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Artigo

Biological activity of *Herissantia crispa* (L.) Brizicky

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RESUMO: "Atividade biológica da *Herissantia crispa* (L.) Brizicky". O extrato metanólico bruto (EMeOH) das partes aéreas da *Herissantia crispa* (L.) Brizicky, planta rica em flavonóides e que não possui estudos farmacológicos, foi testada para avaliar sua atividade sob os parâmetros comportamentais e determinar a dose letal 50 (DL_{50}) em camundongos; atividade antimicrobiana e antiulcerogênica. O EMeOH (5000 mg/kg, v.o. ou 2000 mg/kg i.p.) não alterou os parâmetros comportamentais e não causou mortes nos animais. A amostra vegetal em estudo inibiu o crescimento bacteriano. O EMeOH (750 mg/kg) apresentou atividade anti-diarréica. O EMeOH (250, 500 e 750 mg/kg) foi capaz de inibir as lesões gástricas induzidas pelo 0,3 M HCl/etanol 60% em camundongos. Desta forma, pode-se concluir que a planta em estudo apresenta atividade antiulcerogênica, entretanto, se faz necessário avaliar tal atividade através de modelos mais específicos e estudar o mecanismo de ação pelo qual a amostra vegetal protege a mucosa gástrica.

Unitermos: *Herissantia crispa*, Malvaecae, avaliação comportamental, atividade antibacteriana, atividade antiulcerogênica.

ABSTRACT: The crude methanol extract (EMeOH) of the aerial parts of *Herissantia crispa* (L.) Brizicky, plant riches in flavonoids and without pharmacological studies, was tested to value its activity under the behaviour parameters and to determine the lethal dose (LD_{50}) in mice; antimicrobial and antiulcerogenic activities. The EMeOH (5,000 mg/kg, v.o. or 2,000 mg/kg i.p.) did not alter the behaviour parameters and there were not mice deaths. The extract inhibited the bacterial growth. The EMeOH (750 mg/kg) showed anti-diarroeal activity. The EMeOH (250, 500 and 750 mg/kg) decreased the gastric lesions induced by 0.3 M HCl/ethanol 60% in mice. In conclusion, the EMeOH presents anti-ulcerogenic activity;, however it is necessary to value the antiulcerogenic activity in more specific models and to study the action mechanism by which the vegetable sample protects the gastric mucosa.

Keywords: *Herissantia crispa*, Malvaecae, behaviour evaluation, antibacterial activity, anti-ulcerogenic activity.

INTRODUCTION

The utilization of medicinal plants to cure human diseases is a fact that is present since antique age (Calixto, 2001). The natural products, like medicinal plants, are font of the synthesis of new bioactive substances (Almeida et al., 2001; Barreto et al., 2004; Rocha et al., 2005; Amaral et al., 2006; Barbosa-Filho et al., 2006a,b, 2007, 2008; Oliveira et al., 2007; Rocha et al., 2007; Saúde-Guimarães & Faria, 2007; Quintans-Júnior et al., 2008; Sousa et al., 2008). The molecular diversity of medicinal plants represents a challenge for the chemists who intend to isolate and determine the structure of active compounds (Hamburger & Hostettmann, 1991).

The secondary metabolites of medicinal plants are compounds produced by plants with the special functions: defense against microorganisms and predators (herbivores), protection against ultra-violet ray, attractions of pollinator animals (Wink, 1990). These secondary metabolites comprise alkaloids, tannins, cumarins, lignans, ligninins, terpenoids, steroids, fatty acids, flavonoids, etc (Waterman, 1992; Pichersky & Gang, 2000; Santos, 2004).

The flavonoids are polyphenolics compounds

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with low molecular mass that is distribuitted on the form $C_6C_3C_6$ and they are found in leguminous, fruits, flowers, and leaves (Harbone & Williams, 2000). The flavonoids show several biological activities, for example, increased skin capillary resistance (Beretz & Cazenave, 1991); have anti-inflammatory action, modifying the metabolism of platelet arachidonic acid, or blocking both cyclooxygenase and lipooxigenase pathways (Landolfi et al., 1984; Corrêa et al., 2008); antiulcerogenic effect (Beil et al., 1995); antioxidant action (Trueba & Sanchez, 2001; Trueba, 2003; Zuanazzi & Montanha, 2004) and antimicrobial activity (Tsuchiya et al., 1996).

The Malvaceae family has 85 genera and 1,500 plants species (Joly, 2002). This family has cosmopolitan distribution and is predominant in the tropics (Joly, 2002; Rocha & Neves, 2000).

Species of the Malvaceae family like *Hibiscus esculentus* and *Malva neglecta* are used in popular medicine for some gastric diseases (i.e. ulcer, stomachache) and they showed antiulcerogenic effect against ulcers induced by ethanol in rats (Gürbuz et al., 2003; Gürbuz et al., 2005).

The species selected for this study was *Herissantia crispa* (L.) Brizicky (Malvaceae), that does not show popular indication, however, it was choosen according to the chemotaxonomic aspect, because it is rich in flavonoids.

Silva et al. (2005) isolated two flavonoids (kaempferol 3,7-di-*O*-α-L-rhamnoside and kaempferol -3-β-*O*-D-(6"-*E*-*p*-cumaril) glycoside) from *H. tiubae,* another plant of the genus *Herissantia*. The kaempferol 3,7-di-*O*-α-L- rhamnoside or lespedin caused vasorelaxing effect in rings of mesenteric artery of rats, pre-tensed with phenylephrine (Silva et al., 2005).

Thus, this study aimed investigate the biological activity of *H. crispa* through *in vitro* experiment, by the antibacterial activity and *in vivo* experiments, by behaviour evaluation, lethal dose determination (LD_{50}), screening anti-ulcerogenic and antidiarrhoeal activities.

MATERIAL AND METHODS

Botanical material and methanol extract preparation

Herissantia crispa was collected in the area of Pedra da Boca, municipality of Araruna in the State of Paraíba. It was identified for Dr. Maria de Fátima Agra, botanist from the LTF/UFPB (Voucher 6237 JPB) and deposited in the Herbarium Lauro Pires Xavier of the Departament of Botany - Universidade Federal da Paraíba (UFPB), Brazil.

The aerial parts (3,000 g) were dried in oven at 50 °C for 4 days, powdered and macerated with methanol for 3 days. The solution extract was filtered and concentrated under reduced pressure / rotaevaporator at 40 °C, resulting in a concentrated methanol extract weighing 50 g. The yield (w/w) of the methanol extract (MeOH).

Animals

Male Swiss mice (27-35 g) were used to do *in vivo* experiments. They were obtained from Laboratório de Tecnologia Farmacêutica (LTF) / Universidade Federal da Paraíba (UFPB). The animals were fed by a certified to Nuvilab CR-diet with free access to water. They were maintained in clear/dark cycles of 12 h at 60 ± 1% of humidity and a temperature of 21.5 ± 2 °C.The experimental protocols were approved by the Institutional Committee for Ethics Animal Research (LTF/UFPB), with register number 0112/06.

Drugs

Gentamicin (10 µg/ml), obtained from SHERING; Lansoprazole (30 mg/kg) from ACHE; Absolute ethanol from Merck, Germany. The EMeOH of *H. crispa* was dissolved with saline solution (0.9%).

Behavior evaluation and lethal dose determination (LD_{50})

Male and female Swiss mice were separated into groups according to the administration via. Doses of 2,000, 1,000, 500, 250 and 125 mg/kg were administrated to the group of intraperitoneal via; while the group of oral via were administrated the doses of 5,000, 2,500, 1,250, and 625 mg/kg. The behavior parameters were observed, like stimulatory, depressor effects and the death, during 4 hours, in the intervals of 30 minutes, 1 hour, 2 hours, 3 hours and 4 hours after the treatment to assess possible clinical or toxicological symptoms (Almeida et al., 1999).

The determination of LD_{50} was evaluated on mice as described by Souza Brito (1994). The control (saline solution 0.9%) and treated groups were observed 30, 60, 120 and 360 min after treatment.

Antibacterial activity

The antibacterial action of EMeOH was evaluated using the bacteria: *Escherichia coli* (ATCC - 11105; ATCC - 10536), *Listeria monocytogenes (*ATCC - 7664*), Yersinea entecrocolytica* (ATCC - 9610), *Shigella flexineri* (MM-412), *Shigella sonnei* (LM-07) and *Salmonella* spp (LM-08), samples stored of the Laboratório de Micologia / Departamento de Ciências Farmacêuticas (DCF)/ UFPB and Laboratório de Microbiologa / DCF / UFPB. The bacteria were grown in Agar Mueller Hinton (DIFCO Lab. Co). The antimicrobial agent used for control was chloramphenicol at 200 µg/mL.

The antibacterial action of EMeOH was performed by Broth Microdiluition Method as described in National Committee for Clinical Laboratpory Standards with 100 mL aliquots of diluted EMeOH and standards antimicrobial agents as controls (gentamicin). Bacterial suspensions were standardized with 0.5 mL Mc Farland

Table 1. Antibacterial activity of EMeOH on yeasts of enterobacteria.

Yeasts	EMeOH (µg/mL)						Cloramphenicol 200 µg/mL	Negative control
	5000	2500	1250	630	320	150		
Escherichia coli ATCC - 11105	-	-	+	+	+	+	-	+
Escherichia coli ATCC - 10536	-	-	+	+	+	+	-	+
Listeria monocytogenes ATCC - 7669	-	-	+	+	+	+	-	+
Shigella flexineri (MM-412)	-	-	+	+	+	+	-	+
Shigella sonnei (LM-07)	-	+	+	+	+	+	-	+
Salmonella spp LM-08	-	+	+	+	+	+	-	+
Yerisinea entecrocololytica (ATCC - 9610)	-	+	+	+	+	+	-	+

+ : growth of bacteria; - : inhibition of bacteria.

Table 2. Antidiarrheal activity of loperamide (2 mg/kg) and EMeOH (250, 500 and 750 mg/kg) in castor oil-induced diarrhea.

Treatment	Dose (mg/kg)	N	Number of wet faeces (mean ± S.D.)	Number of total faeces (mean ± S.D.)
Saline	-	6	4.7 ± 0.8	6.3 ± 1.0
Loperamide	2	5	1.6 ± 0.5 **	2.0 ± 1.2 **
EMOH	250	6	3.5 ± 2.3	6.2 ± 3.1
	500	5	5.0 ± 1.8	5.8 ± 0.8
	750	6	1.5 ± 0.6 **	2.7 ± 1.6 **

The results are the mean ± S.D. ANOVA: $F_{(4.23)} = 8.5$ for number of wet faeces; $F_{(4,23)} = 7.2$ for number of total faeces; $p < 0.05$. Followed Dunnett´s test: ** $p < 0.01$ compared with the control group (saline).

Table 3. Effects of lansoprazole and EMeOH of *Herissantia crispa* on 0.3 M HCl/ethanol 60% - induced gastric ulcer in mice.

Treatment	Dose (mg/kg)	N	I.L.U. (mean ± S.D.)	Inhibition (%)
Saline	-	6	267.70 ± 45.23	-
Lansoprazole	30	6	112.50 ± 29.17 **	60
EMOH	125	6	213.30 ± 63.85	20
	250	6	134.17 ± 21.10**	50
	500	6	129.83 ± 31.30 **	52
	750	6	103.70 ± 33.13 **	61

The results (I.L.U.) are the mean ± S.D. ANOVA: $F_{(5.30)} = 16.3$; $p < 0.05$. Followed Dunnett´s test: ** $p < 0.01$ compared with the control group (saline).

standard (NCCLS, 2000; Cleeland & Squires, 1991). The minimum bactericidal concentrations were determined by the emergence of a blue color (resazurin) at the wells indicating absence of growth (Mann & Markham, 1998).

Diarrhoeal induced by castor oil

The experimental was performed according by Awouters et al. (1978) with some modifications. The animals was fasted by 12 h and they were distributed in groups who received an oral administration of EMeOH from *H. crispa* at the respective doses of 250, 500, 750 mg/kg and loperamide (2 mg/kg) or saline (10 mL/kg). After one hour, these animals were treated by castor oil (0.7 mL / animal) orally. The severity of diarrheal was observed during 4 hours, and some parameters were analyzed, like total number of faeces and the number of liquid faeces.

Ethanol/HCl-induced gastric lesions

The experimental was performed according to Mizui & Doteuchi (1981). After a 24 h fasting, rats (n = 6 animals for group) received an oral administration of EMeOH from *H. crispa* at the respective doses of 125, 250, 500, 750 mg/kg and lansoprazole (30 mg/kg)

or saline (10 mL/kg). Fifty minutes after treatment, all rats received 0.2 mL of 0.3 M HCl/ethanol 60% to induce gastric ulcer. The animals were killed 1 h after treatment with the ulcerogenic agent and the stomachs removed and opened along the grater curvature. The ulcerative lesions index (U.L.I.) was calculated according to the methodology described by Szelenyi & Thiemer (1978).

Statistical analysis

The results of LD_{50} and were expressed in mean ± S.D. followed by Student´s t-test using GarphPad Instat, Version 3.00, 1997. The antiulcerogenic activity was expressed in mean ± S. D. The results were analyzed by One-way analysis of variance (ANOVA) followed by Dunnett´s test, with the level of significance $p < 0.05$. The software used was GarphPad Instat, Version 3.00, 1997.

RESULTS AND DISCUSSION

In this work, the biological activities of the EMeOH from *H. crispa* were examined. To investigate the effect of *H. crispa* EMeOH on the central nervous system (CNS), we used the behavior evaluation model in mice (Almeida et al., 1999) and to determine the lethal dose (LD_{50}) on mice, we used the method as described by Souza Brito (1995). These methods were used as an initial part of the pharmacological study of this work. The EMeOH, on the doses and intervals of time valuated, did not alter the behavior parameters and did not cause death in the animals (data not shown). These results suggest that the EMeOH did not cause changes on the central nervous system (CNS), on these conditions valued.

The acute diarrhea is defined like a disease that there is a lost of 200 g of faeces on the frequency of three or more times a day, during 14 days; the persistent diarrhea corresponds a period larger than 14 days, and if this disease lasts 30 days or more time, it is defined like chronic diarrhea (Gadewar & Fosano, 2005).

The diarrhea is a major cause of mortality in children around the world (Pickering, 2004). *Salmonella* and *Shigella* species, *Escherichia coli* (Pickering, 2004), *Listeria monocytoglues* (Ooi & Lorber, 2005), *Yersinia enterocolytica* (Abel-Haq et al., 2000) are the pathogens involved with this disease. The use of antimicrobial agents for treatment of the diarrhea is limited because of the resistance among enteric pathogens. The reason for the resistance is probably associated with the excessive or inappropriate use of antimicrobial agents (Pickering, 2004; Gadewar & Fosano, 2005). The research of the medicinal plants with antimicrobial activity is increasing, with the objective of finding a drug or phytoconstituent with antimicrobial properties and less collateral effects. The EMeOH of *H. crispa* at 5,000 and 2,500 μg/mL inhibited, respectively, the grown of 100% and 57% of yeasts tested in this work (Table 1) and this extract had activity against castor oil - induced diarrhea (Table2).

The peptic ulcer is a disease that shows formation of erosions in the mucosa, reaching the muscular layer of any part of the gastrointestinal tract (Brzozowski, 2003). The ulcer localized in the stomach is called gastric ulcer. The gastric ulcers are produced when defenses (mucous, prostaglandin, blood flow, etc.) are decreased and/or the aggressive factors (HCl, ethanol, *Helicobacter pylori*, stress etc) are increased (Bandyopadhyay et al., 2001).

The ethanol is an inductive agent of gastric lesions, what mimics the ulcer in the human, because it causes cell damage and disturbance on the blood flow (Brzozowski, 2003); it provokes arteriolar dilatation, vasoconstriction and degranulation of mast cells, resulting in hyperemia (Oates & Hakkinenn, 1988). Kvietys et al. (1990) observed the involvement of neutrophils on the inflammatory process induced by ethanol, that attack the gastric mucosa and this releases inflammatory mediators that are responsible by recruitment of neutrophils. The oxidative stress is also involved on the pathogenesis caused by ethanol, hence the generation of free radicals causes cell and tissue damages, resulting on the gastric lesions (Repetto & Llesuy, 2002).

The oral administration of HCl/ethanol solution in mice causes necrotizing lesions in gastric mucosa; it is caused by decrease of mucous layer and the increase of acid secretion (Mizui & Doutechi, 1981). This factor occurs because that agent causes oxidative stress and lipid peroxidation and DNA fragmentation, resulting in ulcerative lesions (Gonçales et al., 2001).

On the model of ethanol-induced gastric lesions, it was observed that lansoprazole (30 mg/kg) and the EMeOH (250, 500 and 750 mg/kg) significantly reduced the gastric lesions. This result indicates that the plant in study has antiulcerogenic activity. Studies carried out by Gürbüz et al. (2005) evaluated the antiulcerogenic activity of *Malva negletcta* (Malvaceae) that showed protective action against gastric lesions induced by ethanol in rats. This result agrees with the protective action observed in the present study with the EMeOH of *H. crispa*.

CONCLUSIONS

The results obtained in this study suggest that the EMeOH of *H. crispa* did not show activity on the central nervous system; and the EMeOH inhibited the grown of the bacteria and it had activity against diarrhea induced by castor oil in mice. The EMeOH had gastroprotective activity on the HCl/ethanol-induced gastric lesions. However, more specific studies must be carried out to elucidate the mechanisms involved in these activities.

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