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Antidiabetic and antihyperlipidemic activity of ethanol extract of Ekor Naga leaves (*Rhaphidophora pinnata (L.f) Schott*) in alloxan-induced male white rats

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ABSTRACT

Antidiabetic and antihyperlipidemic have a very close relationship for Mellitus Diabetics. In previous research, Ekor Naga leaves (*Rhaphidophora pinnata* (L.f) Schott) had an antihyperglycemic effect. The effect was obtained from the presence of secondary metabolites, namely alkaloids, flavonoids, tannins, saponins, and steroids. This research is expected to be a further test of the antidiabetic and antihyperlipidemic effects of alloxan-induced male white rats. This research used an experimental method. The treatment group was divided into four groups, namely negative control (Na CMC 0,5%), positive control (10 mg/kg BW of glibenclamide), group one (250 mg/kg BW of Ekor Naga leaves extract), and group two (500 mg/kg BW of Ekor Naga leaves extract). Data were taken from blood sugar levels on the days 0^{th}, 7^{th}, 10^{th}, and 14^{th}. Total cholesterol, triglyceride, LDL, and HDL levels were observed on the 14^{th} day. Results were analyzed by one-way ANOVA test. The followed by Duncan's test. The result of ethanol extract from Ekor Naga leaves showed antidiabetic and antihyperlipidemic activity in alloxan-induced rats, which had a statistically significant difference relative the negative control ($p<0,05$) decreased the levels of blood glucose, total cholesterol, HDL, LDL, triglycerides. Where the best group is two (500 mg/kg BW of Extract) and followed by group one (250 mg/kg BW of Extract). We concluded that Ekor Naga leaves extract provides activity in the treatment option for patients with diabetes and hyperlipidemia.

Keywords: antidiabetic, antihyperlipidemic, Ekor Naga leaves, alloxan

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INTRODUCTION

Diabetes mellitus is a metabolic disorder disease that occurs chronically and is caused by many factors with characteristics of high blood sugar levels. Hyperglycemia and hyperlipidemia are one of the main characteristics of diabetes mellitus, which can trigger complications (Hartanti & Budipramana, 2020; Pappachan et al., 2019; Salehi et al., 2019). Therefore, efforts to control blood sugar levels are the primary goal to delay the development of complications in patients with diabetes mellitus (Sun et al., 2021; Febrinasari et al., 2020; Maruhashi & Higashi, 2021).

The incidence of diabetes mellitus constantly increase throughout the world. According to the International Diabetes Federation (IDF), in 2021, it is estimated that at least 537 million people aged 20-79 years old in the world will suffer from diabetes mellitus, or equivalent to a prevalence rate of 9.3% of the total world population. Furthermore, the incidence rate is predicted to reach 643 million in 2030 and 783 million in 2045(IDF, 2021). Indonesia alone in 2019 has reached 10.7% of the total population (Kementrian kesehatan republik indonesia, 2020).

The use of traditional medicine as an antidiabetic and antihyperlipidemic agent in humans needs to go through many stages, namely preclinical trials and clinical trials, to prove its safety if used in the long term by patients with diabetes mellitus. Ekor Naga leaves (*Rhaphidophora pinnata (L.f) Schott*) is a plant widely used by the community to treat various diseases. Preclinical testing on the effectiveness of the Ekor Naga leaves as an antihyperglycaemic has been carried out by Lestari et al., (2021); the results showed that the ethanol extract of the Ekor Naga leaves effectiveness as an antihyperglycaemic with the best group of 375 mg/KgBW. In addition, research conducted by Makhdalena (2006) stated that a group of 300 mg/Kg BW ethanol extract of Ekor Naga leaves was effective in lowering cholesterol and triglyceride levels which are factors that trigger cardiovascular disease. Reducing glucose, cholesterol, and triglyceride levels are being thought to be due to the content of secondary metabolites such as flavonoids, alkaloids, and tannins, which are antioxidants that work by inhibiting the alpha-glucosidase enzyme and act as cardioprotective (Gallagher et al., 2003; Utaminingrum et al., 2020). In addition, the content of terpenoids also plays a role in stimulating insulin from the pancreas so that blood glucose level is down (Sani et al, 2017).

The literature survey revealed that there is no experimental evidence of the plant's antidiabetic and antihyperlipidemic effects. Based on these problems, the researchers are interested in further testing the effect of Ekor Naga leaves extract as antihyperglycemic as a controller of blood sugar and cholesterol levels in white male rats induced by Alloxan.

MATERIALS AND METHOD

Materials

Fresh Ekor Naga leaves were taken from Jambi City Jambi Province In Juli 2021, ethanol (PT. Brataco), Na CMC (PT. Brataco), aqua dest, sulfuric acids 2 N, Dragendorff's reagent, Meyer's reagent, Wagner's reagent, Alloxan (Sigma Aldrich), ammonia (PT. Brataco), paraffinic acid (PT. Brataco), trifluoroacetate (Sigma Aldrich), aspirin, glibenclamide, acetic anhydrous, concentrated sulfuric acid (Merck), HCl 2 N (Merck), $FeCl_3$ 1% (Merck), Mg powder, and H_2SO_4 10% (Merck).

Methods

Ekor Naga leaves extract

Ekor Naga (*Rhaphidophora pinnata* (L.f) Schott) leaves were extracted using the maceration method using 70% ethanol as solvent. The powder was put into a vessel, then added 70% ethanol solvent in a ratio of 1:10 until the powder was completely submerged, then covered and left for five days protected from light while stirring. Then the mixture was filtered, and the dregs were maceration again with a 70% ethanol filter until submerged and left for two days, then simmered and poured so that the macerate was obtained. The macerate was then concentrated with a rotary evaporator at a temperature of not more than 40^{o}C, and a thick extract was obtained. The viscous extract obtained was

then stored in the refrigerator in the Rotary Evaporator, and the extract obtained was calculated for the yield. The extracts obtained were subjected to phytochemical screening.

Ekor Naga leaves extract antidiabetic and antihyperlipidemic test

This study used white male rats weighing 200-250 grams with healthy and normal conditions. The number of test animals used in the study was 20 tails. The treatments were divided into four groups, namely:

Group I : Negative Control had been given Na. CMC 0,5%
Group II : Positive Control had been given glibenclamide 10 mg/Kg BW
Group III : Ekor Naga leaves extract with a group of 250 mg/Kg BW
Group IV : Ekor Naga leaves extract with a group of 500 mg/Kg BW

All test animals were given alloxan monohydrate 150 mg/Kg BW intraperitoneally as an inducer of diabetes mellitus. The administration was carried out for three days by comparing the initial and final glucose. If it had exceeded 200 mg/dL, the rats were considered to have diabetes. Observations of blood sugar levels were carried out on days 0^{th}, 7^{th}, 10^{th}, and 14^{th}. Blood glucose was monitored using blood glucose test diagnostic strips. Meanwhile, measurements of cholesterol, triglyceride, LDL, and HDL levels were carried out on day 14^{th} were determined with the use of commercially available enzyme kits.

Data Analysis

Analysis of research data was carried out in three ways, namely descriptively (extract characteristics) and using the SPSS 23 program 2-way ANOVA test (blood sugar levels), 1-way ANOVA (total cholesterol, triglycerides, LDL, and HDL) with a 95% level of confidence.

RESULT AND DISCUSSION

Plant determination

The determination of the Ekor Naga plant was carried out at the "Plant Biosystematics Laboratory" Department of Biology, Faculty of Mathematics and Natural Sciences, Tadulako University, with the number 240/UN28.1.28/BIO/2021, stating that the sample used in this study was the Ekor Naga plant from the family Araceae and species *Epipremnum pinnatum* (L.) England.

Ekor Naga (Rhaphidophora pinnata (L.f) Schott) leaves extract

Ekor Naga leaves extract is obtained by extraction by maceration method, which involves immersing plant material (simplicia powder). The advantage of extraction using the maceration method is that it uses simple equipment and does not use heating so that the material does not decompose. The maceration process used as much as 700 g of Simplicia powder using 70% ethanol solvent to obtain 61 grams of extract.

Phytochemical screening

Phytochemical screening is the preliminary stage in conducting research by describing the class of compounds contained in the plant greetings used. The results can be seen Table 1. The results of the phytochemical examination showed that the ethanol extract of Ekor Naga leaves contained secondary metabolites of flavonoids, alkaloids, saponins, tannins, steroids, and phenols. The results were similar to previous studies conducted by Sumaiyah et al., (2018), Pascila et al. (2020), Lestari et al. (2021) and Tarigan et al. (2021).

Table 1. Phytochemical screening

Phytochemical test	Observation result
Flavonoids	+
Alkaloids	+
Saponins	+
Tannins	+
Steroids	+
Terpenoid	-
Phenol	+

Note: (+) = Positive contains compounds
(-) = Negative contains compounds

Antidiabetic and antihyperlipidemic activity test of ethanol extract of Ekor Naga leaves (Rhaphidophora pinnata (L.) Engl.)

The results of the antidiabetic test can be seen in Table 2. This test is supported by data on the value of total cholesterol, triglycerides, LDL, and HDL in white male rats induced by Alloxan and treated with Ekor Naga leaves extract. This research has an ethical clearance number 3094/UN 28.1.30/KL/2021, which was carried out by the ethics committee of the Falculty of Medicine Tadulako University.

The positive control used in this study was glibenclamide. Glibenclamide is one of the sulfonyl urea diabetes therapy drugs which is commonly used in the community. The mechanism of action of glibenclamide in inhibiting blood sugar by stimulating pancreatic beta cells to produce insulin in larger quantities (AlFaris et al., 2020; Prasathkumar et al., 2021).

The results of the antidiabetic test showed a significant difference in each treatment on day 14th. There had been decreassing in blood sugar levels except for the negative control. Where statistically were showed a significant difference ($p < 0.05$). The results can be seen Table 2. These results indicate that the Ekor Naga leaves extract has an effect as an antidiabetic and antihyperlipidemic agent in alloxan-induced rats. The best results were being shown at group two which is 500 mg/kg BW, with blood sugar levels on day 14th being 50 mg/dL. The standard value for rat blood sugar levels is 50-135 mg/dL. These results were indicated that the administration of Ekor Naga leaves extract has a significant effect in giving the antidiabetic effects of Ekor Naga leaves extract to alloxan-induced male white rats.

Table 2. Average blood glucose levels during 14 days treatment in diabetic rats ± SD

Treatment	Blood Glucose Treatment (mg/dL) ± SD			
	Day 0	Day 7	Day 10	Day 14
Negative Control	267.5 ± 0.71^{a}	272.0 ± 2.83^{a}	226.3 ± 0.42^{a}	137.33 ± 0.28^{a}
Positive Control	240.0 ± 1.41^{a}	149.7 ± 0.50^{c}	60.7 ± 1.77^{c}	54.33 ± 0.14^{c}
Group I (250mg/KgBW)	261.2 ± 0.78^{a}	230.8 ± 0.73^{a}	221.0 ± 1.41^{a}	76.00 ± 0.66^{b}
Group 2 (500mg/KgBW)	286.5 ± 0.71^{a}	167.0 ± 1.41^{b}	206.0 ± 1.41^{b}	50.00 ± 5.66^{c}

Note:
Different lowercase superscripts on the same column indicated a significant difference ($p<0,05$)

In the case of diabetes mellitus, hyperlipidemia is one type of comorbidity that arises as a result of insulin resistance. Insulin resistance will have the effect of increasing lipolysis from stored fat reserves, thereby affecting the lipotic action of hormones and the mobility of fatty acids in the body (Yuan et al., 2021). The condition of hyperlipidemia is characterized by measuring the values of total cholesterol, triglycerides, LDL, and HDL. The results were showed that in diabetic rats, alloxan induction could affect the normal values of total and LDL cholesterol in the body, which were 10-54

mg/dL and 7-27.2 mg/dL, respectively (Parasuraman et al., 2019; Srivastava et al., 2020). The high value of total cholesterol and LDL in the negative control can be seen in the negative control.

The results showed an improvement in total cholesterol and LDL value after being treated with Ekor Naga leaves extract. The best group for reducing total cholesterol and LDL is Group 2 (500mg/Kg BW) of Ekor Naga leaves extract with total and LDL cholesterol values obtained are 78.00 mg/dL and 35 mg/dL, respectively and followed by a group of 1 (250 mg/Kg BW) of Ekor Naga leaves extract. The results can be seen Table 3.

Table 3. The average value of total cholesterol, triglycerides, LDL, and HDL in diabetic rats ± SD

Treatment	Total Cholesterol (mg/dL) ± SD	Triglycerides (mg/dL) ± SD	LDL (mg/dL) ± SD	HDL (mg/dL) ± SD
Negative Control	85.3 ± 6.81^{d}	66.5 ± 1.53^{a}	43.3 ± 6.67^{c}	38.0 ± 21.50^{d}
Positive Control	74.0 ± 9.54^{a}	49.7 ± 10.02^{c}	35.7 ± 10.02^{a}	51.3 ± 4.04^{a}
Group 1 (250mg/KgBW)	79.7 ± 10.51^{c}	54.3 ± 22.28^{b}	37.7 ± 10.44^{b}	42.0 ± 4.58^{c}
Group 2 (500mg/KgBW)	78.0 ± 0.71^{b}	46.7 ± 3.23^{c}	35.0 ± 1.41^{a}	43.5 ± 9.19^{bc}

Note:
Superscripts with different lowercase letters showed significant differences ($P<0.05$)

The secondary metabolites as antidiabetic and antihyperlipidemic compounds are flavonoids, alkaloids, steroids, tannins, and saponins. Flavonoids are a collection of hydroxylated phenolic substances that have a crucial role as free radical scavengers or antioxidants. The protection provided by flavonoids on the body's biological system is comes from the ability to transfer hydrogen, activate antioxidant enzymes, chelate metal catalysts, and inhibit oxidase. The study showed that oxidative stress increases significantly in patients with diabetes mellitus, both type I and type II (Aslam et al., 2018; Li et al., 2019).

Flavonoids which act as antioxidants had protected from the adverse effects caused by free radicals in people with diabetes mellitus, including hyperglycemia and hyperlipidemia. In addition, flavonoids also act as an inhibitor of α-glucosidase enzymes in people with diabetes mellitus [(11)]. The α-glucosidase enzyme is an exocarbohydrate that plays a role in the catalysis of glucose from carbohydrates. If the enzyme has inhibited, the metabolism in the body will cause a decrease in blood glucose levels (Bao et al., 2016; Sarian et al., 2017).

The function of flavonoids is also supported by the presence of alkaloids that have a role as diabetes therapeutic agents working through stimulation of various systems in the body such as inhibition of α-glucosidase enzyme, blockade of PTP-1B, deactivation of DPP-IV, increasing insulin sensitivity and modulating oxidative stress (Singh et al., 2017; Ajebli et al., 2020; Muhammad et al., 2021). Other than that, flavonoids and alkaloids as antioxidants also play a role in inhibiting the modification of LDL oxidation, reducing HMG-CoA reductase activity of the enzyme Acyl-CoA cholesterol acyltransferase (ACAT), and reducing cholesterol absorption in the gastrointestinal tract so that cholesterol levels, triglyceride, and LDL decrease while HDL is increased (Pradana et al., 2016).

Steroid compounds, tannins, and saponins are also antioxidant agents which support the role of flavonoids. The results showed that steroids, tannins, and saponins also have polyphenolic compounds that can reduce blood glucose and lipid levels in people with diabetes mellitus (Ezzat et al., 2017; Hussain & Ikram, 2020; Wang et al., 2019). The mechanism of action for improving the value of cholesterol, triglycerides, LDL, and HDL is through the process of inhibiting the absorption of cholesterol in the intestines, causing cholesterol not to be absorbed and excreted through the feces so that the conversion of cholesterol into bile acids increases as an effort to maintain bile acid depots. Consequently, there is an increase in LDL uptake followed by a decrease in total cholesterol and triglycerides with an increase in HDL values in the blood (Ahmed et al., 2020).

CONCLUSION

Based on the study results above, it can be concluded that the ethanolic extract of the Ekor Naga leaves has an effect as antidiabetic and antihyperlipidemic, and has a statistically significant difference ($p<0.05$) when compared to the negative control. The best group in reducing blood sugar and cholesterol levels in white male rats induced by Alloxan was group 2 (500mg/kg BW) followed by group 1 (250mg/kg BW).

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