

# Antiulcerogenic activity of the extracts of *Struthanthus marginatus*

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**Abstract:** The gastroprotective action of the aqueous extract (AE) and the hydroalcoholic extract obtained from the leaves of *Struthanthus marginatus* (Desr.) Blume, Loranthaceae, were performed with *in vivo* models in rodents using: ethanol, indomethacin or stress-induced ulcers, determination of gastric secretion and the mucus production. The scavenger activity of AE *in vitro* was tested by the DPPH method. The treatment with the extracts (125-1000 mg/kg) significantly inhibited ulcerative lesions in comparison with the negative control groups in all the models evaluated and demonstrated greater effectiveness of the aqueous extract. Regarding the model of gastric secretion, a reduction in volume of gastric juice and total acidity was observed, as well as an increase in the gastric pH. The treatment of rats raised the gastric mucus production. Significant DPPH scavenging activity was evident in the AE. No sign of toxicity was observed. These results show that *S. marginatus* possesses gastroprotective activity. There are indications that the mechanisms involved in anti-ulcer activity are related to a decrease in acid secretion and an increase in gastric mucus content. Also, there is evidence for the involvement of antioxidant activity in the gastroprotective mechanism.

## Introduction

Peptic ulcer is one of the most common gastrointestinal problems seen in clinical practice. While its pathophysiology is complex, there is a consensus among the great majority of authors that the lesion results from an imbalance between aggressive factors (gastric acid secretion, alcohol consumption, nonsteroidal antiinflammatory drugs, smoking, and *Helicobacter pylori* infection) and the defensive function of the mucosa (secretion of mucus, bicarbonate, prostaglandins, blood flow and epidermal growth factors). Emotional stress and the production of reactive oxygen species are also factors that can influence the development of lesions in the digestive mucosa (Das & Banerjee, 1993; Chan & Leung, 2002; Kwiecien et al., 2002).

*Struthanthus marginatus* (Desr.) Blume is a parasitic plant, popularly known as “erva-de-

passarinho”, together with other species of the Loranthaceae family (Correa, 1984). In the state of Maranhão, northern Brazil, it is recommended for stomach ailments. Other popular uses include disorders of respiration (bronchitis and hemoptysis) and leucorrhoea (Brandão et al., 2009).

There are only few scientific studies that refer *S. marginatus*. The species contains high levels of trace elements, including silicon, manganese, iron, copper and zinc, and such a composition may explain the use of the plant for wound healing, since the biochemical processes involved in wound healing depend on enzyme activity that relies, in turn, on the presence of trace elements (Pereira & Felcman, 1998). On the other hand, the literature does contain references to the biological activity of other species of the *Struthanthus* genus. For example, the ethanolic extract of the aerial parts of *S. orbicularis* has been shown to neutralize the effect of the venom of *Bothropus asper* in mice (Nuñez

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et al., 2004). In other work, rutin extracted from *S. subtilis* exhibited cytotoxic activity in four human tumor cell lines (HEp-2, MCF-7, MKN-45, HT-29) (Cordero et al., 2003). The antimicrobial activity of *S. vulgaris* was demonstrated with a 70% hydroalcoholic extract of dried leaves and fractions obtained from the same extract, tested against samples of Gram positive and Gram negative bacteria (Vieira et al., 2005). Meanwhile, results reported by Lorenzana-Jiménez et al. (2006) suggested a potential hypotensive effect of the methanolic extract of leaves of *S. venetus* in anesthetized rats.

Considering that peptic ulcer is a multifactorial condition, and that important determining factors include damage to the mucosa by ethanol, the use of nonsteroidal antiinflammatory agent, and the occurrence of stress, the objective of this study was to determine the antiulcerogenic potential of extracts of the leaves of *S. marginatus*.

## Material and Methods

### Plant material

Leaves of *Struthanthus marginatus* (Desr.) Blume, Loranthaceae, were collected from São Jose de Ribamar, Maranhão, Brazil, between August and October 2006. The plant was authenticated by Dra. Marie Sugiyama from Instituto de Botânica, São Paulo-SP, Brazil. A specimen of the plant was deposited in the Herbarium "Maria Eneyda P. Kauffman Fidalgo" of this institution under voucher number 397.724.

### Preparation of the extracts

The leaves of the plant were dried at room temperature (35-37 °C) and ground. The aqueous extract (AE) was prepared by infusion of the leaves 72 °C for 30 min. The infusion was filtered, concentrated under vacuum (at 55 °C) and freeze-dried (yield 26%). The hydroalcoholic extract (HAE) was prepared by maceration of the leaf powder in 70% ethanol, with replacement of the solvent every 72 h. The solvent was concentrated under vacuum (at 55 °C) providing a yield of 42.6%.

### Phytochemical screening

A phytochemical analysis of extracts for the detection of various classes, such as anthocyanins, anthocyanidins, flavones, flavonols, xanthenes, chalcones, flavanonols, leucoanthocyanidins, flavanones, catechins, tannins hydrolysable, tannins condensable, phenols, steroids, triterpenes and alkaloids was carried out according to standard procedures

(Matos, 1997).

### Detection of radical scavenging compounds by DPPH method

The AE (400 µg) was tested for its antioxidant activity (AA) starting with a thin layer chromatography (TLC) screening, using upper phase of mixture of n-buthanol: acetic acid and water (BAW) (40:10:50). After the chromatograms were sprayed with a 0.2% methanol (80%) solution of the free radical 2, 2-difenil-1-picrilhidrazil (DPPH). The DPPH reagent was detected as yellow spots on a violet background. The quantification of the antioxidant activity of the aqueous extract (AE) was accessed on the basis of radical scavenging effect of DPPH solution (0.006% w/v). Different dilutions of the extract amounting to 2.0 mL were added to 1.0 mL of DPPH solution. These solution mixtures were kept in dark for 30 min and optical density was measured at 517 nm using SP-2000 UV Spectrophotometer. All determinations were performed in duplicate (Guimarães et al., 2010).

### Animals

Wistar rats (160-220 g) and Swiss mice (20-32 g) of either sex were obtained from the Animal House of Universidade Federal do Maranhão, for use in the experiments. The animals were allowed at least three days for acclimatization to the animal room conditions (24 °C) before experiments and were maintained on a standard pellet diet and water *ad libitum*. Food was withdrawn 12-16 h before the experiment, but animals were allowed free access to water. For each group 5 or 6 animals were used. All experiments followed a protocol approved by the Committee for Ethics in Animal Experimentation of the Universidade Estadual do Maranhão, Brazil (Protocol number 879/2008) in accordance with the Federal Government legislation on animal care.

### Evaluation of acute toxicity

The acute toxicity studies were performed in male and female Swiss albino mice (n=5 per sex). A single dose of AE or HAE (5 g/kg) was administered orally (*p.o.*) to groups of animals, which were fasted for 12 h prior the administration. Animals receiving water served as control. The mice were observed for signs and symptoms associated with the extracts administration at 0, 5, 10, 20, 30, 60, 120, 240 and 480 min after and then once a day for the next fourteen days and any changes in behavior or manifestations of toxic symptoms.

#### Anti-ulcer study

Fasted rats were treated with AE or HAE (125-1000 mg/kg), the standard antiulcer drug omeprazole (20 mg/kg) or water (vehicle, 10 mL/kg, *p.o.*, n=6). Gastric lesions were induced after 1 h by 75% ethanol (0.25 mL/100 g, *p.o.*), according to Robert et al. (1979) or indomethacin (10 mg/kg, *s.c.*), according to Rao et al. (1997) or stress (cold restraint at 4 °C for 2 h), according to Tariq et al. (1987). The animals were sacrificed 1 or 6 h after treatments with ethanol or indomethacin, respectively, and immediately after the stress exposure. The stomachs were removed and the mucosa washed and examined under a stereoscope to score the number of ulcers and to determine the ulcer index (UI) according to Vela et al. (1997).

#### Acid secretory parameters study

Pyloric ligation was performed in rats under light anesthesia according to Shay et al. (1945). The AE or HAE (250-1000 mg/kg), omeprazole (20 mg/kg) or water (vehicle, 10 mL/kg), was injected intraduodenally (*i.d.*). The animals were sacrificed 4 h after, the stomach was dissected out and the gastric secretion collected (n=6). The mucosal surface of the stomach was washed with 2 mL of distilled water and the final volume and pH were measured. Total acidity was determined by titrating with 0.1 N sodium hydroxide using phenolphthalein as indicator.

#### Gastric mucus study

The method described by Corner et al. (1974) was employed, with modifications. Fasted rats were treated with AE or HAE (250-1000 mg/kg), misoprostol (100 µg/kg) or water (vehicle, 10 mL/kg, *p.o.*, n=6). The animals were sacrificed 1 h after the treatment and half of the stomachs were immediately transferred to 0.1% Alcian blue solution in 0.16 mM sucrose and 50 mM sodium acetate (pH 5.8). After 2 h the segments were rinsed twice with 250 mM sucrose solution for 15 and 45 min, and the dye complexed with the gastric mucus was extracted with 500 mM magnesium chloride solution shaken intermittently for 2 h. The extract was mixed with 5 mL of diethyl ether and centrifuged at 3600 rpm for 10 min, and the amount of Alcian blue in the aqueous phase was determined spectrophotometrically at 598 nm.

#### Intestinal motility in mice

Mice were treated with AE and HAE (500 and 1000 mg/kg), scopolamine (200 mg/kg) or vehicle (water 0.1 mL/10 g, *p.o.*, n=6), 60 min. prior to the

administration of a 5% charcoal suspension in 1% guar gum (0.1 mL/10 g body weight, *p.o.*). After 30 min, the animals were killed by cervical dislocation and their stomachs and small intestines were removed. The distance traveled by the charcoal plug from the pylorus to the cecum was measured and expressed as a percentage of the total intestinal length (Carlini et al., 2010; Rao et al., 1997).

#### Statistical analysis

Results were expressed as mean±SEM. Significant differences between the treated groups and the control were determined by ANOVA and Newman-Keuls multiple comparison test. The degree of significance was set at  $p < 0.05$ .

## Results

#### Phytochemical screening

The phytochemical screening determined the presence of alkaloids, triterpenes and catechins on HAE only. Tannins hydrolysable are on two extracts. Flavanonols and flavanones are present in higher proportions on AE. The procedures were negative for the rest of the classes.

#### Antioxidant activity of AE

The preliminary qualitative determination of antioxidant activity of AE by TLC on silica gel with BAW (40:10:50, upper phase) revealed 0.4 mmol/L of DPPH radical, suggesting the existence of substances with antioxidant activity, as evidenced by the presence of yellow spots on the purple background, resulting from reduction of the DPPH radical with retention factor  $R_f = 0.89$  to AE and 0.97 to quercetin. The AE was effective at scavenging free radicals at all concentrations tested (Table 1).

**Table 1.** Values of antioxidant activity (%AA) of the aqueous extract (AE) of *Struthanthus marginatus* and the standard (quercetin).

| Concentration<br>µg/mL | Quercetin<br>(%AA) | AE<br>(%AA) |
|------------------------|--------------------|-------------|
| 0.5                    | 82.58±1.33         | 76.58±2.03  |
| 2.0                    | 86.50±3.06         | 82.75±2.91  |
| 10.0                   | 87.64±1.79         | 86.53±4.54  |

The results are expressed as mean±SD.

#### Toxicological results

For the toxicity evaluation, a single dose (5 g/kg,

*p.o.*) of the extracts was administered to animals. During the observation period after the administration the animals were all in good condition, we did not observe any sedation or other behavioral changes and there was no significant difference between the weights of treated animals and the controls. At autopsy, no significant change or lesion was observed in the viscera of any animal.

*Effect of extracts on gastric lesions induced by ethanol or indomethacin or stress*

The pretreatment of the animals with both extracts decreased gastric lesions induced by ethanol. The extent of inhibitions for the respective doses employed (AE or HAE 125, 250 and 500 mg/kg) was 65.4, 86 and 91% or 29.5, 41.3 and 58.4%. The AE (125, 250 and 500 mg/kg) exhibited a protective effect against indomethacin-induced gastric lesions and the extent of inhibition for the respective doses employed, compared to vehicle group, was 55.4, 76.2 and 68.4%. Against indomethacin-induced ulceration the HAE protected only at higher doses (500 and 1000 mg/kg), with a decrease of 57.6 and 68.1% in gastric lesion scores, respectively. The pretreatment of the animals with AE (125, 250 and 500 mg/kg) or HAE (250, 500 and 1000 mg/kg) also decreased the gastric lesions induced by stress reducing the lesions by 36.4, 60.7 and 61% or 47.8, 54.8 and 64%, respectively. Omeprazole, the positive control included in the study also offered significant protection in every model (Table 2).

**Table 2.** Effects of aqueous extract (AE), hydroalcoholic extract (HAE) of *Struthanthus marginatus* and omeprazole (*p.o.*) on gastric lesions in rats.

| Treatment (mg/kg) | Gastric lesions |              |           |
|-------------------|-----------------|--------------|-----------|
|                   | Ethanol 75%     | Indomethacin | Stress    |
|                   | Ulcer index     |              |           |
| Vehicle           | 92.3±15.5       | 55.4±8.5     | 27.2±2.0  |
| Omeprazole 20     | *41.1±9.2       | *9.0±1.1     | *11.0±1.5 |
| AE 125            | *31.9±8.1       | *24.7±4.4    | *17.3±2.7 |
| AE 250            | *12.9±2.9       | *13.2±3.4    | *10.7±2.2 |
| AE 500            | *8.3±0.6        | *17.5±3.7    | *10.6±1.6 |
| HAE 125           | 65.1±5.7        | -            | -         |
| HAE 250           | *54.2±7.8       | 39.3±6.9     | *14.2±3.1 |
| HAE 500           | *38.4±7.0       | *23.5±3.5    | *12.3±1.8 |
| HAE 1000          | -               | *17.7±4.9    | *9.8±0.9  |

The results are expressed as mean±S.E.M, n=5-6. \**p*<0.05 versus control (ANOVA, followed by Newman-Keuls multiple comparison test).

*Effect of extracts on gastric secretion*

The effects of extracts on gastric secretion are shown in Table 3. Control rats with 4 h pylorus ligation produced 6±0.3 mL of secretion with a pH of 2.03±0.28

and a total acidity of 0.27±0.06 mEq[H<sup>+</sup>]/L/4 h. Secretion was reduced with administration of AE (1000 mg/kg) by 39%, and with HAE (250 to 1000 mg/kg) by 36.8, 44.9 and 37.6%, respectively. Treatment with AE (500 mg/kg) or HAE (1000 mg/kg) raised the pH by 2.03 and 2.09 units, respectively. Treatment with AE (1000 mg/kg) or HAE (500 mg/kg) also reduced total acidity by 70.4 and 74.1%, respectively.

**Table 3.** Effect of aqueous extract (AE), hydroalcoholic extract (HAE) of *Struthanthus marginatus* and omeprazole on gastric secretion of 4 h pylorus-ligated rats.

| Treatment (id)      | Volume (mL) | pH       | Total acidity mEq [H <sup>+</sup> ]/L/4h |
|---------------------|-------------|----------|--|
| Control             | 6.0±0.3     | 2.0±0.3  | 0.27±0.06                                |
| Omeprazole 20 mg/kg | 3.3±0.5*    | 5.7±0.3* | 0.04±0.01*                               |
| AE 250 mg/kg        | 5.0±0.6     | 3.0±0.4  | 0.18±0.04                                |
| AE 500 mg/kg        | 5.3±0.6     | 4.1±0.5* | 0.25±0.03                                |
| AE 1000 mg/kg       | 3.6±0.5*    | 3.6±0.2* | 0.08±0.01*                               |
| HAE 250 mg/kg       | 3.8±0.4*    | 3.9±0.6* | 0.14±0.03                                |
| HAE 500 mg/kg       | 3.3±0.2*    | 3.4±0.4  | 0.07±0.01*                               |
| HAE 1000 mg/kg      | 3.7±0.4*    | 4.1±0.6* | 0.16±0.04                                |

The results are expressed as mean±S.E.M, n=6. \**p*<0.05 versus control (ANOVA, followed by Newman-Keuls multiple comparison test).

*Effect of extracts on gastric mucus*

The highest dose tested of AE or HAE (1000 mg/kg) raised the gastric mucus production by 80.5 and 93.6%, respectively (control 11.2±0.6 µg of Alcian blue/g of tissue). Misoprostol, the positive control included, significantly raised the amount of gastric mucus, by 99.7% (Table 4).

**Table 4.** Effect of aqueous extract (AE), hydroalcoholic extract (HAE) of *Struthanthus marginatus* and misoprostol on mucus amount in rats.

| Treatment ( <i>p.o.</i> ) | Dose/kg | Alcian blue µg/g of tissue | Increase (%) |
|---------------------------|---------|----------------------------|--------------|
| Control                   | -       | 11.2±0.6                   | -            |
| Misoprostol               | 100 µg  | 22.3±2.6                   | 99.7%*       |
| AE                        | 250 mg  | 14.2±3.3                   | 27.4%        |
| AE                        | 500 mg  | 13.8±0.4                   | 23.8%        |
| AE                        | 1000 mg | 20.2±2.3                   | 80.5%*       |
| HAE                       | 250 mg  | 15.4±1.5                   | 38.0%        |
| HAE                       | 500 mg  | 13.1±0.8                   | 17.0%        |
| HAE                       | 1000 mg | 21.7±3.7                   | 93.6%*       |

The results are expressed as mean±S.E.M, n=6. \**p*<0.05 versus control (ANOVA, followed by Newman-Keuls multiple comparison test).

*Effect of extracts on intestinal transit in mice*

The pretreatment of mice with AE or HAE (500 and 1000 mg/kg, *p.o.*) did not alter the charcoal intestinal transit (control 56.6±2.4%). Scopolamine (200 mg/kg, *p.o.*), the positive control, reduced this parameter by 53.4%.

## Discussion

The results of this study show, in acute models of gastric ulceration induced by a necrotizing agent (ethanol), inhibition of the biosynthesis of prostaglandin (indomethacin) and maintaining the animal in a cold environment (stress), that the oral administration of extracts of the plant *Struthanthus marginatus* provides protection against gastric lesions induced by all the ulcerogenic agents employed. However, we observed a difference in relation to the effectiveness of the aqueous and hydroalcoholic extracts. In the model of ethanol-induced ulceration, when the same doses of the two extracts were used (125-500 mg/kg) there were clear differences in relation to the UI, which was 2.0 to 4.6 times higher in the animals treated with the HAE. When ulceration was induced by indomethacin the reduction in the ulcerogenic index in the rats treated with the AE (500 mg/kg) was 68%, the same as that in the animals that received the HAE (1000 mg/kg), even though the dose of the latter was twice that of the former, emphasizing the greater effectiveness of the AE in relation to the HAE. With regard to the model of stress-induced ulceration the doses employed of the EA, which reduced the ulcerogenic index by a statistically significant amount, were half of the HAE doses. Thus, the AE showed itself to be more effective compared to the HAE in all of the models studied, something which may be explained by the composition of the extracts since the phytochemical screening demonstrated greater proportions of flavononols and flavanones in the AE, despite the existence of hydrolysable tannins in equal proportions in the two extracts.

The presence of these compounds in plant extracts has suggested antiulcerogenic activity in various studies. For example, flavonoids are compounds reported to have gastroprotective activity in experimental models of gastric ulceration (Baggio et al., 2007; Gurbuz et al., 2009; Zduníc et al., 2009). Tannins, followed by flavonoids, are the main components of the methanolic extract of *Mouriri elliptica*, a plant with gastroprotective activity (Moleiro et al., 2009).

We determined the activity of the extracts against the production of gastric secretion. The extracts of *S. marginatus* reduced in vivo the volume and the acidity of gastric secretion. In our analysis of the AE we found that the assessment parameters for gastric secretion were reduced with double the dose required for a reduction in the UI (that is, 1000 mg/kg AE

reduced the volume of gastric secretion by 38% and the total acidity by 70%). Meanwhile, the three doses of the HAE (250 to 1000 mg/kg) significantly reduced the volume of gastric secretion, as well as affecting the acidity, with the pH increasing by 1.89 and 2.1 when HAE was administered at the doses of 250 mg/kg and 1000 mg/kg, respectively. Considering that acid secretion is an important aggressor in the mucosa, an increase in pH and a reduction of total acidity induced by the plant extracts may constitute part of the process of mucosal protection afforded by the extracts (Jain et al., 2007, Massignani et al., 2009).

Our experiments also showed that the extracts of *S. marginatus* (1000 mg/kg) increased the production of mucus, indicating that the protective effect of the plant itself may be related, in part, to this activity, since the production of mucus is an important factor in the defense of the gastrointestinal mucosa against ulcerogenic agents (Werther, 2000; Laine et al., 2008).

The AE of *S. marginatus* was found to be more effective antiulcerogenic agent, then we chose to examine its activity as a scavenger of free radicals. The *in vitro* test carried out by means of the reaction with DPPH showed that the AE possesses significant antioxidant activity, something which also could contribute to the protective effect of the extract on the gastric mucosa (Berenguer et al., 2006, Galati et al., 2003, Potrich et al., 2010).

This effect was not accompanied by a change in intestinal transit, thereby eliminating a possible anticholinergic or adrenergic effect.

Any toxicity for the extracts of *S. marginatus* was detected, a result which justifies further research into the antiulcerogenic activity of the plant indicated by its popular use.

Taken together these results demonstrate gastroprotective activity in the extracts of leaves of *S. marginatus*, probably brought about through a decrease in gastric secretion, stimulation of mucus production as well as the antioxidant activity of the extract. Such results justify the popular use of this plant for gastric disturbances and contribute to its pharmacological validation, thereby indicating the plant's phytotherapeutic potential. Studies are underway to identify the active compound and to further clarify its mechanism of action.

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