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EVALUATION OF A POLYHERBAL FORMULATION IN GASTRIC ULCER MODELS INDUCED BY NAPROXEN AND ACETIC ACID IN WISTAR RATS

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ABSTRACT
Background: Gastric ulcers remain a prevalent gastrointestinal disorder, often exacerbated by non-steroidal anti-inflammatory drugs (NSAIDs) like Naproxen and irritants such as acetic acid. The investigation focuses on evaluating the gastroprotective properties of a formulation composed of standardized extracts from traditionally used medicinal plants, evaluated in Wistar rat models with experimentally induced gastric ulcers. **Methodology**: Ulcers were induced using Naproxen (NSAID-induced model) and acetic acid (chronic ulcer model) to mimic acute and chronic ulcerative conditions. The polyherbal formulation was administered orally at graded doses prior to ulcer induction. Ulcer index, gastric volume, pH, and histopathological parameters were assessed to determine protective effects. **Results**: The polyherbal formulation significantly reduced ulcer index in a dose-dependent manner, with the highest dose (1180 mg/kg) lowering the index to 0.44 ± 0.02 in Naproxen-induced ulcers (67.45% protection) and to 2.21 ± 0.01 in acetic acid-induced ulcers (61.25% protection), closely approaching omeprazole's efficacy. **Discussion**: The formulation demonstrated a significant reduction in ulcer index and improved gastric mucosal integrity, with notable restoration of antioxidant defense mechanisms. Histological studies revealed reduced mucosal damage and inflammation compared to control groups. **Conclusion**: These outcomes recommend that the polyherbal formulation utilizes a protective effect against gastric ulcers, likely through cytoprotective, anti-inflammatory, and antioxidant mechanisms. The study supports the therapeutic potential of polyherbal combinations in managing gastric ulcers and encourages further clinical investigation.

INTRODUCTION

Gastric ulcers are a prevalent digestive condition resulting from a disrupted balance between the protective mechanisms and harmful factors acting on the stomach lining [1]. The mucosal barrier can be compromised by various harmful factors, including non-steroidal anti-inflammatory drugs (NSAIDs), Helicobacter pylori infection, stress, alcohol consumption, and increased gastric acid secretion, which can lead to ulcer formation [2]. NSAIDs, such as naproxen, are particularly known to cause gastric mucosal damage by inhibiting prostaglandin synthesis, which reduces mucus and bicarbonate secretion, and impairs mucosal blood flow [3]. In parallel, chronic ulcer models using agents like acetic acid closely mimic human ulcer pathology and are widely used for evaluating healing and regeneration processes [4]. Conventional

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therapeutic agents for ulcers, such as H_2 blockers and PPIs (proton pump inhibitors), though effective, may be associated with adverse effects and relapse [5]. Hence, there is a growing interest in developing safer, herbal-based therapies with minimal side effects. Herbal medicine offers a rich repository of bioactive compounds with therapeutic potential. Polyherbal formulations, which combine multiple herb extracts, offer synergistic effects through diverse mechanisms such as cytoprotection, antioxidant activity, and anti-inflammatory action [6]. The present study focuses on evaluating a polyherbal formulation (PHF) that comprises hydroalcoholic extracts of *Sphaeranthus indicus*, *Allium sativum*, *Azadirachta indica*, *Madhuca indica*, *Ficus religiosa*, and *Glycyrrhiza glabra*, all of which have demonstrated antiulcer and antioxidant properties in earlier studies. This study aimed to evaluate the gastroprotective potential of PHF in models of gastric ulcers induced by naproxen and acetic acid in Wistar rats. This study aimed to assess the ulcer-protective potential of the novel formulation by examining changes in antioxidant activity and tissue histopathology, thereby highlighting its possible therapeutic significance.

MATERIALS AND METHODS

Drugs and Chemicals

Naproxen and acetic acid were procured from a certified vendor and used without further purification. Omeprazole was used as a standard antiulcer agent. All remaining chemicals and solvents employed in the study were of analytical purity [7].

Collection and identification of chemical constituents

The herbal ingredients utilized in the polyherbal formulation, *Sphaeranthus indicus*, *Allium sativum*, *Azadirachta indica*, *Madhuca indica*, *Ficus religiosa*, and *Glycyrrhiza glabra*, were sourced from a certified local supplier and authenticated by a botanist from the Department of Botany, Madhav University. The plant materials were carefully washed to remove dirt and foreign particles, shade-dried to preserve phytoconstituents, and converted into a coarse powder through mechanical milling. The ground materials were kept in airtight containers for further use in formulation [8]. Initial phytochemical analysis was performed on each of the plant extracts to identify the major classes of chemical constituents [9–13]. Phytochemical evaluation confirmed the presence of various constituents, including alkaloids, flavonoids, tannins, essential oils, glycosides, and saponins, which are recognized for their roles in gastroprotection, anti-inflammatory activity, and antioxidant properties. These bioactive constituents were considered to contribute synergistically to the polyherbal formulation's antiulcer potential [14].

Extraction of phytoconstituents

The dried and coarsely powdered plant materials, *Sphaeranthus indicus Linn* (whole plant), *Allium sativum* (fruit), *Azadirachta indica* (leaves), *Madhuca indica* (bark), *Ficus religiosa* (root), and *Glycyrrhiza glabra* (root), were subjected to hydroalcoholic extraction to obtain the phytoconstituents [15]. Each plant material was passed through a 16-mesh sieve and macerated separately using a hydroalcoholic solvent (ethanol: water, 1:1) in a 3,000 mL volume, maintained at ambient temperature for one week, with periodic agitation to facilitate effective extraction [16]. After the initial maceration, the process was repeated with fresh solvent to ensure complete extraction. The combined extracts were filtered and air-dried. The dried extracts were gathered, measured, and preserved in sealed airtight containers until further use in the preparation of the polyherbal formulation [15,17–20].

Polyherbal Formulation (PHF)

A polyherbal formulation (PHF) was developed in this study to explore its potential in treating gastric ulcers, drawing upon traditional medicine principles that emphasize the synergistic action of multiple plant components. The formulation included hydroalcoholic extracts of six medicinal plants—*Sphaeranthus indicus*, *Allium sativum*, *Azadirachta indica*, *Madhuca indica*, *Ficus religiosa*, and *Glycyrrhiza glabra*—all known for their gastroprotective and antioxidant properties. Each plant was subjected to standardized hydroalcoholic extraction (ethanol: water, 1:1) through a 7-day maceration process with periodic stirring. The extracts were filtered, evaporated, and combined in fixed proportions based on prior screening data. The resulting mixture was homogenized and diluted with purified water to a final volume of 20 mL for oral use [21]. The PHF was given at four dose levels: 15%, 25%, 50%, and 100% of the therapeutic dose (1180 mg/kg). Its antiulcer efficacy was assessed in Wistar rats using Naproxen- and acetic acid-induced models of acute and chronic gastric ulcers. This formulation process aimed to maximize the therapeutic synergy of phytochemicals, targeting multiple ulcer-related mechanisms, including oxidative stress, inflammation, and mucosal degradation. The favorable outcomes in preclinical models highlight PHF’s promise as a natural, multi-targeted alternative to conventional antiulcer drugs [22].

Experimental Animals

Adult male Wistar rats, weighing 180–250 g, were housed under standard laboratory conditions, including a temperature of 25 ± 2°C, relative humidity of 55 ± 5%, and a 12-hour light/dark cycle, with free access to food and water [23]. Approval for experimenting was obtained from the Institutional Animal Ethics Committee (IAEC), and all experimental protocols were conducted in accordance with CPCSEA regulations [24].

INDUCTION OF GASTRIC ULCERS

Naproxen-Induced Ulcer Model

Before inducing ulcers, the animals were deprived of food for 24 hours. Ulcers were induced with oral administration of Naproxen at a dose of 20 mg/kg once daily for three consecutive days. The animals were then treated with the PHF or omeprazole for 7 days. On day eight, the rats were euthanized, and their stomachs were extracted and analyzed for ulcer index [25].

Acetic Acid-Induced Ulcer Model

Rats were anesthetized with an intraperitoneal injection of ketamine at 50 mg/kg. Subsequently, they received 0.05 mL of glacial acetic acid to the anterior serosal surface of the stomach through a cylindrical tube [26]. After 60 seconds, the area was rinsed with saline. Animals were treated with PHF or omeprazole for 10 days, after which ulcer indices were evaluated.

EVALUATION PARAMETERS

Ulcer Index and Percentage Protection

Gastric ulceration was evaluated macroscopically by examining the inner mucosal surface of the rat stomachs. After experimental induction of ulcers (via Naproxen, or acetic acid), the stomachs were collected, longitudinally opened along the greater curvature, washed with saline, and assessed for ulcer lesions [27,28]. The ulcerated area was measured using a dissecting microscope or digital caliper, and the Ulcer Index (UI) was calculated based on lesion severity and area. Ulcer inhibition was quantified using the following equation: The mathematical formula for calculating the ulcer index and percentage protection is as follows:

$$\boldsymbol{Ulcer\ Index\ (UI)} = \frac{(\boldsymbol{Unhealed\ ulcer\ area\ in\ treated\ group})}{(\boldsymbol{Ulcer\ area\ in\ control\ group})} \times \mathbf{100}$$

$$\%\ \boldsymbol{Protection} = \frac{(\boldsymbol{UI\ of\ control} - \boldsymbol{UI\ of\ treated})}{\boldsymbol{UI\ of\ control}} \times \mathbf{100}$$

A detailed description of the ulcer scoring method, including both lesion size and severity scale. The criteria specify that ulcers were scored based on severity: 0 = Normal mucosa, 1 = Red coloration, 2 = Spot ulcers, 3 = Hemorrhagic streaks, 4 = Ulcers >3 mm, 5= Perforation.

The measurement of lesion size was carried out using digital calipers, and the cumulative score per animal was used to derive the ulcer index. This provided a quantitative measure of the gastroprotective effect of the polyherbal formulation (PHF) in different experimental models.

Histopathological Studies

Samples of stomach tissue from each group were immersed in 10% formalin for fixation [29] and processed for paraffin embedding. Using a microtome, 5 µm-thick slices were obtained and stained with H&E dye. The stained samples were later examined under a light microscope to observe the structural features of the gastric lining [30]. Parameters such as mucosal erosion, ulceration, edema, inflammatory cell infiltration, and blood vessel congestion were assessed. Histopathological findings provided corroborative evidence for the macroscopic outcomes and confirmed the protective effect of PHF on gastric tissue architecture [31].

Statistical analysis

Data are presented as mean ± SEM & and statistical evaluation was performed using GraphPad Prism version 5.0. To assess statistical significance ($p<0.05$), data were subjected to two-way ANOVA with Bonferroni correction & one-way ANOVA with Dunnett's multiple comparison test [27,32].

RESULT AND DISCUSSION

The Percentage Yield of extracts

Hydroalcoholic extraction of six medicinal plants was carried out using maceration with ethanol: water (1:1) at room temperature. The hydroalcoholic extraction yielded varying quantities of plant constituents, with *Sphaeranthus indicus* showing the highest yield (51%), followed by *Madhuca indica* (45.6%), *Azadirachta indica* (45%), *Allium sativum* (38%), *Ficus religiosa* (28%), and *Glycyrrhiza glabra* (20%).

Effect of PHF on Naproxen-Induced Ulcers

The polyherbal formulation (PHF) exhibited significant gastroprotective activity in the naproxen-induced ulcer model. Naproxen administration caused pronounced gastric mucosal injury, evidenced by a high ulcer index in the induction control group across the 10th, 20th, and 30th days (1.66 ± 0.03, 1.41 ± 0.02, and 1.10 ± 0.01, respectively) [33]. In contrast, treatment

with the standard drug omeprazole (30 mg/kg) led to a substantial reduction in ulcer index to 0.91 ± 0.03, 0.56 ± 0.01, and 0.16 ± 0.01, respectively ($p<0.05$ to $p<0.001$), confirming its efficacy as shown in Table 1. PHF administered at various concentrations (15%, 25%, 50%, and 100% of the effective dose) produced a graded reduction in ulcer index. At 1180 mg/kg (100% dose), PHF significantly reduced the ulcer index to 0.85 ± 0.01, 0.75 ± 0.01, and 0.44 ± 0.02 on days 10, 20, and 30, respectively ($p<0.05$ to $p<0.001$), nearing the protection level of omeprazole (67.45% protection vs. 72.63%). Similar dose-related improvements were observed at 590 mg/kg (48.52% protection) (Figures 1 and 2).

Acetic Acid-Induced Ulcers

The polyherbal formulation (PHF) also demonstrated significant antiulcer activity in the acetic acid-induced chronic ulcer model [35,36]. The induction control group exhibited a high ulcer index of 10.87 ± 0.12 and an ulcerated area of 74.48 ± 9.24 mm², reflecting severe mucosal damage (**Table 2**). Treatment with the standard drug omeprazole (30 mg/kg) resulted in a marked reduction in both the ulcer index (2.00 ± 0.09) & ulcerated area (14.35 ± 4.89 mm²), with high statistical significance (***$p < 0.001$), corresponding to a protection rate of 70.12%. The PHF, administered at increasing doses, showed reductions in ulcer parameters. At 1180 mg/kg (100% dose), the ulcer index significantly decreased to 2.21 ± 0.01, and the ulcerated area was 15.02 ± 5.36 mm², yielding 61.25% protection—comparable to omeprazole ($p<0.001$). Similarly, the 590 mg/kg dose (50%) reduced the ulcer index to 2.67 ± 0.01 and ulcerated area to 18.35 ± 8.47 mm² ($p<0.001$). Lower doses (15% and 25%) showed modest protective effects with less statistical significance, indicating a clear dose-response relationship (Figures 3 & 4).

Table 1: Effect of PHF on Naproxen-Induced Ulcers

Group	10 Days (UI)	20 Days (UI)	30 Days (UI)
Induction Ctrl (Naproxen 30mg/kg., p.o)	1.66 ± 0.03	1.41 ± 0.02	1.10 ± 0.01
Reference standard (Omeprazole 30mg/kg, p.o)	0.91±0.03*	0.56±0.01**	0.16±0.01***
PHF 15%	1.25 ± 0.03	1.10 ± 0.07	0.69 ± 0.04*
PHF 25%	1.18 ± 0.02	0.91 ± 0.01	0.51 ± 0.02*
PHF 50%	0.94 ± 0.01*	0.80 ± 0.01**	0.48 ± 0.02***
PHF 100%	0.85 ± 0.01*	0.75 ± 0.01**	0.44 ± 0.02***

All data were analyzed using two-way ANOVA followed by the Bonferroni test [34]. *UI = Ulcer Index; *p<0.05, **p<0.01, ***p<0.001 vs Induction Contro

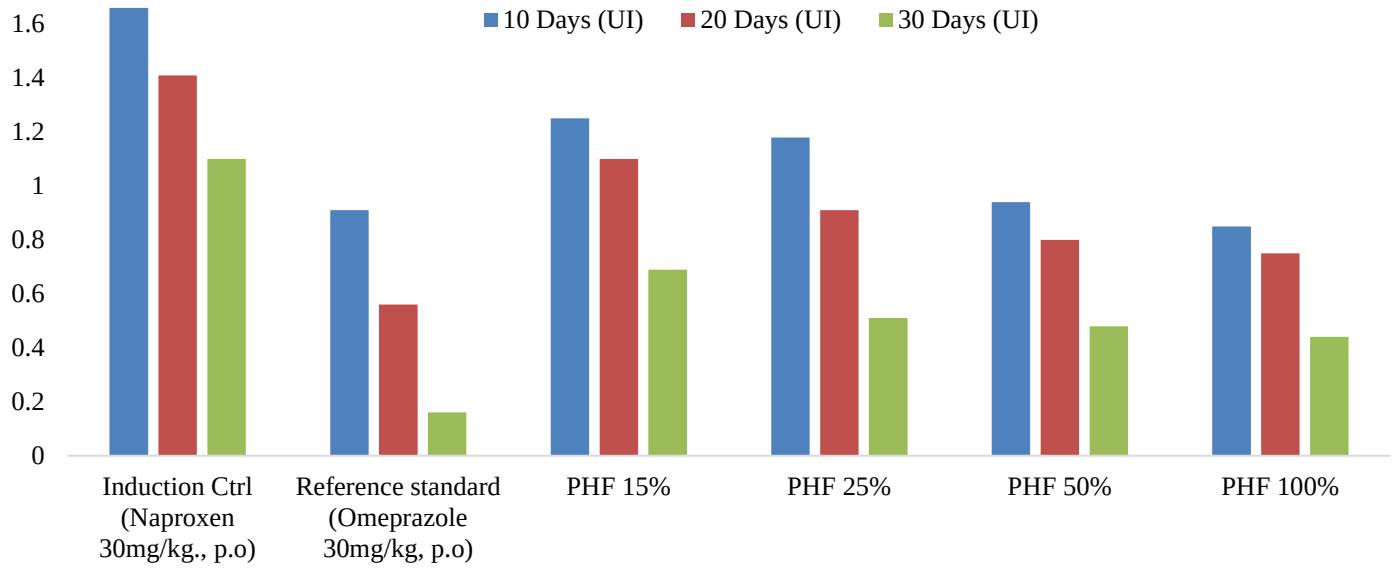

Figure 1: Histogram representing the effect of PHF on ulcer index (UI) in Naproxen-induced ulcers at 10, 20, and 30 days. Values are expressed as mean ± SEM (n =3). Treatment groups include Induction Control (Naproxen 30 mg/kg, p.o.), Reference Standard (Omeprazole 30 mg/kg, p.o.), and PHF at 15%, 25%, 50%, and 100%. Data were analyzed using two-way ANOVA followed by Bonferroni's post hoc test. *p < 0.05, **p < 0.01, *p < 0.001 vs. Induction Control.

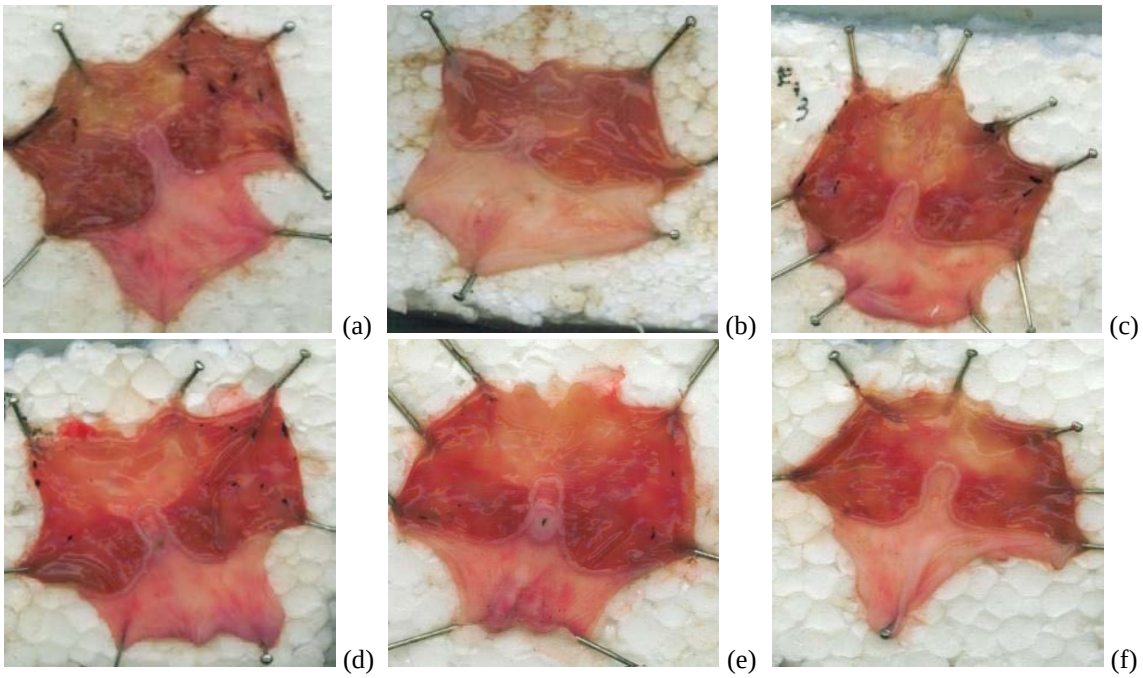

Figure 2: Morphological alterations in the pyloric antrum tissue of rats in the Naproxen-induced ulcer model. a) Naproxen Control group, b) Standard Omeprazole, c) PHF 15%, d) PHF 25%, e) PHF 50%, f) PHF 100%. Groups include Control (Naproxen), Standard (Omeprazole, 30 mg/kg), and PHF treatments at 15%, 25%, 50%, and 100% concentrations.

Table 2: Effect of PHF on Acetic Acid-Induced Ulcers

Group	Ulcerated area (mm²)	Ulcer Index
Induction Ctrl (Acetic acid)	74.48 ± 9.24	10.87 ± 0.12
Omeprazole (30mg/kg, p.o)	14.35±4.89***	2.00±0.09***
PHF 15%	58.94 ± 7.34ns	8.59 ± 0.04ns
PHF 25%	19.98 ± 2.07**	2.97 ± 0.02**
PHF 50%	18.35 ± 8.47***	2.67 ± 0.01***
PHF 100%	15.02 ± 5.36***	2.21 ± 0.01***

***UI = Ulcer Index; *p<0.05, **p<0.01, ***p<0.001 vs Induction Control**

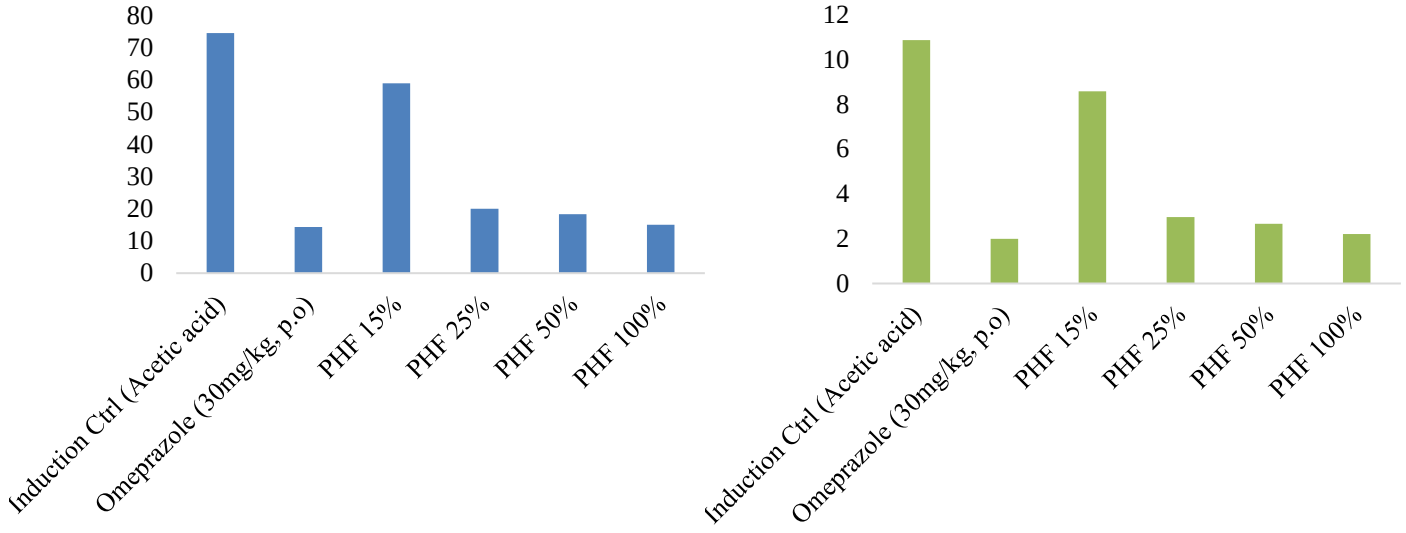

Figure 3: Histogram illustrating the effect of PHF on acetic acid–induced gastric ulcers in rats. Bars represent mean ± SEM (n=3) for ulcerated area (mm²) and ulcer index (UI). Treatment groups include Induction Control (acetic acid), Standard (Omeprazole, 30 mg/kg, p.o.), and PHF at 15%, 25%, 50%, and 100%. Data were analyzed using two-way ANOVA followed by Bonferroni's post hoc test. ns = not significant; *p < 0.05, **p < 0.01, *p < 0.001 vs. Induction Control.

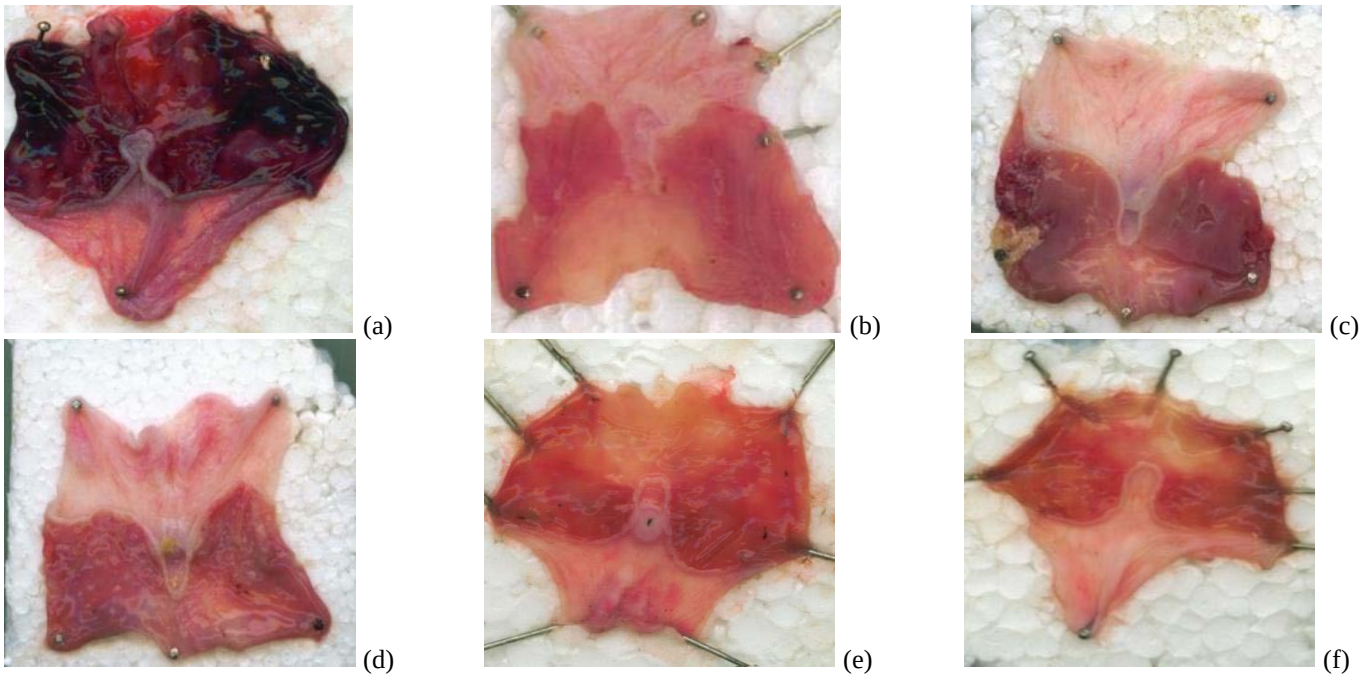

Figure 4: Morphological alterations in the gastric mucosa of rats in the acetic acid–induced ulcer model, a) Acetic acid-induced control group, b) Standard omeprazole 30mg/kg, c) PHF 15%, d) PHF 25%, e) PHF 50%, f) PHF 100%. Treatment groups include Control (acetic acid), Standard (Omeprazole, 30 mg/kg), and PHF at concentrations of 15%, 25%, 50%, and 100%.

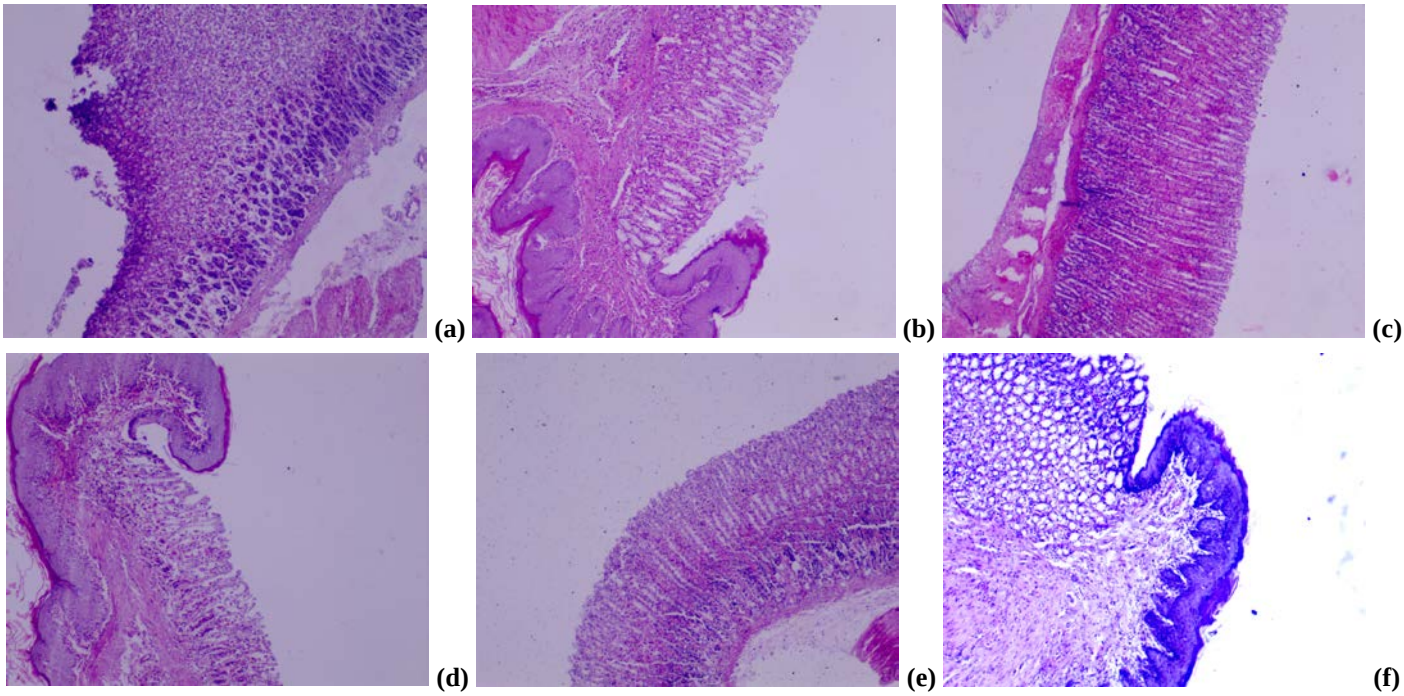

Figure 5: Histopathological changes in the pyloric antrum tissue of rats in Naproxen-induced ulcers: The Naproxen-treated group shows ulcer formation and mononuclear cell infiltration, a) Naproxen (Stomach):- Presence of ulcer (Arrow), and Infiltration of MNC, H&E 10 X, b) Std. (N) (Stomach):- No abnormality Detected, H&E 4 X, c) PHF 15% (Stomach):- Infiltration of MNC, H&E 4 X, d) PHF 25% (Stomach):- Desqamation of Epithelium, H&E 4 X, e) PHF 50% (Stomach):- No abnormality detected H&E 4 X f) PHF 100% (Stomach):- No abnormality detected, H&E 4 XThe standard control (Std. N) and PHF (50% and 100%) groups exhibit standard mucosal architecture without abnormalities. PHF 15% shows mild inflammatory cell infiltration, while PHF 25% reveals epithelial desquamation.

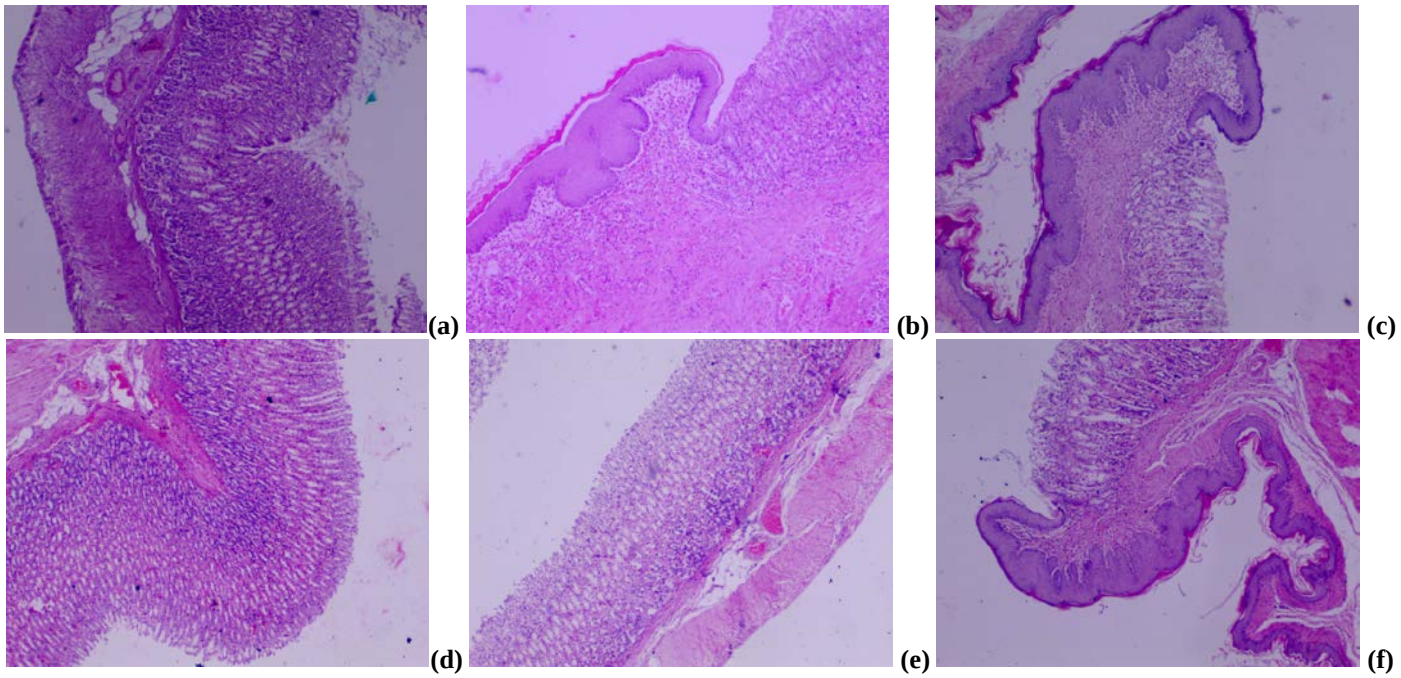

Figure 6: Histopathological changes in the pyloric antrum tissue of rats in Acetic acid-induced ulcers: The acetic acid-treated group shows ulcer formation, a) Acetic acid (Stomach):- Presence of ulcer, H&E 4 X, b) Std. (Stomach):- No Abnormality Detected, H&E 4 X, c) PHF 15 % (Stomach):- No abnormality detected, H&E 4 X, d) PHF 25 %. (Stomach):- Minimal congestion, H&E 4 X, e) PHF 50 % (Stomach):- No Abnormality detected, H&E 4 X, f) PHF 100 %. (Stomach):- No abnormality detected, H&E 4 XPHF 25% group exhibits minimal congestion, while PHF 15%, PHF 50%, and PHF 100% groups, along with the standard control, display normal mucosa without detectable abnormalities.

Histopathological Studies

Histological assessment revealed that PHF-treated groups preserved mucosal architecture and reduced inflammation, congestion, and necrosis compared to induction controls [37–39]. High-dose PHF groups displayed nearly standard histological profiles (Figure 5 & Figure 6).

Statistical Analysis

The results are shown as mean ± SEM and were evaluated using one-way or two-way ANOVA, followed by Dunnett's or Bonferroni post hoc tests. Statistical significance was considered significant at a p-value of less than 0.05 [40].

The current study evaluated the gastroprotective efficacy of a polyherbal formulation (PHF) composed of *Sphaeranthus indicus, Allium sativum, Azadirachta indica, Madhuca indica, Ficus religiosa, and Glycyrrhiza glabra* in Wistar rats using Naproxen- and acetic acid-induced gastric ulcer models. Both models effectively simulated acute and chronic ulcerative conditions, allowing a comprehensive assessment of the formulation's protective potential. The PHF demonstrated a significant reduction in ulcer index and improved gastric parameters such as pH, mucin content, and volume. Notably, the 1180 mg/kg dose of PHF approached the efficacy of the standard drug omeprazole, providing up to 67.45% and 61.25% protection in Naproxen and acetic acid-induced ulcers, respectively. Histopathological evaluations corroborated these findings, showing preserved mucosal architecture and reduced inflammatory cell infiltration in PHF-treated groups [41]. The antiulcer effects may be attributed to the synergistic actions of bioactive compounds in the formulation, such as flavonoids, saponins, tannins, and glycosides. These compounds likely enhance mucosal defense by exerting antioxidant, anti-inflammatory, and cytoprotective effects [42]. Overall, the findings suggest that the PHF effectively mitigates ulcerative damage, promotes mucosal healing, validates its traditional use, and encourages further pharmacological and clinical investigations.

CONCLUSION

The present study demonstrated that the standardized polyherbal formulation (PHF), comprising *Sphaeranthus indicus, Allium*

sativum, *Azadirachta indica*, *Madhuca indica*, *Ficus religiosa*, and *Glycyrrhiza glabra*, significantly reduced ulcer indices and restored gastric mucosal integrity in both Naproxen- and acetic acid-induced gastric ulcer models in Wistar rats. The antiulcer activity of the formulation increased with dose, with the highest dose (1180 mg/kg) providing ulcer protection comparable to that of the standard drug, omeprazole.

Histopathological findings affirmed the formulation's antioxidant, anti-inflammatory, and cytoprotective mechanisms. However, the study is limited to preclinical models, and further studies are required to validate the efficacy, safety & mechanisms of action in clinical settings. Additionally, the interaction of individual phytoconstituents and their pharmacokinetic profiles was not explored in this work. Given the increasing incidence of NSAID-induced ulcers and the growing demand for safer, plant-based therapies, this study underscores the relevance of polyherbal approaches as promising alternatives. The findings provide a foundation for future translational research and development of standardized herbal antiulcer therapeutics aligned with global trends in integrative medicine.

The study presents strong preclinical evidence supporting the antiulcer potential of a polyherbal formulation (PHF) composed of *Sphaeranthus indicus, Allium sativum, Azadirachta indica, Madhuca indica, Ficus religiosa, and Glycyrrhiza glabra*. To advance PHF towards clinical use, further research is needed. Future directions include mechanistic studies to clarify molecular pathways, such as prostaglandin synthesis, nitric oxide signaling, mucosal repair, and cytokine-mediated inflammation. The isolation and characterization of bioactive compounds through LC-MS/MS, HPLC, and NMR will aid in standardization and facilitate regulatory approval. Pharmacokinetic and pharmacodynamic studies are crucial for determining absorption, metabolism, and optimal dosing. Innovative formulation strategies (e.g., nanoemulsions or phytosomes) can improve bioavailability, while stability testing under ICH guidelines will ensure shelf-life and storage conditions. Comprehensive chronic toxicity assessments are needed to establish long-term safety. Translational research should include clinical trials that focus on efficacy, symptom relief, mucosal healing, and quality of life, aligning with AYUSH and CDSCO protocols. Given its antioxidant and anti-inflammatory properties, the PHF's therapeutic scope may extend to other gastrointestinal disorders, such as GERD, IBS, and IBD. These steps are critical for the successful clinical translation of PHF.

FINANCIAL ASSISTANCE
NIL

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTION
Kiran Niuratti Khodake contributed to conceptualization and visualization. He also contributed to writing, editing, and reviewing the manuscript's first draft. Sushil Bhargav supervised the whole study. He reviewed and edited the manuscript's first draft.

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