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Anti-acid and anti-secretory activities of the aqueous extract of *Microdesmis keayana* J. Léonard (Pandaceae) leaves on gastric hypersecretion induced in Wistar rats

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ABSTRACT

Introduction: Gastric acid hypersecretion is a major contributing factor to peptic ulcer disease. This study aimed to evaluate the anti-secretory and anti-acid activities of the aqueous leaf extract of *Microdesmis keayana* (AEMk) in experimental models of gastric hypersecretion in Wistar rats, based on its traditional use against ulcer.

Methods: Three experiments were conducted on 42 rats each (6 animals/group). In the pyloric ligation model, rats were divided into 7 groups: negative control, ulcer control, positive controls (cimetidine 12 mg/kg, Maalox 50 mg/kg), and three groups orally treated with AEMk (125, 250, 500 mg/kg). The rats were sacrificed 6 hours after pyloric ligations. In the models of hypersecretion induced by carbachol or histamine, with atropine and ranitidine as positive controls, respectively, the same group division was applied, with the secretagogue injected one hour after pylorus ligation. The rats were sacrificed five hours thereafter. Macroscopic and anti-secretory parameters, such as ulceration area, gastric acidity and pH were determined.

Results: AEMk reduced gastric acidity and volume versus ulcer control ($P<0.05$) and increased pH ($P<0.05$). In the pyloric ligation model, AEMk significantly ($P<0.05$) reduced ulcer area to 96.81%, like cimetidine (89.97%) and Maalox (88.59%). AEMk inhibited carbachol-induced ulcers by 87.39–93.82% (versus atropine 89.17%) and histamine-induced ulcers by 83.16–94.79% (versus ranitidine 93.31%).

Conclusion: The aqueous leaf extract of *M. keayana* demonstrated significant anti-secretory and gastroprotective activity in experimental models. Further studies involving extract standardization, mechanistic pharmacological investigations, and toxicity assessments are required before its therapeutic potential can be established.

Implication for health policy/practice/research/medical education:
The results of this study suggest that *Microdesmis keayana* J. Léonard is a promising source of an anti-ulcer agent and warrant further research to confirm its efficacy and safety.

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Introduction

The stomach secretes hydrochloric acid and digestive enzymes that promote the breakdown of the alimentary bolus into chyme. However, an acid hypersecretion can lead to gastrointestinal pathologies such as gastro-duodenal ulcers and gastritis, thereby compromising the integrity of the gastric mucosa (1-3). Gastric acid secretion is regulated by several mediators, including histamine and acetylcholine, which stimulate parietal cells through H_2 and muscarinic receptors, respectively (4). In a meta-analysis study, the prevalence of peptic ulcer was evaluated to 8.4% of the world population (5). The annual incidence is estimated to be between 0.1% and 0.3% in Western countries, while higher prevalences are reported in Asia and Africa (6). Doffou et al (7) reported a hospital prevalence of 26.9% in Côte d'Ivoire in 2020. Pharmacological management of acid-related disorders includes agents that suppress gastric acid secretion or enhance mucosal

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protection, including proton-pump inhibitors, H_2-receptor antagonists, antacids, and other gastroprotective agents. Despite their clinical efficacy, limitations associated with adverse effects, drug interactions, and long-term use have encouraged continued investigation of alternative therapeutic agents (8). These treatments aim to reduce acid secretions or enhance mucosal protection. Medicinal plants have therefore attracted interest as potential sources of gastroprotective agents. *Microdesmis keayana* is traditionally used for healing and analgesic purposes involving the skin and mucous membranes, suggesting potential pharmacological activity relevant to mucosal protection. However, its anti-secretory and anti-acid effects in experimental models of gastric hypersecretion have not been adequately characterized (9,10). This study aimed to provide an initial in vivo pharmacological validation of *M. keayana's* antiulcer potential. The expected results should demonstrate a multimodal action involving histaminergic and cholinergic pathways. Comparison with standard drugs will allow for an assessment of its relative efficacy. This research will help strengthen the scientific basis for its traditional use. Our working hypothesis is that the aqueous leaf extract of this species exhibits significant anti-secretory and anti-acid activities, thereby contributing to its gastroprotective profile.

Material and Methods

Materials

Plant

Fresh leaves of *Microdesmis keayana* J. Léonard (Pandaceae) (Figure 1) were collected in June 2023 in the town of Alépé (Côte d'Ivoire), located between latitudes "5°13'04.49 and 5°55'22.06" N and longitudes "3°25'25.25 and 3°57'46.64" W. Botanical authentication was performed by Prof. BAKAYOKO Adama, a botanist at the Swiss Center for Scientific Research in Côte d'Ivoire. A reference herbarium specimen was deposited at this institution under registration number CSRS N° 634, associated with the unique barcode 005166.

Animals

Wistar rats of both sexes were housed in conventional cages and maintained at 25 °C with a 12/12-hour light-dark cycle. They weighed 150-170 g and were 8-10 weeks old. They were given standard pellets (IVOGRAIN) *ad libitum* and had free access to water (11). The protocol was approved by the ethics committee for animal experimentation at our university. The code was N° 001/CEEA/2023.

Drugs and chemicals

They were composed of misoprostol (Cytotec®, Pfizer, Germany), ranitidine (Bristol Myers Squibb, USA), cimetidine (Sigma, USA), NaOH (Sigma, USA), histamine (Sigma, USA), carbachol (Sigma, USA), ether (Sigma, USA), aluminum hydroxide (Maalox®, Sanofi Aventis, France), and atropine (Sigma, USA).

Methods

Preparation of the aqueous extract from the leaves of M. keayana

Fresh leaves were air-dried at the Laboratory of Physiology, Pharmacology, and Pharmacopoeia Hall for two weeks, then ground into powder using an electric grinder (RETSH, SM 100, Germany). One hundred grams of *M. keayana* leaf powder were mixed with 1 liter of distilled water and decocted for 15 minutes. The obtained solution was filtered using Whatman No. 1 filter papers. To the residue, 500 mL of distilled water was added and then boiled for 10 minutes. The obtained filtrates were mixed and dried in an oven at 45 ℃ for 48 hours (12). A brown powder of 22 g was obtained and was used as the aqueous extract of the leaves of *M. keayana* (AEMk).

Phytochemical screening

The phytochemical screening of AEMk was carried out according to the tube characterization techniques described by Bekro et al (13) for the detection of polyphenols, tannins, flavonoids, saponins, sterols and coumarins. This experimental procedure was repeated three times.

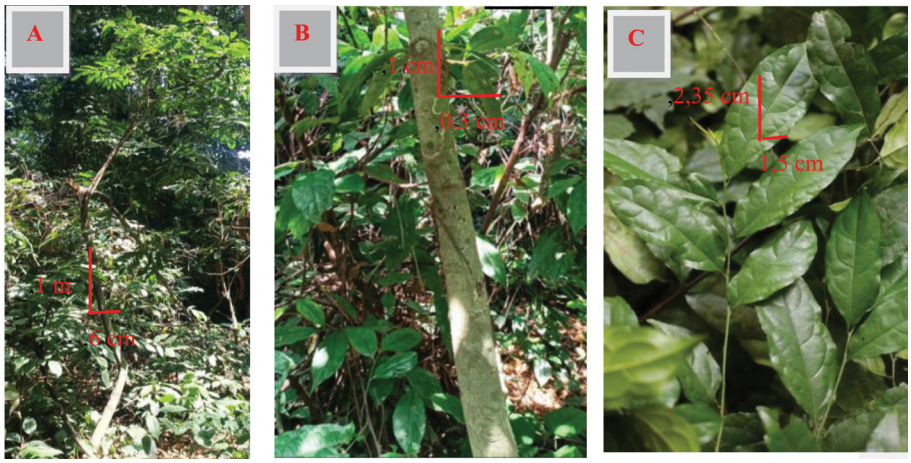

Figure 1. Photograph of the different parts of *Microdesmis keayana* J. Léonard (Pandaceae). A: Tree, B: Trunk, C: Leaves.

Evaluation of the anti-secretory activity of AEMk in rats

The method used was described by Shay (14). Forty-two fasted rats for 24 hours were divided randomly into seven groups of six rats each. Group 1 (non-ulcerative or negative control) and group 2 (ulcerative or pylorus ligated control) were gavaged with distilled water orally at 1 mL/100 g body weight. Those in groups 3 and 4 received cimetidine (12 mg/kg) and Maalox (antacid for mucosal protection) (50 mg/kg) by oral route. As for groups 5 to 7, they were orally administered with AEMk at doses of 125, 250, and 500 mg/kg, respectively. One hour after administration of the different solutions, an incision of about 3 cm was made under the last rib of the rats in groups 2 to 7, which had been anesthetized with ether earlier to perform a pyloric ligation. Six hours after the pyloric ligation, the animals were anesthetized by ether overdose. Then, macroscopic parameters (score, surface, and index of ulceration) and gastric mucus, juice volume, acidity, and pH were determined.

Evaluation of the anti-hypersecretion activity of the aqueous extract of M. keayana leaves in rats

a. Evaluation of the anti-hypersecretion effect of AEMk in carbachol-induced hypersecretion

The method carried out by Perfusion et al (15) was used for this experiment. Forty-two rats were fasted for 24 hours and randomly divided into 7 groups of 6 rats each. The rats in group 1 (non-ligated control), those in group 2 (ligated control), and those in group 3 (carbachol control), received distilled water at 1 mL/100 g. The rats in groups 5 to 7 were treated with AEMk at 125, 250 and 500 mg/kg, respectively. The different solutions were orally administered. Atropine (1 mg/kg) was subcutaneously injected into rats in group 4 just before the pylorus ligation. One hour after administration of the different solutions, pyloric ligation was performed in all rats except those in group 1. One hour after the ligation, the rats in groups 3 to 7 received carbachol (1 mg/kg) *via* the subcutaneous route. The animals were then sacrificed using an overdose of ether five hours after the injection of carbachol. The stomach of each rat was opened and then macroscopic and gastric secretion indices were measured.

b. Evaluation of the anti-hypersecretion effect of AEMk in histamine-induced hypersecretion

In this experiment, the rats from control groups 1 and 2 were treated as described above in carbachol-induced hypersecretion. Group 3, corresponding to the histamine hypersecretion control group, received distilled water (1 mL/100 g). Group 4 was gavaged with ranitidine (50 mg/kg). As for the rats in groups 5 to 7, they were pretreated with AEMk (125, 250 and 500 mg/kg). All the solutions were administered orally. One hour after the administration of the different substances, all the animals, except those of group 1, were pylorus ligated under ether anesthesia. One hour after pyloric ligation, pyloric-ligated animals received histamine subcutaneously at 2.5 mg/kg. Five hours later, the animals were sacrificed by overdose of ether, and their stomachs were removed and opened. Macroscopic and gastric secretion indices were evaluated (15).

Pylorus ligation procedure

One hour after oral administration of the different test solutions, rats in groups 2 to 7 were anesthetized using ether. A midline abdominal incision of approximately 3 cm was made just below the last rib to expose the stomach. The pylorus was carefully isolated and ligated with a thread without causing damage to the surrounding blood vessels. The abdominal incision was then sutured. Six hours after pyloric ligation, the animals were euthanized by an overdose of ether. The stomachs were excised and opened along the long curvature, and gastric contents were collected for analysis. Macroscopic examination was performed to determine ulcer score, ulcerated surface area, and ulcer index. Gastric mucus content was quantified, and gastric juice was analyzed for volume, total acidity, and pH (14).

Measurement of gastric acidity

After the rats were sacrificed, the stomach of each rat was opened, the gastric contents were collected, and the pH was measured using a pH meter (HANNA HI 9025, USA). The contents were thereafter centrifuged at 3000 rpm for 10 minutes. One milliliter of the supernatant was taken from each tube and titrated using a sodium hydroxide (NaOH, 0.1 N) solution to determine gastric acidity. Gastric acidity was calculated using the following formula (1):

$$Acidity\,(mEq/L\ per\ 100\,g) = \frac{Volume\ of\ NaOH \times Normality\ of\ NaOH}{0.1} \times 100 \quad (1)$$

Measurement of macroscopic parameters

The mucus was collected and weighed. The ulcerations were classified according to the gastric lesion classification scale described (16): Absence of ulcer (0), dilation of blood vessels or presence of redness (1), small ulcer marks (1), dilation of blood vessels and presence of ulcer marks (1.5), ulcers ≥3 mm long ≤5 mm long (2), ulcers >5 mm long (3). The stomach was photographed, and the ulcerated surface was measured using ImageJ software. The results obtained allowed the calculation of the index, the percentage of inhibition, and the ulceration surfaces using the formulas described by Zakaria et al (17).

$$UI = \frac{\text{Degree of ulceration of the group} \times \text{percentage of ulcerated rats in the group}}{100} \quad (2)$$

$$DUG = \frac{\text{Sum of points assigned to gastric lesions (score)}}{\text{Number of ulcerated rats in the group}} \quad (3)$$

With UI: group ulceration index and DUG: degree of group ulceration.

$$I = \frac{(USc - USp)}{USc} \times 100 \quad (4)$$

which I = Inhibition percentage of ulcerations in the treated group; USc = Ulceration surface of control group (Ulcerative control); and USp= Ulceration surface of treated groups.

Statistical analysis

The results were expressed as the mean ± standard error of the mean (SEM). The normality of the data was first verified using the Shapiro-Wilk test, and the homogeneity of variances was assessed using Levene's test. Data following a normal distribution and exhibiting homogeneous variances were analyzed using a one-way analysis of variance (ANOVA 1), followed by Turkey's post-hoc test for multiple comparisons between the treatment groups and the control group. Differences were considered statistically significant at a P value <0.05. All analyses were performed using GraphPad Prism software version 8.01 (San Diego, California, USA).

Results

Results of the phytochemical screening

The phytochemical screening of AEMk revealed the presence of polyphenols, tannins, flavonoids, saponins and coumarins (Table 1).

Effect of the aqueous extract of *M. keayana* leaves on pyloric ligation-induced ulcers in rats

Effect of the aqueous extract of Microdesmis keayana leaves on macroscopic parameters

Figure 2 indicates images of the rats' stomachs following the various treatments, and Table 1 shows the effect of the various treatments on macroscopic parameters after rats' pyloric ligation (ulcer surface area, score, ulcer index, and inhibition percentage). The results revealed no ulceration in the stomach mucosa in the negative control group (group 1); therefore, the score and ulceration index were null (Figure 2A). However, in control group 2, where rats' stomachs were ligated (Figure 2B), the results indicated that the ulceration area, the score, and the ulceration index significantly ($P<0.001$) increased compared to the negative control (group 1). The values of these parameters were respectively 69.1 ± 2.09 mm²; 2.86 ± 0.61, and 2.5 ± 0.60 (Table 1). Furthermore, groups pretreated with AEMk at 125, 250, and 500 mg/kg exhibited significantly lower scores ($P<0.001$) compared to group 2 (Figure 2E, 2F, 2G). The score values decreased from 2.23 ± 0.1 (125 mg/kg) to 0.66 ± 0.10 (500 mg/kg) (Table 2). At these same doses, a significant decrease ($P<0.001$) in the ulceration areas and ulceration indices was also observed compared to the control group 2. The ulceration areas diminished from 35.10 ± 0.39 mm² (125 mg/kg) to 2.2 ± 0.20 mm² (500 mg/kg) (Table 2). As for the ulceration indices, they decreased from 1.84 ± 0.23 to 0.41 ± 0.98 for AEMk doses varying from 125 to 500 mg/kg. These decreases corresponded to inhibition percentages ranging from 49.21% (125 mg/kg) to 96.81% (500 mg/kg) (Figure 2E, 2F, 2G). The 50% efficiency dose (ED_{50}) of AEMk was 233.878 mg/kg. The pretreatment of rats with cimetidine (12 mg/kg) (Figure 2D) and Maalox (50 mg/kg) (Figure 2C) induced significant decreases ($P<0.001$) in the score, ulceration area, and ulceration index compared to the control group 2. This corresponded to ulceration inhibitions of 88.59% for Maalox (50 mg/kg) and 89.97% for cimetidine (12 mg/kg).

Table 1. Phytochemical compounds of the aqueous extract of *Microdesmis keayana* leaves

Phytochemical compounds	Reagents	Aqueous extract of *Microdesmis keayana* leaves
Polyphenols	$FeCl_3$ test	+
Flavonoids	Cyanidine test	+
Tannins	$FeCl_3$ test Stiasny test	+
Coumarins	KOH test	+
Saponins	Foam test	+
Sterols	Libermann test	-

(+): Compounds found; (-): Compound absent.

Effect of the aqueous extract of Microdesmis keayana leaves on gastric secretions

The effect of the aqueous extract of *M. keayana* leaves on gastric secretions is summarized in Table 3. The results disclosed gastric volume and acidity of 7.21 ± 0.19 and 93.5 ± 2.51 mEq/L, respectively, with a gastric pH of 1.77 ± 0.13 in pylorus ligated control rats (group 2) pretreated with distilled water. However, in groups pretreated with AEMk (125, 250, and 500 mg/kg), the volume of gastric content and gastric acidity were significantly ($P<0.001$) decreased compared to the control group 2. The values of gastric volume varied from 4.82 ± 0.12 mL (125 mg/kg) to 2.81 ± 0.25 mL (500 mg/kg). Gastric acidity also dropped from 76.7 ± 2.25 to 64.6 ± 2.36 (mEq/L) in the same dose range. As for the pH of the gastric content, it significantly rose ($P<0.001$) in rats pretreated with AEMk (125 to 500 mg/kg), from 3.64 ± 0.11 (AEMk, 125 mg/kg) to 5.65 ± 0.29 (AEMk, 500 mg/kg) compared to that of the control group 2, which was 1.77 ± 0.13. The pH of the gastric contents of the rats that received cimetidine (12 mg/kg) and Maalox (50 mg/kg) also significantly ($P<0.001$) increased, reaching 5.23 ± 0.21 and 5.90 ± 0.23, respectively, resulting in a reduction of gastric acidity with values of 64.8 ± 2.05 mEq/L and 65.9 ± 1.93 mEq/L, respectively (Table 3). The mucus produced by rats in group 2 decreased significantly ($P<0.001$) compared to that in the control group 1. The recorded values were 152 ± 0.35 mg for group 1 and 47.3 ± 0.21 mg for group 2. AEMk caused a significant increase ($P<0.001$) in mucus production compared to the control group 2. The mucus weighed 66.8 ± 0.11 mg for the dose

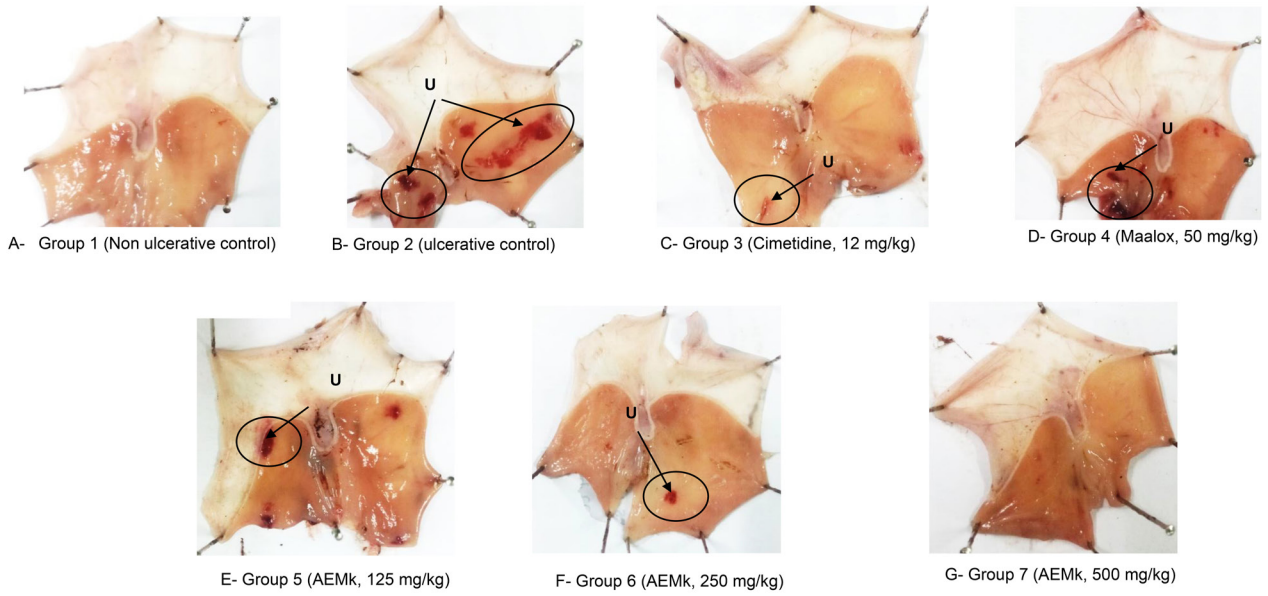

Figure 2. Photographs of the rats' stomachs after different pretreatments in the pyloric ligation model rats. AEMk: Aqueous extract of the leaves of Microdesmis keayana; U: Ulceration.

Table 2. Macroscopic parameters of gastric ulcers induced by pyloric ligation after various pretreatments in rats

Groups	Treatment (mg/kg)	US (mm²)	Score	UI	I (%)
Group 1	D.W	00.00±0.00	00.00±0.00	00.00±0.00	_
Group 2	D.W	69.1±2.09***	2.86±0.61***	2.5±0.6***	_
Group 3	Cimetidine 12	6.93± 0.30###c	1.25± 0.11###a	0.9± 0.53###a	89.97
Group 4	Maalox 50	7.88±0.50###c	1.50± 0,22##a	1.02± 0.73###a	88.59
Group 5	AEMk 125	35.10±0.39###a	2.23± 0.10###c	1.84±0.23###a	49.21
Group 6	AEMk 250	14.9±1.07###b	1.91±0.15###a	1.45± 0.62###a	78.44
Group 7	AEMk 500	2.2±0.2###d	0.66±0.10###d	0.41± 0.98###a	96.81

*** $P<0.001$: significant difference between groups 1 and 2. ## p<0.01, ### $P<0.001$: significant difference between group 2 and groups 3, 4, 5, 6, and 7. The values assigned with the same letter in the same column are similar. Group 1: non-ulcerative control, Group 2: ulcerative control (Pyloric ligation), Group 3: Cimetidine, Group 4: Maalox, Group 5: AEMk at 125 mg/kg, Group 6: AEMk at 250 mg/kg, Group 7: AEMk at 500 mg/kg (n= 6). AEMk: Aqueous extract of the leaves of *Microdesmis keayana*; US: Ulceration surface, UI: Ulceration index, I (%): Inhibition percentage. D.W: Distilled water.

Table 3. Effect of aqueous extract of the leaves of *Microdesmis keayana* (AEMk) on gastric secretions after pyloric ligation in rats

Groups	Treatment (mg/kg)	Gastric volume (mL)	Gastric pH	Gastric acidity (mEq/L)	Mucus (mg)
Group 1	D.W	nd	nd	nd	152±0.35
Group 2	D.W	7.21±0.19	1.77±0.13	93.5±2.51	47.3±0.21***
Group 3	Cimetidine 12	2.52±0.32###a	5.23±0.21###a	64.8±2.05###a	69.8±0.12###b
Group 4	Maalox 50	2.62±0.22###a	5.90±0.23###a	65.9±1.93###a	73.4±0.11###b
Group 5	AEMk 125	4.82±0.12###b	3.64±0.11###b	76.7±2.25###c	66.8±0.11c
Group 6	AEMk 250	3.43±0.15###a	4.25±0.25###a	73.0±1.75###b	72.7±0.13###b
Group 7	AEMk 500	2.81±0.25###a	5.65±0.29###a	64.6±2.36###a	86.7±0.12###a

*** $P<0.001$: Significant difference between groups 1 and 2. ### $P<0.001$: significant difference between group 2 and groups 3, 4, 5, 6 and 7. The values assigned with the same letter in the same column are similar. Group 1: non-ulcerative control, Group 2: ulcerative control (Pyloric ligation), Group 3: Cimetidine, 12 mg/kg, Group 4: Maalox, 50 mg/kg b.w, Group 5: AEMk at 125 mg/kg, Group 6: AEMk at 250 mg/kg, Group 7: AEMk at 500 mg/kg (n= 6). D.W: Distilled water; nd: not-determined.

of 125 mg/kg and attained 86.7 ± 0.12 mg for the dose of 500 mg/kg (Table 3).

Effect of the aqueous extract of *Microdesmis keayana* leaves on carbachol-induced hypersecretion in rats

Effect of the aqueous extract of Microdesmis keayana leaves on macroscopic parameters

Figure 3 illustrates the macroscopic changes in the stomachs of rats following the various treatments. Table 4 depicts the results of the effects of AEMk leaves on carbachol-induced hypersecretion in rats on macroscopic parameters. No ulceration was observed in the gastric mucosa of the rats in group 1 (non-ulcerative control); hence the score and ulceration index are zero (Figure 2A). In group 2 (ulcerative control group), large stomach ulcerations were noted (Figure 2B). These ulcerations measured 47.9 ± 0.51 mm². A score of 2.33 ± 0.21 and ulceration index of 2.34 ± 0.13 were also recorded. However, in group 3, the ligated control rats that received only carbachol and were pretreated with distilled water (Figure 3C) showed significant increases ($P<0.05$; $P<0.001$) in the ulceration index (2.51 ± 0.53) and the ulceration area (57.3 ± 0.3 mm²) compared to group 2. The pretreatment of the rats in group 4 with atropine (1 mg/kg) only revealed less ulcerations areas of the stomach (Figure 3D). The ulceration areas were significantly reduced ($P<0.001$) compared to group 3. These surfaces measured 5.59 ± 0.32 mm², which corresponded to an inhibition percentage of 89.17%. The groups pretreated with AEMk at doses ranging from 125 to 500 mg/kg exposed moderate lesions as well. Their gastric mucosa disclosed dose-dependent decreases in damage and lesions (Figure 3E, 3F, 3G) compared to group 3 (Figure 3C). Indeed, as shown in Table 3, ulceration areas significantly ($P<0.001$) dropped from 15.6 ± 0.42 to 4.20 ± 0.24 mm², equivalent to an inhibition percentage attaining 93.82 % at 500 mg/kg. Moreover, the score and the ulceration index decreased significantly ($P<0.001$) compared to group 3. These values ranged from 1.08 ± 0.15 (AEMk, 125 mg/kg.) to 0.25 ± 0.17 (AEMk, 500 mg/kg) for the score and from 0.54 ± 0.16 (AEMk, 125 mg/kg) to 0.24 ± 0.12 (AEMk, 500 mg/kg) for the ulceration index.

Effect of the aqueous extract of Microdesmis keayana leaves on carbachol-induced gastric secretions in rats

Table 5 displays the effect of AEMk on gastric secretions induced by carbachol. Group 1 had no observable gastric ulceration. Group 3 (Ligated + Carbachol) showed a very significant increase ($P<0.001$) in the gastric volume, which was 8.24 ± 0.69 mL compared to group 2 (Ligated control), where it was 5.80 ± 0.37 mL.

Significant diminutions ($P<0.001$) in the volume of gastric content in animals pretreated with AEMk 125, 250, and 500 mg/kg were observed compared to those in group 3. The values of gastric volume fluctuated between 5.13 ± 0.21 mL (AEMk 125 mg/kg) and 3.83 ± 0.81 mL (AEMk 500 mg/kg), while that of group 3 was 8.24 ± 0.69 ml. The pH of the gastric content, initially impaired by carbachol in group 3 (1.44 ± 078) as compared to group 2 (2.34 ± 0.11), significantly ($P<0.001$) rose in animals pretreated with AEMk (125-500 mg/kg). It climbed to 4.21 ± 0.44 for AEMk at 500 mg/kg. The use of atropine followed the same tendency as AEMk, with a pH value of 4.09 ± 0.25. The gastric acidity of the groups that received AEMk was significantly ($P<0.001$) lower than that of group 3. The values oscillated between 76.2 ± 3.13 mEq/L (AEMk 125

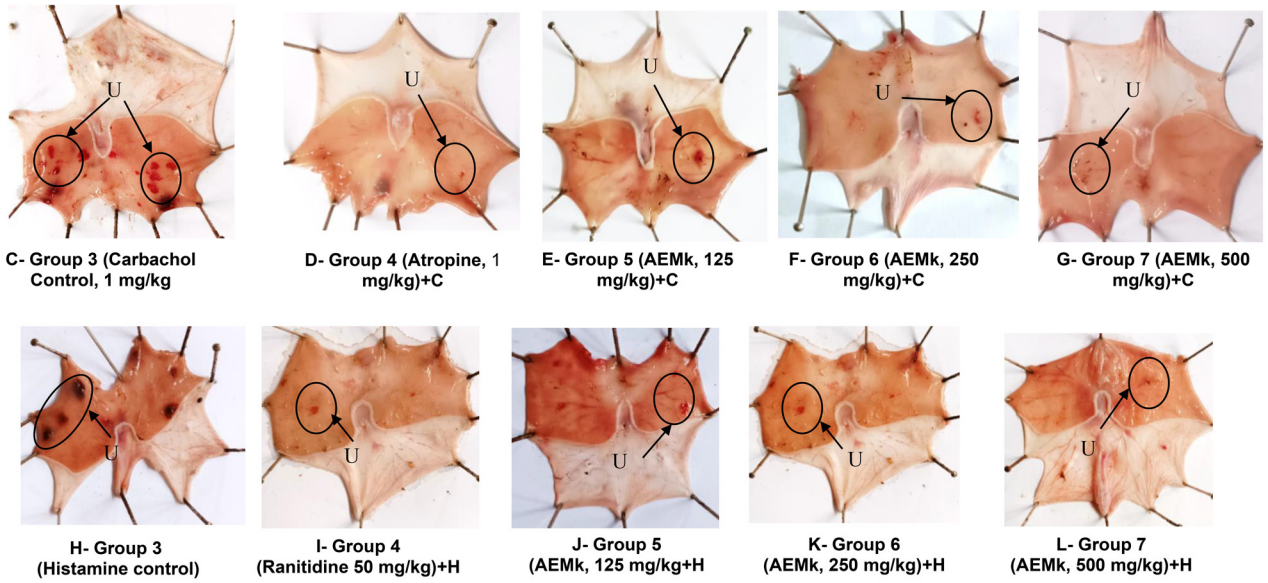

Figure 3. Photographs of the different gastric lesions induced by carbachol and histamine in the pyloric ligation model following various pretreatments. U: Ulceration; C: Carbachol (1 mg/kg), U: Ulceration; H: Histamine (2.5 mg/kg).

Table 4. Macroscopic parameters of carbachol-induced ulcerations after different pretreatments in rats

Groups	Treatment (mg/kg)	US (mm²)	Score	UI	I (%)
Group 1	D.W	00.00±0.00	00.00±0.00	00.00±0.00	nd
Group 2	D.W	47.9±0.51 $^{\Delta\Delta\Delta}$	2.33±0.21 $^{\Delta\Delta\Delta}$	2.34±0.13 $^{\Delta\Delta\Delta}$	nd
Group 3	D.W+C	57.3±0.3***	2.58±0.27	2.51±0.53*	nd
Group 4	Atropine 1+C	5.59± 0.32$^{\#\#\#d}$	0.25± 0.11$^{\#\#\#a}$	0.28± 0.37$^{\#\#\#a}$	89.17
Group 5	AEMk 125+C	15.6±0.42$^{\#\#\#a}$	1.08± 0.15$^{\#\#\#b}$	0.54±0.16$^{\#\#\#a}$	87.39
Group 6	AEMk 250+C	8.61± 0.32$^{\#\#\#b}$	0.75±0.11$^{\#\#\#a}$	0.33± 0.75$^{\#\#\#a}$	91.86
Group 7	AEMk 500+C	4.20±0.24$^{\#\#\#c}$	0.24±0.17$^{\#\#\#a}$	0.24± 0.12$^{\#\#\#a}$	93.82

$^{\Delta\Delta\Delta}$ $P<0.001$: significant difference between groups 1 and 2. *** $P<0.001$: significant difference between group 2 and group 3. $^{\#\#\#}$ $P<0.001$: significant difference between group 3 and groups 4, 5, 6, and 7. The values assigned with the same letter in the same column are similar. Group 1: non-ulcerative control, Group 2: ulcerative control (Pyloric ligation), Group 3: Carbachol control, Group 4: Atropine (1 mg/kg), Group 5: AEMk at 125 mg/kg, Group 6: AEMk at 250 mg/kg, Group 7: AEMk at 500 mg/kg (n= 6). AEMk: Aqueous extract of the leaves of *Microdesmis keayana*; US: Ulceration surface, UI: Ulceration index, I (%): Inhibition percentage, nd: non-determined. C: Carbachol (1 mg/kg b.w.); D.W: Distilled water

Table 5. Parameters of gastric secretions induced by carbachol after the different pretreatments

Groups	Treatment (mg/kg)	Gastric volume (mL)	Gastric pH	Gastric acidity (mEq/L)	Mucus (mg)
Group 1	D.W	nd	nd	nd	138±6.82
Group 2	D.W	5.80±0.37	2.34±0.11	89.2±2.39	40.7±4.79$^{\Delta\Delta\Delta}$
Group 3	D.W+C	8.24±0.69***	1.44±0.78***	121±4.33***	25.8±1.89***
Group 4	Atropine 1+C	3.99±0.61$^{\#\#\#a}$	4.09±0.25$^{\#\#\#a}$	54.7±2.08$^{\#\#\#c}$	95.3±3.37$^{\#\#\#a}$
Group 5	AEMk 125+C	5.13±0.21$^{\#\#\#a}$	3.25±0.71$^{\#\#\#a}$	76.2±3.13$^{\#\#a}$	74.5±5.04$^{\#\#\#b}$
Group 6	AEMk 250+C	4.61±0.61$^{\#\#\#a}$	4.04±0.6$^{\#\#\#a}$	66.0±1.79$^{\#\#\#b}$	99.3±2.58$^{\#\#\#a}$
Group 7	AEMk 500+C	3.83±0.81$^{\#\#\#a}$	4.21±0.44$^{\#\#\#a}$	59.3±1.94$^{\#\#\#b}$	117±4.56$^{\#\#\#c}$

$^{\Delta\Delta\Delta}$ $P<0.001$: significant difference between groups 1 and 2. *** $P<0.001$: significant difference between group 2 and group 3. $^{\#\#\#}$ $P<0.001$: significant difference between group 3 and groups 4, 5, 6, and 7. The values assigned with the same letter in the same column are similar. Group 1: non-ulcerative control, Group 2: ulcerative control (Pyloric ligation), Group 3: Carbachol control, Group 4: Atropine, Group 5: AEMk at 125 mg/kg., Group 6: AEMk at 250 mg/kg, Group 7: AEMk at 500 mg/kg (n= 6). AEMk: Aqueous extract of the leaves of *Microdesmis keayana*, nd: Non-determined. C: Carbachol (1 mg/kg); D.W: Distilled water

mg/kg) and 59.3 ± 1.94 mEq/L (AEMk 500 mg/kg) (Table 5). As for the collected mucus, it significantly ($P<0.001$) fell to reach a value of 25.8 ± 1.89 mg in group 3 compared to the mucus quantity of 40.7 ± 4.79 mg recorded in group 2 (Table 5). The amount of mucus in groups pretreated with AEMk was significantly ($P<0.001$) higher than that of group 3. It varied from 74.5 ± 5.04 mg (AEMk, 125 mg/kg) to 117 ± 4.56 mg (AEMk 500 mg/kg) (Table 5). The amount of mucus was significantly ($P<0.001$) augmented compared to that of the rats in control group 3, reaching 95.3 ± 3.37 mg when rats were pretreated with atropine.

Effect of the aqueous extract of *Microdesmis keayana* leaves on histamine-induced hypersecretion in rats

Effect of the aqueous extract of Microdesmis keayana leaves on macroscopic parameters

Figure 3 and Table 6 show the results of the effect of the aqueous extract of *M. keayana* leaves on histamine-induced hypersecretion in rats. The animals of group 1 (non-ulcerated) that were pretreated with distilled water (1 mL/100 g) had no ulceration (Figure 2). The ulcerated mucosa of rats (ligated) in group 2 exhibited rounded lesions of dark reddish colour in the glandular area of the stomach (Figure 2B). The ulceration surface, the score and the ulceration index were 54.3 ± 1.07 mm², 2.17 ± 0.16 and 2.24 ± 0.40, respectively. In ligated rats' groups that received histamine (group 3), more pronounced dark red ulcers on the glandular portion of the stomach were observed compared to group 2 (Figure 3H). The values of the ulceration index and areas significantly ($P<0.05$; $P<0.001$) increased compared to those of group 2. They were 68.2 ± 0.42 mm² for the ulceration area, 2.50 ± 0.22 for the score, and 2.60 ± 0.16 for the ulceration index.

The pretreatment of the rats with AEMk (125 to 500 mg/kg) caused a significant reduction in the lesions of the gastric mucosa (Figure 3J, 3K, 3L). This reduction resulted in significant drops ($P<0.001$) in the score, surface, and ulceration index compared with those of control group 3. The values diminished from 11.5 ± 0.52 mm² to 3.56 ± 0.08 mm² for the ulceration area, from 1.17 ± 0.15 to 0.16 ± 0.08 for the score and from 0.58 ± 0.24 to 0.24 ± 0.17 for the ulceration index. This corresponded to inhibition percentages ranging from 83.16% to 94.79%.

The administration of ranitidine (50 mg/kg) resulted in a significant decrease ($P<0.001$) in the ulcerations observed in rats, bringing the gastric mucosa almost back

Table 6. Macroscopic parameters of gastric ulcers induced by histamine after various pretreatments in rats

Groups	Treatment (mg/kg)	US (mm²)	Score	UI	I (%)
Group 1	D.W	00.00±0.00"""	00.00±0.00"""	00.00±0.00"""	nd
Group 2	D.W	54.3±1.07"""	2.17±0.16"""	2.24±0.40"""	nd
Group 3	D.W+H	68.2± 0.425***	2.50± 0.22	2.60± 0.16*	nd
Group 4	Ranitidine 50+H	4.56±0.12$^{###b}$	0.16± 0.1$^{###b}$	0.26 ± 0.42$^{###a}$	93.31
Group 5	AEMk 125+H	11.5 ±0·52$^{###a}$	1.17± 0.15$^{###a}$	0.58±0.24$^{###a}$	83.16
Group 6	AEMk 250+H	4.15 ± 0.15$^{###b}$	0.83±0.12$^{###a}$	0.37± 0.25$^{###a}$	93.93
Group 7	AEMk 500+H	3.56 ± 0.08$^{###b}$	0.16±0.08$^{###b}$	0.24± 0.17$^{###a}$	94.79

""" $P<0.001$: significant difference between group 1 and group 2. *** $P<0.001$: significant difference between group 2 and group 3. ### $P<0.001$: significant difference between group 3 and groups 5, 6, and 7. The values assigned with the same letter in the same column are similar. Group 1: non-ulcerative control, Group 2: ulcerative control (Pyloric ligation), Group 3: Histamine, Group 4: Ranitidine, Group 5: AEMk at 125 mg/kg, Group 6: AEMk at 250 mg/kg, Group 7: AEMk at 500 mg/kg (n= 6). AEMk: Aqueous extract of the leaves of *Microdesmis keayana*; US: Ulceration surface, UI: Ulceration index, I (%): Inhibition percentage, nd: Non-determined. D.W: Distilled water; H: Histamine (2.5 mg/kg).

to normal (Figure 3I) with an inhibition rate of 93.31% (Table 6).

Effect of the aqueous extract of Microdesmis keayana leaves on histamine-induced gastric hypersecretion in rats

The effects of AEMk on histamine-induced gastric hypersecretion in pylorus ligated rats are indicated in Table 7. In group 1 (non-ligated control group), no secretion was measured. However, in group 2 (ligated control), the gastric content volume was 6.45 ± 0.17 mL with a gastric pH of 2.34 ± 0.99 and a gastric acidity of 88.8 ± 1.99 mEq/L. The subcutaneous injection of histamine (2.5 mg/kg) to group 3 rats induced a significant rise ($P<0.001$) in gastric volume (8.03 ± 0.44 mL) and gastric acidity (118 ± 1.39 mEq/L) compared to group 2, with a significant fall ($P<0.001$) in gastric pH, which was 1.49 ± 0.89. The ligated rats pretreated with ranitidine (50 mg/kg) and AEMk at 125, 250, and 500 mg/kg and administered with histamine (2.5 mg/kg) displayed significantly ($P<0.001$) lower values in the gastric volume and acidity compared to group 3. The gastric volume of rats that received AEMk decreased from 5.63 ± 0.52 to 3.24 ± 0.31 mL at extract doses of 125-500 mg/kg, whereas that of rats pretreated with ranitidine was 2.37 ± 0.5 ml. As for gastric acidity, values ranged from 78.7 ± 1.48 to 69.5 ± 1.54 mEq/L across the same AEMk dose range and reached 72.2 ± 1.66 mEq/L with ranitidine. However, a significant augmentation ($P<0,001$) of gastric pH was recorded in rats gavaged with AEMk (125, 250, and 500 mg/kg) and ranitidine. Values rose from 3.60 ± 0.45 (AEMk, 125 mg/kg) to 4.34 ± 0.3 (AEMk, 500 mg/kg). For ranitidine, it was 4.43 ± 0.3. The amount of mucus recorded in rats pretreated with AEMk (125, 250 and 500 mg/kg) showed a significant hike ($P<0.001$) when compared to the control group 3. The values shifted from 74.5 ± 5.04 mg in rats that received AEMk at 125 mg/kg to 117 ± 4.56 mg for rats that received AEMk at 500 mg/kg (Table 7).

Discussion

Pharmacological evaluation of AEMk has demonstrated its ability to counteract both excessive gastric acid production and secretory hyperactivity in rat models with pyloric ligation, as well as in cases of hypersecretion induced by histamine and carbachol. Pyloric ligation leads to prolonged accumulation of gastric juice in the stomach (18). Indeed, after pyloric ligation, gastric contents can no longer be evacuated into the duodenum, leading to gastric distension and prolonged stimulation of parietal cells.

Table 7. Parameters of gastric secretions induced by histamine after the different treatments

Groups	Treatment (mg/kg)	Gastric volume (mL)	Gastric pH	Gastric acidity (mEq/L)	Mucus (mg)
Group 1	D.W	nd	nd	nd	125±2.07
Group 2	D.W	6.45±0.17	2.34±0.99	88.8±1.99	34.8±2.95^{ΔΔΔ}
Group 3	D.W+H	8.03±0.44***	1.49±0.89***	118±1.39***	23.7±2.06***
Group 4	Ranitidine 50+H	2.37±0.5$^{###b}$	4.17±0.13$^{###a}$	72.2±1.66$^{###b}$	95.3±3.37$^{###a}$
Group 5	AEMk 125+H	5.63±0.52$^{###a}$	3.60±0.45$^{###a}$	78.7±1.48$^{###a}$	74.5±5.04$^{###c}$
Group 6	AEMk 250+H	4.13±0.32$^{###a}$	4.18±0.15$^{###a}$	70.7±1.26$^{###b}$	99.3±2.58$^{###a}$
Group 7	AEMk 500+H	3.24±0.31$^{###b}$	4.34±0.3$^{###a}$	69.5±1.54$^{###b}$	117±4.56$^{###b}$

$^{ΔΔΔ}P<0.001$ significant difference between group 1 and group 2. *** $P<0.001$: significant difference between group 2 and group 3. ### $P<0.001$: significant difference between group 3 and groups 4, 5, 6, and 7. The values assigned with the same letter in the same column are similar. Group 1: non-ulcerative control, Group 2: ulcerative control (Pyloric ligation), Group 3: Histamine, Group 4: Ranitidine, Group 5: AEMk at 125 mg/kg, Group 6: AEMk at 250 mg/kg, Group 7: AEMk at 500 mg/kg (n= 6). AEMk: Aqueous extract of the leaves of *Microdesmis keayana*; nd: Non-determined. D.W: Distilled water; H: Histamine (2.5 mg/kg).

This stimulation leads to hyperactivation of H_2-histamine receptors, muscarinic (M_3) receptors, and gastrin (CCK2) receptors, promoting the production of hydrochloric acid (19,20). These arguments could explain the significant increase in gastric volume and acidity, as well as the origin of the large ulceration areas observed in the control group rats, whose stomachs were ligated. However, the results revealed that AEMk (125-500 mg/kg) restored secretory and macroscopic parameters. These effects can be attributed to the extract's rich phytochemical composition.

Microdesmis keayana contained saponins, flavonoids, and tannins. This result is in accordance with that of Zamblé et al (21). Saponins help maintain the integrity of the gastric mucosa by stimulating mucus production and strengthening the muco-bicarbonate barrier through positive regulation of mucosal proteins and enzymes that protect against ulceration (22). As for tannins, they bind to mucins and form a protective film on the surface of the mucosa, creating a physical barrier against aggressive agents and thereby increasing tissue resistance (23). Furthermore, flavonoids and tannins possess well-established antioxidant properties that also contribute to the observed gastroprotective effects. However, attributing these effects to specific molecules requires in-depth phytochemical analyses, including chromatographic fractionation and mass spectrometry characterization, to identify and confirm the responsible bioactive compounds. These results are consistent with the observations reported by Goze et al (12), who demonstrated an increase in mucus secretion and a decrease in gastric acid production following the administration to rats of a 70% hydro-ethanolic extract derived from the bark of the *Terminalia superba* (Combretaceae) trunk. Likewise, *Indukanta ghritam* and *Leonotis nepetaefolia* have been shown to have protective effects on gastric ulcers induced by pyloric ligation in rats (24,25). AEMk could protect the gastric mucosa by significantly reducing gastric secretions. To elucidate the action mechanism of AEMk, a study was undertaken on its effect on hypersecretion induced by carbachol and histamine in rats. The results indicated that the hypersecretion control rats exhibited large ulceration plaques accompanied by high gastric secretion with a low pH. Subcutaneous injection of carbachol leads to gastric hypersecretion in ligated rats. Carbachol, a synthetic cholinergic agonist, has a significant effect on the activity of gastric muscarinic receptors, particularly through its regulatory effects on both acid secretion and gastric motility (26).

In this study, both AEMk and atropine, at the doses tested, caused a significant increase in gastric pH, accompanied by a marked decrease in gastric volume and acid secretion. AEMk could act like atropine, which is an inhibitor of gastric acid secretion. Atropine is known to inhibit acid secretion by cholinergic blockade and is used to evaluate the underlying mechanisms of hypersecretion (4). AEMk could contain anticholinergic substances whose effects are similar to those of atropine. Similar observations were reported by Vandi et al (27), who demonstrated the anticholinergic activity of the aqueous extract of the root bark of *Diospyros mespiliformis* (Ebenaceae) administered at doses of 200 and 400 mg/kg to rats.

Histamine-induced hypersecretion in pylorus ligated rats elicited significant increases in gastric volume and acidity and a decrease in gastric juice pH. Histamine plays a key role in the onset and progression of gastric ulcers. It is a key mediator of gastric acid secretion. It interacts with H_2 receptors to influence the integrity of the gastric mucosa and thus increases acid production (28). This increase in acid secretion can contribute to the development of gastric ulcers, especially when the protective mechanisms of the gastric mucosa are compromised. Histamine-induced gastric ulceration is mediated not only by increased acid secretion but also by vasospastic effects, which can alter gastric blood flow and exacerbate mucosal damage (29,30). Pretreatment of rats with AEMk (125 to 500 mg/kg) and ranitidine significantly reduced gastric content volume, gastric acidity, and increased gastric juice pH compared to rats in group 3 (histamine control rats). In addition, the marked increase in gastric mucus production played a key role in the significant reduction in mucosal ulceration observed in animals that had received prior treatment. The effect of AEMk in rats pretreated with this extract at the studied doses was similar to that of rats pretreated with ranitidine. Consequently, the mechanism of action of AEMk appears to be similar to that of ranitidine. Indeed, ranitidine is used to treat ulcers by reducing the production of gastric acid. Its main mechanism of action consists of blocking H_2 histamine receptors on the parietal cells of the stomach, which decreases the formation of cAMP and, consequently, gastric acid secretion, eventually promoting ulcer healing (31-33). More elaborate experiments are required to verify this hypothesis. Vandi et al, Amir et al, and Vaibhav et al (27,34,35) obtained similar results with aqueous extract of *Diospyros mespiliformis* (Ebenaceae) root bark, aqueous extract of *Withania coagulans* (Solanaceae) fruit, and hydroalcoholic extract of *Ficus glomerata* (Moraceae) leaves, respectively. Previous studies have shown that aqueous extracts obtained from the root bark of *Diospyros mespiliformis* and the fruit of *Withania coagulans* were comparable to those of the standard antagonists of carbachol and histamine in the pyloric ligation model and that they protected the gastric mucosa against gastric acid.

The lack of histopathological analysis is a limitation of this study. Although macroscopic parameters showed a significant reduction in gastric lesions, a microscopic evaluation could have confirmed the integrity of the mucosa, the depth of the lesions, and the extent of inflammatory infiltration. Furthermore, the proposed antihistaminic and anticholinergic effects are based on indirect pharmacological approaches using ranitidine and atropine as standards. Further studies, especially, receptor

binding assays or studies on isolated parietal cells are needed to confirm these mechanisms of action.

Conclusion

The aqueous extract of *M. keayana* leaves (AEMk) exhibits anti-secretory and anti-acid activities, as evidenced by an increase in gastric mucus production and inhibition of acid secretion. These effects may result from modulation of cholinergic and histaminergic pathways, probably linked to the secondary metabolites of tannins, saponins and flavonoids in the extract. The results suggest a possible involvement of muscarinic receptors and H_2-histaminic receptors; however, this hypothesis must be confirmed by receptor-binding studies, the use of selective pharmacological antagonists or experiments on isolated cells.

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Authors' contribution

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Conflict of interests

The authors declared no conflict of interest.

Ethical considerations

The protocol was approved by the ethics committee for animal experimentation at our university. The code was N° 001/CEEA/2023. All experimental procedures were conducted in accordance with European Community guidelines (Directive 86/609/EEC of November 24, 1986).

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