Antiulcerogenic Activity of Four Extracts Obtained from the Bark Wood of *Quassia amara* L. (Simaroubaceae)

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Quassia amara L., a neotropical forest shrub of the Simaroubaceae family, is widely used in Caribbean folk medicine and in some northern states of Brazil for the treatment of gastric ulcers. This plant is a source of numerous compounds including both β-carbonile and cantin-6 alkaloids as well as, primarily, the bitter compounds known as quassinoids. We analyzed the possible antiulcerogenic activities of four extracts of different polarities: 70% ethanol (70% EtOH), 100% EtOH, 100% dichloromethane (DCM), and 100% hexane (HEX) obtained from *Quassia amara* bark. All extracts, administered at doses of 5000 mg/kg orally and 1000 mg/kg intraperitoneally, caused neither toxicity or death. In the indomethacin/bethanechol-induced gastric ulcer, 70% EtOH, 100% EtOH, DCM and HEX extracts, 100 mg/kg, *p.o.*, inhibited the gastric ulcer (22.5, 23.4, 50.5, 46.8%, respectively). 70% EtOH, 100% EtOH, DCM, and HEX extracts reduced the gastric injury induced by the hypothermic restraint–stress test in mice (70.7, 80, 60, 82.7%, respectively). In the pylorus ligature of the mouse stomach, following pre-treatment with a single intraduodenal administration of 100 mg/kg of each extract, only 70% EtOH did not change the biochemical parameters of gastric juice. 100% EtOH, DCM and HEX extracts presented decreased gastric juice content, increased pH values and decreased acid output. We also determined the antiulcerogenic activity on HCl–EtOH-induced gastric ulcers in mice at four doses (25, 50, 75, 100 mg/kg, *p.o.*), then evaluated the possible dose-dependent relation and calculated the ED_{50} values. Except for 70% EtOH at a dose of 25 mg/kg, the other extracts showed significantly activity ($p < 0.05$). The free mucous amount in the gastric stomach content was also evaluated. All extracts showed significant increases ($p < 0.05$) of free mucous. This effect was abolished when the animals were pre-treated with indomethacin. Prostaglandin synthesis was evaluated by the administration of HEX extracts by the oral route (100 mg/kg). Prostaglandin synthesis was significantly, increased by 52.3% ($p < 0.05$), and this effect was abolished with prior administration of indomethacin. We concluded that *Quassia amara* is a probable source for a new drug to treat gastric ulcers, and the mechanism of its activity relates to cytoprotective factors, such as mucous and prostaglandins, but there is still the possibility that antisecretory activity is involved in its antiulcerogenic effect.

Key words   *Quassia amara*; phytochemical analysis; antiulcerogenic activity

Gastric ulcers are among the most important diseases in the world. The gastric mucosa is continuously exposed to potentially injurious agents such as acid, pepsin, bile acids, food ingredients, bacterial products, and drugs.[1] These agents have been implicated in the pathogeneses of gastric ulcer, such as an increase in gastric acid and pepsin secretion, a decrease in gastric blood flow, the suppression of endogenous generation of prostaglandins, inhibition of mucosal growth and cell proliferation, and alteration of gastric mobility.[2]

The current therapy for this disease continues to have, as one of its major goals, the control of *Helicobacter pylori* as well as H^+/K^+-ATPase, acid secretion and a subsequent reversal of mucosal damage and inflammation.[3]

Many pharmaceutical products have been employed for the treatment of gastroduodenal ulcer and peptic disease, and for decreasing mortality and morbidity rates, but they are not completely effective and produce many adverse effects. Moreover, these pharmaceutical products are too expensive.[4] Plant extracts are some of the most attractive sources of new drugs and have been shown to produce promising results for the treatment of gastric ulcer.[5]

Simaroubaceae is a large botanical family with pantropical distribution; only a few representatives occur in temperate regions. *Quassia amara* L., a representative of this family, is a

neotropical forest shrub or small tree reputed in traditional medicine to have good effect on stomach diseases, especially gastric ulcers. In Brazil, this species is found in a region from the border with Guiana to the state of Maranhão. It is popularly known in Latin American as "Amargo", "Hombre Grande", "Simaruba", "Pau Quassia", "Murubá", "Murupá" and "Quina de Caiena".[6]

This plant is a source of several compounds which include both β-carbonile and cantin-6 alkaloids, as well as, primarily, the bitter components known as quassinoids, a group of substances belonging to the terpens class. Antimalarial, antifeedant and antifertility pharmacological activities are atributted to these quassinoids.[7]

In considering the use of this plant in Brazilian folk medicine and the several chemical substances isolated and identified from *Quassia amara* bark, we have performed a study of the antiulcerogenic effects for four different extracts of this species using standard rodent models of induced gastric ulcer.

MATERIALS AND METHODS

Drugs and Chemicals   Bethanechol, hydrochloric acid (HCl), cimetidine, diazald, ethanol, hexane, indomethacin, lansoprazole, methanol and dichloromethane (Sigma Chemi-

cal Co., St. Louis, MO, U.S.A.) were used in this study. Indomethacin was prepared in sodium bicarbonate (5%), and extracts were dissolved in 12% Tween 80®. All substances were prepared immediately before use. The reagents used were of analytical grade.

Animals All experiments were performed on male Swiss mice (30 ± 5 g) obtained from the Animal House (CEMIB-UNICAMP) in Campinas, SP. The animals were fed a certified Nuvilab CR-a® (Nuvital) diet with free access to tap water, and were housed in a 12 h light/dark cycle at a humidity of 50% and a temperature of 24 ± 1 °C. All experiments were done in the morning. The experimental protocols were approved by the Animal Use and Care Committee of Unicamp. All of the experiments were conducted in accordance with the recommendations of the Canadian Council on Animal Care.[8]

Extract Preparation The bark of *Quassia amara* L. was collected and identified by botanists from the Enda Caribe Institute, Santo Domingo, Dominican Republic (Exsicata 2114, RD, 84374). The dried bark (5 kg) was powdered in a mill and extracted by maceration for one week with the following organic solvents of increasing polarity: HEX, DCM, 100% EtOH and 70% EtOH. After each extraction, the solutions were filtered through filter paper and the solvents were evaporated in a rotavapor at reduced pressure in order to separate the raw extract from the solvent. Extractions afforded 8.0 g of HEX, 19.5 g of DCM, 52.5 g of 100% EtOH and 93.5 g of 70% EtOH extracts.

Phytochemical Analysis The *Quassia amara* extracts were analyzed using thin-layer chromatography (TLC) plates (0.1 mm thick, silica gel G Merck, Art. 7731) eluted with toluene–acetone–acetic acid (70 : 30 : 0.5, v/v/v) or *n*-butanol acetic-acid water (BAW, 65 : 15 : 25, v/v/v), according to their polarities. The spots were identified under short-wave UV light and plates were sprayed further with iodoplatinate and anisaldehyde–sulfuric-acid reagents or developed with a re-sublimated iodine vapor.

These extracts were also analyzed by HPLC-ES-MS. Twenty milligrams of each extract were dissolved with methanol and filtered through a 0.45 μm Millex filter. Twenty microliters of each extract were injected into the HPLC-ES-MS system (RP18, Phenomenex, $25 \, \text{cm} \times 4.6 \, \text{mm} \times 5 \, \mu\text{m}$, 1 ml/min, ES positive mode+70V).

Pharmacological Assays. Nonsteroidal Antiinflammatory Drug (NSAID)-Induced Gastric Ulcers in Cholinomimetic-Treated Mice The experiment was performed by the method of Rainsford, 1978.[9] In this model, gastric ulcer was induced using indomethacin (30 mg/kg, s.c.) and bethanechol (5 mg/kg, i.p.), administered to mice after a 24 h fast. The extracts 70% EtOH, 100% EtOH, DCM and HEX from *Quassia amara* (100 mg/kg), cimetidine (100 mg/kg) or Tween were administered orally 30 min before the induction of gastric ulcer. The animals were killed by cervical dislocation 4 h after treatment with the ulcerogenic agents; the stomachs were removed and inflated with 4% formalin in buffered saline, and the gastric damage was determined by the methodology of Szelenyi and Thiemer, 1978.[10]

Hypothermic Restraint-Stress Ulcer The experiment was performed by the method of Levine (1971),[11] with some modifications. After 24 h of starvation, the animals received an oral administration of 70% EtOH, 100% EtOH, DCM and HEX extracts from *Quassia amara* (100 mg/kg), cimetidine (100 mg/kg) or Tween (10 ml/kg). One hour after treatment, mice were immobilized in a restraint cage at 4 °C for 3 h to induce gastric ulcer. The animals were killed and the stomachs removed and opened along the greater curvature to determine the lesion index.

Determination of Gastric Secretion The assay was performed by the method of Shay (1945)[12] with a few modifications. All groups of mice were fasted for 24 h, with free access to water. Immediately after pylorus ligature, 70% EtOH, 100% EtOH, DCM and HEX extracts from *Quassia amara* (100 mg/kg), cimetidine (100 mg/kg) as positive control, or the vehicle, Tween, were administered intraduodenally. The animals were killed 4 h later by cervical dislocation; the abdomen was opened and another ligature was placed around the esophagus, close to the diaphragm. The stomachs were removed and the gastric content collected to determine the total amount of gastric-juice acid (ml) and pH values. Distilled water (5 ml) was added, and the resultant solution was centrifuged at 3000 rpm for 10 min. Total acid in the gastric secretion was determined in the supernatant volume by titration to pH 7.0 with 0.01 N NaOH.

HCl/Ethanol-Induced Ulcer The antiulcerogenic activity of the four extracts obtained from *Quassia amara* in this model was assessed in mice, as described by Mizui and Doteuchi (1983).[13] Mice were divided into 6 groups which were fasted for 24 h prior to oral dosing with the vehicle, 12% Tween 80® (10 ml/kg), lansoprazole (30 mg/kg), 70% EtOH, 100% EtOH, DCM or HEX (25, 50, 75 and 100 mg/kg). Fifty minutes after the treatments, all animals received orally 0.2 ml of a 0.3 M HCl/60% EtOH solution. Animals were killed 1 h after the administration of HCl/EtOH solution; the stomachs were excised, inflated by an injection of saline (2 ml) and opened along the greater curvature. Then the stomachs were fixed in 5% formalin for 30 min and the ulcerative lesion index (ULI) was calculated. The ED_{50} values were also calculated by linear regression.

Determination of Mucous in Gastric Content This assay was performed according to the methodology described previously by Sun *et al.*,[14] with some modifications. Mice were fasted for 24 h, under anesthesia, the abdomen incised and the pylorus ligated. The 70% EtOH, 100% EtOH, DCM and HEX extracts (100 mg/kg body weight (kg)) of *Quassia amara* or vehicle were administered intraduodenally after the pylorus ligature. The animals were killed by cervical dislocation 4 h after the drug treatments. The stomach content was immersed in 10 ml 0.02% alcian blue in 0.16 M sucrose/0.05 M sodium acetate, pH 5.8, and incubated for 24 h at 20 °C. The alcian blue binding extract was centrifuged at 3000 rpm for 10 min. The absorbance of the supernatant was measured at 615 nm using a light spectrophotometer U/2000 (Hitachi, Japan). The free mucous in the gastric content was calculated from the amount of alcian blue binding (mg/wet tissue (g)).

Determination of Prostaglandin Synthesis The assay was performed by the method of Curtis *et al.*[15] Thirty minutes after treatment with the vehicle, vehicle plus indomethacin (20 mg/kg, s.c.), HEX (100 mg/kg, *p.o.*) or HEX plus indomethacin, the rats were killed by cervical dislocation and the abdomen opened. The Sham group without treatment experienced the general conditions of the experi-

Table 1. Effects of *Quassia amara* Extracts and Cimetidine on Indomethacin/Bethanecol and Hypothermic Restraint Stress Induced Gastric Ulcer in Mice

Gastric lesion models	Treatments (*p.o.*)	Dose (mg/kg)	*n*	Ulcerative index (mm)	Inhibition (%)
Indomethacin/Bethanechol	Control	—	8	11.1±2.6	—
	Cimetidine	100	8	4.8±2.1***	56.8
	70% EtOH	100	8	8.6±2.3*	22.5
	100% EtOH	100	8	8.5±1.5*	23.4
	DCM	100	8	5.5±1.6***	50.5
	HEX	100	6	5.9±1.7***	46.8
Stress	Control	—	6	7.5±1.2	—
	Cimetidine	100	6	3.3±1.6***	57.3
	70% EtOH	100	6	2.2±0.8***	70.7
	100% EtOH	100	6	1.5±0.8**	80.0
	DCM	100	6	3.0±1.1***	60.0
	HEX	100	6	1.3±0.5**	82.7

The results are the mean±S.E.M. ANOVA: $F_{(5,42)}=11.739$ ($p<0.05$) for indomethacin/bethanecol and $F_{(5,30)}=27.097$ ($p<0.05$) for hypothermic restraint stress model. Dunnett's test: $*p<0.05$, $**p<0.01$, $***p<0.0001$.

Table 2. Effects of *Quassia amara* Extracts and Cimetidine Administered Intraduodenally (i.d.) on the Biochemical Parameters of Gastric Juice Obtained from Pylorus–Ligature Mice

Treatments (i.d.)	Dose (mg/kg)	*n*	pH (Units)	Volume gastric juice (ml)	Total gastric acid (μEq/4h)
Control	—	20	3.1±1.0	469.5±230.9	11.2±3.9
Cimetidine	100	15	5.8±1.1***	257.8±150.9**	7.5±5.4**
70% EtOH	100	18	3.8±1.4	454.6±227.6	8.7±3.4
100% EtOH	100	18	4.8±1.4***	302.0±134.0*	7.0±3.3**
DCM	100	17	4.7±1.7**	300.6±225.6*	7.8±3.2*
HEX	100	18	5.0±1.5***	292.2±175.2*	6.5±2.8***

The results are the mean±S.E.M. ANOVA: $F_{(5,100)}=9.036$ ($p<0.05$) for pH; 3.895 ($p<0.05$) for gastric juice and 3.920 ($p<0.05$) for total acid. Dunnett's test: $*p<0.05$; $**p<0.01$; $***p<0.0001$.

mental group. Samples of the corpus (full thickness) were excised, weighed and suspended in 1 ml of 10 mM sodium phosphate buffer, pH 7.4. The tissue was minced finely with scissors, then incubated at 37 °C for 20 min. Prostaglandin in the buffer was measured using an enzyme immunoassay (RPN222-Amersham).

Statistical Analysis The results are presented as the mean±standard error of the mean (S.E.M.), and were compared using one-way analysis of variance (ANOVA), followed by Dunnet's pairwise test. *p* values of less than 0.05 were considered significant.

RESULTS AND DISCUSSION

Traditionally, medicinal plants have been used in folk medicine throughout the world to treat various diseases, especially gastric ulcer. There are several types of experimental models for evaluating anti-ulcer drugs.

We evaluated the preventive effects of 70% EtOH, 100% EtOH, DCM and HEX extracts obtained from *Quassia amara* bark in mice using the different standard experimental models of induced gastric ulcer.

It is already known that the suppression of prostaglandin synthesis by NSAIDs, such as indomethacin, results in increased susceptibility to mucosal injury and causes gastroduodenal ulcerations.[16] The co-administration of cholinomimetic agents, such as bethanechol, promotes a synergism with NSAIDs in the gastric lesion induced by the increased secretion of acid and pepsin in the stomach.[17]

The antiulcerogenic effect of these extracts in the NSAID/Cholinomimetic-induced lesion model (Table 1), mainly the

DCM and HEX, demonstrated significantly reduced damage to these gastric lesions ($p<0.05$) compared with the respective control and, suggested the probable involvement of these extracts with the cytoprotective mechanism by increasing mucous and/or prostaglandin synthesis.

Gastric stress ulceration is a serious complication which may occur in patients with burns, surgery or central-nervous-system trauma. Stress-induced ulcers are probably mediated by histamine release, with an enhancement of acid secretion and a reduction in mucous production. Moreover, vagal over-activity has been suggested as the principal factor in stress-induced ulceration.[2]

In the gastric ulcer induced by hypothermic-restraint stress, again all the extracts showed significant activity ($p<0.05$), and the obtained inhibitions index for extracts were more effective than those obtained for the positive control, cimetidine (70.7, 80, 60, 82.7, respectively), considering the fact that both extracts and cimetidine were used at same dose, 100 mg/kg *p.o.*, (Table 1). Antisecretory mechanisms, such as reduced histamine secretion and increased mucous synthesis, are responsible for this activity.

In the next step we showed the biochemical effects of *Quassia amara* extracts on gastric-juice parameters obtained after submitting the mice to pylorus ligature using all of the treatments, extracts and positive and negative control administered intraduodenally (Table 2). We observed that 100% EtOH, DCM and HEX, as well as the cimetidine positive control, significantly decreased the gastric acid secretion ($p<0.05$), increased the pH values and promoted reduced acid output. The 70% EtOH did not show significant results in the parameters evaluated.

Table 3. Effects of *Quassia amara* Extracts and Lansoprazole on HCl/EtOH-Induced Gastric Ulcer in Mice

Treatments (*p.o.*)	Dose (mg/kg)	n	Ulcerative index (mm)	Inhibition (%)	r	ED_{50} (mg/kg)	p
Control	—	8	35.4±5.2	—	—	—	—
Lansoprazole	30	8	7.4±1.1***	79.1	—	—	—
70% EtOH	25	8	33.3±6.6	5.9			
	50	8	26.5±4.4***	25.1	**0.98	7.0	**0.003
	75	8	16.4±2.9***	53.7			
	100	8	12.6±2.1***	64.4			
100% EtOH	25	8	22.8±2.7***	35.6			
	50	8	16.8±3.1***	52.5	*0.92	7.2	*0.03
	75	8	15.0±1.7***	57.6			
	100	8	12.1±4.2***	65.8			
DCM	25	8	16.1±1.6***	54.5			
	50	8	16.0±2.8***	54.8	0.50	—	0.4
	75	8	5.6±2.0***	83.8	—	—	—
	100	8	5.6±2.0***	83.8	—	—	—
HEX	25	8	13.5±3.0***	61.9			
	50	8	13.6±1.7***	61.6	*0.92	5.3	*0.03
	75	8	6.0±2.1***	83.1			
	100	8	2.5±1.9***	92.9			

The results are the mean±S.E.M. ANOVA: F values: $F_{(17,126)} = 54.470$ ($p<0.05$). Dunnett's test: * $p<0.05$; ** $p<0.01$; *** $p<0.0001$.

Robert *et al.*,[18] showed that E series prostaglandins (PGEs) inhibit gastric acid secretion in dogs and rats. Subsequent studies confirmed this inhibitory effect of PGE_2 and its analogs in both monkeys and man. In addition, PGI_2, $PGF_{2\alpha}$, and their analogs, were shown to have similar acid-suppressant properties.[16] Probably, the activities exhibited by these extracts are responsible for the synthesis of mucous, phospholipid, bicarbonate and prostaglandins, consequently promoting the inhibition of gastric-acid secretion. Moreover, it is important to remember that the compound(s) present in the extracts of *Quassia amara* by intraduodenal administration were absorbed and then arrived at the stomach to promote effects.

Considering the efficacy of these extracts led us to perform another HCl–EtOH-induced gastric-ulcer experiment using four dose levels (25, 50, 75, 100 mg/kg) for each extract, all of them administered orally. In this experiment we tried to establish the ED_{50} value for each extract and the possible dose-dependent relation of the obtained effect. As shown in Table 3, only 70% EtOH at a dose of 25 mg/kg was not significant in the inhibition of gastric ulcer. The 70% EtOH, 100% EtOH and HEX were dose-dependent ($p<0.05$), and the ED_{50} values were, respectively, 7.0, 7.2 and 5.3 mg/kg.

The balance of defensive and aggressive factors is thought to be important in maintaining gastric mucosal integrity.[19] The formation of gastric mucosal lesions by necrotizing agents such as HCl and EtOH has been reported to involve the depression of these gastric defensive mechanisms.[20] HCl–EtOH-induced gastric ulcers also promote stasis in gastric blood flow which contributes to the development of the hemorrhagic and necrotic aspects of tissue injury.[2]

It has been found that EtOH-induced ulcers are not inhibited by antisecretory agents such as cimetidine, but are inhibited by agents that enhance mucosal defensive factors such as prostaglandins.[21] These results show that *Quassia amara* extracts have an antiulcerogenic effect related to cytoprotection activity.

In looking for a possible mechanism for the increase in mucosal protective factors, we also investigated free mucous production after the administration of the 70% EtOH, 100% EtOH, DCM and HEX extracts (100 mg/kg, *p.o.*), and prostaglandin synthesis with an HEX extract of *Quassia amara*. We observed that all of the extracts significantly increased the "free" mucous in the gastric juice (14.8, 14.3, 27.1, 52.4%, respectively) (Table 4). When indomethacin was subcutaneously administered 30 min before treatment with the extracts or controls, the increase of this mucous was halted.

As shown in Table 5, HEX extract increased the synthesis of prostaglandin levels (52.3%). However, it was not significantly different from the sham group or negative control.

Several compounds, such as β-carbonile alkaloids, indole alkaloids and steroids, are presented in the extracts obtained from *Quassia amara*,[22] moreover, the bitter principle quassinoids are the most interesting group of substances present in these extracts. Our phytochemical analyses by TLC and HPLC-ES-MS confirmed the presence of these quassinoids (mainly quassin and neoquassin) in all of the extracts (data not shown).

These quassinoids probably are responsible for the observed antiulcerogenic activity. Raji and Bolarinwa,[23] showed that orally administered quassin reduced the plasma level of testosterone hormone and consequently promoted antifertility action in animals. Aston *et al.*,[24] showed that sexual hormones such as testosterone, when exogenously administered, aggravated the gastroduodenal ulcer induced by cysteamine in rats. In addition, Adeniyi,[25] observed that in orchidoctemized rats, with testosterone synthesis inhibited, a reduction of gastric-acid secretion occurred compared with that of normal rats. Montoneri & Drago,[26] in contrast, showed that the elevation of endogenous progesterone levels and the administration of exogenous progesterone increased the layer of mucous in the stomach and duodenum, and protected the cysteamine-induced ulcer.

There are many additional works relating exogenous testosterone with an improvement in the ability to increase the number of receptors of endogenous vasopressin, an important aggressive factor of gastrointestinal mucosa,[27,28]

Table 4. Effect of *Quassia amara* Extracts Administered by the Intraduodenal Route on Alcian Blue Binding to Free Gastric Mucous from Pylorus–Ligature Mice

Treatments	Dose (mg/kg)	n	Alcian blue bound [mg/wet tissue (g)]	Alcian blue bound (%)
Sham	–	6	2.1±0.1	—
Sham+indomethacin	10 ml/kg+30	6	2.0±0.1*	−4.8
Tween	10 ml/kg	6	2.1±0.09	—
Tween+indomethacin	10 ml/kg+30	6	2.0±0.1	−4.8
70% EtOH	100	6	2.4±0.07*	14.8
70% EtOH+indomethacin	100+30	6	2.1±0.1	—
100% EtOH	100	6	2.4±0.08*	14.3
100% EtOH+indomethacin	100+30	6	2.0±0.06	—
DCM	100	6	2.7±0.4***	27.1
DCM+indomethacin	100+30	6	1.9±0.2***	−9.5
HEX	100	6	3.2±0.4***	52.4
HEX+indomethacin	100+30	6	2.0±0.1	—

The results are the mean±S.E.M. ANOVA following F values: $F_{(11,60)}=20.748$ ($p<0.05$) for alcian blue bound. Dunnett's test: $*p<0.05$; $***p<0.0001$.

Table 5. Effects of HEX Extract from *Quassia amara* on Prostaglandin Synthesis by the Gastric Mucosa of Rats

Treatments	Dose (mg/kg)	n	Prostaglandin synthesis (pg/mg)	Increase (%)
Sham	—	6	133.0±16.4	—
Tween (*p.o.*)	10 ml/kg	6	140.3±29.2	5.5
Tween (*p.o.*)+indomethacin (s.c.)	10 ml/kg+30	6	45.3±19.6 ***	−65.9
HEX (*p.o.*)	100	6	202.5±63 **	52.3
HEX (*p.o.*)+indomethacin (s.c.)	100+30	6	33.3±21.1 ***	−75.0

The results are the mean±S.E.M. ANOVA following F values: $F_{(4,25)}=25.4$ ($p<0.05$). Dunnett's test: $**p<0.01$; $***p<0.0001$.

while orchidectomy decreases these receptors as well as the vasopressin levels in the plasma.[29] It is probable that quassinoids (quassin and neoquassin) are the compounds responsible for antiulcerogenic activities exhibited in all of the performed experiments.

We conclude that 70% EtOH, 100% EtOH, DCM and HEX extracts obtained from *Quassia amara* provide an excellent preventive effect in gastric ulcer models. The main compounds are the quassinoids, and the mechanism of this effect is probably related to prostaglandins and mucous synthesis. However, the antisecretory mechanism is still possible in this activity. The fact that low doses obtain the best effects, with no toxicity at a dose of 5000 mg/kg, is crucial, demonstrating the high efficacy and security of these extracts.

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