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RESEARCH ARTICLE

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Effect of turmeric (*Curcuma longa* L.) extract on gastric histopathology of diclofenac sodium-induced rats

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ABSTRACT

Background: Prolonged use of diclofenac sodium can cause gastric mucosal damage through cyclooxygenase inhibition and oxidative stress. Turmeric (*Curcuma longa* L.) contains curcumin and other bioactive compounds with potential gastroprotective properties.

Objective: To determine the dose-dependent gastroprotective effect of turmeric extract against diclofenac sodium-induced gastric mucosal injury in rats.

Methods: This experimental study used 28 male Sprague-Dawley rats randomly allocated into four groups (n=7): normal control, negative control (diclofenac 10 mg/kgBW for 7 days), and two treatment groups receiving turmeric extract at 100 mg/kgBW (P1) or 200 mg/kgBW (P2) for 14 days following diclofenac induction. Gastric tissues were evaluated histopathologically using a qualitative description.

Results: The negative control group showed severe erosion and inflammatory infiltration. Both treatment groups demonstrated gastroprotective effects with minimal epithelial damage and no inflammatory changes. The 200 mg/kgBW dose showed superior protection compared to 100 mg/kgBW.

Conclusion: Turmeric extract provides dose-dependent gastroprotection against diclofenac-induced gastric injury, with 200 mg/kgBW demonstrating superior efficacy.

Keywords: Diclofenac sodium, gastroprotection, turmeric extract, gastric histopathology

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are medications commonly used to relieve pain and inflammation, such as in arthritis (rheumatoid arthritis, osteoarthritis), and to reduce fever, swelling, and redness [1]. According to the World Health Organization (WHO) Essential Medicines List Model, NSAIDs are a widely used class of drugs due to their proven therapeutic efficacy [2]. In Indonesia, there were 24,496 types of NSAIDs stored in 20,561 households [3]. The Essential Medicines Lists (EMLs) revealed that of the 100 countries for which data was available, 74 reported using diclofenac sodium [4]. Global sales of NSAIDs accounted for nearly 40%, with the most commonly used types being diclofenac sodium and ibuprofen [5].

Prolonged or inappropriate use of diclofenac sodium can trigger gastrointestinal problems such as dyspepsia, diarrhea, constipation, nausea, vomiting, and gastritis [6]. In the gastrointestinal tract, inappropriate consumption can cause gastric irritation including erosion, bleeding, ulcers, and perforation [7]. Long-term use of diclofenac sodium not only provides benefits in reducing inflammatory symptoms but can also interfere

with the protective mechanisms of the gastric mucosa [8]. The gastric mucosal damage caused by diclofenac sodium is due to its acidic properties and inhibition of cyclooxygenase enzymes, which reduces prostaglandin synthesis. The highly acidic gastric environment can cause mucosal injury and decrease mucosal blood flow, mucus secretion, bicarbonate secretion, and other defense factors of the gastric lining. Diclofenac sodium is also involved in oxidative stress of mucosal cells, which is an etiopathogenic factor that causes gastritis and gastric ulcers [9].

Research has demonstrated that diclofenac sodium administration at a dose of 10 mg/kgBW for 7 days in rats can cause damage to the epithelium of the gastric mucosa [10]. Studies in rats given diclofenac sodium at similar doses showed necrosis of the gastric mucosa with severe dilatation of blood vessels in the lamina propria accompanied by edema and inflammatory cell infiltration (neutrophils), as well as congestion and necrosis in the mucosal layer [11].

The adverse effects of diclofenac sodium can be minimized using antioxidants that can neutralize free radicals [12]. Antioxidants are compounds that counteract the negative effects of free radicals in the body, preventing continued oxidation in body cells. Sources of antioxidants can be obtained through herbal plants or traditional medicine [13]. According to Basic Health Research 2018, approximately 31.4% of households in Indonesia use traditional medicine [14]. Indonesia has numerous herbal plants with medicinal properties, one of which is turmeric [15].

Turmeric (*Curcuma longa* L.) is a tropical plant from the *Zingiberaceae* family [16]. Turmeric rhizomes, particularly curcumin, are known to have many pharmacological effects including antibacterial, anticarcinogenic, anti-inflammatory, and antioxidant properties [17]. Turmeric contains curcumin and secondary metabolic compounds that have been shown to counteract free radicals, making curcumin the most important bioactive component in turmeric [18]. The curcumin content is recognized as the most active component in turmeric with gastroprotective effects that can inhibit damage and protect the gastric mucosal epithelium [19].

White rats (*Rattus norvegicus*) are frequently used as experimental animals in research [20]. Male white rats are particularly suitable as experimental animals because they have approximately 90% genetic similarity to humans and possess relatively fast metabolic capabilities, making them more sensitive for studies related to body metabolism [21].

Research has shown that curcumin in turmeric extract has protective activity by inhibiting excessive gastric acid secretion [22]. Studies demonstrated that administration of turmeric extract at doses of 100 mg/kgBW and 200 mg/kgBW was able to reduce the severity of gastric ulcers and showed gastroprotective activity in improving rat gastric histopathology [23]. Similarly, research indicated that turmeric extract at these doses has gastroprotective properties that can protect the rat gastric mucosa against damage caused by acetylsalicylic acid induction, as evidenced by reduced lesion number and area, as well as decreased mast cells and eosinophils [24].

However, previous studies primarily investigated acetylsalicylic acid-induced gastric damage rather than diclofenac sodium specifically. While both are NSAIDs, they may cause gastric injury through varying pathophysiological mechanisms and severities. Systematic histopathological evaluation comparing the efficacy of different turmeric extract doses specifically against diclofenac sodium-induced gastric mucosal damage remains limited. This study aims to investigate the dose-dependent gastroprotective effects of turmeric extract (100 mg/kgBW versus 200 mg/kgBW) against diclofenac sodium-induced gastric mucosal damage through comprehensive histopathological analysis.

Methods

This study employed a laboratory experimental research design using a true experimental posttest-only control group design. The sample size was determined using Federer's formula, yielding six rats per group, which was adjusted to seven rats per group after applying a dropout rate calculation.

Table 1. Intervention timeline

Phase	Days	Normal Control	Negative Control	P1	P2
Acclimatization	1–7	—	—	—	—
Ulcer induction	8–14	Water	Diclofenac	Diclofenac	Diclofenac
Termination	15	—	Euthanasia	—	—
Treatment	15–28	Water	—	Turmeric 100 mg/kg	Turmeric 200 mg/kg
Final termination	29	Euthanasia	—	Euthanasia	Euthanasia

Animal preparation and ethical considerations

Male Sprague-Dawley rats (*Rattus norvegicus*) were used as experimental subjects. All experimental procedures were approved by Faculty of Livestock, Marine and Fishery, Universitas Nusa Cendana, under approval number 107/1.KT/KEPPKP/VII/2024. And conducted in accordance with ethical guidelines for animal research. The animals were housed in standard laboratory conditions with controlled temperature (22-24°C), humidity, and a 12-hour light-dark cycle. Prior to experimental interventions, all animals underwent a 7-day acclimatization period with standard pellet feed (BR-1) and distilled water provided *ad libitum*. The rats were randomly allocated into four groups (n=7 per group): normal control, negative control, treatment group 1 (P1), and treatment group 2 (P2).

Preparation of test materials

Diclofenac sodium was prepared by dissolving pharmaceutical-grade sodium diclofenac powder in distilled water to achieve the desired concentration for oral administration at a dose of 10 mg/kg body weight. The solution was prepared fresh daily, with the volume adjusted according to individual body weights.

Treatment protocol

Following the 7-day acclimatization period (Days 1-7), the experimental intervention commenced on Day 8 according to the following protocol (Table 1):

1. Phase 1: Gastric ulcer induction (Days 8-14). The negative control group and both treatment groups (P1 and P2) received oral administration of diclofenac sodium at 10 mg/kg body weight once daily for 7 consecutive days to induce gastric mucosal injury. The normal control group received only distilled water during this period via the same oral route and volume.
2. Phase 2: Negative control termination (Day 15). On Day 15, immediately following the 7-day diclofenac administration period, rats in the negative control group were humanely euthanized to assess the extent of gastric mucosal damage without therapeutic intervention.
3. Phase 3: Therapeutic intervention (Days 15-28). Beginning on Day 15, treatment group P1 received oral administration of turmeric extract at 100 mg/kg body weight, while treatment group P2 received 200 mg/kg body weight, both administered once daily for 14 consecutive days. During this phase, the normal control group continued to receive only distilled water.
4. Phase 4: Final termination (Day 29). On Day 29, following completion of the 14-day treatment period, rats from the normal control group and both treatment groups (P1 and P2) were humanely euthanized for specimen collection and analysis.

Histopathological examination

Fixed gastric tissue samples were processed using standard paraffin embedding technique. Tissues underwent dehydration through a graded series of alcohol concentrations, cleared in xylene, and infiltrated with molten paraffin wax. The embedded tissues were sectioned at 4-5 µm thickness using a rotary microtome. Tissue

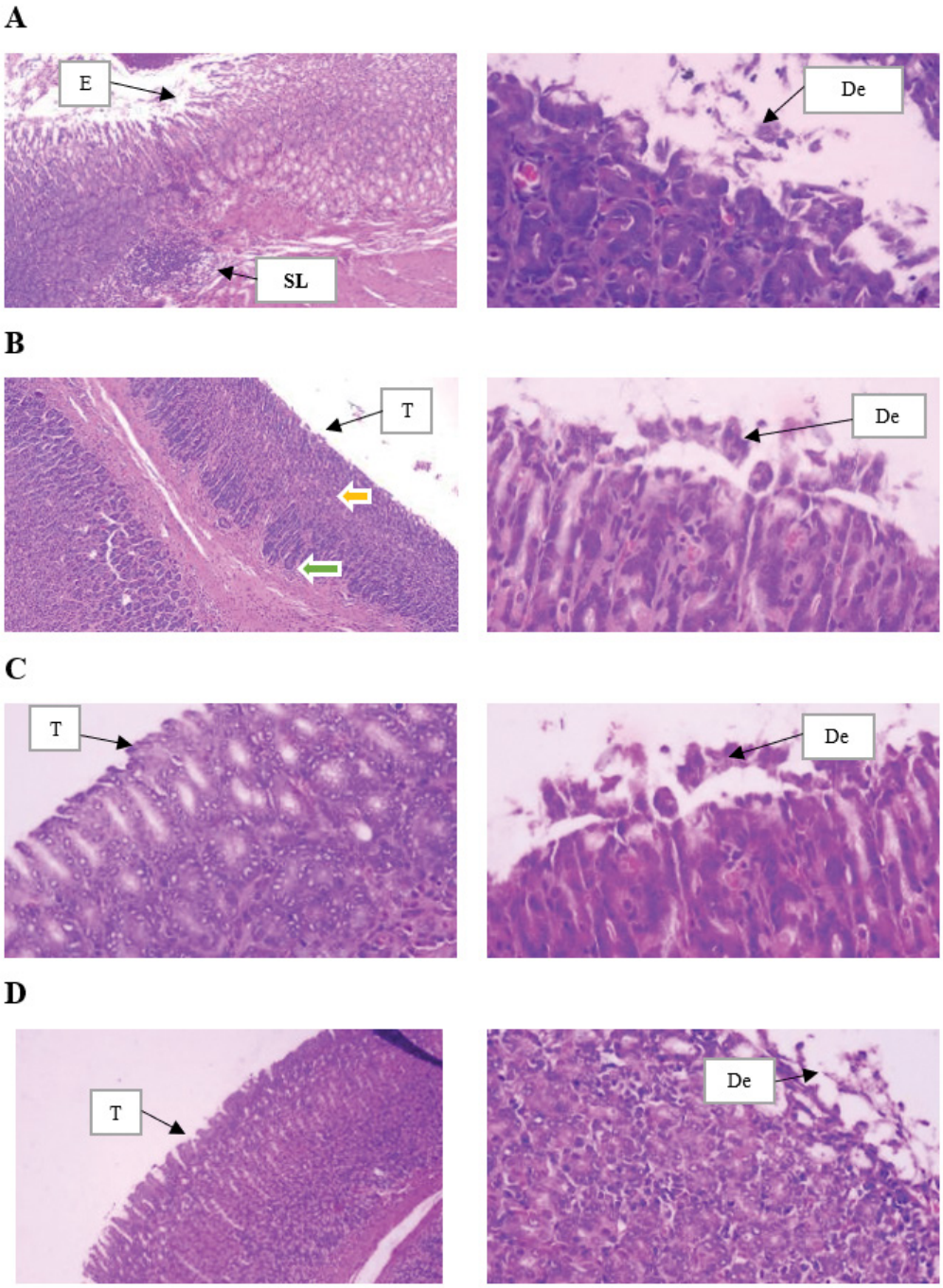

Figure 1. Histological sections of gastric tissues from each experimental group stained with hematoxylin and eosin. (**A**) Negative control Group: E = showing erosion, De = desquamation, and SL = lymphocyte inflammatory cell accumulation. (**B**) Normal control Group: T = no pathological changes found, yellow arrow = parietal cell, green arrow = chief cell, De = desquamation. (**C**) Treatment Group 1 (turmeric extract 100 mg/kgBW): T = not found, De = desquamation. (**D**) Treatment Group 2 (turmeric extract 200 mg/kgBW): T = not found, De = desquamation.

sections were deparaffinized and stained using the Hematoxylin and Eosin (H&E) protocol. Stained sections were examined under a light microscope at 400× magnification to assess gastric mucosal integrity and epithelial changes.

Results

Negative control group examination

The negative control group, which received diclofenac sodium (10 mg/kgBW) without treatment, exhibited the most severe gastric mucosal damage.

All specimens (7/7) demonstrated erosion characterized by partial loss of the gastric mucosa extending into the lamina propria. Desquamation of superficial epithelial cells was observed throughout, accompanied by inflammatory cell infiltration, predominantly lymphocytes, in the submucosal region (Figure 1A).

Normal control group examination

The normal control group, receiving only standard feed and distilled water, showed predominantly intact gastric mucosal architecture. Rats exhibited completely normal histology with well-preserved epithelial lining, intact parietal and chief cells, and no inflammatory infiltration. Minimal desquamation was observed, likely attributable to handling stress or mechanical factors from gavage procedures (Figure 1B).

Treatment group 1 (p1 - 100 mg/kgBW) examination

Rats treated with turmeric extract at 100 mg/kgBW demonstrated marked improvement compared to the negative control group. Rats showed normal gastric histology, exhibited superficial desquamation without progression to erosion or ulceration. Notably, no inflammatory cell infiltration was observed in any specimen from this group, indicating effective gastroprotection (Figure 1C).

Treatment group 2 (p2 - 200 mg/kgBW) examination

The higher dose of turmeric extract (200 mg/kgBW) provided superior gastroprotective effects. Rats displayed completely normal gastric mucosa, showed only minimal desquamation. Similar to P1, no erosion, ulceration, or inflammatory infiltration was detected in any specimen, demonstrating enhanced mucosal protection at this dosage (Figure 1D).

Discussion

The present study demonstrates the gastroprotective efficacy of turmeric extract against diclofenac sodium-induced gastric mucosal injury in rats. Diclofenac sodium exerts its therapeutic effects by inhibiting cyclooxygenase (COX), which exists as two isoenzymes: COX-1 and COX-2. COX-1 is constitutively expressed and involved in the production of prostaglandins that maintain gastric mucosal integrity, while COX-2 is primarily induced during inflammation. The non-selective inhibition of COX-1 leads to decreased prostaglandin synthesis, compromising the gastric mucosal defense mechanisms including mucus secretion, bicarbonate production, and adequate mucosal blood flow [25].

This reduction in prostaglandin levels creates an imbalance that favors reactive oxygen species (ROS) production and subsequent oxidative stress [26]. Elevated ROS can induce cellular damage through multiple pathways: DNA structural alterations, protein oxidation, lipid peroxidation of cellular membranes, and ultimately apoptosis [27]. These cumulative effects manifest as structural changes in the gastric mucosal epithelium, including the erosion and desquamation observed in our negative control group. Prolonged exposure to diclofenac sodium can progress to more severe pathology, including ulceration and perforation.

The negative control group exhibited severe gastric mucosal damage characterized by erosion and inflammatory cell infiltration, confirming the ulcerogenic potential of diclofenac sodium at 10 mg/kgBW for 7 days. This finding is consistent with previous studies demonstrating that diclofenac administration induces gastric mucosal injury through COX-1 inhibition and oxidative stress [10,11]. The presence of submucosal lymphocyte infiltration indicates an inflammatory response to the mucosal injury, representing the body's attempt to initiate tissue repair processes. The erosive changes observed reflect the breakdown of gastric mucosal defensive factors under the sustained toxic effects of diclofenac sodium [28,29].

Interestingly, the normal control group demonstrated minimal desquamation in some specimens despite receiving no ulcerogenic agents. This observation can be attributed to environmental stressors inherent to experimental conditions. Handling stress activates the sympathetic nervous

system and hypothalamic-pituitary-adrenal axis, leading to increased cortisol secretion. Elevated cortisol levels can stimulate parietal cells to increase gastric acid production while simultaneously inhibiting prostaglandin synthesis, thereby reducing mucosal protective mechanisms [30]. Additionally, the mechanical trauma associated with oral gavage procedures may contribute to superficial epithelial cell shedding without affecting deeper mucosal layers [31,32]. These stress-induced changes highlight the importance of proper acclimatization and standardized handling protocols in experimental research.

Both treatment groups (P1 and P2) demonstrated marked improvement in gastric histopathology compared to the negative control group, with the absence of erosion, ulceration, or inflammatory infiltration. Importantly, the desquamation observed in these groups appears mechanistically distinct from that in the negative control group. The lack of inflammatory cell infiltration suggests that the epithelial shedding in treated animals results primarily from mechanical factors (gavage trauma) and handling stress rather than diclofenac-induced toxicity or inflammatory processes.

The dose-dependent protective effect observed between P1 (100 mg/kgBW) and P2 (200 mg/kgBW) indicates that higher concentrations of turmeric extract provide enhanced gastroprotection. This finding aligns with previous research demonstrating gastroprotective properties of turmeric extract at similar doses against other NSAIDs [23,24]. However, it is important to note that acetylsalicylic acid (aspirin) and diclofenac sodium may induce gastric injury through partially different pathophysiological mechanisms, making direct comparisons challenging. While both inhibit COX enzymes, their relative selectivity, pharmacokinetic properties, and additional toxic effects may differ.

The gastroprotective effects of turmeric extract can be attributed to its rich phytochemical composition, particularly curcumin and associated secondary metabolites including flavonoids, alkaloids, saponins, tannins, and steroids. These compounds exert their protective effects through multiple complementary mechanisms.

Curcumin, the primary bioactive component of turmeric, demonstrates potent antioxidant and anti-inflammatory properties. It scavenges ROS directly and enhances endogenous antioxidant enzyme systems, thereby mitigating oxidative stress-induced cellular damage [12]. Curcumin also modulates inflammatory pathways by inhibiting nuclear factor-kappa B (NF-κB) activation and reducing pro-inflammatory cytokine production.

Flavonoids present in turmeric extract contribute to gastroprotection through several mechanisms: increasing mucosal prostaglandin levels, reducing histamine secretion from mast cells, and providing direct antioxidant activity that neutralizes free radicals [33]. These actions help prevent ulcer and erosion formation in the gastrointestinal tract.

The alkaloid content of turmeric inhibits H^+-K^+-ATPase (proton pump) activity in parietal cells, thereby reducing gastric acid secretion while promoting mucus production and increasing gastric pH [22,34]. This dual action creates a more favorable environment for mucosal healing and protection.

Saponins function as gastroprotective agents by activating defensive factors of the gastric mucosa, including enhanced mucus secretion and improved mucosal blood flow. Tannins exert cytoprotective effects on the gastric mucosa through astringent properties that may precipitate surface proteins, forming a protective layer over the mucosa [34].

The synergistic interaction of these phytochemical constituents likely accounts for the comprehensive gastroprotective effects observed in our study, addressing multiple pathological pathways simultaneously.

Our findings support and extend previous research on turmeric's gastroprotective properties. Studies have demonstrated that turmeric extract at doses of 100 and 200 mg/kgBW provides significant protection against NSAID-induced gastric injury [23,24]. However, most previous investigations focused on aspirin-induced gastric damage rather than diclofenac sodium specifically. Given the distinct pharmacological profiles of different NSAIDs, our study provides valuable evidence for turmeric

extract's efficacy specifically against diclofenac-induced gastric injury, which is clinically relevant given diclofenac's widespread use globally.

Several limitations of the current study warrant consideration. First, the sample size of seven rats per group, while statistically adequate based on Federer's formula, is relatively small and may limit the generalizability of findings. Second, the study evaluated gastric histopathology at a single time point following treatment completion. A longitudinal assessment with multiple time points would provide more comprehensive information about the temporal dynamics of gastric injury development and healing processes.

Finally, while histopathological assessment provides valuable structural information, the clinical significance and translatability of these findings to human applications remain uncertain. Interspecies differences in gastric physiology, drug metabolism, and dietary factors must be considered when extrapolating animal study results to clinical practice.

Despite these limitations, our findings suggest that turmeric extract may have potential as an adjunctive gastroprotective agent for patients requiring long-term NSAID therapy. The dose-dependent effect observed indicates that optimization studies are warranted to determine the minimum effective dose and maximum safe dose in both animal models and eventually human subjects.

Future research should address the identified limitations by incorporating larger sample sizes, longitudinal assessments, comprehensive biochemical analyses, and functional gastric measurements. Investigations into the bioavailability of curcumin and strategies to enhance its absorption would be valuable for clinical translation. Additionally, comparative studies directly evaluating turmeric extract against conventional gastroprotective agents would help establish its therapeutic position.

Ultimately, well-designed randomized controlled clinical trials are necessary to establish the efficacy, safety, optimal dosing, and cost-effectiveness of turmeric extract as a gastroprotective agent in humans. Such studies should particularly focus on populations at high risk for NSAID-induced gastropathy, including elderly patients, those with previous peptic ulcer disease, and individuals requiring long-term NSAID therapy for chronic conditions.

Conclusion

Turmeric extract demonstrates gastroprotective effects against diclofenac sodium-induced gastric mucosal injury in rats. The higher dose (200 mg/kgBW) provided better protection than the lower dose (100 mg/kgBW), as evidenced by reduced histopathological damage scores and preservation of mucosal integrity. These findings suggest that turmeric extract may have potential as an adjunctive gastroprotective agent in patients requiring long-term NSAID therapy. However, further dose-optimization studies and clinical trials are needed to establish therapeutic efficacy and safety in humans.

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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

ML, ALSA, RRW, and KL designed the study. ML and RRW collected the data. ML and ALSA analyzed the data. ML and ALSA drafted the manuscript. KL supervised the project. All authors reviewed and approved the final manuscript.

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