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Antidiabetic activity test result of fractionation of Bengkal Leaves (*Nauclea orientalis* L.) on male white mice

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Abstract

Background: Bengkal leaves (*Nauclea orientalis* L.) are a plant that contains flavonoids, which are active substances that have been demonstrated to reduce blood glucose levels (i.e., they are antidiabetic). The pharmacological activity of a decoction of Bengkal leaves (*Nauclea orientalis* L.), which has been used in the community as an antidiabetic, has yet to be determined. This research was conducted to test the activity of Bengkal leaf fractions (*Nauclea orientalis* L.), which were used as an antidiabetic in male white mice that had been previously induced with alloxan.
Method: This research employs a quasi-experimental approach utilizing a static-group comparison design. The test animals utilized in this study were 35 male white mice, which were divided into seven groups. The first group served as the negative control (tragacanth), the second as the positive control (alloxan), the third as the comparison group (glibenclamide), the fourth as the ethanol extract group, the fifth as the n-hexane fraction, the sixth as the ethyl acetate, and the seventh as the Bengkal leaf water, with a dose of 150 mg/kg BW. Subsequently, the blood glucose levels of the mice were monitored on days 1, 3, and 7 to ascertain the efficacy of the treatment. Subsequently, a *one-way ANOVA* statistical test was employed to ascertain the most efficacious day. Subsequently, the post hoc Duncan test should be employed to ascertain the optimal fraction that exhibits a degree of efficacy comparable to that of glibenclamide 5 mg. This will allow us to ascertain whether the Bengkal leaf fraction (*Nauclea orientalis* L.) is efficacious in the treatment of diabetes. Ultimately, the efficacy of the Bengkal leaf fraction as an antidiabetic drug will be determined.
Results: The administration of various fractions of Bengkal leaves to male white mice induced by alloxan has been observed to elicit antidiabetic activity.
Conclusion: The administration of the ethyl acetate fraction derived from Bengkal leaves has been observed to exhibit antidiabetic activity in male white mice that are nearly equivalent to that of glibenclamide. The ethyl acetate fraction of the Bengkal leaf exhibits promise as a potential antidiabetic pharmaceutical agent.

Keywords: Bengkal leaves, Flavonoids, Fractionation, Antidiabetic, Alloxan.

INTRODUCTION

People have used Bengkal leaves (*Nauclea orientalis* L.) as a traditional medicine for antidiabetes (1). The form used is ten leaves with simple processing using only water as a boiling agent (2). If people continue to use these boiled preparations without knowing their level of effectiveness, the desired therapeutic effect will not be achieved. Errors can come from processing and dosage aspects. Error factors in processing can come from the age of the leaves used and the boiling time, while the dosage is related to the number of leaves and the rules for use. This can become a habit of using the wrong drugs in society over a sustained period (3). With the information above, it is necessary to know whether the processing method in the community is effectively used for anti-diabetes.

Liquid extract of Nauclea orientalis stem bark has the effect of reducing doxorubicin-induced oxidative stress, inflammation, apoptosis, and DNA fragmentation in Wistar rats (4). Nauclea orientalis leaf extract showed the highest activity for the DPPH inhibition assay. Other research states that 10% *Nauclea orientalis* soaking has an

attractant effect, making it useful as an alternative vector control for Dengue Hemorrhagic Fever (DHF) (5). The residue, ethyl acetate fraction, hexane fraction, and *Nauclea orientalis* L. leaf extract have antibacterial activity against *Escherichia coli* and *Staphylococcus* bacteria (6). The study also showed that Bangkal leaf extract has antibacterial activity against *Staphylococcus aureus* which has an inhibition zone in the moderate to strong category (7).

The identification of secondary metabolites of Bengkal leaves (*Nauclea orientalis* L.) has been tested qualitatively using phytochemical screening and confirmation tests using the TLC test. In this test, the results obtained were the content of Bengkal leaves (*Nauclea orientalis* L.), namely the terpenoid group from essential oils, saponins, triterpenoid carotenoids, phenol groups from simple phenols, tannins, phenolic acids and flavonoids (8,9). With the flavonoid content as hyperglycemia, flavonoids can act as antidiabetics (2). Previous research showed that 70% ethanol extract from *Nauclea subdita* leaves could reduce blood glucose levels in white mice (1). In previous studies, it was found that there was effectiveness in using Bengkal leaf infusion (*Nauclea orientalis* L.) as an antidiabetic in mice (10).

However, there has been no research to prove the activity of the results of fractionation of the ethanol extract of Bengkal leaves (*Nauclea orientalis* L.) and to determine the best type of fraction as an antidiabetic, it is necessary to carry out research entitled Antidiabetic Activity Test Results of Fractionation of Bengkal Leaves (*Nauclea orientalis* L.) on animals male white mice. Further research will carry out topic development toward the best dose fraction test, LD 50 and RBO tests, SGPT and SGOT tests, pathology tests, isolation using column chromatography, and therapeutic drug monitoring tests (calculating drug levels in the blood).

METHOD

The method used is quasi-experimental research using a static-group comparison design, namely research that creates two groups of research objects consisting of a control group and an intervention group (11).

This research will be carried out in approximately 5 months at the Phytochemistry and Pharmacology Laboratory, Department of Pharmacy, Health Polytechnic, Ministry of Health, Jambi in 2024 with a certificate number suitable for research ethics, namely LB.02.06/2/029/2024 which has been issued by KEPK Poltekkes Kemenkes Jambi.

The research procedure's conduct

Extraction

Fresh Bengkal leaves are sorted, washed until clean then chopped, then air-dried. Then powdered using a simplicia blender and weighed. A total of 1 part of the sample powder was put into a maceration container and 10 parts of 70% ethanol solvent were added. The maceration process was carried out for 3 days, stirring occasionally. The maserate is separated by filtering and then evaporated using a rotary evaporator until a thick extract is obtained (12).

Fractionation

The 70% ethanol extract of Bengkal leaves was fractionated using water and n-hexane as a solvent in a ratio of 1:1 in a separating funnel, then shaken sufficiently, then left until two layers were formed, namely the n-hexane layer and the water layer, then the two layers were separated. This treatment was carried out several times in repetition until the n-hexane layer appeared clear and a sample solution of the n-hexane fraction was obtained. Then the water layer was fractionated again using ethyl acetate solvent, carried out several times in the same way as the above treatment until a sample of the water fraction and a sample of the ethyl acetate fraction were obtained. All parts of the n-hexane, ethyl acetate, and water fractions were evaporated using a rotary evaporator to obtain a thick fraction sample (13–17).

The use of materials and instruments

Preparation of Test Animals

The experimental test animals used can be calculated using the formula (11): (t-1) (r-1) ≥ 15,

(t-1) (r-1) ≥ 15

(7-1) (r-1) ≥ 15
6 (r-1) ≥ 15
6r = 15 + 6
r 21/6 = 3,5 = 4+1 = 5
Information :
t : Group
r : Number of test animals
so that one treatment group uses five mice. So, for seven treatment groups, thirty-five mice were used.

Preparation of drug solutions, carriers, and diabetes inducers

a. Glibenclamide 5 mg solution
5 mg x 0.0026 = 0.013 mg (0,65mg/kgBW). Take 1 tablet of Glibenclamide, put it in a mortar, then grind it until it is homogeneous, then add 10 ml of 0.5% tragacanth suspension, take 1 ml of the solution then dilute it with 0.5% tragacanth suspension until you get a 7.7 ml solution, then stir the glibenclamide suspension solution until homogeneous (18,19).

b. Preparation of Tragacant suspension 0.5%
Weigh out 0.5 g of Tragacanth then spread it in hot water twenty times, let it sit for fifteen minutes, then grind it, then add the remaining water until 100 ml is obtained (20).

c. Preparation of 175 mg/kgBW Alloxan solution
175 mg/kgBW x 0.02 kg = 3.5 mg. 3.5 mg/0.2 ml x 10 ml = 175 mg. Weigh 175 mg of Aloxan into a glass beaker then add 10 ml Aqua Pro injection, stir until homogeneous (19,21,22).

Treatment of Test Animals

The test animals used in this study were 30 male white mice (*Mus musculus*) aged 2-3 months with a body weight of 20-30 grams which were divided into 6 test groups. Male white mice were first adapted for approximately 1 week in a cage and given standard food and sufficient drinking water during the adaptation period. All groups of mice were made diabetic except the negative control group by injecting alloxan at a dose of 175 mg/kgBW intraperitoneally with a volume of 0.2 ml/20g. After that, the next day the blood sugar level is checked, if there is a statistically significant increase then the treatment can be continued by continuing to provide food and drink, if necessary, giving a 10% sugar solution. Next, tragacanth, alloxan, glibenclamide, ethanol extract of Bengkal leaves 150 mg/kgBW, n-hexane fraction of Bengkal leaves 150mg/kgBW, ethyl acetate fraction of Bengkal leaves 150mg/kgBW and wastewater fraction of Bengkal leaves 150mg/kgBW were administered to the 7 groups of mice. Then check the blood sugar levels of the mice on days 1, 3, and 7 of the experimental animals.

Data collection and analysis techniques

After treatment, the blood glucose levels of the test animals are measured and displayed as a table. Then it was analyzed statistically using *ANOVA* analysis.

RESULTS

After carrying out the research, data was obtained as follows:

Table 1. Percentage of Decrease in Blood Glucose Levels of Test Animals

No.	Treatment Group	Blood Glucose Levels of Test Animals (mg/dL)										
		Fast	Diabetic	Days to-								
				1	SD	%	3	SD	%	7	SD	%
1.	Control negative	125,2	209,5	192,4	6,877	8,16	194	6,204	7,39	194,6	6,107	7,11
2.	Control positive	109	218,7	177	7,582	19,06	122,8	7,049	43,85	91	12,980	58,39
3.	Comparison	110,5	207,4	130,2	7,293	37,22	112,4	8,142	45,80	99,4	4,393	52,07
4.	Ethanol Extract of Bengkal leaves	120,4	212,6	191,6	5,941	9,87	185,8	6,723	12,60	180,8	7,328	14,95
5.	n-Hexane fraction of Bengkal leaves	106,2	203,3	181	6,324	10,96	173,2	6,300	14,80	166,2	6,379	18,24
6.	Ethyl acetate fraction of Bengkal leaves	112,7	208,2	132,6	7,635	36,31	114,8	8,318	44,86	102,2	4,658	50,91
7.	Wastewater fraction of Bengkal leaves	121,1	210,5	174,2	13,292	17,24	146,6	19,138	30,35	108,4	11,371	48,50

DISCUSSION

Fresh samples of Bengkal leaves were taken as much as 1 kg and obtained 678.9 g of dry simplicia powder with a yield of 67.89%. Furthermore, it was macerated with 6 liters of 96% ethanol solvent for 5 days while stirring occasionally. The maceration results were evaporated with a rotary evaporator to obtain 196.89 g of extract with a yield of 29%. Then 10 g of the extract was fractionated with n-hexane and ethyl acetate solvents and then evaporated with a rotary evaporator to obtain each fraction yield as follows:

Table 2. Yield Determination Result Data

No.	Faction Name	Extract Weight (g)	Fraction Yield (%)
1.	*n*-hexane	0,26	2,6
2.	Ethyl acetate	0,35	3,5
3.	Water	1,88	18,8

The percentage of yield obtained from each fraction is different, this is due to the difference in the ability to attract compounds from each solvent used in the fractionation process. The percentage of yield from the water fraction is greater than the ethyl acetate and n-hexane fractions. From table 2 it can be seen that the compounds contained in Bengkal leaves are more polar.

Table 3. Phytochemical Test Results of Bengkal Leaf Extract (*Nauclea orientalis* L.)

No.	Extract	Test results				
		Alkaloid	Flavonoid	Triterpenoids/Steroids	Tannin	Saponins
1.	Ethanol extract	+	+	-	+	+
2.	n-Hexane Fraction	-	-	+	-	-
3.	Ethyl Fraction Acetate	+	+	-	+	-
4.	Water Fraction	+	+	-	+	+

Information:

\+ = Contains secondary metabolite compounds
− = Does not contain secondary metabolite compounds

From Table 3 it is known that the secondary metabolite content in the ethanol extract of Bengkal leaves positively contains flavonoids, saponins, tannins, and alkaloids. The n-hexane fraction positively contains triterpenoids/steroids. The ethyl acetate fraction positively contains alkaloids, flavonoids, and tannins. The water fraction positively contains alkaloids, flavonoids, tannins, and saponins.

Based on table 3 above, shows that when using polar and semi-polar solvents, more secondary metabolite compound groups were identified compared to non-polar solvents.

Testing of the antidiabetic activity of fractionated extract of Bengkal leaves was conducted to determine whether the fraction has antidiabetic activity and to determine the fraction that provides the best blood glucose-lowering activity. The test animals consisted of 7 groups, namely negative control given 0.5% tragacanth, positive control given 150 mg/kgBW alloxan, comparator namely glibenclamide 0.65 mg/kgBW, and each fraction with a dose of 150 mg/KgBW.

From Table 1 above, it can be seen that the percentage of blood glucose levels in mice after alloxan induction is > 200 mg/dL. Alloxan is a diabetogenic agent used to induce test animals to become hyperglycemic. Alloxan induction is carried out intraperitoneally. When alloxan is injected intraperitoneally, alloxan will quickly penetrate the plasma membrane and enter β cells through the intermediary of glucose transporter 2 (GLUT2) (23).

After being given treatment for 1, 3, and 7 days, all groups of test samples experienced a decrease in blood glucose levels. The negative control group of Tragacanth 0.5% experienced a decrease in blood glucose levels with a low percentage compared to the test sample group. The group with the highest percentage of reducing blood glucose levels was glibenclamide which was the comparative control.

From Table 1 above, it can be seen that the negative control group experienced a decrease in blood glucose after being given 0.5% Tragacanth suspension. Based on the study, this is due to the metabolic process in the body of mice and diuresis so that blood glucose levels in the body of mice can be reduced. Next is the comparison group, namely the group of diabetic mice that received glibenclamide suspension treatment of 5 mg/KgBW. Glibenclamide is an oral antidiabetic sulfonylurea generation II with a working mechanism that can stimulate pancreatic β cells to release insulin which can control blood sugar levels in the body (24). In the positive control group, there was a decrease in blood glucose levels of 91 mg/dL over 7 days. The decrease in blood glucose levels began on the 3rd day by 177 mg/dL with a diabetic blood glucose level of 218.7 mg/dL.

The Bengkal leaf ethanol extract group experienced a decrease in blood glucose levels of around 14.95% whereas the results of administering the Bengkal leaf ethanol extract were able to reduce the blood glucose levels of mice by 180.8 mg/dL within 7 days. Administration of the Bengkal leaf ethanol extract experienced a decrease in blood glucose levels starting on the 3rd day by 191.6 with a diabetic blood glucose level of 212.6 mg/dL.

The n-hexane fraction group experienced a decrease in blood glucose levels of around 18.24% and the administration of this fraction was able to reduce blood glucose levels in mice on the 3rd day by 181 mg/dL. In the water fraction, there was a decrease in blood glucose levels of 48.50%. The decrease in blood glucose levels that occurred in the water fraction was lower than the ethyl acetate fraction, which was 102.2 mg/dL within 7 days. The decrease in blood glucose levels began to occur on the 3rd day.

Based on the research results, each group of test samples has a different percentage of ability to reduce blood glucose levels in mice. This is related to the ability of pharmacological activity of secondary metabolite compounds dissolved in each fraction. The potential for large antidiabetic activity is given by the water fraction of ethanol extract of Bengkal leaves compared to other fractions. Secondary metabolites found in the water fraction, for example, are flavonoids. Flavonoids are polar polyphenol compounds so they tend to dissolve in polar solvents and are slightly soluble in semipolar solvents (25). The research conducted (26) also showed that the polar water fraction showed the ability to reduce blood glucose in diabetic mice.

Flavonoid compounds can lower blood glucose levels with their ability as antioxidants. Antioxidants that can convert ROS into H_2O can prevent excessive ROS production, thus reducing oxidative damage. The research (27) states that antioxidants will bind to free radicals so that they can reduce insulin resistance. The mechanism of action of flavonoids as antidiabetics is their ability to inhibit GLUT 2 (Glucose Transporter type 2), inhibit the enzyme phosphodiesterase, and reduce oxidative stress in people with diabetes mellitus (28). Previous research from (29) states that flavonoids, one of the metabolites of basil leaves, work as an antidiabetic by increasing insulin secretion by increasing the influx of Ca^{2+} ions through calcium channels so that the exocytosis process occurs from insulin granules and causes insulin to be secreted into the blood circulation.

The results of this study are in line with research by (1) stating that the ethanol extract of taya leaves (*Nauclea subdita* (Korth) Steud) was able to reduce blood sugar levels in mice that had been given alloxan. The greatest effectiveness of the 70% ethanol extract of Taya leaves was for extract test III but was still low compared to the positive control.

Table 4. Normality Test

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Standardized Residual for Levels_Sugar_Blood	,067	105	,200*	,984	105	,229

After conducting a normality test, it can be seen from the *Shapiro-Wilk* value that the significance value is > 0.05, so the research data in Table 1 is stated to be normally distributed, so it can be concluded that the research data is normal (Table 4).

Table 5. Homogeneity Test

Levene's Test of Equality of Error Variances[b]

		Levene Statistic	df1	df2	Sig.
Blood Sugar Levels	Based on Mean	2,382	20	84	,103
	Based on Median	1,018	20	84	,452
	Based on the Median and with adjusted df	1,018	20	43,112	,463
	Based on trimmed mean	2,362	20	84	,003

Then in the homogeneity test, it can be seen that the significance value is > 0.05, so the research data is declared homogeneous (Table 5). Based on the data above, this study has met the requirements to be continued to the *ANOVA* test stage, where the data is normally distributed and the variance is homogeneous. After that, the ANOVA test was carried out and the data was obtained as in Table 6.

From the results of the *ANOVA* test on the group of mice, it can be seen that the significance value is <0.05, so it can be interpreted that there is a significant difference in the blood sugar levels of mice between groups in each research data, in the significance value of the observation day there is a significant difference indicated by the p-value <0.05, meaning that there is an effect of the observation day on the blood sugar levels of experimental animals, for the relationship between the treatment group and the observation day, the significance value is <0.05, so there is a relationship between the treatment group and the observation day (Table 6).

Furthermore, to find out whether this Bengkal leaf fraction has effectiveness and to find out the best dose in lowering the blood sugar levels of mice, a further test was carried out, namely the *Duncan post hoc* test. After the *Duncan post hoc* test, the data was obtained as in Table 7.

Table 6. *ANOVA* Test

Tests of Between-Subjects Effects

Dependent Variable: Blood Sugar Levels

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	134412,400[a]	20	6720,620	87,476	,000
Intercept	2394105,000	1	2394105,000	31161,649	,000
Group_Mice	99024,533	6	16504,089	214,817	,000
Day_Observation	19983,829	2	9991,914	130,055	,000
Group_Mice * Day_Observation	15404,038	12	1283,670	16,708	,000
Error	6453,600	84	76,829		
Total	2534971,000	105			
Corrected Total	140866,000	104			

Table 7. *pos hoc Duncan* Test

Blood Sugar Levels

Duncan[a,b]

Group Mice	N	Subset 1	2	3	4	5	6
Comparison	15	114,00					
Ethyl Acetate Fraction	15	116,53					
Negative control	15		130,27				
Residual fraction (water)	15			143,07			
n-Hexane Fraction	15				173,47		
Ethanol Extract	15					186,07	
Positive control	15						193,67
Sig.		,431	1,000	1,000	1,000	1,000	1,000

After further testing (*post hoc*) *Duncan* found that the values in the ethyl acetate fraction group and the comparison group had the same effectiveness, whereas this group had a different effect from the other groups. The ethyl acetate fraction group approached its value with the comparison group, so it can be concluded that the dose group in the ethyl acetate fraction group has better effectiveness than the other dose groups.

With the above results, it turns out that the Bengkal leaf fraction is proven to be able to reduce blood sugar levels in mice. These results also follow previous research which found that 70% ethanol extract of Bengkal leaves at a dose of 150mg/20gBW can reduce blood sugar levels in mice that have been given alloxan.

CONCLUSIONS

Based on the results of the research that has been done, it can be concluded that each fraction has the activity of lowering blood sugar levels in male white mice induced by alloxan, the ethyl acetate fraction of Bengkal leaves has better activity than other test groups based on the *Duncan* test. The ethyl acetate fraction of Bengkal leaves is almost equivalent to the effect of glibenclamide.

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