Gastroprotective Activity of *Sterculia striata* A. St. Hil. & Naudin (Malvaceae) in Rodents

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The *Sterculia striata* ethanolic extract (Ss-EtOH) inhibited gastric lesions induced by ethanol, HCl/ethanol, and ischemia/reperfusion, but not those induced by indomethacin, and did not alter the gastric secretion. Ss-EtOH restored the catalase activity and content of non-protein sulfhydryl groups in the stomach of mice treated with ethanol. The gastroprotection induced by Ss-EtOH in the ethanol-induced gastric lesion model was abolished by N^G-nitro-L-arginine methyl ester (L-NAME) pretreatment, suggesting the involvement of nitric oxide and antioxidant compounds, but not prostaglandins, in this activity. Lupeol obtained from Ss-EtOH promoted gastroprotection as well as the extract at the same dose, and it must therefore contribute to the observed effects.

Key words: Gastroprotective, Nitric Oxide Synthase, *Sterculia striata*

Introduction

Sterculia striata A. St. Hil. & Naudin (Malvaceae) (The Angiosperm Phylogeny Group, 2003) is a tree popularly known in Brazil as "chichá", "pau-rei", and "castanheiro-do-mato" and can be found in the Cerrado and Caatinga ecoregions in the Brazilian northeast (Corrêa, 1984). This species has economic importance as a medicine to treat furuncles and as an ornamental plant (Costa *et al*., 2010), as well as in human consumption (Corrêa, 1984).

Preliminary phytochemical investigations of the oil obtained from seeds of *S. striata* detected the presence of cyclopropenoid fatty acids (Chaves *et al.*, 2004), and the ethanolic extract obtained from stem barks of *S. striata* provided a mixture of sitosterol and stigmasterol (0.8%), sitosterol-3-*O*-*β*-D-glucopyranoside (0.24%), and four pentacyclic triterpenoids: lupeol (5.2%), 3-*β*-*O*-acyl-lupeol (0.04%), lupenone (0.32%), and betulinic acid (0.09%). Lupeol (Fig. 1) is the major chemical constituent obtained (Costa *et al.*, 2010). In this pioneering study, chemical structures were identified by ^{1}H and ^{13}C NMR spectral data analysis and comparison with literature data. The phenolic content, determined according to the Folin-Ciocalteu procedure, was (63.94 ± 5.59) mg of gallic acid equivalents (GAE) per gram of ethanolic extract (Costa *et al.*, 2010). Data in the literature indicate anti-inflammatory and gastroprotective activities for these chemical constituents (Navarrete *et al.*, 2002; Sánchez-Mendoza *et al.*, 2010; Lira *et al*., 2009).

Therefore, based on chemical constituents with a possible gastroprotective activity obtained from *Sterculia striata* ethanolic extract (Ss-EtOH), the aim of this study was to investigate the gastro-

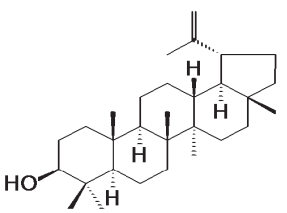

Fig. 1. Chemical structure of lupeol, the major chemical constituent of *S. striata* stem bark.

protective activity of Ss-EtOH in gastric ulcers induced by different agents in mice and rats and to evaluate mechanisms of action involved in this activity. Aiming to compare the Ss-EtOH activity with that of its major constituent, we also assessed the gastroprotective activity of lupeol in models of gastric ulcers induced by ethanol and ethanol/HCl.

Material and Methods

Plant material

The plant material was collected in November 2004 in the city of Oeiras, Piauí, Brazil. A *S. striata* specimen was submitted to taxonomic identification and a voucher specimen was deposited at the Graziella Barroso Herbarium of the Federal University of Piauí, Teresina, Brazil (TEPB 10165). Stem bark (1800 g) was dried at room temperature, pulverized, and macerated in ethanol (95%) in a stainless steel container. Successive extractions were performed, followed by evaporation of the solvent, resulting in 67 g (3.7% yield) of the ethanolic extract (Ss-EtOH).

Animals

Male or female Swiss mice (25–30 g) and Wistar rats (180–220 g) were obtained from the Sectorial Vivarium of the Medicinal Plants Research Center of the Federal University of Piauí, Teresina, Brazil. Animals were housed at (24 ± 2) °C under a 12 h light/12 h dark cycle, and they had free access to standard pellet diet and water. They were fasted over 18 h and acclimatized to the test environment for 2 h before experimentation. All experiments followed experimental protocols submitted to and approved by the Animal Research Ethics Committee of the Federal University of Piauí, Teresina, Brazil (protocol number 12/2008).

Chemicals and drugs

The following drugs and chemicals were used: absolute ethanol (Quimex, São Paulo, SP, Brazil), carbenoxolone (Sigma-Aldrich, St. Louis, MO, USA), indomethacin (Indocid 50 mg; Merck Sharp & Dohme, São Paulo, SP, Brazil), cimetidine (Glaxo Smith Kline, Rio de Janeiro, RJ, Brazil), ranitidine (Sigma-Aldrich, St. Louis, MO, USA), N^G-nitro-L-arginine methyl ester (L-NAME) (Sigma-Aldrich, St. Louis, MO, USA), L-arginine (L-ARG) (Sigma-Aldrich, St. Louis, MO, USA), EDTA (Reagen, Colombo, PR, Brazil), Tween 80 (Sigma-Aldrich, Seelze, Germany), *N*-acetylcysteine (NAC) (Sigma-Aldrich, St. Louis, MO, USA), 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB) (Sigma-Aldrich, St. Louis, MO, USA), Tris and sodium hydroxide (Cristália, São Paulo, SP, Brazil), lupeol (isolated from the Ss-EtOH).

The Ss-EtOH extract was first solubilized in 1.0% Tween 80 and then diluted in saline solution (0.9% NaCl). Other drugs were dissolved either in saline solution or distilled water. Ss-EtOH extract and drug concentrations were adjusted for treatment to yield 10 mL/kg body weight.

Acute toxicity studies

The acute toxicity was determined according to the method described by Miller and Tainter (1944) with some modifications. Mice were divided into six groups of ten animals each and fasted for 18 h with free access to water, and then treated orally with saline (control group) and Ss-EtOH (500 or 2000 mg/kg body weight), and intraperitoneally (i.p.) with saline (control group) and Ss-EtOH (500 or 1000 mg/kg body weight). Animals were evaluated 1, 2, 3, 4, 24, 48, and 72 h after administration to assess possible toxicological symptoms and number of deaths. After observation for 14 d, mice were euthanized by cervical dislocation, and liver, lungs, spleen, heart, and kidneys were removed and weighed.

Absolute ethanol-induced gastric ulcer

Swiss mice (n = 8) were fasted for 18 h with free access to water and then orally treated with vehicle (1.0% Tween 80, 10 mL/kg body weight), carbenoxolone (100 mg/kg body weight), a gastric cytoprotective agent, Ss-EtOH (6.25, 12.5, 25, and 50 mg/kg body weight), or lupeol (25 mg/kg body weight). After 1 h, gastric lesions were induced by oral administration of absolute ethanol (0.2 mL/animal, p.o.). Then, animals were euthanized by cervical dislocation 30 min after ethanol administration, their stomachs were removed, opened along the greatest curvature, and gastric lesions area was measured by planimetry, using a transparent paper. The lesion area in each animal was measured in mm^2 according to Robert *et al.* (1979). The lesion area was calculated as follows: lesion area (%) = lesion area (mm^2) · 100/total area (mm^2).

HCl/ethanol-induced gastric ulcer

Swiss mice (n = 7) were fasted for 18 h with free access to water and then orally treated with vehicle (1.0% Tween 80, 10 mL/kg body weight), carbenoxolone (100 mg/kg body weight), Ss-EtOH (6.25, 12.5, 25, and 50 mg/kg body weight), or lupeol (25 mg/kg body weight). After 1 h, gastric lesions were induced by 0.3 M HCl/60% ethanol solution (0.2 mL/animal, p.o.). Then, animals were euthanized by cervical dislocation 1 h after HCl/ethanol administration, their stomachs were removed and opened along the greatest curvature to determine the lesion area (mm^2) (Robert *et al.*, 1979; Mizui and Douteuchi, 1983).

Indomethacin-induced gastric ulcer

Wistar rats (n = 8) were fasted for 18 h with free access to water and then orally treated with vehicle (1.0% Tween 80, 10 mL/kg body weight), cimetidine (100 mg/kg body weight), a H_2 receptor antagonist, or Ss-EtOH (25 and 50 mg/kg body weight). After 1 h, gastric lesions were induced by subcutaneous administration of indomethacin (30 mg/kg, s.c.). Then, animals were euthanized by cervical dislocation 6 h after induction of gastric ulcers, their stomachs were removed, opened along the greatest curvature, rinsed with saline, and examined under a stereomicroscope (PZO-Labimex, Warsaw, Poland). The extent of gastric mucosal lesions was measured by score as described by Szabo *et al.* (1985) with some modifications. Quantity and diameter of erosions were calculated, mean scores for each group were compared with the control group, and inhibition percentage of ulceration was determined (Szabo *et al.*, 1985; Bhargava *et al.*, 1973).

Ischemia- and reperfusion-induced gastric ulcer

Wistar rats (n = 5) were fasted for 18 h with free access to water and then orally treated with vehicle (1.0% Tween 80, 10 mL/kg body weight), NAC (750 mg/kg body weight, i.p.) or Ss-EtOH (6.25, 12.5, 25, and 50 mg/kg, p.o.). After 30 min, under anesthesia by sodium thiopental (25 mg/kg body weight, i.p.), the celiac artery blood flow was interrupted by a microvascular clamp. After 30 min, the clamp was removed and reperfusion was established. Then, animals were euthanized 1 h after induction of reperfusion, their stomachs were removed, opened along the greatest curvature, and the gastric lesion area was measured by planimetry (mm^2) (Robert *et al.*, 1979; Ueda *et al.*, 1989).

Determination of gastric secretion in pylorus-ligated rats

Pylorus ligation was performed in groups of ten rats as described by Shay *et al.* (1945) and was done through a midline abdominal incision under anesthesia (sodium thiopental, 25 mg/kg body weight, i.p.). Ss-EtOH was intraduodenally administered as 25 mg/kg body weight in 5 mL/kg body weight volume. Control animals received vehicle (5 mL/kg body weight), and the standard group received ranitidine (50 mg/kg body weight), a H_2 receptor antagonist, by the same route. The abdomen was sutured, and animals were allowed to recover from anesthesia. Rats were euthanized 4 h after treatment by an overdose of sodium thiopental, the abdomen was opened, and another ligature was placed around the esophagus close to the diaphragm. Stomachs were removed, and gastric juice solution was collected. Distilled water (3 mL) was added, and the total solution was centrifuged at 4465 x g for 30 min. The volume, pH value and total acidity of gastric secretion were determined in the supernatant. The total acidity output was determined by titration to pH 7.0 with 0.1 M NaOH in a pH-meter (WTW 330i; Wissenschaftlich-Technische Werkstätten GmbH & Co. KG, Weilheim, Germany) and expressed as mEq/h gastric juice (Shay *et al.*, 1945).

Quantification of non-protein sulfhydryl (NP-SH) groups

Stomachs were first treated with vehicle without ethanol (Sham), vehicle, Ss-EtOH (25 and 50 mg/kg body weight, p.o.) or NAC (750 mg/kg body weight, i.p.). A model in which gastric lesions were induced by absolute ethanol was used to analyse the role of NP-SH groups in gastroprotection induced by Ss-EtOH. The amount of NP-SH in gastric mucosa was determined according to Sedlak and Lindsay (1968). The absorbance was measured at 412 nm within 5 min after addition of 0.05 mL of 0.01 M DTNB diluted in methanol using a white homogenate. The values were derived from a standard curve for cysteine and expressed as μg NP-SH/g tissue.

Catalase activity

Mice were pretreated with vehicle without ethanol (Sham), vehicle, Ss-EtOH (25 and 50 mg/kg body weight) or NAC (750 mg/kg body weight, i.p.). Next, they were treated with absolute ethanol (Robert *et al.*, 1979) to analyse the role of catalase (CAT) in gastroprotection induced by Ss-EtOH. CAT activity was measured for 6 min according to Beers and Sizer (1952) by following the absorbance at 240 nm, and CAT activity was defined as the amount of enzyme decomposing 1 mmol of H_2O_2 per min. The results were expressed as mmol/(min 100 mg tissue).

Role of nitric oxide on the gastroprotective effect of Ss-EtOH

The role of nitric oxide in the gastroprotective effect induced by Ss-EtOH (25 mg/kg body weight, p.o.) was evaluated as follows: mice were pretreated with vehicle, L-ARG (600 mg/kg body weight, i.p.) or Ss-EtOH alone, or with their respective combinations with L-NAME (20 mg/kg body weight, i.p.) before the induction of the gastric lesions with absolute ethanol. While Ss-EtOH was administered 1 h prior to ethanol, L-NAME and L-ARG were given 30 min before (Olinda *et al.*, 2008).

Statistical analysis

The results are expressed as mean ± standard error of the mean (S.E.M.). The statistical significance for differences between groups was calculated by analysis of variance (ANOVA) and Tukey's post test. The differences between groups were regarded as significant at $p < 0.05$. All analyses were performed using GraphPad Prism™ 5.0 (GraphPad Software, San Diego, CA, USA).

Results

Acute toxicity studies

A single administration of Ss-EtOH, 2000 mg/kg body weight by oral route or 1000 mg/kg body weight by intraperitoneal route, did not produce any immediate death or signs of acute toxicity in treated animals. During the following 14 days after administration of Ss-EtOH, all animals were euthanized. At the autopsy, no significant changes or lesions were observed in internal organs of each animal. Therefore, no toxicological effects were observed for Ss-EtOH in mice.

Effect on gastric ulcer induced by absolute ethanol

Oral administration of Ss-EtOH (12.5, 25, and 50 mg/kg body weight) decreased the area of gastric lesions in mice by 40.4%, 72.9%, and 48.9%, respectively, compared with the control group ($p < 0.05$). Carbenoxolone (100 mg/kg body weight) and lupeol (25 mg/kg body weight) also decreased the area of gastric lesions by 65.4% and 76.4%, respectively (Table I).

Effect on gastric ulcer induced by acidified ethanol

In gastric ulcers induced by HCl/ethanol, Ss-EtOH (12.5, 25, and 50 mg/kg body weight, p.o.) significantly ($p < 0.05$) protected the gastric mucosa of mice by 21.7%, 56.5%, and 40.0%, respectively, compared to the control group. Under these conditions, carbenoxolone (100 mg/kg body weight, p.o.) and lupeol (25 mg/kg body weight) also reduced the area of gastric lesions by 43.0% and 41.0%, respectively (Table I).

Effect on gastric ulcer induced by indomethacin

Ss-EtOH (25 and 50 mg/kg body weight, p.o.) did not inhibit formation of gastric ulcers induced by indomethacin, suggesting that the gastroprotective effect of Ss-EtOH does not involve prostaglandins or leukotrienes. The administration of cimetidine (100 mg/kg body weight, p.o.) was effective in reducing (99.6%) the area of gastric lesions (Table I).

Effect on gastric ulcer induced by ischemia and reperfusion

The administration of Ss-EtOH (12.5, 25, and 50 mg/kg body weight, p.o.) and *N*-acetylcysteine (750 mg/kg body weight, i.p.) reduced the area of lesions by 46.5%, 58.2%, 42.8%, and 60.5%, respectively (Table I).

Determination of gastric secretion in pylorus-ligated rats

Ss-EtOH (25 mg/kg body weight) altered neither the pH value of the gastric secretions (3.46 ± 0.55) compared with vehicle (3.40 ± 0.39), nor the volume of gastric secretion [(2.77 ± 0.230) mL] compared with the control [(2.62 ± 0.448) mL]. Likewise, total acidity was not reduced by Ss-EtOH [(0.051 ± 0.0120) mEq/h] com-

pared to the control [(0.040 ± 0.0090) mEq/h]. On the other hand, it was reduced by ranitidine [(0.0043 ± 0.0010) mEq/h] (Table II).

Quantification of non-protein sulfhydryl (NP-SH) groups

Compared with non-treated animals [Sham, (854.3 ± 88.7) μg NP-SH/g tissue], oral administration of Ss-EtOH (25 or 50 mg/kg body weight) and *N*-acetylcysteine (750 mg/kg body weight) significantly restored ($p < 0.05$) the NP-SH levels [(577.1 ± 62.6), (705.6 ± 155.0), and (587.4 ± 72.0) μg NP-SH/g tissue, respectively] that had been reduced ($p < 0.001$) in gastric lesions induced by absolute ethanol [(227.1 ± 38.8) μg NP-SH/g tissue] in mice (Fig. 2).

Determination of the catalase activity

The catalase activity in the stomach of mice was (3.06 ± 0.17) mmol/(min 100 mg tissue) (Sham) and after ethanol administration, it was significantly ($p < 0.001$) reduced to (0.94 ± 0.07) mmol/(min 100 mg tissue) (vehicle). After prior treatment with Ss-EtOH (25 and 50 mg/kg body weight) or *N*-acetylcysteine (750 mg/kg body weight), the catalase activity increased to (1.70 ± 0.15), (1.63 ± 0.09), and (1.79 ± 0.19) mmol/(min 100 mg tissue), respectively, and it was statistically significant ($p < 0.001$) compared to the control (vehicle) (Fig. 3).

Role of nitric oxide in the gastroprotective effect of Ss-EtOH

Oral administration of Ss-EtOH (25 mg/kg body weight) and L-ARG (600 mg/kg body weight) significantly decreased ($p < 0.05$) the area of gastric lesions induced by absolute ethanol to (5.58 ± 0.83) and (10.40 ± 1.50) mm², respectively, compared with the control group [(28.97 ± 1.83) mm²]. The prior administration of the nitric oxide synthase inhibitor L-NAME (20 mg/kg body weight) was able to reverse Ss-EtOH- [(35.48 ± 4.30) mm²] or L-ARG-induced gastroprotection [(34.50 ± 2.38)

Table I. Effects of *S. striata* ethanolic extract (Ss-EtOH), lupeol, carbenoxolone, *N*-acetylcysteine (NAC), and cimetidine in different gastric lesion models in rodents. Each group represents the mean ± S.E.M. for 6–10 animals. *$p < 0.05$ compared to respective control group (ANOVA one way and Tukey test).

Gastric lesion model	Treatment	Dose (mg/kg body weight)	Area of gastric lesion [mm²]	Inhibition/protection (%)
Absolute ethanol (mice)	Control (saline)	-	20.74 ± 1.14	0.0
	Ss-EtOH	6.25	18.92 ± 2.25	8.7
		12.5	12.35 ± 2.54*	40.4
		25	5.62 ± 0.83*	72.9
		50	10.59 ± 0.76*	48.9
	Lupeol	25	4.90 ± 1.06*	76.4
	Carbenoxolone	100	7.17 ± 1.40*	65.4
HCl/ethanol (mice)	Control (saline)	-	28.93 ± 1.94	0.0
	Ss-EtOH	6.25	26.25 ± 2.73	9.3
		12.5	22.64 ± 3.26*	21.7
		25	12.59 ± 2.75*	56.5
		50	17.37 ± 1.74*	40.0
	Lupeol	25	17.06 ± 2.60*	41.0
	Carbenoxolone	100	12.43 ± 1.84*	43.0
Ischemia/reperfusion (rats)	Control (saline)	-	33.23 ± 2.53	0.0
	Ss-EtOH	6.25	38.33 ± 1.91	0.0
		12.5	17.79 ± 4.93*	46.5
		25	13.88 ± 3.35*	58.2
		50	18.99 ± 3.43*	42.8
	NAC	750	13.13 ± 1.47*	60.5
Indomethacin (rats)	Control (saline)	-	35.54 ± 3.32	0.0
	Ss-EtOH	25	32.40 ± 9.68	8.8
		50	26.22 ± 5.16	26.2
	Cimetidine	100	0.14 ± 0.14*	99.6

mm²], its respective substrate. These data suggest NO synthase involvement in gastroprotection by Ss-EtOH (Fig. 4).

Discussion

Natural products have attracted great interest of the scientific community due to their potential bioactivity. Several plants are used for treatment of gastrointestinal disorders, especially gastritis, gastric ulcers, and dysenteries, as well as a food source. However, some of them have not been subjected to pharmacological or toxicological studies.

The present work is the first report on the gastroprotective activity of the ethanolic extract obtained from *Sterculia striata* stem bark (Ss-EtOH) in rodents, regarding catalase activity, concentra-

Table II. Effects of *S. striata* ethanolic extract (Ss-EtOH) and ranitidine on pH value, total acidity of gastric secretion, and gastric juice volume in pylorus-ligated rats. Each group represents the mean ± S.E.M. for 10 animals. ANOVA one way variance analysis and Tukey test show that the p value ($^*p < 0.05$) is significant compared with the control group.

Treatment	Dose (mg/kg body weight)	Gastric secretion
		pH
Control (saline)	-	3.40 ± 0.39
Ss-EtOH	25	3.46 ± 0.55
Ranitidine	50	6.74 ± 0.15*
		Total acidity [mEq/h]
Control (saline)	-	0.040 ± 0.0090
Ss-EtOH	25	0.051 ± 0.0120
Ranitidine	50	0.0043 ± 0.0010*
		Volume [mL]
Control (saline)	-	2.62 ± 0.448
Ss-EtOH	25	2.77 ± 0.230
Ranitidine	50	1.60 ± 0.188*

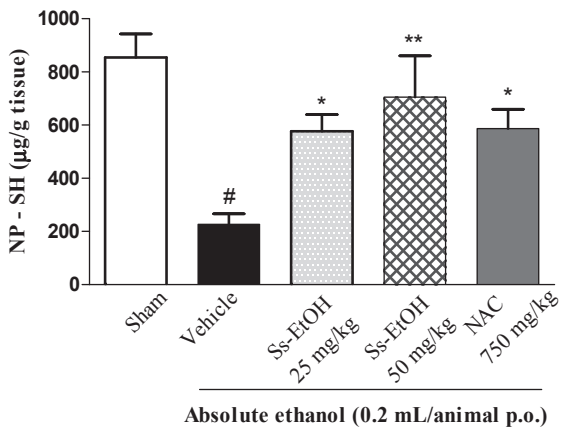

Fig. 2. Effect of Ss-EtOH (25 and 50 mg/kg body weight) and NAC (750 mg/kg body weight) on the content of NP-SH groups in the gastric wall of mice treated with absolute ethanol. The results are means ± S.E.M. of 7 animals/group. $^*p < 0.05$ compared to the control and $^{\#}p < 0.05$ compared to Sham (ANOVA and Tukey test).

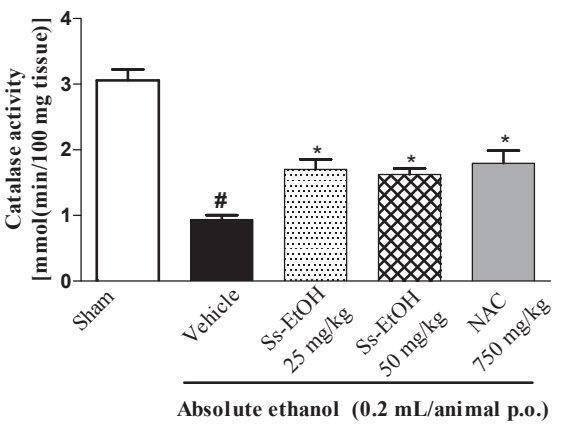

Fig. 3. Effect of Ss-EtOH (25 and 50 mg/kg body weight) and NAC (750 mg/kg body weight) on the catalase activity in the gastric wall of mice treated with absolute ethanol. The results are means ± S.E.M. of 7 animals/group. $^*p < 0.05$ compared to the control and $^{\#}p < 0.05$ compared to Sham (ANOVA and Tukey test).

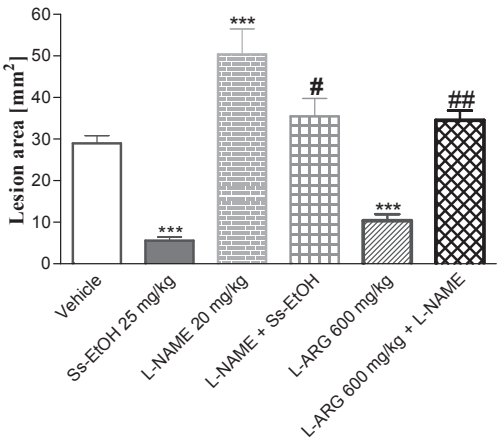

Fig. 4. Effect of pretreatment of mice with L-NAME (20 mg/kg body weight) on the gastroprotective activity of Ss-EtOH (25 mg/kg body weight) and L-ARG (600 mg/kg body weight). The results are means ± S.E.M. of 6–8 animals/group. $^{***}p < 0.001$ compared to the control, $^{\#}p < 0.05$ compared to Ss-EtOH, and $^{\#\#}p < 0.01$ compared to L-ARG (ANOVA and Tukey test).

tion of NP-SH groups, and nitric oxide involvement.

The protection of the gastric mucosa against injuries in response to ethanol and HCl/ethanol can be mediated by several mechanisms, including defensive factors of the gastric mucosa such as an increase in mucus and bicarbonate production, reduction of gastric secretion volume or neutralization of total acidity.

Ethanol induces lesions in the gastric mucosa by reducing mucus production and bicarbonate secretion (Oates and Hakkinen, 1988; Samonina *et al*., 2004) and causing disorders in the local microcirculation, leading to ischemia, increase of free radicals, decrease of prostaglandin levels and non-protein sulfhydryl (NP-SH) groups. Hemorrhage may also occur, as well as an increase in histamine release by mastocyte degranulation (Repetto and Llesuy, 2002; Siegmund, 2003; Woods *et al*., 1988). According to Mizui and Douteuchi (1983), oral administration of HCl/ethanol solution in mice produces necrotic lesions in the gastric mucosa, especially due the high fragility of the protective mucus layer and exacerbation of peptic acid secretion. Thus, ethanol induces the formation of gastric ulcers and the presence of HCl accelerates this process.

In gastric lesions induced by ischemia and reperfusion in rats, ischemia is hardly injurious to the gastric mucosa, and subsequent reperfusion of ischemic tissue causes several complications including tissue lesions associated with systemic damages, such as free radicals accumulation which attack and damage cell membranes, thereby promoting the attraction of neutrophiles and the release of inflammatory mediators (Ribeiro and Yoshidaw, 2005). Likewise, one of the most important factors underlying gastric lesions after reperfusion is the formation of reactive oxygen species by the hypoxanthin-xanthin oxidase system (Ueda *et al*., 1989).

Induction of gastric ulcers by non-steroidal anti-inflammatory drugs (indomethacin) involves inhibition of cyclooxygenases I and II, resulting in the reduction of prostaglandins production. Prostaglandins E_2 and I_2 act on mucus and bicarbonate synthesis and on regulation of acid secretion and blood flow in the gastric mucosa (Curtis *et al.*, 1995; Halter *et al.*, 2001). Indomethacin is also able to increase the leukotriene production, especially of leukotriene C4, which leads to vasoconstriction of the gastric mucosa of rats, which in turn leads to a stasis in submucosal arterioles and venules (Whittle *et al*., 1985).

In pylorus-ligated rats, Ss-EtOH was analysed and compared with the action of ranitidine (50 mg/kg body weight), a H_2 receptor antagonist. As a result of the pylorus ligation, ulcerations are formed due to gastric hypersecretion, probably stimulated by the vago-vagal reflex observed in gastric distension promoted by an increase in the gastric volume after pylorus obstruction. This procedure stimulates the secretion of gastrin, which stimulates parietal cells of the gastric tract to secrete HCl (Toda and Herman, 2005).

Organisms have enzymatic systems which scavenge reactive oxygen species and prevent their destructive actions (Kwiecien *et al*., 2002). Catalase is an endogenous antioxidant enzyme which accelerates hydrogen peroxide disproportionation into water and molecular oxygen (Ribeiro and Yoshidaw, 2005; Halliwell, 1990; Cnubben *et al*., 2001). NP-SH groups represent another antioxidant system which participates in the protection of the gastric mucosa by binding to free radicals, forming disulfide bonds between mucus constituents, and hinder their dissociation (Avila *et al*., 1996). These groups are primarily present in reduced glutathione, which alleviates oxidative stress by scavenging free radicals, reducing peroxides, and forming complexes with electrophilic compounds, thereby protecting cellular structures (Klaassen *et al*., 1985; Hayes and Mclellan, 1999; Kimura *et al*., 2001).

Nitric oxide (NO) enhances the blood flow in the gastric mucosa and stimulates mucus production, besides inhibiting neutrophile adherence to endothelial cells. NO is synthesized by nitric oxide synthase (NOS) from oxygen (O_2) and L-arginine. L-NAME inhibits NOS, thus decreasing the production of NO and consequently the gastric blood flow, leading to an increase in vascular resistance and a decrease in superoxide dismutase activity, thereby causing an increase in reactive oxygen species (Toda and Herman, 2005).

Oral administration of Ss-EtOH inhibited gastric lesions induced by ethanol, HCl/ethanol, and ischemia/reperfusion, but it was not effective in protecting the gastric mucosa of indomethacin-induced ulcers. Intraduodenal administration of Ss-EtOH did not change the pH value, volume, and total acidity of the gastric secretion in pylorus-ligated rats. Additionally, Ss-EtOH restored the catalase activity and the level of NP-

SH groups in the stomach wall of mice that were depleted by oral treatment with ethanol. Moreover, the gastroprotective activity of Ss-EtOH against oral administration of absolute ethanol was abolished in mice previously treated with L-NAME.

The present study suggests that *Sterculia striata* ethanolic extract has gastroprotective activity against gastric mucosal damage induced by ethanol, HCl/ethanol, and ischemia and reperfusion, probably acting by activation of cytoprotective mechanisms such as elevation of the levels of NP-SH groups, catalase activity, and the NOS pathway, but neither through the involvement of prostaglandins nor the inhibition of gastric acid secretion. The phytochemical investigation of stem barks from *Sterculia striata* by chromatographic methods led to the isolation of sitosterol, stigmasterol, and sitosterol-3-*O*-*β*-D-glucopyranoside, besides pentacyclic triterpenoids, lupeol, 3-*β*-*O*-acyllupeol, lupenone, and betulinic acid. Pure lupeol, the major chemical constituent of Ss-EtOH, protected against ethanol- and HCl/ethanol-induced gastric ulcers with an efficacy comparable to that of the extract (25 mg/kg body weight).

Our results demonstrate for the first time that the ethanolic extract of the stem bark of *S. striata* has gastroprotective activity in different models. Since lupeol is present in Ss-EtOH at very low concentrations and demonstrates a gastroprotective activity, it must partially contribute to the observed effects. Other well-known gastroprotective compounds, like *β*-sitosterol and sigmasterol, are also present in this extract and could also contribute to the gastroprotective effect.

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