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GASTROPROTECTIVE POTENTIAL OF DOLICHANDRONE FALCATA EXTRACT VIA MODULATION OF OXIDATIVE STRESS, INFLAMMATION, AND MUCOSAL HEALING

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ABSTRACT

Background: *Dolichandrone falcata*, traditionally used for gastrointestinal disorders, has demonstrated antiulcer activity, but the underlying protective mechanisms remain unclear. This study evaluated the methanolic extract of *D. falcata* for gastroprotective, antioxidant, and anti-inflammatory activities using ethanol- and pylorus-ligation–induced ulcer models in rats. **Methodology:** Wistar rats were divided into control, standard, and treatment groups. Ulcers were induced by ethanol or pyloric ligation. The extract (100, 200, and 400 mg/kg) and omeprazole (20 mg/kg) were administered orally. Ulcer index, gastric parameters, oxidative stress markers [malondialdehyde (MDA), glutathione (GSH), superoxide dismutase (SOD), catalase (CAT)], and inflammatory cytokines [TNF-α, IL-6] were assessed, supported by histopathological examination. **Results and Discussion:** The extract produced a dose-dependent reduction in the ulcer index in both models, with 76.6% protection at 400 mg/kg, comparable to omeprazole (79.7%). Histology revealed marked restoration of the gastric mucosa with minimal necrosis. MDA levels decreased significantly, while GSH, SOD, and CAT levels were elevated toward normal. TNF-α and IL-6 were markedly suppressed, indicating a reduction in oxidative and inflammatory injury. **Conclusion:** *D. falcata* extract demonstrated potent gastroprotective effects through antioxidative, anti-inflammatory, and mucosal-healing mechanisms. This is the first biochemical and cytokine-based validation of its traditional use, suggesting strong potential for developing *D. falcata* as a plant-derived therapeutic for ulcer management.

INTRODUCTION

Peptic ulcer disease (PUD) is characterized by damage to the mucosa of the stomach or duodenum. This results from an imbalance between defensive mechanisms, such as mucus secretion and mucosal blood supply, and aggressive forces, such as acid and pepsin [1]. Although pharmacological treatments, including antacids, proton pump inhibitors, and H2-receptor blockers, are frequently used, their long-term use can pose challenges. These synthetic agents have been linked to problems like treatment resistance, recurrent symptoms, and possibly an

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increased risk of cancer [2]. As a result, plant-based substitutes are becoming increasingly popular because they are considered safer and have more adaptable pharmacological effects. In the past, traditional healthcare systems have relied heavily on medicinal plants to treat peptic ulcers and other gastrointestinal disorders. One such plant used in conventional medicine to reduce inflammation, promote wound healing, and treat digestive issues is Dolichandrone falcata (Bignoniaceae), also locally known as Medshingi [3]. Research on its phytochemical composition has identified bioactive compounds with anti-inflammatory, gastroprotective, and antioxidant properties, including flavonoids, phenolic compounds, alkaloids, and tannins [4]. Animal models have been used in experimental research to support the antiulcer effectiveness of D. falcata extract. In particular, methanolic extracts have been shown to reduce gastric secretions and ulcer indices in both ethanol-induced and pyloric ligation-induced ulcer models [5]. Furthermore, similar protective benefits have been demonstrated with herbal tablet formulations that include this extract, supporting the feasibility of developing oral medicinal treatments derived from this plant [6]. However, the biochemical processes underlying its ulcer-healing ability remain incompletely understood. Because ulcer formation has a complex etiology, a dual strategy that includes tissue-level and molecular investigations is crucial. Histopathological assessments can show tissue regrowth, immune cell infiltration, and mucosal injury. At the same time, the evaluation of biological indicators of inflammation and oxidative stress provides important information on the physiological changes induced by the plant extract [7]. Because it encourages lipid peroxidation and weakens antioxidant defenses, oxidative stress plays a major role in ulcerogenesis. Furthermore, mucosal injury is exacerbated by pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which sustain the inflammatory response [8].

In light of this, the current study aims to evaluate the therapeutic efficacy of Dolichandrone falcata extract in experimental models of stomach ulceration. The study's main objectives are to assess its effects on inflammatory cytokine modulation, augmentation of the antioxidant system, and mucosal healing. It is anticipated that the results will confirm the plant's traditional uses and provide scientific evidence for its use in phytotherapeutic treatments for gastric ulcers. Previous studies have demonstrated the antiulcer potential of herbal agents via suppression of oxidative stress and inflammatory pathways. However, no detailed biochemical or cytokine-based elucidation of *D. falcata*'s mechanism has been reported. Therefore, this study represents the first comprehensive evaluation of the methanolic extract of *D. falcata*, correlating biochemical antioxidant activity, cytokine modulation, and histopathological recovery in ethanol- and pylorus-ligation-induced ulcer models. This integrative approach bridges ethnomedicinal knowledge with molecular validation.

MATERIALS AND METHODS

Extract Preparation

The air-dried powdered bark of *Dolichandrone falcata* (500 g) was macerated in methanol (1:5 w/v) at 40 °C for 72 h with intermittent stirring. The extract was filtered and concentrated under reduced pressure at 45 °C using a rotary evaporator to obtain a dark-brown semisolid mass (yield ≈ 12.4% w/w). Doses (100–400 mg/kg p.o.) were selected based on preliminary pharmacological screening and literature reports indicating effective gastroprotective activity of similar methanolic extracts at 100–500 mg/kg.

Experimental Animals and Ethics

A recognized laboratory animal center provided young Wistar albino rats of both sexes, weighing 150-200 g. The animals were kept under carefully regulated conditions, with a 12-hour light/dark cycle, a constant ambient temperature of 22 ± 2 °C, and a relative humidity of 50%-60%. In addition to unrestricted access to water, a properly nourished pellet diet was provided. The Institutional Animal Ethics Committee (IAEC) approved all animal-related procedures, and they were carried out in compliance with the guidelines established by the Government of India's Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). The study protocol was approved by the Institutional Animal Ethics Committee (IAEC No.: SCOP/IAEC/2024/14) in accordance with CPCSEA guidelines. Separate sets of animals were used for ethanol- and pylorus-ligation-induced models to avoid cross-interference. All data were analyzed following confirmation of normal distribution (Shapiro–Wilk test) and homogeneity of variance (Levene's test) [9].

Ulcer Induction Models

Two commonly utilized animal models—the pyloric ligation paradigm and the ethanol-induced stomach ulcer type—were employed to assess the gastroprotective efficacy of Dolichandrone falcata extract.

Ethanol-Induced Gastric Ulcer Model

Before the experiment, the animals were allowed unlimited access to water and fasted for 24 hours. Subsequently, they were randomly assigned to five groups of six animals each. These comprised three test groups that received oral doses of 100, 200, and 400 mg/kg of methanolic extracts of Dolichandrone falcata over seven days, a control group, and a conventional treatment group that received omeprazole at 20 mg/kg. Absolute ethanol was administered orally on the last day as a dose of 1 mL for 200 g of body mass, which caused stomach ulcers. The animals were put to sleep an hour after being exposed to ethanol, and their stomachs were extracted, opened along the larger curvature, and checked for inflammatory lesions. A systematic grading system was used to calculate the ulcer index [10].

Model of Pyloric Ligation

The animals were given ether for light anesthesia after fasting for the entire night before the surgery. The abdominal cavity was accessed by making a midline incision, and the pylorus was carefully tied off to avoid damaging nearby blood vessels. The animals were then allowed time to regain consciousness after the incision was sealed. Animals in various groups were given a vehicle, a common reference medication, or an oral extract of Dolichandrone falcata one hour before surgery. The animals were killed four hours after pyloric ligation, and the contents of their stomachs were taken out to measure the volume, pH, and overall acidity. Lesion severity and ulcer index were also assessed in the separated stomach tissues [11].

Histopathological Study

Stomach tissues from each experimental group were collected and stored in 10% buffered formalin for 1 day. Following fixation, the samples were cleaned with xylene, embedded in paraffin, and dehydrated using a series of graded ethanols. A microtome was used to obtain 5 µm-thick sections, which were subsequently stained with eosin and hematoxylin (H&E). To identify histological alterations, such as mucosal destruction, epithelial disintegration, inflammatory cell infiltration, and edema & hemorrhagic symptoms, the stained slides were examined under a microscope. To facilitate comparison of the various groupings, representative photomicrographs were obtained [12].

Biochemical Analysis

Gastrointestinal mucosal tissues were homogenized in cooled phosphate buffer and centrifuged to examine the role of oxidative damage in ulcerogenesis and to evaluate the extract's preventive effect. The resulting supernatant was utilized in the following manner to estimate oxidative stress biomarkers:

- Using the thiobarbituric acid reactive substances (TBARS) method, malondialdehyde (MDA) levels, a marker of lipid peroxidation, were determined and expressed as nmol MDA per milligram of protein [13].
- Ellman's reagent was used to quantify reduced glutathione (GSH), and absorbance was measured at 412 nm [14].
- The ability of Superoxide Dismutase (SOD) to prevent pyrogallol from auto-oxidizing was measured using a spectrophotometer set to 420 nm [15].
- The rate at which hydrogen peroxide degraded was used to calculate the activity of catalase (CAT), and absorbance at 240 nm was recorded [16].

The Lowry technique was used to quantify each sample's total protein content to standardize enzymatic activity [17].

Measurement of Cytokines Inflammatory

Following the manufacturer's instructions, ELISA kits were used to measure interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels in gastric tissue homogenates (Sigma-Aldrich). Utilizing a microplate reader, absorbance was measured at 450 nm. Cytokine concentrations, which were represented in picograms each milligram of tissue protein, were computed using standard calibration curves [18].

Analysis of Statistics

Means ± the standard error around the average (SEM) is how the findings are displayed. Tukey's post hoc test was used for multiple pairwise comparisons following one-way ANOVA. Statistical significance was defined as a p-value < 0.05. GraphPad Prism version 9.0 for Windows (GraphPad Software, San Diego, California, USA) was used for all statistical analyses and graphical representations.

RESULT AND DISCUSSION

Results

Gross Ulcer Indices and Protection Rates

In both ethanol-induced and pylorus-ligation-induced models, the consumption of Dolichandrone falcata extracts demonstrated a dose-responsive trend in lowering stomach ulceration. The ulcer index significantly decreased after receiving treatment via omeprazole, a well-known, conventional anti-ulcer drug. Interestingly, results comparable to those of omeprazole were obtained when the extract was administered at 400 mg/kg, confirming substantial anti-ulcer potential.

Table 1: Effect of *Dolichandrone falcata* Extract on Ulcer Index and Protection Rate in Ethanol-Induced Ulcer Model

Group	Ulcer Index (Mean ± SEM)	%Protection
Control	12.8 ± 0.36	–
Standard(Omeprazole)	2.6 ± 0.22***	79.7%
Extract 100 mg/kg	8.2 ± 0.33**	35.9%
Extract 200 mg/kg	5.4 ± 0.27**	57.8%
Extract 400 mg/kg	3.0 ± 0.25***	76.6%

Values are expressed as mean ± SEM, n = 6.

p < 0.01, ***p < 0.001 compared to control group.

The results reveal that the ulcer index decreased in a dose-dependent manner, with a 400 mg/kg dose having effects akin to those of omeprazole. This implies that the extract may have gastroprotective effects, possibly due to its antioxidant properties & capacity to protect the gastric mucosa.

Histological Findings

The gastroprotective activity of Dolichandrone falcata extracts was confirmed by microscopic analysis of stomach tissues. Significant pathological changes, such as significant mucosal injury, infiltration of inflammatory cells, interstitial fluid retention, and hemorrhagic symptoms, were found in the control group that was not treated. Important Points to Note:

• **Group under Control:** Widespread necrosis, bleeding, and intense neutrophilic infiltration, all of which indicated severe acute inflammation, were indicative of extensive damage to the stomach mucosa.

Standard Drug Group: The gastric lining was largely preserved, exhibiting only minor superficial erosions, suggesting effective protection.

Extract at 100 mg/kg: The mucosal layer showed mild-to-moderate disruption, with slight tissue swelling.

- **Extract at 200mg/kg:** Mucosal structure partially recovered, suggesting anti-inflammatory and gradual healing.
- **Extract at 400 mg/kg:** With little indications of inflammation and a well-preserved secretory structure, the stomach epithelium seemed to have almost completely healed (Figure 1).

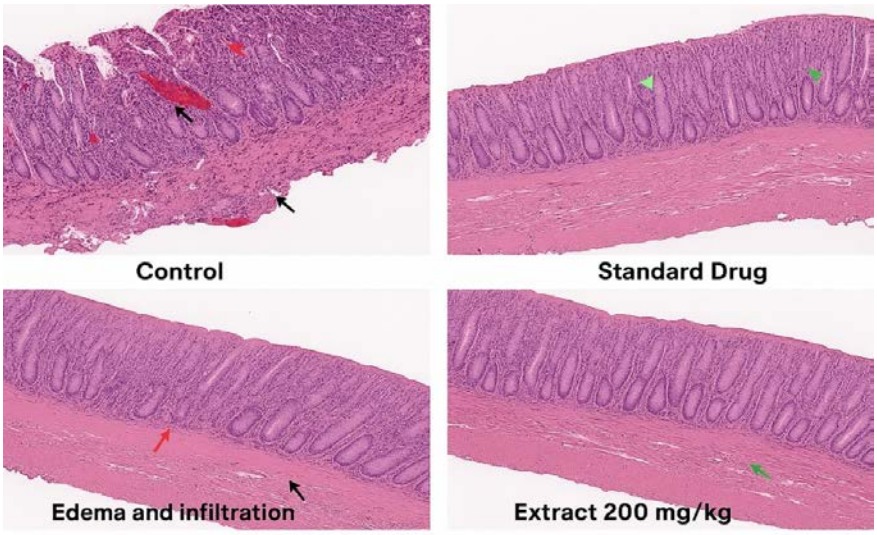

Figure 1: Representative histopathological micrographs of gastric mucosa in ethanol-induced ulcer model (H&E, ×40).
Arrows indicate key histopathological features, including necrosis (black), edema (red), and mucosal regeneration (green).

Effective tissue preservation was demonstrated by histological analysis, which showed that gradual mucosal recovery correlated with the administered dose.

Levels of Antioxidant Enzymes

While antioxidant defenses were restored after treatment with the extract, stress markers were markedly changed in the control group (Table 2).

Table 2: Effect of *D. falcata* Extract on Oxidative Stress Markers

Group	MDA (nmol/mg)	GSH (µmol/g)	SOD (U/mg)	Catalase (U/mg)
Control	6.82 ± 0.24	1.62 ± 0.12	1.34 ± 0.10	1.80 ± 0.15
Standard	2.21 ± 0.17***	3.95 ± 0.18***	3.42 ± 0.21***	4.25 ± 0.19***
Extract 100 mg/kg	5.10 ± 0.22**	2.18 ± 0.14*	2.11 ± 0.17*	2.98 ± 0.13*
Extract 200 mg/kg	3.60 ± 0.19**	2.95 ± 0.16**	2.84 ± 0.15**	3.60 ± 0.18**
Extract 400 mg/kg	2.45 ± 0.20***	3.72 ± 0.19***	3.25 ± 0.20***	4.02 ± 0.16***

Values are expressed as mean ± SEM, n = 6. , *p < 0.05, **p < 0.01, ***p < 0.001 compared to control.

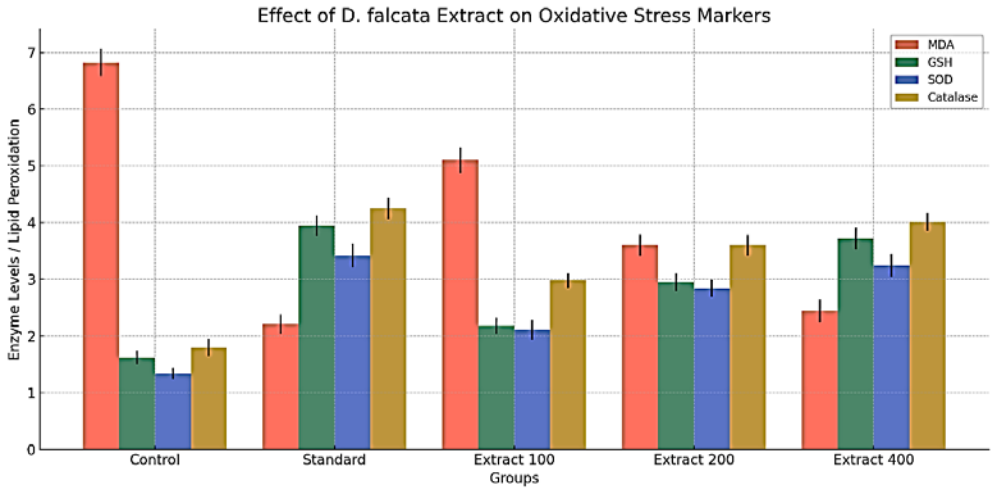

Figure 2: Effect of D. falcata Extract on MDA, GSH, SOD, and Catalase Levels

Lower levels of malondialdehyde (MDA) indicated a significant reduction in lipid peroxidation following the injection of Dolichandrone falcata extract. Furthermore, the extract contributed to the restoration of the body's antioxidant defense system, as evidenced by increased glutathione (GSH) levels and improved catalase and superoxide dismutase (SOD) activities. These results imply that the extract helps maintain the health of the stomach mucosa by preventing damage brought on by oxidative stress. Pearson correlation analysis revealed a significant negative correlation between MDA levels and mucosal regeneration score ($r = –0.86$, $p < 0.01$) and a positive correlation between GSH levels and histopathological recovery ($r = 0.81$, $p < 0.05$), supporting the biochemical-histological relationship (Figure 2).

Changes in Inflammatory Biomarkers

The injection of Dolichandrone falcata extracts resulted in a significant decrease in inflammatory markers, whereas the control group's gastric tissues showed elevated expression of inflammatory cytokines (Table 3). A notable reduction in both IL-6 and TNF-α levels evidences the extract's anti-inflammatory properties. This effect may promote tissue repair and protect the stomach lining from damage. The observed suppression of TNF-α and IL-6 may involve modulation of the NF-κB signaling pathway, which regulates pro-inflammatory gene expression. In contrast, the enhancement of antioxidant enzymes suggests activation of the Nrf2-HO-1 defense axis, thereby contributing to mucosal repair (Figure 3).

Table 3: Effect on Inflammatory Cytokines (pg/mg tissue protein)

Group	TNF-α (pg/mg)	IL-6 (pg/mg)
Control	87.3 ± 3.6	64.5 ± 2.8
Standard	32.1 ± 2.1***	28.4 ± 1.9***
Extract 100 mg/kg	65.7 ± 2.9*	48.2 ± 2.2*
Extract 200 mg/kg	45.6 ± 2.5**	36.7 ± 2.0**
Extract 400 mg/kg	33.8 ± 2.3***	30.1 ± 1.8***

Values are expressed as mean ± SEM, n = 6., *p < 0.05, **p < 0.01, ***p < 0.001 compared to control.

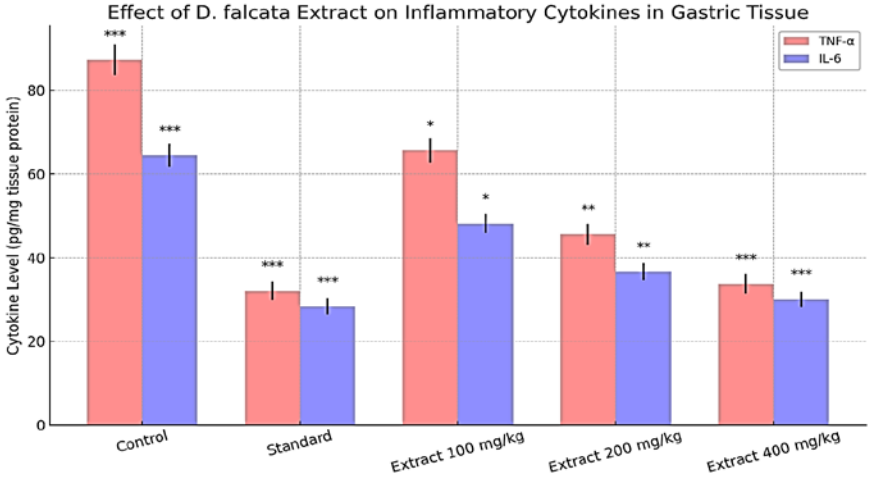

Figure 3: Effect of D. falcata Extract on TNF-α and IL-6 Levels in Gastric Tissue of Treated Rats

DISCUSSION

Assessment of Dolichandrone falcata Extract's Gastroprotective Potential. Several experimental parameters, including ulcer index persistence, histological evaluation, antioxidant enzyme analysis, and assessment of inflammatory cytokines, were systematically used to examine the gastroprotective properties of the Dolichandrone falcata extract. In combined ethanol-induced and pyloric ligation models, the extract demonstrated dose-dependent gastroprotection, underscoring its potential to prevent gastric mucosal injury.

Reduction in Ulcer Index and Dose-Responsive Protection

Compared with the untreated control, injection of D. falcata extract significantly reduced the number of mucosal lesions in the ethanol-induced ulcer model. The extract has protective benefits comparable to those of omeprazole at a dose of 400 mg/kg. A favorable relationship between dose and efficacy was demonstrated by a steady increase in protection rates, ranging from 35.9% at 100 mg/kg to 76.6% at 400 mg/kg. The extract's function in preserving mucosal stability and preventing ethanol-induced gastric injury is evidenced by the observed decrease in the ulcer index.

Histopathological Observations Supporting Mucosal Recovery

Microscopic analyses supported the extract's gastroprotective effectiveness and validated the gross pathological findings. Significant mucosal loss, epithelial disintegration, hemorrhagic regions, necrotic tissue & significant inflammatory infiltration, all indicators of severe stomach ulceration, were seen in the ulcer control group. These characteristics were noticeably attenuated in a dose-dependent manner upon stimulation with D. falcata extract. The 200 mg/kg group exhibited significant regenerative alterations, whereas the 100 mg/kg group showed only minor mucosal erosion. At 400 mg/kg, there was almost complete restoration of normal stomach architecture, minimal inflammation, and intact glands, suggesting that anti-inflammatory and regenerative effects may have mediated mucosal repair.

Attenuation of Oxidative Stress

A major contributor to the formation of stomach ulcers, oxidative stress is caused by excessive oxidized lipids and weakened antioxidant mechanisms. Increased malondialdehyde, or MDA, levels in untreated mice suggested more severe lipid peroxidation. MDA levels were significantly reduced by D. falcata extract treatment in a dose-dependent manner. Concurrently, levels of antioxidant enzymes, such as reduced glutathione (GSH), catalase, and superoxide dismutase (SOD), were markedly restored, particularly at the highest dose (400 mg/kg), mirroring the effects of omeprazole. These results suggest that the extract protects stomach tissue by enhancing the activity of endogenous antioxidants and reducing oxidative damage.

Regulation of Inflammatory Cytokines

Tumour necrosis factor-alpha (TNF-α) & interleukin-6 (IL-6) are inflammatory markers associated with worsening mucosal injury and with the prevention of recovery. The control samples had significantly greater levels of pro-inflammatory markers, which were noticeably reduced after extract treatment. TNF-α and IL-6 levels significantly decreased after therapy with D. falcata extracts, particularly at doses of 200 and 400 mg/kg, with results comparable to those obtained with the reference standard. This implies that the extract has anti-inflammatory properties, which promote mucosal healing and reduce further damage.

Mechanistic Insights into Gastroprotective Action

Dolichandrone falcata's therapeutic effectiveness seems to result from a confluence of pharmacological mechanisms. These include downregulating inflammatory mediators, promoting mucosal regeneration, strengthening antioxidant defenses, and inhibiting lipid peroxidation. Taken together, these processes enhance the stomach's mucosa's resistance to aggressive substances such as ethanol and gastric acid and accelerate the repair of pre-existing lesions. Although the findings substantiate the antiulcer efficacy of *D. falcata*, certain limitations exist. Acute and sub-chronic toxicity studies were not performed, and phytochemical quantification of major constituents remains pending. Furthermore, the study utilized acute ulcer models; future research should explore chronic or stress-induced models and isolate active compounds responsible for the observed effects.

The present findings are consistent with earlier reports on herbal agents possessing comparable gastroprotective activities. For instance, *Rutaecarpine* and *Gallic acid* demonstrated ulcer-healing effects by activating the Nrf2/HO-1 pathway and suppressing inflammatory cytokines [13,14]. Similarly, extracts of *Sedum dendroideum* and *Bassia indica* have been shown to

enhance mucosal regeneration via polyphenolic constituents that reduce oxidative stress and inhibit the HMGB1/TLR4/NF-κB axis [15–17]. These correlations reinforce that *D. falcata* acts through shared mechanistic pathways, supporting its ethnopharmacological use for gastrointestinal protection. The phytochemical profile of *D. falcata* includes flavonoids, phenolics, tannins, and alkaloids, which are known to exert potent antioxidant and anti-inflammatory actions.

Flavonoids and phenolic compounds scavenge reactive oxygen species, upregulate Nrf2-mediated antioxidant enzyme expression, and suppress NF-κB signaling, thereby reducing pro-inflammatory cytokine production. These bioactives likely contribute to the observed restoration of GSH, SOD, and CAT activities and the attenuation of TNF-α and IL-6 levels. Thus, the extract's gastroprotective potential can be attributed to a synergistic interplay between its phytochemical constituents and their modulation of oxidative and inflammatory pathways.

CONCLUSION

The findings demonstrate that the methanolic extract of *Dolichandrone falcata* effectively prevents experimentally induced gastric ulcers through synergistic anti-inflammatory, antioxidant, and mucosal-healing mechanisms. The extract restored gastric integrity, reduced ulcer severity, and improved histological architecture in a dose-dependent manner. Significant reductions in malondialdehyde (MDA) and elevations in glutathione (GSH), catalase, and superoxide dismutase (SOD) confirmed attenuation of oxidative stress. Suppression of pro-inflammatory cytokines, including TNF-α and IL-6, further validated its protective role during mucosal recovery. These findings indicate that *D. falcata* exerts gastroprotection by modulating oxidative and inflammatory pathways while enhancing tissue regeneration. This study provides the first biochemical and cytokine-based evidence supporting the plant's traditional therapeutic use. Future investigations focusing on the isolation of active phytoconstituents and the involvement of molecular pathways such as NF-κB and Nrf2 may advance its potential development as a plant-derived antiulcer agent.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Sagar Kamble conceived and designed the study. Ajay Salvi, Shivaji Patil, and Shashikant Modekar performed the experiments and collected the data. Sachin Kothawade contributed to data interpretation, manuscript review, and overall guidance. Sagar Kamble drafted the initial manuscript, and all authors reviewed, edited, and approved the final version.

ABBREVIATIONS

CAT – Catalase; CPCSEA – Committee for the Purpose of Control and Supervision of Experiments on Animals; D. falcata – Dolichandrone falcata; ELISA – Enzyme-Linked Immunosorbent Assay; GSH – Reduced Glutathione; H&E – Hematoxylin and Eosin; IAEC – Institutional Animal Ethics Committee; IL-6 – Interleukin-6; MDA – Malondialdehyde; PUD – Peptic Ulcer Disease; SEM – Standard Error of Mean; SOD – Superoxide Dismutase; TBARS – Thiobarbituric Acid Reactive Substances; TNF-α – Tumor Necrosis Factor-alpha

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