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Antidiarrhea Activity of Ethanol Extract of Rambutan Leaves (*Nephelium lappaceum* L.) in Capsule Form on Male Mice

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Abstract

Background*: Diarrhea is characterized by changes in stool form to soft or liquid, with an intensity of bowel movements more than three times a day. One of the plants used as an alternative treatment for diarrhea is rambutan, particularly its leaves. Previous studies have shown that rambutan leaf extract can treat diarrhea.* ***Objective****: The purpose of this study was to determine the antidiarrhea activity of ethanol extracts of rambutan leaves containing tannins and flavonoids that inhibit intestinal motility.* ***Methods****: This study was conducted experimentally using the intestinal transit method, which measures the length of the intestine passed through a marker. The smaller the ratio between the length of the intestine and the marker, the greater the decrease in intestinal motility in the mice. Group 1: loperamide HCl at a dose of 4 mg/kg BW; Group 2: placebo; Group 3: FI, FII, and FIII capsules at doses of 50 mg, 100 mg, and 150 mg.* ***Results****: The test results showed that Formulations 1, 2, and 3 had activities of 23.3%, 26.8%, and 32.3%, respectively. The capsule with the best results was formulation 3, at a dose of 150 mg. Compared with the positive control, the effectiveness of this capsule was 22% higher than that of loperamide.* ***Conclusion****: The results of this study showed that rambutan leaves extracted in capsule form effectively treats diarrhea. The one-way ANOVA test showed a significant difference between the FI, FII, and FIII groups ($p < 0.05$).*

Keywords*: antidiarrhea, capsule, intestinal transit, rambutan, tannin*

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INTRODUCTION

Diarrhea is a disease characterized by changes in the form of stool that becomes runny, with an intensity of bowel movements more than three times a day. Diarrhea can cause loss of fluids in the body, disruption of acid-base balance, dehydration, and even death. In 2018, diarrhea sufferers were toddlers who were served in health facilities, with as much as 40.90% of the estimated diarrhea in health facilities (Wahyuni, 2021). One of the treatments for diarrhea is antidiarrheal drugs that can reduce peristaltic movements in the intestines. Drugs used in the treatment of diarrhea are divided into several categories: antidiarrhea antipyretic, antipyretic, antipyretic, motility, adsorption, and anti-secretion properties (Hermansyah & Parinding, 2022). Rambutan plants are used to treat diarrhea. One part of the rambutan plant that can be used for antidiarrheal treatment is the leaves that contain tannins and flavonoids, which are astringent by shrinking the mucous membranes and shrinking the pores so that they can inhibit the release of excess fluids and electrolytes (Fadilah et al., 2023). Based on the research conducted by Suherman et al. (2013), the ethanol extract of rambutan leaves has antibacterial activity that is effective in suppressing the development of *Escherichia coli*. With the potential of rambutan leaves as an antibacterial agent, it is hoped that rambutan leaves can be used as an antidiarrheal agent caused by bacteria. To enable the public to utilize rambutan leaf extract as a remedy for diarrhea, it is essential to develop a capsule formulation of this substance. In addition, rambutan leaf extract in capsule form was also used to maintain the stability of the extract and facilitate marketing. Compared with other forms, capsule preparations are easier to use and can eliminate the odor of the extract preparation. In addition, the dry extract contained fewer bacterial cells.

MATERIALS AND METHODS

Material

Chemical material

Rambutan leaves and 96% ethanol (PT. Dipa Prasada Husada, Tasikmalaya), Loperamide HCl (PT. Nufarindo, Semarang), gelatin (PT. Dipa Prasada Husada, Tasikmalaya), avicel PH 101 (PT. Dipa Prasada Husada, Tasikmalaya), aerosil (PT. Dipa Prasada Husada, Tasikmalaya), stearic acid (PT. Dipa Prasada Husada, Tasikmalaya), lactose (PT. Dipa Prasada Husada,Tasikmalaya), 2N HCl (PT.Dipa Prasada Husada, Tasikmalaya), Mg powder (PT. Dipa Prasada Husada, Tasikmalaya), and $FeCl_3$ (PT. Dipa Prasada Husada, Tasikmalaya).

Reagent

Dragendorff reagent, Wagner reagent, and Lierbermann-Buchard reagent

Equipment

Glassware (Pyrex, Indonesia), water bath (B-One), digital scale (Radwag), oven (Memmert Un55 Oven, Germany), surgical instruments, rotary evaporator (Nanbei, China), oral sonde, surgical scissors, and tweezers were used.

Method

Extraction

Extraction of rambutan leaves (*Nephelium lappaceum* L.) using maceration was used because flavonoid compounds are not resistant to heating. The 96 ethanol was used because it is a universal solvent that can attract polar compounds such as flavonoids and tannins. This maceration method uses 500 g of rambutan leaf powder and 5000 mL of 96% ethanol (Hermansyah & Parinding, 2022). The extraction was performed for 3 × 24 h. The extract was filtered through a filter paper until the filtrate was obtained. To obtain a thick extract, the solvent was evaporated using a Rotary Vacuum Evaporator at 60°C.

Phytochemical screening

Phytochemical screening was conducted to determine the content of secondary metabolite compounds in rambutan leaf powder and extract. Tests were conducted on flavonoids, tannins, alkaloids, saponins, polyphenols, steroids, and terpenoids (Wahid and Safwan, 2020).

a. Flavonoid Test

One gram of the sample was added to 1 mL of hydrochloric acid solution and 1 g of magnesium powder. A positive indication was indicated by a color change to pink (Putri et al., 2021).

b. Tannin Test

One gram of the sample was mixed with three drops of 1% gelatin solution. The presence of a white residue was a positive indication (Putri et al., 2021).

c. Alkaloid Test

A total of 1 g of the sample was mixed with 5 mL of chloroform and 5 mL of ammonia and then divided into three test tubes. Each test tube was prepared using Mayer's and Dragendorff's reagents. A positive indication for Mayer's reagent is the presence of a white or yellow residue, whereas, for Dragendorff reagent, a positive result is indicated by the presence of an orange to red residue (Putri et al., 2021).

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Table 1. Formulation of rambutan leaf ethanol extract capsules

Ingredients	Function	Composition (mg)			
		F0	**FI**	**FII**	**FIII**
Rambutan leaf extract	Active Ingredients	-	50	100	150
agar-agar	Binder	35	35	35	35
Avicel PH 101	Filler	60	60	60	60
Aerosil	Lubricants	3	3	3	3
Stearic Acid	slide	8	8	8	8
Lactose	Filler	194	144	94	44
	Total	300	300	300	300

d. Saponin Test

A total of 1 g of the sample was mixed with 10 mL of hot distilled water, shaken for 5 min, and left for 5 min. Positive saponin results were seen in the form of a thick foam of approximately 1-10 cm, which was stable. The addition of 2N HCl did not eliminate the foam (Putri et al., 2021).

e. Polyphenol Test

Three total of a 1 g of sample were added to 3 drops of 0.1% $FeCl_3$ solution. Positive indications include a color change to blue, green, bluish-green, brownish-green, or blackish blue (Susanti et al., 2019).

f. Steroid and Terpenoid Tests

A sample weighing 1 g was placed in a cup, and then 1 mL of chloroform and five drops of Liebermann-Burchard reagent were added. The presence of steroids in the sample is indicated by the formation of a blue or green ring, while a positive indication of terpenoids is indicated by a color change to dark green (Nurjannah et al., 2022).

Capsule formulation

The capsule formulation was based on previous research, with different doses of active ingredients of rambutan (50 mg, 100 mg, and 150 mg). The capsule formulation of rambutan leaf ethanol extract is shown in Table 1, which involves different doses of the active ingredients of rambutan leaf extract: 50 mg, 100 mg, and 150 mg. This concentration was chosen based on the results of previous studies, which have proven to be effective in reducing diarrhea.

Rambutan leaf ethanol extract capsules were prepared with four variations of the extract concentration. The thick extract was mixed with Avicel PH 101 at a much of 1:1, then ground homogeneously, and dried in an oven for 30 min at a temperature of 50 °C. The temperature was constant throughout the process, and a fan assisted the oven. The ingredients were weighed according to the concentrations specified in the formula (FI, FII, and FIII). Lactose and dry extract were placed in a mortar and stirred until homogeneous, and Avicel PH 101, Aerosil, and gelatin were added gradually, stirred until homogeneous, and then dried in an oven at a temperature of 40-50°C for 24 h. Stearic acid was added as the outer phase, stirred homogeneously, sieved, and placed into capsule shell number 1 with a weight of 300 mg each. During the capsule preparation process, consistency in capsule size, weight, and integrity was ensured.

Capsule weight uniformity test

Ten capsules were taken, each capsule was weighed, and the average deviation was calculated.

Disintegration time test

Six capsules of rambutan leaf ethanol extract F0, FI, FII and FIII were inserted into the disintegration test tool. A pH 1,2 buffer solution is commonly used in gastrointestinal simulations. The disintegration time requirement was <15 min (Wulandari et al., 2021).

Antidiarrheal activity test

White Swiss Webster mice (Mus musculus) were used as the test animals. The criteria for the mice used were healthy male mice, healthy, 2-3 months old, and weighing 1.5 kg, around 20-30 grams. Before treatment, the mice were acclimatized to an average room temperature of 23-29ºC. This period was carried out for seven days with the aim that the test animals were in the same environmental conditions as the environmental conditions when they were treated. The mice were placed in a cage measuring 40 × 30 × 12 cm. A total of 25 mice were used, consisting of five groups, with each group consisting of five mice. Then, the preparation of positive control tests, negative controls, F0, FI, FII, and FIII were performed. Each test animal received a different preparation, namely loperamide HCl, which was administered to the control group at a dose of 0.0104 mg/20 g BW. F0 is a negative control that does not contain active substances in the rambutan leaf extract capsule test group: FI (dose 1) 50 mg, FII (dose 2) 100 mg, and FIII (dose 3) 150 mg. After 45 min of test preparation, all mice were orally administered a carbo adsorbent (norit powder) marker suspension. Marker suspensions are used to track intestinal transit time by slowing down intestinal movement and

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adsorbing diarrhea-causing substances. Norit powder is used as a suspension marker because of its black color, and it does not affect the intestines. After 65 min of administration of the marker suspension, the mice were dissected from the neck. Surgery was performed by observing the intestines and measuring the length of the marker in the intestine (Ambari, 2019).

The submission of the code of ethics is stated to be in accordance with the 7 (seven) WHO 2011 standards, namely social values, scientific values, equal distribution of burdens and benefits, risks, inducements/exploitation, confidentiality and privacy, and consent after explanation referring to the 2016 CIOMS guidelines. The fulfillment of the indicators for each standard suggests this. Animal experiment ethics test certificate number: No.039/E.02/KEPK BTH/V/2024.

The data obtained were calculated using the formula for the percentage of activity and effectiveness. The data were then analyzed using the SPSS (Statistical Product and Service Solution) computer program. Normal and homogeneous data were then tested using ANOVA parameters. Based on the results of the one-way ANOVA, a significance value (ρ <0.05) was obtained, indicating that there was a significant difference between the test groups based on the comparison of the ratio of intestinal length to the ratio of marker length. The LSD Post Hoc Test was conducted to clarify the findings of ANOVA and determine which test groups showed significant differences compared to the other groups (Rusdiah & Ghina S.N., 2021).

RESULTS AND DISCUSSION

Extraction

Based on the processing of fresh rambutan leaf, it is as much as 6kg, with the final result in the form of powder obtained being as much as 1.38kg. The average drying loss is 2.64%. The results of drying loss obtained in repetition 1 were 2.4%, in repetition 2 were 2.86%, and in repetition 3 were 2.66%, with an average of 2.64% in accordance with the provisions (<10%) and met the requirements permitted for drying loss parameters. In drying loss with provisions of <10%, the powder can be stable, prevent the growth of microorganisms, and be efficient as a treatment.

The extraction process produced a yield of 28.62%. From the data obtained, the yield of rambutan leaf ethanol extract was good because >10% means that the active compounds contained in the rambutan leaf ethanol extract were high (Deti et al., 2021).

Phytochemical screening

The results of the phytochemical screening showed a positive flavonoid content test, indicated by the formation of orange amyl alcohol. The addition of magnesium powder and hydrochloric acid in the test resulted in a reduction of the flavonoid compound, resulting in an orange reaction, which is characteristic of the presence of flavonoid compounds in the sample. Tests for tannin and polyphenol levels using $FeCl_3$ reagents. In tannin compounds, it is indicated by the formation of a white precipitate, whereas in polyphenol compounds, it is indicated by the formation of a greenish-black color (Susanti et al., 2022). A positive saponin content test is indicated by the appearance of stable foam as high as 1 cm for ± 10 min, which does not disappear after the addition of 2N HCl. The foam is formed because saponins have hydrophobic and hydrophilic molecular structures. When saponins are mixed with hot water, they form micelles that are trapped in the air to create a foam (Putri et al., 2021). Tests for steroid and terpenoid contents using anhydrous and concentrated H_2SO_4 solutions.

The formation of a blue or green ring indicates positive steroid results. This reaction occurs between the theory and specific reagents and produces a colored complex that suggests the presence of steroids in the test sample. Meanwhile, a positive terpenoid result indicates a color change to dark green. This reaction occurs when terpenoids and reagents react to produce a complex compound with a dark green color as an indicator of the presence of terpenoid compounds (Rosdianah, 2021). Alkaloid content tests are carried out using Mayer, Dragendorff, and Wagner reagents. The results obtained are in the form of a white precipitate in Mayer's reagent, an orange precipitate in Dragendorff's reagent, and a light brown to yellow precipitate in the Wagner reaction. The formation of this precipitate is caused by the nitrogen atoms in the alkaloid, which have free electrons that can replace iodine ions in the reagent through covalent bonds (Putri et al., 2021).

Testing of physical properties of preparations

The rambutan leaf ethanol extract capsules were manufactured using the wet granulation method, in which the thick extract was dried with Avicel PH 101 to prevent degradation, regulate water content, physical stability, and dose control. The results of the physical evaluation of the rambutan leaf ethanol extract capsules are shown in Table 2.

The results of the flow time test showed that the dose of rambutan leaf extract can affect the flow rate to achieve therapeutic effects at the target site. The results

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of the humidity test showed differences caused by the composition of the rambutan leaf ethanol extract formulation, such that the more extract used, the higher the value of the results obtained. Compressibility tests were carried out to ensure that the capsule formulation had good powder flow, physical stability, and optimal release of the active ingredients. The results of the compressibility test showed a significant difference between specific gravity and compressive specific gravity, with a requirement of 5-15%. The angle of the repose test affects the homogeneity, efficiency, and final quality of the product, and the test results show that the greater the extract used, the greater the resulting angle (Suparman, 2019). In the weight uniformity test, there were differences in the average test values caused by several factors, namely the type of raw material used, production process, and environmental conditions, which can also affect the stability of the preparation. Several factors affected the results of the disintegration time test, including the composition of the preparation, the size of the preparation, the stability of the preparation, the pH value, and the test method used. This is because the higher the dose of rambutan leaf extract, the longer the disintegration time (Wulandari et al., 2021).

The results of the antidiarrheal activity test using the intestinal transit method were used to determine the antidiarrheal activity of rambutan leaf ethanol extract by measuring the distance travelled by the marker to the intestines of each mouse. The results of the rambutan leaf ethanol extract capsule test group with various doses showed that the average antidiarrheal activity ratio tended to be lower than that of the negative control, indicating that the test group had antidiarrheal activity (Hermansyah & Parinding, 2022; Sukmawati et al., 2020). The results of antidiarrheal activity are shown in Figure 1

Table 2. Evaluation Results of Rambutan Leaf Ethanol Extract Capsule Preparations

Test Parameters	F0	FI	FII	FIII
Flow Time (second)	4.14	4.83	4.25	3. 46
Humidity (%)	2.75	2.79	3.76	3.48
Compressibility (%)	11	8.8	12.8	13
Rest Corner	35.5º	31.7º	33.4º	36.1º
Weight Uniformity (mg)	376.6 ± 1.35	376.7 ± 1.26	376.6 ± 1.11	376.9 ± 1.51
Disintegration time (second)	5.47 ± 0.04	6.65 ± 0.29	9.87 ± 0.60	11. 66 ± 0 . 76

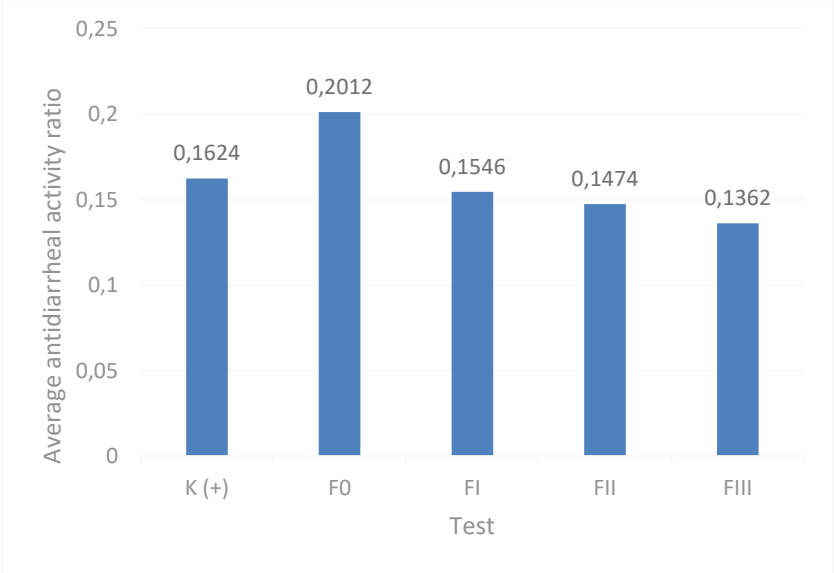

Figure 1. Average Antidiarrhea Activity Ratio

Information:
K (+) : Group given Loperamide HCl in 1.5% Na CMC
F0 : Group given capsules without extract
F I : Group given 50 mg rambutan leaf extract capsules
F II : Group given 100 mg rambutan leaf extract capsules
F III : Group given 150 mg rambutan leaf extract capsules

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Referring to Figure 1. regarding the difference in the ratio of intestines passing through the marker suspension. In the capsule test group in formulation 0, there was no antidiarrheal activity, so the resulting intestinal ratio was high. Formulation I showed good antidiarrheal activity with an effectiveness percentage of 120%. Meanwhile, in the test group with rambutan leaf ethanol extract capsules in formulation II with a dose of 100 mg and formulation III with a dose of 150 mg, the ratio results exceeded the positive control, indicating that the test group had an antidiarrheal effect. The smaller the ratio between the total length of the intestine and the length of the intestine passed through by the marker, the stronger the antidiarrheal effect of the test group (Lina & Astutik, 2020; Santosa et al., 2023). Compared to the 50 mg dose, the 100 mg and 150 mg doses showed superior antidiarrheal effects because the higher the dose, the more compounds contained therein. Tannins and flavonoids act as antibacterial agents and reduce intestinal contractions during diarrhea.

Data analysis

In the data analysis study using the one-way ANOVA test, this test begins with a normality test using the Shapiro-Wilk test with a 95% confidence level. The results of the study showed a significant value ($\rho > 0.05$), which means that the samples tested were normally distributed. A homogeneity test was then performed, which produced a significance value ($\rho > 0.05$). Based on the results of the one-way ANOVA, a significance value ($\rho < 0.05$) was obtained, which showed that there was a significant difference between the test groups based on the comparison of the ratio of the length of the small intestine to the marker length ratio. The LSD post hoc test was conducted to confirm the ANOVA results and to determine which test groups showed significant differences between the other test groups. Based on the LSD post hoc test, there was a significant difference between the loperamide HCl and formula 0 groups with a significant result ($p < 0.05$). Meanwhile, a comparison between the test groups of rambutan leaf ethanol extract capsules (*Nephelium lappaceum* L.) showed a significant difference with a significance value ($p > 0.05$) (Tari et al., 2020) (Fadilah & Susanti, 2020).

CONCLUSION

Ethanol extract of rambutan leaves (*Nephelium lappaceum* L.) can be stated that ethanol extract capsules of rambutan leaves (*Nephelium lappaceum* L.) have antidiarrheal activity with the best dose of 150 mg with an effectiveness percentage of 32.2%. This formulation of the rambutan leaf extract can be utilized in practical applications after a toxicity test is performed. Compared with the current study, this will allow rambutan extract to be used as an alternative treatment for diarrhea. A limitation of this study is that stability and toxicity tests were not performed to ensure the safety and stability of the preparation.

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AUTHOR CONTRIBUTIONS

Conceptualization, N.N.F.; Methodology, A.N.; Software, W.N.A.; Validation, N.N.F.; Formal Analysis, W.N.A.; Investigation, A.R.; Resources, A.R.; Data Curration; S.R.; Writing - Original Draft, N.N.F.; Writing - Review & Editing, N.N.F.; Visualization, S.R.; Supervision, W.N.A.; Project Administration, W.N.A.; Funding Acquisition, N.N.F.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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