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Preliminary Studies on Gastric Anti-ulcerogenic Effects of *Averrhoa carambola* in Rats

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SUMMARY. In this study we investigated the anti-ulcerogenic potential of the water-alcohol extract of leaves of *Averrhoa carambola* (ACE). The acute effects of ACE administered by oral gavage on anti-ulcer activity were investigated in the following ulcer models in rats: lesions induced by acidified ethanol, indomethacin and acute stress. ACE, at doses of 800 and 1200 mg/Kg, *p.o.*, only showed significant anti-ulcer activity in the acidified-ethanol-induced ulcer model in rats. ACE tested by indomethacin and acute stress ulcerogenic models did not show this activity. The results suggest low anti-ulcer activity with different mechanisms of action for the anti-ulcerogenic activity observed for ACE.

RESUMEN. "Estudios Preliminares sobre los Efectos Gástricos Antiúlcera de *Averrhoa carambola* en Ratas". El potencial antiúlcera del extracto hidroalcohólico de las hojas de *Averrhoa carambola* (ACE) fue investigado en los modelos experimentales de úlcera: lesiones inducidas por etanol acidificado, indomethacin y estrés agudo. ACE a las dosis de 800 y 1200 mg/Kg, sólo mostró actividad antiúlcera significante en el modelo inducido por etanol-acidificado. ACE en modelos experimentales de ulcera inducidos por la indometacina y por el estrés agudo no han demonstrado effectividad. Los resultados indican que la actividad antiúlcera del extracto es baja y presenta diferentes mecanismos de acción.

INTRODUCTION

Gastric ulcers are believed to be due to an imbalance between acid and pepsin along with weakness of the mucosal barrier [1]. The gastric mucosa is continuously exposed to potential injurious agents such as acid, pepsin, bile acid, bacterial products and drugs [2].

Averrhoa carambola (L.) (Oxalidacea), known as star fruit or carambola, is believed to have originated in Sri Lanka. The plant has been cultivated in Southeast Asia and Malaysia for many centuries and has acquired a number of regional names [3]. In India, the ripe fruit is administered to stop hemorrhages and to relieve bleeding hemorrhoids. The dried fruit and the juice are said to antagonizes fevers. In Brazil, carambola is recommended as a diuretic in kidney and bladder complaints, and is believed to be beneficial in the treatment of eczema. The aim of the present investigation was to evaluate the aerial parts (leaves) of *A. carambola* for possible anti-ulcer activity.

MATERIAL AND METHODS

Plant material

Fresh aerial parts (leaves) of *Averrhoa carambola* L. (Oxalidaceae) were collected in September 2000 in the medicinal garden of the State University of Maringá (Universidade Estadual de Maringá, UEM), Paraná, Brazil. A voucher specimen (HUM nº 8101) has been deposited in the Herbarium of the Department of Biology.

Preparation of extract

The dried and powdered plant material (2.3 Kg) was macerated with ethanol/water (1:1) (7 L x 3) at room temperature for 10 h each time, with shaking. The extract was slowly evaporated to remove the organic solvent and lyophilized using a freeze-dryer to yield a dark

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brown residue (158 g). The final lyophilized product constituted about 6.8% of the original dried material. Aqueous suspensions were prepared from this lyophilized product and used in all tests. Phytochemical analysis [4,5] gave positive results for tannins and triterpenes.

Animals

All experiments were performed with male Wistar rats, 180-220 g. The animals were housed under standard laboratory conditions and maintained on a standard pellet diet and water ad libitum. The animals were deprived of food for 24 h before experimentation but allowed free access to tap water throughout. All experiments were carried out using 8-10 animals per group.

Anti-ulcer activity

The effect of the *Averrhoa carambola* extract (ACE) on gastric lesions was evaluated using three experimental lesion models: lesions induced by acidified ethanol, indomethacin and acute stress. The rats were deprived of food for 24 h, but water was allowed. Acidified-ethanol-induced ulcers were induced according to the method described by Szabo [6], by intragastric instillation of 5 mL/Kg of a solution of 60% ethanol and 40% 0.3 M HCl solution. Ulcers were also induced by indomethacin (30 mg/Kg, s.c.) according to the method described by Hayden and West [7]. The method described by Nagura [8] was used to induce stress ulcers. The ACE, cimetidine, or a solution of 0.9% NaCl was administered to different groups of animals 30 min before administration of the acidified-ethanol or indomethacin solutions. One hour after the administration of the necrotizing agents, the animals were killed by ether inhalation and each stomach was examined for gastric lesions. In the method for stress-induced ulcers, after intragastric administration of saline, cimetidine, or ACE, each animal was immobilized in a cylindrical cage and immersed vertically in water to the level of the xiphoid for 17 h at 23°-25°. After this time, the animals were put down and evaluated for gastric lesions. The stomachs were removed and opened along the smaller curvature. The ulcer index was evaluated according to severity and scored using an arbitrary scale: 1= petechial hemorrhage or minute pinpoint ulcers; 2=small ulcers; 3=more than two ulcers, with mainly large ulcers.

STATISTICAL ANALYSIS

Results are reported as means ± SEM and were analyzed statistically by analysis of variance (ANOVA) followed by the Tukey test. P values of less than 0.05 were considered significant.

RESULTS

The Table 1 summarizes the results obtained in the experimental models of ulceration in rats. Cimetidine (100 mg/Kg), the reference drug, significantly reduced the ulcerative index in all three models of gastric mucosal lesions tested. ACE was not effective against ulcers induced by indomethacin or by stress. The pretreatment with ACE showed significant, dose-dependent anti-ulcer and cytoprotective effects against gas-

Ulcer inducing agent	Treatment	Dose (mg/Kg)	Number of animals	Ulcer index
Acidified ethanol	*A. carambola*	400	9	34.89 ± 3.39
		800	11	20.73 ± 3.42*
		1200	10	8.90 ± 1.58*
	Cimetidine	100	8	20.00 ± 3.63*
	NaCl 0.9%	-	15	32.10 ± 1.99
Indomethacin	*A. carambola*	400	10	24.30 ± 3.44
		800	10	16.80 ± 2.63
		1200	10	24.80 ± 3.65
	Cimetidine	100	9	2.56 ± 0.85*
	NaCl 0.9%	-	9	18.78 ± 2.91
Stress	*A. carambola*	400	12	16.58 ± 2.33
		800	12	16.67 ± 2.03
		1200	12	14.33 ± 2.01
	Cimetidine	100	12	6.17 ± 1.30*
	NaCl 0.9%	-	12	18.17 ± 1.85

Table 1. Effects of *Averrhoa carambola* extract (aerial parts) on gastric ulcers induced by ulcerogenic drugs, necrotizing agents and stress. *Values are mean ± S.E.M.; $P<0.05$ *vs.* control (saline).

tric ulcers experimentally induced by acidified ethanol at the higher doses (800 and 1200 mg/Kg) studied. The effect was comparable to that of cimetidine.

DISCUSSION

Ulcers are caused due to an imbalance between mucosal integrity and aggressive factors. For maintenance of the mucosal integrity, different therapeutic agents, including plant extracts, are used to inhibit gastric acid secretion or to stimulate the mucosal defense mechanism by increasing the mucosal production of the surface epithelial cells, or by interfering with mediators synthesis [9] . The present study was carried out to evaluate the anti-ulcer activity of ACE against different animal models of ulcers.

According to the experimental models used in this study, indomethacin induce ulcer formation by depleting cytoprotective PGs, e.g. PGE_2 and PGI_2, in the cyclooxygenase pathway of arachidonic acid metabolism [10]. PGE_2 and PGI_2 of gastric and duodenal mucosa are responsible for mucus producting and maintaining cellular integrity of the gastric mucosa [11]. In the HCl/EtOH-induced gastric ulceration, HCl causes severe damage to gastric mucosa [12], whereas ethanol produces necrotic lesions by direct necrotizing action which in turn reduces defensive factors like the secretion of bicarbonate and production of mucus [13]. During stress, vagal over-activity leads to histamine release, which increases acid secretion [14].

In this study, ACE prevented acute, gastric mucosa injury induced by ethanol-acid method, the protective action was produced at a highest, but not a lowest dose of the extract. The mechanism underlying this action in unknown. However, as a first step, the extract should be fractioned and further studied. In contrast, the extract did not decrease the ulcerative index in indomethacin stress models, suggesting a mechanism of action independent of the prostaglandin or cyclo-oxygenase pathway and of the central mechanisms in this process.

In phytochemical studies of plants with anti-ulcer properties, activity due to the presence of triterpenes, flavonoids, and mucilage was observed [15]. As ACE contains these constituents, the partial anti-ulcer activity could be due their effects. On the other hand, the mucilage present in ACE could act directly to protect the gastric mucosa, avoiding gastric damage induced by necrotizing agents.

Further studies using more specific methods are required to elucidate the mode of action and better evaluate the therapeutic value of treatment with aerial parts (leaves) of *A. carambola*.

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