dose, representing a clinically meaningful endpoint not consistently reported in prior studies.

Several limitations should be considered when interpreting these findings. The sample size of seven rats per group, while calculated using the Federer formula with dropout adjustment, may limit statistical power for detecting subtle differences and restrict generalizability. The study's single time point assessment precludes understanding of temporal progression of injury and recovery, and the absence of biochemical correlations with serum biomarkers (ALT, AST, ALP, bilirubin) and oxidative stress markers (malondialdehyde, superoxide dismutase, glutathione) limits interpretation of hepatoprotective mechanisms. Additionally, the specific curcuminoid content of the turmeric extract was not quantified, which affects reproducibility and mechanistic understanding. The evaluation of only one diclofenac dose (10 mg/kg BW) and treatment duration (7 days) prevents comprehensive toxicity profiling. While mechanisms were inferred from literature, direct measurement of molecular markers would provide mechanistic confirmation. Finally, interspecies differences in drug metabolism and physiology complicate extrapolation to clinical applications without human equivalent dose calculations and clinical trials.

These findings suggest potential therapeutic value of turmeric supplementation for mitigating

NSAID-induced hepatotoxicity in populations requiring chronic NSAID therapy. However, clinical translation requires dose optimization through allometric scaling, comprehensive evaluation of long-term safety and drug interactions, and development of standardized bioavailable curcumin formulations. Importantly, this study employed a co-administration model, leaving uncertain whether turmeric extract can reverse established hepatotoxicity. Future research should address these gaps through larger studies incorporating biochemical markers, dose-response and time-course evaluations, mechanistic investigations using molecular techniques, assessment of therapeutic rather than solely preventive administration, investigation of bioavailability-enhancing formulations, and ultimately, clinical trials in at-risk populations.

Conclusion

This study demonstrates that turmeric extract provides hepatoprotection against diclofenac sodium-induced liver injury in rats. Histopathological examination revealed that the 200 mg/kg BW dose effectively prevented hepatocellular necrosis and reduced parenchymatous and hydropic degeneration compared to the 100 mg/kg BW dose. These findings suggest that turmeric extract's antioxidant and anti-inflammatory properties may mitigate NSAID-induced hepatotoxicity. However, further studies incorporating biochemical markers, larger sample sizes, mechanistic investigations, and dose-response evaluations are necessary to confirm these preliminary findings.

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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

GIPH and ALSA handled conceptualization and methodology. GIPH, ALSA and MR managed data curation, investigation and analysis. GIPH and ALSA prepared the draft and performed review. MR supported project administration and data acquisition. ALSA and AST provided supervision and final approval of the manuscript.

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