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Gastroprotective effect of the crude ethanolic extract from the stem barks of *Piptadenia viridiflora* (Kunth) Benth. (Fabaceae)

[Efecto gastroprotector del extracto etanólico crudo de la corteza de *Piptadenia viridiflora* (Kunth) Benth. (Fabaceae)]

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Abstract: The objective of this work was to evaluate the gastroprotective activity of the crude ethanolic extract (CEE) from the stem barks of Piptadenia viridiflora using the acute models of inducing gastric ulcers by ethanol, ethanol-acidified, and ischemia-reperfusion, and correlating this response with the antioxidant activity, as well as, analyze the chemical profile of the extract by high-performance liquid chromatography coupled to diode array detector (HPLC-DAD). For this purpose, mice and rats were used. The ethanol ulcer induction test showed that CEE at doses of 100 and 200 mg/kg promoted 70% and 80% of gastroprotection, respectively. In the gastric ulcer induction test by acidified-ethanol and ischemia-reperfusion, CEE (200 mg/kg) promoted 66% and 90% of gastroprotection in animals, respectively. In conclusion, this species has gastroprotective activity, and this response is possibly related to the antioxidant activity, as well as the presence of flavonoids detected in CEE of P. viridiflora.

Keywords: Gastric ulcer; Gastroprotection; Flavonoids; *Piptadenia viridiflora*; Fabaceae.

Resumen: El objetivo de este trabajo fue evaluar la actividad gastroprotectora del extracto etanólico crudo (CEE) de Piptadenia viridiflora, utilizando los métodos de inducción de úlceras gástricas agudas por etanol, etanol acidificado y de isquemia-reperfusión, y correlacionando esta respuesta, con la actividad antioxidante, así como, perfil químico de la muestra. Para ello se utilizaron ratones (Swiss) y ratas (Wistar). Como resultado, la prueba de inducción de úlceras por etanol mostró que la CEE a dosis de 100 y 200 mg/kg promovió 70% y 80% de gastroprotección, respectivamente. En la prueba de inducción de úlcera gástrica por etanol acidificado e isquemia-reperfusión, la CEE (200 mg/kg) promovió 66% y 90% de gastroprotección en animales, respectivamente. Concluimos que la especie tiene una acción gastroprotectora y que esta respuesta posiblemente esté relacionada con la actividad antioxidante, así como con la presencia de flavonoides detectados en la CEE de P. viridiflora.

Palabras clave: Úlcera gástrica; Gastroproteccion; Flavonoides; *Piptadenia viridiflora*; Fabaceae.

INTRODUCTION

Peptic ulcers are injuries that occur in the stomach, duodenum and more rarely in the esophagus (Malik *et al*., 2021), due to multifactorial processes, which involve an imbalance in the production and release of harmful and protective agents of the gastric mucosa. Annually, approximately two hundred thousand people are hospitalized with the diagnosis of gastric ulcers (Eraslan *et al.*, 2020). The appearance of these lesions is linked to the excessive consumption of some drugs, such as alcohol, non-steroidal anti-inflammatory drugs (NSAIDs) and cigarettes, infection by *Helicobacter pylori* bacteria, and episodes of stress and anxiety (Mousa *et al.*, 2019).

The main damaging agent of the gastric mucosa is hydrochloric acid (HCl), produced by parietal cells and secreted in the lumen of the stomach (Megha *et al.*, 2020). The reduction of gastric protection mechanisms [mucus and bicarbonate secretion (HCO_3^-), decreased blood microcirculation in the region, among others], added to oxidative stress, promoted by HCl, and substances, such as ethanol, for example, trigger reactions that culminate in tissue necrosis of the tissue layers of the stomach (Serafim *et al*., 2020).

The usual treatment for this condition is the use of synthetic drugs, proton pump inhibitors H^+/K^+ ATPase (omeprazole), histamine H2 receptor inhibitors (H2 blockers) and cytoprotective drugs (Silva *et al*., 2020). These drugs are associated with many side effects, ranging from inhibition of vitamin $B_{12,}$ absorption to bone damage and cardiac arrhythmias (Mahmoud & El-Ghffar, 2019; (Khémiri & Bitri, 2019). Despite the dominance of the use of these synthetic drugs, the incidence of hospitalizations has enabled a greater demand for alternative treatments based on medicinal plants, which enable fewer side effects, and greater patient compliance with treatment (Hut *et al.*, 2017).

Based on this premise, our research group used the species *Piptadenia viridiflora* (Kunth) Benth. to carry out this study. This is an angiosperm belonging to the Fabaceae family (subfamily Mimosoideae), popularly known in Brazil as "espinheiro", "icarape", "jacinto", "soroca" and "surucucu". This species is predominant in the Brazilian Caatinga biome, due to its great adaptation to dry and arid climates (Pessoa *et al*., 2010).

Previous studies have demonstrated the presence of flavonoids and antioxidant activity in this plant species (Costa *et al*., 2016; Macêdo, 2017), as well as antibacterial (Trentin *et al.*, 2011) and anthelminthic (Costa *et al.*, 2016) activities. Flavonoids are recognized by their antioxidant and anti-inflammatory properties (Chen *et al*., 2019). As previously mentioned, oxidative stress, as well as inflammatory processes, are mechanisms related to the appearance of gastric lesions. This species is widely used in folk medicine in the city of São Raimundo Nonato, located in the state of Piauí, Brazil, for the treatment of heartburn. The lack of scientific studies on the medicinal use of this species for the treatment of gastric diseases enabled the interest of our research group to investigate the possible gastroprotective action of the species *P. viridiflora* through methods of inducing gastric damage in animal models.

MATERIALS AND METHODS

Plant material

Barks of *P. viridiflora* were collected in March 2018, in São Raimundo Nonato, state of Piauí, Brazil (coordinates: 9°05'91.64" S, 42°65'99.86" W). Then, the botanic material was taken to UNIVASF, Petrolina, Pernambuco, Brazil. The plant material was dried at room temperature, and then pulverized in a knife mill. All procedures for access to genetic patrimony and associated traditional knowledge were carried out and the project was registered in SisGen (#AF591AC). The species was identified by comparison with the voucher specimen deposited at the Herbarium Vale do São Francisco (HVASF) at the Federal University of Vale do São Francisco (UNIVASF), under registration number #28.

Extract preparation

The stem barks (550 g) were submitted to maceration with ethanol 95% (2 L) during three days. It was carried out three extractions. The extractive solution obtained was concentrated in rotatory evaporator at reduced pressure (45°C) affording the crude ethanolic extract (CEE), which weighed 105 g (yield of 19%).

DPPH radical scavenging assay

The antioxidant property of CEE was investigated by using the 2,2-diphenyl-1-picrylhydrazyl free radical (DPPH) as a reagent according to previous work (Mensor *et al*., 2001). Also, ascorbic acid (AA) and butylhydroxyanisole (BHA) samples were evaluated. The samples were dissolved in 96% ethanol in order to obtain solutions with a concentration of 1 mg/mL. Subsequently, these stock solutions were diluted in different concentrations (243, 81, 27, 9, 3, and 1 μg/mL) in ethanol, in a final volume of 10 mL. These samples were added in glass cuvettes with 1.0 cm of optical path, and then 1 mL of the DPPH alcoholic

solution (5.0 µg/mL) was added to all samples, except for those corresponding to the blank. Absorbance was measured at 518 nm in a spectrophotometer. Antioxidant activity (%AA), expressed as percentage of DPPH radical scavenging activity was calculated using the following equation:

$$\%AA = [(Ac - As)/ Ac] \times 100$$

Where **Ac** is the absorbance of the control, and **As** is the absorbance of the sample. All tests were performed in triplicate (Mensor *et al*., 2001).

High-performance liquid chromatography coupled to diode array detector (HPLC-DAD) analysis

HPLC-DAD analysis was performed using a Shimadzu Prominence® HPLC system equipped with two binary pumps (LC-20AD), degassing unit (DGU-20A), automatic sampler (SIL-20AHT), column oven (CTO-20A), module communication bus (CBM-20A), diode array detector (SPD-M20A) and a reverse phase column. To perform the analysis, methanolic solution (1 mg/mL) of the CEE was prepared, which was subjected to analysis by HPLC-DAD, using an octadecylsilane column (250 x 4.6 mm, 5 µm, C 18, Agilent®) as stationary phase and mobile phase composed of 2 solvents: solvent A: 0.1% of trifluoroacetic acid in ultrapure water and solvent B: methanol, with a flow of 0.6 mL/min in gradient. The stationary phase was maintained at 30ºC, the injected volume was 35 µL and the analysis was monitored from 190 to 800 nm. The data obtained were processed using the software Shimadzu® LC solution 1.0. The results were analyzed from the comparison with chromatograms of standard reference substances: caffeic acid, chlorogenic acid, gallic acid, protocatechuic acid, chrysin, epicatechin, fisetin, galocatechin, hesperedin, naringenin, quercetin, isoquercetin, resveratrol, rutin, scopoletin, cirsiliol, harman, hesperetin, isovitexin and vitexin, at concentration of 200 µg/mL (Torres *et al.*, 2018).

Animals

All experimental protocols were approved by the Ethics Commission on the use of Animals (CEUA) of the Federal University of Vale do São Francisco (UNIVASF) with the registration number #0016/270219. Swiss male mice (30 to 45 g) and male Wistar rats (200 to 300 g), aged 6 to 10 weeks, were obtained from the UNIVASF vivarium (147 mice and 77 rats). The animals were housed at a temperature of 22 ± 2°C, under a 12 h light-dark cycle, with free access to standard rodent food and water *ad libitum*. All animals were fasted for 14 h before the experiments, were carried out and euthanized with a lethal subcutaneous injection of Thiopental (100 mg/kg), according to Brazilian Resolution No. 1000, of May 11, 2012, of the Federal Council of Veterinary Medicine (CFMV, 2012).

The experiments were carried out evaluating the formation of gastric ulcers and the effect of gastroprotection. The area of gastric lesions was measured by computerized planimetry using the ImageJ-NIH® Software.

The calculation of the formation of gastric lesions was performed by correlating the total measurement of each stomach and the injured areas and mm^2 of area.

$$\text{Ulcer index\%} = (\text{sum of injury areas} / \text{total area}) \times 100$$

The gastroprotection calculation was achieved by correlating the percentage values of ulcer index in the control-vehicle group (UIC) and in the treated groups (UIT).

$$\text{Gastroprotection} = (UIC - UIT) \times 100/UIC$$

Acute gastric ulcer induced by ethanol

This model was used to determine the ability of CEE to prevent the formation of acute gastric ulcers in the stomach lining, according to adaptations of the method described by Morimoto *et al*. (1991). For this purpose, a positive control group (carbenoxolone 100 mg/kg) was used; a negative control group - vehicle (saline 0.1 mL/100 g); and the test group, CEE, at doses of 100 and 200 mg/kg. After 14 h fasting, male mice received this previous pretreatment by gavage, orally. After 1 h, the animals received absolute ethanol (lesion-inducing agent); half an hour after the induction of the lesions, the animals were euthanized and their stomachs removed and opened by the greater curvature to measure the areas of gastric lesions.

Acute gastric ulcer induced by acidified ethanol

Acute gastric ulcer induced by acidified ethanol model was used to determine the ability of CEE to prevent the formation of acute gastric ulcers in deeper layers of the stomach, according to adaptations of the method described by Mizui & Doteuchi (1983). Thus, the positive control group (carbenoxolone 100 mg/kg) was used; a vehicle-negative control group (saline 0.1 mL/100 g); and the CEE test group at doses of 100 and 200 mg/kg. After 14 h fasting, male

mice received this previous pretreatment by gavage, orally. After 1 h the animals received 0.3 M absolute acidified ethanol with HCl (lesion inducing agent); half an hour after injury induction, the animals were euthanized and their stomachs removed and opened by the greater curvature to measure the areas of gastric lesion.

Acute gastric ulcer induced by ischemia-reperfusion

This acute ulcer induction method is performed through a surgical process, which ischemia and the reperfusion of oxygen gas (O_2) is induced to form the lesions. In this test, a positive control group *N*-acetylcysteine (200 mg/kg) was used; a negative control group-vehicle (saline 0.1 mL/100 g), and the test group (CEE dose 200 mg/kg). After 14 h fasting, male rats received this previous pretreatment by gavage, orally. After 30 min of the previous pretreatment, the anesthetic state was induced in the animals. The anesthetics xylazine (50 mg/kg) and ketamine (5 mg/kg) were administered (intramuscularly) in all groups; an interval of 15-20 minutes was given for complete sedation of the animals. Then an opening was made in the animals' abdomen to expose the celiac artery, where a clamp was placed in order to stop blood flow to the stomach. The clamp remained in the artery for 30 min, after removal, it was counted 1 hour for blood reperfusion, then the animals were euthanized and their stomachs removed and opened by the greater curvature to measure the areas of gastric lesions (Yoshikawa *et al*., 1989).

Statistical analysis

The statistical analysis was made using the Analysis of Variance (one-way ANOVA) and the results were expressed as mean ± standard error of the mean. For *in vivo* tests, one-way ANOVA was used, followed by Dunnett's post-test. The analyses were performed using the GraphPad Prism 9.0 software, and the differences between the groups were considered statistically significant at $p<0.05$.

RESULTS

DPPH radical scavenging assay

The antioxidant activity of the samples, determined by the DPPH radical scavenging capacity, was expressed as a percentage of antioxidant activity (%AA) and CE_{50} (minimum effective concentration to reach 50% of the maximum effect). The results found for this test are shown in Figure No. 1.

Figure No. 1 expresses the response of antioxidant activity in relation to the increase in the concentration of the samples. The CEE presented 95.47% of antioxidant activity and CE_{50} of 16.03 ± 0.59 µg/mL. The AA and BHA standards showed 97.77% and 86.21% of antioxidant activity, and CE_{50} of 27.00 ± 1.8 and 59.66 ± 0.9 µg/mL, respectively.

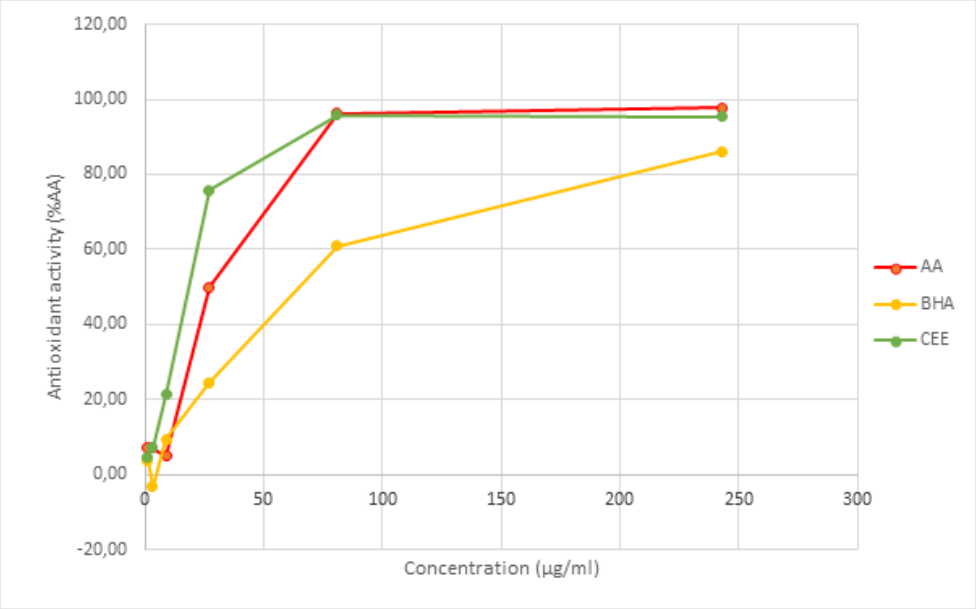

Figure No. 1
Analysis of the scavenging of the radical 2,2-diphenyl-1-picrilhidrazil (DPPH). Correlation of the antioxidant activity of the samples in relation to the increase of their concentrations. AA: Ascorbic acid; BHA: Butylhydroxyanisole; CEE: Crude ethanolic extract

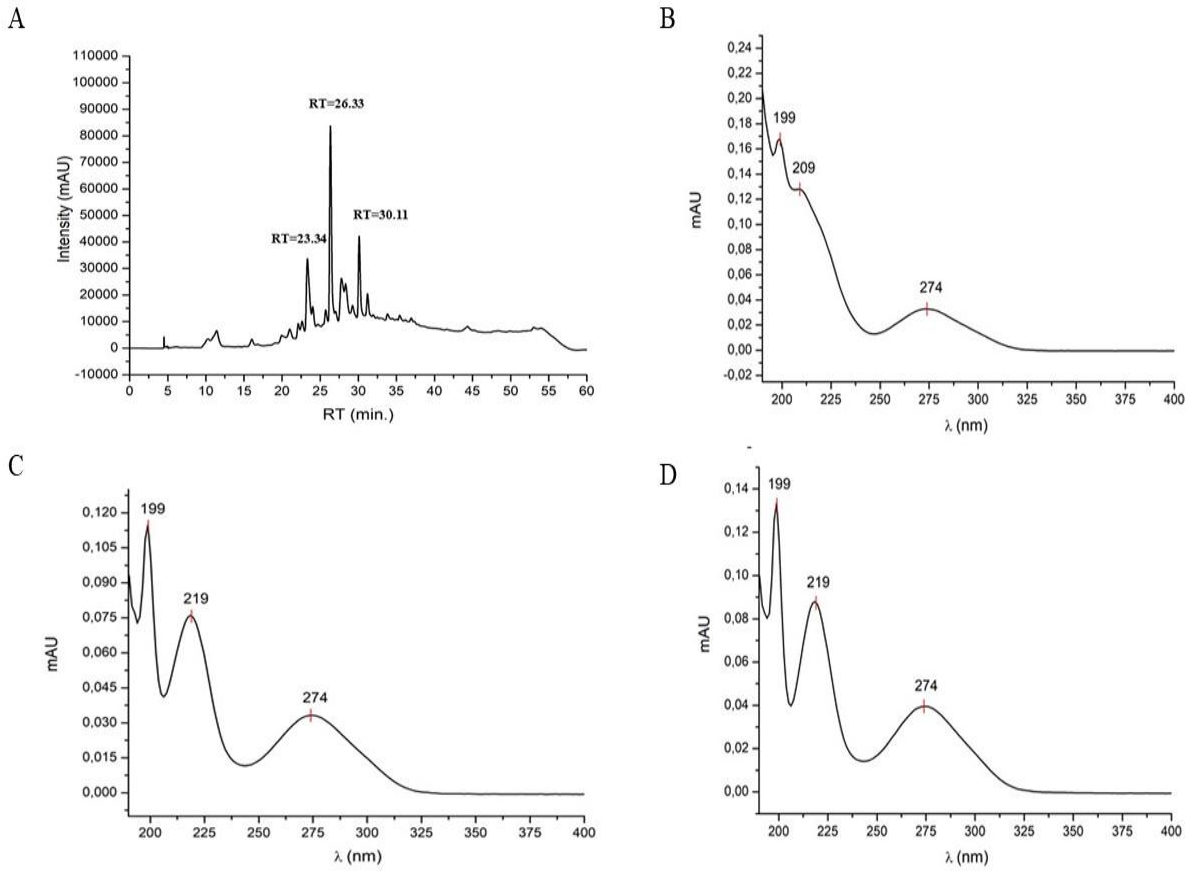

Figure No. 2
Chromatogram obtained after analysis by high-performance liquid chromatography coupled to diode array detector (HPLC-DAD) of crude ethanolic extract (CEE). A) Chromatographic profile at 270 nm; B) UV spectrum at the retention time 23.34 min; C) UV spectrum at the retention time of 26.33 min; D) UV spectrum at the retention time in 30.11 min

HPLC-DAD analysis

It was not possible to identify the substances present in the crude ethanolic extract of *P. viridiflora* through the comparison of retention times and maximum absorption spectra of the analytical standards.

However, the compounds with retention times at 23.34, 26.33, and 30.11 min showed ultraviolet (UV) absorption bands at the wavelengths of 219 and 274 nm (Figure No. 2), characteristics for the presence of flavonoids (Santi *et al.*, 2014).

Acute gastric ulcer induced by ethanol

The purpose of this test was to promote lesions in the gastric mucosa of mice. The negative control group (vehicle) formed 5.54 ± 1.06% of ulcerated area. The CEE groups at doses of 100 and 200 mg/kg, and the positive control group, carbenoxolone at a dose of 100 mg/kg, formed 1.65 ± 0.42%, 1.10 ± 0.29%, and 1.08 ± 0.15% of ulcerated area, respectively. Thus, the groups presented 70%, 80% and 80% of gastroprotective effect, respectively. The results are shown in the Figure No. 3, which, are observable, macroscopically, in the representative stomachs of each group, also exposed in Figure No. 3.

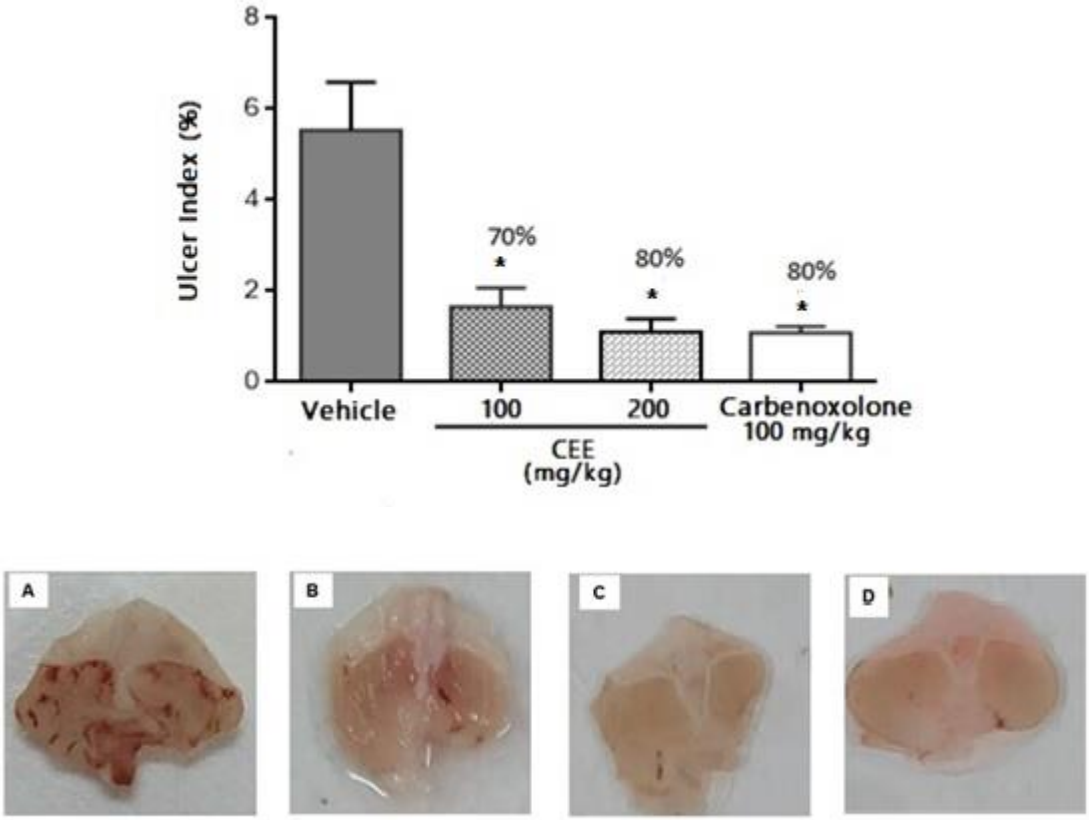

Figure No. 3
The results were expressed by ANOVA one way as the mean ± S.E.M. (n = 7-8 / group), followed by Dunnett's posttest, * $p<0.05$. The figure shows the induction of acute gastric lesions with absolute ethanol and the correlation between the relative area of injury of the treated groups, in relation to the vehicle group (control group). In the images, the correlation of open stomachs representative of each group is expressed. (A) control group - vehicle; (B) CEE 100 mg/kg; (C) CEE 200 mg/kg; (D) carbenoxolone 100 mg/kg. CEE: Crude ethanolic extract

Acute gastric ulcer induced by acidified ethanol
The purpose of this test was to promote lesions in the deeper layers of the mice's stomach. The negative control group (vehicle) formed 15.5 ± 1.6% of ulcerated area. The CEE group at a dose of 100 mg/kg formed 13.5 ± 0.83% of ulcerated area and had no gastroprotective effect, while the CEE group at a dose of 200 mg/kg, and the carbenoxolone group at a dose of 100 mg/kg formed 5.27 ± 1.43% and 0.98 ± 0.15% of gastric lesion, respectively. Thus, both had 66.0% and 93.6% of gastroprotective effect, respectively. The results are shown in the Figure No. 4. These results are observable, macroscopically, in the representative stomachs of each group, also exposed in Figure No. 4.

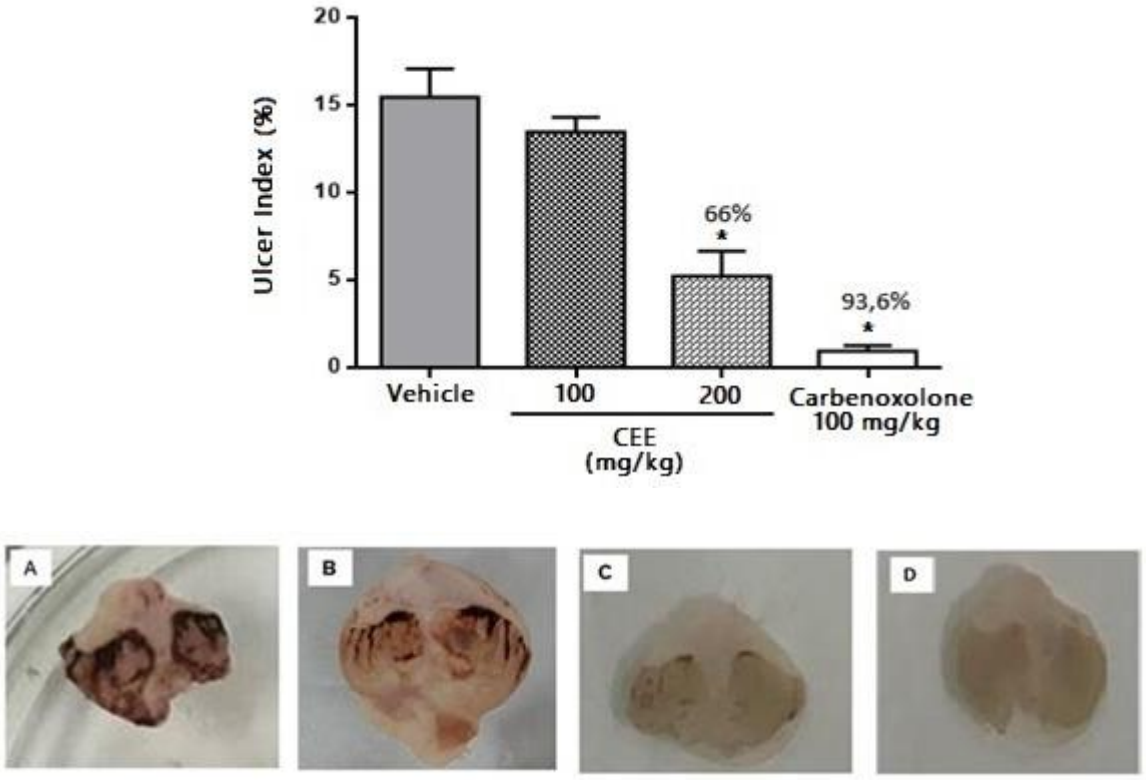

Figure No. 4
The results were expressed by ANOVA one way as the mean ± S.E.M. (n = 7-8 / group), followed by Dunnett's posttest, * *p*<0.05. The figure shows the induction of acute gastric lesions with acidified ethanol and the correlation between the relative lesion area of the treated groups, in relation to the vehicle group (control group). In the images, the correlation of open stomachs representative of each group is expressed. (A) control group - vehicle; (B) CEE 100 mg/kg; (C) CEE 200 mg/kg; (D) carbenoxolone 100 mg/kg. CEE: Crude ethanolic extract.

Acute gastric ulcer induced by ischemia-reperfusion
The purpose of this test was to promote gastric lesions through ischemia, and mainly via reperfusion of oxygen gas in the stomach. The vehicle group formed 10.6 ± 1.92% of ulcerated area. The CEE groups at the dose of 200 mg/kg and *N*-acetylcysteine at the dose of 200 mg/kg formed 1.07 ± 0.33% and 0.12 ± 0.04% of ulcerated area, respectively. Thus, both had 90% and 97% of gastroprotective effect, respectively. The results are expressed in Figure No. 5, and these results are observable, macroscopically, in the stomachs representative of each group, also exposed in this figure.

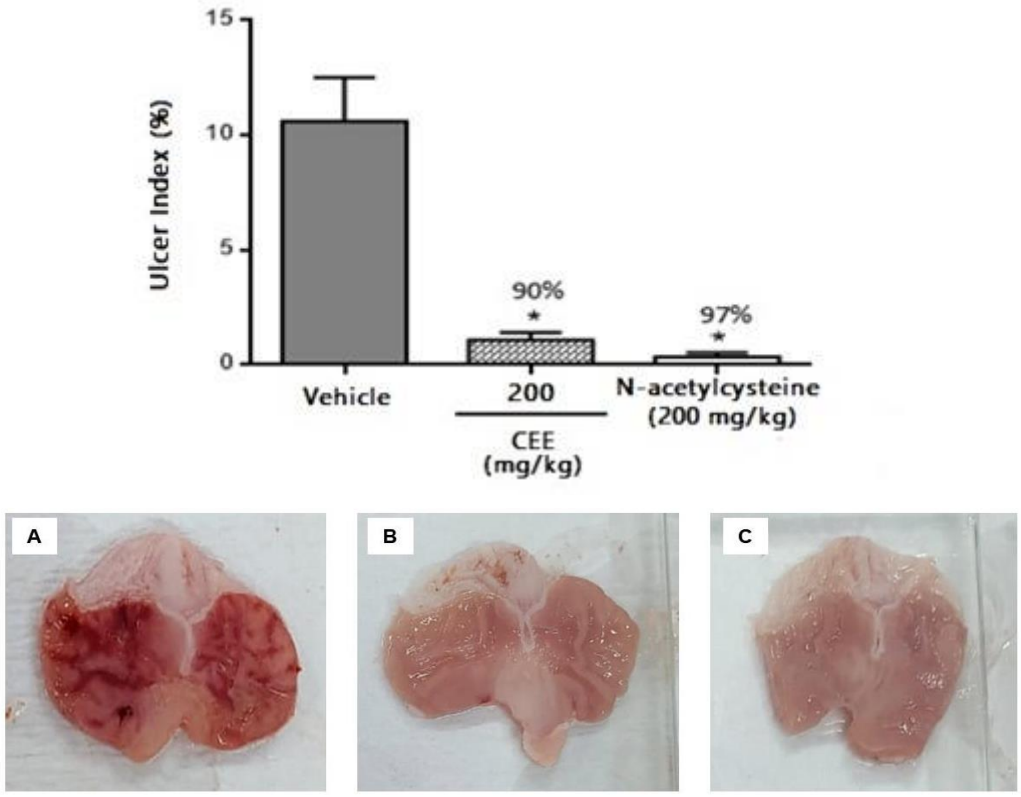

Figure No. 5
The results were expressed by ANOVA one way as the mean ± S.E.M. (n = 7-8 / group), followed by Dunnett's posttest, * $p<0.05$. The figure shows the induction of acute gastric lesions for ischemia-reperfusion and the correlation between the relative lesion area of the treated groups, in relation to the vehicle group (control group). In the images, the correlation of open stomachs representative of each group is expressed. (A) control group - vehicle; (B) CEE (B) CEE 200 mg/kg; (C) *N*-acetylcysteine 200 mg/kg. CEE: Crude ethanolic extract.

DISCUSSION

Previous studies have demonstrated antioxidant activity *in vitro*, and the presence of phenolic compounds in the bark, and flavonoids in the leaves of the species *Piptadenia viridiflora* (Costa *et al.*, 2016; Macêdo, 2017). In the study of Costa *et al*. (2016), HPLC analyses revealed flavonoids as the major components of *P. viridiflora* extracts, which showed high *in vitro* egg hatching inhibition after removal of tannins, suggesting that flavonoids were responsible for the anthelminthic effect. However, the flavonoids responsible for the biological effect were not identified in the study.

In this study, we determined the antioxidant capacity of CEE obtained from stem bark of *P. viridiflora* using the DPPH radical scavenging method. The analysis of the results of this test showed that CEE has a high antioxidant capacity, close to the AA standard and higher than the BHA standard. In addition, the minimum effective concentration to achieve half of the maximum response of antioxidant activity, was lower in the CEE, therefore, CEE was more effective as antioxidant in relation to the standards used. In the HPLC analysis, UV absorption bands characteristic of flavonoids were found.

It was not possible to identify the substances present in the extract of *P. viridiflora* through the comparison of retention time and maximum absorption spectra at the analytical standards. Therefore, no similarity to any of the evaluated analytical standards was found. These compounds are under investigation. Previous studies with *Piptadenia* species have shown the presence of the flavonoid

galetin 3,6-dimethyl ether as the main chemical constituent in *P. stipulacea* (Queiroz *et al.*, 2010; Vasconcelos *et al*., 2015).

These compounds have high sequestering capacity of reactive oxygen species (ROS), in addition to anti-inflammatory action (Biela *et al.*, 2020). ROS as well as inflammatory processes are directly involved in the emergence of gastric ulcerative lesions induced by ethanol and in the ischemia-reperfusion process (Rahman *et al.*, 2020; Omayone *et al.*, 2020).

Ethanol acts on the gastric mucosa causing injuries directly and indirectly. It works by disintegrating the protective mucus-bicarbonate barrier, due to the production of ROS and the exaggerated inflammatory process in the region (Karampour *et al.*, 2019). When oxidized, ethanol produces ROS ($O_2^{\bullet}$, $OH^{\bullet}$, H_2O_2), responsible for the lipid peroxidation of membranes, thus, ethanol acts by decreasing mucus production, blood circulation in the stomach, cell proliferation and promoting changes in permeability and depolarization of mitochondrial membranes, these processes precede cell death, and the consequent appearance of gastric ulcerations (Rahman *et al.*, 2020).

When acidified, ethanol stimulates a cascade of reactions promoted by pro-inflammatory cytokines, leukocytes and ROS, which cause and intensify tissue necrosis, leading to the appearance of lesions in layers of tissue deeper in the stomach, culminating in the appearance of gastric ulcers with perforation and bleeding (Prazeres *et al.*, 2019). From the results obtained in this study, we observed that in the ethanol acute gastric ulcer induction test, the CEE in the tested doses, promoted gastroprotection when compared to the vehicle group.

In the gastric ulcer induction test induced by acidified ethanol, the dose of 200 mg/kg of CEE promoted gastroprotection in animals. However, the dose of 100 mg/kg of CEE was not sufficient to generate this response. In both tests, carbenoxolone, a drug with cytoprotective action (Bluman *et al*., 2019), also promoted gastroprotection in animals. The justification for the results found with CEE, can be given through the possible participation of the action of the flavonoids detected in the sample, however, to validate this data, it is necessary to carry out additional studies using other methodologies, for example, gastric lesions induced by acetic acid and ibuprofen-induced gastric ulcer.

In the acute gastric ulcer induction model due to reperfusion-ischemia, the group tested with CEE and the *N*-acetylcysteine group (mucolytic substance) (Savva *et al.*, 2019) presented gastroprotection when compared to the vehicle group. The induction of ulcers by this method occurs through the ischemic process and blood reperfusion, however, it is the latter process, the main determinant for the appearance of these lesions, because when it returns, the blood brings with it free radicals derived directly from oxygen gas, culminating in oxidative stress (Ohara *et al*., 2020). Studies indicate that oxidative stress is the central mechanism of formation of gastric lesions induced by this method (Omayone *et al*., 2020). Thus, the gastroprotective effect promoted by CEE in animals, may be related to the antioxidant response found in the DPPH radical sequestration test, in addition, we can infer that flavonoids may be related to this activity, since they are compounds that present high scavenging capacity of free radicals and therefore antioxidant activity (Chen *et al*., 2019).

CONCLUSIONS

In this study we reported, for the first time, the gastroprotective effect of the species *Piptadenia viridiflora* and concluded that this species has gastroprotective and antioxidant activity. However, additional studies are needed to accurately determine the mechanisms of action and the substances involved in this response.

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