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Preclinical gastroprotective activity of an *Eugenia brasiliensis* Lam. (Myrtaceae) extract

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Abstract

Gastric ulcers are lesions of the mucous coating membrane of the stomach characterized by burning and epigastric pain as symptoms, which are empirically relieved by *Eugenia brasiliensis* Lam. (Myrtaceae) extracts. However, there are no studies which evaluated sistematically its gastroprotector potential. Thus, this study aimed to assess the gastroprotector effectiveness of an acetonic extract obtained from leaves of *Eugenia brasiliensis* in reducing gastric ulcers in rats. Animals were divided in groups and submitted to alcohol and indomethacin models of gastric lesion after previous treatment with the extract and to acetic acid-induced ulcer followed by six days exposure to the extract. Ethanol-induced gastric lesion was reduced by 30 and 100 mg/Kg of the extract in 36% and 68%, respectively. Indomethacin-induced gastric lesion area was reduced by 30, 100 and 300 mg/Kg of the extract in 66%, 88% and 73%, respectively. Acetic acid-induced gastric ulcer was reduced in 72% by 100 mg/Kg extract. Data indicate that *Eugenia brasiliensis* acetonic extract was effective in reducing gastric lesion in all models tested, which can be attributed to modulation of the inflammatory response and antioxidant activity enhancement by polyphenols, resulting in direct contribution to decrease cell damage which brings consequent gastric ulcer reduction.

Keywords: *Eugenia brasiliensis*. Phytomedicines. Phytotherapy. Gastritis. Gastric ulcer.

Introduction

Gastrointestinal ulcers are lesions in the lining of gastric and duodenal mucosa that develop when defense mechanisms are not sufficient to contain aggressive agents, including excessive gastric acidity, *Helicobacter pylori* infection, prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs), stress, excessive alcohol consumption and smoking[1].

Currently, their treatment is based mainly on the use of proton pump inhibitors (PPIs) or histamine H2 receptor antagonists, which promote an intense decrease in gastric acid secretion in order to protect the mucosa, lead to gastric healing and prevent recurrence of lesions by reducing gastric acid secretion. PPIs are associated with antibacterials when *H. pylori* eradication is required[2].

However, H2 blockers can cause adverse reactions, although not very prevalent, not negligible, such as vomiting, abdominal pain, diarrhea, gastroenteritis, headache, drowsiness, pneumonia[3]. As short-term adverse effects, PPIs can cause nausea, diarrhea, constipation, flatulence, dizziness, less prevalent headache, but prolonged use can result in important adverse effects, such as reduced absorption of vitamin B12, iron and calcium, in addition to pulmonary or intestinal infections, which are related to chronic hypochlorhydria. PPIs have also been associated in the long term with chronic kidney disease and hepatotoxicity [4]. The risk of gastric tumor development due to hypergastrinemia in response to the long-term use of PPIs remains under investigation[5].

Compounds from plants may constitute a new source of substances with alternative therapeutic potential to existing drugs. Attention is drawn to *Eugenia brasiliensis* Lam. (Myrtaceae), which has been shown to be anti-inflammatory in preclinical models of peritonitis[6] and pleurisy[7], in addition to extracts and compounds isolated from its leaves inhibiting cyclooxygenase enzymes[8]. Anti-inflammatory and antinociceptive effect in preclinical models of visceral and somatic inflammatory pain has also been evidenced[9], however, there are no studies on gastroprotection.

Therefore, the aim of this study was to evaluate the gastroprotective properties of an extract of *Eugenia brasiliensis*, known as “grumixama”, in preclinical models of prevention and treatment of gastritis and ulcer.

Material and Method

Ethical aspects

All tests were carried out only after approval of the project by the Ethics in Animal Use Committee (CEUA) of the University of Joinville Region (UNIVILLE), as stated in Opinion number 014/2017, issued on May 29, 2017.

Design, study location and period

This was a preclinical study carried out at the UNIVILLE Pharmacology Laboratory, from May to August 2018.

Study protocol

Animals

Wistar female rats (*Rattus norvegicus*) were used (eight per group) weighing between 200-250 g and purchased from the Animal Facility of the Federal University of Santa Catarina and kept in the Sectorial Animal Facility of the Pharmacology Laboratory of Univille under controlled temperature (20 ± 2 ºC), lighting (12-hour light/dark cycle, with light on at 7 a.m. and off at 7 p.m.) and free access to water and food. The experimental procedures adopted in this study were submitted to the approval of the guidelines of the Ethics Committee for the Use of Animals (CEUA) of Univille. In all proposed experimental models, the animals were euthanized by intraperitoneal injection of pentobarbital (100 mg/Kg).

Eugenia brasiliensis extract

Fresh leaves from *Eugenia brasiliensis* Lam., Myrtaceae, were collected in Florianópolis, Santa Catarina state (27º36'.13.65"S, 48º31' 14.75"W), in March 2012. Plant material was identified by Dr. Daniel de Barcellos Falkenberg from the Botany Department of Federal University de Santa Catarina (UFSC), and a voucher specimen was deposited in the herbarium FLOR of the same institution under registry number 34675[7].

The plant material was dried and milled, totaling 1813 g of material. This material was macerated in hydroalcoholic solution (92.8%, w/w−1) for seven days. The extract was filtered and solvent evaporated in a rotary evaporator (below 60°C) coupled with a vacuum condenser, and concentrated to a reduced volume. After total evaporation of the solvent, 192.5 g of crude extract was obtained, which represents a yield of 10.62% of plant material. Preparation of EAF fraction An aliquot of 117 g from the crude extract was resuspended in water and the mixture was stored under refrigeration (2–8 ºC) over night and filtered. The aqueous solution was defatted by washing with dichloromethane. Ethyl acetate fraction was prepared by liquid-liquid partition, yielding 23.87 g[7].

Ethanol-induced gastric lesions

An adaptation of the methodology described by[10] was adopted. The animals were treated with the extract vehicle (0.9% saline solution, dose of 0.1 mL/100g) orally (p.o.) or *Eugenia brasiliensis* acetonic extract (30, 100 or 300 mg/Kg, p.o.) and after 60 minutes, they received pro-analysis ethanol (P.A., 99.9%) (1 mL, v.o.) or 0.9% saline solution (1 mL, v.o.). One hour after ethanol administration, the animals were euthanized by injecting pentobarbital (100 mg/Kg) intraperitoneally (i.p.) and their stomachs were removed, opened along the smaller curvature, gently washed with distilled water and stretched out on a Styrofoam plate and extended to the analysis of gastric lesions. Total injured area (cm²) of each stomach was quantified using the ImageJ® Version 1.57K program, from photographs of the stomach mucous membranes.

Indomethacin-induced gastric lesions

Animals received 0.9% saline solution (0.1 mL/100 g, v.o.) or acetone extract at doses of 30, 100 and 300 mg/Kg orally after fasting for 12 hours and water ad libitum. One hour later, saline (0.1 mL/100 g, p.o.) or indomethacin (40 mg/kg, p.o.) was administered[11]. Six hours after administration of indomethacin, the animals were euthanized by i.p. of pentobarbital (100 mg/Kg) and their stomachs removed, opened along the smaller curvature, gently washed with distilled water and stretched out on a Styrofoam plate and

extended for the analysis of gastric lesions. Total injured area (cm²) of each stomach was quantified using the ImageJ® Version 1.57K program, from photographs of the stomach mucous membranes.

Acetic acid-induced gastric ulcer

The animals were deprived of food for 12 hours, then anesthetized with xylazine and ketamine (10 mg/Kg and 90 mg/Kg, respectively, i.p.). The abdominal wall was opened, and the stomach exposed and 500 µL of 80% acetic acid was applied to the serous layer of the anterior gastric wall. After one minute of application, the acetic acid was removed and the site was washed with 0.9% saline solution. The stomach was relocated into the abdominal cavity, followed by internal and external sutures, and the animals were observed until they regained consciousness after surgery[12]. Control animals were applied saline to the serous layer.

The animals remained on food restriction until the next day, but with free water consumption. Twenty-four hours after surgery, the animals had access to food twice a day for one hour. On the second day after surgery, 100 mg/Kg of the extract of *Eugenia brasiliensis* was administered once a day orally for six days and controls received saline (0.1 ml/100 g orally) once a day for six days. One day after the last administration, the animals were euthanized by pentobarbital (100 mg/Kg, i.p.) and their stomachs removed, opened along the smaller curvature, gently washed with distilled water and stretched out on a Styrofoam plate and extended for the analysis of gastric lesions. Total injured area (cm²) of each stomach was quantified using the ImageJ® Version 1.57K program, from photographs of the stomach mucous membranes.

Results analysis and statistics

Data are presented as mean ± standard error of mean (SEM) of the injured gastric area (cm^2). One-way analysis of variance (ANOVA) followed by Tukey's *post-hoc* test was performed using the Graphpad Prism 6.0 program to demonstrate a statistically significant difference between groups, considered for $p < 0.05$ values.

Results and Discussion

Animals given ethanol and treated with saline solution one hour before showed a significantly larger area of gastric lesion than animals who were given saline as ethanol control, while animals that received ethanol and were treated one hour before with acetonic extract of *Eugenia brasiliensis* 30 and 100 mg/Kg significantly presented reduction of, respectively, 36% and 68% of ethanol-induced damaged area, while 300 mg/Kg did not reduce gastric damage. No statistically significant difference between 30 and 100 mg/Kg was found. Animals that received saline solution and were previously treated with the 300 mg/Kg extract presented minimum gastric damage area. Animals treated only with saline solution presented no gastric lesions **(TABLE 1)**.

Data present mean ± SEM of the injured area. Animals (n = 8) received 0.9% saline solution (0.1 mL/100 g, p.o.) or extract (EXT30, EXT100 and EXT300 mg/kg, p.o.) one hour before being treated with 0.9% saline solution (1 mL, p.o.) or absolute ethanol (1 mL, p.o.). *Statistically significant difference in relation to the group that received saline ($p < 0.001$). **Statistically significant difference in relation to the group that received saline one hour of ethanol ($p< 0.008$).

TABLE 1: Effect of ethyl acetonic *Eugenia brasiliensis* extract on ethanol-induced gastric injury.

Group	Area (cm^2)
Saline-saline	0
Saline-EXT300 mg/Kg	0.003 ± 0.001
Ethanol-saline	1.481 ± 0.066*
Ethanol-EXT 30 mg/Kg	**0.965 ± 0.153****
Ethanol-EXT 100 mg/Kg	**0.484 ± 0.160****
Ethanol-EXT 300 mg/Kg	1.548 ± 0.152

Source: the authors (2023).

Animals that received indomethacin and were treated with saline solution one hour before this showed an injured area significantly higher than controls, while those who were given acetonic extract of *Eugenia brasiliensis* 30, 100 and 300 mg/Kg presented significant reduction of injured area of, respectively, 66%, 88% and 73%. There was statistically significant difference between doses. Animals that received saline solution and were previously treated with the extract at a dose of 300 mg showed minimum lesion area and animals treated only with saline solution presented no gastric lesions **(TABLE 2)**.

TABLE 2: Effect of ethyl acetonic *Eugenia brasiliensis* extract on indomethacin-induced gastric injury.

Group	Area (cm^2)
Saline-saline	0
Saline-EXT300 mg/Kg	0.002 ± 0.001
Indomethacin-saline	0.232 ± 0.020*
Indomethacin -EXT 30 mg/Kg	**0.079 ± 0.022****
Indomethacin -EXT 100 mg/Kg	**0.027 ± 0.006****
Indomethacin -EXT 300 mg/Kg	**0.062 ± 0.016****

Source: the authors (2023).

Data present mean ± SEM of the injured area. Animals (n = 8) received 0.9% saline solution (0.1 mL/100 g, p.o.) or extract (EXT30, EXT100 and EXT300 mg/kg, p.o.) one hour before being treated with 0.9% saline solution (1 mL, p.o.) or indomethacin (40 mg/Kg, p.o.). *Statistically significant difference in relation to the group that received saline ($p < 0.001$). **Statistically significant difference in relation to the group that received saline one hour before indomethacin ($p < 0.001$).

Animals that suffered gastric injury by acetic acid and were treated with saline for six days showed significant larger area of gastric lesion **(TABLE 3)** compared to saline controls, while the animals that underwent gastric injury induction and received 100 mg/Kg *Eugenia brasiliensis* extract for seven days showed a significant 72% reduction of the injured area. Animals that received saline solution in the stomach serosa and were treated with saline or extract (100 mg/Kg) for six days did not present stomach lesions. Only 100 mg/Kg was selected for this test due to the previously mentioned described results (there was no significant difference between 30 and 100 mg/Kg effect in ethanol and indomethacin models and 300 mg/Kg did not reduce ethanol gastric lesion area).

TABLE 3: Effect of ethyl acetonic *Eugenia brasiliensis* extract on acetic acid-induced gastric injury.

Grupo	Área (cm^2)
Saline-saline	0
Saline-EXT100 mg/Kg	0
Acetic acid-saline	0.759 ± 0.077
Acetic acid-EXT 100 mg/Kg	**0.211 ± 0.035***

Source: the authors (2023).

Data present mean ± SEM of the injured area. Animals (n = 8) received 0.9% saline solution (0.1 mL/100 g, p.o.) or extract (EXT100 mg/kg, p.o.) twice a day for six days after stomach injury with 0.9% saline solution or 80% acetic acid for one minute. *Statistically significant difference in relation to the group that received vehicle *in situ* and saline solution for six days ($p < 0.001$). **Statistically significant difference in relation to the group that received acetic acid *in situ* and saline solution for six days ($p < 0.001$).

Ethanol oral administration in rats causes lesions presenting hemorrhagic rays throughout the stomach body and histological analysis showed typical characteristics of ethanol damage to the mucosa, presented by damage in the deep layers, with necrosis, hemorrhage, hyperemia surrounding gastric glands, numerous cells infiltration in the gastric epithelium and dilated blood vessels[13].

After ingestion, ethanol activates inflammation and oxidative stress: the first causes the recruitment of leukocytes, which increase the expression of the nuclear factor kappa-b (NF-KB), triggering the release of pro-inflammatory cytokines, such as the tumor necrosis (TNF-alpha) and interleukin-1beta[14]. These cytokines and other pro-inflammatory mediators increase macrophages and neutrophils chemotaxis and the expression of free radicals, causing damage to the gastric epithelium and destruction of cell membrane stability[14].

In this study, ethanol-induced lesions were significantly reduced by the ethyl acetonic extract of *Eugenia brasiliensis* 30 and 100 mg/Kg. The ethyl acetone extract of *Eugenia brasiliensis* used in the present study is composed of the flavonoids catechin, isoquercetin, galangin and apigenin[7], which may exert anti-inflammatory and antioxidant activities, possibly mediators of the gastroprotective effect observed. The anti-inflammatory effect may be related to lower COX-2 activity and lower production of pro-inflammatory cytokines or greater expression of protective factors (mucus and bicarbonate secretion). This same extract was also effective in reducing carrageenan-induced pleurisy by reducing leukocyte migration, exudation, and nitric oxide production[7]. The anti-inflammatory effect was also evidenced through reduction of ear oedema mediated by croton oil and arachidonic acid in mice by an extractive acetonic fraction of *Eugenia brasiliensis* containing quercetin, catechin and gallocatechin[15].

Polyphenols are bioactive molecules with promising potential in the management of peptic ulcer[16]. Thus, the intense generation of reactive oxygen species that occurs during gastric ulcer formation can be reduced by antioxidant substances, such as polyphenols, justifying their gastroprotective action[17]. The 300 mg/Kg dose was not effective, possibly due to the high concentration of several types of compounds, which may have resulted in loss of action specificity or even gastric lesion.

The administration of indomethacin promoted a significant increase in lipid peroxidation in the gastric mucosa, in addition to marked inhibition of the antioxidant enzymes superoxide dismutase (SOD) and

catalase (CAT), increased levels of TNF- α, necrosis and desquamation of the surface of the stomach mucosa, leukocyte infiltration and fibrosis[18], validating this gastritis model.

In the present study, animals that received indomethacin developed gastric mucosal lesions that were significantly reduced by the ethyl acetonic extract of *Eugenia brasiliensis* at all doses. Unrefined extracts containing tannins are used worldwide to treat gastric ulcers, as they react with the proteins of the tissues with which they come into contact, forming a layer that protects the stomach, increasing its resistance to mechanical injury or chemical irritation. In addition, antioxidant activity was evidenced for tannins in several experimental models, in addition to promoting tissue repair[19].

The presence of polyphenols also activates the antioxidant system, preventing cell damage and lipid peroxidation by excess free radicals in humans[20] and polyphenols contribute to increased expression of metalloproteinases in the gastric tissue that are involved in the regeneration, re-epithelialization and remodeling of the mucous layer, influencing its rearrangement and secretory capacity[21].

The application of acetic acid causes the development of ulcers very similar to those of the human organism in pathological terms and healing mechanisms, being widely used in the investigation of antiulcerogenic compounds[22]. The injury caused by acetic acid penetrates the muscular, submucosal and mucosal layers of the stomach. The formed ulcer becomes chronic in 2-3 days and heals completely within 2-3 weeks without perforation[22].

The application of acetic acid induces a state of acute and chronic oxidative stress, marked by a decrease in SOD activity and gluthatione levels, an increase in lipid peroxidation, in addition to also involving prostaglandins, growth factors, nitric oxide and cytokines[23].

There is a correlation between interleukin-1β and TNf-α increase with the ulcer density in the gastric mucosa since they are cytokines with chemotactic and neutrophil activating properties that maintain the local inflammatory response[24]. It was also described that nitric oxide (NO) produced by NO synthase induced in excessive amounts can form peroxynitrite and hydroxyl radicals that promote tissue damage and NO synthase is increased in the gastric mucosa when there is an ulcer[25].

Treatment with the 100 mg/Kg extract for seven days promoted significant 72% reduction of gastric lesion, evidencing the healing properties for the already installed lesion. It is possible that the extract modified the expression of the pro-inflammatory cytokines involved, increased the secretion of bicarbonate and prostaglandins, or reduced the secretion of gastric acid, which contributed significantly to reducing the extent of the lesion.

The presence of compounds such as phenols, hydrolysable and condensed tannins, flavonoids, chalcones and aurones, flavonols, xanthones, catechins, free steroids, saponins and resins is found in an acetonic extract of stem and leaves of *Eugenia brasiliensis*[26]. The presence of flavonoids capable of inhibiting the synthesis of TNF–α and blocking the phospholipase enzymes, COX-1 and COX-2 or lipoxygenases[27] may contribute to the positive effects regarding the antiulcerogenic properties observed in this study, since *Eugenia brasiliensis* also expresses flavonoids, although to a lesser extent than tannins and polyphenols[26]. However, no other studies were found concerning the effectiveness of *Eugenia brasiliensis* extracts in gastritis models for comparison.

Tannins can stimulate tissue repair and carry out enzymatic and protein regulation in order to influence wound healing processes, burns and inflammation, stimulating the formation a protective layer (tannin-protein complex and/or polysaccharide) on injured tissues, allowing tissue repair processes[19].

Limitations of this study include no evaluation of extract toxicity, as well as direct comprehension of mechanisms of action involved in the gastroprotective effect, but which were discussed based on the current literature available. However, the unprecedented contribution is highlighted in terms of validating the popular use of *Eugenia brasiliensis* preparations and their gastroprotective activity through a systematic scientific study.

Conclusion

In conclusion, the ethyl acetone extract of *Eugenia brasiliensis* showed a significant capacity to reduce gastric lesions induced by ethanol and indomethacin at different doses and by acetic acid at 100 mg/Kg, possibly related to substances with antioxidant and anti-inflammatory properties. New studies to clarify which signaling pathways were directly affected in what intensity and toxicity profile might be future approaches.

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None.

Conflict of interests

There is no conflict of interests.

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Contribution

Study design: AJC; MHRM; Lima DDL; EMP
Data curation: AJC; MHRM; Lima DDL; EMP
Data collect: AJC; MHRM; MDA; DDDM; Lima DDL; EMP
Data analysis: AJC; MHRM; MDA; DDDM; DDL; Pereira EMP
Writing of the original manuscript: AJC; MHRM; MDA; EMP
Proofreading and Editing: MDA; DDDM; DDL; EMP.

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