Research Article

Gastroprotective Effect of the Aqueous Fraction of *Tamarindus indica* L. Leaves Against Aspirin-Induced Gastric Injury in Mice

Efek Gastroprotektif Fraksi Air Daun Asam Jawa (*Tamarindus indica* L.) terhadap Cedera Lambung pada Mencit yang Diinduksi Aspirin

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ABSTRACT

Tamarindus indica L. leaves contain bioactive compounds, particularly tannins and saponins, which may contribute to gastric mucosal protection. This study aimed to evaluate the gastroprotective effect of the aqueous fraction of *T. indica* leaves in aspirin-induced gastric injury in mice. Twelve mice were randomly divided into four groups (n = 3): normal control, negative control, and two treatment groups receiving the aqueous fraction at doses of 6 mg/30 g and 12 mg/30 g body weight prior to aspirin induction. Gastroprotective activity was assessed through macroscopic observation and histopathological examination of gastric tissues. Aspirin administration caused gastric mucosal injury characterized by erosion, ulceration, and hemorrhage. Treatment with the aqueous fraction reduced gastric damage and improved epithelial integrity. The dose of 12 mg/30 g body weight showed the most pronounced protective effect. These findings suggest that the aqueous fraction of *T. indica* leaves has potential gastroprotective activity.

ABSTRAK

Daun asam jawa (*Tamarindus indica* L.) mengandung senyawa bioaktif, terutama tanin dan saponin, yang berpotensi melindungi mukosa lambung. Penelitian ini bertujuan mengevaluasi efek gastroprotektif fraksi air daun asam jawa pada cedera lambung yang diinduksi aspirin pada mencit. Dua belas mencit dibagi secara acak ke dalam empat kelompok (n = 3), yaitu kontrol normal, kontrol negatif, serta dua kelompok perlakuan yang menerima fraksi air dengan dosis 6 mg/30 g dan 12 mg/30 g berat badan sebelum induksi aspirin. Aktivitas gastroprotektif dinilai melalui pengamatan makroskopik dan pemeriksaan histopatologi jaringan lambung. Pemberian aspirin menyebabkan kerusakan mukosa lambung yang ditandai dengan erosi, ulkus, dan hemoragi. Pemberian fraksi air menurunkan tingkat kerusakan mukosa dan memperbaiki integritas epitel. Dosis 12 mg/30 g berat badan menunjukkan efek protektif paling kuat. Hasil ini menunjukkan bahwa fraksi air daun asam jawa berpotensi sebagai agen gastroprotektif alami.

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1. INTRODUCTION

Gastrointestinal disorders, particularly those involving the stomach, remain common health problems in many populations. One of the most frequently reported conditions is peptic ulcer disease, which occurs when the balance between aggressive factors—such as gastric acid, pepsin, and certain medications—and the protective mechanisms of the gastric mucosa is disrupted. Among these factors, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been widely associated with gastric mucosal injury. Aspirin, one of the most commonly used NSAIDs, can impair mucosal defense primarily through inhibition of prostaglandin synthesis. Prostaglandins play an important role in maintaining gastric mucosal integrity by regulating mucosal blood flow, mucus secretion, and bicarbonate production (Kvietys et al., 2014). Consequently, prolonged or excessive use of aspirin may increase the risk of gastric mucosal damage. Because of this effect, aspirin is frequently employed as an inducer of gastric injury in experimental studies investigating gastroprotective agents (Santoso, 2017).

In recent years, increasing attention has been directed toward the exploration of plant-derived compounds as potential gastroprotective agents. This interest is partly driven by the need to identify alternatives that may reduce the adverse effects associated with long-term use of synthetic drugs. Tamarind (*Tamarindus indica* L.) is a plant that has long been used in traditional medicine and has been reported to possess various pharmacological properties. Previous studies have indicated that different parts of *T. indica* contain bioactive compounds with potential anti-ulcer activity (Karmana, 2024; Kumar et al., 2011). In particular, methanolic extract of *T. indica* seeds has shown antiulcer effects in experimental models, supporting the pharmacological potential of this plant (Kumar et al., 2011). Tannins, for example, are known to interact with proteins on the mucosal surface, forming a protective layer that may help reduce the penetration of irritant substances and limit gastric acid exposure (Kumar et al., 2011; Raja et al., 2008).

Although these findings suggest the potential of *T. indica* leaves in gastric protection, studies specifically evaluating the biological activity of individual fractions of the extract remain limited. Fractionation can help concentrate certain groups of compounds and may allow a clearer assessment of their pharmacological effects. The aqueous fraction, in particular, is expected to contain polar compounds such as tannins and saponins that may contribute to mucosal protection. Therefore, further investigation is needed to evaluate the gastroprotective effect of this fraction using an experimental model of gastric injury.

Based on these considerations, the present study aimed to evaluate the gastroprotective potential of the aqueous fraction of *T. indica* leaves against aspirin-induced gastric mucosal injury in mice (*Mus musculus*). The gastroprotective activity of the fraction was assessed through macroscopic observation and histopathological examination of gastric tissues in mice. The findings of this study are expected to provide additional evidence regarding the potential role of *T. indica* leaves as a source of plant-derived gastroprotective agents.

2. METHODS

2.1. Instruments and Materials

The instruments used in this study included a glass stirring rod, scalpel No. 21 (GEA Medical, Bandung, Indonesia), blender HR210 (Philips, Jakarta, Indonesia), freeze dryer Lyovapor L-200 (Buchi, Flawil, Switzerland), rotary evaporator RV 10B (IKA, Staufen, Germany), porcelain crucibles, a 500 mL separatory funnel (Pyrex, Corning Inc., New York, USA), cannula, mortar and pestle, light microscope CX23 (Olympus, Tokyo, Japan), microtome RM2235 (Leica Microsystems, Wetzlar, Germany), laboratory oven (Memmert, Schwabach, Germany), 1 mL dropper pipette (Pyrex®, Corning Inc., New York, USA), analytical balance NT-A600 (Newtech, Shanghai, China), vials, and maceration containers.

The materials used included aluminum foil, aspirin tablets 80 mg (Aspilet®, PT Kalbe Farma Tbk., Jakarta, Indonesia), distilled water (Onemed® Water One, Surabaya, Indonesia), ethanol 70% and ethanol 96% (Onemed®, Surabaya, Indonesia), parchment paper, filter paper (Whatman No. 1, Maidstone, UK), and analytical grade n-hexane (Merck®, Darmstadt, Germany).

2.2. Plant Material

The plant material consisted of tamarind leaves (*T. indica*) collected from Takalar Regency, South Sulawesi, Indonesia. Mature leaves were harvested directly from the tree and selected based on their dark green coloration.

2.3. Experimental Procedures

a. Study Location

The experimental procedures were conducted at the Pharmaceutical Biology Laboratory and Pharmacology Laboratory of Universitas Almarisah Madani. Histopathological analysis was performed at the Anatomical Pathology Laboratory of Hasanuddin University Teaching Hospital, Makassar, Indonesia.

b. Preparation of Dried Tamarind Leaf Simplicia

Fresh tamarind leaves were subjected to wet sorting to remove foreign materials, damaged leaves, and contaminated samples. The leaves were washed with running water and air-dried at room temperature until completely dried, indicated by brittle leaves when crushed. The dried material was subsequently re-sorted to remove incompletely dried or damaged samples (Rahimah et al., 2022).

c. Preparation of Tamarind Leaf Ethanol Extract

A total of 600 g of dried tamarind leaf simplicia were ground into powder using a blender. The powdered material was extracted by maceration using 96% ethanol at a ratio of 1:10 (w/v). Remaceration was carried out several times until a clear filtrate was obtained. The combined filtrates were concentrated using a

rotary evaporator to obtain a viscous extract. The extract was then weighed to determine extraction yield (Rahimah et al., 2022).

d. Fractionation of Tamarind Leaf Extract

The ethanol extract of tamarind leaves was fractionated using liquid–liquid extraction with n-hexane and distilled water. The extract was dissolved in distilled water and transferred into a separatory funnel. n-Hexane was then added, and the mixture was shaken thoroughly before being allowed to stand until two layers formed: the upper n-hexane layer and the lower aqueous layer. The layers were separated, and the process was repeated several times until a clear aqueous fraction was obtained. The aqueous fraction was subsequently dried using a freeze dryer (Rahimah et al., 2022).

e. Preparation of Test Samples

Preparation of Aqueous Fraction. The aqueous fraction of tamarind leaf extract was prepared at doses of 6 mg/30 g body weight (BW) and 12 mg/30 g BW. For the 6 mg/30 g BW dose, 60 mg of the fraction was dissolved in 10 mL of distilled water. The same procedure was applied for the 12 mg/30 g BW dose by dissolving 120 mg of the fraction in 10 mL of distilled water.

Preparation of Aspirin Suspension. An aspirin tablet (80 mg, Aspilet®) was pulverized using a mortar and pestle. A total of 265.78 mg of the powder was weighed and gradually dissolved in distilled water until the final volume reached 30 mL, producing an aspirin suspension equivalent to 3.15 mg/mL.

f. Experimental Design

This study used mice as experimental animals and received ethical approval from the Health Research Ethics Committee of Universitas Muslim Indonesia–Ibnu Sina Hospital (No. 042/A.1/KEPK-UMI/II/2022). The animals used were healthy mice weighing 25–30 g and free from physical abnormalities.

A total of 12 mice were randomly divided into four groups (n = 3 per group). Prior to treatment, the animals were acclimatized for one week under laboratory conditions. After acclimatization, treatments were administered for 14 consecutive days according to the experimental design shown in **Table 1**. The aqueous fraction of tamarind leaves and aspirin suspension were administered orally at a volume of 1 mL/30 g BW.

Table 1. Experimental design of treatment groups

Group	Treatment
I	Normal control
II	Aspirin control (3.15 mg/30 g BW)
III	Aqueous fraction of *T. indica* leaves (6 mg/30 g BW) + aspirin (3.15 mg/30 g BW)
IV	Aqueous fraction of *T. indica* leaves (12 mg/30 g BW) + aspirin (3.15 mg/30 g BW)

g. Histopathological Examination

After 14 days of treatment, the mice were sacrificed ethically and the stomach tissues were collected for histopathological examination. The stomachs were rinsed with physiological NaCl solution and fixed in 10% buffered formalin for 24 h. The tissues were dehydrated using graded ethanol, cleared with xylene, and infiltrated with molten paraffin before being embedded into paraffin blocks (Bancroft & Gamble, 2008).

The paraffin blocks were sectioned using a microtome at a thickness of 4–5 μm and mounted on glass slides. The sections were stained with hematoxylin and eosin (H&E) following standard procedures including deparaffinization, rehydration, staining, and mounting (Kmiec, 2016). The slides were examined under a light microscope at magnifications of $100\times–400\times$ to evaluate mucosal condition, epithelial damage, inflammatory cell infiltration, and changes in gastric gland structure. Histopathological changes were evaluated descriptively to determine the degree of tissue damage caused by the treatments (Shackelford et al., 2002).

h. Gastric Damage Assessment and Statistical Analysis

Gastric damage was evaluated semi-quantitatively based on macroscopic observations (score 0–4) and histopathological assessment (score 0–3). These scores were used to calculate the gastric damage index according to the method described by Szabo and Hollander (1989).

The data were presented as median values and analyzed using the Kruskal–Wallis test followed by the Mann–Whitney post hoc test. The correlation between macroscopic and histopathological scores was analyzed using Spearman's correlation test. A p-value < 0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1. Yield Extraction and Fractionation

The extraction of dried tamarind leaves was performed using the maceration method with 96% ethanol. From 600 g of dried simplicia, 130 g of viscous extract were obtained, corresponding to a yield of 21.7%. Ethanol was selected as the extraction solvent because of its suitability for biological applications and its ability to extract a wide range of secondary metabolites with varying polarity, including flavonoids, saponins, tannins, alkaloids, and phenolic compounds (Azwanida, 2015). Maceration was chosen as it allows the diffusion of chemical constituents under relatively mild conditions, thereby minimizing degradation of thermolabile compounds (Tiwari et al., 2011).

The ethanol extract was subsequently fractionated using water and n-hexane through liquid–liquid extraction. Fractionation is commonly applied to simplify the chemical composition of crude extracts and to enrich compounds based on polarity. In the present study, the aqueous fraction was selected for further biological evaluation because polar constituents such as tannins and saponins are expected to be more soluble in water and have previously been associated with gastroprotective activity (Ameh & Eze, 2010; Senguttuvan et al., 2014).

3.2. Macroscopic Evaluation of Gastric Mucosa

Macroscopic examination revealed distinct differences in gastric morphology among the experimental groups (**Table 2**). The normal control group exhibited reddish-white gastric mucosa with a wavy surface structure, indicating preserved gross morphology of the gastric tissue. In contrast, the aspirin control group displayed pale mucosa with a wavy and wrinkled surface, suggesting the presence of gastric injury following aspirin induction.

These macroscopic alterations may be associated with impaired mucosal perfusion resulting from the inhibition of prostaglandin synthesis by aspirin (Pal, 2021; Takeuchi, 2012). Prostaglandins are known to contribute to the maintenance of mucosal blood flow and protection of gastric epithelial cells. Previous studies have also described aspirin-induced gastric injury as being accompanied by pale mucosal surfaces, irregular folding, and distortion of gastric morphology, which may reflect mucosal irritation and changes in gastric motility (Satapathy et al., 2024; Singh et al., 2008).

Administration of the aqueous fraction of *T. indica* leaves was associated with an improved macroscopic appearance compared with the aspirin control group (**Table 2**). In the group receiving 6 mg/30 g BW, the gastric mucosa appeared slightly pale to reddish-white with a wavy surface, indicating partial protection. Meanwhile, the group treated with 12 mg/30 g BW showed reddish-white mucosa with a wavy surface that more closely resembled the normal control group. These observations suggest that the aqueous fraction may reduce the extent of aspirin-induced macroscopic gastric alterations.

Table 2. Macroscopic gastric appearance, histopathological score, and gastric damage index in mice treated with the aqueous fraction of *T. indica* leaves

Group	Treatment	Macroscopic appearance	Macroscopic score	Histopathological score	Gastric damage index (GDI)
I	Normal control	Reddish-white mucosa with a wavy surface	0	0	0[a]
II	Aspirin control (3.15 mg/30 g BW)	Pale mucosa with a wavy and wrinkled surface	2	3	5[c]
III	Aqueous fraction of *T. indica* leaves (6 mg/30 g BW) + aspirin	Slightly pale to reddish-white mucosa with a wavy surface	1	2	3[b]
IV	Aqueous fraction of *T. indica* leaves (12 mg/30 g BW) + aspirin	Reddish-white mucosa with a wavy surface	0	1	1[ab]

Note: Data are presented as median values (n = 3 per group). Different superscript letters indicate significant differences among groups at $p < 0.05$ according to the Kruskal–Wallis test followed by the Mann–Whitney post hoc test. BW, body weight; GDI, gastric damage index.

3.3. Histopathological Observations

Histopathological examination further supported the macroscopic findings (**Figure 1**). The gastric mucosa of the normal control group showed intact epithelial structure without observable pathological lesions. In contrast, the aspirin control group exhibited clear signs of gastric injury, including erosion, ulceration, and hemorrhage.

Ulcerative lesions represent mucosal damage extending beyond the epithelial layer into deeper mucosal or submucosal layers and are commonly accompanied by inflammatory responses and bleeding. Erosion generally refers to more superficial injury confined to the epithelial layer, while hemorrhage reflects vascular damage within the mucosa and is frequently associated with more severe gastric injury (Laine et al., 2008).

The histological alterations observed in the aspirin control group can be explained by both local and systemic mechanisms of aspirin-induced gastric injury. Locally, aspirin acts as a weak acid that can diffuse into gastric epithelial cells under acidic conditions and become trapped intracellularly through an ion-trapping mechanism, leading to cellular injury and epithelial disruption (Beck et al., 2000). Systemically, aspirin irreversibly inhibits cyclooxygenase enzymes, particularly COX-1, resulting in decreased synthesis of protective prostaglandins such as PGE_2 and PGI_2. These mediators play important roles in mucus secretion, bicarbonate production, and maintenance of mucosal blood flow; therefore, their reduction weakens gastric mucosal defense mechanisms and increases susceptibility to acid-mediated injury (Takeuchi & Amagase, 2018).

In the group receiving the aqueous fraction at 6 mg/30 g BW, erosive and ulcerative changes were still observed in some samples, suggesting that the protective effect at this dose was limited. In contrast, the group treated with 12 mg/30 g BW showed better preservation of gastric mucosal architecture and did not display severe lesions comparable to those observed in the aspirin control group (**Figure 1**).

3.4. Gastric Damage Scores and Gastroprotective Activity

The integrated assessment of gastric injury, based on macroscopic score, histopathological score, and gastric damage index (GDI), is summarized in **Table 2**. The aspirin control group showed the highest GDI value, indicating the most severe gastric damage. Administration of the aqueous fraction reduced the GDI at both dose levels, with the 12 mg/30 g BW group showing the lowest value among the treatment groups.

A similar trend was observed in the macroscopic and histopathological scores. The aspirin control group exhibited the

highest scores, while the normal control group showed no detectable gastric injury. The group treated with 6 mg/30 g BW displayed intermediate scores, whereas the group treated with 12 mg/30 g BW demonstrated lower damage scores, suggesting a greater protective effect at the higher dose.

Statistical analysis indicated significant differences in gastric damage among the experimental groups ($p < 0.05$). The treatment groups showed lower gastric damage scores compared with the aspirin control group. In addition, the agreement between macroscopic and histopathological observations supports the reliability of the evaluation of gastric injury in the present study. Similar correlations between gross gastric lesions and histological changes have been reported in previous studies of gastric mucosal injury (Laine et al., 2008; Oates & Hakkinen, 1988).
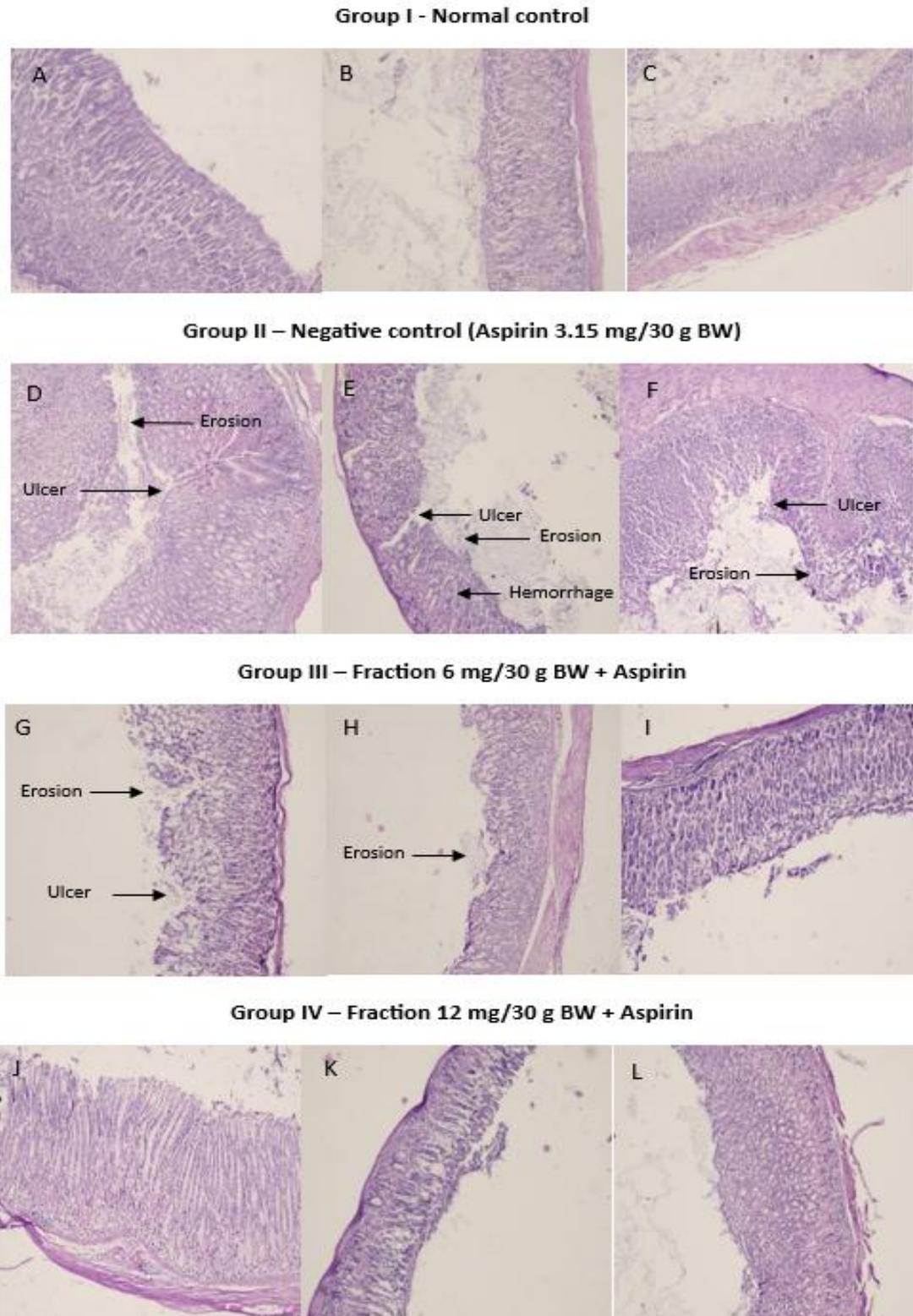
Figure 1. Representative histopathological features of gastric tissues in experimental mice. Group I, normal control; Group II, negative control (aspirin, 3.15 mg/30 g BW); Group III, aqueous fraction of *T. indica* leaves (6 mg/30 g BW) plus aspirin; Group IV, aqueous fraction of *T. indica* leaves (12 mg/30 g BW) plus aspirin. Gastric lesions observed in the aspirin control group included erosion, ulceration, and hemorrhage.

3.5. Possible Contribution of Bioactive Compounds

The observed gastroprotective activity may be associated with bioactive constituents present in tamarind leaves. Previous phytochemical studies have reported that ethanol extracts of *T. indica* leaves contain several secondary metabolites, including tannins, flavonoids, anthraquinones, and saponins, with tannins and saponins often representing major components (Bhadoriya et al., 2011; Karmana, 2024).

Tannins may contribute to mucosal protection by precipitating proteins on the mucosal surface and forming a protective barrier that limits the penetration of gastric acid and pepsin (Borrelli & Izzo, 2000). In addition, tannins possess antioxidant and anti-inflammatory properties that may help reduce oxidative stress and inflammatory responses in gastric tissues (Chanudom & Tangpong, 2015).

Saponins have also been reported to enhance gastric mucosal defense by stimulating mucus secretion and increasing endogenous prostaglandin production, including prostaglandin E_2, which plays a role in maintaining mucosal integrity (Alharbi et al., 1994; Zakaria et al., 2002). Furthermore, saponins may stabilize epithelial cell membranes and contribute to antioxidant activity, thereby reducing cellular damage caused by oxidative stress (Devi et al., 2007).

Overall, the findings suggest that the aqueous fraction of *T. indica* leaves was associated with reduced aspirin-induced gastric injury in mice, as indicated by improved macroscopic morphology, lower gastric damage scores, and better preservation of histological structure. Within the tested dose range, the 12 mg/30 g BW dose showed the most favorable gastroprotective profile.

4. CONCLUSION

This study indicates that the aqueous fraction of *T. indica* leaves was associated with reduced gastric mucosal injury in aspirin-induced mice, as reflected by improved macroscopic gastric appearance, lower gastric damage scores, and better preservation of histological architecture compared with the aspirin control group. Among the tested doses, the fraction administered at 12 mg/30 g body weight showed the most favorable protective profile under the experimental conditions. The observed effects may be related to polar bioactive constituents of *T. indica* leaves, including tannins and saponins, which have been reported to contribute to gastric mucosal defense. However, the present study was limited to morphological and semi-quantitative assessments, and the underlying molecular mechanisms were not investigated. Further studies involving phytochemical characterization, mechanistic evaluation, and expanded experimental models are therefore required to better understand the potential role of *T. indica* leaf fractions in gastroprotective research.

AUTHOR CONTRIBUTIONS

Conceptualization, S.R.; methodology, S.R. and M.I.; validation, S.R., M.I., and D.N.P.; formal analysis, S.R.; investigation, S.R. and M.I.; resources, S.R.; data curation, S.R.; writing—original draft preparation, S.R.; writing—review and editing, S.R., M.I., and D.N.P.; visualization, S.R.; supervision, D.N.P.; project administration, S.R.; funding acquisition, S.R. All authors have read and agreed to the published version of the manuscript.

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Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ROLE OF THE FUNDERS

The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) USE

During the preparation of this manuscript, the author(s) used ChatGPT (OpenAI) to assist in improving the clarity, structure, and readability of the text. After using this tool, the author(s) carefully reviewed, edited, and verified the entire content to ensure that it accurately reflects their own ideas and interpretations. The author(s) take full responsibility for the integrity and originality of the published work.

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