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Plinia peruviana (Poir.) Govaerts (jabuticaba) extract inhibits the development of gastric ulcers in animal models through gastroprotective mechanisms

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ABSTRACT

Plinia peruviana, commonly known as "jabuticabeira," is a native Brazilian species widely used in traditional medicine to manage gastrointestinal disorders, including diarrhea, abdominal pain, and intestinal dysfunctions. This study assessed the gastroprotective activity and explored the mechanisms of action of a hydroethanolic extract from *Plinia peruviana* peels (EHPP) in mice models of acute gastric lesions. EHPP was obtained through hydroethanolic maceration, followed by lyophilization and phytochemical characterization. Gastroprotective effects at oral doses of 100, 250, and 500 mg/kg were examined in mice models of gastric injury induced by ethanol, acidified ethanol, and indomethacin. The investigation concentrated on the roles of gastric mucus synthesis, sulfhydryl (SH) groups, the nitric oxide (NO) pathway, α2-adrenergic receptors, and myeloperoxidase (MPO) activity to clarify the mechanisms involved. Phytochemical analysis showed that gallic acid and ellagic acid were the major phenolic compounds in the extract. EHPP significantly reduced the gastric lesion index in all models: by 62.3%, 70.4%, and 41.5% (ethanol); 77.6%, 78.5%, and 37.7% (acidified ethanol); and 44.3%, 47.3%, and 39.4% (indomethacin), respectively. The gastroprotective effect was linked to stimulation of mucus production, involvement of SH groups, the NO pathway, α2-adrenergic receptor activation, and MPO inhibition. In conclusion, EHPP exhibits substantial gastroprotective effects through multiple mechanisms, including enhancement of mucus secretion and modulation of oxidative and inflammatory pathways. These results support the traditional use of *Plinia peruviana* for gastrointestinal disorders and illustrate its potential for the development of phytotherapeutic drugs.

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1. Introduction

Gastric disorders, principally ulcers with an estimated prevalence of approximately 10% worldwide, represent an important global health concern, making a considerable contribution to morbidity and mortality. (Raafat et al., 2020). The underlying pathophysiology involves an imbalance between protective and aggressive factors affecting the gastric mucosa (Tarnawski & Ahluwalia, 2021). Protective factors include the production of a mucous bicarbonate barrier, adequate blood flow, antioxidant activity, prostaglandins, and related mediators. Conversely, aggressive factors stress, encompass excessive alcohol consumption, *Helicobacter pylori* infection, frequent use of non-steroidal anti-inflammatory drugs (NSAIDs), and oxidative stress (Gong et al., 2024; Pandey et al., 2019).

Gastric ulcer treatment typically relies on antacids, histamine H2 receptor antagonists, irreversible proton pump inhibitors, or potassium-competitive acid blockers (Nesello et al., 2017). While these medications demonstrate efficacy, prolonged use is associated with a range of adverse effects (Zakaria et al., 2016). Consequently, there is increasing interest in alternative natural therapeutic strategies that may complement or reduce reliance on conventional treatments.

"Jabuticabeira", belonging to the Myrtaceae family, is a tree native to Brazil with several botanical species, including *Plinia peruviana* (Poir.) Govaerts (Waller et al., 2020). In Brazil, it predominates in the Southern and Southeastern regions, where it is traditionally used in the treatment and prevention of gastrointestinal disorders, including diarrhea and intestinal inflammation, as reported in ethnopharmacological and experimental studies (Cruz & Kaplan, 2004; Graziela Moraes et al., 2021; Pitz et al., 2016a).

The "jabuticaba fruit" has a rich chemical composition, particularly rich in bioactive compounds with potential health benefits (Bocker & Silva, 2025). Recent research has identified significant concentrations of phenolic acids, including gallic acid, ellagic acid, and p-coumaric acid (de Oliveira et al., 2024), as well as cinnamic acid derivatives. Flavonoids such as quercetin and anthocyanins, notably cyanidin-3-O-glucoside and delphinidin-3-O-glucoside, are found in the fruit's skin (Fernandes et al., 2022). Furthermore, the presence of D-psicose, D-glucose, and citric acid in peel extracts demonstrates the fruit's chemical diversity (Pinc et al., 2023). This diverse composition suggests that jabuticaba holds promise for applications in the food and pharmaceutical industries.

Recent studies on jabuticaba have highlighted its potential to alleviate intestinal inflammation and endotoxemia associated with obesity, provide sun protection through antioxidant activity, and promote wound healing (Cefali et al., 2021; Rodrigues et al., 2021). Additionally, jabuticaba has demonstrated anti-inflammatory, hypoglycemic, hypolipidemic, and analgesic activities (T. G. da S. Brito et al., 2021), as well as chemopreventive properties (Holkem et al., 2021), antimicrobial effects (Fidelis et al., 2020) and non-cytotoxicity (Lamas et al., 2020).

Given the chemical constituents of jabuticaba fruit and the documented anti-inflammatory, healing, and antioxidant activities, the present study investigates the gastroprotective potential of this species and the possible mechanisms of action.

2. Materials and methods

2.1. Plant material and extract preparation

Fruits of *Plinia peruviana* were collected from the Araripe Plateau in Crato, Ceará, Brazil, in January 2020 (S 7°13′00.6" – W 39°22′15.1″). The collection was authorized by the Chico Mendes Institute for Biodiversity Conservation (ICMBio), the agency responsible for FLONA – Araripe (permit number 78582-1). A specimen was identified by Dr. Maria Arlene Pessoa da Silva and deposited in the Dardano de Andrade Lima Herbarium at the Regional University of Cariri (URCA, Crato-CE, Brazil), under voucher number 14.430. The botanical name *Plinia peruviana* was confirmed using *The Plant List* (www.theplantlist.org), accessed on July 23, 2025.

The fresh fruit peels were used for the preparation of the hydroalcoholic extract of *Plinia peruviana* (EHPP). The material was ground using an industrial blender (4 L, 1200 W, 18,000 rpm; Evitra, Itajobi, SP, Brazil) and then immersed in 2 L of water/ethanol PA solution (1:1 v/v), remaining stored for 72 h. After this period, the extract was filtered, stored, and frozen. After solidification, the material was subjected to lyophilization (Freeze dryer, Liobras, São Carlos, SP, Brazil). The EHPP was kept in a desiccator until the assays were performed. The extraction yield was 5.92% (w/w), based on fresh weight, corresponding to the lyophilized hydroethanolic extract obtained from *Plinia peruviana* peels.

2.2. Mass spectrometry analysis by electrospray ionization (ESI-MS)

2.2.1. Sample preparation

The dried extract was reconstituted in 1 mL of a methanol-water solvent mixture (2:1, v/v). Subsequently, 10 μL of ammonium hydroxide was added for negative-ionization mode, or 10 μL of formic acid for positive-ionization mode, to optimize ionization efficiency.

2.2.2. Instrumentation and ESI-MS parameters

Mass spectrometry (MS) analyses were conducted on a hybrid Quadrupole-Orbitrap instrument (Q-Exactive™, Thermo Scientific, Bremen, Germany) with high resolution and mass accuracy, coupled to a heated electrospray ionization source (HESI-II). Electrospray ionization (ESI) was operated in both negative (−3.1 kV) and positive (+3.8 kV) ion modes. The source conditions were maintained as follows: capillary temperature at 320 °C, S-lens RF level adjusted to 45 V, sheath gas flow of 8 L min^{-1}, and auxiliary gas flow of 5 L min^{-1}, using high-purity nitrogen (N_2, >99.9%).

2.2.3. Fragmentation conditions

Tandem mass spectrometry (MS/MS) experiments utilized collision-induced dissociation (CID) within the high-energy collisional dissociation (HCD) cell. Normalized collision energies of 20, 25, and 30 eV were applied to systematically assess fragmentation behavior at different energy levels.

2.2.4. Compound annotation

Mass spectrometry data files in (.raw) format were converted to the open standard (.mzML) using the MSConvert tool from the ProteoWizard package (Palo Alto, CA, USA). Data analysis was conducted via the GNPS web platform (https://gnps.ucsd.edu/ProteoSAFe/static/gnps-splash.jsp) to extract compound-related information. Molecular annotations were achieved by comparing experimental MS/MS spectra with the GNPS spectral library, utilizing tools such as Molecular Networking for spectral organization and similarity-based analysis (Wang et al., 2016) for spectral organization and similarity-based analysis. Further annotations were refined using the MS-DIAL software to improve molecular feature identification. (Tsugawa et al., 2019).

2.3. Animals and ethical aspects of research

Swiss mice (*Mus musculus*) of both sexes, weighing 25–30 g, were utilized in the experiments. Inclusion of both sexes enabled assessment of sex-based differences in disease progression and treatment response (Gulati et al., 2015; Khalil et al., 2007). Group sample sizes were determined using statistical software (e.g., G*Power). Animals were housed at 22 ± 2 °C under a 12-h light/dark cycle, with a relative humidity of 55%–65%, and ad libitum access to filtered water and commercial chow (Presence, Purina, Brazil). Mice were fasted for 12 h before the initiation of experiments. For all protocols, euthanasia was performed using a CO_2 inhalation chamber. Each group comprised three animals of each sex, randomly selected. All procedures were conducted in accordance with the ethical principles established by Brazilian

Federal Law No. 11.794/2008, which regulates the use of animals for scientific purposes. The study was approved by the URCA Animal Use Ethics Committee under license number 00103/2021.1.

2.4. Investigation of the in vivo gastroprotective activity of EHPP

In the case of lesions produced by ethanol or acidified ethanol, stomach tissues were scanned, digitized, and subsequently analyzed through computerized planimetry using ImageJ software (Bethesda, MD, USA). The extent of injury was calculated as the percentage of the total gastric mucosal surface. For indomethacin-induced lesions, the severity was graded by quantifying gastric damage according to the following scoring system: 0 (absence of lesions); 1 (slight edema); 2 (edema with hemorrhage); 1–2 (punctate lesions); 1–3 (broad lesions); 5 (multiple punctiform lesions); and 6 (diffuse lesions distributed throughout the mucosa), as described by (Zinkievich et al., 2010). The doses of EHPP used (100, 250, and 500 mg/kg) were selected based on a value equal to or less than 10% of the orally administered dose of 5000 mg/kg used for estimating the median lethal dose (LD_{50}), which did not induce toxicity or mortality (data not shown).

2.4.1. Gastric lesion induced by ethanol, acidified ethanol with hydrochloric acid (HCl), and indomethacin

For each ulcer-inducing protocol, mice were allocated into five experimental groups (n = 6). The animals received oral treatments consisting of NaCl (0.9%), omeprazole (30 mg/kg, proton pump inhibitor), or EHPP at doses of 100, 250, and 500 mg/kg. One hour later, gastric injury was induced by either ethanol (96%) 0.2 mL/animal, p.o., or acidified ethanol (0.3 mol HCl in 60% ethanol, 0.2 mL/animal, p.o.). Following 30 min of exposure to ethanol and 1 h for acidified ethanol, the mice were euthanized, stomachs excised, opened along the greater curvature, rinsed, and prepared for lesion assessment as described above.

In a separate set of experiments, animals were treated orally with NaCl (0.9%), omeprazole (30 mg/kg), or EHPP (100, 250, 500 mg/kg). After 1 h, gastric damage was induced by subcutaneous injection of indomethacin (10 mg/kg), a nonsteroidal anti-inflammatory agent. Treatments were repeated 3 h after the administration of indomethacin, and 6 h later, the mice were euthanized, stomachs collected, and lesions quantified following the same methodology.

2.4.2. Physical barrier test

Mice were assigned to three experimental groups (n = 6) and received treatments with NaCl (0.9%, p.o.) or EHPP (100 mg/kg) administered either orally or intraperitoneally. In the intraperitoneal group, ethanol (96%, 0.2 mL/animal, p.o.) was administered 30 min after EHPP injection, whereas for the oral treatment groups, ethanol was given 1 h after NaCl or EHPP administration. Thirty minutes following ethanol exposure, the animals were euthanized, stomachs excised, and gastric injury assessed as described above.

2.5. Contribution of gastroprotective pathways to the mechanism of action of EHPP

2.5.1. Prostaglandin involvement determination test

Mice were allocated into five groups (n = 6). The first three groups received either NaCl (0.9%, p.o.), EHPP (100 mg/kg, p.o.), or misoprostol (0.016 mg/kg, p.o.), which is a PGE2 agonist. The remaining two groups were pre-treated with indomethacin (10 mg/kg, p.o.) 2 h before administration of EHPP or misoprostol. After 1 h of oral treatment, or 30 min for intraperitoneal administration, 96% ethanol (0.2 mL/animal, p.o.) was administered. Thirty minutes following ethanol exposure, the animals were euthanized, and their stomachs were excised (Rafatullah et al., 1990), and the gastric lesion area was measured as previously described.

2.5.2. Determination of gastric mucus adherence

Six mice were randomly assigned to three experimental groups and received oral administration of NaCl (0.9%), EHPP (100 mg/kg), or misoprostol (0.016 mg/kg). Gastric injury was induced 1 h later by administering 96% ethanol (0.2 mL/animal, p.o.). Thirty minutes after ethanol exposure, the animals were euthanized, and their stomachs were excised and rinsed. The gastric mucosa was removed, weighed, and incubated in 10 mL of 0.1% Alcian blue solution for 2 h for staining. Excess dye was eliminated with 0.25 mol/L sucrose. Mucus-bound dye was extracted using 5 mL of 0.5 mol/L magnesium chloride. Subsequently, 3 mL of the blue supernatant was mixed with 3 mL of ethyl ether and shaken vigorously to form an emulsion. Following centrifugation (Centrifuge NF 800R, Ankara, Turquia) at 3000 × g for 10 min at ambient temp, the aqueous phase was collected, and the residue discarded. Alcian blue concentration was measured spectrophotometrically (Biochrom Libra S22 UV/vis Spectrophotometer, Waterbeach, Cambridge) at 598 nm. The quantity of dye bound to gastric mucus was determined from a standard curve and reported as μg Alcian blue per mL per gram of tissue (Rafatullah et al., 1990).

2.5.3. Involvement of ATP-dependent potassium channels

Mice were divided into five experimental groups (n = 6). The first three groups received either oral NaCl (0.9%), oral EHPP (100 mg/kg), or intraperitoneal diazoxide (3 mg/kg), which is a K^+ channel activator. The remaining two groups were pretreated with the K^+ channel blocker glibenclamide (5 mg/kg, intraperitoneally) 30 min before administration of EHPP or diazoxide. Gastric injury was induced with 96% ethanol (0.2 mL/animal, orally) 1 h after oral treatments or 30 min after intraperitoneal injections. Thirty minutes after ethanol administration, animals were euthanized, stomachs were excised, and the area of gastric lesions was quantified as previously described.

2.5.4. Involvement of histamine (H2) receptors

Mice were allocated to five groups (n = 6). The first three groups received NaCl (0.9%, p.o.), EHPP (100 mg/kg, p.o.), or ranitidine (40 mg/kg, i.p.), an H2 histamine receptor antagonist. The remaining two groups were pretreated with histamine (2 mg/kg, i.p.) 30 min before EHPP or ranitidine administration. Following 1 h of oral or 30 min of intraperitoneal treatment, animals received 96% ethanol (0.2 mL/animal, p.o.). Thirty minutes after ethanol administration, animals were euthanized, stomachs excised, and gastric lesion areas measured as previously described.

2.5.5. Involvement of sulfhydryl groups

Mice were divided into five experimental groups (n = 6). The first three groups received either oral NaCl (0.9%), oral EHPP (100 mg/kg), or intraperitoneal carbenoxolone (100 mg/kg) and were then treated with N-ethylmaleimide (NEM), a sulfhydryl group blocker. One hour after oral treatments or 30 min following intraperitoneal injections, gastric injury was induced with 96% ethanol (0.2 mL/animal, p.o.). Thirty minutes later, animals were euthanized, stomachs were excised, and the gastric lesion area was quantified as previously described.

2.5.6. Involvement of α2-Adrenergic receptors

Mice were divided into five experimental groups (n = 6). The first three groups received either oral NaCl (0.9%), oral EHPP (100 mg/kg), or intraperitoneal clonidine (0.05 mg/kg), an α_2-adrenergic receptor agonist. The remaining two groups were pretreated with the selective α_2-adrenergic antagonist yohimbine (2 mg/kg, i.p.) 30 min before administration of EHPP or clonidine. Gastric lesions were induced with 96% ethanol (0.2 mL/animal, p.o.) 1 h after oral treatments or 30 min after intraperitoneal injections. Thirty minutes later, animals were euthanized, stomachs were excised, and the area of gastric lesions was quantified as previously described.

2.5.7. Involvement of nitric oxide way and nitrite/nitrate dosage

Mice were divided into five experimental groups (n = 6). The first three groups received either oral NaCl (0.9%), oral EHPP (100 mg/kg), or intraperitoneal L-arginine (600 mg/kg), which serves as a precursor for nitric oxide (NO) synthesis. The remaining two groups were pre-treated with the nitric oxide synthase inhibitor L-NAME (20 mg/kg, i.p.) 30 min before administration of EHPP or L-arginine. Gastric lesions were induced with 96% ethanol (0.2 mL/animal, p.o.) 1 h after oral treatments or 30 min after intraperitoneal injections. Thirty minutes later, the animals were euthanized, stomachs were excised, and the area of gastric lesions was quantified as previously described.

Nitrite and nitrate concentrations were determined using the Griess method. The Griess reagent was prepared by mixing equal volumes of 5% phosphoric acid, 0.1% N-1-naphthylenediamine (NEED), 1% sulfanilamide in 5% phosphoric acid, and distilled water. For the assay, 100 μL of 10% homogenate supernatant, prepared in potassium phosphate buffer, was combined with 100 μL of Griess reagent. For the blank, 100 μL of reagent was mixed with 100 μL of buffer. A standard curve was established using serial dilutions of nitrite (100, 50, 25, 12.5, 6.25, 3.12, and 1.56 μmol). Absorbance was measured at 540 nm.

2.5.8. Involvement of the enzyme myeloperoxidase

Gastric tissue samples were collected from animals subjected to absolute ethanol-induced gastric ulcer, weighed, and homogenized (0.05 g tissue/mL) in hexadecyltrimethylammonium bromide (HTAB) solution using a Polytron homogenizer. Samples were kept on ice, sonicated for 25 min, and centrifuged (Centrífuga NF 800R, Ankara, Turquia) at 4100 rpm for 8 min at ambient temperature. The supernatant was collected for myeloperoxidase (MPO) activity determination. The method is based on the quantification of MPO released from damaged tissue. MPO activity was measured following the protocol described by (Bradley et al., 1982), using 0.0005% hydrogen peroxide as the substrate. One unit of MPO was defined as the amount capable of converting 1 μmol of hydrogen peroxide to water per minute at 22 °C. The change in optical density of the reaction mixture, containing o-dianisidine, was monitored over time by spectrophotometry (Biochrom Libra S22 UV/vis Spectrophotometer, Waterbeach, Cambridge) at 600 nm. Results were expressed as MPO units (UMPO) per μL of lavage fluid.

2.6. Statistical analysis

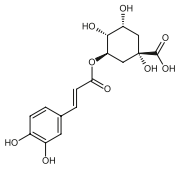
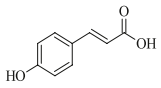
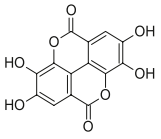
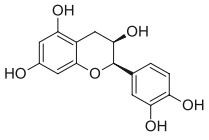
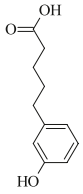
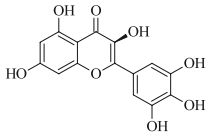
Data are reported as mean ± standard error of the mean (SEM). Group comparisons were conducted using analysis of variance (ANOVA) with Dunnett's post hoc test. All statistical analyses were performed using GraphPad Prism version 8.0.2 (GraphPad Software Inc., La Jolla, CA, USA). Statistical significance was defined as a p-value less than 0.05.

3. Results

3.1. Phytochemistry

The unequivocal identification of chlorogenic acid (caffeoylquinic

Table 1
Compound annotation results for hydroethanolic and pure extracts of *Plinia peruviana* via molecular networking analysis.

Precursor ion	Product mass (*m/z*)	Adduct	Molecular formula	Metabolite name	Chemical structure	Chemical class
353.103	191.056	[M-H] $^-$	$C_{16}H_{18}O_9$	Caffeoylquinic acid		Organic acid
163.040	119.050 93.034	[M-H] $^-$	$C_9H_8O_3$	p-coumaric acid		Organic acid
301.067	256.062 228.133 184.756	[M-H] $^-$	$C_{14}H_6O_8$	Ellagic acid		Organic acid
289.072	245.082 203.071 109.029	[M-H] $^-$	$C_{15}H_{14}O_6$	(−)-Epicatechin		Flavonoid
191.019	147.029 135.058 102.899	[M-H] $^-$	$C_{11}H_{14}O_3$	5-(3-Hydroxyphenyl) valeric acid		Fatty acid
317.067	271.077 179.011 151.004	[M-H] $^-$	$C_{15}H_{10}O_8$	Myricetin		Flavonoid

acid) was established through analysis of its hydrolytic cleavage using negative-mode electrospray ionization mass spectrometry (ESI-MS), as observed in Table 1. The rupture of the ester group at the C3 carbon of the quinic cyclitol core generated the diagnostic fragment *m/z* 191.056, corresponding to the [quinic acid – H]-ion, characteristic of stereoselective deacylation (Yang et al., 2022). For p-coumaric acid, the decarboxylation (-CO_2) of the carboxyl group resulted in the ion *m/z* 163.040 → 119.050, a pattern consistent with conjugated rearrangements of the phenylpropanoid system, corroborating its structural identification (Lambert de Malezieu et al., 2019).

In the case of ellagic acid, a sequential loss of CO_2 *m/z* 301.067 → 256.062 was observed, followed by retro-Diels-Alder (RDA) cleavage of the benzopyranochromone core, a typical mechanism of dimeric polyphenols. For (−)-epicatechin, the fragmentation *m/z* 289.072 → 245.082 corresponds to decarboxylation of the C-ring, while the transition *m/z* 289.072 → 109.029 arises from heterolytic cleavage of the C-O ether bond in the B-ring, generating the [$C_6H_5O_2$]-ion, a pattern aligned with the disintegration of flavan-3-ols (de Sousa Dias et al., 2022).

For 5-(3-hydroxyphenyl) valeric acid, the fragments *m/z* 191.019 → 147.029 (CO_2 loss) and *m/z* 191.019 → 102.899 (β-cleavage of the phenylpropanoid group) confirmed its structure, with the *m/z* 102.899 ion corresponding to the [C_6H_5O]-anion, typical of substituted aromatic systems. Myricetin exhibited dominant fragmentation *m/z* 317.067 → 179.011, attributed to cleavage of the heterocyclic ether in the C-ring with formation of the protonated flavylium ion, a characteristic pattern of trihydroxylated flavanols (Bai et al., 2020).

3.2. Acute toxicity and screening for the gastroprotective activity of EHPP

3.2.1. Non-clinical acute oral toxicity — LD_{50}

Oral administration of EHPP at 5000 mg/kg did not result in mortality or observable signs of toxicity in the animals, indicating that the extract is non-toxic *in vivo*.

3.2.2. Acute gastric lesions induced by ethanol, acidified ethanol, and indomethacin

Administration of ethanol successfully induced gastric lesions. Oral pretreatment with EHPP at doses of 100, 250, and 500 mg/kg significantly reduced lesion formation by 62.3%, 70.4%, and 41.5%, respectively, compared with the control group (Fig. 1A). Likewise, in the acidified ethanol-induced ulcer model, EHPP treatment at the same doses resulted in reductions of 77.6%, 78.5%, and 37.7%, respectively, relative to controls (Fig. 1B). The positive control group treated with omeprazole (30 mg/kg, orally) showed 93.5% and 94.0% inhibition of lesion development, respectively. In the indomethacin-induced gastric lesion model, EHPP at 100, 250, and 500 mg/kg significantly reduced lesion area by 44.3%, 47.3%, and 39.4%, respectively, compared with the control group (Fig. 1C). Omeprazole (30 mg/kg) treatment resulted in 85.37% inhibition.

To assess whether the observed effect was solely mediated by a physical barrier, EHPP at 100 mg/kg was administered orally and intraperitoneally. The results (Fig. 1D) demonstrated reductions in ulcerative area of 64.0% and 54.0%, respectively, compared with the control group. No statistically significant difference in ulcerative lesion inhibition was observed between the two administration routes. This finding indicates that the effect is attributable to the systemic action of the extract's chemical compounds rather than to a local physical barrier.

3.3. Contribution of gastroprotective pathways to the mechanism of action of EHPP

Among the tested doses of EHPP (100, 250, and 500 mg/kg), the 100 mg/kg dose was selected for the assays investigating the signaling mechanisms involved in its gastroprotective activity. Statistical analysis showed that increasing the dose to 250 or 500 mg/kg did not yield a significantly higher reduction in gastric lesions compared to 100 mg/kg. Thus, 100 mg/kg was defined as the optimal dose, representing the lowest dosage required to achieve maximum gastroprotection without a plateau-induced waste of the extract. Moreover, using a lower dose is

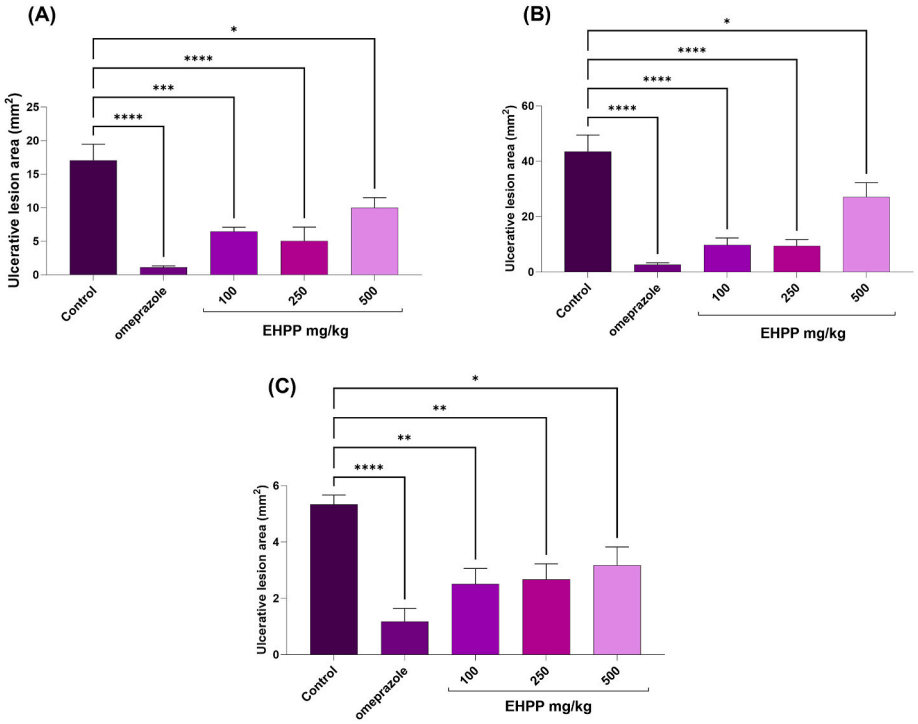


Fig. 1. Effect of EHPP on gastric lesions induced by ethanol **(A)**, acidified ethanol **(B)**, and indomethacin **(C)** in mice. Experimental groups included control (0.9% NaCl, orally), omeprazole (30 mg/kg, orally), and EHPP (100, 250, 500 mg/kg, orally). Data are presented as mean ± SEM (n = 6 per group). Statistical analysis was performed using one-way ANOVA followed by *Dunnett's post hoc test* (*p < 0.5, **p < 0.01, ***p < 0.001, and ****p < 0.0001). ns – not significant.

preferable, as it reduces the risk of adverse effects, offers a better safety profile, and allows for more rational use of the extract.

3.3.1. Involvement of ATP-dependent potassium channels and H_2 receptors

EHPP, administered at 100 mg/kg (p.o.), significantly reduced ethanol-induced gastric lesions by 74.5% compared to the control group. Similarly, diazoxide (3 mg/kg, i.p.), a potassium channel opener, reduced lesions by 65.0%. To investigate the involvement of potassium channels, glibenclamide (5 mg/kg, i.p.), a potassium channel blocker, was administered before diazoxide or EHPP. EHPP maintained its inhibitory effect in the presence of glibenclamide, indicating that glibenclamide did not reverse its gastroprotective action. Under KATP-channel blockade, EHPP continued to provide significant gastroprotection, suggesting that KATP channels are not essential to its mechanism of action. In contrast, glibenclamide significantly reversed the protective effect of diazoxide (Fig. 2A). As discussed in sections 3.3.2 and 3.3.3, gastroprotective mechanisms mediated by nitric oxide (NO) and prostaglandins may be influenced by EHPP's effects on KATP channels, as these channels represent a recognized final common pathway for several endogenous mechanisms.

EHPP extract at 100 mg/kg (p.o.) demonstrated significant gastroprotective activity in mice and was evaluated for potential involvement with histaminergic H_2 receptors. Both EHPP and ranitidine (40 mg/kg, i.p.), an established H_2 receptor antagonist, significantly reduced gastric lesions by 63.4% and 50.8%, respectively, compared to the control group. To determine whether this effect involved the histaminergic pathway, histamine (2 mg/kg, i.p.), a stimulator of gastric acid secretion, was administered before treatment. Histamine partially reversed the protective effect of ranitidine but did not significantly affect EHPP's gastroprotective action. These findings suggest that H_2 receptors are not directly involved in the mechanism by which EHPP protects the gastric mucosa (Fig. 2B).

3.3.2. Involvement of prostaglandins E_2 (PGE_2)

Analysis of prostaglandin involvement demonstrated that groups treated with misoprostol (0.016 mg/kg, orally), a synthetic analog of PGE_2, and EHPP (100 mg/kg, orally) showed statistically significant reductions in gastric lesions of 75.7% and 74.0%, respectively, compared to the control group. To elucidate the underlying mechanism, indomethacin (10 mg/kg, orally), a non-selective cyclooxygenase (COX) inhibitor, was administered before misoprostol and EHPP treatment. This intervention partially reversed the gastroprotective effects in both groups, suggesting that the PGE_2 pathway may contribute to EHPP's effects (Fig. 3A).

Gastric mucus production increased significantly by 180.4% and 127.7% in groups treated orally with misoprostol (0.016 mg/kg) and EHPP (100 mg/kg), respectively, compared to the control group (0.9% NaCl, p.o.). Given that misoprostol acts as an agonist of prostaglandin EP3 receptors, these findings suggest that EHPP-induced mucus production may be partially mediated through modulation of this pathway (Fig. 3B).

3.3.3. Involvement of the nitric oxide (NO) pathway and nitrate/nitrite quantification

In examining the role of nitric oxide (NO), groups treated orally with L-arginine (600 mg/kg) and EHPP (100 mg/kg) exhibited significant inhibition of ethanol-induced gastric lesions, with reductions of 73.9% and 55.5%, respectively, compared to the control group. The involvement of NO was further confirmed by pretreatment with L-NAME (20 mg/kg, i.p.), an inhibitor of nitric oxide synthesis, which abolished the cytoprotective effects of both L-arginine and EHPP (Fig. 4A). NO activates its receptor through soluble guanylyl cyclase, leading to increased cGMP levels. This increase can promote the opening of KATP channels in vascular smooth muscle and other cell types. The opening of KATP channels results in cellular hyperpolarization and facilitates vasodilation, thereby improving gastric mucosal microcirculation, which is essential for resisting and repairing injuries.

Furthermore, assessment of nitrite and nitrate levels, byproducts of endogenous NO metabolism, revealed that groups treated with EHPP and L-arginine exhibited significantly increased nitrite levels (74.9% and 52.5%, respectively) compared with the control group (Fig. 4B). These findings support the involvement of nitric oxide in the gastroprotective mechanism induced by EHPP.

3.3.4. Involvement of sulfhydryl groups (-SH groups) and α_2 adrenergic receptors

Oral administration of carbenoxolone (100 mg/kg) and EHPP (100 mg/kg) resulted in 51.5% and 61.2% inhibition of gastric lesions, respectively, compared to the control group (Fig. 5A). To assess the involvement of sulfhydryl groups in gastroprotection, N-ethylmaleimide (NEM), a sulfhydryl group inhibitor, was administered as a pretreatment. This intervention completely reversed the gastroprotective effects of both EHPP and carbenoxolone, suggesting that sulfhydryl groups are likely involved in EHPP's protective mechanism.

Oral administration of clonidine (0.05 mg/kg) and EHPP (100 mg/kg) significantly reduced ethanol-induced ulcerative lesions by 74.4% and 78.3%, respectively, compared to the control group. When yohimbine was administered, a partial reversal of the gastroprotective effects of both clonidine and EHPP was observed (Fig. 5B), suggesting that α2 adrenergic receptors contribute to the gastroprotective effect of EHPP.

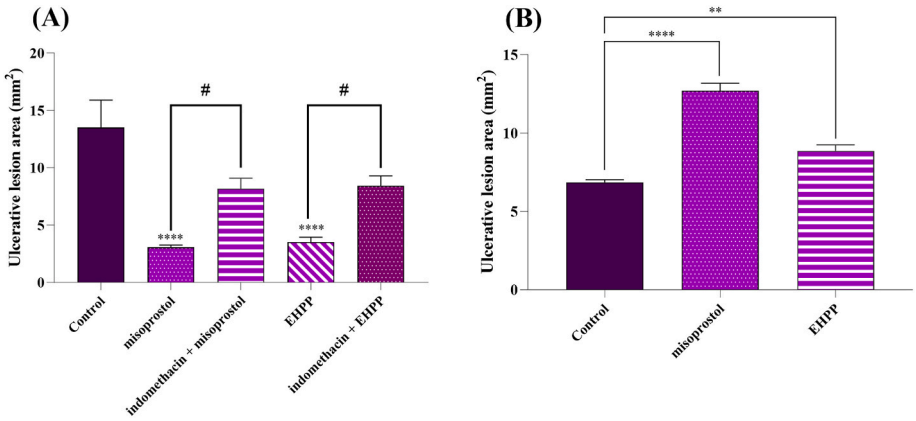


Fig. 2. Role of ATP-dependent potassium channels (A) and H_2 receptor signaling (B) in the gastroprotective effect of EHPP (100 mg/kg) on acute gastric lesions induced by ethanol. Data are presented as mean ± SEM (n = 6 animals per group). Statistical analysis was performed using one-way ANOVA followed by *Dunnett's post hoc test* (*p < 0.5, ***p < 0.001, and ****p < 0.0001). ns – not significant.

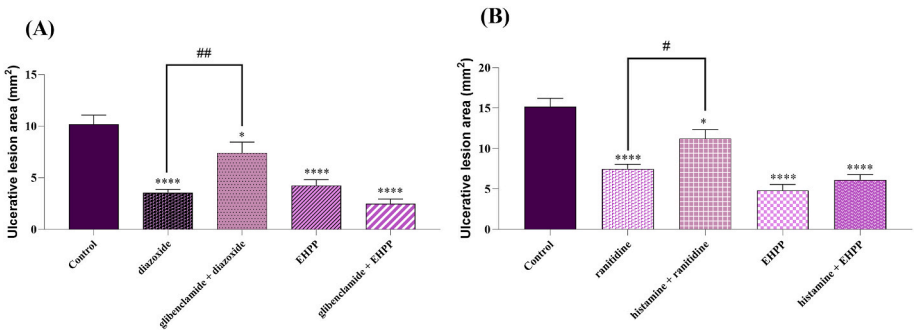


Fig. 3. Role of PGE_2 in the gastroprotective effect of EHPP (100 mg/kg) on acute gastric lesions induced by ethanol. (A) Gastric lesion area; **(B)** Mucus production assessed by *Alcian blue* staining. Data are presented as mean ± SEM (n = 6 animals per group). Statistical analysis was performed using one-way ANOVA followed by *Dunnett's post hoc test* (*p < 0.5, **p < 0.01, and ****p < 0.0001). ns – not significant.

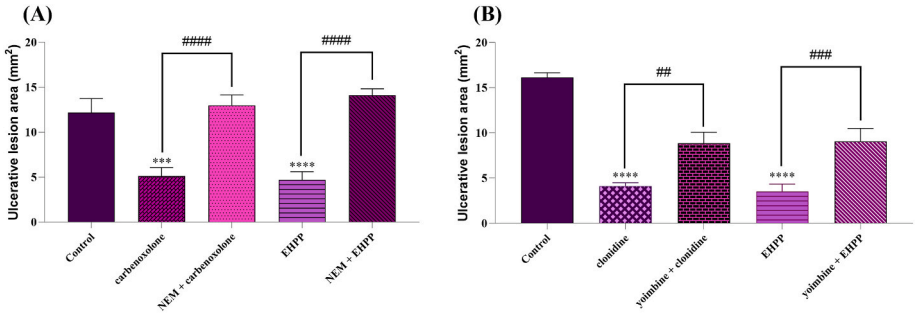


Fig. 4. Role of the nitric oxide (NO) pathway in the gastroprotective effect of EHPP (100 mg/kg) on acute gastric lesions induced by ethanol. **(A)** Ulcerative lesion area; **(B)** Percentage of nitrite/nitrate levels. Data are presented as mean ± SEM (n = 6 animals per group). Statistical analysis was performed using *one-way* ANOVA followed by Dunnett's post hoc test *p < 0.5, **p < 0.01, and ****p < 0.0001). ns – not significant.

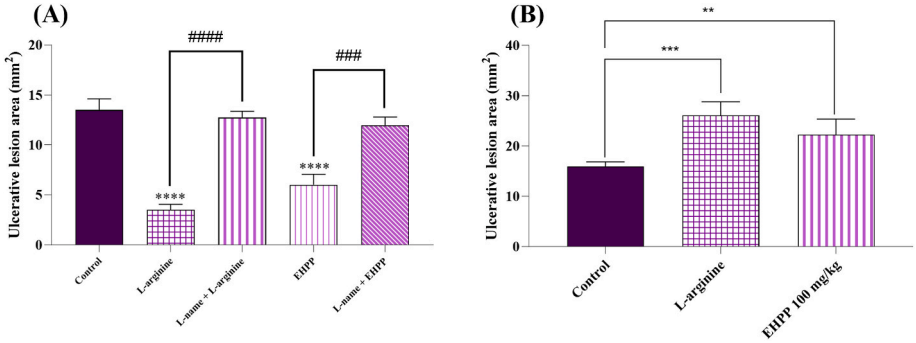


Fig. 5. Role of sulfhydryl (-SH) groups **(A)** and α_2-adrenergic receptors **(B)** in the gastroprotective effect of EHPP (100 mg/kg) on acute gastric lesions induced by ethanol. Data are presented as mean ± SEM (n = 6 animals per group). Statistical analysis was performed using *one-way* ANOVA followed by *Dunnett's post hoc test* (**p < 0.01, ***p < 0.001, and ****p < 0.0001). ns – not significance.

3.3.5. Myeloperoxidase (MPO) activity

The EHPP extract (100 mg/kg) and omeprazole (30 mg/kg) significantly reduced myeloperoxidase (MPO) activity by 49.8% and 64.8%, respectively, compared with the control group, indicating reduced inflammation in gastric tissue (Fig. 6). These results indicate that both treatments may produce downstream anti-inflammatory and antioxidant effects, thereby preserving mucosal perfusion and cellular homeostasis. This observation aligns with findings on the activation of ATP-dependent potassium (KATP) channels, which can reduce neutrophil recruitment and activation, limit oxidative stress, and, indirectly, decrease inflammatory markers such as MPO, as described in Section 3.3.2.

4. Discussion

Histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs) are commonly used as reference drugs to reduce gastric acidity and treat ulcers or gastric inflammation. Omeprazole, a PPI, has demonstrated antioxidant and anti-inflammatory properties (Abed et al., 2020; Kedika et al., 2009), modulate neutrophil activity (Fowler et al., 2024), and improves mucosal defense and microcirculation in certain experimental studies. H2RAs, including nizatidine and ranitidine, decrease acidity by blocking H2 receptors and influence mucosal blood flow, barrier function, and inflammatory signaling in specific models, which may provide modest protection independent of acid suppression (Liu et al., 2016). However, prolonged use of H2 antagonists or PPIs is linked to significant adverse effects (Meng et al., 2023; Yibirin et al., 2021), underscoring the need for alternative therapies.

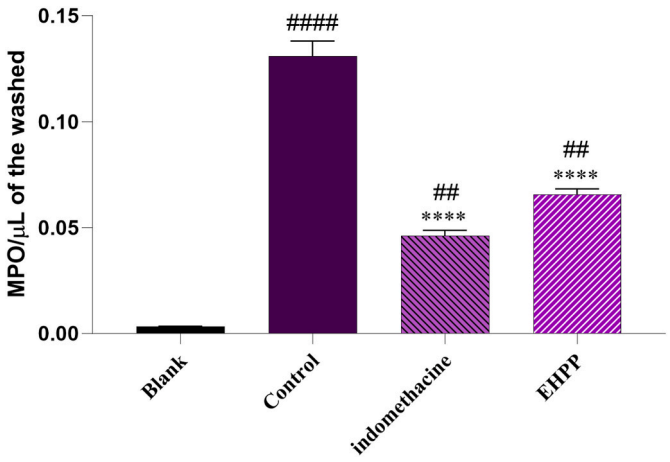


Fig. 6. Myeloperoxidase (MPO) activity in gastric tissue of animals treated with EHPP (100 mg/kg) and exposed to ethanol. Data are presented as mean ± SEM (n = 6 animals per group). Statistical analysis was performed using one-way ANOVA followed by *Dunnett's* post hoc test (*p < 0.5 and ****p < 0.0001).

Highlighting the necessity for alternative therapeutic options. Natural compounds derived from medicinal plants have shown promising potential for treating ulcers and gastritis (Singh & Easwari, 2022).

The anti-inflammatory and gastroprotective effects of fruits have been documented in the literature (Alcântara et al., 2026). A randomized controlled trial demonstrated that consumption of jabuticaba confers potential health benefits, including a reduction in the glucose curve and proinflammatory cytokine IL-6 (Geraldi et al., 2024). The present study was conducted on the premise that the extract derived from the fruit peels of *Plinia peruviana* (EHPP) may possess gastroprotective properties. This hypothesis was supported by significant inhibition observed in all *in vivo* models utilized. Furthermore, the study sought to elucidate the mechanisms underlying EHPP's gastroprotective effects. To the best of the authors' knowledge, this is the first report to demonstrate the gastric-protective activity of the fruit peel of this species, underscoring its potential as a therapeutic agent.

Phytochemical characterization of EHPP identified secondary metabolites and bioactive compounds, including caffeoylquinic acid, p-coumaric acid (Boeing et al., 2021), ellagic acid (Eldesoqui et al., 2025), (−)-epicatechin, 5-(3-hydroxyphenyl) valeric acid, and myricetin (Ansari et al., 2025; Park et al., 2021), substances commonly associated with gastroprotective activity due to their high antioxidant effect. These substances are commonly associated with gastroprotective activity due to their significant antioxidant properties. They play a critical role in neutralizing reactive oxygen species (ROS), thereby preventing lipid peroxidation and degradation of the mucosal barrier (Pitz et al., 2016b).

Additionally, the detection of polyphenols such as gallic acid and ellagic acid supports the hypothesis that these secondary metabolites are primary contributors to the observed gastroprotective effects (Graziela Moraes et al., 2021). Beyond their direct antioxidant effects, gallic acid and ellagic acid have been reported to modulate signaling pathways involved in gastric mucosal defense, including the regulation of inflammatory mediators, enhancement of endogenous antioxidant enzymes, and preservation of epithelial integrity. Therefore, the marked gastroprotection observed with EHPP may result not only from ROS scavenging but also from the modulation of cellular pathways that limit tissue injury and accelerate mucosal recovery. This interpretation is consistent with the reduction in MPO activity and the participation of nitric oxide and prostaglandins demonstrated in the present study. Previous findings from the research group have demonstrated that ellagic acid and gallic acid exhibit gastroprotective activity (S. A. Brito et al., 2018).

The gastroprotective effects of EHPP are likely not due to a single compound, but rather to synergistic interactions among its constituents. Flavonoids and phenolic acids may enhance antioxidant activity by reducing ROS production, inhibiting lipid peroxidation, and modulating endogenous antioxidant enzymes (Prabhu et al., 2021; Sies, 2015; Wagner & Ulrich-Merzenich, 2009). These findings reinforce the hypothesis that the pharmacological activity of the extract is associated with multi-component and multi-target mechanisms characteristic of complex natural products. The ability of EHPP to protect against ethanol- and acidified ethanol-induced lesions is particularly relevant because these models are strongly associated with oxidative stress, microvascular dysfunction, and disruption of the mucus barrier rather than excessive acid secretion. Therefore, the efficacy of EHPP in these models suggests that its protective effect is primarily related to cytoprotective and antioxidant mechanisms. This interpretation is supported by the phytochemical profile of the extract, which is rich in phenolic compounds known to preserve membrane integrity, reduce oxidative injury, and modulate inflammatory responses. The ethanol-induced injury model is widely used to evaluate the gastroprotective efficacy of various substances, as it replicates the mechanisms of ulceration observed in humans (Sohail et al., 2023). Gastric mucosal damage results from reduced blood flow, which impairs mucus and bicarbonate secretion by oxyntic and pyloric cells (Marriott & Gregory, 2024). Ethanol or acidified ethanol causes lesions mainly via direct cytotoxicity, disrupting the mucus/bicarbonate barrier, inducing microvascular injury, and triggering oxidative stress and inflammation, rather than acid hypersecretion. Ethanol also promotes histamine release, calcium influx, leukotriene production, and ROS activation—key factors in gastric lesion pathogenesis (Al Asmari et al., 2016). Indomethacin is another main agent for inducing gastric ulcers experimentally; it inhibits COX and thus reduces gastroprotective prostaglandins such as PGE2 (Malfertheiner et al., 2009).

EHPP exhibited a significant cytoprotective effect across all experimental models, suggesting involvement of mucus barriers. To determine whether this effect was due to local action, such as the formation of a physical barrier over the gastric mucosa, an assay was performed using both oral and systemic (i.p.) administration of EHPP. EHPP maintained its gastroprotective activity regardless of the route of administration, indicating that the effect is systemic.

In the next step, a series of experiments was designed to gain insights into the probable cytoprotective mechanism of action of EHPP. The involvement of prostaglandins and nitric oxide is mechanistically consistent with the phytochemical composition of EHPP. Polyphenols such as ellagic acid, gallic acid, epicatechin, and myricetin have been reported to enhance endothelial nitric oxide synthase activity, improve microcirculation, and stimulate cytoprotective signaling pathways associated with prostaglandin production. Consequently, the observed dependence on NO and PGE2 may represent a downstream biological response triggered by the coordinated action of these phenolic constituents. The simultaneous participation of sulfhydryl groups further suggests that preservation of the redox environment is an important component of the gastroprotective effect. This demonstrates that the effect of EHPP is multi-target, which is reasonable given that various secondary metabolites are present in the extract and that action on distinct targets and synergistic interactions are plausible, particularly when dealing with an extract from medicinal plants. Fig. 7 illustrates the gastroprotective mechanisms of EHPP.

PGE2 plays a crucial role in gastric mucosal protection. It mediates blood flow, mucus secretion, and pH regulation (Wallace, 2008). Production of NO is essential for maintaining mucosal integrity. This elevated production was confirmed by higher levels of nitrite and nitrate, both byproducts of endogenous NO metabolism. Moreover, myeloperoxidase activity, an enzyme in neutrophils important for defense, was reduced in EHPP-treated groups. This suggests lower neutrophil recruitment and a weaker inflammatory response (Santin et al., 2013).

α2-adrenergic receptors have been implicated in inhibiting acid secretion and regulating intestinal motility (Pitz et al., 2016b). The protection induced by EHPP was reversed by the selective α2 antagonist

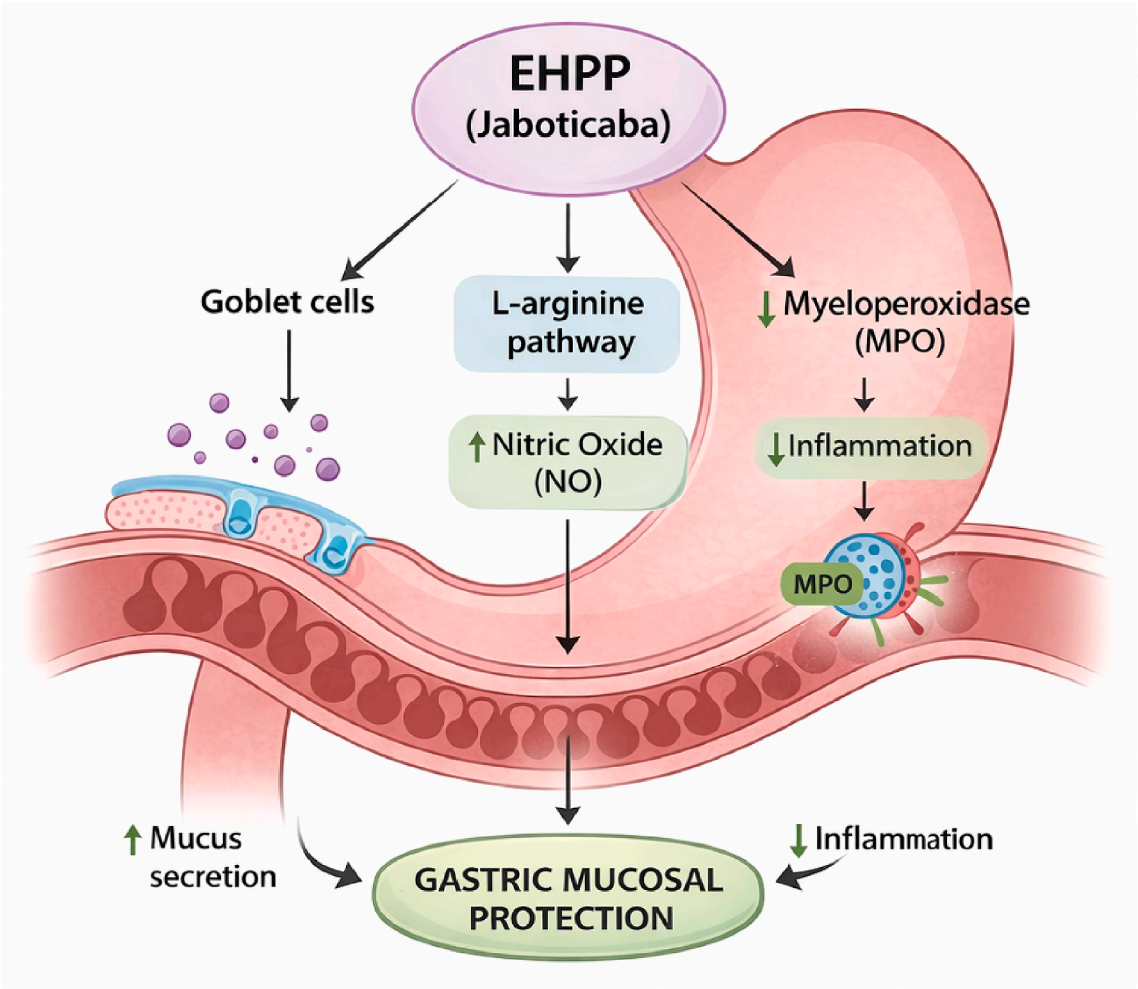


Fig. 7. Gastroprotective mechanisms of the hydroalcoholic extract of *Plinia peruviana* (EHPP). EHPP stimulates mucus secretion by goblet cells, promotes nitric oxide (NO) synthesis from L-arginine, involves sulfhydryl groups (–SH), and inhibits the enzyme myeloperoxidase (MPO), contributing to the maintenance of gastric mucosal integrity and the reduction of inflammation.

yohimbine, suggesting a possible role for these receptors in the gastroprotective activity. Furthermore, sulfhydryl groups are recognized for their antioxidant properties and for their role in stabilizing gastric mucus (Balan et al., 2014; Sanchez et al., 2005). In the study, the involvement of sulfhydryl compounds was evident, indicating that the gastroprotective effect of EHPP also depends on their presence. The involvement of K+ channels and H2 histamine receptors was initially ruled out, as they did not modify the cytoprotective effect of EHPP. Similarly, the participation of muscarinic cholinergic receptors was excluded. Finally, it is important to note that, while prostaglandins, nitric oxide, α2-adrenergic receptors, and sulfhydryl groups are clearly involved in EHPP's effects, other factors—such as gastric emptying—may also contribute to its overall cytoprotective activity.

5. Conclusion

Available evidence demonstrates that the ethanolic extract of *Plinia peruviana* (EHPP) may exhibit gastroprotective activity, possibly through multiple mechanisms such as stimulation of prostaglandin-mediated mucus secretion, activation of α2-adrenergic receptors, nitric oxide synthesis, participation of sulfhydryl (SH) groups, and the impact of myeloperoxidase (MPO) activity. These findings suggest the potential of *Plinia peruviana* as a source of bioactive compounds that can be explored in therapeutic strategies aimed at the prevention and treatment of gastric lesions, although more clinical evidence is needed to confirm its efficacy.

6. Limitations

This study utilized only acute murine ulcer models (ethanol/acidified ethanol and indomethacin) to assess the gastroprotective effects of EHPP. While these models effectively capture short-term mucosal injury, they do not adequately reflect the complex pathophysiology of chronic or recurrent ulcer disease, such as persistent inflammation, impaired healing, and relapse. The absence of comprehensive safety assessments and long-term evaluations further restricts conclusions regarding sustained efficacy and translational relevance. Additionally, the use of a crude hydroethanolic extract of EHPP complicates the identification of the roles and interactions of individual constituents, including gallic and ellagic acids and other peel metabolites. This limitation also hinders the elucidation of dose–response relationships and structure–activity correlations. Therefore, future research should employ chronic ulcer and ulcer-healing models, alongside bioassay-guided fractionation and pharmacokinetic profiling, to more robustly determine efficacy, identify active components, clarify mechanisms of action, and enhance reproducibility and translational applicability.

Despite these limitations, the study provides valuable insights and demonstrates clinical potential. The findings indicate that EHPP consistently conferred protection in various injury models, with efficacy linked to increased mucus production, involvement of SH/NO pathways,

α2-adrenergic signaling, and decreased MPO activity. These results suggest that effective gastroprotection is mediated by cytoprotective, antioxidant, and anti-inflammatory mechanisms. Furthermore, the study established connections between traditional use, quantifiable outcomes, and plausible biological mechanisms. Additional assays utilizing identified compounds or isolated constituents may serve as a preclinical foundation for the development of standardized phytotherapeutic candidates. Collectively, these findings justify further investigation using chronic or healing models, fraction-guided validation, and comprehensive safety and translational studies.

CRediT authorship contribution statement

Isabel Sousa Alcântara: Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Renata Torres Pessoa:** Resources, Investigation, Formal analysis. **Lucas Yure Santos da Silva:** Writing – original draft, Visualization, Methodology, Investigation. **Roger Henrique Souza da Costa:** Validation, Resources, Methodology. **Aparecida Barros da Silva:** Validation, Resources. **Tarcisio Mendes Silva:** Resources, Methodology. **Samara Alves Brito:** Writing – original draft, Methodology, Formal analysis, Data curation. **Anita Oliveira Brito Pereira Bezerra Martins:** Writing – original draft, Resources, Formal analysis, Data curation. **Jean Carlos Pereira Sousa:** Writing – original draft, Methodology, Investigation. **Andréa Rodrigues Chaves:** Validation, Methodology, Investigation, Formal analysis. **Ricardo Neves Marreto:** Writing – original draft, Methodology, Funding acquisition, Formal analysis. **Francisco Sandro Menezes Rodrigues:** Writing – original draft, Visualization, Validation, Formal analysis. **Irwin Rose Alencar de Menezes:** Writing – original draft, Supervision, Project administration, Data curation, Conceptualization. **Almir Gonçalves Wanderley:** Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization.

Ethics approval

This study was submitted to, and its research protocol approved by, the Ethics Committee on the Use of Animals at URCA, under license number 00103/2021.1.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Irwin Rose Alencar de Menezes reports was provided by Regional University of Cariri.

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Data availability

All data supporting the findings of this study are available from the corresponding author upon reasonable request.

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