Trop J Nat Prod Res, September; 8(9): 8314 - 8320 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Analgesic, Anti-Inflammatory and Anti-Gastric Ulcer Potential of Aqueous Leaf Extract of *Emilia sonchifolia* in Rats

Mercylyn Ezinne Uche[1,2], Chinyere Godwin Chinyere[1], Celestine Nwabu Ekweogu[2], Rutherford Ikenna Esiaba[1], Promise Nwankpa[2], Eziuche Amadike Ugbogu[1]*

[1]*Department of Biochemistry, Faculty of Biological Sciences, Abia State University, PMB 2000, Uturu, Abia State, Nigeria*
[2]*Department of Medical Biochemistry, Faculty of Basic Medical Sciences, Imo State University, PMB 2000, Owerri, Imo State, Nigeria*

ARTICLE INFO

Article history:
Received: 05 May 2024
Revised: 10 August 2024
Accepted: 14 August 2024
Published online: 01 October 2024

ABSTRACT

Emilia sonchifolia is used in traditional medicine for the treatment of wounds, diabetes, inflammation and ulcer. This study aims to investigate the analgesic, anti-inflammatory and anti-ulcer effects of the aqueous leaf extract of *Emilia sonchifolia* (ALEES). In the acute toxicity test, ALEES was administered up to 5 g/kg body weight via oral route. In the ulcer experiments, Group II–VI rats were pretreated with 1000 mg/kg ethanol or ibuprofen before Group III rats received 20 mg/kg omeprazole and Group IV–VI rats received various doses of ALEES. In the anti-inflammatory and analgesic studies, group II rats received 100 mg/kg acetylsalicylic acid (ASA). For the ulcer, anti-inflammatory and analgesic studies, rats were administered ALEES at doses of 200, 400 and 600 mg/kg body weight while group I served as a normal control. In ethanol-induced ulcer, rats administered 600 mg/kg ALEES showed a higher percentage (%) ulcer inhibition compared to standard drug (omeprazole) treated group ($p<0.05$). The % ulcer inhibition in the ibuprofen-induced ulcer test did not exhibit any significant changes ($p>0.05$) between the group treated with 600 mg/kg ALEES and the omeprazole group. In addition, there was no significant anti-inflammatory activity between ALEES at a dose of 600 mg/kg (52.78%) and ASA at a dose of 100 mg/kg (66.61%), however, ASA had a stronger analgesic effect compared to all ALEES-treated groups ($p<0.05$). The results of this study suggest that ALEES is safe and has the potential to be used as an anti-ulcer and anti-inflammatory agent.

Keywords: Analgesic, Anti-ulcer, Anti-inflammatory, *Emilia sonchifolia*.

Introduction

Medicinal herbs are widely used around the world to treat various health problems such as inflammation, diarrhoea, diabetes, and ulcers.[1] These plants have a vast reservoir of phytoconstituents and are currently considered as reliable sources for the development of new drugs.[2,3,4] Peptic ulcers are open sores on the gastric mucosa and the inner lining of the stomach. People who drink alcohol excessively have a higher risk of developing gastric and peptic ulcers. In addition, the inappropriate use of non-steroidal anti-inflammatory drugs (NSAIDs) in conjunction with *Helicobacter pylori* infection are associated with increase in annual incidence rate of ulcer.[5] Moreover, individuals exposed to chronic environmental and psychological stress, and those who skip meals (fasting) are also predisposed to peptic ulcer.[6] The NSAIDs such as aspirin, which are acidic in nature, directly irritate the mucosa, inhibit the enzyme cyclooxygenase and reduce the synthesis of prostaglandin and thromboxane.[7,8] Prostaglandin and thromboxane play a gastroprotective role by increasing gastric secretion, which protects stomach from its acidic environment.

***Corresponding Author. Email:** amadike.ugbogu@abiastateuniversity.edu.ng

Tel: +234-81-6755-0663

Citation: Uche, ME, Chinyere, CG, Ekweogu, CN, Nwankpa, P, Ugbogu, EA. Analgesic, anti-inflammatory and anti-gastric ulcer potential of aqueous leaf extract of *Emilia sonchifolia* in rats. Trop J Nat Prod Res. 2024; 8(9): 8314-8320. https://doi.org/10.26538/tjnpr/v8i9.10

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

Drugs such as diclofenac, ibuprofen, indomethacin and piroxicam also cause ulcers in the gastrointestinal tract (GIT) by inducing reactive oxygen species that induce the production of inflammatory cytokines such as tumour necrosis factor (TNF)-α and nuclear kappa factor B (NF-κB).[9,10] All of these contribute to the overproduction of gastric acid and pepsin, and to the breakdown of some defense mechanisms of the GIT including secretion of the mucus, the release of the peptide hormone secretin and the formation of bicarbonate.

If left untreated, complications of peptic ulcer disease (PUD) such as gastric outlet obstruction, upper gastrointestinal bleeding, perforation, adhesions, gastroesophageal reflux and aspiration of gastric contents can pose life-threatening risks.[11,12] The various treatment options for gastric and duodenal ulcers include dietary and lifestyle adjustments, avoidance of random fasting, use of antacids, H_2 antagonists such as ranitidine and cimetidine, and proton pump inhibitors such as rabeprazole and omeprazole. In people with *H. pylori* infection, triple therapy with proton pump inhibitors, H_2 receptor blockers and antibiotics such as amoxicillin, clarithromycin, ciprofloxacin, metronidazole and tinidazole has been shown to be effective in eradicating the bacteria.[13,14,15] Pain, a key symptom of inflammation along with swelling, heat and redness, is often associated with suffering and places a significant financial burden on individuals and society.[16,17] The NSAIDs and opioid analgesics are used in pain management as they can relieve pain via antinociceptive mechanisms. Anti-inflammatory drugs used to treat peptic ulcers and inflammation have been shown to block the effects of endogenous anti-inflammatory substances such as prostaglandin, histamine and leukotrienes.[18] Studies have shown that tricyclic antidepressants, NSAIDs, natural products and G-protein-coupled receptor inhibitors have antinociceptive properties and are suitable for the treatment of both acute and chronic pain. However, prolonged use of these NSAIDs, opiates, proton pump inhibitors and antihistamines often leads to a number of side effects, including gastrointestinal ulcers and

bleeding, cerebrovascular accidents and respiratory centre depression in the brain.[16,19] Opioid addicts often experience drowsiness, irrational behaviour, hypotension, delirium and mental retardation.[20,21] The commonly administered drug omeprazole for peptic ulcers has been associated with adverse effects such as immunosuppression, calcium and magnesium deficiency and bone fragility.[22,23] Therefore, it is essential to explore medicinal plants and their bioactive constituents as potential alternatives to conventional drugs to treat these health conditions.

Emilia sonchifolia, a perennial plant of the Asteraceae family, is native to SouthEast Asia but widely distributed across Nigeria.[24] It grows up to 60 cm tall and is commonly found between July and October in SouthEast Nigeria. Throughout its long history, this plant has been used in traditional medicine to treat a variety of ailments, including cuts, wounds, gastropathy, diabetes, inflammation, asthma, diarrhoea and tooth decay.[25,26] *Emilia sonchifolia* is valued in traditional Chinese medicine for its anti-inflammatory properties and its effectiveness against tumours, viruses and bacterial infections.[27] Several scientific studies have reported that *E. sonchifolia* has hepatoprotective, immunomodulatory, wound healing, antioxidant, anti-inflammatory, and anti-ulcer properties.[28,29] Although the leaves of *E. sonchifolia* are used in traditional medicine to treat ulcers, pain and inflammation, there is little scientific evidence to support these claims. This study therefore investigated the analgesic, anti-inflammatory and anti-ulcer effects of the aqueous leaf extract of *Emilia sonchifolia* (ALEES) in albino rats.

Materials and Methods

Collection and identification of plant

The leaves of *Emilia sonchifolia* were collected on 26th February, 2023 in Umuguma in Owerri West LGA, Imo State, Nigeria. The plant was authenticated by an experienced taxonomist from Michael Okpara University of Agriculture, Umudike (MOUAU), Nigeria. The website http://www.worldfloraonline.org/taxon/wfo-0000017704, accessed on 10th March, 2023, was used to verify the classification of the plant. A specimen was kept in the herbarium with specimen number: MOUAU/ZEB/HERB/21/0022.

Preparation of ALEES

The harvested leaves of *Emilia sonchifolia* were carefully separated from the stem and then thoroughly washed with distilled water. They were then air-dried for 24 hrs. To prepare the aqueous leaf extract of *Emilia sonchifolia* (ALEES), 500 g of dried leaves were mixed with 25 mL of distilled water and processed using an electric blender. After blending, the resulting mixture was filtered and concentrated in a hot air oven, yielding a greenish-colored pasty extract.

Experimental Animals

Male albino rats weighing 150 to 170 g were purchased from MOUAU. Prior to the start of the study, a two-week acclimatization period was used to acclimatize the rats to the laboratory conditions. The rats were kept in a 12-hr light/dark cycle, with humidity 35- 60% and temperatures 25- 28 ºC. The rats had constant access to water and normal rat food for the duration of the study. The study adhered with the ethical guidelines set out in the World Health Organization 1998 criteria on appropriate laboratory techniques, as well as United States legislation for laboratory animals. On 25th August, 2020, Abia State University granted ethical clearance (ABSU/REC/BMR/088) for the study.

Analgesic activity of ALEES

The protocol of Adeyemi et al.[32] was used with minor modifications. Five groups (n = 6/group) of thirty rats weighing 150-170 g were used. The rats were administered different oral treatments: group I (normal control), group II (positive control) received 100 mg/kg acetylsalicylic acid, and the ALEES groups were treated as follows: III=200, IV=400 and V=600 mg/kg of ALEES. The rats in each group received 10 mL/kg (0.6%) acetic acid intraperitoneally after 30 minutes, and the number of writhes of each rat was counted from 0- 30 minutes.

$$\text{Inhibition (\%)} = \frac{\text{Number of writhes in control- Number of writhes in test}}{\text{Number of writhes in control}} \times 100 \ldots \text{equ I}$$

Anti-Inflammatory activity of ALEES

With minor modifications, the protocol described by Orieke et al.[33] was applied. Five groups (n = 6/group) of thirty rats weighing 150-170 g were used. The rats were administered different oral treatments: group I (control), group II (positive control) received 100 mg/kg acetylsalicylic acid, and the ALEES groups were treated as follows: III=200, IV=400 and V=600 mg/kg of ALEES.

After 30 minutes of oral treatment, the rats received an injection of 0.1 mL of egg albumin into the subplantar area of the right hind paw to induce paw oedema. The paw circumferences of the treatment and control groups were then determined at 0, 30, 60 and 120 minute intervals using calipers. The extent of the oedema was determined by the difference between the initial and final paw circumferences.

$$\text{\% Increase in paw circumference (c) at induction} = \frac{\text{C at induction - C prior induction}}{\text{C prior induction}} \times 100 \ldots\ldots \text{equ II}$$

$$\text{\% Decrease in paw circumference (c) at intervals} = \frac{\text{C at induction - C at inter}}{\text{C at induction}} \times 100 \ldots \text{equ III}$$

$$\text{\% Anti-inflammatory activity at 120 min} = \frac{\text{Mean fall in test - Mean fall in control}}{\text{Mean fall in control}} \times 100 \ldots \text{equ IV}$$

Ulcer study

Ibuprofen-induced ulcer study

A total of eighteen rats, weighing 150-170 g, were subjected to a 24-hr fasting period and then divided into six groups (group 1-VI) according to their body weight. Group I, which served as a normal control, received distilled water. Group II, which served as a negative control, was not treated. Group III received omeprazole (20 mg/kg body weight), while the ALEES groups were treated as follows: III=200, IV=400 and V=600 mg/kg ALEES before ulcer induction.

Ethanol-induced ulcer study

A total of eighteen rats, weighing 150-170 g, were subjected to a 24-hr fasting period and then divided into six groups (group 1-VI) according to their body weight. Group I, which served as a normal control, received distilled water. Group II, which served as a negative control was not treated. Group III received omeprazole (20 mg/kg body weight), while the ALEES groups were treated as follows: III=200, IV=400 and V=600 mg/kg ALEES before ulcer induction.

Groups II–VI rats received oral administration of 1000 mg/kg body weight ibuprofen or ethanol to develop ulcers 30 minutes after the pre-treatments, while group I rats received no treatment at all. All rats sacrificed by cervical dislocation one (1) hour after the lesion was established.[35]

Suction ulcers, 1.0; hemorrhagic streaks, 1.5; normal stomach, 0.0; red coloration, 0.5; ulcers > 3 < 5 mm, 2.0; ulcers > 5 mm, 3.0.

2.6.3 Calculation of ulcer index

This is measured according to the method described by Goel and Sairam[36]. The ulcerated lesion of the incised stomach is read with a magnifying glass.

$$\text{Ulcer index} = \frac{\text{amount of ulcers per rat (UA) + ulcer severity score (US) + ulcer \% in rats (UP)}}{10} \times 100 \ldots\ldots \text{V}$$

$$\text{Ulcer \% in rats (UP)} = \frac{\text{Total ulcers in a group}}{\text{Total number of animals}} \times 100 \ldots\ldots \text{VI}$$

$$\% \text{ inhibition} = \frac{\text{ulcer index of the control group (negative) (UIC)} - \text{ulcer index of the test group (UIT)}}{\text{ulcer index of the control group (negative) (UIC)}} \times 100 \ldots\ldots \text{VII}$$

Statistical analysis

The mean ± SD was used to represent the data. Statistical analysis was performed using RTM software (version 3.0.3). The post-hoc Tukey test ($p \leq 0.05$) in conjunction with one-way analysis of variance was used to determine statistical differences between groups.

Results and Discussion

In our acute toxicity evaluation, administration of ALEES at doses up to 5 mg/kg did not result in any toxicity signs, behavioural changes or death, indicating that ALEES can be used for therapeutic applications without adverse effects.

Rats treated with 600 mg/kg ALEES showed a percentage pain inhibition of 45.59%. This result was significantly lower ($p<0.05$) than that of the standard drug (acetylsalicylic acid), which resulted in 70.97% pain inhibition (Table 1). Earlier studies by Faseela et al.[40] reported that *E. sonchifolia* contains flavonoids, tannins and alkaloids. Studies by Nwafor and Okwuasaba [41] and Tijani et al.[42] have shown that flavonoids, tannins and alkaloids have the ability to inhibit prostaglandin synthesis, leading to a reduction in inflammation and pain relief. In addition, previous studies have shown that the limonene contained in *E. sonchifolia* has anti-inflammatory and analgesic effects.[43,44]

Table 1: Effects of ALEES on writhes and pain inhibition in rats

Group	Writhes in 30 mins	% Pain inhibition
Normal control	38.67±2.5^{c}	-
Acetylsalicylic acid (100 mg/kg)	10.67±2.08^{a}	70.97±5.46^{c}
200 mg/kg ALEES	31.00±2.65^{c}	20.02±7.43^{a}
400 mg/kg ALEES	26.33±1.15^{b}	31.78±2.99^{a}
600 mg/kg ALEES	21.00±3.05^{b}	45.59±7.77^{b}

Mean ± SD (n=6). Values in the same row bearing different letter of the alphabet are statistically significant (P<0.05).

Inflammation is characterized by heat, pain, redness and swelling and is usually induced in experimental animals by the use of egg albumin, capsaicin or carrageenan models.[28] The inflammation and oedema induced by egg albumin are usually triggered by the release of mediators histamine and serotonin.[45] These mediators facilitate the increase in vascular permeability, the development of oedema and the movement of white blood cells to the site of injury.[46,47] The oedema resulting from increased vascular permeability is triggered by non-neurogenic stimulation mediated by autacoids and by neurogenic stimulation triggered by bradykinin. The latter induces the release of substance P from nerve endings, which in turn mediates the release of histamine from mast cells, resulting in oedema.[48] In this study, there was no significant ($p>0.05$) anti-inflammatory effect between rats treated with 600 mg/kg ALEES (52.78%) and those treated with 100 mg/kg acetylsalicylic acid (standard drug) (66.61%), as shown in Table 2. This finding underpins the anti-inflammatory effect of ALEES. The results of our anti-inflammatory study are consistent with the reports of Essien et al.[28] and Faseela et al.[40] Limonene, D-carvone, and oleic acid, identified by researchers as being present in *E. sonchifolia*, are bioactive phytochemicals with anti-inflammatory properties.[49-51] Inhibition of substance P release and histamine production may be the plausible mechanisms by which ALEES exerts its anti-inflammatory effects.

Ulcers are defined as lesions that can manifest on the skin, mucous membranes and inner linings of various organs, including the stomach and duodenum. The etiology of ulcers is multifactorial and includes bacterial infections and excessive gastric acid secretion. Gastric ulcers significantly affect the quality of life of affected individuals by causing severe abdominal pain, bloating, vomiting blood, and possible intestinal obstruction, among other symptoms.[52] In our ethanol-induced ulcer study, rats administered with 600 mg/kg ALEES had the highest percentage ulcer inhibition and a significant reduction in ulcer scores compared to rats treated with 20 mg/kg omeprazole (standard drug) (Table 3, Fig. 1). Furthermore, when comparing the omeprazole-treated group with the rats administered 600 mg/kg ALEES in the ibuprofen-induced ulcer study, no effects ($p>0.05$) were observed on the metrics of ulcer number, ulcer perforation, ulcer index, ulcer score and percentage ulcer inhibition (Table 4, Fig. 2). The NSAIDs such as ibuprofen, have been identified as agents that can induce gastric ulcers by activating inflammatory cells, which in turn stimulate the production of cytokines and lead to oxidative stress.[5] The presence of a variety of phytochemicals in ALEES may play a role in improving gastric ulcer parameters and reducing gastric mucosal breakdown in rats pre-treated with ALEES.[40] Tannins, for example have astringent and vasoconstrictor effects that may help prevent the development of gastric ulcers, while carbohydrates help form a protective layer over the ulcer preventing direct contact with harmful substances.[5] In addition, it is believed that the bioactive substances contained in ALEES, such as limonene, D-carvone, hexadecane and oleic acid, may help prevent the development of gastric ulcers caused by ulcerogenic and necrotic substances such as ethanol.[50,51,53] Also, ALEES has wound healing effect[54] and regeneration, which may possibly contribute to its potentials to prevent gastric ulcer.[55]

Table 2: Anti-inflammatory activities of ALEES in rats

			ALEES (mg/kg)		
Treatment	**Normal control**	**ASA, 100 mg/kg**	**200**	**400**	**600**
Initial PC (mm)	22.33±0.58^{a}	22.67±0.58^{a}	23.00±1.00^{a}	22.33±0.58^{a}	22.67±0.58^{a}
Induction PC (mm) at 60 min	33.33±1.53^{a}	27.67±0.58^{a}	31.67±0.58^{a}	31.33±0.58^{a}	29.00±1.00^{a}
Post Induction PC (mm) at 120 min	34.33±2.08^{a}	26.83±0.29^{a}	30.67±0.58^{a}	29.67±0.58^{a}	28.33±0.58^{a}
Rise in PC Value (mm)	12.00±1.73	4.17±0.29^{a}	7.67±1.53^{b}	7.33±1.15^{b}	5.67±1.15^{a}
% Anti-inflammatory activity	-	66.61±34.74^{b}	36.11±12.73^{a}	38.89±9.62^{a}	52.78±9.62^{b}

Mean ± SD (n=6). Values in the same row bearing different letter of the alphabet are statistically significant (P<0.05). PC, Paw circumference. ASA, acetylsalicyclic acid.

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Table 3: Gastroprotective effect of ALEES on ethanol-induced ulcers in albino rats

Parameter	Group I (Normal Control)	Group II (Negative Control)	Group III (Omeprazole 20mg/kg)	ALEES Group IV (200 mg/kg)	ALEES Group V (400 mg/kg)	ALEES Group VI (600 mg/kg)
Number of ulcers	0.00±0.00^{a}	6.33±0.58^{c}	2.67±0.58^{b}	3.67±0.58^{b}	3.33±1.53^{b}	2.00±1.00^{b}
Ulcer score	0.00±0.00^{a}	14.33±1.53^{d}	4.67±1.53^{c}	6.33±1.15^{c}	4.33±1.53^{b}	2.67±1.15^{b}
Ulcer perforation	0.00±0.00^{a}	100.00±0.00^{d}	48.33±7.64^{c}	65.00±8.66^{b}	51.67±7.64^{b}	43.33±5.77^{c}
Ulcer Index	0.00±0.00^{a}	12.07±0.21^{d}	5.57±0.97^{c}	7.50±1.04^{b}	5.93±1.07^{b}	4.80±0.78^{c}
Percentage Ulcer Inhibition	100.00±0.00^{a}	0.00±0.00^{d}	53.61±8.09^{c}	37.50±8.66^{b}	50.55±8.91^{c}	60.00±6.51^{c}

Values represent the mean for N=3.Values in the same row bearing different alphabets are not significantly different from each other at p<0.05.

Table 4: Gastroprotective effect of ALEES on Ibuprofen-induced ulcers in albino rats

Parameter	Group I (Normal Control)	Group II (Negative Control)	Group III (Omeprazole 20 mg/kg)	ALEES (mg/kg) Group IV (200 mg/kg)	ALEES (mg/kg) Group V (400 mg/kg)	ALEES (mg/kg) Group VI (600 mg/kg)
Number of ulcers	0.00±0.00^{a}	7.00±1.00^{c}	2.23±0.58^{b}	6.33±0.58^{c}	4.33±0.58^{b}	3.33±0.58^{b}
Ulcer score	0.00±0.00^{a}	14.83±1.61^{d}	3.17±0.76^{b}	12.00±0.50^{c}	9.50±0.50^{c}	6.83±1.04^{b}
Ulcer perforation	0.00±0.00^{a}	100.00±0.00^{d}	45.00±5.00^{b}	83.33±2.89^{c}	58.33±2.89^{b}	53.33±5.77^{b}
Ulcer Index	0.00±0.00^{a}	12.18±0.25^{c}	5.22±0.67^{b}	10.17±0.37^{b}	7.22±0.37^{b}	6.68±069^{b}
Percentage Ulcer Inhibition	100.00±0.00^{d}	0.00±0.00^{a}	58.53±5.14^{c}	16.53±3.03^{b}	40.75±3.03^{c}	45.13±5.66^{c}

Values represent the mean for N=3.Values in the same row bearing different alphabets are significantly different from each other at p<0.05

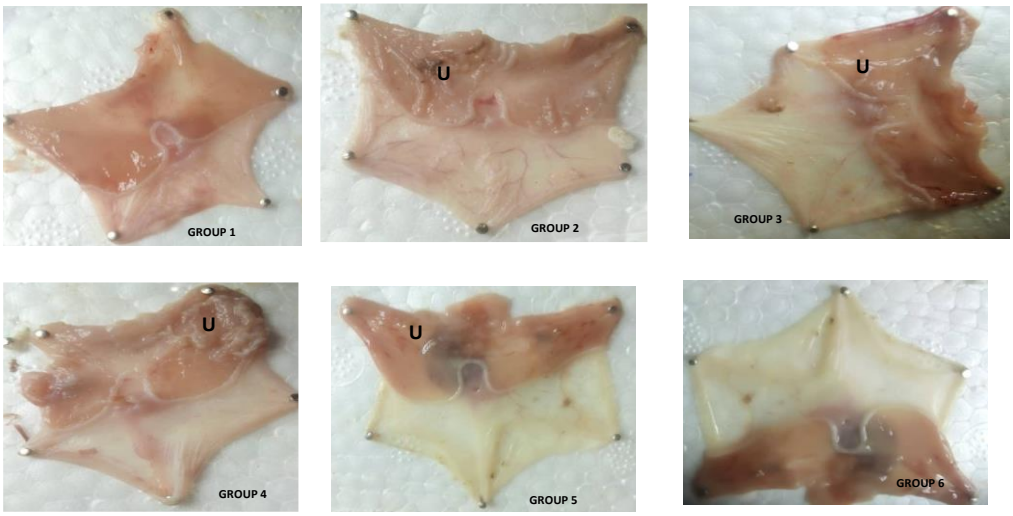

Figure 1: Macroscopic view of incised ethanol-induced ulcerated stomach of animals pretreated with omeprazole and different doses of ALEES. Group 1(Normal control), Group II (Negative control), Group III (Omeprazole, 20 mg/kg), Group IV, V and VI received 200, 400 and 600 mg/kg ALEES respectively.

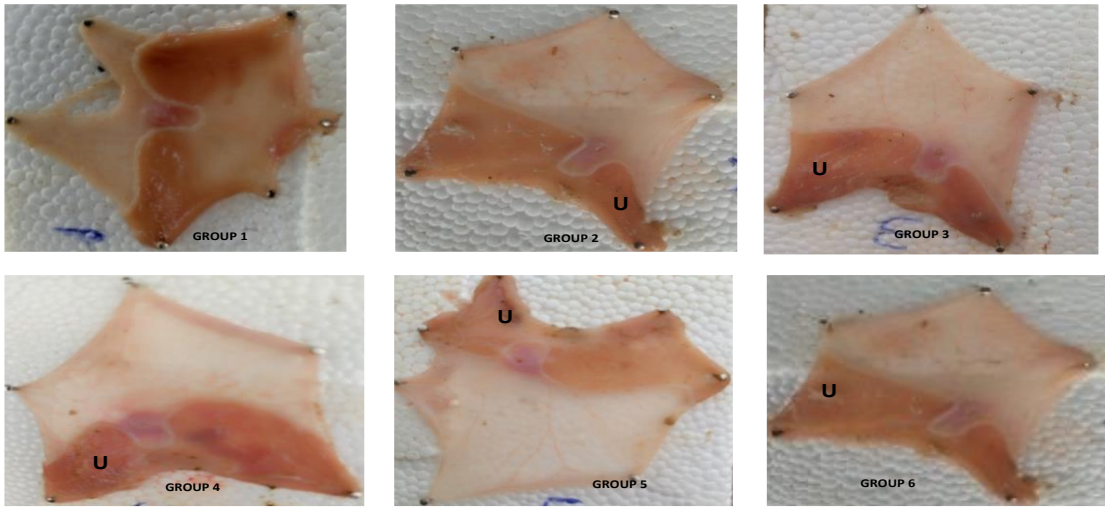

Figure 2: Macroscopic view of incised ibuprofen-induced ulcerated stomach of animals pretreated with omeprazole and different doses of ALEES. Group 1(Normal control), Group II (Negative control), Group III (Omeprazole, 20 mg/kg), Group IV, V and VI received 200, 400 and 600 mg/kg ALEES respectively

Conclusion

In conclusion, administration of the aqueous leaf extract of *Emilia sonchifolia* (ALEES) at doses up to 5 mg/kg did not cause any sign of toxicity, behavioural changes, or death, thus suggesting that ALEES can be used for therapeutic purposes without adverse effects. In addition, this study indicated that ALEES has anti-inflammatory, anti-ulcer and mild analgesic effects, hence supporting its use in traditional medicine for the treatment of these diseases. However, the authors recommend chronic toxicity testing as well as human clinical trials for the anti-inflammatory and anti-ulcer properties of ALEES to determine potential long-term side effects associated with its use and the ideal dosage for the treatment of these diseases.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

References

1. Akubugwo EI, Emmanuel O, Ekweogu CN, Ugbogu OC, Onuorah TR, Egeduzu OG, Ugbogu EA. GC-MS analysis of the phytochemical constituents, safety assessment, wound healing and anti-inflammatory activities of *Cucurbita pepo* leaf extract in rats. Sci Pharm. 2022; 90(64). https://doi.org/10.3390/scipharm90040064.
2. Iweala EJ, Uche ME, Dike ED, Etumnu LR, Dokunmu TM, Oluwapelumi AE, Okoro, BC, Dania OE, Adebayo AH, Ugbogu EA. *Curcuma longa* (Turmeric): Ethnomedicinal uses, phytochemistry, pharmacological activities and toxicity profiles—A review. Pharmacol Res Modern Chin Med. 2023; 6: 100222. https://doi.org/10.1016/j.prmcm.2023.100222.
3. Ugbogu EA, Okoro H, Emmanuel O, Ugbogu OC, Ekweogu CN, Uche M, Dike ED, Ijioma SN. Phytochemical characterization, anti-diarrhoeal, analgesic, anti-inflammatory activities and toxicity profile of *Ananas comosus* (L.) Merr (pineapple) leaf in albino rats. J Ethnopharmacol. 2024; 319(2):117224. doi: 10.1016/j.jep.2023.117224.
4. Ekweogu CN, Akubugwo EI, Emmanuel O, Nosiri CI, Uche ME, Adurosakin OE, Ijioma SN, Ugbogu EA. Phytochemical profiling, toxicity studies, wound healing, analgesic and anti-inflammatory activities of *Musa paradisiaca* L. Musaceae (Plantain) stem extract in rats. J Ethnopharmacol. 2024; 117639. https://doi.org/10.1016/j.jep.2023.117639.
5. Nabil M, El Raey MA, Abdo W, Abdelfattah M, El-Shazly A, Sobeh M, Mahmoud MF. Gastro-protective effects of *Albizia anthelmintica* leaf extract on indomethacin-induced gastric ulcer in wistar rats: In silico and *in vivo* studies. Antioxidants 2021; 10(2):176.
6. Lawal F, Garba K, Shuai'bu AB, Chedi BAZ. Evaluation of the antiulcer activity of aqueous seed extract of *Moringa oleifera* Lamarck (Moringaceae). Trop J Nat Prod Res. 2018; 2(3):140-144. doi.org/10.26538/tjnpr/v2i3.8.
7. Peura DA. Prevention of nonsteroidal anti-inflammatory drug–associated gastrointestinal symptoms and ulcer complications. Am J Med. 2004; 117:63–71.
8. Sohail R, Mathew M, Patel KK, Reddy SA, Haider Z, Naria M, Habib A, Abdin ZU, Razzaq C, Akbar A. Effects of non-steroidal anti-inflammatory drugs (NSAIDs) and gastroprotective NSAIDs on the gastrointestinal tract: A narrative review. Cureus. 2023; 3:15(4):e37080. doi: 10.7759/cureus.37080.
9. Bandyopadhyay D, Chattopadhyay, A. Reactive oxygen species-induced gastric ulceration: Protection by melatonin. Cur Med Chem. 2006; 13:1187–1202.
10. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochem Pharmacol. 2020; 180:114147. doi: 10.1016/j.bcp.2020.114147.
11. Lau JY, Sung JJ, Metz DC, Howden CW. Systematic review of the epidemiology of complicated peptic ulcer: incidence, recurrence, risk factors and mortality. Gastroenterol. 2008; 134:30-32.
12. Papanikolaou IS, Siersema PD. Gastric outlet obstruction: current status and future directions. Gut and Liver 2022; 16(5):667-675. doi: 10.5009/gnl210327.
13. Yuan Y, Padol IT, Hunt RH. Peptic ulcer disease today. Nat Rev Gastroenterol Hepatol. 2006; 3:80–89. doi: 10.1038/ncpgasthep0393.
14. van Soest EM, Siersema PD, Dieleman JP, Sturkenboom M, Kuipers EJ. Persistence and adherence to proton pump inhibitors in daily clinical practice. Aliment Pharmacol

Therapeut. 2006; 24:377–385. doi: 10.1111/j.1365-2036.2006.02982.x.
15. Wang J, Zhang G, Hu X, Liu Y, Bao Z Huang Y. Two-week triple therapy has a higher *Helicobacter pylori* eradication rate than 1-week therapy: A single-center randomized study. Saudi J Gastroenterol. 2015, 21(6):355-359. doi: 10.4103/1319-3767.170951.
16. Enegide C, Akah PA, Ezike AC, Ameh SF, Ezenyi IC, Okhale SE. Evaluation of the antioxidant, antinociceptive and anti-inflammatory activities of *Combretum nigricans* ethanolic leaf extract Trop J Nat Prod Res. 2024; 8(6): 7554-7560. https://doi.org/10.26538/tjnpr/v8i6.35.
17. Basbaum AI, Bautista DM, Scherrer G and Julius, D. Cellular and molecular mechanisms of pain. Cell 2010; 139:267–284. doi: 10.1016/j.cell.2009.09.028.
18. Kuna L, Jakab J, Smolic R, Raguz-Lucic N, Vcev A, Smolic M. Peptic ulcer disease: A brief review of conventional therapy and herbal treatment options. J Clin Med. 2019; 8(2):179. doi: 10.3390/jcm8020179.
19. Bavry AA, Khaliq A, Gong Y, Handberg EM, Cooper-DeHoff RM, Pepine CJ. Harmful effects of NSAIDS among patients with hypertension and coronary artery disease. Am J Med. 2011; 124:614–620. doi: 10.1016/j.amjmed.2011.02.025.
20. Porreca F, Ossipov MH. Nausea and vomiting side effects with opioid analgesics during treatment of chronic pain: Mechanisms, implications, and management options. Pain Mgt. 2009; 10:654–662. doi: 10.1111/j.1526-4637.2009.00583.x.
21. Passik SD, Lowery A. Psychological variables potentially implicated in opioid-related mortality as observed in clinical practice. Pain Mgt. 2011; 12(02):S36-S42. doi: 10.1111/j.1526-4637.2011.01130.x.
22. Sivri B. Trends in peptic ulcer pharmacotherapy. Fund Clin Pharmacol. 2004; 18:23–31. doi: 10.1111/j.1472-8206.2004.00203.x.
23. Yanagihara GR, de Paiva AG, Neto MP, Torres LH, Shimano AC, Louzada MJ, Annoni R, de Oliveira P. Effects of long-term administration of omeprazole on bone mineral density and the mechanical properties of the bone. Revista Brasileira de Ortopedia, 2015; 50(2):232-238. doi: 10.1016/j.rboe.2015.03.002.
24. Ogundajo AL, Ewekeye T, Sharaibi OJ, Owolabi MS, Dosoky NS, Setzer WN. Antimicrobial activities of sesquiterpene-rich essential oils of two medicinal plants, *Lannea egregia* and *Emilia sonchifolia*, from Nigeria. Plants 2021; 10(3):488. doi: 10.3390/plants10030488.
25. Narayanan V.PS, Kathirason SG, Elango P, Subramanian R, Gurusamy A. *Emilia sonchifolia* leaf extract-mediated green synthesis, characterization, *in vitro* biological activities, photocatalytic degradation and in vivo *Danio rerio* embryo toxicity of copper nanoparticles. RSC Adv. 2023; 13(24), 16724–16740. https://doi.org/10.1039/d3ra00454f.
26. Siu TY, Kong BL, Wong KH, Wu HY, But GW, Shaw PC, Lau DT. Characterization and phylogenetic analysis of the complete chloroplast genome of *Emilia sonchifolia* (L.) DC. Mitochondrial DNA. Part B Res. 2023; 8(1): 20–22. https://doi.org/10.1080/23802359.2022.2055980.
27. Yu SS, Zhao RL, Lin MX, Wu Y, Shu-Gui C, Yu FY, Song WW, Zhu H. Occurrence of phytoplasma belonging to 16SrII group associated with Witches'-broom symptoms in *Emilia sonchifolia* in Hainan Island of China. Plant Dis. 2021; https://doi.org/10.1094/PDIS-01-21-0043-PDN.
28. Essien GE, Nwidu LL, Nwafor PA. Anti-inflammatory and analgesic potential of methanolic extract of *Emilia sonchifolia* (Compositae) leaves in rodents. Afr J Biomed Res. 2009; 12: 199–207.
29. Kallivalappil G, Kuttan G. Evaluation of the anti-inflammatory and urotoxicity ameliorative effects of γ-humulene containing active fraction of *Emilia sonchifolia* (L.) DC. Inflammopharmacol. 2019; 27: 409–420. doi: 10.1007/s10787-017-0423-3.
30. Care Animal Use Committee. Guidelines for the capture, handling, and care of mammals as approved by the American Society of Mammalogists. J Mammal. 1998; 1416-1431.
31. National Research Council (NRC-US). Committee for the Update of the Guide for the Care and Use of Laboratory Animals. Guide for the Care and Use of Laboratory Animals. 8th edition. Washington (DC): National Academies Press (US). 2011; https://www.ncbi.nlm.nih.gov/books/NBK54050/ doi: 10.17226/12910
32. Adeyemi OO, Okpo SO, Okpaka O. The analgesic effect of the methanolic extract of *Acanthus montanus*. J Ethnopharmacol. 2004; 90:45-48.
33. Orieke D, Ohaeri OC, Ijeh II, Ijioma SN. Gastrointestinal and uterine smooth muscles relaxant and anti-inflammatory effects of *Corchorus olitorius* leaf extract in laboratory animal models. J Ethnopharmacol. 2020; 247: 112224.
34. Sivaraman D, Muralidharan P. Anti-ulcerogenic evaluation of root extract of *Ficus hispida* Linn. in aspirin ulcerated rats. Afr J Pharm Pharmacol. 2010; 4: 079-082.
35. Rasika DB, Mahendra AG, Sneha JA, Subodh CP. Anti-ulcer activity of ethanolic extract of leaves of *Sesbania grandiflora* linn. Int J Pharm Pharmaceut Sci. 2010; 2(4): 206-209.
36. Goel R, Sairam K. Anti-ulcer drugs from indigenous sources with emphasis on *Musa Sapientum*, *Tamrabhasma*, *Asparagus Racemosus* and *Zingiber officinale*. Indian J Pharmacol. 2002; 34(2): 100-110.
37. Emmanuel O, Uche ME, Dike ED, Etumnu LR, Ugbogu OC, Ugbogu EA. A review on *Garcinia kola* heckel: traditional uses, phytochemistry, pharmacological activities, and toxicology. Biomarkers 2022; 27(2): 101–117. https://doi.org/10.1080/1354750X.2021.2016974.
38. Okoro BC, Dokunmu TM, Okafor E, Sokoya IA, Israel EN, Olusegun DO, Bella-Omunagbe M, Ebubechi UM, Ugbogu EA, Iweala, EEJ. The ethnobotanical, bioactive compounds, pharmacological activities and toxicological evaluation of garlic (*Allium sativum*): A review. Pharmacol Res Modern Chin Med. 2023; 8: 100273. https://doi.org/10.1016/j.prmcm.2023.100273.
39. Ukpai OM, Ijioma SN, Kanu K, Orieke D, Chinedu-Ndukwe PA, Ugwuanyi KC, Ugbogu EA. Phytochemical composition, toxicological profiling and effect on pup birth weight of *Corchorus olitorius* leaf extract in rats: Implications for fetal macrosomia control. J Ethnopharmacol. 2024; 117170. https://doi.org/10.1016/j.jep.2023.117170.
40. Faseela A, Aparna G, Jishidha A, Nidhi R. In vitro anti-inflammatory and anti-ulcer activities of aqueous extract of *Emilia sonchifolia*. World J Bio Pharm Health Sci. 2023; 15:176-186.
41. Nwafor PA, Okwuasaba FK. Antinociceptive and anti-inflammatory effects of methanolic extract of *Asparagus pubsences* root in rodents. J Ethnopharmacol. 2003; 84:125-129.
42. Tijani AY, Ugoru MO, Salawu, O.A. Antipyretic, anti-inflammatory and antidiarrhoeal properties of *Faidherbia albida* in rats. Afr J Biotechnol. 2008; 7 (6):696-700.
43. Omkulthom A, Omar N, Omer A, Ashwag A, Raffaele, C. Separation and evaluation of potential antioxidant, analgesic, and anti-inflammatory activities of limonene-rich essential oils from *Citrus sinensis* (L.). Open Chem. 2022; 20: 1517-1530.
44. Yingjie H, Wen-Xue C, Zhichang S. Antimicrobial activity and mechanism of limonene against *Staphylococcus aureus*. J Food Safety. 2021; 41: 1-3.

45. Barung EN, Dumanauw JM, Duri MF, Kalonio D.E. Egg white-induced inflammation models: A study of edema
46. Pharmaceut Technol Res. 2021; 12(2):109-112. doi: 10.4103/japtr.JAPTR_262_20.
47. Yong YK, Sulaiman N, Hakim MN, Lian GE, Zakaria ZA, Othman F, Ahmad Z. Suppressions of serotonin-induced increased vascular permeability and leukocyte infiltration by *Bixa orellana* leaf extract. BioMed Res Int. 2013:463145.
48. Patil KR, Mahajan UB, Unger BS, Goyal SN, Belemkar S, Surana SJ, Ojha S, Patil CR. Animal models of inflammation for screening of anti-inflammatory drugs: Implications for the discovery and development of phytopharmaceuticals. Int J Mol Sci. 2019; 20:1–38.
49. Paterson KJ, Zambreanu L, Bennett DL, McMahon, S.B. Characterisation and mechanisms of bradykinin-evoked pain in man using iontophoresis. Pain 2013; 154(6):782-792. doi: 10.1016/j.pain.2013.01.003.
50. Pina L, Serafini M, Oliveira M, Sampaio L, Guimarães J, Guimarães A. Carvone and its pharmacological activities: A systematic review. Phytochem. 2022; 196: 0031-9422. https://doi.org/10.1016/j.phytochem.2021.113080.
51. Corrêa A, Weimer P, Rossi R, Hoffmann J, Koester L, Suyenaga E, Ferreira, C. Lime and orange essential oils and d-limonene as a potential COVID-19 inhibitor: Computational, in chemico, and cytotoxicity analysis. Food profile and histological change of rat's paw. J Adv Biosci. 2023; 51: 2212-4292. https://doi.org/10.1016/j.fbio.2022.102348.
52. Santa-María C, López-Enríquez S, Montserrat-de la Paz S, Geniz I, Reyes-Quiroz ME, Moreno M, Palomares F, Sobrino F, Alba G. Update on anti-inflammatory molecular mechanisms induced by oleic acid. Nutrients 2023; 15(1):224. doi:10.3390/nu15010224.
53. Jaiswal F, Awani R, Wal P, Wal A, Singh S. Peptic ulcer: a review on etiology, pathogenesis and treatment. Asian J Pharmaceut Edu Res. 2021; 10:1-17.
54. Bouyahya A, Mechchate H, Benali T, Ghchime R, Charfi S, Balahbib A, Burkov PV, Mubarak M, Shariati M, Lorenzo J, El Omari, N. Health benefits and pharmacological properties of carvone. Biomolecules. 2021; 11:1803.
55. Uche ME, Chinyere G.C, Ekweogu CN, Nwankpa P, Ugbogu EA. Phytochemical analysis, toxicity assessment, and wound healing properties of *Emilia sonchifolia* L. leaf extract in rats. South Afr J Bot. 2024; 172:736-746. https://doi.org/10.1016/j.sajb.2024.07.065.
56. Zhang W, Lian Y, Li Q, Sun L, Chen R, Lai X, Lai Z, Yuan E, Sun S. Preventative and therapeutic potential of flavonoids in peptic ulcers. Molecules. 2020; 11: 25(20):4626.