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Gastroprotective Effects of *Da Khoi Cot*, A Traditional Vietnamese Polyherbal Decoction, Against Indomethacin-Induced Gastric Ulcer in *Wistar* rats

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ABSTRACT

The effective management of gastric ulcers, particularly those induced by non-steroidal anti-inflammatory drugs (NSAIDs), remains challenging due to the adverse effects and relapse associated with conventional therapies. *Da Khoi Cot* (DKC), a Vietnamese traditional decoction composed of six medicinal herbs, has been used for gastrointestinal disorders, but its efficacy has not been scientifically validated. This study evaluated the gastroprotective effects of DKC in an indomethacin-induced gastric ulcer model in rats. *Wistar* rats were pretreated orally for 7 days with either DKC (24 or 48 mL/kg/day) or misoprostol (50 µg/kg/day). Gastric ulcers were induced by indomethacin (40 mg/kg). Ulcer severity was assessed macroscopically and histopathologically. MDA, GSH in gastric tissue, TNF-α in serum, as well as AST, ALT, creatinine, and urea levels, were evaluated. DKC at 48 mL/kg/day significantly reduced the ulcer index, and both doses significantly reduced the number of gastric lesions compared to the ulcer control group ($p < 0.05$). Histopathological analysis demonstrated significant improvements in mucosal integrity, with reduced inflammation and hemorrhage. The decoction also produced a marked antioxidant effect, significantly decreasing gastric MDA and increasing GSH levels ($p < 0.05$-0.001). DKC pretreatment also considerably suppressed the indomethacin-induced rise in serum TNF-α ($p < 0.01$). No significant alterations in hepatic or renal function markers were observed. DKC exerts significant gastroprotective effects against indomethacin-induced gastric ulceration while maintaining a favorable safety profile. These results provide the first preclinical evidence supporting DKC's potential as an adjunctive therapy for NSAID-associated gastric ulcers.

Keywords: *Da Khoi Cot*, Gastric Ulcer, Herbal Medicine, Indomethacin, Antioxidant, Anti-Inflammation

Introduction

Peptic ulcer disease (PUD), encompassing gastric ulcers (GU) and duodenal ulcers (DU), remains a substantial global health burden with approximately 4 million new cases diagnosed annually worldwide and a lifetime prevalence of 5-10%.[1–4] GU is particularly concerning due to its association with bleeding, perforation, and malignant transformation.[5] GU pathogenesis involves disruption of mucosal defenses by gastric acid, pepsin, oxidative stress, and, critically, *Helicobacter pylori* infection and prolonged NSAID use.[6,7] Indomethacin provokes gastric ulceration by inhibiting prostaglandins and amplifying oxidative and inflammatory damage, making it a well-established experimental model.[8,9] Current PUD management includes *H. pylori* eradication with triple therapy (PPI plus clarithromycin and amoxicillin) or vonoprazan-based regimens,[10,11] and for NSAID-induced ulcers, strategies emphasize NSAID discontinuation, COX-2 inhibitor substitution, or co-prescription of gastroprotectants, such as misoprostol.

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Despite these advances, significant challenges persist: incomplete prevention of recurrence, adherence issues, PPI-associated adverse effects (micronutrient malabsorption, renal disease, infection risk, rebound hypersecretion),[12] limited H_2RA efficacy,[13] escalating antimicrobial resistance undermining *H. pylori* eradication,[14] and persistent mucosal injury risk in NSAID users despite co-therapy. These limitations underscore the need for safer, multi-targeted alternatives, such as herbal medicines that offer pleiotropic activities—antioxidant, anti-inflammatory, antisecretory, cytoprotective, and anti-*H. pylori* effects—with favorable safety profiles.[15–18] Polyherbal formulations are particularly promising, as synergistic phytochemical interactions may enhance gastroprotection while minimizing the side effects of synthetic drugs. *Da Khoi Cot* (DKC) is a Vietnamese traditional polyherbal decoction composed of *Ardisia sylvestris* Pitard, *Radix Paeonia lactiflorae*, *Oldenlandia capitellata* Kuntze, *Amomum aromaticum* Roxb., *Fructus Aurantii immaturus*, and *Sepiae endoconcha.* Individual components demonstrate gastroprotective properties*: Radix Paeonia lactiflorae* and paeoniflorin reduce gastric acid secretion and oxidative injury while enhancing mucosal defenses;[19] *Amomum* species demonstrate anti-ulcer activity regulating gastric acid and inflammatory pathways;[20,21] *Fructus Aurantii immaturus* protects against ethanol- and NSAID-induced damage through mucus stimulation and prostaglandin preservation;[22,23] and *Sepiae endoconcha* provides mucosal protection in indomethacin models.[24]

While individual DKC components show gastroprotective activity, the complete formulation has not been systematically evaluated in standardized preclinical models. This represents a critical knowledge gap, as polyherbal efficacy cannot be predicted from individual

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constituents due to potential synergistic, additive, or antagonistic interactions.[25–28] Furthermore, the complete formulation's safety profile requires systematic assessment. This study evaluated DKC's anti-gastric ulcer effects in an indomethacin-induced model in *Wistar* rats, providing preclinical evidence to support its therapeutic potential as an adjunctive or alternative therapy for NSAID-associated gastric ulcers**.**

Materials and Methods

Plant material

The *Da Khoi Cot* (DKC) decoction used in this study was manufactured by Nam Son Medicine Joint Stock Company, Vietnam. The standardized herbal formulation comprised the following botanical components with their respective quantities per 100 mL of final product: *Ardisiae sylvestris* Pitard (18 g), *Radix Paeoniae lactiflorae* (6 g), *Oledenlandia capitellata* Kuntze (20 g), *Amomum aromaticum* Roxb. (6 g), *Fructus Aurantii immaturus* (8 g), and *Sepiae endoconcha* (12 g). The total weight of raw materials per 100 mL decoction was 70 g. The decoction was prepared using an automatic herbal decoction and packaging machine (KTP-EP-25, Korean). Each batch consisted of 60 doses and was preserved in 100-mL glass bottles under controlled storage conditions: temperature 2–8°C and humidity under 75%. All herbal components were authenticated according to the Vietnamese Pharmacopoeia 5th edition standards.[29] The extract was supplied in liquid form and designed for oral administration.

Experimental animals

Wistar rats of both sexes, weighing 170–230 g, were used for the study. The animals were sourced from the National Institute of Hygiene and Epidemiology in Hanoi, Vietnam, and were acclimated for 7 days prior to the experiment. Animals were maintained under standard laboratory conditions: temperature (22–25°C), humidity (45–65%), and a 12-hour light/dark cycle. They were provided with *ad libitum* access to standard laboratory food and water throughout the study. All animal procedures were conducted at the Laboratory of the Department of Pharmacology, Hanoi Medical University. The study protocol was approved by the Vietnam University of Traditional Medicine's Ethical Review Board (Approval No. 333/QD-HVYDCT, dated January 23, 2025) and was conducted in strict accordance with institutional ethical guidelines.

Experiment design

The anti-ulcerogenic effect of the liquid polyherbal extract DKC was evaluated in a rat model of indomethacin-induced gastric ulcer at a dose of 40 mg/kg.[30–32]

Rats were randomly divided into five groups (n = 10 per group) with an equal male-to-female ratio to minimize sex-related variability. The rats in each group received either the test extract or distilled water orally (via gavage) for 7 consecutive days, as follows: Group 1 (Normal control): distilled water 10 mL/kg b.w./day, Group 2 (Ulcer control): distilled water 10 mL/kg b.w./day, Group 3 (Reference control): misoprostol 50 µg/kg b.w./day, Group 4: DKC 24 mL/kg b.w./day, and Group 5: DKC 48 mL/kg b.w./day.

The selected doses were based on the DKC safety profile from previous toxicity studies, the recommended dosage for each herb in the Vietnamese Pharmacopeia 5th edition guidelines, and traditional medicinal usage.[29]

Animals were fasted for 18 hours (with free access to water) prior to indomethacin administration to standardize gastric conditions. One hour after the final pretreatment dose, rats in groups 2–5 were given a single oral dose of indomethacin (40 mg/kg). Six hours following indomethacin administration, the animals were euthanized by pentobarbital (20 mg/kg, i.p.) for evaluation of study parameters. All animals were coded, and investigators were blinded to group allocation to minimize bias.

Blood sample analysis

Blood samples were collected via cardiac puncture immediately after sacrifice. Serum was separated by centrifugation at 3,000 rpm for 10 minutes at 4°C and used for the determination of alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and urea levels using a semi-automatic biochemical analyzer (Erba Chem 5 V3, Germany).

The concentrations of tumor necrosis factor-alpha (TNF-α) were determined using commercial sandwich enzyme-linked immunosorbent assay (ELISA) kits (Cloud-Clone Corp., USA; Catalog numbers: SEA133Ra). The assays were performed following the manufacturer's protocol, and absorbance was read immediately at 450 nm using a microplate reader (BioTek, USA). Concentrations were determined from standard curves generated for each assay.[33]

Tissue homogenate analyses

For oxidative stress parameters, gastric tissue homogenates were prepared by excising a 100-mg portion of the stomach, rinsing it with ice-cold saline, and homogenizing it in ice-cold phosphate-buffered saline (PBS, pH 7.4) at 10% w/v using a tissue homogenizer. The homogenate was centrifuged at 10,000 rpm for 15 minutes at 4°C, and the supernatant was used for assays.

Malondialdehyde (MDA) levels, as a marker of lipid peroxidation, were determined using a high-performance liquid chromatography system (Shimadzu, Japan) with visible detection at 532 nm, following the method of Grotto et al..[34] Briefly, 500 µL of the supernatant was deproteinized with 500 µL of trichloroacetic acid 10% w/v, centrifuged, and 100 µL of the resulting supernatant was reacted with 125 µl of H_3PO_4 6% and 125 µl of thiobarbituric acid 0.8% (Sigma-Aldrich Chemicals Pvt. Ltd., USA). Results were expressed as nmol MDA/100 mg tissue, using a standard curve prepared with malondialdehyde bis (dimethylacetal) (Sigma-Aldrich Chemicals Pvt. Ltd., USA).

Reduced glutathione (GSH) levels were measured using a high-performance liquid chromatography system (Shimadzu, Japan) with C18 columns and derivatization with Ellman's reagent (DTNB) (Sigma-Aldrich Chemicals Pvt. Ltd., USA), following the method of Garcia et al.[35] Briefly, 500 µL of the supernatant was deproteinized with 500 µL of trichloroacetic acid 10% w/v, centrifuged, and the resulting supernatant was reacted with DTNB in phosphate buffer (pH 8.0). Absorbance was measured at 330 nm, and results were expressed as µg GSH/100 mg tissue, using a standard curve prepared with GSH (Sigma-Aldrich Chemicals Pvt. Ltd., USA).

Macroscopic evaluation

Rats were sacrificed by laparotomy under anesthesia, and the stomach and duodenum were exposed. The gastrointestinal tract from the esophagus (adjacent to the cardia) to the proximal small intestine (3 cm distal to the pylorus) was excised. The stomach and duodenum were opened along the greater curvature using scissors, rinsed with 0.9% sodium chloride solution, and the ulcerated surface was gently blotted with filter paper to remove excess fluid. The specimens were fixed on a foam board with pins, and the gastric mucosa was examined under a 10× magnifying lens. The ulcer index (UI) was determined based on the severity of gastric ulceration, scored according to the scale described by Raish et al. (2021),[36] as shown in Table 1. To ensure precision and minimize error, assessment and scoring of the lesions in the coded samples were conducted by a single investigator. To mitigate the risk of measurement bias, the outcome assessor was blinded to the group allocations. The percentage of ulcer inhibition was calculated using the following formula:

$$\% \text{ Ulcer Inhibition} = \frac{(\text{UI in control} - \text{UI in test}) \times 100}{\text{UI in control}}$$

Histopathological evaluation

A section of the gastric tissue from the glandular region was fixed in 10% neutral buffered formalin for 24 hours. The tissues were then processed routinely, embedded in paraffin, sectioned at 5 µm thickness, and stained with Hematoxylin and Eosin (H&E). The stained sections were examined under a light microscope by a pathologist unaware of the group allocations. Histological changes were evaluated using the scoring system by Simões et al.,[37] which assesses five parameters on a scale of 0-3: depth of the erosion, depth of ulcer lesion, hemorrhage, inflammation, and apoptosis.

Phytochemical characterization

The total phenolic content of the DKC decoction was determined using the Folin-Ciocalteu method,[38] and was found to be 4.75 ± 0.04 mg of

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gallic acid equivalents per mL. The total flavonoid content, quantified via the Dowd method,[39] was 74.65 ± 1.43 µg of quercetin equivalents per mL. Values represent the mean ± standard deviation (SD) of five independent replicates.

Table 1: Macroscopic scoring criteria according to the scale of Raish M *et al.*[36]

Description of gastric mucosa	Score
Normal stomach	0
Red coloration	0.5
Hemorrhagic spots	1
1-5 small ulcers	2
Many small ulcers	3
Many small and large ulcers	4
Stomach full of ulcers with perforations	5

Statistical analysis

All data are expressed as the mean ± standard deviation (SD). Statistical analysis was performed using SPSS software (Version 26.0). Multiple groups were compared by one-way analysis of variance (ANOVA) followed by Tukey's post-hoc comparisons tests for parametric data. For histological grading, nonparametric tests (Mann-Whitney U test) were used. A p-value of less than 0.05 was considered statistically significant.

Results and Discussion

The present study provides the first systematic preclinical evaluation of the Vietnamese traditional decoction *Da Khoi Cot* (DKC) for its gastroprotective effects in an indomethacin-induced gastric ulcer model in rats. The findings demonstrate that oral pre-treatment with DKC confers significant, dose-dependent protection against indomethacin-induced gastric injury. This was evidenced by a marked reduction in the number of gastric lesions, improved histopathological scores, and a restoration of the gastric antioxidant balance. Importantly, these therapeutic effects were achieved without any detectable signs of hepatic or renal toxicity, highlighting a favorable safety profile.

The gastroprotective effects of the DKC decoction against indomethacin-induced gastric ulcers were evaluated through macroscopic, histopathological, blood, and gastric homogenate analyses.

Effect of DKC on macroscopic gastric lesions

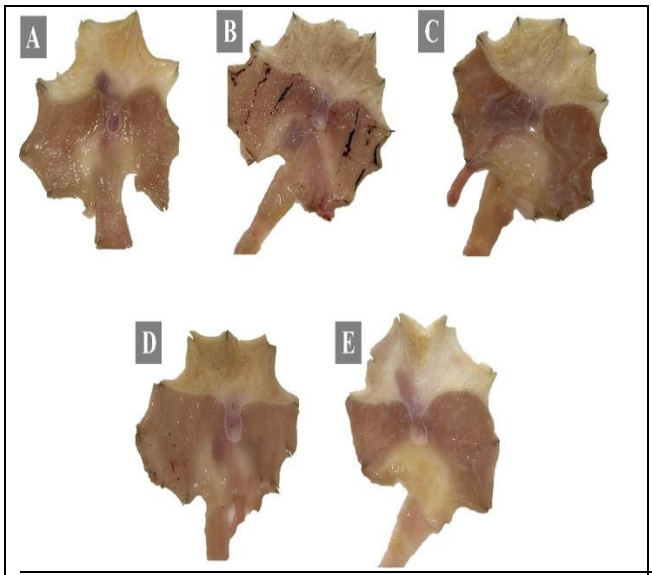
Pretreatment with DKC demonstrated a protective effect on the gastric mucosa, as evidenced by macroscopic examination. The ulcer control group exhibited a 100% ulcer incidence with a mean ulcer index (UI) of 4.00. Administration of DKC at 24 mL/kg/day and 48 mL/kg/day reduced the UI to 3.40 ± 1.26 and 3.10 ± 1.29, respectively. Although these reductions represented inhibition rates of 15.0% and 22.5%, they did not reach statistical significance compared to the ulcer control group ($p > 0.05$). (Figures 1 and 2)

A more sensitive measure of mucosal damage, the number of individual lesions, showed significant improvements with DKC treatment. The ulcer control group had a mean of 23.20 ± 8.57 lesions. Both doses of DKC also produced significant reductions: the number of lesions decreased to 15.00 ± 6.57 in the low-dose group ($p < 0.05$) and to 11.80 ± 8.43 in the high-dose group ($p < 0.01$). (Figure 1)

Representative macroscopic images visually corroborated these findings. The normal control group showed intact gastric mucosa, while the ulcer control group displayed numerous hemorrhagic spots and ulcers. The misoprostol and DKC-treated groups showed a clear, dose-dependent reduction in the severity and number of these lesions. (Figure 1)

Experimental gastric ulcer models are indispensable for investigating disease pathogenesis and evaluating novel therapeutic agents.[40,41] The indomethacin-induced ulcer model is particularly relevant as it closely mimics the key pathophysiological mechanisms of NSAID-induced gastropathy in humans, primarily through the inhibition of prostaglandin synthesis and the induction of oxidative stress and inflammation.[42,43] The dose of 40 mg/kg used in the present study has been well-established in numerous previous investigations and consistently produces severe gastric ulceration within 6 hours, making it an appropriate model for testing gastroprotective interventions.[30,44,45] The 100% ulcer incidence observed in our untreated model group confirms the reliability and reproducibility of this model.

Our macroscopic evaluation revealed an interesting discrepancy between the ulcer index scoring and the quantitative lesion count. While the ulcer index showed only numerical reductions with DKC treatment without reaching statistical significance (15.0% and 22.5% inhibition at 24 and 48 mL/kg, respectively), the quantitative lesion count demonstrated statistically significant dose-dependent reductions (35.3% and 49.1% reduction, $p < 0.05$ and $p < 0.01$, respectively). This apparent discrepancy can be explained by the inherent limitations of categorical scoring systems such as the ulcer index. The Raish scoring system assigns the same categorical score to stomachs with different numbers of ulcers within a given severity range.[36] For example, a stomach with one large ulcer and a stomach with multiple large ulcers may both receive a score of 4 ("many small and large ulcers"). This ceiling effect reduces the sensitivity of the ulcer index to detect moderate improvements in lesion number, particularly when severe ulceration is present.



Group (*n = 10*)	Red coloration	Hemorrhagic spots	Small ulcers	Large ulcers	Nu les
Ulcer control	0.1 ± 0.32	4.5 ± 4.36	13.1 ± 7.55	5.1 ± 4.18	23.
Misoprostol (50 µg/kg)	0.1 ± 0.32	1.2 ± 2.83	2.9 ± 3*	0.9 ± 1.38*	5.1
DKC decoction (24 mL/kg)	0.3 ± 0.49	1.1 ± 3.48	9 ± 5.93	4.6 ± 3.21	15.
DKC decoction (48 mL/kg)	0.2 ± 0.43*	0.2 ± 0.43	8.5 ± 6.23	2.9 ± 2.97	11.

Figure 1: Macroscopic evaluation of gastroprotective effects of DKC decoction against indomethacin-induced gastric ulcers. (A-E) Representative photographs of excised rat stomachs from each experimental group. (A) Normal control, (B) Ulcer control (Indomethacin 40 mg/kg), (C) Misoprostol (50 µg/kg), (D) DKC (24 mL/kg), (E) DKC (48 mL/kg). The ulcer control group (B) shows extensive hemorrhagic streaks and lesions, which are reduced in the treatment groups (C-E). Data are expressed as mean ± SD (n=10). *, **, *** *compared to the ulcer control group ($p < 0.05$, $p < 0.01$, and $p < 0.001$).*

Effect of DKC on histopathological examination

Microscopic examination of the gastric tissue provided further evidence of DKC's gastroprotective effects. The untreated ulcer model group displayed severe histopathological alterations, including deep mucosal erosion, extensive epithelial cell loss, submucosal edema, and significant inflammatory cell infiltration. (Figure 3)

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In contrast, the groups pre-treated with DKC showed considerable improvement. The 24 mL/kg DKC group exhibited mild mucosal erosion limited to the upper one-third of the epithelium with very mild inflammatory infiltration. The 48 mL/kg DKC group also showed moderate erosion, but with only mild inflammation and scattered lymphocytes. The misoprostol-treated group showed the best protection, with only minimal signs of lymphocytic infiltration in the lamina propria. (Figure 3)

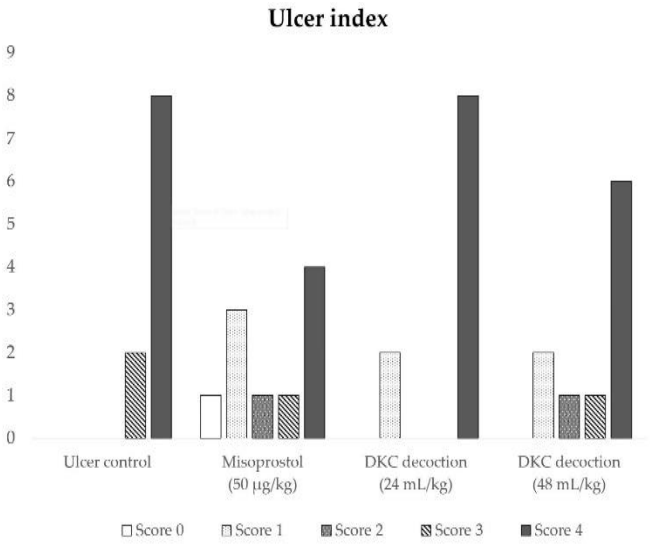

Figure 2: Distribution of ulcer index scores across experimental groups. The chart displays the frequency distribution of ulcer index scores (0–4) for individual animals in each treatment group (n = 10 per group). Score 0 = normal stomach; Score 1 = red coloration or hemorrhagic spots; Score 2 = 1–5 small ulcers; Score 3 = many small ulcers; Score 4 = many small and large ulcers. No animals in any group exhibited Score 5 (stomach full of ulcers with perforations).

Histopathological scoring quantified these observations. While the reduction in the depth of erosion and ulcerative lesions by DKC was not statistically significant ($p > 0.05$) (Figures 4A-B), both doses of DKC (24 and 48 mL/kg) and misoprostol significantly reduced the proportion of gastric samples with grade 2 inflammatory and hemorrhagic lesions compared to the ulcer model group ($p < 0.05$ and $p < 0.01$, respectively) (Figures 4C-D). No sample showed apoptotic injuries.

Microscopic examination provided detailed insights into the cellular and tissue-level protective effects of DKC. The most striking findings were the significant reductions in hemorrhagic lesions and inflammatory cell infiltration in DKC-treated groups. These histopathological improvements are clinically relevant because hemorrhage and inflammation are key indicators of acute mucosal injury and correlate with the risk of serious complications such as gastrointestinal bleeding and perforation.[46,47] The ability of DKC to reduce hemorrhage suggests that it preserves microvascular integrity and prevents the vascular disruption that typically accompanies NSAID-induced injury.[41] The anti-inflammatory effects indicate that DKC modulates the inflammatory cascade triggered by indomethacin, thereby limiting secondary tissue damage from inflammatory mediators and infiltrating leukocytes. Interestingly, while DKC significantly improved hemorrhage and inflammation scores, the reductions in erosion depth and ulcer depth did not reach statistical significance. This pattern suggests that DKC's primary protective mechanisms involve modulation of inflammatory responses and vascular protection rather than complete prevention of initial epithelial disruption. This is consistent with the antioxidant and anti-inflammatory properties of the individual herbal components, which would be expected to primarily target secondary injury mechanisms (inflammation, oxidative stress) rather than the direct prostaglandin-depletion effects of indomethacin. The decoction reduces aggressive factors in the gastric environment. Constituents such as *Amomum aromaticum* and *Citrus aurantium* have been shown to inhibit gastric acid secretion and pepsin activity while maintaining prostaglandin synthesis, thus diminishing acid- and enzyme-mediated mucosal injury, which is one of the primary targets in peptic ulcer therapy.[21–23] *Sepiae endoconcha* further promotes epithelial restitution, contributing to the preservation and repair of the gastric mucosal barrier—another central therapeutic target in gastritis and peptic ulcer management.[24] *Ardisia sylvestris* Pitard supplies flavonoids, tannins, and other phenolic compounds with documented antioxidant and antimicrobial activities, which may further reduce oxidative stress and microbial challenge. These factors are known to aggravate gastritis and peptic ulcer pathology.[49] This dose-dependent protective effect is also consistent with previous research demonstrating that multi-component herbal formulations often exert their therapeutic actions through complementary and synergistic mechanisms.[15,25–27]

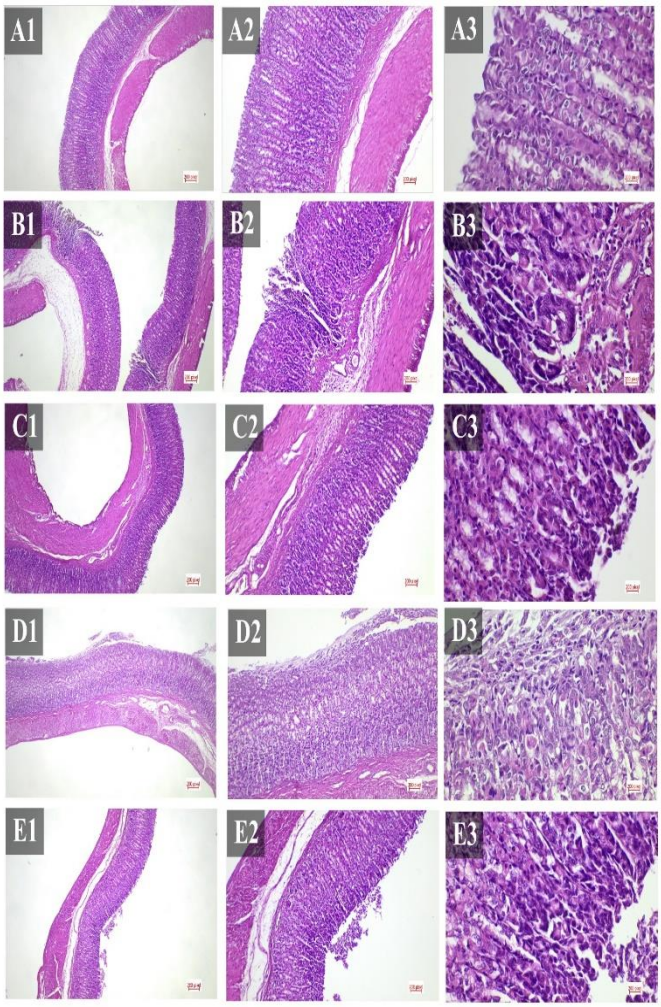

Figure 3: Histological analysis of gastric tissue in the indomethacin-induced ulcer model. Hematoxylin and eosin (H&E)-stained gastric tissue sections at three magnifications: 40× (panels 1), 100× (panels 2), and 400× (panels 3). **(A1–A3)** Normal control—preserved mucosal architecture with intact epithelium, normal glandular structures, and no inflammatory infiltration. **(B1–B3)** Ulcer control—severe pathological alterations including deep mucosal erosion extending into the submucosa, extensive epithelial cell loss, marked submucosal edema, hemorrhage, and dense inflammatory cell infiltration. **(C1–C3)** Misoprostol (50 µg/kg)—well-preserved mucosal integrity with minimal erosion and only slight lymphocytic infiltration in the lamina propria. **(D1–D3)** DKC decoction (24 mL/kg)—mild mucosal erosion limited to the superficial epithelium with minimal inflammatory infiltration. **(E1–E3)** DKC decoction (48 mL/kg)—moderate improvement in mucosal architecture with reduced erosion depth and mild scattered lymphocytic infiltration.

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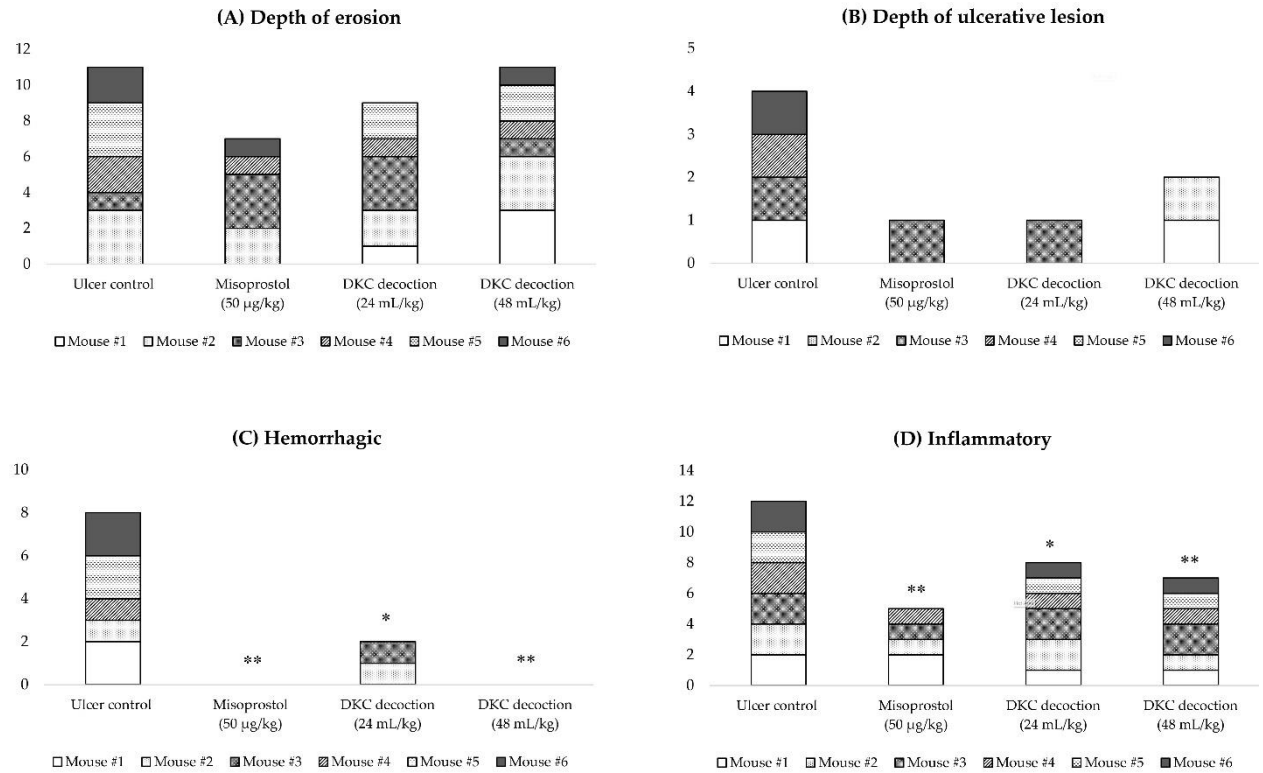

Figure 4: Quantitative histopathological scoring of gastric mucosal injury. Microscopic evaluation of gastric tissue damage in indomethacin-induced peptic ulcers following pretreatment with DKC decoction or misoprostol. Histological parameters were scored according to the system of Simões et al. (2019) on a scale of 0–3: (A) Depth of erosion score; (B) Depth of ulcerative lesion score; (C) Hemorrhage score; (D) Inflammation score. Data are presented as individual values (n = 10 per group). The normal control group exhibited a score of 0 for all parameters in all animals. *, ** *compared to the ulcer control group ($p < 0.05$, $p < 0.01$).*

Effect of DKC on oxidative stress and proinflammatory markers

The gastroprotective mechanism of DKC was further investigated by assessing oxidative stress in gastric tissue and systemic inflammation via serum analysis. Induction of ulcers with indomethacin significantly increased lipid peroxidation in the gastric mucosa, as indicated by elevated MDA levels, and depleted the key antioxidant, GSH, in the ulcer control group compared to the normal control ($p < 0.05$). Pretreatment with DKC effectively reversed this oxidative imbalance. Both the low (24 mL/kg/day) and high (48 mL/kg/day) doses of DKC significantly decreased MDA levels ($p < 0.05$ and $p < 0.001$, respectively) and significantly increased GSH levels ($p < 0.05$ and $p < 0.001$, respectively) compared to the ulcer control group. The effect of the high dose was particularly pronounced. (Figure 5A-B)

Concurrently, the systemic inflammatory response was assessed by measuring the level of the proinflammatory cytokine TNF-α in serum. A remarkable increase in serum TNF-α was observed in the ulcer control group compared to the normal control ($p < 0.001$). This inflammatory cascade was significantly mitigated by pretreatment; the misoprostol group showed a highly significant reduction in TNF-α ($p < 0.001$), and both the low and high doses of DKC also produced significant decreases compared to the ulcer control ($p < 0.01$). (Figure 5C)

Oxidative stress is a hallmark of NSAID-induced ulcerogenesis, where indomethacin suppresses prostaglandins, leading to reactive oxygen species (ROS) overproduction, lipid peroxidation, and depletion of endogenous antioxidants. In our model, the ulcer control group showed significantly elevated gastric MDA and reduced GSH compared to normal controls. DKC pretreatment reversed these changes: the 24 mL/kg b.w./day dose significantly lowered MDA and raised GSH ($p < 0.05$), while the 48 mL/kg b.w./day dose produced more robust effects ($p < 0.001$). This dose-dependent redox modulation highlights antioxidative activity as a primary gastroprotective mechanism, consistent with evidence that phytochemical-rich extracts mitigate NSAID-induced mucosal injury by scavenging ROS and bolstering antioxidant defenses.[16,19] Individual DKC components contribute to the antioxidative activity of the decoction. *Ardisia sylvestris* Pitard contains flavonoids, tannins, coumarins, and anthraquinones, exhibiting strong 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging.[49] *Radix Paeonia lactiflorae* (via paeoniflorin) upregulates heat shock protein-70 (HSP-70), reduces oxidative injury, enhances mucosal defenses, and provides gastroprotective effects against various ulcerogens, including HCl/ethanol, immersion stress, and NSAIDs models.[19,50]

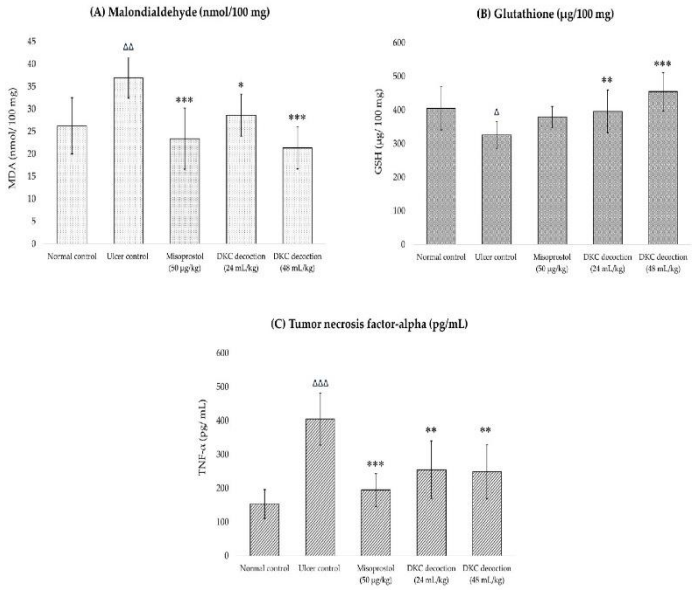

Figure 5: Effects of DKC decoction on oxidative stress and proinflammatory markers in gastric tissue and serum. Biochemical assessment of gastroprotective mechanisms following

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pretreatment with DKC decoction or misoprostol in the indomethacin-induced gastric ulcer model. (A) Malondialdehyde (MDA) levels in gastric tissue homogenates—a marker of lipid peroxidation and oxidative damage. (B) Reduced glutathione (GSH) levels in gastric tissue homogenates—an indicator of endogenous antioxidant capacity. (C) Serum tumor necrosis factor-alpha (TNF-α) concentrations—a marker of systemic inflammatory response. Data are expressed as mean ± SD (n = 8 per group). $^{\Delta}$, $^{\Delta\Delta}$, $^{\Delta\Delta\Delta}$ *compared to the normal control group (p < 0.05, p < 0.01, and p < 0.001); *, **, *** compared to the ulcer control group (p < 0.05, p < 0.01, and p < 0.001).*

The standardized formulation HT074 (combining *Paeonia* with *Inula britannica*) similarly decreases MDA, boosts GSH, and preserves mucosal integrity in NSAID-induced ulcers.[19] *Oldenlandia capitellata* ethanol extract lowers MDA and H_2O_2, while elevating GSH, total antioxidant capacity, superoxide dismutase (SOD), catalase, and glutathione peroxidase in indomethacin models.[51] Essential oils from *Amomum aromaticum* Roxb. attenuate oxidative stress via PI3K/AKT pathway modulation.[21] *Fructus Aurantii immaturus* (and d-limonene) shows antioxidant effects in ethanol- and NSAID-lesions.[22,23] Finally, *Sepiae endoconcha* decreases MDA, enhances SOD, and elevates prostaglandin E_2 and epidermal growth factor, promoting restitution.[24] These collective actions explain DKC's potent antioxidant profile.

Inflammation also exacerbates NSAID-induced gastric damage, with proinflammatory cytokines like TNF-α playing a pivotal role.[52,53] Indomethacin triggers TNF-α release, which promotes neutrophil infiltration, endothelial dysfunction, and amplified ROS production, culminating in mucosal erosion and ulceration.[54] In our study, serum TNF-α levels surged in the ulcer control group compared to normal controls, reflecting systemic inflammation. Pretreatment with DKC significantly attenuated this: both doses reduced TNF-α, with effects comparable to misoprostol. This suggests DKC's anti-inflammatory activity contributes to its gastroprotection, potentially by interrupting the TNF-α-neutrophil axis observed in indomethacin models. DKC's components likely mediate this via nuclear factor-kappa B (NF-κB) inhibition, a key regulator of TNF-α expression.[55] *Radix Paeonia lactiflorae* suppresses NF-κB and cyclooxygenase-2 (COX-2), reducing cytokine release in ulcer models.[19,50] *Oldenlandia capitellata* modulates immunity by lowering white blood cell counts and improving phagocytic indices, while directly decreasing TNF-α in gastric inflammation.[51] Future studies should explore DKC's effects on downstream mediators (e.g., interleukin-6 [IL-6]) to fully delineate its anti-inflammatory cascade.

These data suggest that *DKC* acts simultaneously on multiple key pathogenic mechanisms of GU, thereby exerting complementary and potentially synergistic pharmacodynamic effects. This multi-target pharmacological profile, which includes the reduction of aggressive factors, enhancement of mucosal defence mechanisms, modulation of inflammatory responses and oxidative stress, and support of epithelial regeneration, is directed at the key therapeutic targets in gastritis and peptic ulcer disease. This integrated mechanism may explain the dose-dependent biochemical and histological improvements observed in the present study.

Assessment of hepatic and renal safety profile

The ulcer control group showed a significant increase in AST and ALT activities compared to the normal control ($p < 0.001$ and $p < 0.05$, respectively), likely reflecting systemic stress from severe ulceration. Crucially, treatment with either dose of DKC did not produce any significant changes in serum AST, ALT, creatinine, or urea levels compared to the ulcer control group ($p > 0.05$). This indicates that the DKC decoction, at the tested doses, did not induce detectable acute hepatotoxicity or nephrotoxicity. (Table 2)

Table 2: Effects of DKC on biochemical markers of liver and kidney function

Treatment *(n = 10)*	AST *(IU/L)*	ALT *(IU/L)*	Creatinine *(mg/dL)*	Urea *(mmol/L)*
Normal control	90 ± 12.12	50.5 ± 9.09	4.47 ± 0.88	58.7 ± 5.68
Ulcer control	127.5 ± 13.01$^{\Delta\Delta\Delta}$	68 ± 10.33 $^{\Delta}$	4.91 ± 0.96	65.5 ± 9.79
Misoprostol (50 µg/kg)	108 ± 13.98	57 ± 10.33	4.74 ± 1	62 ± 9.37
DKC decoction (24 mL/kg)	113.1 ± 23.22	66.7 ± 13.54 $^{\Delta}$	4.74 ± 1.51	64.5 ± 4.36
DKC decoction *(4*8 mL/kg)	120.2 ± 24.87 $^{\Delta\Delta}$	65.7 ± 16.9	5.01 ± 1.21	65 ± 8.24

Data are presented as mean ± SD (n=10). AST: aspartate aminotransferase; ALT: alanine aminotransferase.
$^{\Delta}$, $^{\Delta\Delta}$, $^{\Delta\Delta\Delta}$ compared to the normal control group ($p < 0.05$, $p < 0.01$, and $p < 0.001$)

Safety is paramount for herbal therapies, especially those intended as adjuncts to NSAIDs. In our model, indomethacin significantly elevated serum AST and ALT levels, indicating hepatic stress resulting from systemic inflammation. The DKC decoction at both doses caused no significant changes in AST, ALT, creatinine, or urea compared to controls ($p > 0.05$), confirming the absence of acute hepato- or nephrotoxicity. This profile contrasts with some synthetic agents, which may induce organ damage with prolonged use.[18]

From a clinical perspective, NSAID-associated GU remains a major therapeutic challenge, particularly in elderly patients and in those with chronic inflammatory conditions requiring long-term NSAID therapy. Conventional prophylactic agents such as PPIs and misoprostol are effective but limited by adverse effects, including diarrhea, electrolyte imbalance, infectious complications, and rebound acid hypersecretion, as well as incomplete prevention of relapse.[11,14] In this context, a multi-component herbal–marine formulation such as DKC, with demonstrated gastric protective effects and a favorable safety profile, may represent a valuable adjunctive or supportive strategy. Potential clinical applications include prophylaxis in high-risk populations, adjuvant therapy to reduce the required dosage of standard drugs and mitigate their side effects, or an alternative option for patients who are intolerant to conventional therapies.

Several limitations of the present study should be acknowledged. First, the specific phytochemicals responsible for the observed effects were not isolated or quantified, which precludes definitive conclusions about concentration-effect relationships. Future studies should focus on bioassay-guided fractionation to identify the lead active compounds. Second, this study utilized only the indomethacin-induced ulcer model. To validate the broad-spectrum efficacy of DKC, its effects should be investigated in other models, such as those induced by ethanol, stress, or *H. pylori* infection. Finally, the short duration of the study limits conclusions about long-term efficacy and potential chronic toxicity. Longer-term studies are warranted to confirm its safety for chronic use. Future research should also include pharmacokinetic and pharmacodynamic studies to better understand the absorption, distribution, and metabolism of DKC, followed by well-designed clinical trials to confirm its efficacy and safety in humans.

In summary, this study provides the first systematic preclinical evidence that DKC decoction exerts significant gastroprotective effects against indomethacin-induced gastric ulceration. Its efficacy is mediated through a combination of antioxidant and anti-inflammatory mechanisms, including the marked suppression of TNF-α, while

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maintaining a favorable hepatic and renal safety profile. These findings offer a robust pharmacological rationale for further research, including the isolation of active compounds, pharmacokinetic studies, validation in multiple ulcer models, and well-designed clinical trials.

Conclusion

The *Da Khoi Cot* (DKC) decoction demonstrated statistically significant gastroprotective effects against indomethacin-induced gastric ulceration in *Wistar* rats, primarily through antioxidant mechanisms (reduced MDA and elevated GSH) and anti-inflammatory actions (including TNF-α suppression). Both tested doses (24 and 48 mL/kg b.w./day) improved macroscopic and histopathological outcomes, with the higher dose showing superior reductions in ulcer index, lesion count, inflammation, and hemorrhage, while maintaining a favorable hepatic and renal safety profile. These findings provide the first systematic preclinical evidence supporting DKC's potential as an adjunctive therapy for indomethacin-associated gastric ulcers, warranting further phytochemical isolation, pharmacokinetic studies, and clinical validation.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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