Anti-ulcerogenic and antisecretory effects of *Celtis iguanaea* (Jacq.) Sargent hexane leaf extract

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ABSTRACT: The *Celtis iguanaea* (Jacq.) Sargent (Cannabaceae) is one of the native species of the Cerrado region of Brazil widely used in folk medicine to treat dyspepsia. The objective of the present study was to evaluate the gastroprotective effect of the *Celtis iguanaea* (Jacq.) Sargent (HE) hexane leaf extract in the lesion and gastric secretion models.Antiulcerogenic activity of the *Celtis iguanaea* (HE) hexane leaf extract was observed with the experimental models, such as indomethacin and pyloric ligation-induced gastric ulcers. In order to evaluate the antisecretory activity of this extract, isolated *Rana catesbeiana* mucosa and pyloric ligation in mice were used. The HE treatment reduced the lesion index of indomethacin and pyloric ligation-induced ulcer. This extract also reduced the gastric acid secretion and total acidity (increasing the gastric pH) in mice. The secretion of H^+ was reduced in the basal values (15.58 ± 1.99 µEq H^+/g/15 min) when isolated *Rana catesbeiana* mucosa was incubated with HE. Intraduodenal administration of HE reduced the gastric secretion produced by bethanecol or histamine. The antiulcerogenic and antisecretory efficacy of HE in this study suggest anticholinergic and antihistaminergic mechanism or interruption of intracellular events that are linked to acid secretion.

Keywords: *Celtis iguanaea,* antiulcerogenic activity, antisecretory activity, Cerrado, hexane extract.

RESUMO: Efeito anti-ulcerogênico e antisecretório do extrato hexânico das folhas de *Celtis iguanaea* (Jacq.) Sargent. *Celtis iguanaea* (Jacq.) Sargent (Cannabaceae) é uma das espécies nativas do cerrado brasileiro, sendo amplamente utilizada na medicina popular para o tratamento de dispepsia. O objetivo do presente trabalho foi avaliar o efeito gastroprotetor do extrato hexânico das folhas de *Celtis iguanaea* (Jacq.) Sargent (EH) em modelos de secreção e de lesões gástricas. A atividade antisecretória do extrato hexânico das folhas de *Celtis iguanaea* (EH) foi avaliada no modelo de mucosa isolada de *Rana catesbeiana* e pelo modelo de ligadura pilórica em camundongos. A avaliação da atividade anti-ulcerogênica do EH foi determinada no modelo de úlceras gástricas induzidas por indometacina e ligadura pilórica. Quando a mucosa de *Rana catesbeiana* isolada foi incubada com o EH, a secreção de H^+ foi reduzida em comparação com o valor basal (15,58 ± 1,99 µEq H^+/g/15 min). O tratamento com o EH reduziu o índice de lesões na úlcera induzida por indometacina e ligadura pilórica. O EH também reduziu o volume de secreção, a acidez total, e aumentou o pH gástrico. A administração intraduodenal reduziu a secreção gástrica produzida por betanecol ou histamina. A eficácia anti-ulcerogênica e antisecretória do EH neste estudo, sugere um mecanismo anticolinérgico e antihistaminérgico ou interrupção de eventos intracelulares que estão ligados à secreção ácida.

Palavras-chave: *Celtis iguanaea*, atividade anti-ulcerogênica, atividade antisecretória, cerrado, extrato hexânico.

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INTRODUCTION

For over a century, gastric ulcer disease has been a major cause of morbidity and mortality (Higham et al., 2002). Factors such as stress, nutritional deficiencies, smoking and continuous ingestion of nonsteroidal–antiinflammatory drugs (NSAIDs) had led to increase in the cases of gastric ulcer (Belaiche et al., 2002). The etiology of gastroduodenal ulcers is usually caused by disequilibrium between aggressive (hydrochloric acid and pepsin) and defensive mucosal factors (blood flow, mucus, bicarbonate secretion, and epithelial layer) (Wallace & Granger, 1996).

The treatment of peptic ulcer is generally based on the inhibition of gastric acid secretion by H_2-antagonists, proton pump inhibitors and antimuscarinic agents (Bighetti et al., 2005). However, prolonged use of these drugs may lead to series of adverse effects (La Vechia & Tavani, 2002; Raghunath et al., 2005). A search for new therapeutic antiulcer agents is therefore as an important element in maintaining of health. In recent time, gastroprotective activity of *Maytenus ilicifolia* (Schrad) Planch (Formigoni et al., 1991; Tabach & Oliveira, 2003), *Croton cajucara* Benth. (Brito et al., 1998; Almeida et al., 2003), *Quassia amara* L. (Toma et al., 2002), *Spiranthera odoratissima* (Silva, 1998) had been reported.

Celtis iguanaea (Jacq.) Sargent (Cannabaceae) is popularly known as esporão-de-galo. The genus *Celtis* has approximately 70 species and widely spread in the temperate region of Cerrado (Cronquist, 1981). This species is a thorny plant, 6-9 feet tall, with rounded crown and branches sticking vertically giving a pyramidal shape to the canopy. It has an erect and cylindrical trunk of 15-30 cm in diameter (Lorenzi & Souza, 1999). Ethnopharmacological studies showed the use of its leaves in the form of infusion for the treatment of asthma and digestive disturbs (Paula, 2009; Silva & Proença, 2008; Tene et al., 2007). Phytochemical analysis of the leaves and stem of *Celtis iguanaea* showed the presence of flavonoids, coumarins and mucilage (Paula et al., 2010). Previous results showed gastroprotective effect of the hexane fraction obtained from the partitioning of *Celtis iguanaea* ethanol leaf extract (Sousa et al., 2012).

The objective of the present study was to evaluate gastroprotective effect of hexane leaf extract of *Celtis iguanaea* (Jacq.) Sargent (HE) in the lesion and gastric secretion models.

MATERIAL AND METHODS

Animals

Male albino Swiss mice weighing 25-35 g (supplied by Central Animal Laboratory, Federal University of Goiás) and *Rana catesbeiana* of both sexes weighing between 80-120 g (provided by Fujioka Ranario) were used in all experiments. The animals were maintained under controlled conditions of temperature with a 12 h dark/light cycle and free access to water and standard food. All experiments were conducted between 8:00 a.m. to 4:00 p.m. and were performed in accordance with the Ethical Principles in Animal Research as adopted by the Brazilian Society of Laboratory Animal Science. The experimental protocols was approved by Research Ethic Council of Federal University of Goiás (Protocol number 106/08).

Plant material

The leaves of *Celtis iguanaea* (Jacq.) Sargent (Cannabaceae), as popularly known esporão-de-galo, were collected in Hidrolândia, GO, Midwest Brazil (16° 53'59,4" S - 49° 13' 29,4" W) with an altitude of 786 m., on September 2008. Samples were authenticated by Prof. Dr. José Realino de Paula, and a voucher specimen was deposited at the Herbarium of the Federal University of Goiás (40.110/UFG).

Preparation of extract

The leaves were oven dried with forced ventilation at 40°C and then crushed to a fine powder. The HE was obtained by exhaustive extraction in Soxhlet apparatus and concentrated under reduced pressure in rotary evaporator. The extraction process yielded 4.81%.

Drugs and chemicals

The following drugs were used: acetylcholine (ACh), carbamil-β-methylcholine chloride (bethanechol), atropine, histamine dihydrochloride (all from Sigma Chemical Co., St. Louis, MO, USA), indomethacin (Indocid® Merck Sharp & Dohme, Brazil), ranitidine (Cloridrato de Ranitidina® Teuto, Brazil). The chemicals used and other solutions were all of analytical grade. All drugs and reagents were prepared immediately before use.

Pharmacological assays

Quantification of H^+ secreted

Rana catesbeiana isolated gastric mucosa was incubated in Ussing chamber (Villegas 1968; Ferreira 2002), for the study of the gastric secretion. After the destruction of central nervous system

(CNS) of a *Rana catesbeiana*, the abdomen was opened longitudinally and the stomach removed and the mucosa was washed in 15 mL of Ringer solution without buffer. The mucosa was then mounted in the Ussing chamber with the luminal side filled with Ringer solution while serous side was filled with buffered ringer solution. Oxygenation was performed by oxygen bubbling. HE concentrations (10, 30, 100, 300 the 1000 µg/mL) were achieved in Ringer solution of serous side after a stabilization period of 60 minutes. The pH of the solution in contact with the luminal side was monitored by a pH adjusted to 6.5 and (initial pH) at 0. 001 N NaOH throughout the experiment.

Nonsteroidal anti-inflammatory drug (NSAID)-induced ulcer

Mice Swiss (n=8) fasted for 16 hr were randomly divided into six groups. Animals were orally treated with vehicle (2% Tween-80 10 mL/kg), ranitidine (50 mg/kg), or HE (25, 50, 100 and 200 mg/kg). One hour after treatment, all the animals received indomethacin (30 mg/kg s.c.) to induce gastric ulcer. Six hours after indomethacin treatment, the animals were sacrificed by cervical dislocation. The stomachs were removed, and opened along the minor curvature. The gastric mucosa was examined for the presence and severity of ulcerative lesions. According to Macaúbas et al. (1988), the degree of lesion score were measured with a ruler and a magnifying glass (10x amplification) and expressed as the mean rate. Parameters for the ulceration index (UI) area; color of the mucosa, loss of mucosal folds, petechial hemorrhages, edema, hemorrhage and number of ulcer.

Pyloric ligation in mice

The pyloric sphincter of mice was ligated surgically, as described by Vissher et al. (1954). HE (100 mg/kg) or vehicle (2% Tween 80 10 mL/kg) were immediately administered intraduodenally (i.d.) and the incision was closed. Four hours later the animals were killed, the stomachs were excised, opened along the smaller curvature and the UI was determined.

The luminal contents were collected, centrifuged for 30 min at 1500 rpm. The volume (mL) and the value of gastric pH were measured. Each sample was titrated against 0.01 N NaOH using the phenolphthalein reagent as an indicator, and the total acid was expressed as microequivalents of H^+ per litre per 4 h (mEq[H^+]/L/4h). This model was also used to establish the effect of HE on secretion induced bethanechol (20 mg/kg s.c.*)* and histamine (30 mg/kg s.c.).

Statistical analysis

Data were showed as mean ± standard error of mean (SEM) and analyzed statistically by one-way ANOVA followed by Student-Newman-Keuls' test as the post hoc test, or Student "t" test unpaired where necessary. Differences between experimental groups were considered statistically significant when $P \leq 0.05$ (Sokal & Rohlf, 1981).

RESULTS AND DISCUSSION

Herbal extracts have been and remain important sources of biologically active compounds. These extracts are crucial to drug development (Nodari & Guera, 2001). In the present study, we evaluated anti-ulcerogenic and antisecretory effects of HE. Recent studies showed that the hexane fraction of the ethanol leaf extract of *Celtis iguanaea* is an effective anti-ulcerogenic and antisecretory agent (Sousa et al., 2012). The chemical study

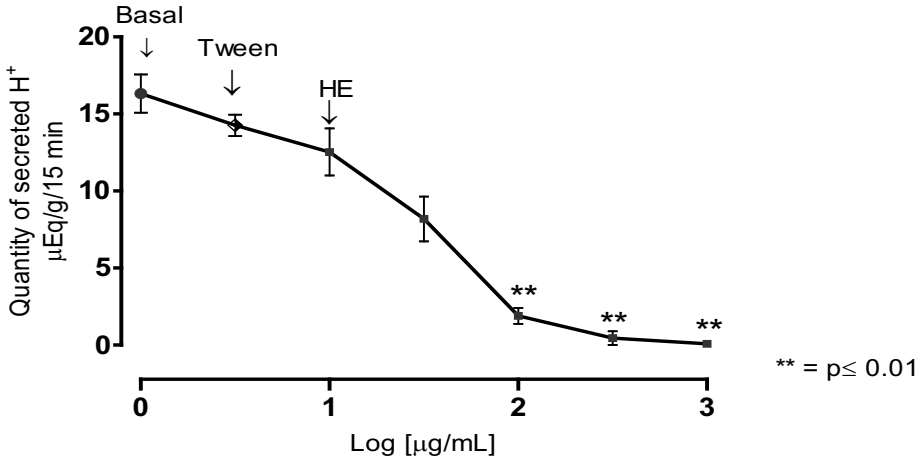

FIGURE 1. Determination of H^+ (µEq/g/15 min.) in the presence of *Rana catesbeiana* stomach mucosa incubated with HE in Ussing chamber. The values are represented with mean ± SEM. ** $P \leq 0.01$ compared to control Tween.

realized by Trevisan et al. (2012) of the hexane fraction allowed the isolation and identification of pentacyclic triterpenes series friedelano, friedelin and epifriedelinol when it was previously isolated from the bark of *Celtis sinensis* the epifriedelinol (Kim et al., 2005). To verify the hypothesis of an activity involving mechanisms of acid secretion, the HE was evaluated in an experimental model of an isolated *Rana catesbeiana* gastric mucosa. It is known that increased secretion of acid may be regarded as an important factor in the formation of ulcer while the reduced secretion of gastric acid would result in decreased ulcerative lesion. We observed that the concentrations of HE (100, 300 or 1000 µg/mL) decreased significantly the basal gastric acid secretion (*P*≤0,01) (Figure 1).

The anti-ulcer activity of HE was studied using *in vivo* acute gastric lesions induced experimentally by indomethacin (Djahanguiri, 1969) or by ligation of the pylorus (Vissher et al., 1954).

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin causes gastroduodenal ulceration by suppression of prostaglandin synthesis (Wallace, 2001). Prostaglandins E_2 and I_2 are known for their ability to inhibit gastric acid secretion and stimulate the secretion of mucus and bicarbonate besides the maintenance of mucosal blood flow. The oral treatment of HE showed a reduction UI proportional to the dose of 50 mg/kg when compared with the control group (Table 1). The ranitidine 50 mg/kg (positive control) decreased the UI by 55.5%. These results suggest possible involvement of prostaglandins and/or mucus in the anti-ulcerative effect of the extract (Table 1). As we did not observe a perfect dose-effect relationship within the range of 50 to 200 mg/kg, we assumed that the doses being tested produce the maximum effect of HE at this range, hence, we opted for 100 mg/kg p.o. that showed similar results with ranitidine to further our study.

In continuation with the study of anti-ulcerogenic activity, we used the pyloric ligation model. Among the various mechanisms involved in the pathogenesis of peptic ulcer induced by pyloric ligation, secretion and accumulation of gastric acid are possibly the most relevant factors (Muthuraman & Soo, 2010). In this model, the HE reduced the UI by 37. 4 %, when compared with the control group (Table 1).

Since the HE showed antisecretory activity in gastric secretion model, we proceeded with the evaluation of possible mechanisms involved. In the model of gastric acid secretion induced by pyloric ligation, treatment with HE (100 mg/kg) reduced the volume of gastric juice and the total acidity while increased pH significantly (p<0,001) when compared to the control group (Table 2).

Acetylcholine released by the postganglionic cholinergic neurons binds to M_3 muscarinic subtype located in the parietal cells, thereby leading to gastric acid secretion (Aihara et al.,2005). The M_3 receptor when stimulated activates phospholipase C by Gq protein that induces generation of IP_3 and diacylglycerol, followed by an increase in intracelular [Ca^{2+}] (Caulfield & Birdsall, 1998). Bethanecol is a selective agonist of muscarinic receptor that increases gastric acid secretion (Schubert, 2000). The pretreatment with HE (100 mg/kg i.d.) or atropine (50 mg/kg i.d.) reduced significantly the volume (mL), total acid secretion and raise the pH in mice after administration of bethanecol (20 mg/kg s.c.) (*P*≤0,001) (Table3).

Histamine stimulates gastric acid secretion

TABLE 1. Effect of HE on indomethacin-induced gastric ulcers or pyloric ligation in mice.

Models	Treatments	Route	Dose (mg/kg)	N	Ulceration index	Reduction %
Indomethacin	*Control*	p.o.	-	8	13.50 ± 0.76	-
	HE		25	8	9.44 ± 1.04 *	30.0
	HE		50	8	8.11 ± 1.00***	39.9
	HE		100	8	6.62 ± 0.32***	50.9
	HE		200	8	6.57 ± 0.48***	51.3
	Ranitidine		50	8	6.00 ± 0.52***	55.5
Pyloric ligation	*Control*	i.d.	-	7	6.77 ± 0.61	-
	HE		100	7	4.42 ± 0.20***	37.4

The values represent the mean ± SEM of the ulceration index (UI) of each group. * $P \leq 0.05$ and *** $P \leq 0.001$ compared with the vehicle treated group. N = number of animals in each group.

TABLE 2. Effects of HE intraduodenally administered on gastric secretion in mice.

Treatments (i.d)	Dose (mg/kg)	N	Volume (mL)	pH	Total acid (mEq[H^+] /L/4h)
Control	-	7	2.55 ± 0.05	2.95	7.5 ± 0.09
HE	100	7	2.15± 0.02***	3.69*	3.10 ± 0.03***

The values represent the mean ± SEM. 7 animals were used in each group. * $P \leq 0.05$ and *** $P \leq 0.001$ compared with the vehicle treated group.

TABLE 3. Effects of intraduodenally administration of the HE, atropine or ranitidine in the pyloric ligation model in mice.

Pre-treatments (i.d.)	Treatments (s.c.) 60 min.	N	Volume (mL)	pH	Total acid (mEq[H^+] /L/4h)
Vehicle 10 mL/kg	Saline 10 mL/kg	9	2,56 ± 0.55	3.27 ± 0.29	5.9 ± 0.92
Vehicle 10 mL/kg	Bethanechol 20 mg/kg	9	2.80 ± 0.07*	2.88 ± 0.15*	10.5 ± 1.00***
HE 100 mg/kg	Bethanechol 20 mg/kg	9 9	2.16 ± 0.05##	5.47 ± 0.36##	2,4 ± 0.86###
Atropine 10 mg/kg	Bethanechol 20 mg/kg		2.20 ± 0.01###	4.80 ± 0.24#	2.0 ± 0.24###
Vehicle 10 mL/kg	Saline 10 mL/kg	9	2.38 ± 0.06	3.68 ± 0.24	4.4 ± 0.42
Vehicle 10 mL/kg	Histamine 30 mg/kg	9 99	2.58 ± 0.06*	2.80 ± 0.05*	16.7 ± 1.90***
HE 100 mg/kg	Histamine 30 mg/kg		2.16 ± 0.05###	3.99 ± 0.24##	7.0 ± 1.20###
Ranitidine 50 mg/kg	Histamine 30 mg/kg		2.20 ± 0.04###	3.42 ± 0.17#	5.5 ± 0.67###

The values represent the mean ± SEM. 9 animals were used in each group. * $P \leq 0.05$ and *** $P \leq 0.001$ compared with the vehicle treated group and # $P \leq 0.05$ ## $P \leq 0.01$ and ### $P \leq 0.001$ compared with the secretagogue.

by binding directly to H_2 receptors on parietal cell. When stimulated adenylate cyclase increases the cAMP, which in turn activates protein kinase A. The activation of this pathway stimulates the proton pump in the parietal cell, and results in acid secretion (Jain et al., 2007). In the same way, the pretreatment with HE (100 mg/kg i.d.) or ranitidine (50 mg/kg i.d.) reduced the volume (mL), total acid and raise the pH in mice after administration of histamine (30 mg/kg s.c.) (Table 3).

The ligation of the pyloric end of the stomach causes accumulation of gastric acid, that could result in peptic ulcers. The drugs capable of reducing the gastric acid secretion are effective in reducing ulcers in this model. The inhibition of secretion stimulated by histamine or bethanechol, may suggest the blockade or inhibition of a common target of the cascade of events that leads to gastric acid secretion.

CONCLUSION

In conclusion, our results suggest that the efficacy of hexane leaf extract of *Celtis iguanaea* in preventing ulcers is based on its anti-ulcerogenic and an antisecretory effect. The blockade of bethanecol and histamine by HE suggested an anticholinergic and antihistaminergic mechanism or an interruption of intracelular events that are linked to acid secretion.

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