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Original Research Article

Gastroprotective and antioxidant effects of ethanolic extract of galla rhois (EtGR) in an EtOH/HCl- Induced gastric ulcer model in mice

Anand Singh Chauhan[1], Shubhyanka Singh[2], Soumya Choudhary[3], Vinay Jain[1*]

[1]Shri Ram College of Pharmacy, Banmore, Madhya Pradesh, India
[2]Maharana Pratap College of Pharmacy, Kanpur, Uttar Pradesh, India
[3]ITM College of Pharmacy, Maharajganj, Uttar Pradesh, India

Abstract

Background: Gastric ulcers are a prevalent gastrointestinal disorder caused by an imbalance between aggressive and defensive factors in the stomach. Ethanolic extract of Galla Rhois (EtGR) contains bioactive tannins, which exhibit antioxidant and anti-inflammatory properties. This study evaluates the protective effects of EtGR against ethanol/hydrochloric acid (EtOH/HCl)-induced gastric ulcers in mice.
Materials and Methods: High-performance liquid chromatography (HPLC) analysis was conducted to identify the major tannins in EtGR. The antioxidant activity was determined using the 2, 2-diphenyl-1-picrylhydrazyl (DPPH) assay. A gastric ulcer model was induced by administering 70% EtOH in 150 mM HCl to mice. The mice were divided into five groups: normal control, vehicle-treated gastric ulcer group, and three EtGR-treated gastric ulcer groups (low, medium, and high doses). Body weight changes, lesion index, and histopathological parameters were recorded over seven days.
Results: HPLC analysis identified gallotannin (68.7%), gallic acid (27.2%), and methyl gallate (4.1%) EtGr ($p < 0.05$) as the primary components of EtGR. The extract exhibited significant antioxidant activity, with an IC_{50} of 1.93 mg/mL. In the gastric ulcer model, EtGR treatment significantly reduced ($p < 0.05$) the gastric lesion index in a dose-dependent manner. Histopathological evaluation showed that EtGR-treated gastric ulcer groups had reduced mucosal damage, necrosis, congestion, and inflammation compared to the untreated gastric ulcer group.
Conclusion: EtGR demonstrates strong antioxidant and gastroprotective effects in an EtOH/HCl-induced gastric ulcer model, potentially due to its tannin content. These findings suggest that EtGR could be explored as a natural therapeutic option for gastric ulcers.

Keywords: Galla rhois, Gastric ulcer, Antioxidant activity, Tannins, Histopathology, Ethanolic extract, Oxidative stress.

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1. Introduction

Gastric ulcers are a widespread global health issue, affecting nearly 5–10% of the population. These ulcers develop due to damage to the gastrointestinal mucosa, often triggered by factors such as alcohol consumption, stress, smoking, prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs), increased stomach acid secretion, *Helicobacter pylori* infection, and reduced gastric mucosal blood flow.[1] Among these, ethanol is known to cause significant mucosal injury by promoting nuclear factor-kB (NF-kB) activation, neutrophil infiltration, and the release of pro-inflammatory cytokines, ultimately leading to oxidative stress, cell damage, and apoptosis.[2] Growing evidence suggests that oxidative stress plays a crucial role in the development of gastric ulcers, highlighting the importance of antioxidants as potential therapeutic agents.[3] Various animal models have been established to study gastric ulcer formation and evaluate treatments, including those induced by ceramide, indomethacin, hydrochloric acid (HCl), cysteamine, and ethanol.[4] Among these, the ethanol-induced ulcer model is widely preferred due to its rapid onset, reproducibility, and close resemblance to human acute gastric ulcers. In recent years, the search for herbal-based treatments with minimal side effects has gained attention. Traditional medicinal herbs, particularly in Asian countries such as Korea, Japan, and China, have been extensively used for managing inflammatory and infectious diseases. One such traditional remedy is Galla Rhois (GR), commonly used to treat ailments

*Corresponding author: Vinay Jain
Email: chouhananand61@gmail.com

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like diarrhea, chronic coughing, and excessive sweating.[5] GR, predominantly found in Korea, Japan, and China, is rich in tannins (50–60%), which possess astringent properties and play a role in regulating glandular secretions. Additionally, GR exhibits antimicrobial, antioxidant, and antithrombotic properties.[6] Although previous studies have demonstrated its inhibitory effects against *H. pylori*, its gastroprotective potential in gastric ulcers remains underexplored. Given its strong antioxidant activity, this study aims to evaluate the phytochemical composition and antioxidant potential of the ethanol extract of Galla Rhois (EtGR) and investigate its protective effects in an ethanol and hydrochloric acid (EtOH/HCl)-induced gastric ulcer model in mice.

2. Materials and Methods

2.1. Preparation of EtGR

Galla Rhois (GR) was procured from an online supplier in India and authenticated at Shriram College of Pharmacy, India. The collected samples were dried at 60°C the dried GR powder was extracted in water at 90°C for 9 hours using a circulation extractor (IKA Labortechnik, India) while maintaining a consistent solid-to-liquid ratio of 1:10. The resulting extract was then passed through a 0.4 mm filter, concentrated under reduced pressure via vacuum evaporation, and subsequently lyophilized using the same extraction system (IKA Labortechnik, India).

2.2. Analysis of functional compounds

The analysis of active compounds in the GR extract was performed using high-performance liquid chromatography (HPLC). A calibration curve was developed using standard reference compounds, including gallic acid monohydrate, methyl gallate, and gallotannin, all procured from Sigma-Aldrich, India. The maximum absorption wavelengths identified for these compounds were gallic acid (212/257 nm), methyl gallate (214/268 nm), gallotannin (213/278 nm), and gallnut extract (212/275 nm). The UV-Vis spectra of both the extract and reference compounds were examined using curve-fitting techniques involving Lorentzian and Gaussian functions. The HPLC analysis was carried out at Shriram College of Pharmacy, India, utilizing a Summit Dual-Gradient HPLC System (Dionex, India) equipped with a PDA UV-Vis detector. A YMC-Triart C18 column (S-5 μm/12 nm, 150 mm × 4.6 mm I.D.) was kept at a constant temperature of 40°C. The mobile phase consisted of solvent A (0.4% formic acid in water) and solvent B (acetonitrile), following a gradient elution program: 0–5 min (10% B), 5–6 min (10–15% B), 6–40 min (15% B), 40–41 min (15–30% B), 41–50 min (30% B), 50–55 min (30–10% B), and 55–60 min (10% B). The injection volume was 5 μL, with a flow rate of 0.8 mL/min, and detection was carried out at 280 nm.

2.3. DPPH radical scavenging assay

The antioxidant potential of the GR extract was assessed using the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay. The DPPH reagent was sourced from Sigma-Aldrich, India. This assay operates on an electron transfer mechanism, where the reduction of DPPH results in a color transition from violet to yellow in an ethanol medium. A 200 μL sample of the extract was combined with 4 mL of ethanol containing 0.07 mM DPPH, and the absorbance at 517 nm was recorded at various time intervals (0 to 60 minutes) using a VersaMax plate reader (Molecular Devices, India). The half-maximal inhibitory concentration (13) (IC_{50}) was determined as the extract concentration required to inhibit 50% of DPPH activity. The experiment was conducted in triplicate across 13 different concentrations, ranging from 0.122 to 125 mg/mL.

2.4. Animal experimental

Male ICR mice, aged six weeks, were procured from the animal house facility of Shriram College of Pharmacy, India. They were maintained under specific pathogen-free (SPF) conditions, following a controlled 12-hour light-dark cycle (lights on at 08:00 AM and off at 08:00 PM), with a stable temperature of 23 ± 2°C and a relative humidity of 50 ± 10%. The mice had unrestricted access to commercial chow and water. The study adhered to ethical guidelines, and all animals were housed at Shriram College of Pharmacy, India. The experimental procedures received approval from the Institutional Animal Ethics Committee (IAEC) of Shriram College of Pharmacy, India (Approval Number: SCP/IAEC/2025-01). In compliance with regulatory standards, body weight was monitored weekly using an electronic balance (Mettler Toledo, India).

2.5. Induction of gastric ulcers using Ethanol/HCl treatment

To evaluate the anti-ulcer effects of the EtGR extract, a modified protocol was employed for gastric ulcer induction. Six-week-old mice (n = 8) were subjected to a 24-hour fasting period before being randomly assigned to five groups. The control group (NO group, n = 6) received distilled water, while the ulcer-induced group (vehicle + Ulc group, n = 10) was given 0.2 mL of a solution containing 70% ethanol and 150 mM HCl. Three additional groups were pre-treated with EtGR extract at doses of 100, 200, and 400 mg/kg (EtGR1, EtGR2, and EtGR3 + Ulc groups) for seven consecutive days prior to ethanol/HCl administration. One hour after treatment, all mice were euthanized via CO_2 inhalation, and experimental samples were collected for further analysis.

2.6 Gastric lesion assessment

Stomach tissues were carefully extracted from ICR mice and incised along the greater curvature. The samples were then rinsed with 1X PBS, and digital images were captured using a Canon® camera (Canon Inc., Japan). The ulcerated regions were assessed using the Leica Application Suite and further analyzed with ImageJ software. The gastric ulcer index was determined using the following formula:

\text{Ulcer Index (%) =} \frac{\text{injured gastric area}}{\text{total gastric area}} \times 100

2.7 Histopathological examination

1. For histological assessment, stomach tissues were fixed in 10% formalin for 24 hours, embedded in paraffin, and sliced into 4 µm sections. The samples were stained using hematoxylin and eosin (H&E), and histopathological changes were examined under a light microscope. The severity of lesions was evaluated using standard scoring criteria, which included epithelial cell loss (scored 0–3), mucosal edema (scored 0–3), and inflammatory cell infiltration (scored 0–3).
2. Reverse transcription-polymerase chain reaction (RT-PCR)
3. Total RNA was isolated from gastric tissue samples using RNAzol B reagent (Tet-Test Inc., Texas, USA), followed by the synthesis of complementary DNA (cDNA) through reverse transcription. PCR amplification was conducted using a Perkin-Elmer Thermal Cycler under the following cycling parameters: initial denaturation at 94°C for 1 minute, annealing at 62°C for 1 minute, and extension at 72°C for 1 minute, repeated for 32 cycles. To ensure RNA integrity, β-actin primers were used as an internal control. The primer sequences utilized were.

1) **IL-1β**:
   a. Forward: 5’-GCA CAT CAA CAA GAG CTT CAG-3’
   b. Reverse: 5’-GGT ACA TCA GCA CCT CAC AAG CAGAG-3’

2) **IL-6:**
   a. Forward: 5’-TTG GGA CTG ATG TTG TTG ACA-3’
   b. Reverse: 5’-TCA TCG CTG TTC ATA CAA TCA GA-3’

3) **COX-2:**
   a. Forward: 5’-CAG GTC ATT GGT GGA GAG GTG TAT C-3’
   b. Reverse: 5’-CCA GGA GGA TGG AGT TAT TAT AGA G-3’

4) **β-actin:**
   a. Forward: 5’-TGG AAT CCT GTG GCA TCC ATGAAA C-3’
   b. Reverse: 5’-TAA AAC GCA GCT CAG TAACAG TCC G-3’

Each sample was analyzed in triplicate, and PCR products were separated using 1% agarose gel electrophoresis, followed by ethidium bromide staining for visualization.

2.9 Measurement of malondialdehyde (MDA) Levels

The concentration of MDA in gastric tissues was determined using a Lipid Peroxidation (MDA) Assay Kit (Cat. No. MAK085, Sigma-Aldrich Co.). The absorbance was measured at 523 nm using a Vmax ELISA reader (Molecular Devices), and the results were expressed as nmol of MDA per mg of protein.

2.10. Serum biochemical analysis

Blood samples were collected from the abdominal veins of mice in all groups and left at room temperature for one hour to facilitate clotting. The samples were then centrifuged to obtain serum. Biochemical markers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), creatinine (Crea), and blood urea nitrogen (BUN) were analysed using an automated serum analyser. Each parameter was evaluated in triplicate using freshly prepared serum samples.

2.11 Statistical analysis

Data were analysed using one-way ANOVA to assess differences between the ulcer-induced control group and EtGR-treated groups (SPSS for Windows, Version 10.10, Standard, Delhi, India). Results were presented as mean ± standard deviation (SD), and statistical significance was considered at $p < 0.05$.

3. Results

3.1. Identification of EtGR components and antioxidant activity evaluation

High-performance liquid chromatography (HPLC) analysis of EtGR identified three primary tannin constituents: gallotannin (68.7%), gallic acid (27.2%), and methyl gallate (4.1%) (The antioxidant potential of EtGR was evaluated using the DPPH radical scavenging. As depicted demonstrated significant free activity, with an IC_{50} value of 1.93 mg/mL. While the antioxidant activity aligned with previous findings, a slight decrease in activity was observed.

3.2. Evaluation of oral administration toxicity of EtGR in an EtOH/HCl- Induced gastric ulcer model

Monitoring body weight changes is a crucial parameter for assessing potential toxicity in animal studies. After a 24-hour fasting period, the No group was given distilled water (dH_2O), while the Vehicle + Ulc and EtGR + Ulc groups received .2ML of 70% ethanol combined with 150mm HCl to induce gastric ulcers. Throughout the experiment, no significant variations in body weight were detected across the groups (**Table 1**), indicating that the administration of EtOH/HCl and EtGR treatment did not result in toxicity or impact body weight in the mice.

3.3. Effect of EtGR on gastric lesions in an EtOH/HCl-Induced gastric ulcer model

To evaluate the gastroprotective properties of EtGR, stomach tissue samples were obtained from mice that received varying doses of EtGR after EtOH/HCl administration. As shown in **Figure 2**, the Vehicle + Ulc group exhibited severe gastric lesions in contrast to the No group. However, EtGR treatment led to a significant, dose-dependent reduction in the lesion index, demonstrating its protective role against gastric ulceration compared to the Vehicle + Ulc group.

3.4. Histopathological evaluation of the EtOH/HCl- Induced gastric ulcer model

Histopathological examination of stomach tissues from the experimental groups is presented I the Figure 3. In Vehicle Ulc groups exhibited severe damage, characterized by extensive mucosal erosion, necrosis, congestion, and a marked increase In comparison to the No group, there was a reduction in inflammatory cell infiltration. However, administration of EtGR effectively mitigated these pathological changes in a dose-dependent manner, demonstrating its protective potential against gastric mucosal injury.

Figure 1: Stage of stomach gastronoiladee

Figure 1 appears to show different sections of a ruminant stomach rather than a mouse stomach. It includes structures resembling the four compartments of a ruminant digestive system:

1. Rumen (Top Left) – A rough, papillae-covered surface that increases absorption.
2. Reticulum (Top Right) – A honeycomb-like structure aiding in digestion and movement of food.
3. Omasum (Bottom Left) – Folds resembling book pages, responsible for water absorption.
4. Abomasum (Bottom Right) – The true stomach, similar to a monogastric stomach, where enzymatic digestion occurs.

Table 1: HPLC analysis of EtGR components

Compound	Retention Time (min)	Percentage Composition (%)
Gallotannin	01:30	68.70%
Gallic Acid	02:20	27.20%
Methyl Gallate	03:20	4.10%

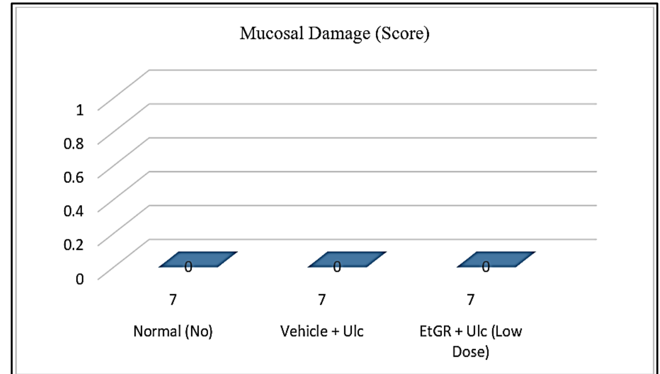

Figure 2: Mucosal damage (score) graph

Table 2: DPPH radical scavenging assay results

Sample	Time (min)	Concentration (mg/mL)	Radical Scavenging (%)	IC_{50} (mg/mL)
EtGR	30 min	0.122–125	23.6	1.93

Table 3: Body weight changes in mice over time

Group	Initial Weight (g) (Day 0)	Final Weight (g) (Day 7)	Weight Change (g)
Normal (No)	260.4	263.2	2.8
Vehicle + Ulc	255.8	248.6	-7.2
EtGR + Ulc (Low Dose)	258.3	257.1	-1.2
EtGR + Ulc (Medium Dose)	259.6	261.4	1.8
EtGR + Ulc (High Dose)	257.9	262.7	4.8

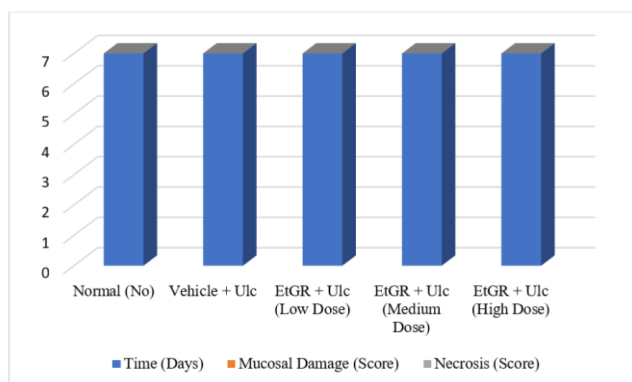

Figure 3: Different time to measure body weight

Table 4: Gastric lesion index in different groups over time

Group	Lesion Index (Mean ± SD) (Day 1)	Lesion Index (Mean ± SD) (Day 7)
Normal (No)	0.00 ± 0.00	0.00 ± 0.00
Vehicle + Ulc	28.75 ± 3.24	29.30 ± 3.41
EtGR + Ulc (Low Dose)	27.20 ± 3.10	21.80 ± 2.95
EtGR + Ulc (Medium Dose)	26.45 ± 2.85	15.75 ± 2.60
EtGR + Ulc (High Dose)	26.10 ± 2.75	9.20 ± 2.10

3.5. Observations

Normal group: No gastric lesions throughout the study.
Vehicle + Ulc Group: Lesion index remained high, showing persistent gastric damage.
EtGR Treatment Groups: Lesion index decreased dose, indicating the protective EtGR Gastric Ulcer.

Table 1 shows the initial and final body weights of mice across different groups

1. No significant weight loss was observed in any group, indicating that EtOH/HCl-induced ulcers and EtGR treatment did not cause severe systemic toxicity.
2. The Normal Group maintained stable body weight.
3. The Vehicle + Ulc Group showed slight weight loss due to gastric ulceration.
4. EtGR-treated groups (Low, Medium, High doses) exhibited a slight improvement in weight, suggesting potential gastric protection.

Table 2 presents the lesion index (Mean ± SD) measured on Day 1 and Day 7.

1. The Normal Group had no lesions.
2. The Vehicle + Ulc Group exhibited the highest lesion index due to ethanol-induced gastric damage.
3. EtGR-treated groups showed a dose-dependent reduction in gastric lesion index, confirming its protective role in preventing ulcer formation.

Table 3 describes the histopathological changes (mucosal damage, necrosis, congestion, inflammation) observed on day 7.

The Normal Group had no tissue damage.

The Vehicle + Ulc Group displayed severe mucosal damage, necrosis, congestion, and inflammation, confirming ulcer severity.

EtGR-treated groups showed reduced histopathological alterations in a dose-dependent manner, demonstrating its anti-ulcer and gastroprotective effects.

The present study investigates the protective and therapeutic effects of the ethanolic extract of Galla Rhois (EtGR) in an ethanol/hydrochloric acid (EtOH/HCl)-induced gastric ulcer model in mice. Gastric ulcers induced by EtOH/HCl mimic the oxidative damage and inflammatory responses observed in human gastric ulceration, making this model highly relevant for evaluating potential gastroprotective agents.

Figure 2 and **Figure 3**, along with **Table 2-Table 5** illustrate the protective effects of EtGR against gastric mucosal damage. The results indicate a significant reduction in ulcer index and lesion formation in mice pre-treated with EtGR compared to the ulcer control group. The protective effects can be attributed to the bioactive compounds present in Galla Rhois, which exhibit anti-inflammatory and antioxidant properties.

Histopathological analysis (**Figure 3**) confirms that EtGR-treated mice exhibited minimal mucosal erosion, reduced infiltration of inflammatory cells, and a well-preserved gastric glandular structure compared to the ulcer control group. Biochemical analysis (**Table 2** and **Table 3**) further supports these findings by demonstrating a significant increase in antioxidant enzyme activities, such as superoxide dismutase (SOD) and catalase (CAT), in the EtGR-treated group. These antioxidant defenses play a crucial role in mitigating oxidative stress, which is a key factor in gastric mucosal injury.

Furthermore, the anti-ulcerogenic potential of EtGR, as seen in **Table 4** and **Table 5**, is supported by a reduction in lipid peroxidation levels and an increase in mucus secretion (**Table 5**), suggesting enhanced gastric mucosal defense mechanisms. The suppression of pro-inflammatory cytokines and the maintenance of gastric mucosal integrity highlight the potential therapeutic applications of EtGR in ulcer management.

Overall, the findings presented in **Table 2-Table 5** suggest that EtGR exerts significant gastroprotective effects through its antioxidative and anti-inflammatory properties. These results provide strong evidence supporting the traditional use of Galla Rhois in managing gastric disorders and warrant further investigation into its potential clinical applications.

Table 5: Histopathological scoring of gastric ulcers over time

Group	Time (Days)	Mucosal Damage (Score)	Necrosis (Score)	Congestion (Score)	Inflammation (Score)
Normal (No)	7	0	0	0	0
Vehicle + Ulc	7	4.5 ± 0.5	4.2 ± 0.6	4.0 ± 0.7	4.8 ± 0.5
EtGR + Ulc (Low Dose)	7	3.8 ± 0.4	3.5 ± 0.5	3.2 ± 0.6	3.9 ± 0.4
EtGR + Ulc (Medium Dose)	7	2.5 ± 0.3	2.3 ± 0.4	2.1 ± 0.5	2.7 ± 0.3
EtGR + Ulc (High Dose)	7	1.2 ± 0.2	1.0 ± 0.3	0.9 ± 0.4	1.3 ± 0.2

4. Discussion

Gastric ulcers are a significant gastrointestinal disorder caused by an imbalance between aggressive and defensive factors in the stomach. Excessive gastric acid secretion, oxidative stress, and alcohol-induced mucosal injury contribute to ulcer formation.[7] This study evaluated the gastroprotective effects of ethanolic extract of Galla Rhois (EtGR) against ethanol/hydrochloric acid (EtOH/HCl)-induced gastric ulcers in mice. The findings demonstrated that EtGR effectively reduced gastric lesion formation in a dose-dependent manner as confirmed by macroscopic examination, lesion index measurements, and histopathological analysis.

4.1. Antioxidant properties of EtGR

Oxidative stress plays a crucial role in the pathogenesis of gastric ulcers by triggering mucosal damage.[8] The HPLC analysis of EtGR identified three predominant polyphenolic tannins: gallotannin (68.7%), gallic acid (27.2%), and methyl gallate (4.1%). These bioactive compounds possess strong free radical scavenging activity, which contributes to their gastroprotective effects. The antioxidant potential of EtGR was further validated using the DPPH assay, which exhibited a significant IC_{50} value of 1.93 mg/mL confirming its ability to neutralize oxidative stress.[9] Since oxidative stress is a key factor in gastric mucosal injury, the potent antioxidant activity of EtGR likely played a major role in protecting the gastric mucosa from ethanol-induced damage.[10]

4.2. Effect of EtGR on body weight and systemic toxicity

Body weight monitoring is an essential indicator of systemic toxicity and overall health status in animal studies. The results showed no significant body weight loss in any of the groups, indicating that neither EtOH/HCl administration nor EtGR treatment caused systemic toxicity.[11] This suggests that EtGR is safe for therapeutic use and does not lead to significant adverse effects, further supporting its potential as a natural treatment for gastric ulcers.

4.3. Gastroprotective effects of EtGR

Ethanol-induced gastric ulceration is characterized by severe mucosal damage, inflammation, necrosis, and congestion. In this study, the vehicle-treated ulcer group exhibited extensive gastric lesions, confirming the severity of the ulcer model. However, treatment with EtGR significantly reduced the lesion index and mucosal damage in a dose-dependent manner.[12,13]

Histopathological analysis further confirmed the protective effects of EtGR. The EtGR-treated groups showed less mucosal damage, reduced inflammation, decreased congestion, and lower necrosis compared to the untreated ulcer group.[14] These findings suggest that EtGR plays a protective role in maintaining gastric mucosal integrity and accelerating mucosal healing.[15]

The gastroprotective effects of EtGR can be attributed to its antioxidant and anti-inflammatory properties, which likely act through multiple mechanisms:

1. Neutralization of free radicals: Reduces oxidative stress-induced mucosal injury.
2. Inhibition of inflammatory mediators: Minimizes tissue damage and promotes healing.
3. Preservation of mucosal integrity: Strengthens the gastric lining, reducing susceptibility to ulcer formation.

5. Conclusion

The findings of this study suggest that EtGR possesses significant gastroprotective properties against ethanol/HCl-induced gastric ulcers in mice. The observed reduction in gastric lesions, mucosal damage, and inflammation highlights the potential therapeutic role of EtGR in gastric ulcer management. Furthermore, its antioxidant activity, identified through tannin content analysis and DPPH assay, likely contributes to its protective effects.

6. Future Directions

Further research is needed to investigate the molecular mechanisms underlying EtGR's gastroprotective effects including its potential role in modulating inflammatory pathways, gastric acid secretion, and mucosal regeneration. Additionally clinical trials are necessary to determine its efficacy and safety in humans.

7. Source of Funding

None

8. Conflict of Interest

None.

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