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Gastroprotective effect test of ekor naga leaves extract (*Rhaphidophora pinnata* (L.f) Schott) on male white rats

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ABSTRACT: *Rhaphidophora pinnata* leaves are one of the herbal plants that have pharmacological effects. Previous research has shown that ekor naga leaves contain secondary metabolites with tonic pharmacological effects, including the ability to heal cut wounds, as well as antihyperglycemic and antidiabetic properties. This research aims to demonstrate the potential of ekor naga leaf extract as a gastroprotective agent. The extract was evaluated using standard methods, including determination of water content, ash content, phytochemical screening, and compound identification by LC-MS. Gastroprotective testing was carried out by dividing the treatment group into six groups, including the Group 1: normal group, Group 2: negative control (Sodium CMC 0.5%), Group 3: positive control (Sucralfate), Group 4: 125mg/KgBW extract, Group 5: 250 mg/KgBW extract, and Group 6: 500mg/KgBW extract. The results of the observations were in the form of gastric ulcer severity scores and histological images of the gastric organs. Gastroprotective testing revealed significant differences between the treatment groups and the negative control group ($p<0.05$). The 500 mg/kgBW extract exhibited the most effective gastroprotective effect, with a 42.5% inhibition rate and minimal inflammation observed both macroscopically and microscopically. These results suggest that ethanol extract from ekor naga leaves may serve as an alternative or complementary therapy for gastritis.

KEYWORDS: Extract; gastroprotective; one way anova*; Raphidophora pinnata*; rats.

INTRODUCTION

Gastric ulcers are a prevalent health issue affecting all age groups. These inflammatory conditions, characterized by lesions on the stomach wall, can potentially escalate to gastroesophageal reflux disease (GERD), a condition that may have fatal consequences [1], [2]. The prevalence of gastric ulcer disease continues to increase annually. The prevalence range for men is 11-14%, while for women, it is 8-11%. In Indonesia, the prevalence ranges from 6% to 15%, with an average age of 20-50 years [3].

Treatments for gastric ulcers, such as ranitidine, antacids, and omeprazole, help reduce stomach acid, but eliminating inflammation requires additional therapy from other drugs [4], [5], [6]. Meanwhile, inflammatory therapy generally causes side effects for the stomach, from increased stomach acid to the potential to trigger ulcers in the stomach, one example of which is therapy using NSAID drugs[7].

Studies have demonstrated that ekor naga leaves possess anti-inflammatory properties. Given their rich content of secondary metabolites, including alkaloids, flavonoids, saponins, steroids, and tannins, these leaves hold promise as a natural remedy for gastric ulcers. These compounds may act synergistically to reduce inflammation and suppress stomach acid production. Ekor naga leaves have a long history of use in traditional medicine and have been extensively investigated for their pharmacological potential. Research has explored their effects in various areas, including anti-inflammatory, wound healing, burn healing, antihyperglycemic, antidiabetic, anti-hyperuricemic, and antihyperlipidemic properties. Additionally, researchers have conducted studies on their acute toxicity and teratogenic effects[8], [9], [10], [11], [12], [13]. The Research conducted by Pan et al. (2019) supports the fact that ekor naga leaves Extract contains active compounds that act as inflammatory inhibitors in Rhaphidophora pinnata leaf extract, which pharmacologically has shown that *Rhaphidophora pinnata* leaf extract inhibits LPS-stimulated mRNA induction that encodes pro-inflammatory cytokines and leukocyte adhesion molecules, such as TNF-α, IL-1β, IL-8, and COX-2 [14].

Based on the potential of the compounds above, researchers believe it is necessary to test the effects of ekor naga leaves Extract as a gastroprotective agent.

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MATERIALS AND METHODS

Materials

Ekor naga leaves from Mendalo (Jambi) and identified by a taxonomist from Padjajaran University, where voucher specimen 07/HB/03, male white rat weighing 200-250 grams which has been approved for use based on the results of an ethical clearance examination conducted by the ethics committee of the Faculty of Medicine and Health Sciences, University of Jambi with number 1394/UN21.8/PT.01.04. All animal treatment and research implementation adheres to the reporting principles of the 2020 ARRIVE guidelines[15], 70% ethanol (Brataco, Indonesia), Na.CMC, sucralfate (Combiphar, Indonesia), formalin, 1% NaOH (Merck, Jerman), 96% ethanol (Brataco, Indonesia), absolute ethanol (Merck, Jerman), hematoxylin (Merck, Jerman), eosin (Merck, Jerman), xylazine (Bimoda, Indonesia), ketamine (Medistar, Indoensia), paraffin (Paraflakes, India), distilled water, gallic acid (Merck, Jerman), 0.9% NaCl (PT. Wıdatra Bhakti, Indonesia), aluminum chloride (Merck, Jerman), sodium acetate (Merck, Jerman), folin-ciocalteu reagent (Merck, Jerman), Quercetin (Merck, Jerman).

Extraction of ekor naga leaves

Ekor naga leaves extraction was performed using the maceration method. Five hundred grams of simplicia powder were placed into a large, dark bottle, and solvent was added until the simplicia was completely submerged. The ratio of the simplicia to the solvent used is 1:10. Then, stirring was performed periodically for two days at room temperature (25±2 °C), and the mixture was protected from light. The maceration outcomes were filtered using filter paper. The dregs have been re-macerated in 2 instances. The maceration consequences have been thickened with the use of a rotary evaporator. The maceration outcomes were then measured for ash content, water content, Ethanol-Soluble Essence content, Water-Soluble Essence content, and phytochemical screening.

Total phenolic content

The determination of total phenolic content was conducted using the Folin-Ciocalteu method, with slight modifications based on the research test procedure by Khan et al[16]. The quantification of phenolics was achieved by using a regression equation derived from a standard curve of gallic acid with concentrations ranging from 5 to 50 ppm. The preparation of the extract sample was carried out by preparing an extract concentration of 250 ppm, by weighing 6.25 mg of extract into a 25 mL measuring flask. Add 25 mL of methanol p.a. Stir using a magnetic stirrer. Testing the phenol content began by taking 1 mL of each solution from each concentration series. Then, add 5 mL of Folin-Ciocalteu solution, let it stand for 8 minutes, and add 4 mL of 1% NaOH. Incubate for 1 hour in a dark room. Absorbance measurement using a maximum wavelength of 730nm. The same process is applied to the blank. The total phenol yield was expressed in mg equivalents of gallic acid per gram of sample (mg GEA/g Extract).

Total flavonoid content

Measurement of total flavonoid levels was performed using the aluminum chloride reagent color reaction method, following the research procedure of Alara et al. with slight modifications. The equation from the quercetin standard curve, with a concentration range of 25-100 ppm, was used [17]. Absorbance was measured at 440 nm using UV Vis Spectrophotometer. Variations in extract concentration were made by preparing a 500 ppm main solution by weighing 12.5 mg of extract, adding 25 mL of methanol p.a., and stirring for 30 minutes using a magnetic stirrer. Then, pipette 0.5 mL of the sample solution, add 1.5 mL of absolute ethanol, 1 mL of 10% $AlCl_3$, 0.1 mL of sodium acetate, and distilled water until the volume reaches 10 mL. Incubate the mixture at room temperature and in a dark place for 30 minutes. Finally, measure the absorbance using a wavelength of 440 nm. The total flavonoid content was determined using a linear regression equation derived from a standard curve of quercetin, and the results were expressed as quercetin equivalents per gram of Extract (mg QE/g Extract)

LCMS Profile

LC-MS was used to identify the chemicals in *Epipremnum pinnatum* leaf extract with minimal adjustments to the work protocols used by Ismed et al [18]. Ten milligrams of *Epipremnum pinnatum* leaf extract was weighed and dissolved in 10 mL of methanol using a measuring flask. This research used an ultra-Performance Liquid Chromatography (UPLC) (LC: ACQUITY UPLC H-Class System, Waters, USA) and a mass spectrometer (Xevo G2-S QTof, Waters, USA). This experiment used a C-18 column (1.8µm 2.1 x 100 mm,

ACQUITY UPLC HSS, Waters, USA) with a column temperature of 500 °C and a room temperature of 250 °C. The mobile phase used in this analysis consisted of a mixture A (water+5 mM ammonium formate) and mixture B (acetonitrile+0.05% formic acid), flow rate using a gradual gradient of 0.2 mL/min for 23 minutes and an injection volume of 5 µL, which had been previously filtered using a 0.2 µm filter syringe. MS analysis used electrospray ionization (ESI) positive charge mode with a mass range of 50-1200 m/z and source and desolvation temperatures of 100 and 350 °C, respectively. Then cone gas flow rate and desolvation of 50L/h and 793L/h were also used sequentially with collision energy varying between 4-60 eV. Polar compounds produced chromatograms first, followed by compounds with lower polarities. The chromatogram peaks were interpreted using the MassLynx application [19].

Gastric ulcer effect test

The gastroprotective effects of ekor naga leaf extract were evaluated in male Wistar rats weighing 200-250 grams. The test animals were acclimatized for a week before the experiment began. The test animals were housed in a room with a controlled temperature of 25±3 °C and a relative humidity of 40-60%, maintained under a 12-hour light-dark cycle. This research has passed an ethical review conducted by the Ethics Committee of the Faculty of Medicine and Health Sciences, University of Jambi, with letter number 1394/UN21.8/PT.01.04. Each treatment group consisted of five rats. Five test animals were chosen because most studies use a range of test animals between 5 and 8 rats [20]. The division of treatment groups is as follows:

Group 1	:	Without Induction and Treatment (Normal)
Group 2	:	Na CMC 0.5% as much as 2 mL (Negative control)
Group 3	:	Sucralfate 180 mg/Kg BW (Positive Control)
Group 4	:	The Extract was given a dose of 125 mg/kg BW.
Group 5	:	The Extract was given a dose of 250 mg/kg BW.
Group 6	:	The Extract was given a dose of 500 mg/kg BW.

The therapy was given for 14 days. After the therapy, the test animals were induced using 96% ethanol except for the normal group, and fasted for 24 hours. On the fifteenth day, the experimental animals were euthanized through anesthesia administered via intraperitoneal injection of ketamine hydrochloride (50mg/kg body weight) and xylazine hydrochloride (10mg/kgBW body weight). Perform gastric removal surgery from the esophagus to the bottom of the pylorus (the distal part connected to the duodenum). Wash the stomach with NaCl solution. Physiology: Observe the ulcer damage index after completion and store the internal organs in 10% formalin. Macroscopic observation will later become a parameter to measure the ulcer index, which includes Ulcer Count Parameters and Ulcer Bleeding Score [21]-[23]. The ulcer index result will be used as the basis for obtaining the percentage value of gastric damage inhibition.

Table 1. Ulcer count parameters.

Score	Ulcer count parameters
1	Normal
2	Bleeding spots
3	Amount of bleeding 1-3 locations
4	Amount of bleeding 4-6 locations
5	Amount of bleeding 7-9 locations
6	Amount of bleeding>9 locations or perforation

Table 2. Ulcer bleeding score.

Score	Ulcer bleeding score
1	Normal
2	Bleeding spot
3	Light bleeding
4	Moderate bleeding
5	Heavy bleeding
6	Perforation / The entire mucosal area is bleeding.

The ulcer index value is determined using the following formula:

UI = UC + UB + 0,1 PU
UI: Ulcer Index
UC : Ulcer Count
UB : Ulcer Bleeding
PU: Percentage of animals affected by ulcers in each treatment group
Meanwhile, the percentage of Ulcer Index (UI) is calculated using the formula:

$$\% \text{ UI} = \frac{\text{UI control} - \text{UI tested}}{\text{UI control}} \text{ x } 100\%$$

Data analysis

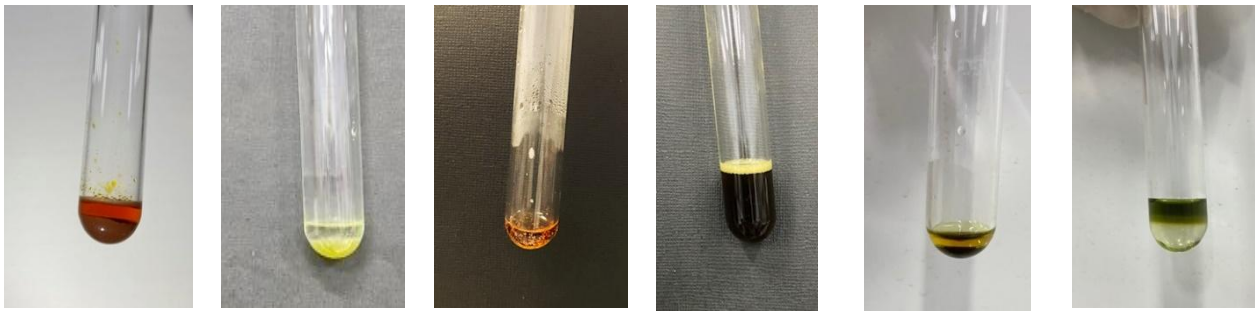
The test data were analyzed using two methods: first, a descriptive approach, namely, Extract testing, and histological description of the stomach organ. Both stomach bleeding scores were analyzed using SPSS 21 software, which consists of several stages. First, normality and homogeneity tests were performed. If these tests were met, the significance value was then measured using the one-way ANOVA method with a 95% confidence level ($p<0.05$). The third stage is the Duncan post hoc test. If the ANOVA test requirements are not met, a significance test employing a nonparametric approach will be used.

▪ RESULTS

The results of the standardization tests conducted on the ekor naga Leaves Extract encompassed the following parameters: water content, ash content, ethanol-soluble extract content, water-soluble extract content, and phytochemical screening.

Table 3. Extract standardization results.

No	Test Parameters	Results (%b/v)
1	Water content	26.94
2	Ash content	13.32
3	Ethanol soluble essence content	54.16
4	Water soluble essence content	60.49



A B C D E F

Figure 1. Phytochemical Screening Results of Ekor naga Leaves Extract. A: Alkaloids with Dragendorff reagent; B: Alkaloids with Mayer reagent; C: Flavonoids; D: Saponins; E: Tannins; F: Steroids.

Figure 1 demonstrates that ekor naga leaf extract contains alkaloids, flavonoids, saponins, tannins, and steroids. The quantitative analysis of total phenolic and flavonoid levels within the ethanol extract of ekor naga leaves is presented in Table 4.

Table 4. Results of Total Phenol and Total Flavonoid Tests content.

Sample	Total phenol content	Total flavonoid content
Ethanol extract of ekor naga leaves	188 mg GAE/gram	72.06 mg QE/grams

The results of the LC-MS analysis yielded a spectral chromatogram with 12 peaks (Figure 1), representing bioactive compounds that interact with the LC column.

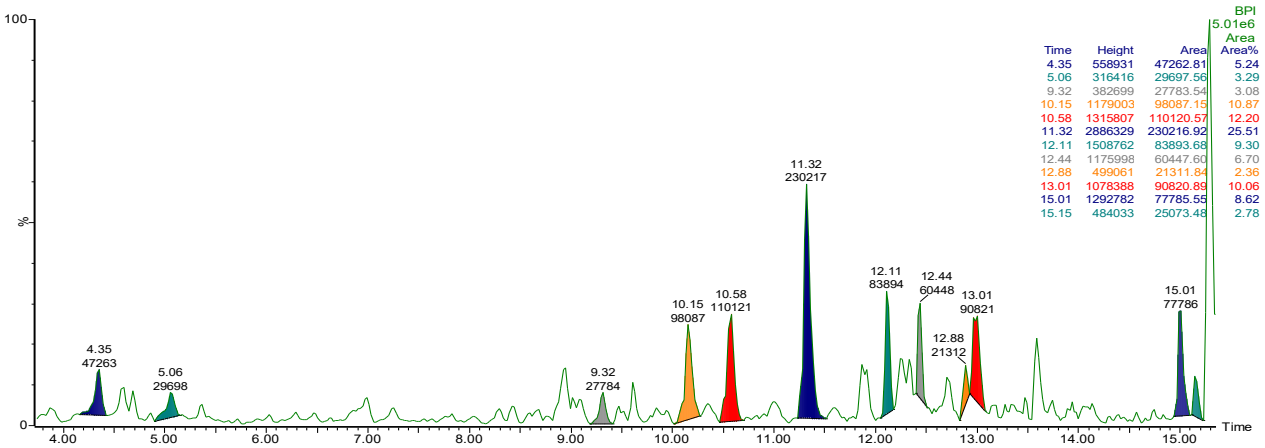
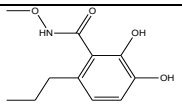
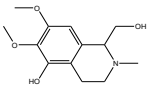
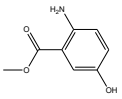
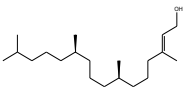
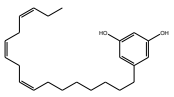
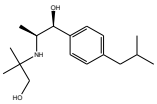
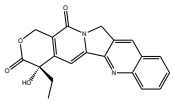
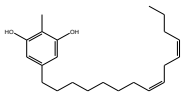
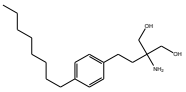
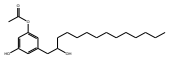
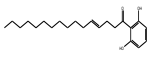


Figure 2. LC-MS chromatograms of ekor naga leaves (*Raphidopora pinnata*) extracts.

Table 5. Tentative metabolites identified in the ekor naga leaves (*Raphidopora pinnata*) extracts through LC-MS fragmentation using positive ionization.

No	Prediction compound	Molecular formula	Calculated mass (m/z)	Molecular weight	RT	Group	Chemical structure
1.	2,3-dihydroxy-n-methoxy-6-propylbenzenecarboximidic acid	$C_{11}H1_5NO_4$	226.1078	213.23	4.35	alkaloid	
2.	1-(hydroxymethyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-1h-isoquinolin-5-ol	$C_{13}H_{19}NO_4$	254.1388	253.29	5.06	alkaloid	
3.	8-methylnonyl 2-amino-5-hydroxybenzoate	$C_{17}H_{27}NO_3$	294.2062	293.40	9.32	alkaloid	
4.	Phytol	$C_{20}H_{40}O$	297.1404	296.53	10.15	hydro-carbon	
5.	5-(heptadeca-8,11,14-trien-1-yl)benzene-1,3-diol	$C_{23}H_{34}O_2$	343.2945	342.52	10.58	phenolic	
6.	6-(deca-1,3,5-trien-1-yl)-2-(hydroxymethyl)-1-methylpiperidin-3-ol	$C_{17}H_{29}NO_2$	280.2306	279.42	11.32	alkaloid	
7.	Camptothecin	$C_{20}H_{16}N_2O_4$	349.2757	348.35	12.11	alkaloid	
8.	2-methyl-5-(pentadeca-8,11-dien-1-yl)benzene-1,3-diol	$C_{22}H_{34}O_2$	331.2633	330.50	12.44	phenolic	
9.	6-(6-hydroxy-2,5-dimethyloct-4-en-1-ylidene)-8-methyl-hexahydroindolizin-8-ol	$C_{19}H_{33}NO_2$	308.2607	307.47	12.88	alkaloid	
10.	Eleostearic acid	$C_{18}H_{30}O_2$	279.2315	278.43	13.01	fatty acid	
11.	3-hydroxy-5-[(2s)-2-hydroxytetradecyl]phenyl acetate	$C_{22}H_{36}O_4$	365.2700	364.5197	15.01	phenolic	
12.	1-(2,6-dihydroxyphenyl)hexadec-4-en-1-one	$C_{22}H_{34}O_3$	365.2687	346.50	15.15	phenolic	

Note: RT: Retention Time

Macroscopic examination of the stomach revealed that the ekor naga leaves extract exhibited gastroprotective properties. Compared to the control group, the 500 mg/kg BW dose demonstrated the most significant ulcer inhibition at 42.5% and an Ulcer Index of 11.5, followed by 250 mg/kg BW and 125 mg/kg BW. This gastroprotective effect was statistically significant ($p<0.05$) (Table 6, Figure 3, and Figure 4).

Table 6. Ulcer calculation results.

Group	Ulcer count score	Ulcer bleeding score	PU	0.1xPU	Ulcer index	Ulcer inhibition
Normal	1.00±0.000[a]	1.00±0.000[a]	0	0	2	-
Na CMC 0.5%	5.00±0.4082[d]	5.00±0.2082[d]	100	10	20	-
Sukralfat 180mg/KgBW	2.4±0.2500[b]	2.00±0.2500[b]	60	6	10.4	52%
125mg/KgBW Extract	4.75±0.4787[d]	3.25±0.2500[c]	80	8	16	20%
250mg/KgBW Extract	3.75±0.4787[c]	3.25±0.2500[c]	80	8	15	25%
500mg/KgBW Extract	2.75±0.4787[b]	2.75±0.4787[b]	60	6	11,5	42.5%

Note :

1. The data analysis employed was a one-way ANOVA with a significance value of 0.05 ($p<0.05$). Significant differences in each treatment can be observed from the superscript letters in the research results.
2. PU: Percentage of animals affected by ulcers in each treatment group

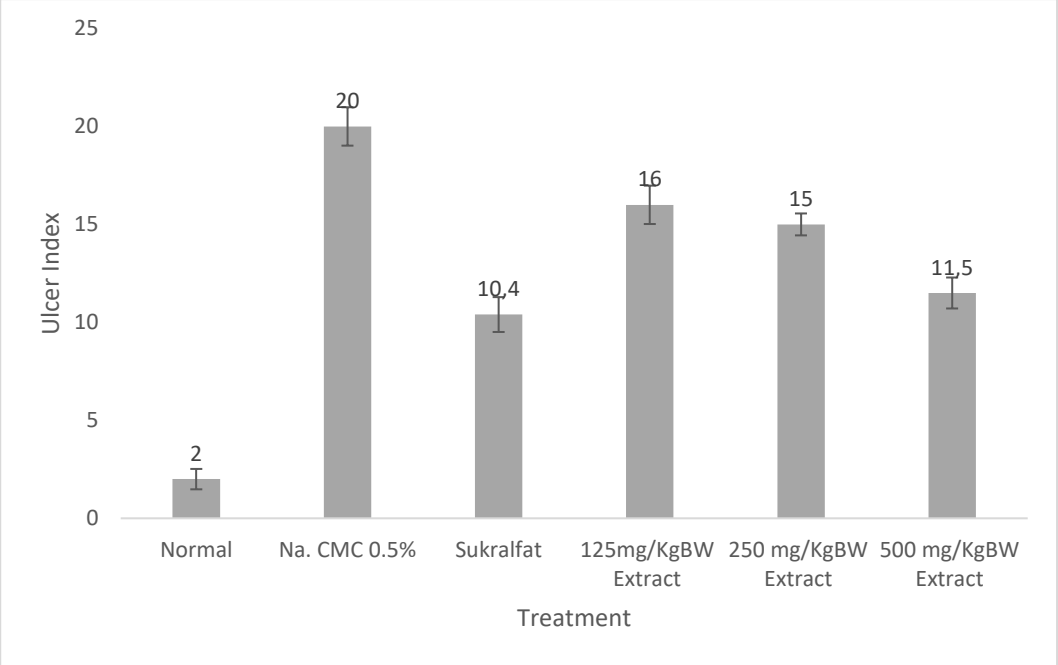


Figure 3. Diagram Ulcer index ımprovement graph in the experimental group.

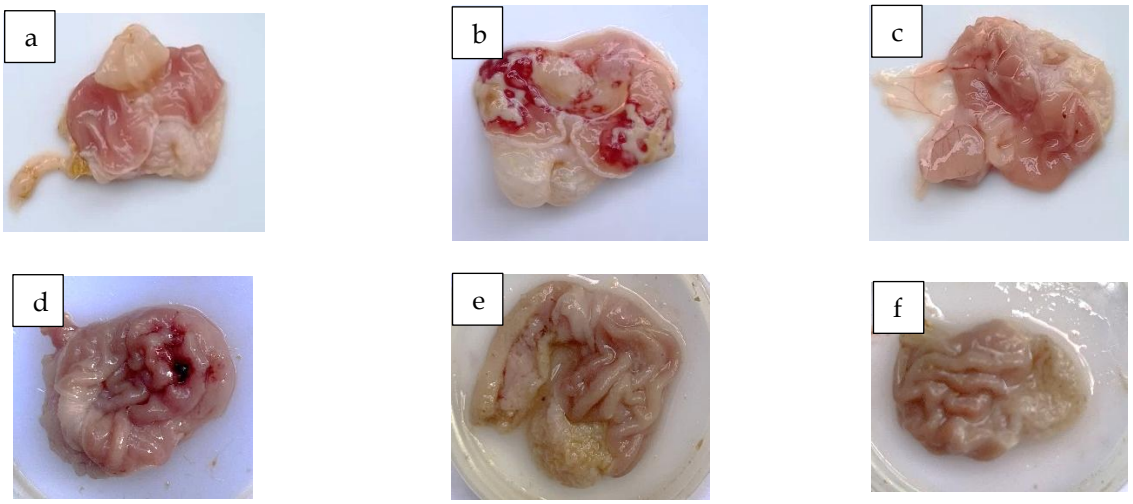


Figure 4. Macroscopic figure of the stomach after treatment; a. normal group, b. NaCMC groups, c. sucralfate 180 mg/KgBW, d. extract 125 mg/KgBW), e. extract 250 mg/KgBW, f. extract 500 mg/KgBW.

The results of microscopic observations show the presence of erosion in the stomach lining, which triggers cell vasodilation (Figure 5).

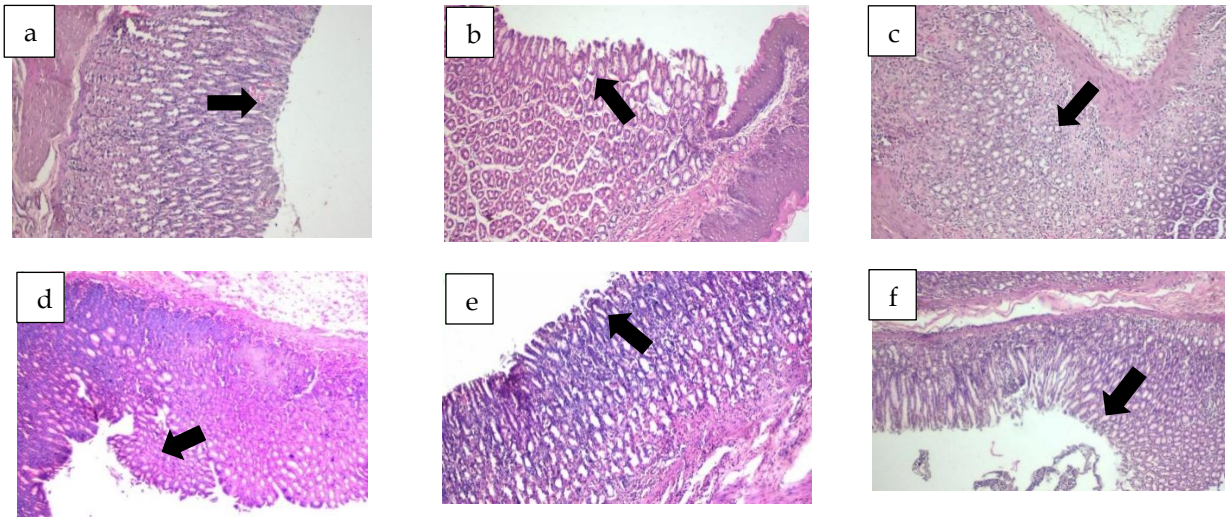


Figure 5. Microscopic view of the stomach; hematoxylin eosin staining; magnification: 100x; arrows in photo a showed deep mucosal layer; a. normal group, b. NaCMC groups, c. sucralfate 180 mg/KgBW, d. extract 125 mg/KgBW), e. extract 250 mg/KgBW, f. extract 500 mg/KgBW.

▪ DISCUSSION

Ekor naga leaves were determined at Padjajaran University with letter number 07/HB/03, which stated that the plants used as samples in this Research were proven to be ekor naga leaves plants (*Rhaphidophora pinnata* (L.) Schott). The ekor naga leaf extract contains alkaloids, flavonoids, saponins, tannins, and steroids. This finding aligns with the literature, specifically the work of Pascila et al. which reports the presence of these secondary metabolites (alkaloids, steroids, flavonoids, saponins, tannins) in ekor naga leaves [10], [24].

Phenolic compounds are compounds found in almost all components of secondary metabolites. The OH-compound content can provide antioxidant activity for repairing damaged tissues resulting from exposure to free radical compounds. While flavonoids are one of the largest metabolite groups with diverse types,

approximately 9,000 types of structures have been recorded as types of flavonoid compounds. This compound is found in almost all herbal plants. The study's results showed that flavonoid compounds play a role in protecting the gastric mucosa from injury. The strong antioxidant activity of phenols and flavonoids can reduce free radical compounds, inhibit oxidizing enzymes, and reduce lipid peroxidation. These activities show that flavonoid compounds are active as gastroprotective agents from the ekor naga leaves extract[24].

The results of the LC-MS analysis yielded a spectral chromatogram with 12 peaks (Figure 1), representing bioactive compounds that interact with the LC column. Six identified compound peaks showed potential as anti-inflammatory agents, potentially preventing inflammation associated with gastric ulcers. The estimated activity of compounds suspected to be present in ekor naga leaves extract based on LC-MS results was traced through a literature review on the NCBI website and previous research. The suspected compounds are: 1-(hydroxymethyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-1H-isoquinolin-5-ol [25], Phytol [26], 6-(deca-1,3,5-trien-1-yl)-2-(hydroxymethyl)-1-methylpiperidin-3-ol [27], Camptothecin [28], 6-(6-hydroxy-2,5-dimethyloct-4-en-1-ylidene)-8-methyl-hexahydroindolizin-8-ol [29] , and Eleostearic acid [30].

The effect of ekor naga Leaves Extract was tested using 96% ethanol as an inducer. Ethanol can damage the gastric mucosa, alter the permeability of the epithelial barrier, and facilitate the back diffusion of hydrochloric acid, thereby damaging the tissue. Ethanol can also induce intracellular oxidative stress, leading to mitochondrial permeability transition and depolarization, which can cause cell death in the gastric mucosa. If the mucosal cells die, it triggers phagocytosis, which can release free radicals [31].

Sucralfate, a standard ulcer medication, served as the positive control in this Research. It functions by adhering to ulcer sites, triggering the release of prostaglandins in the stomach lining, which enhances local protection. This involves aiding in the repair of the gastric mucosa by increasing the protective barrier of phospholipids and stabilizing mucus production. Notably, sucralfate binds to the basic fibroblast growth factor (bFGF), a crucial factor in ulcer healing. bFGF stimulates the growth of new tissue (granulation tissue), the formation of new blood vessels (angiogenesis), and the proliferation of smooth muscle cells, all of which contribute to ulcer healing [32]. The results of microscopic observations show the presence of erosion in the stomach lining, which triggers cell vasodilation. Vasodilation of cells observed under a microscope was a response of the gastric mucosa due to decreased mucus secretion. Vasodilation occurs because, in the gastric mucosal layer, there are cells that can produce HCl in the blood vessels and fundus. Vasodilation of the mucosa would cause increased HCl production. Vasodilation is mediated by the mechanism of COX-1 and COX-2, where COX-1 converts PGH2 into prostaglandins and thromboxane, thereby maintaining homeostasis. COX-2 would convert PGH2 into PGE2 by various mechanisms. Prostaglandin E2 (PGE2) was what would cause vasodilation. PGE2 would also cause increased vascular permeability, leading to increased blood flow and enlarged capillary pores. If the capillary pores enlarge, it would cause plasma proteins to exit and enter the inflamed tissue [33], [34], [35].

Ekor naga leaves contain secondary metabolites, specifically flavonoids, which exhibit cytoprotective activity against the gastric mucosa by binding free radicals and acting as antioxidants, thereby increasing mucus production and exhibiting antisecretory effects. Flavonoids will increase the content of mucosal prostaglandins, decrease histamine secretion from mast cells by inhibiting histidine decarboxylase, and inhibit the growth of *Helicobacter pylori*. Ekor naga leaves also contain secondary metabolite compounds of alkaloids, which can increase gastric pH. Steroids work by inhibiting the phospholipase A2 enzyme, which is involved in arachidonic acid synthesis, and thereby prevent the production of inflammatory mediators. Saponins activate protective factors in the mucous membrane, and tannins can protect the stomach by increasing the irritant defense factor, as well as providing antioxidants and anti-inflammatory properties, thereby helping to repair tissue [5].

▪ CONCLUSION

The conclusion from the results of the Research above is that there is an effect of administering the ethanol extract of ekor naga leaves on gastroprotective healing, with the best dose being group 6, namely 500 mg/KgBW. This Research has shown that the ekor naga leaves extract has the potential to be developed as an alternative gastroprotective therapy. Further Research is needed to isolate and quantify the bioactive compounds that play a gastroprotective role.

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