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Original Article

Total Phenol Content and Gastric Anti-Ulcer Activity of Hydroalcoholic Extract of *Persea caerulea* (Ruiz & Pav.) Mez. Bark

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ABSTRACT

Objective: Determine the content of total phenols and evaluate the gastroprotective effect of the extract of *Persea caerulea* (Ruiz & Pav.) Mez. in mice with induced gastric ulcer**. Material and Methods:** The bark of *Persea caerulea* was macerated in 70% ethanol and the phenol content was determined using the Folin-Ciocalteu method. The female *Mus musculus* Balb/c specimens were distributed in the following groups: White Control Group, without indomethacin dosing; Negative Control Group, dosing with indomethacin; Positive Control Group treated with ranitidine at a dose of 50 mg/kg; Groups *P. caerulea* treated with extract at doses of 50 mg/kg, 100 mg/kg and 200 mg/kg. Gastric ulcer was induced with indomethacin orally at a dose of 50 mg/kg, the procedure was repeated 12 hours later; Gastroprotective treatment was administered 60 minutes after each dose of indomethacin, 6 hours after the last dose, sodium pentobarbital was euthanized and the stomach was resected to determine ulceration using the Marhuenda Scale. **Results:** Higher percentages of gastric ulcer inhibition were obtained in the *P. caerulea* 100 mg/kg (80%) and *P. caerulea* 200 mg/kg (85.71%) groups. **Conclusions:** Extract of *Persea caerulea* (Ruiz & Pav.) Mez., At doses of 100 and 200 mg/kg of body weight, has a gastric antiulcerative effect which is related to its content of total polyphenols.
Key words: Gastric Ulcer, Mice, Indomethacin.

INTRODUCTION

Gastric ulcer is a common disease of the digestive system[1], caused by stomach acids that damage its lining, causing pain, and sometimes bleeding. Peptic ulcer (gastric or duodenal) is the cause of dyspepsia in approximately 10% of people.[2] Current therapeutic treatments are highly dependent on Western medicine; however, numerous studies have shown that medicinal plants can effectively treat gastric ulcer in many animal models, through different mechanisms, which include stimulation of the proliferation of mucous cells, inhibition of secretion of gastric acid and H^+/K^+ ATPase activity, activity, and antimicrobial properties.[1]

Use of medicinal plants plays a fundamental role in disease prevention.[3] Medicinal plant-based drugs are considered as alternatives for treatment, since they have fewer or no side effects, compared to the appearance of many side effects from the use of synthetic drugs.[4-5]

Persea caerulea (Ruiz & Pav.) Mez (*P. caerulea*) is a plant belonging to the Lauraceae family and grows between 350 and 2200 meters above sea level (MASL).[6] Studies determined the presence of metabolites such as kaempferol-3-O-α-L-rhamnopyranoside, quercetin-3-O-α-L-rhamnopyranoside, quercetin-3-O-β-glucoside, and scopoletin[7]; Coumarins and flavonoids, isofraxidine, campesterol, stigmasterol and β-sitosterol were also found.[8]

MATERIAL AND METHODS

Vegetal material

The barks of *Persea caerulea* (Ruiz & Pav.) Mez were collected in San Martín Region, Perú.

Experimental animals

Thirty female *Mus musculus* Balb/c mice, 12 to 14 weeks old and weighing between 30 to 35 g, were used and received balanced food and water ad libitum. All procedures were approved by the Ethics Committee of the School of Medicine, Universidad Nacional de Trujillo for the care and use of animals (COD document. N° 002 - 2020)

Preparation of the hydroalcoholic extract

Barks were washed repeatedly with distilled water, then it was completely dried in a stove at 45°C. Barks dried were ground in a manual mill until obtaining a fine powder. 50 g of this fine powder were macerated in 500 mL of 70% ethanol in amber hermetic sealed flasks with stirring for 5 min daily for 7 days. Subsequently, it was vacuum filtered with filter paper and put in porcelain capsules for drying up in stove at 45 °C; dry extract was kept in amber bottle in refrigeration (2 to 4 °C) until it was used.[9]

Determination of total phenol content

It was determined with the Folin-Ciocalteu reagent. A calibration curve with gallic acid as a standard was obtained, It was prepared by adding 2 milligrams of

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Gallic acid in 10 ml of methanol as stock solution, concentrations of 100, 50, 25 and 12.5 µg/ml were prepared. Then 0.5 mL of each standard and extract were mixed with 2.5 mL of Folin-Ciocalteu 50% and 2.5 mL of distilled water, and incubated for 5 min at 40 °C. Finally, 2 mL of Na_2CO_3 solution was added (7.5%, w/v). The final mixture was shaken and incubated for 15 min at 40 °C. The absorbance of all standards and samples was measured at 765 nm using a UV-Vis spectrophotometer. The results were expressed as mg Gallic acid equivalents (GAE)/g extract.[10]

Evaluation of gastric antiulcer activity

The mice were divided into 6 groups of 5 mice each one. Blank Control Group: 5 days of 0.5 mL p.o. of physiological saline solution (PSS); 24 hours of fasting: 1st induction with 0.5 mL of PSS + 0.5 mL of PSS; 12 hours later: 2nd induction with 0.5 mL of PSS + 0.5 mL of PSS. Negative Control Group: 5 days of PSS (0.5 mL p.o.); 24 hours of fasting: 1st induction with indomethacin 50 mg/kg p.o. + 0.5 mL of SSF; 12 hours later: 2nd induction with indomethacin 50 mg/kg p.o. + 0.5 mL of PSS. Positive Control Group: 5 days of ranitidine 50 mg/kg p.o.; 24 hours of fasting: 1st induction with indomethacin 50 mg/kg p.o. + ranitidine 50 mg/kg p. o.; 12 hours later: 2nd induction with indomethacin 50 mg/kg p.o. + ranitidine 50 mg/kg p.o. Groups *P. caerulea* 50 mg/Kg, 100 mg/Kg and 200 mg/kg p.o.: 5 days of extract; 24 hours of fasting: 1st induction with indomethacin 50 mg/kg p.o. + extract; 12 hours later: 2nd induction with indomethacin 50 mg/kg p.o. + extract.

For five consecutive days, gastroprotective treatments were administered to the mice, then they were fasted for 24 hours; After this time, the first induction of ulceration was carried out with 50 mg/Kg of indomethacin; 12 hours later the first gastric ulcer induction, the second dose of indomethacin (50 mg/Kg) was administered; 60 minutes after indomethacin administration, the gastroprotective substance[11-12] was administered. After 6 hours of this last dosage, euthanasia was carried out with a dose of 60 mg/kg i.p. of sodium pentobarbital to each experimental animal, following the animal bioethics standards[13-15], after this step, a laparotomy was performed to extirpate the stomach; The extirpated stomach was cut through the greater curvature; then it was extended and PSS was added to make observations.

Determination of the ulceration index and percentage of ulceration inhibition

Marhuenda Scale was used to determine Ulceration Index, considering the magnitude of the lesion observed in the gastric mucosa (loss of continuity or rupture of the same), for which a vernier caliper was used to measure the length of the ulcerative wounds. Furthermore, the number of ulcers and the presence or absence of bleeding were counted.[16]

Percentage of ulceration inhibition of each experimental animal was calculated, with respect to the ulceration index of the positive control group, as follows:

$$\%\ inhibición = \frac{I.U.GCP - I.U.P.}{I.U.GCP}\ x\ 100$$

U.I.CPG= mean ulceration index of positive control group

I.U.P = ulceration index of the problem group, per experimental animal

The mean values of the inhibition percentages of each working group, as well as their standard deviation, were determined.

RESULTS

Determination of total phenol content

The amount of total phenols of the hydroalcoholic extract of the bark of *P. caerulea* was determined by the Folin-Ciocalteu method and 315.11 ± 0.97 mg were found expressed as Gallic acid equivalents (GAE) per gram of dry extract. The determination was made in triplicate.

Macroscopic observation of stomachs

Results of macroscopic study present differences in degrees of ulcerative gastric lesion. Negative Control Group present a large number of ulcerations and petechiae unlike the Positive Control Group that received Ranitidine drug, only small petechiae were observed. While the *P. caerulea* Groups shows a lower number of gastric ulcerations and petechiae, this effect being dose dependent. The ulceration index and the percentage of ulceration inhibition were calculated using the Marhuenda Scale.

Percent inhibition of ulceration

Results of the observational analysis applying the Marhuenda Scale, allows obtaining the ulceration index, which is finally expressed as a percentage of ulceration inhibition.

DISCUSSION

The Negative Control Group shows the effect generated by the induction of gastric ulcer with indomethacin when ulcers and bleeding are observed in the gastric mucosa compared to the normal structure of a stomach of the White Control Group (Fig. 1). NSAIDs can cause gastric damage by inhibiting cyclooxygenase (COX) and reducing prostaglandin production.[17] COX is the key enzyme for translating arachidonic acid into PG, which includes at least 2 isomerases: COX-1 and COX-2; COX-1 is primarily involved in maintaining the integrity of the gastric mucosa and regulating gastric acid secretion and blood flow, while COX-2 is involved in the repair process of damaged mucosa by promoting PG production in the inflammatory response.[18-20] Prostaglandin E2 (PGE2) is one of the main metabolites of arachidonic acid, it is well recognized as a protective cellular factor to repair damaged gastric mucosa by inhibiting gastric acid secretion, increasing blood flow in gastric mucosa and promoting protein synthesis and cell renewal.[21]

In addition, Epidermal Growth Factor (EGF) induces the JAK/STAT signaling pathway and the phosphatidylinositol pathway, which is related to immunity and proliferation, which is why a notable reduction in EGF concentration has been reported in gastric ulcers in a large sample of patients.[22-23] Indomethacin induces gastric mucosa damage in several mechanisms[24], but activation of p38 MAPK is one of the most important factors in activating endoplasmic reticulum stress and further damage.[25] *In vitro* experiments demonstrate that p38 MAPK and JNK are involved in the loss of barrier function induced by indomethacin in gastric cell line, and this barrier loss occurs through the loss of the barrier protein occludin from the junctions narrow. The protective effect of the inhibition of p38 MAPK on the tight binding protein occludin and, therefore, on the mucosal barrier, was further demonstrated in ex vivo studies using gastric mucosa in murine models.[26-27]

Administration of Ranitidine prevented damage to a high degree of the gastric mucosa (Figure 1). Ranitidine is a very common histamine H2 receptor antagonist and has a more prominent effect on basal acid secretion and a less profound effect on acid production.[28] While the experimental animals treated with extract of *P. caerulea* showed a higher percentage of inhibition of ulceration compared to Negative Control group, observing a reduction in gastric damage produced by the administration of indomethacin, in addition, doses of 100 and 200 mg/kg of P. caerulea showed a similar effect to Ranitidine (Figure 2).

The tissue damage observed in the gastric mucosa is associated with the intense generation of free radicals such as reactive oxygen species that cause oxidative stress and the consequent damage to the mucosa; These free radicals also alter the function of the cellular antioxidant enzyme

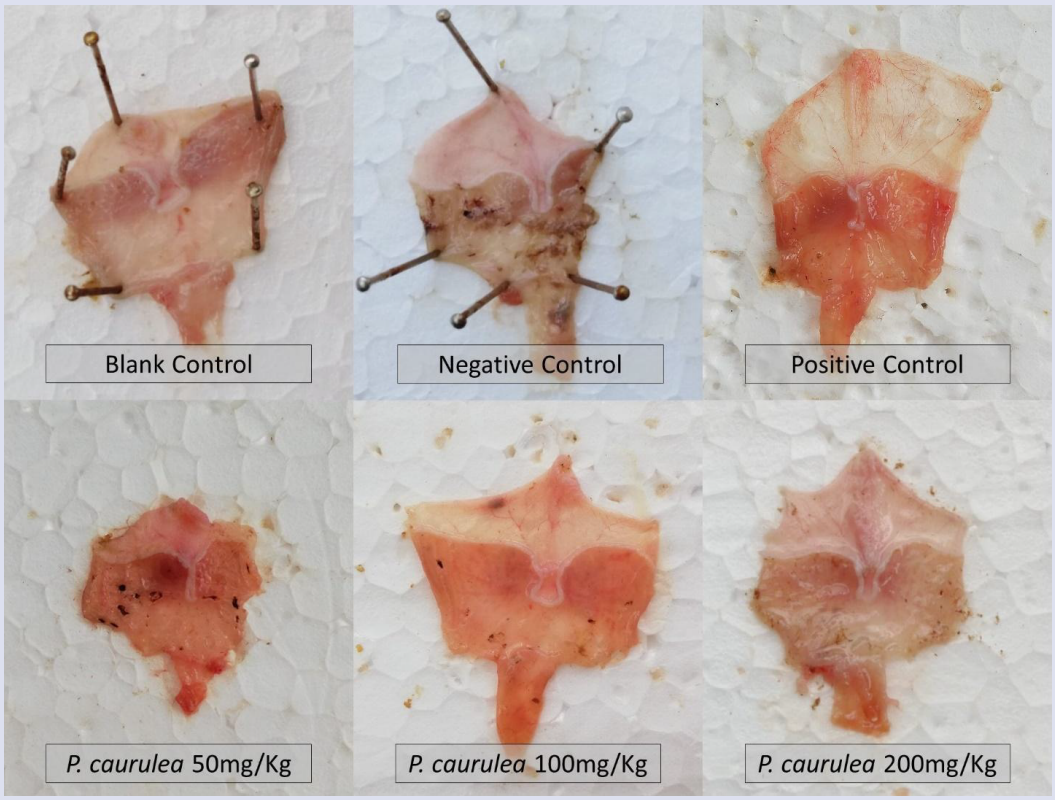

Figure 1: Macroscopic observation of the effect of Persea caerulea (Ruiz & Pav.) Mez on induced gastric ulcer in mice.

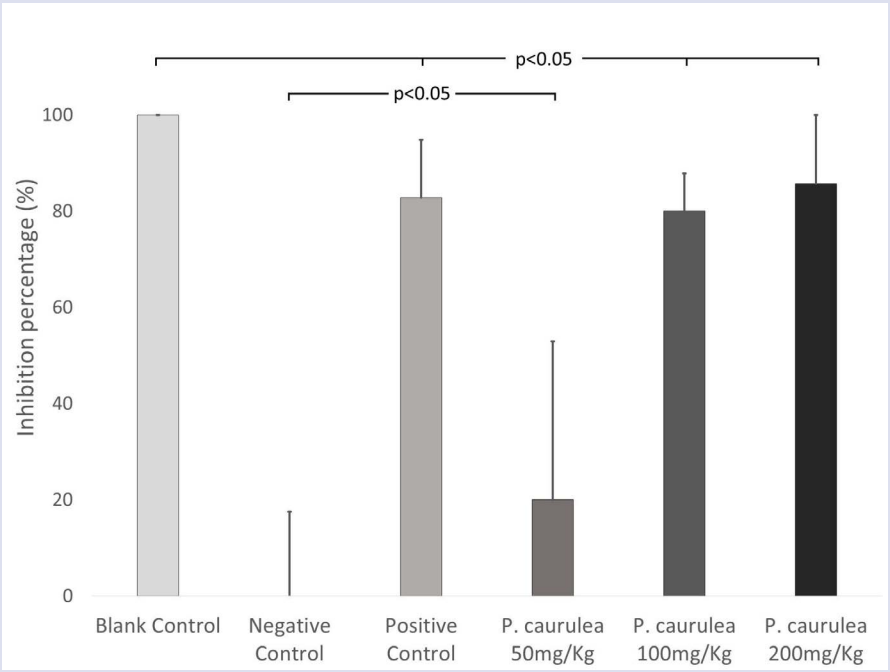

Figure 2: Gastric antiulcer effect of *Persea caerulea* extract (Ruiz & Pav.) Mez expressed as a percentage of ulceration inhibition. n = 5, p <0.05.

that acts as an important cellular defense against oxidative stress, leading to aggravated tissue damage during gastroduodenal ulceration.[29] Free radicals initiate microvascular permeability, generating additional infiltration of plasma cells and macrophages into gastric endothelial cells, leading to inflammation.[30]

Polyphenols are one of the most abundant secondary metabolites, they are ubiquitously present in fruits and vegetables, and are considered an integral part of the human diet. Polyphenols consist of a wide variety of chemical structures based on substitutions of the basic chemical structure of polyphenols, polymerization, and degree of oxidation[29]. Polyphenols reported in *P. caerulea*, such as: quercetin, kaempferol-3-O-α-L-rhamnopyranoside, kaempferol-3-O-α-L-arabinopyranoside, quercetin-3-O-α-L-rhamnopyranoside, quercetin -3-O-β-glucoside[8], would give the extract of this plant the gastroprotective activity, which

is related to the quantified in total polyphenols of the hydroalcoholic extract of *P. caerulea* expressed in mg of Gallic acid.

Quercetin has gastroprotective activity and is due to antioxidant activity that reduces lipoperoxidation. Research has shown that quercetin has an effective antiulcer activity, protects and prevents changes in biochemical and morphological parameters observed after induction of ulcer with ethanol in rats.[31] Thiobarbituric acid reactive substances in the gastric mucosa, an index of lipoperoxidation, were increased by ethanol ulcer injury, but the increase was inhibited by quercetin administration.[32] Also, a pharmaceutical preparation combining famotidine and quercetin was used to increase the treatment of gastric ulcer, this combined treatment showed absence of signs of inflammation or bleeding and significantly prevented the indomethacin-induced decrease in glutathione levels and decreased the levels of malondialdehyde.[33] Quercetin has an antioxidant effect and can protect the gastric mucosa against indomethacin-induced gastric ulceration than famotidine.[34]

Kaempferol, like quercetin, is a common type of flavonoid with antioxidant and anti-inflammatory properties.[35] Kaempferol can protect the stomach by inhibiting neutrophil accumulation and myeloperoxidase activity, regulating pro-inflammatory cytokine levels, and enhancing NO production to maintain gastric mucosal glycoprotein levels.[36] Kaempferol reduces the expression of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-8) and the production of IL-8 in H. pylori-infected gastric adenocarcinoma cells.[37] In a model of gastric injury by ethanol, kaempferol significantly decreased the ulcer index, increased the preventive index, completely protected the mucosa from injury and conserved gastric mucosa glycoprotein, decreased myeloperoxidase activity and cytokine levels. proinflammatory.[36]

The extract of *P. caerulea* has an effect similar to ranitidine and it is postulated that this effect is mainly due to the action of compounds such as quercetin and kaempferol, polyphenols reported in *P. caerulea* that have antioxidant and anti-inflammatory activity.[30,32,35]

CONCLUSION

The hydroalcoholic extract of the bark of *Persea caerulea* (Ruiz & Pav.) Mez, at doses of 100 and 200 mg/Kg, has a gastric antiulcer effect similar to that of ranitidine, and this activity is related to the content of polyphenols totals.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

ACP and CSC carried out the preparation of the first draft and preparation of the extract. MSC and MLS performed gastric ulcer induction, MVA and FHC administered the treatments. WAD collected the plant species. LGE and OPS carried out the evaluation with the Marhuenda Scale and determination of percentages of ulceration inhibition. CAV and VVLT performed the quantification of total polyphenols. MGB and JHV performed the statistical analysis. AGS and WSG designed tables and figures.

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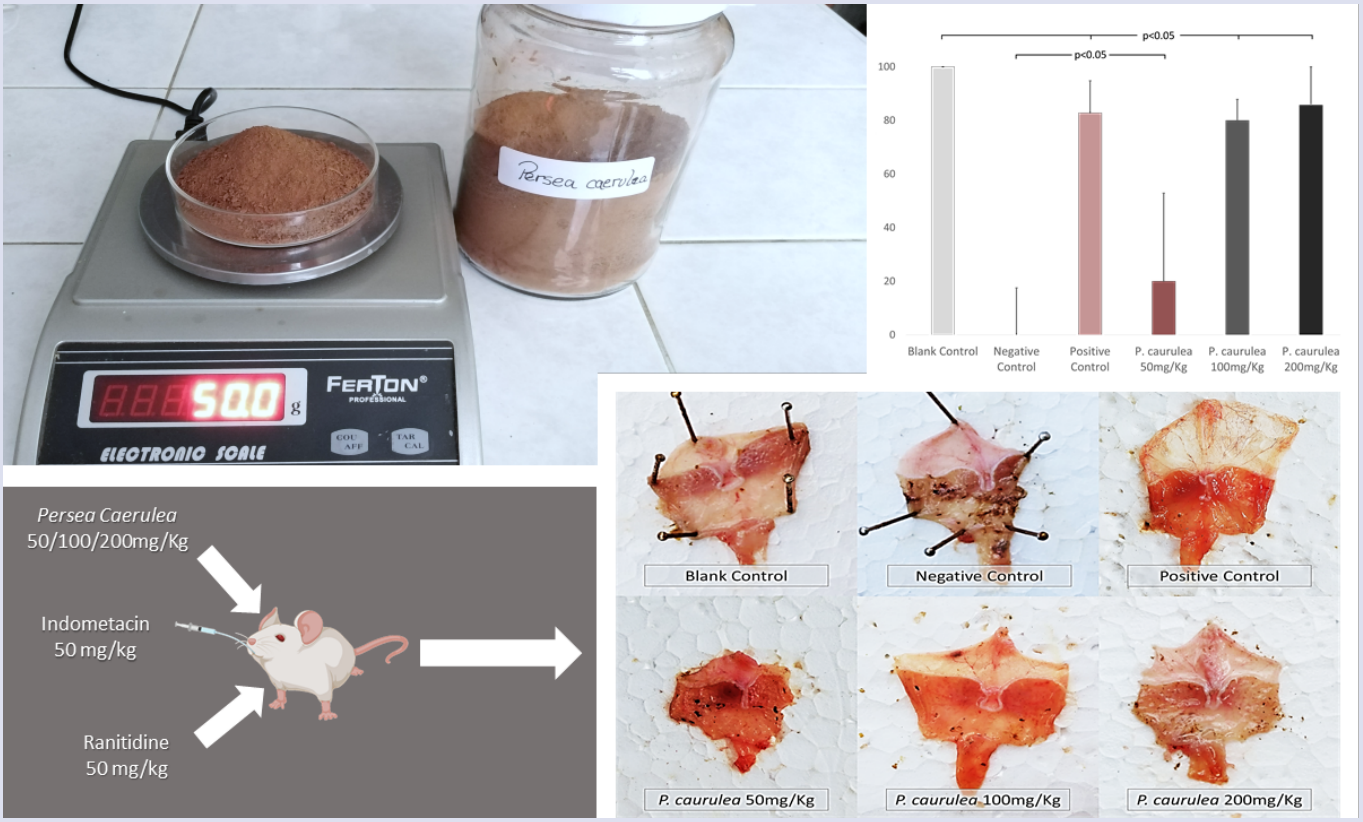
GRAPHICAL ABSTRACT



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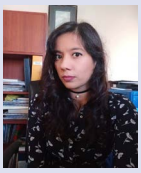

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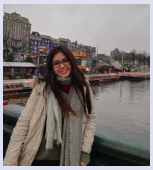

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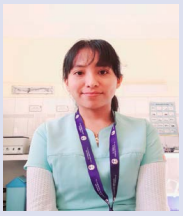

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