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Effectiveness of Ethanol Extract of Rambai Fruit Peel (*Baccaurea motleyana* Mull. Arg.) on the Hematological Profile of Diabetic Mice

Efektivitas Ekstrak Etanol Kulit Buah Rambai (Baccaurea motleyana Mull. Arg.) terhadap Profil Hematologi Mencit Diabetes

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ABSTRAK

Penelitian ini bertujuan mengetahui pengaruh ekstrak etanol kulit buah rambai (*Baccaurea motleyana* Mull. Arg.) terhadap profil hematologi mencit jantan (*Mus musculus*) guna mengetahui dosis yang efektif dalam meningkatkan profil hematologi mencit jantan, serta untuk mengetahui toksisitas ekstrak etanol kulit buah rambai. Penelitian ini menerapkan Rancangan Acak Lengkap (RAL) yang terdiri dari enam perlakuan, yaitu mencit diabetes yang diberi akuades (kontrol negatif) (P1), mencit diabetes yang diberi obat glibenklamid (kontrol positif) (P2), serta mencit diabetes yang diberi ekstrak etanol kulit buah rambai pada dosis 200 mg/kg berat buah (bb) (P3), 400 mg/kg bb (P4), 800 mg/kg bb (P5), dan 1.600 mg/kg bb (P6). Terdapat empat replikasi untuk masing-masing perlakuan. Data yang diperoleh dianalisis secara statistik menggunakan ANOVA dan diuji lanjut menggunakan uji Duncan (DMRT) pada tingkat kepercayaan 95%. Hasil studi ini menunjukkan bahwa ekstrak etanol kulit buah rambai berpengaruh nyata terhadap kadar hemoglobin, jumlah eritrosit, dan jumlah leukosit mencit jantan. Dosis terbaik untuk meningkatkan kadar hemoglobin adalah 400 mg/kg bb. Dosis terbaik untuk meningkatkan jumlah eritrosit adalah 1600 mg/kg bb. Semua dosis perlakuan ekstrak mampu meningkatkan jumlah leukosit.

Kata kunci: Diabetes, Hemoglobin, Kulit buah rambai, Toksisitas.

ABSTRACT

*This study aims to determine the effect of ethanol extract of rambai fruit peel (*Baccaurea motleyana *Mull. Arg.) on the hematological profile of male mice (*Mus musculus*), to determine the effective dose in increasing their hematological profile, and to determine the toxicity of the ethanol extract of rambai fruit peel. This study applied completely randomized design (CRD) consisting of six treatments: diabetic mice treated with distilled water (negative control) (P1), diabetic mice treated with glibenclamide drug (positive control) (P2), and diabetic mice treated with ethanol extract of rambai fruit peel at a dose of 200 mg/kg fruit weight (fw) (P3), 400 mg/kg fw (P4), 800 mg/kg fw (P4), and 1,600 mg/kg fw (P6). There were four replications for each treatment. The data obtained were statistically analyzed using ANOVA and further tested using DMRT at a 95% confidence level. The results show that the ethanol extract of rambai fruit peel significantly affected the hemoglobin levels, the number of erythrocytes, and the number of leukocytes of the mice. The best dose to increase the hemoglobin levels was 400 mg/kg fw. The best dose to increase the number of erythrocytes was 1600 mg/kg fw. All extract doses was able to increase the number of leucocytes.*

Keywords: *Diabetes, Hemoglobin, Rambai fruit peel, Toxicity.*

INTRODUCTION

The hematological profiles, both in human and animal, are very important to be known or studied. Hematological profile is one aspect of blood physiology that can determine a person's health status, such as injury, infection, or decreased body function due to stress (Ihedioha et al., 2004). Problems or disorders in organs can be caused by disease occurrence, as well as by problems related to blood or blood function. Abnormal blood parameters can also cause problems or disorders in other organs (Astawan et al., 2011). Anemia, polycythemia, and leucopenia are several problems that can be caused by imbalances in blood substance levels. In general, it is known that too few red blood cells or hemoglobin can cause anaemia (Hall, 2016).

The results of the 2013 Basic Health Research (*Riskesdas*) showed that 21.7% of the Indonesian population was suffering from anemic. In Indonesia, toddlers in the age of 12 to 59 months are more likely to be anemic. Iron deficiency is one of the causes of anaemia, but low hemoglobin levels along with low number of erythrocyte are also one of the primary causes of anaemia. Thus, treatment on this matter should be performed appropriately. Hemoglobin levels will increase rapidly, either through blood transfusion or through iron and folic acid therapy. This is preferably conducted recently because natural ingredients are considered better than synthetic ingredients (Moeljanto, 2002). Therefore, there must be an effort to keep the stable amount of blood in the body in order to maintain a good hematological profile of the body.

Diabetes mellitus is characterized by blood glucose levels that exceed normal limits. This can occur when the body does not produce enough insulin for the body in order to function properly. Beta (ß) cells in the pancreas produce the hormone insulin that helps blood glucose entering cells. Insulin is then converted into energy or ATP needed by other body tissues (Hongdiyanto, 2014).

Alkaloids, flavonoids, and phenolics are active ingredients found in rambai fruit from the *Baccaurea* genus (Gunawan et al., 2016). These antioxidants can chelate excess free radicals in pancreatic ß cells (Suarsana et al., 2010). According to Elfirati (2018), ethanol extract of rambai fruit peel contains several phytochemical compounds, such as flavonoids, saponins, terpenoids, and phenolics.

A study by Ismawati (2018) showed that various compounds contained in rambai fruit peel have the potential to reduce blood glucose levels in mice suffering from diabetes. A study on hypoglycemia mice by Ceriana et al. (2019a) also showed that mice experienced a decrease in blood glucose levels, which also had an impact on glycogen levels in the liver (Sari et al., 2018). It was also reported that rambai fruit peel extract increased the body weight of mice (Ceriana et al., 2019b) and it was safe to be used as a medicine. According to Amalia et al. (2019), rambai fruit peel extract did not cause clinical symptoms in mice, especially in organs such as the liver (Ceriana et al., 2019c; Ceriana et al., 2022), kidney, heart, and spleen (Ceriana et al., 2023).

Based on the aforementioned background, this study was conducted to investigate the profile of ethanol extract of rambai fruit peel (*Baccaurea motleyana* Mull. Agr.) with the aim to determine the effectiveness of ethanol extract of rambai fruit peel on the hematological profile of male mice. The parameters observed were the blood glucose levels, the hemoglobin levels, the number of erythrocytes (hematocrite), the number of leucocytes, and leucocyte differentiation.

MATERIALS AND METHOD

Location and Time of Research

The ethanol extract preparation for treatment was conducted at the Microbiology Laboratory, Department of Biology, Faculty of Mathematics and Natural Sciences (FMIPA), Syiah Kuala University. The experimental animals were acclimatized and tested at the Pharmacology Laboratory of Atjeh Institute. Blood profile analysis was conducted at the Zoology

Laboratory, Department of Biology Education, Faculty of Tarbiyah and Teachership, Ar-Raniry State Islamic University. Overall, this study was conducted from February to July 2022.

Tools and Materials

The tools used were glucometer (Nesco), analytical balance, dropper pipette, measuring cup, beaker, funnel, sieve, maceration container, mortar, pestle, spuid, mice rearing cage, gastric feeding tube, surgical scissors, hemoglibinometer, cross set, hemoglobinometer, hemocytometer, and rotary vacuum evaporator, dilution tube, and stirring rod. The materials used were rambai fruit (*Baccaurea motleyana* Mull. Agr.), 24 male mice (*Mus musculus*) as the experimental animals, filter paper, alloxan, glibenclamide drug, distilled water, All Feed-4 rations, wood husk, glucose test strips, hydrochloric acid, EDTA, 96% of ethanol solvent, 0.1 N of HCl, Hayem solution, and Turk solution.

Research Design

This study used completely randomized design (CRD) consisting of six treatments for diabetic mice: distilled water (negative control) (P1), glibenclamide drug (positive control) (P2), rambai fruit peel extract at a dose of 200 mg/kg fruit weight (fw) (P3), 400 mg/kg fw (P4), 800 mg/kg fw (P5), and 1,600 mg/kg fw (P6). There were four replications for each treatment.

Work Procedures

Preparation of rambai fruit peels

The peels of rambai fruit (*Baccaurea motleyana* Mull. Agr.) were separated from the flesh and washed thoroughly. The peels were then dried using an oven at 50^{o}C.

Extraction of rambai fruit peel

The extraction method used was the maceration or soaking method using a solvent. First, the rambai fruit peels were cut into small pieces, washed thoroughly with running water, then dried by aerating the peels on newspaper to produce dry simplisia. Next, the simplisia was soaked in 96% of ethanol solvent at a ratio of 1:2 and stirred occasionally. Soaking was carried out in a maceration container for 2 x 24 hours. After that, the results of maceration (filtration) were filtered, which resulted in a filtrate. The simplisia was soaked twice to produce the most filtrate. The results of the first and second filtration were collected and concentrated using a rotary vacuum evaporator to produce a thick extract. The extract was then freed from ethanol by heating it in a water bath.

Induction of alloxan

In this study, alloxan was used as the diabetogenic substance. Alloxan was administered intraperitonially at a dose of 200 mg/30 gr fw, which is the typical dose that causes hyperglycemia in mice. The mice were observed for four days. After four days, a glucometer was used to check their glucose levels. The mice with glucose levels of more than 200 mg/dl were separated and could be used for treatment. On the fifth day, the chosen mice began to be treated with ethanol extract of rambai fruit peel (*Baccaurea motleyana* Mull. Agr.).This was counted as the first day of rambai peel ethanol extract treatment (H1).

Application of ethanol extract of rambai fruit peel on the mice

Prior of treatment with ethanol extract of rambai fruit peel, the blood glucose of mice was measured. In this study, mice with glucose levels of more than 200 mg/dl were used. A total of 24 mice were used as experimental animals and were subjected to six treatment groups as follows.

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Table 1. Treatment group of mice.

No.	Name (Label)	Description of Treatment
1.	Negative control (P1)	Diabetic mice + distilled water
2.	Positive control (P2)	Diabetic mice + glibenclamide drug at a dose of 0.0195 mg/30 gr fw
3.	Extract Treatment 1 (P3)	Diabetic mice + ethanol extract of rambai fruit peel at a dose of 200 mg/kg fw
4.	Extract Treatment 2 (P4)	Diabetic mice + ethanol extract of rambai fruit peel at a dose of 400 mg/kg fw
5.	Extract Treatment 3 (P5)	Diabetic mice + ethanol extract of rambai fruit peel at a dose of 800 mg/kg fw
6.	Extract Treatment 4 (P6)	Diabetic mice + ethanol extract of rambai fruit peel at a dose of 1,600 mg/kg fw

Prior to treatment, the mice were fasted for 12 hours. Next, using a gastric feeding tube for mice, the diluted treatment solution was injected to provide oral treatment to the mice. After 14 days of treatment with ethanol extract of rambai fruit peel, a glucometer was used to measure the blood glucose of the mice. The tail end of the mice was cut to obtain blood. After the blood came out of the mice's tail, a blood glucose measuring strip was attached to the blood and inserted into the glucometer.

Hematological measurement

a. Hemoglobin levels

In the hemometer dilution tube, a drop of 0.1 N of hydrochloric acid (HCl) was introduced until reached the mark of 2. Then, the blood of EDTA-treated mice was drawn until reached the exact line of 0.5. The blood was put into the base pipette (being careful not to cause air bubbles) and the contents of the pipette were rinsed using 0.1 N of HCl solution. Then, the contents of the tube were mixed with the blood and HCl. Next, a stirring rod was used to stir the drops of distilled water until the color resulted on the hemoglobinometer was the same as the standard color. The dilution tube was then read to determine the hemoglobin levels.

b. Number of erythrocytes

The number of erythrocytes was counted using a hemocytometer.

c. Number of leucocytes

The number of leucocyte was counted using four grid fields, including a grid field for counting erythrocytes, each of which measures an area of 1 x 1 mm^2 (Figure 1).

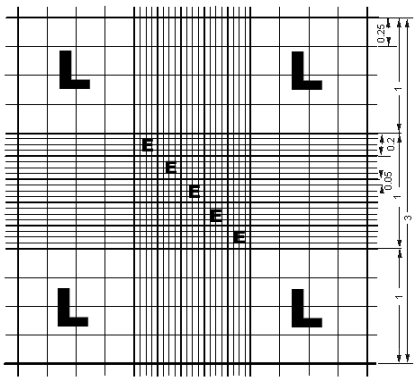

Figure 1. Pattern of how to count the number of leucocytes using a hemocytometer in the form of chamber measuring 1 x 1 mm^2 (Letter L). Letter E indicates the counting pattern.

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Data analysis and processing

The data obtained was then statistically processed using ANOVA (analysis of differences) in SPSS version 22. Then, if it was found that the treatments had an impact on the hemoglobin profile of the mice, Duncan's multiple range test (DMRT) at the 95% confidence level was performed to figure out the differences among the treatments.

RESULTS AND DISCUSSION

Extraction Result

The yield percentage of the extraction was 5.384%.

Phytochemical Content

The results of the phytochemical test of ethanol extract of rambai fruit peel (*Baccaurea motleyana* Mull. Agr.) are presented in Table 2.

Table 2. Phytochemical content of ethanol extract of rambai fruit peel (*Baccaurea motleyana* Mull. Agr.).

Phytohemical Content	Testing Reagent	Detected (+) or Undetected (-)
Alkaloid	Mayer	-
	Wagner	-
	Dragendorff	-
Steroid	Liebermann-Buchard Test	-
Terpenoid	Liebermann-Buchard Test	+
Saponin	Shaking	+
Flavonoid	0.5 of Mg dan HCl	+
Phenolic	$FeCl_3$	+

As seen from Table 2, the ethanol extract of rambai fruit peel contains four phytochemical compounds: terpenoids, saponins, flavonoids, and phenolics.

Results of Alloxan Induction

Prior to treatment, the blood glucose levels of all mice were first checked as the initial blood glucose levels. Then alloxan was given to them to cause diabetes. After all mice were diabetic, their blood glucose levels were measured using a glucometer. The average of blood glucose levels of mice before and after being induced with alloxan are presented in Table 3.

Table 3. The average blood glucose levels of the mice before and after alloxan induction.

Average of Blood Glucose Levels (mg/dl)	
Prior to Alloxan Induction	**After Alloxan Induction**
117.458 ± 18.486	403.125 ± 126.131

Source: Primary data

As seen in Table 3, the average of blood glucose levels of the mice before alloxan induction is 117.458 mg/dl, and that of after alloxan induction is 403.125 mg/dl. According to Sun (2016), the blood glucose levels of mice normally ranges from 88–112 mg/dl. Thereby, it was then necessary to figure out the blood glucose level of the mice after treatment. For this reason, the measurement of blood glucose levels of the mice treated with ethanol extract of rambai fruit peel (*Baccaurea motleyana* Mull. Agr.) was conducted to evaluate its antidiabetic properties.

Blood Glucose Levels

For 14 days, the ethanol extract of rambai fruit peel (*Baccaurea motleyana* Mull. Agr.) was administered to the mice subjected to hyperglycemia. This aimed to examine its antidiabetic properties in these experimental animals. During this period, all mice were given the treatment. Table 4 shows the average blood glucose levels of the mice after alloxan induction (pre-test) and after treatment (post-test).

Table 4. The average blood glucose levels of the mice after alloxan induction (pre-test) and after treatment (post-test).

No.	Treatment	Average of Blood Glucose Levels (mg/dl) ± SD	
		Pre-test	Post-test
1.	Negative control (P0)	284 ± 45,798	209.75 ± 8,057
2.	Positive control (P1)	471.75 ± 85,908	87.25 ± 14,430
3.	Dose of 200 mg/kg fw (P2)	409.5 ± 109,381	122 ± 42,544
4.	Dose of 400 mg/kg fw (P3)	384.75 ± 182,381	115.5 ± 34,539
5.	Dose of 800 mg/kg fw (P4)	409.75 ± 82,5	99 ± 10,165
6.	Dose of 1,600 mg/kg fw (P5)	459 ± 172,437	76.5 ± 16,94107

Source: Primary data

Table 4 presents the average of blood glucose levels of the mice after alloxan induction and after treatment with ethanol extract of rambai fruit peel (*Baccaurea motleyana*). The results show that there was a significant decline in the blood glucose levels of the mice after treatment.

Hemoglobin Levels

Table 5 presents the statistical test results on the hemoglobin levels of the mice.

Table 5. The average hemoglobin levels of the mice treated with ethanol extract of rambai fruit peel (*Baccaurea motleyana* Mull. Arg.).

No.	Treatment	Average of Hemoglobin Levels ± SD
1.	Negative control (P1)	$8.5000 \pm 0{,}58^{a}$
2.	Positive control (P2)	$10.0000 \pm 0{,}00^{b}$
3.	Dose of 200 mg/kg fw (P3)	$10.7500 \pm 0{,}50^{bc}$
4.	Dose of 400 mg/kg fw (P4)	$12.5000 \pm 1{,}00^{d}$
5.	Dose of 800 mg/kg fw (P5)	$11.5000 \pm 1{,}29^{cd}$
6.	Dose of 1,600 mg/kg fw (P6)	$11.7500 \pm 0{,}96^{cd}$

Description: Numbers followed by different superscript letter in the same column indicate significant difference based on the results of DMRT ($p < 0.05$).

Table 5 shows that the result of negative control (P2) is significantly different compared to the results of all other treatments. In addition, the results of P3, P4, P5, and P6 treatments are significantly higher than the result of negative control, in which P4 treatment produced the highest result. This shows that the application of ethanol extract of rambai fruit peel can increase hemoglobin levels in the blood of mice. Particularly, extract dose of 400 mg/kg fw is the best dose to increase the hemoglobin levels.

Number of Erythrocytes

Table 6 presents the statistical test results on the number of erythrocytes of the mice.

Table 6. The average number of erythrocytes of the mice treated with ethanol extract of rambai fruit peel (*Baccaurea motleyana* Mull. Arg.)

No.	Treatment	Average Number of Erythrocytes ± SD
1.	Negative control (P1)	4,452,500 ± 6
2.	Positive control (P2)	5,910,000 ± 7
3.	Dose of 200 mg/kg fw (P3)	4,827,500 ± 4
4.	Dose of 400 mg/kg fw (P4)	6,190,000 ± 2
5.	Dose of 800 mg/kg fw (P5)	6,810,000 ± 1
6.	Dose of 1,600 mg/kg fw (P6)	10,840,000 ± 3

Description: Numbers followed by different superscript letter in the same column indicate significant difference based on the results of DMRT ($p < 0.05$).

As seen in Table 6, the dose of 1600 mg/kg fw produced the highest average number of blood erythrocytes compared to that of all other treatments. This shows that this dose was able to effectively increase the number of erythrocytes in the blood of mice.

Number of Leucocytes

Table 7 presents the statistical test results on the number of leucocytes of the mice.

Table 7. The average number of leucocytes of the mice treated with ethanol extract of rambai fruit peel (*Baccaurea motleyana* Mull. Arg.).

No.	Treatment	Average Number of Leucocytes ± SD
1.	Negative control (P1)	$4,160 \pm 4^{a}$
2.	Positive control (P2)	$4,921 \pm 4^{b}$
3.	Dose of 200 mg/kg fw (P3)	$4,765 \pm 7^{b}$
4.	Dose of 400 mg/kg fw (P4)	$4,714 \pm 1^{b}$
5.	Dose of 800 mg/kg fw (P5)	$4,734 \pm 1^{b}$
6.	Dose of 1,600 mg/kg fw (P6)	$5,067 \pm 2^{b}$

Description: Numbers followed by different superscript letter in the same column indicate significant difference based on the results of DMRT ($p < 0.05$).

As seen in Table 7, the doses of 200 mg/kg fw, 400 mg/kg fw, 800 mg/kg fw, and 1600 mg/kg fw produced results that are significantly higher than that of negative control (P1), but not significantly different from that of positive control (P2). Meanwhile, negative control (P1) produced the lowest result than that of all other treatments. This indicates that the treatment of ethanol extract of rambai fruit peel was able to increase the number of blood leukocytes in mice.

The results showed that the compound content of ethanol extract of rambai fruit peel (*Baccaurea motleyana* Mull. Arg.) can reduce blood glucose levels of mice. Phytochemical test results show that the ethanol extract of rambai fruit peel contains saponins, phenolics, terpenoids, and flavonoids.

Saponin compounds in rambai fruit peel have the potential to inhibit digestive enzymes for carbohydrates, modulate glucose-regulating enzymes such as in Platykodi root, and increase insulin secretion in *Momordica cymbalaria* (Lee & Choi, 2013). Besides, saponin compounds exhibit the following functions: i) inhibit the activities of a-amylase and a-glucosidase enzymes, which are important catalyzer for converting carbohydrates into glucose, ii) have the potential to slow down and prolong the duration of carbohydrate digestion, and iii) reduce glucose absorption, which can directly prevent an increase in blood glucose concentration after meals (Sales, 2012).

Terpenoid compounds have the ability to control the activity of perioxisome proliferator activity receptors (PPARs). PPARs are nuclear receptors that regulate gene transcription and are involved in various cellular metabolisms, including carbohydrate metabolism. By stimulating PPARs, the transcription of insulin-sensitive genes will change, which means the insulin becomes

more sensitive to the rise in blood glucose. As a result, the sensitivity of insulin to rising blood glucose may increase, which in turn may lead to the development of insulin resistance.

Rambai fruit skin contains flavonoids that play an important role to regenerate pancreatic cells and stimulate insulin secretion (Dheer & Bhatnagar, 2010). Flavonoids also function to lower blood glucose levels by reducing glucose uptake and controlling the expression activity of enzymes involved in carbohydrate metabolism (Brahmachari, 2011). Therefore, it can be concluded that secondary metabolite compounds of ethanol extract of rambai fruit peel can reduce blood glucose levels.

CONCLUSIONS

Based on the results of this study, it can be concluded that the ethanol extract of rambai fruit peel was able to increase the hemoglobin levels of the mice at doses of 400 mg/kg fw, 800 mg/kg fw, and 1,600 mg/kg fw, where the dose of 400 mg/kg produced the best result. The extract also was able to produce the highest number of erythrocytes at a dose of 1,600 mg/kg fw and leukocytes at all doses of extract treatment.

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