Jurnal Farmasi Galenika (*Galenika Journal of Pharmacy*) (e-Journal) 2025; 11 (2): 93 – 105
ISSN: 2442-8744 (electronic); 2442-7284 (printed)
Journal Homepage: https://bestjournal.untad.ac.id/index.php/Galenika
DOI: 10.22487/j24428744.2025.v11.i2.17657

Ethanolic Extract of *Cyclea barbata* Leaves as a Promising Natural Candidate for Anti Peptic Ulcer

(*Ekstrak Etanol Daun Cyclea barbata sebagai Kandidat Alami Antitukak Lambung*)

Dyah Ratna Ayu Puspita Sari [1*], Putu Yudha Ugrasena[2], Ni Putu Rika Mahayani[3]

[1]Progran Studi Farmasi, Fakultas Matematika dan Ilmu Pengetahuan Alam, Universitas Tadulako, Palu, Indonesia.*
[2]Departemen Farmakologi dan Terapi, Fakultas Kedokteran, Universitas Udayana, Denpasar, Indonesia
[3] Program Studi D3 Farmasi, Fakultas Kesehatan, Institut Teknologi dan Kesehatan Bintang Persada, Denpasar, Indonesia.

Article Info:
Received: 23 July 2025
in revised form: 24 July 2025
Accepted: 28 October 2025
Available Online: 30 October 2025

Keywords:
Peptic ulcer
Cyclea barbata
Ulcer Index
Gastric pH.

Corresponding Author:
Dyah Ratna Ayu Puspita Sari
Progran Studi Farmasi
Fakultas MIPA
Universitas Tadulako
Palu
90245
Indonesia
email: ayupuspitadyah8@gmail.com

ABSTRACT

Background: Peptic ulcer disease (PUD) is a persistent gastrointestinal disorder characterized by mucosal damage in the stomach or duodenum. *Cyclea barbata* leaves have been reported to contain bioactive compounds with gastroprotective potential. **Objectives:** This study aimed to evaluate the protective effects of 70% ethanolic extract of *C. barbata* leaves on ethanol-induced gastric ulcers in rats. **Methods:** Thirty male rats were randomly divided into six groups. The groups consisted of a normal control, a negative control (Na CMC 0.5%), a positive control (ranitidine 13.5 mg/kg BW), and three treatment groups that received *C. barbata* ethanolic extract at doses of 100, 200, and 400 mg/kg BW. Treatments were administered orally for 14 consecutive days, and the animals were sacrificed on day 15. Ulcer count, ulcer diameter, ulcer index, and gastric pH were measured. **Results:** The negative control group exhibited an average of 6.4 ulcers. Administration of ranitidine and all tested concentrations of *C. barbata* extract significantly reduced the number of ulcers compared to the negative control. The most pronounced effect was observed at 400 mg/kg BW, yielding an average of 1 ulcer and a significantly lower ulcer index ($p < 0.05$). In contrast, gastric pH values did not differ significantly among the treatment and negative control groups ($p > 0.05$). **Conclusions:** The findings indicated that the ethanolic extract of *C. barbata* leaves exerted gastroprotective activity, with the 400 mg/kg BW dose demonstrating the strongest ulcer-preventive effect.

How to cite (APA 6th Style):
Sari, D. R. A. P., Ugrasena, P. Y., Mahayani, N. P. R. (2025). Ethanolic extract of *Cyclea barbata* leaves as a promising natural candidate for anti-peptic ulcer. *Jurnal Farmasi Galenika: Galenika Journal of Pharmacy (e-Journal), 11*(2), 93-105. doi:10.22487/j24428744.2025.v11.i2.17657

INTRODUCTION

Peptic ulcer disease (PUD) affects approximately four million individuals worldwide each year, with an estimated lifetime prevalence of 5–10% in the general population. Globally, there are considerable disparities in healthcare systems' approaches to the prevention, diagnosis, treatment, and follow-up of PUD (Abbasi et al., 2022). The condition significantly contributes to morbidity and mortality globally, underscoring its effect on public health (S. D. Waldman, 2024). Recent studies have demonstrated a global decline in the prevalence and burden of PUD from 1990 to 2019. In Indonesia, the prevalence of PUD varies among studies and across geographical regions. A study in Jakarta reported a prevalence of 14.3% among patients undergoing endoscopy, with higher rates in males and individuals over 46 years of age (Akbar et al., 2020). In 2019, South Asia, encompassing Indonesia, exhibited the highest age-standardized prevalence rate, with a favourable correlation between socioeconomic position and PUD rates (Xie et al., 2022).

Peptic ulcer disease (PUD) is a chronic gastrointestinal disorder marked by mucosal injury in the stomach or duodenum (Amandeep et al., 2012; Kaushik, 2023). The primary etiological factors include Helicobacter pylori infection and prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs) (Amandeep et al., 2012; Kaushik, 2023; Pandey et al., 2019). *H. pylori* inhabits the stomach mucosa, resulting in inflammation and immune system impairment (Kaushik, 2023). Nonsteroidal anti-inflammatory drugs (NSAIDs) influence prostaglandin synthesis, undermining gastric mucosal integrity (Amandeep et al., 2012; Kaushik, 2023). Additional contributing factors encompass stress, tobacco use, spicy cuisine, and nutritional inadequacies (Amandeep et al., 2012). The development of peptic ulcers is influenced by a variety of factors, including both endogenous and exogenous factors, and free radicals are closely associated with both conditions (Bhattacharyya et al., 2014). Free radicals are directly correlated with peptic ulcers, as they induce oxidative damage, resulting in lipid peroxidation, mucosal injury, and DNA damage. This damage compromises the gastric mucosa's integrity, contributing to the development and exacerbation of peptic ulcers (Pathan et al., 2013). Free radicals, particularly reactive oxygen species (ROS), contribute to cellular damage and inflammation, exacerbating ulcer formation. Treatment strategies focus on diminishing acid secretion, neutralising present acid, and safeguarding the affected region to facilitate healing (Amandeep et al., 2012).

Pharmacological treatment for peptic ulcers employs pharmacological agents including Proton Pump Inhibitors (PPIs) as the primary option (omeprazole, lansoprazole), H2 Receptor Antagonists (ranitidine, cimetidine), antacids, and sucralfate. Although these synthetic drugs are effective, long-term PPI and H_2RA use is associated with multiple adverse effects, including fundic gland polyps, increased risk of gastrointestinal infections, gastric cancer, neuroendocrine tumors, gut microbiota alterations, pathogen overgrowth, and osteoporosis (Sung et al., 2009). Therefore, an alternative treatment from natural

ingredients with relatively low side effects is needed. *Cyclea barbata*, commonly known as green grass jelly, exhibits a range of pharmacological activities that highlight its potential in traditional and modern medicine. This plants contribute to its diverse therapeutic potential, which includes antibacterial, antioxidant, anti-inflammatory, gastroprotective, immunomodulatory, anti-cholesterol, and analgesic effects (Febrianto et al., 2022; Gangga et al., 2017; Handayani et al., 2018; Soka, 2025; Sori et al., 2018). *Cyclea barbata* has been traditionally used in Indonesia for its medicinal properties, particularly in treating digestive disorders like gastritis and peptic ulcers. Its use is favored due to the perceived lower side effects compared to synthetic drugs(Febrianto et al., 2022; Santi et al., 2017). The plant's analgesic and anti-inflammatory properties further support its traditional use in managing gastric discomfort and inflammation. The ethanolic extract of C. barbata leaves contains phenolic compounds, alkaloids, flavonoids, tannins, saponins, coumarins, steroids, and triterpenoids (Febrianto et al., 2022; W. Zhang et al., 2020a). The plant's extracts have shown promising results in traditional used and preclinical studies, indicating their potential to be developed into new therapeutic agents for peptic ulcers.

The ethyl acetate extract from *C. barbata* leaves has flavonoids, tannins, phenolic chemicals, and terpenoids (Mahadi et al., 2018). Furthermore, a study conducted by Puspita Sari & Yanuarty (2022) indicated that the ethyl acetate fraction derived from *C. barbata* leaves comprises flavonoids, tannins, terpenoids, and phenolic compound. Ethanol extract of *C. barbata* leaves exhibits antibacterial activity against *Staphylococcus aureus* and *Vibrio parahaemolyticus* with an inhibition zone diameter of 11.12 mm (Arrosyid et al., 2019). Based on the research by Gangga et al (2017) shows the antioxidant activity of 96% ethanol extract with an IC50 value of 83.28 ppm. The ethanol extract of *C. barbata* leaves also has anti-inflammatory activity with a percentage reduction in edema in the dosage groups of 1.875, 3.75, and 7.5 mg/kgBB of 30.09%, 32.09%, and 36.75%, respectively. According to these findings, the anti-inflammatory efficacy of the 7.5 mg/kg BW ethanol extract of *C. barbata* leaves is nearly identical to that of the positive control Natrium Diclofenac, which is 38.43% . Another study conducted by Handayani et al. (2018) showed that the ethyl acetate extract of *C. barbata* could inhibit lipoxygenase activity by 53.76%, resulting in an IC50 value of 0.267 µg/mL. While the studies highlight the potential of *Cyclea barbata* as a natural remedy for peptic ulcers, further research is needed to elucidate its efficacy, mechanisms, and safety profile. Therefore, this study aimed to evaluate the gastroprotective effects of a 70% ethanolic extract of C. barbata leaves in ethanol-induced peptic ulcer rat models.

MATERIAL AND METHODS

Materials

The sample of green grass jelly leaves occurred in the Perkutatan Region, Jembrana Regency, Bali Province. 70% ethanol (Brataco), 80% ethanol (Brataco), aquadest (Brataco), ranitidine HCl

(Hexpharm), 0,5 % Na-CMC (Sigma Aldrich), 0,9% NaCl (Widatra Bhakti), 10% BNF (Buffered Neutral Formalin), Phytochemical reagents (Nitra Kimia).

Methods

Sample Collection and Preparation

Green grass jelly (*Cyclea barbata*) leaves were collected in the Perkutatan region, Jembrana Regency, Bali Province, Indonesia. Plant identification was verified at the UPT Balai Konservasi Tumbuhan, Kebun Raya "Eka Karya" LIPI, Bedugul, Bali. The freshly collected leaves were washed, sorted, and air-dried for five days. The dried samples were ground to a fine powder using a blender.

Extraction and Phytochemical screening

The green grass jelly leaves were extracted using the maceration method with 70% ethanol for 5 days. The filtrate were evaporated with a rotary evaporator at 50 ^{o}C until a viscous extract is obtained. Phytochemical screening of the ethanol extract of green cincau leaves conducted includes screening for compounds in the alkaloid, phenolic, tannin, flavonoid, saponin, terpenoid, and steroid (Sari et al., 2023, 2025).

Experimental

The study was conducted after the approval issued by Institutional Animal Ethics Committee of STIKES Bina Usada Bali (160/EA/KEPK-BUB-2021). A total of 30 male Wistar rats (*Rattus norvegicus*) were employed and randomly allocated into six groups of five animals each. Prior to treatment, the rats underwent a 14-day acclimatization period with free access to standard pellets and water. Group I served as the normal control, receiving only diet and water, while Group II acted as the negative control and was administered 0.5% Na-CMC suspension. Group III as the positive control, treated with ranitidine suspension at a dose of 13.5 mg/kg body weight. Groups IV, V, and VI were given oral doses of green grass jelly leaf extract at 100, 200, and 400 mg/kg body weight, respectively. All treatments were provided once daily for 14 consecutive days. On day 14, one hour after treatment, all groups except the normal control were orally challenged with 80% ethanol at a dose of 1 ml/200 g body weight, followed by a 24-hour fasting period. On day 15, the animals were euthanized, and abdominal dissection was performed to excise the stomach. Gastric fluid was collected by ligating the upper duodenum and the esophagus at the cardia, followed by intragastric injection of 2 ml physiological saline. Afterwards, the two sections were cut and the gastric fluid was withdrawn with a syringe. Centrifuged at 300 rpm for 10 minutes. The supernatant was collected, and the pH of the gastric fluid was determined using a pH meter. A macroscopic assessment of the gastric was performed to assess the quantity and dimensions of lesions/ulcers present on the gastric mucosa. The stomach was incised along the larger curvature, washed

with a 0.9% NaCl solution, distributed on a flat surface, and the resulting ulcers were then examined (Puspita Sari & Yanuarty, 2022).

Evaluation of Macrospic Ulcer Index and Gastric pH

pH measurement was conducted on the supernatant of the centrifuged gastric fluid using a pH meter (Fisher Scientific). The displayed number represents the pH value of gastric fluid. Observation of the peptic ulcer index was conducted visually by examining the surface of the gastric. Quantifying the number of ulcers and measuring ulcers diameters. An evaluation was performed by quantifying the severity of ulcer development. Assessment of ulcers was developed using the modified Szabo et al. (1985) scoring method (Table 1)

Table 1. Scoring of Peptic Ulcer

Score	Gastric appearance
0	Normal
1	Hyperemia
2	Hemmorhage petechiae
3	Hemmorhage ecchymoses
4	Hemmorhage purpura
5	Erosion

Description:

Hyperemia is a condition characterized by the dilation of blood vessels and an excessive accumulation of blood constituents. Erosion refers to the separation of the superficial mucosal epithelium. Hemorrhage refers to the extravasation of blood components from blood arteries into surrounding tissues. Petechiae are little hemorrhagic lesions ranging from 0.1 to 0.2 cm in size. Ecchymoses are areas of hemorrhage ranging from 0.2 to 3.0 cm in size. Purpura are hemorrhagic lesions over 3 cm in diameter (Szabo et al., 1985).

The ulcer index is determined by employing the following formula:

$$U = (U_N + U_S + U_p) \times 10^{-1}$$

Description:

U : Ulcer Index

U_N : Average number of ulcers per test animal

U_S : Average severity of ulcers

U_P : Percentage of animals with ulcers

Data Analysis

The obtained data on gastric pH and peptic ulcer index were analyzed using SPSS software with the Least Significant Difference (LSD) test.

RESULTS AND DISCUSSION

Extraction and Phytochemical Screening

The extraction of 400 grams of C. barbata leaf simplicia yielded 82.36%, and the results of the phytochemical screening are presented in Table 2.

Table 2. Result Of Phytochemical Screening of *C. barbata* leaves Extract

No	Phytochemical Screening	Result
1	Alkaloid	-
2	Phenol	+
3	Flavonoids	+
4	Tannins	+
5	Triterpenoid	+
6	Steroid	-
7	Saponins	+

According to Table 1, the phytochemical screening of the 70% ethanol extract of green grass jelly leaves reveals the presence of secondary metabolites, specifically Phenols, Tannins, Saponins, Flavonoids, and Triterpenoids. This study contains neither alkaloids nor steroids. Gangga et al. (2017) discovered that the 96% ethanol extract of green grass jelly leaves, obtained from maceration extraction, included phenols, alkaloids, flavonoids, tannins, saponins, triterpenoids, steroids, and coumarins.

Macroscopic Ulcer and Gastric pH

Macroscopic evaluation of gastric ulcers is crucial for assessing mucosal injury and for predicting malignancy risk. A risk stratification score based on ulcer severity, ulcer diameter, and ulcer count can help identify high-risk ulcers requiring follow-up (Brindle et al., 2022; De Francesco et al., 2024). Although macroscopic evaluations provide immediate insights into the efficacy of gastroprotective treatments, they are part of a broader assessment that includes histological and biochemical analyses. These comprehensive evaluations help elucidate mechanisms of action—such as anti-inflammatory, antioxidant, and anti-apoptotic pathways—which contribute to the overall gastroprotective effects (Fu et al., 2018). Ethanol was used as a negative control since numerous preclinical studies utilizing animal models have demonstrated ethanol-induced effects, and such induction has recently been explored to evaluate its relevance in human conditions.

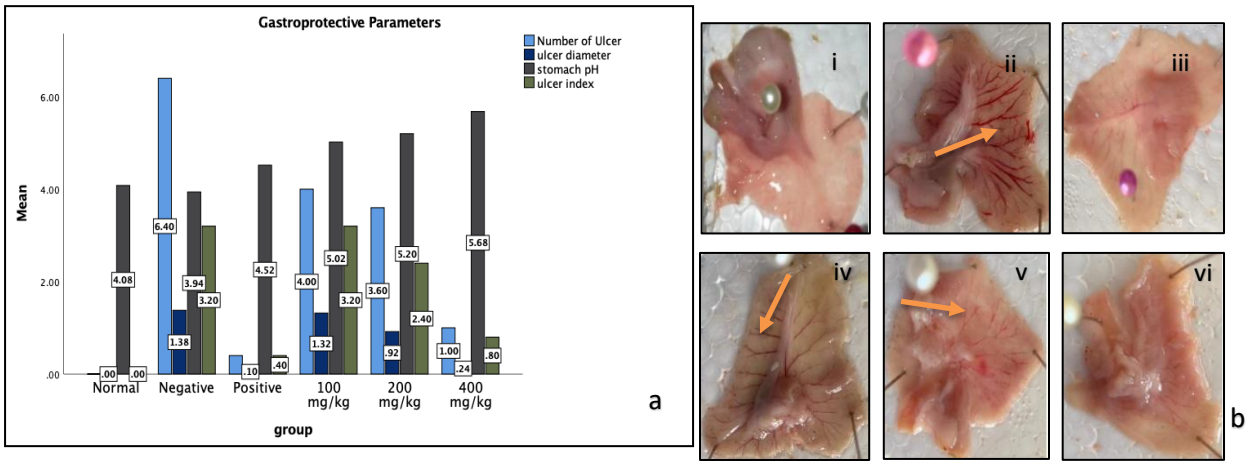

Figure 1. (a) Comparison the number of ulcer, ulcer diameter and ulcer index of each group; (b) macroscopic observation of each group i: normal; ii: negative; iii: positive (Ranitidine); iv: 100mg/kg; v: 200mg/kg; vi: 400 mg/kg.

Figure 1a. shows the potential of *C. barbata* extract against several gastroprotective parameters, such as number of ulcers, diameter of ulcers, ulcer indexes and pH stomach. Macroscopic observations of the stomach show differences among groups in ulceration, hemorrhage, and hyperemia, as presented in Figure 1b. The negative control group showed an average of 6.4 ulcers. Both the positive control (ranitidine) and all tested doses of the ethanolic extract of *C. barbata* reduced the number of ulcers. The most pronounced reduction was observed at 400 mg/kg BW, with an average of one ulcer, and a significantly lower ulcer index ($p < 0.05$). Post hoc LSD analyses showed that 200 mg/kg BW and 400 mg/kg BW significantly ($p < 0.05$) reduced ulcer number compared with the negative control (see Table 3).

Table 3. Comparison Of The Parameters And Statistics Analysis

Groups	Number of ulcer	Ulcer diameters (mm)	Stomach pH	Ulcer index
Normal	0*	0*	4,08	0*
Negative	6,40	1,38	3,94	3,20
Positive (ranitidine)	0,10*	0,40*	4,52	0,40*
C.barbata 100 mg/kg	4,00	1,32	5,02	3,20
C. barbata 200 mg/kg	3,60*	0,92	5,20	2,40
C. barbata 400 mg/kg	1,00*	0,24*	5,68	0,80*
Kruskall wallis Significance (95%)	<0,05	<0,05	>0,05	<0,05

* : LSD significance (< 0,05) against negative control

Table 3 shows the results of the ulcer diameter at each concentration of *C. barbata* extract being smaller than the negative control. Likewise, the positive control gave significant results (P<0.05). However, the

extract with the dosage 400 mg/kg BW gave significant results on changes in ulcer diameter 0.24 mm ($P<0.05$) compared to the negative control. Macroscopic observation in figure 1b (vi) shows almost no bleeding and slight ulceration. The ulcer index shows that the ethanol extract of *C. barbata* has the potential to be gastroprotective with an ulcer index concentration value of 400 mg/kg 0.80 which is significantly different ($P<0.05$) from the negative control. Gastric pH analysis revealed no significant differences between the control and treatment groups receiving various doses of C. barbata ($p > 0.05$), although a trend toward higher pH values was observed in the treated groups.

Recent investigations have highlighted the gastroprotective potential of *C. barbata* extracts against drug-induced gastric ulceration. Specifically, leaf extracts of *C. barbata* demonstrated protective activity against aspirin-induced ulcers in murine models. In the present study, animals receiving cincau leaf infusions across all tested doses exhibited notable ulcer-protective effects, with significant differences observed between treatment groups and the negative control ($p=0.002$). Administration of *C. barbata* leaves at 2.5 mg/kg BW, 5 mg/kg BW, and 10 mg/kg BW conferred gastric protection, with the magnitude of the effect increasing in a dose-dependent manner.(Handayani et al., 2018; Siregar & Miladiyah, 2011).

Mechanism as anti ulcer

Cyclea barbata, a medicinal plant traditionally used in ethnopharmacology, is rich in secondary metabolites such as alkaloids, flavonoids, and phytoecdysones. These bioactive constituents are associated with multiple pharmacological properties, particularly gastroprotective activities that involve antioxidant and anti-inflammatory mechanisms.(Febrianto et al., 2022; Wang et al., 2019). Based on the study by Handayani et al (2018), *C. barbata* Mier. leaf extracts contain total flavonoid 21.62 mgQE/g and had activity to inhibit lipoxygenase as anti-inflammatory agent. Recent studies show that flavonoids demonstrate significant anti ulcer activity through various mechanisms, including antioxidant and anti-inflammatory effects. A review highlighted the potential of flavonoids in preventing peptic ulcers, emphasizing their cytoprotective properties (Afzal et al., 2022; C. Serafim et al., 2020; W. Zhang et al., 2020b).

Furthermore, acute exposure to ethanol has been shown to cause gastric abnormalities, including pronounced damage to the villi structure. The ulcerogenic action of ethanol is mainly attributed to its ability to compromise the gastric mucosal barrier, promote the generation of reactive oxygen species, trigger lipid peroxidation, and activate inflammatory cascades that ultimately lead to epithelial cell necrosis(Kuo et al., 2024; Yang et al., 2024). Ethanol is frequently employed as an ulcer-inducing agent due to its reproducibility, rapid induction of mucosal injury, and its strong clinical relevance as a key risk factor for peptic ulcer disease (Alomair et al., 2022; C. A. de L. Serafim et al., 2021; Simon et al.,

2022). In overdose conditions, ethanol administration in murine models typically produces hemorrhagic lesions and may modulate several pro-inflammatory mediators (Afzal et al., 2022). *C.barbata* ethanolic extract contains flavonoids (phytochemical screening), and the likely mechanisms underlying reductions in ulcer index, ulcer number, and ulcer size are antioxidant activity and anti-inflammatory effects via modulation of inflammatory pathways (C. Serafim et al., 2020; W. Zhang et al., 2020b). Flavonoids are known for their potent antioxidant properties, which scavenge free radicals and reducing oxidative stress in the gastric mucosa (Singh et al., 2018). This activity is crucial in preventing damage to the gastric lining caused by reactive oxygen species (ROS) generated during inflammation or exposure to harmful substances like ethanol (Boudebbaz et al., 2025; Du et al., 2023). As anti inflammatory agents, flavonoids demonstrate notable anti-inflammatory activity by attenuating the release of pro-inflammatory cytokines and regulating key inflammatory signaling cascades. Evidence indicates that flavonoids suppress the NF-κB pathway, leading to decreased expression of mediators such as TNF-α and IL-6. Moreover, their ability to influence the PI3K/AKT pathway contributes to reduced apoptosis and enhanced cellular survival within the gastric mucosa, thereby mitigating ulcer severity(Du et al., 2023; Guo et al., 2024). Zhang et al (2024) showed that flavonoids influence various cellular signaling pathways that are critical for maintaining gastric mucosal integrity. The AMPK/PI3K signaling pathways are involved in the protective effects of Dendrobium officinale flavonoids against ethanol-induced gastric ulcers, highlighting their role in regulating apoptosis and autophagy (Zhang et al., 2024). The study of Lin et al (2023) showed that TLR4/NF-κB and TRPV1 signaling pathways are also modulated by flavonoids, contributing to their gastroprotective effects by reducing inflammation and promoting mucosal healing (Lin et al., 2022). Previous investigations have highlighted that plant-derived flavonoids can alter gastric pH, an effect attributed to the gastroprotective activity of *C. barbata* extract. Similarly, more recent evidence has demonstrated the involvement of flavonoids in regulating gastric pH and providing protective effects against peptic injury (Afzal et al., 2022). Flavonoids enhance the gastric mucosal defense by increasing the production of protective factors such as mucus and prostaglandins. This strengthens the gastric barrier and protects against ulcerogenic factors (W. Zhang et al., 2020a). Overall, flavonoids are key phytochemicals in *C. barbata* and present a promising avenue for developing effective treatments for peptic ulcers.

CONCLUSION

The ethanolic extract of *Cyclea barbata* leaves contains phenolic compounds, alkaloids, flavonoids, tannins, saponins, coumarins, steroids, and triterpenoids, which contribute to its pharmacological and gastroprotective effects, particularly through antioxidant and anti-inflammatory activities. Macroscopic gastric observations showed variations in ulceration, hemorrhage, and hyperemia among the groups. Treatment with *C. barbata* extract at all concentrations reduced ulcer formation, with the 400 mg/kg

BW dose showing the most significant effect ($P<0.05$). This concentration reduced ulcer diameter to 0.24 mm and yielded an ulcer index of 0.80, both significantly different from the negative control ($P<0.05$). Minimal bleeding and mild ulceration were observed macroscopically. Although gastric pH did not differ significantly between groups ($p > 0.05$), the flavonoids in the extract likely play a central role in its gastroprotective action. Overall, the ethanolic extract of *C. barbata* shows promising potential as a natural gastroprotective agent for peptic ulcer management.

CONFLICT OF INTEREST

The authors declare no conflict of interest

REFERENCES

Abbasi-Kangevari, M., Ahmadi, N., Fattahi, N., Rezaei, N., Malekpour, M.-R., Ghamari, S.-H., Moghaddam, S. S., Azadnajafabad, S., Esfahani, Z., Kolahi, A.-A., Roshani, S., Rezazadeh-Khadem, S., Gorgani, F., Naleini, S. N., Naderimagham, S., Larijani, B., & Farzadfar, F. (2022). Quality of care of peptic ulcer disease worldwide: A systematic analysis for the global burden of disease study 1990-2019. *PloS One*, *17*(8), e0271284. https://doi.org/10.1371/journal.pone.0271284

Afzal, M., Alharbi, K. S., Alenezi, S. K., Alshammari, M. S., Alomar, F. A., & Kazmi, I. (2022). Europinidin Enhances Healing through Modulating Antioxidant Processes in Experimentally Induced-Stomach Ulcer Condition. *International Journal of Pharmacology*, *18*(7), 1509–1520. https://doi.org/10.3923/ijp.2022.1509.1520

Akbar, F. N., Tjakradidjaja, F. A., Hendarto, H., Ridho, S., Nursyahidah, -, & Rahma, L. A. (2020). Proportion of Peptic Ulcer Patients Based on Esophagogastroduodenoscopy (EGD) Examination at Jakarta Haji Hospital 2015-2018. *International Journal of Human and Health Sciences (IJHHS)*, *5*(1), 27. https://doi.org/10.31344/ijhhs.v5i1.228

Alomair, M. K., Alabduladheem, L. S., Almajed, M. A., Alobaid, A. A., Alkhalifah, E. A. R., Younis, N. S., & Mohamed, M. E. (2022). Achillea millefolium Essential Oil Mitigates Peptic Ulcer in Rats through Nrf2/HO-1 Pathway. *Molecules*, *27*(22). https://doi.org/10.3390/molecules27227908

Amandeep, K., Robin, S., Ramica, S., & Sunil, K. (2012). *PEPTIC ULCER: A REVIEW ON ETIOLOGY AND PATHOGENESIS*. https://api.semanticscholar.org/CorpusID:30105756

Arrosyid, M., Sutaryono, & Muliana, R. (2019). Uji Efektivitas Ekstrak Etanol Daun Cincau Hijau (Cyclea barbata Miers) Terhadap Bakteri Staphylococcus aureus. *CERATA Jurnal Ilmu Farmasi*, *10*(2), 45–50. https://doi.org/10.61902/cerata.v10i2.87

Bhattacharyya, A., Chattopadhyay, R., Mitra, S., & Crowe, S. E. (2014). Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases. *Physiological Reviews*, *94*(2), 329–354. https://doi.org/10.1152/physrev.00040.2012

Boudebbaz, K., Brouk, M., Laalem, R., & Zabaiou, N. (2025). Gastroprotective Properties of Flavonoid-Rich Extract of Pulicaria odora Against Ethanol-Induced Gastric Ulcer in Mice. *Heliyon*, *11*(1), e41625. https://doi.org/10.1016/j.heliyon.2025.e41625

Brindle, W. M., Grant, R. K., Smith, M., Suddaby, M., Wallace, A., Gillespie, S. L., Church, N. I.,

Noble, C. L., Penman, I. D., Plevris, J. N., Robertson, A. R., Watson, E. F., Selinger, C. P., Kalla, R., & Masterton, G. S. M. (2022). Risk stratifying gastric ulcers: Development and validation of a scoring system. *Frontline Gastroenterology*, *13*(2), 111–118. https://doi.org/10.1136/flgastro-2020-101759

De Francesco, V., Zullo, A., Amato, A., Bergna, I., Bendia, E., Giorgini, G., Buscarini, E., Manfredi, G., Cadoni, S., Cannizzaro, R., Realdon, S., Ciuffi, M., Ignomirelli, O., Da Massa Carrara, P., Finucci, G., Somma, A. Di, Frandina, C., Loria, M., Galeazzi, F., … Manta, R. (2024). Prevalence of Endoscopic and Histological Lesions at Upper Endoscopy: A Cross-Sectional, Multicentre Study in Clinical Practice. *GE Portuguese Journal of Gastroenterology*, 1–8. https://doi.org/10.1159/000537685

Du, K., Zheng, C., Kuang, Z., Sun, Y., Wang, Y., Li, S., & Meng, D. (2023). Gastroprotective effect of eupatilin, a polymethoxyflavone from Artemisia argyi H.Lév. & Vaniot, in ethanol-induced gastric mucosal injury via NF-κB signaling pathway. *Journal of Ethnopharmacology*, 116986. https://doi.org/10.1016/j.jep.2023.116986

Febrianto, S., Praharsini, F. V., Annas, Z. F., & Hanifa, N. I. (2022). Cyclea barbata L. Miers.: Penggunaan tradisional, fitokimia, dan aktivitas farmakologi. *Sasambo Journal of Pharmacy*, *3*(2), 69–82. https://doi.org/10.29303/sjp.v3i2.178

Fu, Y., Wu, H., Cui, H., Li, Y., & Li, C. (2018). Gastroprotective and anti-ulcer effects of oxymatrine against several gastric ulcer models in rats: Possible roles of antioxidant, antiinflammatory, and prosurvival mechanisms. *Phytotherapy Research*, *32*(10), 2047–2058. https://doi.org/10.1002/PTR.6148

Gangga, E., Purwati, R., & Farida, Y. (2017). Penetapan Parameter Mutu Ekstrak yang Memiliki Aktivitas sebagai Antioksidan dari Daun Cincau Hijau (Cyclea barbata L.Miers.). *Jurnal Ilmu Kefarmasian Indonesia*, *15*(2), 236–243.

Guo, Y., Wu, Y., Huang, T., Huang, D., Zeng, Q., Wang, Z., Hu, Y., Liang, P., Chen, H., Zheng, Z., Liang, T., Zhai, D., Jiang, C., Liu, L., Zhu, H., & Liu, Q. (2024). Licorice flavonoid ameliorates ethanol-induced gastric ulcer in rats by suppressing apoptosis via PI3K/AKT signaling pathway. *Journal of Ethnopharmacology*, 117739. https://doi.org/10.1016/j.jep.2024.117739

Handayani, N. F., Elya, B., & Puspitasari, N. (2018). Cyclea Barbata leaf extract: Lipoxygenase inhibitory activity and phytochemical screening. *International Journal of Applied Pharmaceutics*, *10*(Special Issue 1), 106–109. https://doi.org/10.22159/ijap.2018.v10s1.22

Kaushik, P. (2023). PEPTIC ULCER : A SURVEY ON ETIOLOGY AND PATHOGENESIS. *International Journal of Creative Research Thoughts (IJCRT)*, *11*(6), 621–631.

Kuo, C. H., Wu, L. L., Chen, H. P., Yu, J., & Wu, C. Y. (2024). Direct effects of alcohol on gut-epithelial barrier: Unraveling the disruption of physical and chemical barrier of the gut-epithelial barrier that compromises the host–microbiota interface upon alcohol exposure. *Journal of Gastroenterology and Hepatology (Australia)*, *39*(7), 1247–1255. https://doi.org/10.1111/jgh.16539

Lin, K., Deng, T., Qu, H., Ou, H., Huang, Q., Gao, B., Li, X., & Wei, N. (2023). Gastric protective effect of Alpinia officinarum flavonoids: mediating TLR4/NF-κB and TRPV1 signalling pathways and gastric mucosal healing. *Pharmaceutical Biology*, *61*(1), 50–60. https://doi.org/10.1080/13880209.2022.2152058

Mahadi, R., Rasyiid, M., Dharma, K. S., Anggraini, L., Nurdiyanti, R., & Nuringtyas, T. R. (2018).

Immunomodulatory and Antioxidant Activity of Green Grass Jelly Leaf Extract (Cyclea barbata Miers.) In Vitro. *Journal of Tropical Biodiversity and Biotechnology*, *3*(3), 73. https://doi.org/10.22146/jtbb.33441

Pandey, A., Saraswat, N., Wal, P., Pal, R. S., Wal, A., & Maurya, D. (2019). A Detailed Review on: Recent Advances, Pathophysiological Studies and Mechanism of Peptic Ulcer. *Res. J. Pharmacology & Pharmacodynamics*, *11*(4), 165–170.

Pathan, I. K., K, N. B., Kumar, K. A., K, I., & Kiran, J. H. (2013). Synthesis and Gastroprotective Evaluation of New Chalcone Derivatives. *Research J. Pharmacology and Pharmacodynamics*, *5*(6), 325–330.

Puspita Sari, D. R. A., & Yanuarty, R. (2022). Potensi Gastroprotektif Fraksi Etil Asetat Daun Cincau Hijau (Cyclea barbata Miers) terhadap Lambung Tikus yang Diinduksi Etanol. *PHARMACY: Jurnal Farmasi Indonesia (Pharmaceutical Journal of Indonesia)*, *19*(2), 263. https://doi.org/10.30595/pharmacy.v19i2.13624

Santi, I., Putra, B., & Wahyuni, S. (2017). UJI EFEK EKSTRAK ETANOL DAUN CINCAU HIJAU (Cyclea barbata Miers) SEBAGAI ANTIINFLAMASI PADA TIKUS PUTIH YANG DIINDUKSI KARAGEN. *Jurnal Ilmiah As-Syifaa*, *9*(1), 58–66. https://doi.org/10.33096/jifa.v9i1.256

Sari, D. R. A. P., Ugrasena, P. Y., Astini, N. P. A. D., & I Gede Agus Sindhu A. (2023). UJI TOKSISITAS EKSTRAK ETANOL 96% DAUN MIANA (Plectranthus scutellaroides R.Br) TERHADAP Artemia salina DENGAN METODE BSLT (Brine Shrimp Lethality Test). *Journal Pharmactive*, *2*(2), 59–64. https://doi.org/10.64036/pharmactive.v2i2.34

Sari, D. R. A. P., Ugrasena, P. Y., & Indraswari, P. I. I. (2025). Pengaruh Perbedaan Ketinggian Tumbuh Daun Miana (Coleus scutellarioides) di Daerah Bali Terhadap Kadar Flavonoid Total. *Herbal Medicine Journal*, *8*(2), 1–10.

Serafim, C. A. de L., Araruna, M. E. C., Alves Júnior, E. B., Silva, L. M. O., Silva, A. O., da Silva, M. S., Alves, A. F., Araújo, A. A., & Batista, L. M. (2021). (-)-Carveol Prevents Gastric Ulcers via Cytoprotective, Antioxidant, Antisecretory and Immunoregulatory Mechanisms in Animal Models. *Frontiers in Pharmacology*, *12*(August), 1–17. https://doi.org/10.3389/fphar.2021.736829

Serafim, C., Araruna, M. E., Alves Júnior, E., Diniz, M., Hiruma-Lima, C., & Batista, L. (2020). A Review of the Role of Flavonoids in Peptic Ulcer (2010–2020). *Molecules*, *25*(22), 1–32. https://doi.org/10.3390/MOLECULES25225431

Simon, L., Souza-Smith, F. M., & Molina, P. E. (2022). Alcohol-Associated Tissue Injury: Current Views on Pathophysiological Mechanisms. *Annual Review of Physiology*, *84*, 87–112. https://doi.org/10.1146/annurev-physiol-060821-014008

Singh, K. D., Chetia, D., & Biplab, D. (2018). NEW FLAVONOID COMPOUND FROM ALLIUM HOOKERI THWAITES AS A GASTROPROTECTIVE AGENT. *International Journal of Pharmacy and Pharmaceutical Sciences*, *10*, 24–30. https://api.semanticscholar.org/CorpusID:59129899

Siregar, I. M., & Miladiyah, I. (2011). Protective effects of Cyclea barbata Miers leaves against aspirin-induced gastric ulcer in mice. *Universa Medicina*, *30*(2 SE-Review Article), 88–94. https://doi.org/10.18051/UnivMed.2011.v30.88-94

Soka, B. G. (2025). Uji aktivitas analgetik ekstrak daun cincau hijau atau daun daluman (cyclea barbata miers) pada mencitsebagai terapi gastritis. *Jurnal Ilmiah PANNMED*, *20*(2), 157–160. https://doi.org/10.36911/pannmed.v20i2.2308

Sori, R. K., O., B., Adiga, S., & Thomas, H. (2018). Evaluation of the antipeptic ulcer activity of the seed extract of sesame (Sesamum indicum) in stress induced peptic ulcers in rats. *International Journal of Basic & Clinical Pharmacology*, *7*(6), 1131. https://doi.org/10.18203/2319-2003.ijbcp20182094

Sung, J. J. Y., Kuipers, E. J., & El-Serag, H. B. (2009). Systematic review: the global incidence and prevalence of peptic ulcer disease. *Alimentary Pharmacology & Therapeutics*, *29*(9), 938–946. https://doi.org/10.1111/j.1365-2036.2009.03960.x

Waldman, S. D. (2024). *79 - Peptic Ulcer Disease* (S. D. B. T.-A. of C. P. S. (Fifth E. Waldman (ed.); pp. 367–373). Elsevier. https://doi.org/https://doi.org/10.1016/B978-0-443-11105-1.00079-0

Wang, X., Zhang, Q., Peng, Y., Li, L., Qu, J., Liu, Y., Xu, S., Ma, S.-G., Li, Y., Zou, Z., Wang, R.-B., & Yu, S. (2019). Two azafluoranthene alkaloids and a phytoecdysone from the stems of Cyclea barbata. *Journal of Asian Natural Products Research*, *21*, 217–226. https://api.semanticscholar.org/CorpusID:73425628

Xie, X., Ren, K., Zhou, Z., Dang, C., & Zhang, H. (2022). The global, regional and national burden of peptic ulcer disease from 1990 to 2019: a population-based study. *BMC Gastroenterology*, *22*(1), 58. https://doi.org/10.1186/s12876-022-02130-2

Yang, S., Liu, G., Xia, X., Gan, D., Xiang, S., & Xiang, M. (2024). α-Mangostin suppresses ethanol-induced gastric ulceration by regulating the Nrf2/HO-1 and NF-κB/NLRP3/caspase-1 signaling pathways and gut microbiota. *Heliyon*, *10*(2), e24339. https://doi.org/10.1016/j.heliyon.2024.e24339

Zhang, W., Lian, Y., Li, Q., Sun, L., Chen, R., Lai, X., Lai, Z., Yuan, E., & Sun, S. (2020a). Preventative and Therapeutic Potential of Flavonoids in Peptic Ulcers. *Molecules*, *25*(20), 4626. https://doi.org/10.3390/MOLECULES25204626

Zhang, W., Lian, Y., Li, Q., Sun, L., Chen, R., Lai, X., Lai, Z., Yuan, E., & Sun, S. (2020b). Preventative and therapeutic potential of flavonoids in peptic ulcers. *Molecules*, *25*(20). https://doi.org/10.3390/molecules25204626

Zhang, Z., Xie, H., Farag, M. A., Li, Z., Wu, Q., & Shao, P. (2024). Dendrobium officinale flowers flavonoids enriched extract protects against acute ethanol-induced gastric ulcers via AMPK/PI3K signaling pathways. *Food Science and Human Wellness*, *13*(6), 3661–3679. https://doi.org/10.26599/FSHW.2023.9250048