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ANTISECRETORY ACTIVITY OF THE STEM BARK AQUEOUS EXTRACT OF *KHAYA GRANDIFOLIOLA* (MELIACEAE) IN RATS OCCURS THROUGH ANTICHOLINERGIC AND ANTIHISTAMINIC PATHWAYS

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ABSTRACT

Aim: The current study investigated the possible mechanism of antisecretory action of *Khaya grandifoliola* in rats. ***Methods:*** Carbachol and histamine-induced hypersecretion, associated with the pylorus ligation technique, were used. The aqueous extract (250-500 mg/kg) was administered by oral or duodenal route and gastric mucosal ulceration, mucus production, pH, gastric volume, and acidity were measured. ***Results:*** Histamine and carbachol raised gastric acidity to 68.89 and 60.00 mEq/L respectively in the control rats. The extract of *K. grandifoliola* (250 and 500 mg/kg), given by oral route significantly ($p< 0.001$) reduced histamine-induced gastric acidity to 41.80 and 40.60 mEq/L, and carbachol-induced gastric acidity to 24.42 and 16.40 mEq/L, with 100 percent inhibition of gastric ulceration by the 500 mg/kg dose in the carbachol model. Intraduodenally-administered extract (250-500 mg/kg) significantly ($p < 0.001$) reduced histamine-induced gastric acidity to 48.73 and 33.84 mEq/L, and carbachol-induced gastric acidity to 26.72 and 26.22 mEq/L. The extract (250-500 mg/kg) significantly reduced ($p < 0.001$) the volume of gastric secretion and significantly increased mucus production in carbachol-induced hypersecretion only. The ulcer inhibition potential in histamine-induced gastric lesion, at the two doses of the extract of *K. grandifoliola*, was low (20.79 % and 48.97 %) by oral route, but increased by intraduodenal route (53.92 % and 83.03 %). In carbachol-induced gastric lesion, 250 mg/kg of extract increased ulcer inhibition potential from 29.93 % by oral route to 67.49 % by duodenal route ***Conclusion:*** The aqueous extract of *K. grandifoliola* has both antisecretory and cytoprotective effects. This antisecretory effect may involve a mechanism common to both cholinergic and histaminic pathways with greater effects elicited through the cholinergic pathway.

KEYWORDS: *Khaya grandifoliola*, gastric ulcer, gastric hypersecretion, antisecretory activity.

INTRODUCTION

In clinical practice, peptic ulcer is one of the most prevalent gastrointestinal disorders, commonly occurring in developed countries. The central role of gastric acid hypersecretion in the etiology of gastro duodenal ulcers is well known.[1] Various other factors can contribute to the formation of gastric ulcer such as the infection of the stomach mucosa by *Helicobacter pylori*,[2] and the frequent use of non-steroidal anti-inflammatory drugs (NSAIDs).[3] Due to the multiple ethology of peptid ulcers, treatment is based on triple therapy which combines antibiotics (Clarithromycin, Metronidazole, Amoxicillin) for the eradication of *H. pylori*, an antiacid for neutralizing the acidity of gastric juice (Sodium bicarbonate, Sodium citrate, Magnesium hydroxide, Aluminium hydroxide, Calcium carbonate), an antisecretory for the reduction of gastric secretion acid which can be either a H_2-receptor antagonist (Cimetidine, Ranitidine, Famotidine) or a proton pump inhibitors (Omeprazole, Lansoprazole, Pantoprazole), or an anticholinergics (Pirenzepine, propantheline, oxyphenonium); in some cases, a prostaglandin analogues (Misoprostol) can be combined with the triple therapy or antiulcer topic (Sucralfate, Carbenoxolone). Unfortunately, this cocktail of drugs is now known to confer simple-to-severe side effects ranging from constipation, diarrhea, itching and dizziness to arrhythmia, abdominal pain, impotence and gynecomastia in men and galactorrhea in women.[4,5,and6] Due to these side effects, there is a need to find new antiulcer compounds with potentially less or no side effects. Medicinal plants have always been the main

sources of new drug candidates for the treatment of various diseases including gastro duodenal ulcer.[7,8] In the West, it is a disease that affects 8 to 10 persons out of 100 residents.[9] The introduction of endoscopy in Africa at the beginning of the 1980s helped to reveal the high degree of prevalence of the disease in the pathology of the black African.[10] The prevalence of gastric ulcers in Cameroon is about 7.2 %.[11] Medicinal plants contain numerous biologically active compounds such as nutrients and phytochemicals which have physiological actions on the human body.[12] The inherent active ingredients are used to cure disease or relieve pain.[13]

Khaya grandifoliola (Meliaceae) is also called African Mahogany, Benin Mahogany, Large-leaved Mahogany, or Senegal Mahogany. It is found in Benin, the Democratic Republic of the Congo, Ivory Coast, Ghana, Guinea, Nigeria, Sudan, Cameroon, Togo and Uganda. It is used in the form of concoction for the treatment of convulsion, cough, stomach ache, fever, threatened abortion, rheumatism, dermatomycosis and malaria fever in Nigeria.[14, 15 and 16] The stem bark of this plant has been scientifically evaluated for some activities. The anti-malaria activity of the stem bark was reported.[17, 18, 19 and 20] The stem bark was also found to possess anti-ulcer property,[21] anti-microbial potentials against both gram positive and gram-negative bacteria especially on some resistant strains of Staphylococcus,[22] anti-inflammatory activity,[23] anti-anaemic,[24, 25] hypoglycaemic, hypoproteinaemic and hypocholesterolaemic effects.[26] *Khaya grandifoliola* extract was also reported as possessing the antioxidant activity and hepatoprotective effect.[27,28] The phytochemical tests showed the presence of limonoids, saponins, tannins, alkaloids, anthraquinones, flavonoids, reducing sugars and phlobatannins in this plant.[29, 30 and 31] Proximate analysis showed that carbohydrates and proteins were high concentrations in *K. grandifoliola*, while the concentrations of minerals such as magnesium, calcium, sodium, potassium, magnesium, iron and manganese were low.[29] A previous study showed that the aqueous extract of *K. grandifoliola* has both cytoprotective and antisecretory activity. In the current experiment, we used the pylorus ligation technique in a series of secretagogue-induced hypersecretion models in order to investigate the possible mechanism of antisecretory action of *K. grandifoliola* in rats.

MATERIAL AND METHODS

Animals

Male Wistar rats (150–220 g) were raised using a standard laboratory diet and tap water in the animal house of the Faculty of Science, University of Yaoundé 1. Prior authorization for the use of laboratory animals in this study was obtained from the Cameroon National Ethics Committee (Reg. No. FWA-IRB00001954).

Extract preparation

The plant material, fresh stem-bark of *Khaya grandifoliola*, was collected in Mbokam village (Jakiri) in the North-West Region of Cameroon (6° 06’ North and 10°39’ East). Botanical identification was done at the National Herbarium in Yaoundé by comparison with existing herbarium specimen No. PM 098 /95. The fresh stem-bark of *K. grandifoliola* was cut up, dried and ground to a powder. 1 kg of the dried material was boiled in 5 liters of water for 30 minutes. The extract solution was filtered through Whatman filter paper No. 3. The resulting filtrate was evaporated at 40°C using a ventilated oven (Jencons-PLS, UK) to obtain 66.35 g of a red powder. The extract re-dissolved readily in distilled water which was used as the vehicle.

Phytochemical tests Bruneton (1993)

Phytochemical tests for the major metabolites of the extract were performed. The aqueous extract of *K. grandifoliola* was screened for the presence of biologically active compounds such as tannins, alkaloids, saponins, flavonoids, anthocyanins, phenols, quinones, coumarins, sterols, triterpenoids, glycosides and proteins. Based on the intensity of coloration, the lather or the precipitate formed during the test, secondary metabolite proportions were characterized as highly present (+++), present (++) or weakly present (+) when the test result was positive, and absent (−) when the test result was negative.

Secretagogue-induced gastric hypersecretion

The extract (250 and 500 mg/kg) was administered by oral route and tested on gastric hypersecretion induced in pylorus ligated rats by histamine (2.5 mg/kg, s.c.) or carbachol (0.5 mg/kg, *s.c.)* injected 1 h after pylorus ligature.[32] The animals were sacrificed 4 h after secretagogue administration and gastric juice was collected and ulcers indices measured.

Secretagogue-induced gastric hypersecretion by intraduodenal route

The hypersecretory effects of the secretagogues were also challenged by the aqueous extract (250-500 mg/kg) administered by intraduodenal route. After laparotomy and pylorus ligation, the extract was introduced into the duodenal lumen using a syringe. The stomach incisions were closed and histamine (2.5 mg/kg) or carbachol (0.5 mg/kg) were administered 1 h later by subcutaneous route.[33] The animals were sacrificed 4 h after secretagogue administration. Gastric juice was collected and mucus production and ulcer indices were measured.

Measurement of gastric acidity

Samples of centrifuged gastric juice (1 mL) were analyzed for hydrogen ion concentration by pH-metric titration with 0.1N NaOH solution

Mucus production assessment

The mucus covering of each stomach was gently scraped using a glass slide and the mucus weighed carefully using a sensitive digital electronic balance.[34]

Statistical Analysis

The data were analyzed using one-way analysis of variance (ANOVA) followed by the student-Newman-keuls test. p values less than 0.05 were considered significant. Values in tables were given as arithmetic means ± standard error of the mean (S.E.M).

RESULTS

Qualitative phytochemical screening of the aqueous extract of *K. grandifoliola* revealed the presence of many phytoconstituents. These included, phenols, saponins, flavonoids, proteins, acids (+++), anthocyanins (++), tannins, alkaloids, ketones, sugars, coumarins; quinines, and amino acids (+). Oils, sterols, triterpenoids, glycosides and resins (-) were absent.

Tables 1 and 2 show the results obtained when, in addition to pylorus ligation, gastric hypersecretion was provoked by the administration of histamine. *K. grandifoliola* (250 and 500 mg/kg) prevented the formation of gastric lesions, inhibition attaining 48.97 % at the dose 500 mg/kg. Cimetidine (100 mg/kg) prevented lesion formation by 62.02 %. Mucus production increased from 39.20 mg in the controls to 57.20 mg for Cimetidine and 95.20 mg for the highest dose of the extract (Table 1). Administration of histamine to the control animals increased gastric acidity to 68.89 ± 1.21 mEq/L (Table 2). Treatment with the extract (250 and 500 mg/kg) resulted in significant reduction (by 39.03 % and 41.07 %) in gastric acidity (41.80 ± 0.92 and 40.60 ± 0.40mEq/L) compared with the controls (68.89 ± 1.29 mEq/L). Cimetidine (100 mg/kg) showed a more significant decrease to 20.64 ± 1.15 mEq/L (70.04 % reduction) compared to the rats treated with the extract. The reductions in acid secretion were not accompanied by a significant reduction in volumes of gastric juice and ulcer indices (except in the rats treated with Cimetidine).

Table 1: Effects of orally-administered *K. grandifoliola* extract on histamine-induced gastric ulcers in rats.

Treatment	Dose (mg/kg)	N	Ulcer index	% ulcerated surface	Inhibition (%)	Mucus production (mg)
Control	-	5	4.17 ± 0.48	2	-	39.20 ± 0.41
K. grandifoliola	250	5	3.30 ± 0.06	0.92	20.79	83.20 ± 11.50**
K. grandifoliola	500	5	2.13 ± 0.4	0.58	48.97	95.20 ± 10.44**
Cimetidine	50	5	1.00 ± 0.06*	0.49	62.02	57.20 ± 5.62

N = 5 rats per treatment; *$p < 0.05$; **$p < 0.01$, statistically significant relative to control

Table 2: Effects of orally-administered *K. grandifoliola* extract on histamine-induced gastric secretion in rats.

Treatment	Dose (mg/kg)	N	Gastric pH	Gastric content (mL)	Gastric acidity (mEq/L)	% Acidity Reduction
Control	-	5	1.89 ± 0.02	4.42 ± 0.34	68.89 ± 1.29	-
K. grandifoliola	250	5	2.69 ± 0.08	5.06 ± 0.45	41.80 ± 0.92***	39.03
K. grandifoliola	500	5	3.40 ± 0.03*	4.12 ± 0.46	40.60 ± 0.40***	41.07
Cimetidine	50	5	3.32 ± 0.63*	4.34± 0.58	20.64 ± 1.15***	70.04

N = 5 rats per treatment; *p < 0.05, ***p < 0.001, statistically significant relative to control

Tables 3 and 4 show the results obtained when, in addition to pylorus ligation, gastric hypersecretion was provoked by the administration of carbachol. *K. grandifoliola* (250 and 500 mg/kg) prevented the formation of gastric lesions, inhibition attaining 100 % at the dose 500 mg/kg. Ranitidine (50 mg/kg) prevented lesions formation by 71.93 %. Mucus production increased from 28.20 mg in the controls to 50.20 mg for Ranitidine and 101.00 mg for the highest dose of the extract (Table 3). Administration of carbachol to the control animals raised gastric acidity to 60.08 ± 0.32 mEq/L (Table 4). Treatment with the extracts (250 and 500 mg/kg) resulted in highly significant reduction (59.9 and 72.6 %) in gastric acidity to 24.40 ± 1.12 and 16.40 ± 0.75 mEq/L. Ranitidine (100mg/kg) showed similar decrease (71.37 %; 17.20 ± 0.49 mEq/L) compared with the rats treated with the extract at the dose of 500 mg/kg. The reduction of acid secretion at 500 mg/kg of extract was accompanied by a significant reduction of ulcers index (inhibition, 100 %).

Table 3: Effects of orally-administered *K. grandifoliola* extract on carbachol-induced gastric ulcers in rats.

Treatment	Dose (mg/kg)	N	Ulcer index	% ulcerated surface	Inhibition (%)	Mucus production (mg)
Control	-	5	3.57 ± 0.43	2.19	-	28.20 ± 4.09
K. grandifoliola	250	5	2.50 ± 0.00	0.81	29.93	59.80 ± 4.96**
K. grandifoliola	500	5	0.00 ± 0.00***	0.00	100	101.00 ± 7.29***
Ranitidine	50	5	1.00 ± 0.06***	0.93	71.93	50.20 ± 4.19**

N = 5 rats per treatment; **p < 0.01; ***p < 0.001, statistically significant relative to control

Table 4: Effects of orally-administered *K. grandifoliola* extract on carbachol-induced gastric secretion in rats.

Treatment	Dose (mg/kg)	N	Gastric pH	Gastric content (mL)	Gastric acidity (mEq/L)	% Acidity Reduction
Control	-	5	1.85 ± 0.17	5.06 ± 0.28	60.08 ± 0.32	-
K grandifoliola	250	5	3.63 ± 0.11**	5.06 ± 0.56	24.40 ± 1.12***	59.9
K grandifoliola	500	5	6.43 ± 0.66***	4.56 ± 0.56	16.45 ± 0.75***	72.62
Ranitidine	50	5	6.27 ± 0.44***	3.4 ± 0.61	17.20 ± 0.49***	71.37

N = 5 rats per treatment; **p < 0.01; ***p < 0.001, statistically significant relative to control

Table 5 and 6 show the effects of duodenally-administered aqueous extract of *K. grandifoliola* on gastric ulceration and secretion induced by histamine in rats. Intraduodenal administration of *K. grandifoliola* aqueous extract (250 and 500 mg/kg) to pylorus ligated rats subjected to histamine-induced hypersecretion produced a highly significant (p < 0.001) decrease (52.82 %) of acid secretion (33.84 ± 0.97 mEq/L), ulcer index (0.70 ± 0.04), and increased inhibition of gastric lesions to 83.03 % for the 500 mg/kg dose. pH values and mucus production increased up to 3.93 ± 0.37 and 95.25 ± 10.44 mg, respectively, for the same dose.

Table 5: Effects of duodenally-administered aqueous extract of *K. grandifoliola* extract on gastric ulceration induced by histamine in rats.

Treatment	Dose (mg/kg)	N	Ulcer index	% ulcerated Surface	Inhibition %	Mucus production (mg)
Control	-	5	4.12 ± 0.37	1.93	-	39.20 ± 0.01
K grandifoliola	250	5	1.50 ± 0.06**	0.22	53.92	83.21 ± 11.10**
K grandifoliola	500	5	0.70 ± 0.04***	0.03	83.03	95.25 ± 10.44***
Cimetidine	50	5	1.90 ± 0.37*	0.74	53.92	57.30 ± 5.17**

N = 5 rats per treatment; * p<0.05; **p < 0.01; ***p < 0.001, statistically significant relative to control

Table 6: Effects of duodenally-administered aqueous extract of *K. grandifoliola* on secretion induced by histamine in rats.

Treatment	Dose (mg/kg)	N	Gastric pH	Gastric content (mL)	Gastric acidity (mEq/L)	% Acidity Reduction
Control	-	5	2.29 ± 0.18	4.42 ± 0.34	71.73 ± 2.20	-
K grandifoliola	250	5	3.64 ± 0.02**	3.66 ± 0.47	48.73 ± 0.47***	32.06
K grandifoliola	500	5	3.93 ± 0.03**	3.75 ± 0.40	33.84 ± 0.97***	52.82
Cimetidine	50	5	4.30 ± 0.34**	2.06 ± 0.04***	23.58 ± 1.79***	67.13

N = 5 rats per treatment; **p < 0.01; ***p < 0.001, statistically significant relative to control

Tables 7 and 8 show the effects of duodenally-administered aqueous extract of *K. grandifoliola* on gastric ulceration and secretion induced by carbachol in rats. Intraduodenal administration of *K. grandifoliola* aqueous extract (250 and 500 mg/kg) to pylorus ligated rats subjected to carbachol-induced hypersecretion produced a highly significant (p < 0.001) decrease of acid secretion to 26.72 ± 0.93 mEq/L at the dose of 250 mg/kg, and to 26.22 ± 2.36 mEq/L at 500 mg/kg (62.64 % and 63.34 % reduction). The ulcer index highly decreased to 1.20 ± 0.05 at 250 mg/kg. Ulcer formation was totally inhibited and gastric mucus production increased (101.00 ± 7.29 mg) significantly for the dose of 500 mg/kg. pH increased to 3.58 ± 0.03 and the volume of gastric juice reduced to 4.58 ± 0.40 for the same dose.

Table 7: Effects of duodenally-administered aqueous extract of *K. grandifoliola* extract on gastric ulceration induced by carbachol in rats.

Treatment	Dose (mg/kg)	N	Ulcer index	% Ulcerated surface	Inhibition %	Mucus production (mg)
Control	-	5	3.69 ± 0.36	2.49	-	56.60 ± 4.02
K grandifoliola	250	5	1.20 ± 0.05*	0.09	67.50	78.80 ± 5.83*
K grandifoliola	500	5	0.00 ± 0.00***	0.00	100	101.00 ± 7.29***
Cimetidine	50	5	1.70 ± 0.09	0.72	53.95	84.00 ± 2.39**

N = 5 rats per treatment; * p<0.05; **p < 0.01; ***p < 0.001, statistically significant relative to control

Table 8: Effects of duodenally-administered aqueous extract of *K. grandifoliola* extract on gastric secretion induced by carbachol in rats.

Treatment	Dose (mg/kg)	N	Gastric pH	Gastric content (mL)	Gastric acidity (mEq /L)	% Acidity Reduction
Control	-	5	2.71 ± 0.09	6.72 ± 0.30	71.52 ± 2.98	-
K grandifoliola	250	5	3.38 ± 0.11**	4.10 ± 0.32***	26.72 ± 0.93***	62.64
K grandifoliola	500	5	3.58 ± 0.03***	4.58 ± 0.40***	26.22 ± 2.36***	63.34
Ranitidine	50	5	4.91 ± 0.16***	2.46 ± 0.14***	34.46 ± 1.30***	51.82

N = 5 rats per treatment; **p < 0.01; ***p < 0.001, statistically significant relative to control

DISCUSSION

Peptic ulcer and gastritis have been associated with multipathogenic factors and could be due to disturbances in natural equilibrium between the aggressive factors (acid, pepsin) and maintenance of the mucosal integrity through the endogenous defense mechanism.[35] Generally, various non-specific and specific methods are used to restore these imbalances ranging from attenuation and possibly blockade of the gastric acid secretion to enhancement of the mucosal defense mechanisms.[36] The present experiments were designed to validate the folk use of *K. grandifoliola* in gastric ulcer treatment and to suggest a possible mode of its antisecretory and cytoprotective action. The results showed that the aqueous extract protected the gastric mucosa against damage induced by carbachol- and histamine-induced hypersecretion associated with the pylorus ligation technique used in rat. Carbachol is a cholinomimetic drug that, like acetylcholine, increases free intracellular calcium. The resulting activation of protein kinase by phosphorylation leads to increased HCl production.[37] Gastric acid plays a major role in the pathogenesis of gastric and duodenal ulcers.[38] Acid secretion can be stimulated by three principals "secretagogues" histamine, acetylcholine and gastrin. The action of these three substances is synergistic in that a small dose of one potentiates the response brought about by a small dose of another. Each has a specific receptor site on the basolateral membrane of the oxyntic/parietal cell. Vagal stimulation and gastrin released by G cells stimulate the release of histamine by the enterochromaffin-like, or mast cells. Acetylcholine binds to M_3-muscarinic receptors causing an increase in parietal cell intracellular calcium. Histamine activates parietal cell H_2 receptors, known to be linked to adenylate cyclase by the cAMP pathway activation. This activation by the cAMP pathway for histamine or calcium-sensitive pathways for muscarinic and gastrin receptors trigger the H^+/K^+ ATPase pump, and through an active transport mechanism, is able to increase the hydrogen ion concentration in the lumen of the stomach and accumulation of gastric acid.[39]

In the current study, histamine-induced basal acid secretion was higher (68.89 ± 1.29 mEq/L) compared to carbachol-induced basal secretions (60.08 ±0.32 mEq/L). These results are in agreement with previous findings[40] which showed that carbachol-induced secretion by parietal cells is fast, small, and transient, whereas histamine-provoked secretion is slow, large, and sustained. The aqueous extract (250 and 500 mg/kg) of *Khaya grandifoliola*, and Ranitidine significantly raised gastric pH and reduced the volume and secretion of gastric acid more in carbachol- than in histamine-treated rats. Further experimentation yielded highly significant reductions of volume and acidity of gastric secretion when the extract was administered by intraduodenal route in both carbachol- and histamine-induced hypersecretion models. These results suggest that the observed reductions in gastric acidity could be due more to a muscarinic receptor blocking activity than histaminic-receptor blocking mechanism. It is worth noting that even in histamine-treated rats, the laparotomy- and pylorus ligation-induced pain constitutes a source of stress which contributes to acid secretion through the cholinergic pathway. When the extract of *K. grandifoliola* (250 and 500 mg/kg) was administered orally in the histamine-induced hypersecretion model, the results showed that the acidity reduced by less than 50 % (39.03 % and 41.07 %) and was accompanied by lower percentages of ulcer inhibition (20.79 % and 48.97 %) compared with the carbachol model where the reduction in acidity reached 59.90 % and 72.62 %, and with 29.93 % and 100 % ulcer inhibition. These results suggest that the extract of *K. grandifoliola* acts more effectively through the inhibition of cholinergic pathways compared with the histaminergic route. Similar cholino-histaminergic antisecretory activity has been shown by the aqueous extract of *Eremomastax speciosa* in rats.[41]

The effects of *K. grandifoliola* aqueous extract may not be attributed to a gastric luminal topical activity alone since the extract was also active when administered by intraduodenal route. A closer examination of the results reveals that when administered orally, the low dose of the extract (250 mg/kg) was more effective in reducing both acid secretion and lesion formation induced by carbachol (60 % and 30%, respectively) compared with histamine (39 % and 21%, respectively). Similar way, the low dose of extract (250 mg/kg), when administered by duodenal route, reduced acid secretion and lesion formation more effectively against carbachol (62 % and 67%, respectively) compared with histamine (32 % and 54%, respectively). The highly significant acid reduction capacity when the extract (250 and 500 mg/kg) was administered by duodenal route both for the histamine (32 % and 53%) and carbachol (63 %) models, is suggestive of the involvement of one or more active secondary metabolites.

In all methods used the cytoprotection obtain was associated with a significant increase in mucus production. We also demonstrated the strong antisecretory and antiulcer actions of *K. grandifoliola* extract against secretagogue-induced hyperacidity. Because secretagogue-induced acid secretion occurs by specific mechanisms, the extract of *K. grandifoliola* may contain two or more antisecretory ingredients acting separately and synergistically. Phenols and flavonoids, present in significant quantities in the extract, are natural plant substances that are well-known for their gastric antisecretory and cytoprotective activities.[8, 36, 42, and 43]

CONCLUSION

The aqueous stem-bark extract of *K. grandifoliola* protected the rat gastric mucosa and inhibited gastric acid secretion. The anti-secretory effect may involve a mechanism common to both cholinergic and histaminic pathways with greater effects elicited through the cholinergic pathway. This may be attributed to the various bioactive compounds present in the extract.

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