Antiulcerogenic activity of the ethanolic extract of *Licania macrophylla* Benth

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Abstract

The *Licania macrophylla* Benth species, popularly known as "anauerá", "anuera", "anoerá", "ana-wyra" and "wayãpi", is widely found in the Amazon. Here, riverine communities use different parts of the plant for the treatment of amoebiasis, dysenteric disorders, wound healing and anti-inflammatory actions. The present study aims to investigate the gastroprotective activity of ethanolic extract of *L. macrophylla* stem bark in experimental animals. For this purpose, different experimental models for gastric ulcer induction were performed, such as absolute ethanol (99.5%), acidified ethanol (60%/0.3M HCl), and the non-steroidal anti-inflammatory drug model (indomethacin). In this study, 25-30g female Swiss mice were used for the absolute and acidified ethanol experimental models, and 200-300g female Wistar rats were used for the non-steroidal anti-inflammatory drug model. Each experimental model was divided into groups of five (5) animals for each tested dose of *L. macrophylla* extract (100, 250 and 625 mg/kg), as well as for the negative (vehicle) and positive (carbenoxolone) control groups. All administrations were performed orally, with a volume ratio of a maximum of 10 ml/kg body weight for mice and 100 ml/kg for rats. After each experiment, stomachs were evaluated to determine the following parameters: total lesion area, ulcer percentage, ulcerative lesion index, cure percentage. Statistical analysis was performed by one-way ANOVA followed by Dunnett post-test, considering significant values when $p<0.05$. The ethanolic extract of *L. macrophylla* showed gastroprotective effect against gastric lesions induced by absolute ethanol, significantly reducing the established parameters (250 and 625 mg/kg), promoting a cure rate of 53.76±5.71% and 84.15±1.89%, respectively. For the experimental protocol performed with acidified ethanol the results showed that the animals treated with the L. macrophylla ethanolic extract at the doses of 250 and 625 mg/kg, lesions decreased significantly when analyzing the established parameters, obtaining as a cure percentage of 52.34±4.83% and 83.86±2.46%, respectively. The ethanolic extract of L. macrophylla in the non-steroidal anti-inflammatory gastric lesion induction model was able to significantly reduce lesions for all doses tested (100, 250 and 625 mg/kg) in the established parameters, with a cure percentage (%) of 84.46±1.33%, 75.00±3.71% and 72.27±2.06%, respectively. In conclusion, *L. macrophylla* extract demonstrates antiulcerogenic activity in the acid and absolute ethanol induction models, as well as in the ulcer model induced by non-steroidal anti-inflammatory drugs with significant gastroprotective activity.

Keywords: Medicinal plants. Crude extract. Anauerá. Gastric ulcer.

INTRODUCTION

Gastric ulcers are lesions that occur in the stomach wall, characterized by bleeding and perforation[1], and are progressive disorders that have a great impact on the patient's quality of life[2].

The emergence of gastric ulcers is considered a multifactorial process that results from the imbalance between the aggressing factors and the mucosal protectors. Among the aggressive factors is the secretion of acid, pepsin and free radicals that originate from stimuli related to living conditions such as stress, smoking, alcohol, continuous use of non-steroidal anti-inflammatory drugs - NSAIDs, ingestion of

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certain foods and the presence of *Helicobacter pylori*. Protective factors include the mucus barrier, bicarbonate, nitric oxide (NO), blood flow, prostaglandins and antioxidant defense[2,3].

Treatment of ulcers is based on restoring the balance of protective and aggressive factors to eliminate pain, promoting healing and preventing recurrent ulcers. With the understanding of the pathogenesis of peptic ulcers, several classes of drugs have emerged such as proton pump inhibitors (omeprazole, lanzoprazole, pantoprazole), H2 receptor antagonists (cimetidine, ranitidine, famotidine and nizatidine) and antibiotics in cases of *H. pylori* infection (amoxicillin). Other drugs have emerged to protect the mucosa as a cytoprotective agent (carbenoxolone, sucralfate, colloidal bismuth) and a prostaglandin analog (misoprostol)[4,5].

Drug therapy for the treatment of gastric ulcer confirms a high recurrence rate of the pathology, besides presenting significant side effects[6]. However, the search for new substances derived from natural products has been one of the main sources of discovery of new drugs with potentially more effective and safer therapeutic effects. Medicinal plants are sources of bioactive compounds such as flavonoids, alkaloids, terpenes, tannins, carotenoids and phenolic compounds. Such compounds contain various biological activities, especially compounds such as flavonoids, terpenoids and tannins, which are attributed to antiulcerogenic activity[7].

The species *Licania macrophylla* Benth, belonging to the family Chrysobalanaceae, popularly known as "anauerá", "anuera", "anoerá", "ana-wyra" and "wayãpi", is a large tree that can reach up to 30 m in height. In the Amazon, it is popularly used for various purposes, such as being a potent antidysentery factor, wound healing, an amoebiasis treatment and having anti-inflammatory activity. According to the literature, no reports of its antiulcerogenic activity were reported[8,9,10,11].

The species *L. macrophylla* possesses, in its chemical composition, compounds such as flavonoids, chalcones and aurones, quinones, free steroids and tannins[8,9,12]. In a study of methanolic extract of *L. macrophylla* stem bark and leaves, activity against bacterial strains tested with *Staphylococcus aureus, Pseudomonas aeruginosa* and *Escherichia coli* were demonstrated[9]. Due to the potential therapeutic potential of this species, this study raises the following question: does the ethanolic extract of this species possess gastroprotective activity?

MATERIALS AND METHODS

The stem bark of the *L. macrophylla* species was collected via waterway in a floodplain in the Maracá community, located on the Urubuzinho River, at the following coordinates (Lat. 0°24'46.83 S Long. 51°27'5.36 W), 32km away from Mazagão Velho, AP. The study material was sent to the Animal Experimentation Laboratory (LEA) of the Federal University of Amapá (UNIFAP). An exsiccate was prepared for the identification of the species and was then deposited in the Amapan Herbarium (HAMAB) of the Amapá State Institute of Scientific and Technological Research (IEPA), Macapá, AP.

To obtain the ethanolic extract of *L. macrophylla*, the bark of the stem was dried at 40ºC for 72h. The material was fragmented and ground in a knife mill and turned powder, which underwent a cold maceration process using 1 kg of powder for every 5L of ethanol (1:5, weight/volume) as an ethanol solvent, agitating every 24 hours for 7 days. The extractive solution obtained was filtered and concentrated by evaporation at a temperature around 50°C. A viscous extract was obtained and was stored in a container for residual evaporation of the solvent until obtaining the dry/crude ethanol extract of L. macrophylla (EELM). The extract obtained a yield of 10.6%. For the experiments, the extract was weighed and solubilized in a solution of 5% DMSO to obtain different concentrations.

Drugs and Reagents Used

To determine antiulcerogenic activity and mechanism of action, hydrochloric acid p.a. (Alphatec), sodium bicarbonate (Alphatec), sodium chloride (Alphatec), ketoprofen (Sanofi) indomethacin (Sigma Aldrich), carbenoxolone (Sigma Aldrich), xylazine (Vetbrands), ketamine (Ceva), ethanolic alcohol (Alphatec), ethyl

alcohol p.a. (Alphatec), dimethylsulfoxide-DMSO (Prolab). All drugs were prepared immediately before use.

Animals

Female Wistar rats (Rattus norvegicus) weighing between 200-300 grams (n=25) and female Swiss mice (Mus muscululus albinus) aged 6-7 weeks and weighing 25-30 grams (n=50) were used. The animals came from the Multidisciplinary Center for Biological Investigations in the area of Laboratory Animal Science - CEMIB, University of Campinas - UNICAMP. The animals were kept in plastic boxes in an experimental room for 7-10 days under controlled conditions of temperature (23±2oC), humidity (50±10%), a 12-hour light-dark cycle, with access ad libitum to Presence® brand ration and filtered water for the experiments.

For euthanasia of the animals after the experiments, ketamine and xylazine 40 and 5 mg/kg respectively, as well as anesthesia were administered intraperitoneally, according to the National Council for Animal Experimentation Control, Resolution Norm No. 13 from September 2013. Carcass disposal proceeded according to item 1.6 of the FCF-IQ/USP Laboratory Animal Care and Procedures Manual 2013.13

Experimental Design

For the evaluation of the antiulcerogenic activity of the extract, gastric ulcer induction experiments were performed based on etiological factors of the disease in man such as absolute ethanol, acidified ethanol and NSAIDs. Each experimental model contained its respective negative/vehicle control groups (5% dimethylsulfoxide - DMSO), positive control (carbenoxolone 200 mg/kg), and test groups of three EELM dose amounts (100, 250, 625 mg/kg). The fasted animals were kept in a special cage with a wire mesh at the bottom (to avoid coprophagia).

At the end of each experimental protocol the stomachs were removed, opened through the greater curvature, washed in physiological solution (0.9% NaCl) and scanned to obtain the images (HP G4050 scanner). After scanning, the obtained images were analyzed using the EARP software to measure the lesioned areas and to determine the following parameters: (a) total lesion area (TLA), (b) percentage of lesion area in relation to the area total stomach, (c) ulcerative lesion index (ULI); (d) inhibition or cure percent[14].

(a) Σ Total Injury Area (mm^2) (TLA);

(b) (b) Percentage of Ulcers: Percentage of Injury Area in relation to Total Stomach Area;

$$\% = \sum \frac{\text{Lesion area}}{\text{Total area of the stomach}} \times 100$$

(c) Ulcerative Lesion Index (ULI)
Level 1: hemorrhaging points ≤ 1mm2
Level 2: 1 to 3mm2 ulcerations
Level 3: Deep ulcerations ≥ 3mm2

$$ILU = (\sum \text{Nível 1}) + (2x \sum \text{Nível 2}) + (3x \sum \text{Nível 3})$$

(d) Inhibition or Cure Percent;

$$CI\% = \frac{100 - \text{ULI treated}}{\text{ULI control}} \times 100$$

Absolute Ethanol-Induced Ulcer Model

The animals were randomly divided into 5 groups (n=5) of Swiss mice. Carbenoxolone 200 mg/kg (positive control), vehicle (negative control) and EELM extract (100, 250 and 625 mg/kg – test groups) were used for their respective treatments. Each treatment was administered orally at a rate of up to 10 ml/kg. After 60 minutes of treatment, 100 ml/kg of the injurious agent (99.5% ethanol) was administered to all animals orally. After 60 minutes of administering

the injurious agent, all animals were euthanized, and their stomachs were opened for analysis and parameter determination[15].

Acidified Ethanol-induced Ulcer Model

After 24 hours of fasting, Swiss mice were divided into 5 groups (n=5). One group received 200 mg/kg carbenoxolone (positive control), another group received vehicle (negative control) and the others the EELM extract at varying doses (100, 250 and 625 mg/kg – test group). All treatments were performed orally. After 50 minutes, 100 mL/kg weight of acidified ethanol (60% ethanol/ 0.3M HCl) was administered. After 60 minutes of administration of the injurious agent, the animals were euthanized to remove their stomachs and determine the parameters[16].

Non-Steroidal Anti-Inflammatory Drug (NSAID)- Induced Ulcer Model

To perform the experiment, after 24 hours of fasting, the animals were divided into 5 groups (n=5) of Wistar rats. The treatments were carried out respectively with carbenoxolone 200 mg/kg (positive control), vehicle control (negative control) and EELM at the doses of 100, 250 and 625 mg/kg (test group), orally. After 1h and 30 minutes, the indomethacin inducing agent (100 mg/kg) was administered orally, and 0.2 ml ketoprofen was applied intramuscularly. The animals were euthanized 12 hours after the injurious stimulus for stomach removal and determining parameters[17].

Statistical analysis

Results were expressed as mean±s.e.m., normality and homogeneity tests were performed, and data distribution was normal for the use of the one-way ANOVA followed by a Dunnett post-test for multiple comparisons. Values were considered significant when $p<0.05$. The program used for these analyses was GraphPad Prism version 5.01.

Ethical Considerations

The treatment protocols to be performed in this study were submitted to the Ethics Committee for Animal Use of the Federal University of Amapá CEUA/UNIFAP, approved under opinion no. 0019/2017.

RESULTS

Absolute Ethanol-Induced Gastric Ulcers

The results showed a significant reduction in the EELM doses of 250 and 625 mg/kg in the parameters evaluated as the Total Lesion Area (TLA), the Ulcerative Lesion Index (ULI) and Ulcer Percentage (%), compared to the vehicle controls. In calculating the Wound Healing Percentage (%), the 250 mg/kg dose healed 53.76% and the 625 mg/kg dose healed 84.15%, as can be seen in Figure 1, Graph 1 and Table 1.

Acidified Ethanol-Induced Gastric Ulcers

Animals treated with EELM at doses of 250 and 625mg/kg had a significant reduction in Total Lesioned Area (TLA), Ulcerative Injury Index (ULI), and Percentage of Ulcers (%) compared with the group of animals treated with the vehicle. The Wound Healing Percentages (%) obtained were 20.27% for the 100 mg/kg dose, 54.34% for the 250 mg/kg dose and 83.86% for the 625 mg/kg dose, as can be seen in Figure 2, Graph 2 and Table 2.

Non-Steroidal Anti-Inflammatory Drug (NSAIDs)-Induced Gastric Ulcers

Regarding the model of gastric ulcer induction with non-steroidal anti-inflammatory agents (indomethacin 100mg / kg + ketoprofen 0.2mL), when assessing the Total Lesioned Area, Ulcerative Lesion Index (ULI), Percentage of Ulcers (%), all doses of the L. macrophylla ethanolic extract (EELM) tested (100, 250, 625 mg/kg) significantly reduced these parameters when compared to the negative control. For the Wound Healing Percentage (%) it was possible to measure 84.45% healing for the 100 mg/kg dose, 75.00% for the 250 mg/kg dose and 72.26% for the 625 mg/kg dose, as may be seen in Figure 3, Graph 3 and Table 3.

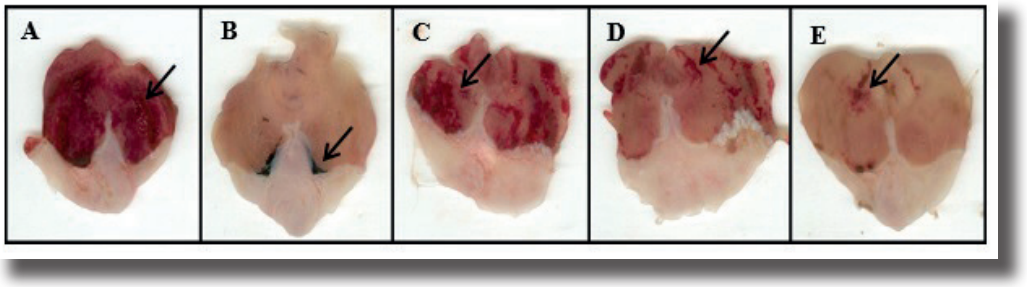
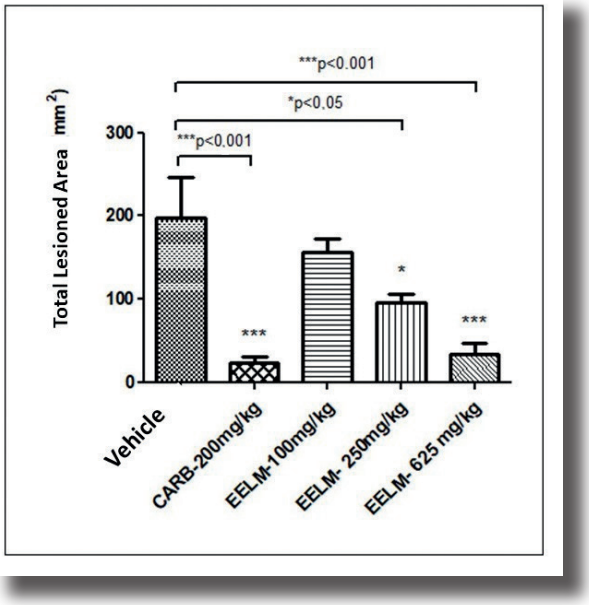


Figure 1 – Stomach images after ulcer induction by absolute ethanol, (A) negative control, (B) positive control; (C) EELM 100 mg/kg; (D) EELM 250 mg/kg; (E) EELM 625 mg/kg.

Graph 1 – Result of the total lesioned area (mm2) parameter in the absolute ethanol-induced gastric ulcer model in mice.



Results were expressed as mean ± s.e.m. (n=5, per group). One-way Analysis of Variance (ANOVA) was used, followed by Dunnett's test: ***p<0.001 comparing the negative control group (vehicle) vs. CARB (200mg/kg) positive control. *p<0.05 comparing the negative control group (vehicle) vs. EELM (250 mg/kg); ***p<0.001 comparing the negative control group (vehicle) vs. EELM (625 mg/kg).

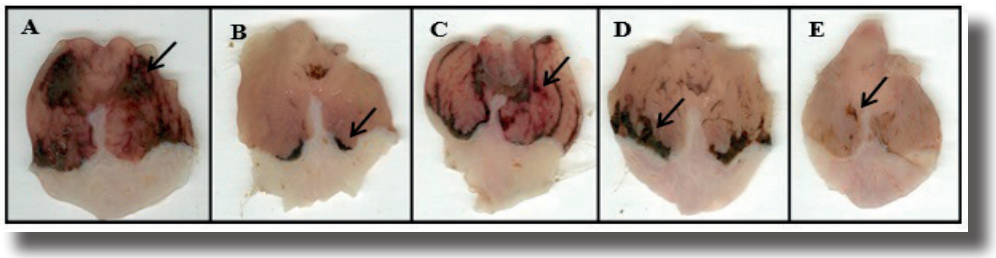
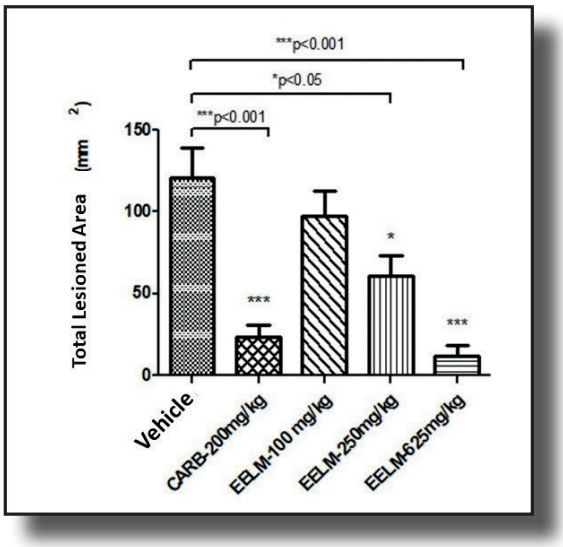


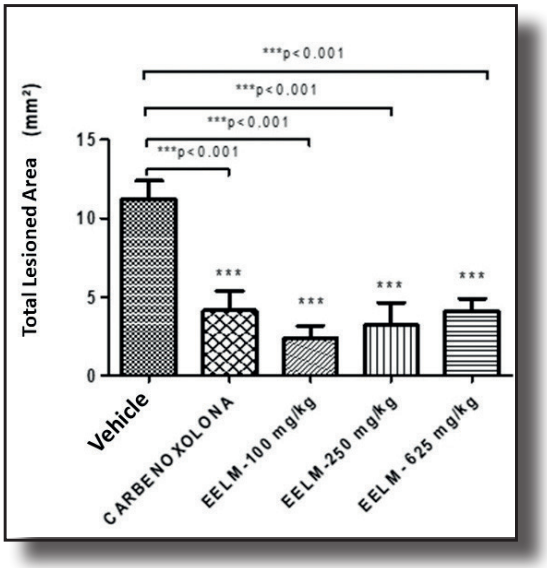
Figure 2 – Stomach images after ulcer induction by acidified ethanol, (A) negative control, (B) positive control; (C) EELM 100 mg/kg; (D) EELM 250 mg/kg; (E) EELM 625 mg/kg.

Graph 2 – Effect of acidified ethanol-induced gastric ulcer model in mice in the total lesioned area (mm2) parameter.



Results were expressed as mean±s.e.m (n=5, per group). One-way analysis of variance (ANOVA) was used, followed by Dunnett's test: ***p<0.001 (Vehicle vs. CARB 200mg/kg). *p<0.05 comparing the negative control group (vehicle) vs. extract (250 mg/kg); ***p<0.001 comparing the negative control group (vehicle) vs. extract (625 mg/kg).

Graph 3 – Parameter total lesioned area (mm2) in the NSAID-induced gastric ulcer model in rats.



Results were expressed as mean ± s.e.m. (n=5, per group). One-way analysis of variance (ANOVA) was used, followed by Dunnett's test: ***p<0.001 Vehicle vs. CARB (200mg/kg). ***p<0.001 comparing the negative control group (vehicle) vs. EELM (at doses of 100, 250, 625mg/kg).

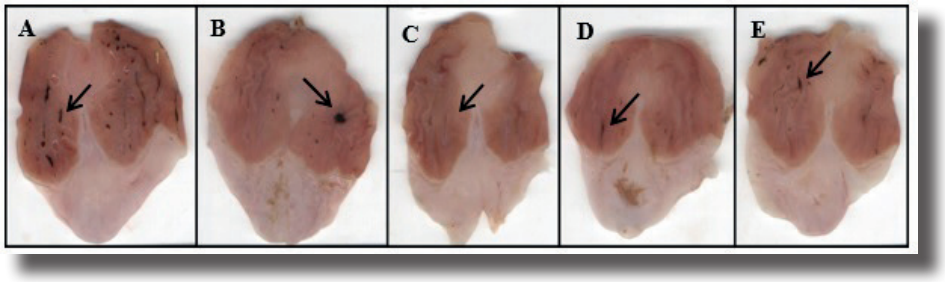


Figure 3 – Stomach images after induction of ulcer by (indomethacin + ketoprofen), (A) negative control; (B) positive control (C) EELM 100 mg/kg; (D) EELM 250 mg/kg; (E) EELM 625 mg/kg.

Table 1 – Absolute ethanol-induced gastric ulcer model in mice concerning the ULI, Ulcer % and Healing % parameters.

Treatment (v.o)	U.L.I.	% of Ulcers	% of Healing
VEHICLE	586.38±19.11	62.64±11.53	0.0-±0.00
CARBENOXOLONE	62.72±3.90+++	8.90±2.83***	21.42%±8.45
EELM 100	460.76±4.47	46.87±3.95	21.42%±8.45
EELM 250	271.17±5.64+	31.84±3.92*	53.76%±5.71
EELM 625	92.92±5.82+++	10.79±1.88***	84.15%±1.89

(ANOVA), followed by Dunnett's test: +++p<0.001 comparing the negative control (Vehicle) vs. positive control (CARB 200mg/kg), ILU. +p<0.05 (EELM at 250mg / kg dose) vs. (Vehicle), ILU. +++ p <0.001 (EELM at 625mg / kg dose) vs. (Vehicle). ***p<0.001 Vehicle vs. CARB (200mg/kg), % of Ulcers. *p<0.05 EELM (250 mg/kg) vs. Vehicle, % of ulcers. ***p<0.001 EELM (625 mg/kg) vs. Vehicle, % of ulcers.

Table 2 – Model of acidified ethanol-induced gastric ulcers in mice concerning ULI, % of Ulcers and Wound Healing % parameters.

Treatment (v.o)	U.L.I.	% of Ulcers	% of Healing
VEHICLE	356.21±5.50	51.42±3.94	0.0±0.00
CARBENOXOLONE	62.72±3.90+++	8.90±2.83***	82.39%±1.53
EELM 100	284.01±5.09	31.90±5.74*	20.27%±2.91
EELM 250	169.77±5.14+	21.24±4.60***	52.34%±4.83
EELM 625	57.50±7.92+++	4.19±2.24***	83.86%±2.46

Results are presented as mean ± s.e.m. One-way analysis of variance (ANOVA) was used, followed by Dunnett's test: +++p<0.001 comparing the negative control (Vehicle) vs. the positive control (CARB 200mg/kg), ULI. +p<0.05 EELM (250 mg/kg) vs. Vehicle, ULI. +++p<0.001 EELM (625 mg/kg) vs. Vehicle ULI. ***p<0.001 Vehicle vs. CARB (200mg/kg), % of ulcers. *p<0.05 EELM (100 mg/kg) vs. Vehicle, % ulcer. ***p<0.001 EELM (250, 625mg/kg) vs. (Vehicle), % of ulcers.

Table 3 – Model of non-steroidal anti-inflammatory gastric ulcers (NSAIDs) in rats, concerning ULI, % of Ulcers and Wound Healing % parameters.

Treatment (v.o)	U.L.I.	% of Ulcers	% of Healing
VEHICLE	20.21±3.08	2.39±0.31	0.0±0.00
CARBENOXOLONE	5.49 ±1.74++	0.71±0.19***	72.85%±2.42
EELM 100	4.54 ±0.37++	0.40±0.14***	84.46%±1.33
EELM 250	5.05±3.26++	0.63±0.26***	75.00%±3.71
EELM 625	5.61±1.49++	0.68±0.14***	72.27%±2.06

Results are presented as mean ± s.e.m. One-way analysis of variance (ANOVA) was used, followed by Dunnett's test: ++p<0.01 Vehicle vs. CARB, ULI ++p<0.01 EELM (at doses of 100, 250, 625mg/kg) vs. Vehicle, ULI.

DISCUSSION

Studies of medicinal plants with possible gastroprotective activities are based on demonstrating the efficacy of new therapeutic alternatives in the treatment or prevention of gastric lesions produced by different harmful agents.

The acute ethanol-induced ulcer model is a primary step in the search for substances with antiulcerogenic potential, as it determines the effectiveness of a test drug, which opens the way for investigating in other models, as well as the mechanisms of action involved in gastroprotective activity[18].

The deleterious effects of ethanol are caused by direct toxic contact to the gastric mucosa compromising its structure by various mechanisms, such as solubilizing the mucus and bicarbonate barrier. This ulcerogenic agent also triggers and inflammatory reaction promoting the release of inflammatory mediators, which induce the activation of granulocytes forming proteases and free radicals, decreasing blood flow thereby causing ischemia, cell death and damage to the gastric mucosa[16].

The acidified ethanol model acts through a local effect on the gastric mucosa. It disrupts its integrity by forming necrotizing lesions by decreasing mucus layer protection, which is caused by the solubilization of the barrier's components releasing access to stomach lumen acid. This model is an appropriate protocol for assessing acute damage[19,20].

Studies have disassembled that compounds such as flavonoids are able to protect the gastric mucosa from necrotizing substances and are effective in the treatment of acute and chronic gastric ulcers. Flavonoids have the ability to inhibit specific enzymes and stimulate some hormones and neurotransmitters and sequester free radicals[21].

The results obtained in this study in the treatments performed within the ulcer models induced by absolute ethanol and acidified ethanol showed that the groups of animals with the EELM in the respective doses of 100, 250 and 625mg/kg caused a considerable gastroprotective effect; similar to that shown by the standard drug, carbenoxolone. The protective response demonstrated by EELM in the absolute ethanol and acidified ethanol experimental protocols suggests that the extract acts as an antiulcerogenic agent, promoting a significant protection of the gastric mucosa with a dose-dependent response tendency.

In the presented model of gastric ulcer induction by NSAIDs, indomethacin was the first choice because of its high ulcerogenic potential compared to other drugs of the same class of drugs[22].

It is pointed out that the effects of NSAIDs are mediated by the inhibition of the type 1 isoform of the enzyme cyclogenase (COX-1) and the type 2 isoform of the enzyme cyclogenase (COX-2), thereby reducing prostaglandin E1 levels (PGE1) and E2 (PGE2). Thus, the prolonged use of this drug is directly associated with the appearance of gastric lesions[23].

According to the literature, compounds such as tannins can play a role in gastric protection. Authors report that tannins from plant extracts can form a physical barrier in the gastric mucosa by binding to mucus proteins, thus, preventing the formation of ulcers and promote healing[24,25].

Another class of mucosal protective compounds are terpenes, which have been reported in studies concerning the antiulcerogenic activity of pentacyclic triterpenes. Terpenes are related to anti-inflammatory activity. This effect occurs through various mechanisms of action such as prostaglandin synthesis (PGs), which are responsible for controlling blood flow, mucus/bicarbonate production and acid secretion among other pathways[26].

The results obtained in the NSAID-induced ulcer model showed that all doses tested (100, 250, 625mg/kg) were able to reduce gastric lesions caused by non-steroidal anti-inflammatory drugs, with the lowest dose showing a significant statistical significance when compared to

the negative control. In this experimental model, there was no dose-dependent activity pattern with the doses tested.

Thus, *L. macrophylla ethanolic* extract acts significantly against mucosal lesions, potentially exerting a gastroprotective effect as observed by different experimental models. There is a need for further studies to elucidate the mechanisms involved in the gastroprotective activity of the extract.

CONCLUSION

The results showed that the ethanolic extract of *L. macrophylla* in the analyzed doses produce a gastroprotective activity against ulcer models induced by absolute ethanol and acidified ethanol. The gastroprotective effect of the L. macrophylla ethanolic extract within the ulcer model induced by non-steroidal anti-inflammatory drugs showed a significant activity at all doses, especially at the lowest dose tested against the induced lesions. The plant species under study has gastroprotective activity regarding the appearance of gastric ulcers induced by different experimental models.

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