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Artigo

Pharmacological studies of ethanolic extracts of *Maytenus rigida* Mart (Celastraceae) in animal models

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RESUMO: "Estudo farmacológico do extrato etanólico de *Maytenus rigida* Mart (Celastraceae) em modelos animais". O extrato etanólico bruto (EEOH) da casca de *Maytenus rigida* Mart (Celastraceae) uma planta da medicina popular do Brasil, foi testado para a atividade antiinflamatória, antiúlcera e antidiarréica em modelos animais. Não foi observado sinal de toxicidade aguda nos animais tratados com doses elevadas do EEOH (5000 mg/kg, v.o. ou 2000 mg/kg i.p.). O extrato nas doses de 250, 500 e 750 mg/kg mostrou um significante efeito inibitório ($P < 0,01$) no edema de pata induzido por carragenina e exibiu propriedade protetora contra a ulceração induzida por etanol em ratos. Também uma atividade antidiarréica ($P < 0,01$) foi observada na diarréia induzida por óleo de rícino em camundongos. O trânsito intestinal foi reduzido significativamente ($P < 0.01$), porém o pré-tratamento não reduziu o peso do conteúdo intestinal em ratos. Os resultados dão suporte à utilização de *Maytenus rigida* na medicina popular do Brasil para o tratamento da inflamação, da úlcera e da diarréia.

Unitermos: *Maytenus rigida*, Celastraceae, antiinflamatória, antiúlcera, antidiarréica.

ABSTRACT: The crude ethanol extract (EEOH) of the bark of *Maytenus rigida* Mart (Celastraceae) a plant used in Brazil herbal traditional medicine, was tested for anti-inflammatory, antiulcer and antidiarrhoeal activities in animal models. No acute toxicological sign was observed in animals treated with the highest dose (5000 mg/kg, p.o. or 2000 mg/kg i.p.) of EEOH. The extract doses of 250, 500 or 750 mg/kg revealed a significant inhibitory effect ($P < 0,01$) in carrageenin-induced rat paw oedema and exhibited ulcer-protective properties against ethanol-induced ulceration in rats. An anti-diarrhoeal activity ($P < 0.01$) was also observed in castor-oil-induced diarrhoeal in mice. The intestinal transit was significantly ($P < 0.01$) reduced, however the pretreatment did not reduce the weight of intestinal contents. These results support the popular applications of *Maytenus rigida* for the treatment of inflammation, ulcer and diarrhoea in Brazil herbal traditional medicine.

Keywords: *Maytenus rigida*, Celastraceae, anti-inflammatory, antiulcer, anti-diarrhoeal.

INTRODUCTION

Recently, there has been a return of the use of plants for the treatment of different diseases, nevertheless, many plants have not been studied for their the claimed biological activity, and thus it is necessary to verify the activity through a pharmacological study.

Plant extracts of the Celastraceae have been used for centuries as insecticide in traditional agriculture, and also for the treatment of many stomachal complications, fever, rheumatoid arthritis and cancer. The *Maytenus* genus is the largest one of the Celastraceae family. Currently, there are about 80 species recognized and distributed all over Brazilian territory (Joffily; Vieira, 2005; Brandão et al 2006).

Many biological activities of this genus were determined experimentally as antiulcerogenic and analgesic (Gonzalez et al., 2001; Silva et al., 2005), antiulcer (Souza-Formigoni et al., 1991; Tabach; Oliveira, 2003; Ferreira et al., 2004; Jorge et al., 2004), antinociceptive, anti-inflammatory (Jorge et al., 2004), antioxidant (Vellosa et al., 2006; Melo et al., 2001) activity of *Maytenus ilicifolia*, antimicrobial (Kloucek et al., 2007) and antileishmanial (Perez-Victoria et al., 1999) activity of *Maytenus macrocarpa*, antimutagenic, antioxidant and antimicrobial of *M. krukovii* (Bruni et al., 2006), DNA Polymerase β-Lyase inhibitory activity from *Maytenus putterlickoides* (Feng et al., 2004).

Maytenus rigida Mart. (Celastraceae) popularly known as "bom-nome", "bom-homem" or "pau-de-colher" is considered a native plant in the northeast of Brazil (Andrade-Lima 1989; Rocha et al., 2004; Agra et al., 2007). In folk medicine, the decoction obtained from the bark of *Maytenus rigida* is used for the treatment

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of inflammatory diseases and gastrointestinal disorders as diarrhoea, dysentery and ulcer (Rocha et al., 2004). Despite the popular use of this species as a medicinal plant, there are no data about its pharmacological effect.

This study aimed at the investigation into the antiinflamatory, gastric antiulcer and antidiarrhoeal activities of the EtOH extract of the barks of *Maytenus rigida* in animal models.

MATERIAL AND METHODS

Animals

Male Swiss albino mice (27-35 g) and male Wistar rats (180-250 g) obtained from the Central Animal House of the Laboratório de Tecnologia Farmacêutica (LTF) of the Universidade Federal da Paraíba (UFPB) were used. The animals were fed by a certified Nuvilab CR-diet, with free access to tap water, and housed on a 12 h light/dark cycle at 60 ± 1 % humidity and a temperature of 21.5 ± 2 °C. The experimental protocols were approved by the institutional Committee for Ethics Animal Research (LTF/UFPB), protocol number 0513/05.

Plant material and ethanolic extracts preparation

Maytenus rigida Mart was collected in the city of Aroeira, Paraíba state, Brazil and identified by Dr. Maria de Fátima Agra, the botanist from the LTF/UFPB. A voucher Agra et al. 3316 (JPB) was deposited in the Herbarium Lauro Pires Xavier of the Departament of Botany of the UFPB, Brazil. The bark (3500 g) of *Maytenus rigida* Mart, was dried in oven at 50 °C for 4 days, powdered and macerated with 96% ethanol for 3 days. The solution was filtered and concentrated under reduced pressure (rotaevaporator) at 40 ºC. The yield (w/w) of the crude ethanol extract (EEOH) was 14%.

Drugs

Cimetidine (100 mg/kg v.o.), atropine (10 mg/kg v.o.), carrageenin (0.1 mL of a 1.0% subplantar suspension) obtained from Sigma Chemical Co. St. Louis, Mo, (USA), lansoprazole (30 mg/kg p.o.), Medley, Brazil, indomethacin (20 mg/kg p.o.), ethanol from Merck, Germany, loperamida (2 mg/kg v.o.),

Table 1. Effects of indomethacin and EEOH of *Maytenus rigida* on Carrageenan-induced paw oedema in rats.

Treatment	Dose mg/kg	paw volume (mL) 1 h	2 h	3 h
Saline		0.35 ± 0.08	0.65 ± 0.07	0.74 ± 0.07
Indomethacin	20	0.20 ± 0.04 ** (43 %)	0.32 ± 0.07 ** (51 %)	0.37 ± 0.07 ** (50 %)
EEOH	250	0.29 ± 0.09 (17 %)	0.46 ± 0.09 ** (29 %)	0.54 ± 0.08 ** (27 %)
	500	0.23 ± 0.05 ** (34 %)	0.35 ± 0.08 ** (46 %)	0.48 ± 0.07 ** (35 %)
	750	0.17 ± 0.06 ** (51 %)	0.32 ± 0.06 ** (51 %)	0.39 ± 0.07 ** (47 %)

The results are mean ± S.D. of mice. ANOVA $F_{(4,70)} = 72$ followed by Bonferroni's test . ** p< 0,01 compared to the saline control.
The % of inhibition vs. control are reported in brackets.

Table 2. Effects of lansoprazole and EEOH of *Maytenus rigida* on ethanol-induced gastric ulcers in rats.

Treatment	Dose (mg/kg)	UI	Inhibition (%)
Saline	-	130 ± 7.9	-
Lansoprasole	100	45 ± 7.3**	65
EEOH	125	117 ± 8.8	10
	250	63 ± 5.9**	52
	500	17 ± 2.7**	87
	750	7 ± 2.6**	95

Results (UI) are mean ± S.D. of mice. ANOVA $F_{(5,30)} = 354.57$ followed by Dunnett's test. **p<0.01 compared to the saline control.

Table 3. Effects of loperamide and EEOH of *Maytenus rigida* on castor oil-induced diarrhoea in mice.

Treatment	Dose (mg/kg)	Total number of faeces in 4 h	Number of wet faeces in 4 h	% Inhibition of diarrhoea
saline	-	25 ± 2.07	17 ± 2.07	-
loperamide	10	8 ±1.58**	5 ± 1.34**	68
EEOH	250	12 ± 2.70**	8 ± 1.58**	52
	500	8 ± 1.64**	3 ± 1.30**	68
	750	5 ± 1.22**	2 ± 0.55**	80

The results are the mean ± S.D. ANOVA $F_{(4,20)}$ = 88 for total number of faeces and $F_{(4,20)}$ = 95 for number of wet faeces followed by Dunnett's test. **p<0.01 compared to the control group.

Table 4. Effects of atropine and EEOH of *Maytenus rigida* on small intestinal transit in rats.

Treatment	Dose (mg/kg)	Peristaltic index	% Inhibition
saline	-	83 ± 6.24	-
atropine	2	53 ± 2.45**	36
EEOH	250	61 ± 4.23**	26
	500	52 ± 4.89**	37
	750	47 ± 1.20**	43

The results are the mean ± S.D. of mice. ANOVA $F_{(4,24)}$ = 63 followed by Dunnett's test. **p<0.01 compared to the control group.

Table 5. Effect of atropine and EEOH *Maytenus rigida* on intraluminal fluid accumulation in the small intestine of rats.

Treatment	Dose (mg/kg)	Weight of intestinal content (g)
saline	-	3.12 ± 0.43
atropine	2	1.95 ± 0.17**
EEOH	250	2.82 ± 0.22
	500	3.10 ± 0.21
	750	3.35 ± 0.16

The results are the mean ± S.D. of mice. ANOVA $F_{(4,24)}$ = 27 followed by Dunnett's test. **p<0.01 compared to the control group.

castor oil (0.7 mL/animals), deactivated charcoal (5% v.o.), gum acacia (5% v.o.). An ethanol extract (EEOH), from the bark of *Maytenus rigida* Mart was dissolved in 0.9% of saline (w/v).

Acute toxicity studies

Acute toxicity studies were performed in mice of either sex as described by Souza Brito (1995). For these studies, mice were divided into five groups, containing 10 animals each. The treated group received EEOH extract in doses of 650, 1250, 2500 or 5000 mg/kg (p.o.) or 250, 500, 1000 or 2000 mg/kg (i.p.) animal weight. Mice were carefully observed 0,5; 1; 2; 3; 4; 24; 48 and 72 h after the treatment to assess possible clinical or toxicological symptoms.

Carrageenin-induced paw oedema in rats

Anti-inflammtory activity was evaluated on basis of the inhibition of the carrageenin-induced hind paw oedema (Winter et al., 1962). The rats were divided into control (salina, 10 ml/kg, p.o.), positive control (indomethacin 20 mg/kg p.o.) and test groups (EtOH extract 250, 500 or 750 mg/kg p.o.) containing five mice in each group. Paw oedema was induced by the injection of 0.1 mL of 1.0% carrageenin suspension in the subplantar region of the left hindpaw. The paw

volume was determined before any treatment (basal volume) and measured at 1, 2 and 3 h after carrageenin injection with a plethysmometer (UGO Basile, Italy). The extract or indomethacin were administered 60 min before carrageenin injection.

Ethanol-induced ulcer

The experiment was performed according to Morimoto et al. (1991). After a 24 h fasting, rats (n = 6) received an oral administration of EEOH from *Maytenus rigida* Mart (125, 250, 500 or 750 mg/kg), lansoprazole (30 mg/kg) or saline (10 mL/kg). One hour after treatment, all rats received 1mL of ethanol to induce gastric ulcer. The animals were killed 1 h after treatment with the ulcerogenic agent and the stomachs removed and opened along the greater curvature. The ulcerative lesion index (U.L.I.) was calculated according to the methodology described by Szelenyi; Thiemer (1978).

Castor oil-induced diarrhea

The method, described by Awouters et al. (1978) with modification, was followed for this study. Briefly, the animals were divided into control (saline), positive control (loperamide 10 mg/kg) and test groups (EEOH 250, 500 or 750 mg/kg), containing five mice in each group. Each animal was placed in an individual cage, the floor was lined with blotting paper and changed every hour. Diarrhoea was induced by oral administration of 0.7 ml castor oil to each mouse, 30 min after the above treatments. During an observation period of 4 h, the total number of faecal output and the number of diarrhoeic faeces excreted by the animals were recorded.

Normal intestinal transit and intestinal fluid accumulation

The method, described by Rao et al. (1997), was followed in this study. The animals were left to starve for 12 h prior the experiment but were allowed free access to water. The animals were divided into control (salina, 10 mL/kg, p.o.), positive control (atropine sulphate 2 mg/kg p.o.) and test groups (EtOH extract 250, 500 or 750 mg/kg p.o.) containing five rats in each. After 60 min, standard charcoal meal (1 mL/rat of a 5% deactivated charcoal suspension in 5% gum acacia) were given to mice orally. Animals were sacrificed 30 min after administration of charcoal meal and the small intestine immediately isolated. Peristaltic index for each mouse was expressed as percentage of the distance traveled by the charcoal meal relative to the total length of the small intestine from pyloric sphincter to ileo-caecal junction of each animal. The intestinal fluid accumulation was indirectly analyzed by enteropooling assay (Rao et al., 1997). Briefly, the intestine was reweighed and the difference between full and empty intestines was calculated.

Statistical analysis

Data was analysed using the program Instat®. The results are expressed as the mean ± S.D. Statistical significance between groups was assessed by one-way analysis of variance (ANOVA) followed by Dunnett's or Bonferroni's test .with the level of significance $p < 0.05$.

RESULTS AND DISCUSSION

As part of this pharmacological study, the acute toxicity of the EEOH obtained from *Maytenus rigida* Mart in mice was first investigated. Increasing doses of EEOH were administered orally (650, 1250, 2500 or 5000 mg/kg) and intraperitoneally (250, 500, 1000 or 2000 mg/kg). In these doses, no signs and symptoms of acute toxicity were observed in all treated mice.

Inflammation is one of the most important processes involved in the defense of an organism; however, it often progresses to painful or chronically harmful diseases needing pharmacological treatment. The inflammatory response involves many effector mechanisms which produce a multiplicity of vascular and cellular reactions. (Ward, 1994).

During the progression of carrageenan-induced edema there is a release of some mediators (Winter et al., 1962; Chattapadhyay et al., 2002). The initial phase is attributed to the release of histamine and 5-HT. A second phase is mediated by kinins and finally in a third phase, the mediator is prostaglandin (Di Rosa et al., 1971; Holsapple et al., 1980).The acute phase of the inflammation is characterized by local vasodilatation and increased capillary permeability resulting in an exudation of fluid the interstitial space (Pedernera et al., 2006).

Carrageenin-induced paw oedema has been frequently used to assess the anti-oedematous effect of natural products. In this model of inflammation the EEOH at 250, 500 and 750 mg/kg inhibited the formation of edema after carrageenin injection with maximum inhibition in paw volume of 29, 46 and 51 % respectively in the second hour (Table 1) compared to the saline control, suggesting that inhibition kinins and/or prostaglandins.

Peptic ulcer is a common injury that may be induced by a variety of factors, such as ethanol, stress, smoking, nutritional deficiencies and noxious agents, including non-steroidal anti-inflammatory drugs (NSAIDs) (To et al., 2001).

Injection of absolute ethanol into the gastric lumen induced gross lesions in the glandular part of stomach (Natele et al, 2001). This gastric damage may be due to stasis in gastric blood flow, which contributes to the development of the hemorrhage and

necrotic aspects of tissue injury. This is direct a action on the gastric epithelium also causing perturbation of mast cells and release of vasoactive mediators such as histamine (Guth et al., 1984; Oates; Hakkinen, 1988). Recent studies have demonstrated that ROS and lipid peroxidation play an important role in the pathogenesis of acute gastric damages induced by ethanol (La Casa et al., 2000). Endogenous glutathione and prostaglandin (PG) levels are also lowered by ethanol while the release of histamine, influx of calcium ions, generation of free radicals and production of leukotrienes are all increased (Glavin; Szabo, 1992). It has been demonstrated that mucosal barrier does not hinder the diffusion of ethanol into gastric mucosa. Therefore, it might be assumed that the relatively lipophilic ethanol can also be taken up by the cells (Dokmeci et al., 2005).

In the model of ethanol-induced ulcers (Table 2), oral administration of the EEOH at doses 250, 500 or 750 mg/kg and lansoprazole (30 mg/kg, positive control) significantly inhibited 52, 87, 95 and 65 % of the ulcerogenic lesions from the ethanol over the gastric surface, respectively. This protection could reflect the inhibition of gastric secretion or an increase in the release of protective substances by the mucosa.

The delayed gastric emptying increases the absorption of orally administered anti-ulcer agents, thus promoting ulcer healing (Bertaccini; Scapignato, 1981). The extract decreased the propulsive movement of charcoal meal through the gastrointestinal tract (GIT) in a dose-dependent manner. This observation was significantly ($P < 0.01$) different from what was seen in the control group (Table 4). The significant delay in gastrointestinal transit caused by EEOH of *Maytenus rigida* is considered to be a beneficial property in ulcer patients.

Diarrhoea is a worldwide problem, especially among children and contributes to morbidity and mortality. It is considered to be the passage of watery bowel contents at a daily rate twice that of a person's usual rate (Raffa et al, 2006). The treatment of the diarrhoeal aims at, among other objectives, to increase resistance to flow (segmental contraction, decrease propulsion and peristalsis) and to increase mucosal absorption or to decrease secretion (Burks, 1991).

Several mechanisms have been previously proposed to induce the diarrhoeal effect of castor oil (Izzo, 1996). These include inhibition of intestinal Na^+,K^+-ATPase activity to reduce normal fluid absorption (Gaginella; Bass, 1978), activation of adenylate cyclase or mucosal cAMP mediated active secretion (Gaginella et al., 1978; Capasso et al., 1994), stimulation of prostaglandin formation (Capasso et al., 1986; Galvez et al., 1993), platelet activating factor (Capasso et al., 1992; Pinto et al., 1992; Mascolo et al., 1996) and most recently nitric oxide (NO) has been claimed to contribute to the diarrhoeal effect of castor oil (Mascolo et al., 1996), that increase the permeability of the epithelial layer to calcium ions and stimulate intestinal secretion (Mascolo et al., 1993).

The EEOH exhibited anti-diarrhoeal activity in the study, when inhibiting significantly ($P < 0.01$) both the frequency of defaecation as well as the wetness of the faecal droppings in mice. The extract (750 mg/kg) produced maximum inhibition (80 % of inhibition) of castor oil-induced diarrhoea in mice (Table 3).

The anti-diarrhoeal effect of the extracts may be related to an inhibition of muscle contractility and motility, as observed by the decrease in intestinal transit by charcoal meal and (Table 4), consequently a reduction in intestinal propulsion, but no inhibition of fluid intraluminal accumulation, where pretreatment of rats with the extract did not reduce significantly the weight of intestinal content (Table 5). Therefore, the anti-transit effect of *Maytenus rigida* may play an important role in its anti-diarrhoeal effect.

CONCLUSION

The results obtained in this study suggest that the ethanol extract of *Maytenus rigida* possesses antiinflamatory, gastric antiulcer and antidiarrhoeal activity, however other studies must be carried out to elucidate the mechanisms involved in these activities. This supports the use of the plant in traditional medicine to treat inflamatory conditions, gastric ulcer and diarrhoea.

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