



Effect of Suruhan Leaves (*Peperomia pellucida* L. Kunth) Extract on Triglyceride Blood Level in Diabetic Rats

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Abstract

Background: Diabetes Mellitus causes complications, such as hypertriglyceridemia. Indonesia has biological wealth diversity that can be exploited in alternative medicine. One of which is Suruhan plants. Flavonoid contents in the plant extract can normalize blood triglyceride levels. **Objective:** This study aims to determine the effect of the Suruhan extract (*Peperomia pellucida* L. Kunth) on blood triglyceride levels in alloxan-induced diabetic white rats. **Methods:** The induction process used alloxan at a dose of 150mg/kgbw intraperitoneally to 12 rats. The rats were divided into 5 research groups, namely normal rats, diabetic rats, and diabetic rats were given various doses of extract. The treatment was carried out for 14 days. Blood samples for triglyceride examination were taken at the end of the study. **Results:** blood triglyceride levels were obtained in the normal group (127.67 mg/dl); and diabetic control group (395.67mg/dl); the dose group was 20mg/kg BW (216mg/dl); the dose group was 40 mg/kg BW (159.33 mg/dl) and the dose group was 80 mg/kg BW (143.33 mg/dl) in the statistical test with one way ANOVA ($p < 0.05$) obtained significance with a value of $p = 0.000$. **Conclusions:** There is an influence of plant extracts (*Peperomia pellucida* [L.] Kunth) administration on the blood reduction of triglyceride levels in diabetic white rats induced by alloxan.

Keywords: diabetes mellitus, suruhan plants (*Peperomia pellucida* [L.] Kunth), triglyceride

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INTRODUCTION

Diabetes Mellitus is a metabolic disorder caused by pancreatic damage, resulting in the inability to produce the hormone insulin (Petersmann *et al.*, 2019). Insulin is a hormone responsible for regulating the balance of sugar in the blood (Latres *et al.*, 2019). Moreover, individuals with diabetes mellitus can experience increased free fatty acids in the blood, parallel to the fluctuation of blood glucose levels (Sobczak *et al.*, 2019). The elevated levels of free fatty acids in the blood can lead to reduced tissue sensitivity to insulin (Kojta *et al.*, 2020). This mechanism explains the correlation between cholesterol levels and diabetes (Wardani *et al.*, 2015).

In 2021, the International Diabetes Federation (IDF) stated that the estimated number of people worldwide suffering from diabetes had reached 643 million by 2030 and this number is projected to reach 783 million by 2045 (International Diabetes Federation, 2021). Meanwhile, the projected population of Indonesia by 2030 suggests that around 21.3 million individuals will be afflicted with diabetes, placing the country in the 6th position globally, after India, China, the United States, Pakistan, Brazil, and Mexico (Infodatin, 2020).

According to data collected by the Jakarta Primary Non-Communicable Disease Risk Factors Surveillance in 2006, it was reported that cases of dyslipidemia occurring in Type 2 Diabetes (DMT2) patients had higher percentages: 67.7% increase in total cholesterol, 54.9% increase in triglycerides, 36.8% decrease in HDL, and 91.7% increase in LDL (Perkeni, 2019). Dietary control remains one of the most desirable avenues for the prevention and management of chronic degenerative diseases such as diabetes. Various plants have been employed in traditional medicine to treat diabetes (Kumar *et al.*, 2021).

Meanwhile, according to a previous study, antihyperglycemic effect ethanol extract from the suruhan leaves (*Peperomia pellucida* L. Kunth) at doses of 56 mg/kg BW, 112 mg/kg BW, and 168 mg/kg BW have been proven to reduce blood glucose levels and improve liver cell damage in male mice (*Mus musculus*) induced with alloxan (Islamy, 2019). The other study reported that suruhan extract at doses of 20 mg/kgBW, 40 mg/kgBW, and 80 mg/kgBW reduced blood glucose in rats sucrose-induced (Salma *et al.*, 2013). Polyphenol and flavonoid compounds in plants *Peperomia pellucida* have strong antioxidant and α -amylase inhibitory activity (Men *et al.*, 2022). The enzyme α -amylase plays a role in breaking down starch into maltose and alpha-

amylase reciprocally inhibits insulin production (Pierzynowski *et al.*, 2023).

Alloxan is one of the drugs used to induce diabetes experimentally because of damage to pancreatic beta cells and damage to insulin work which can trigger hyperglycemia (Ibrahim *et al.*, 2023). Alloxan accumulates in pancreatic beta cells and generates reactive oxygen species, has a significant necrotizing, and reduces the number of β -cells resulting in insulin deficiency (Lenzen, 2008; Radenković *et al.*, 2016).

This research was conducted to determine the influence of the ethanol extract from the suruhan leaves on blood triglyceride levels in rats induced with alloxan. This study was based on the correlation between diabetes mellitus and blood cholesterol and lipid condition. This study also explored the dose-dependent effects of suruhan leaf extract on blood glucose and triglyceride levels in alloxan-induced diabetic rats.

MATERIALS AND METHODS

Tools

The tools used include a syringe (Onemed 3ml, Indonesia), analytical scale (Precisa, Switzerland), digital scale (SF 400, China), measuring cylinder, test tube, beaker glass, erlenmeyer flask, rotary evaporator (RV 10 digital V, USA), semi-auto chemistry analyzer photometer (Sunostik SBA 733), glucose test meter, and glucose meter strips (GlucoDR, Korea), EDTA tube (K2 3ml, China), stirring rod, spoon, oral probe, cage, rat feeding, and drinking area.

Materials

The materials used include suruhan leaves powder from the Research Institute for Spices and Medicinal Plants (BALITTRO) Bogor-West Java with determination at Indonesian Institute of Sciences (LIPI) with reference number 465/IV/DI.01/3/2021. Ethanol 96% (Unbranded, Indonesia), alloxan monohydrate (Sigma Aldrich, Germany), triglyceride reagent (Sigma Aldrich, Germany), Sprague-Dawley rats (BPOM, Indonesia), aquadest (Unbranded, Indonesia), sodium carboxymethyl cellulose (Na CMC, Wealthy, Indonesia), sodium chloride 0.9%, NaCl 0.9% (Wida, Indonesia).

Animals

Fifteen male rats (*Rattus norvegicus*) of the Sprague-Dawley strain, aged three months, weighing approximately 150-250 grams. The sample size in this study was calculated using the formula minimum and maximum sample sizes for analysis of variance (ANOVA) Design (Arifin & Zahiruddin, 2017). The Sprague-Dawley rats used as test animals must be

healthy and obtained from the Experimental Animal Facility of The National Agency of Drugs and Food Control (BPOM), the Republic of Indonesia. The rats were maintained properly and according to the applicable ethical guidelines.

Method

Alloxan Preparation

In this study, a dose of 150 mg/kgbw of alloxan in 0.9% NaCl solution was used (Ibrahim *et al.*, 2023). During the induction process, a total of 15 healthy rats were first acclimated for 7 days. This was followed by the alloxan induction phase on rats that had been fasted for 18 hours. The rats were weighed to determine the amount of alloxan to be administered to each rat, with a dosage of 150 mg/kg BW. Subsequently, the rats' blood glucose levels were examined through the caudal vein using a glucometer, two hours after the blood glucose level examination. Subsequently, alloxan induction was administered to the rats intraperitoneally, once at the initial stage of the study. Blood glucose level was checked within 72 hours following the induction procedure to ascertain the degree of glucose elevation, indicating a successful induction.

Preparation of Suruhan Extracts

The plant material used is the powder of the Suruhan leaves plant (*Peperomia pellucida* L. Kunth). The parts utilized were the leaves and stems in good condition, free from damage and mold. The powdered plant material was then extracted using the maceration method with 96% ethanol (Abubakar & Mainul, 2021). A total of 500 grams of powdered material were dissolved in 96% ethanol with solvent replacement every 24 hours for 3 days. After that, the residue was filtered. Then the residue was macerated again with ethanol 96% for 2 days and filtered as the mixing filtrate. Finally, the filtrates were mixed and then evaporated with a rotary evaporator at 60°C to obtain a thick extract. Subsequently, in the concentrated extract, organoleptic assessments were conducted, and the chemical content of the extract was identified through a flavonoid content test. A plant extract suspension was prepared with a mixture of 1% Na CMC (sodium carboxymethyl cellulose) in a total volume of 3 ml for each dose of 20 mg, 40 mg, and 80 mg (Salma *et al.*, 2013).

Flavonoid Screening

The presence of flavonoids in the ethanol extract of Suruhan was identified using the Willstatter test (Rao *et al.*, 2016; Thi *et al.*, 2020). A crude extract of 5 ml was dissolved in ethanol and filtered. Added 0.1 g of magnesium powder (Mg), 1 ml HCL and 2 ml of amyl alcohol. Shake the mixture and allow it to separate. The

presence of red, yellow, or orange coloration in the amyl alcohol layer indicates the presence of flavonoids.

Experimental Design

After induced diabetes with alloxan and blood glucose analysis at level >200 mg/dL, the rats were randomly divided into five groups (n =3 per group as follows; Group 1 represented the normal group, not induced and without treatment. Group 2 served as the DM control, induced of alloxan without treatment. Group 3 was induced and treated with 20 mg/kgbw of Suruhan leaves extract. Group 4 was induced and treated with 40 mg/kg BW of Suruhan leaves plant extract. Lastly, Group 5 was induced and treated with 80 mg/kg BW weight of Suruhan leaves extract. Before administering the treatment, the rats were measured to determine the amount of extract that could be given based on their dosage. The administration of the treatment was conducted orally using an oral probe and carried out daily for 14 days (Salma *et al.*, 2013; Yuliani *et al.*, 2016). During the treatment, there were variations in the dosages of the Suruhan leaf extract according to the predetermined groups. The Suruhan leaves extract was given orally to the rats at a maximum volume of 1% of their body weight. One day after the last administration of the extract, the rats' blood glucose levels were measured. The rats' body weights were recorded, and some rats were sacrificed to collect blood from the heart for the examination of their blood triglyceride levels. This was carried out because measuring blood triglyceride levels required a significant amount of blood, at least 3 ml, to be centrifuged and produce serum (Mahdi *et al.*, 2020).

Statistical Analysis

The results are expressed as mean \pm SD. Differences between groups were assessed by one-way ANOVA using the Statistical Package for Social Sciences (SPSS for Windows, version 22.0). Post hoc testing was performed for inter-group comparisons using the least significance difference (LSD) P-values < 0.05 were considered as significantly altered.

RESULTS AND DISCUSSION

Body weight changes

The body weight was analyzed during the 14 days of the experiment. The body weight changes in all diabetic and non-diabetic rats are represented in Table 1. Rats' body weight increased in the Normal Group and three group rats with diabetes with Suruhan extract treatment.

Table 1. Body weight before and after being treated with suruhan extract

Group	Body Weight Before Treatment (gram)	Body Weight After Treatment (gram)	Percent BodyWweight Changes (%)
Normal	204.67 ± 2.31	277.67 ± 17.01	26.14 ± 3.81*
DM	189.67 ± 35.85	184.33 ± 37.29	-3.08 ± 2.26
DM+20	211.33 ± 53.20	223.67 ± 54.15	5.66 ± 0.91*
DM+40	176 ± 13.23	208.33 ± 24.66	15.21 ± 4.03*
DM+80	219.33 ± 81.46	249.33 ± 65.16	13.56 ± 8.82*

Note: The sign (-) in the number indicates the percent decrease in body weight. Values are expressed as the mean ± standard deviation (STD); *= $P < 0.05$ vs Diabetic Group. Normal group (Rats without induced and treatment), DM (Rats Induced diabetes without treatment), DM+20 (Rats diabetes with treatment suruhan extract dose 20mg/kg BW), DM+40 (Rats diabetes with treatment suruhan extract dose 40mg/kg BW) and DM+80 (Rats diabetes with treatment suruhan extract dose 80mg/kg BW)

Table 2. Blood glucose levels of alloxan-induced diabetic rats treated with suruhan extract

Group	Blood Glucose levels before Treatment (mg/dL)	Blood Glucose levels after Treatment (mg/dL)	Percent decrease in blood glucose levels (%)
Normal	104 ± 14.73	143.67 ± 12.34	27.49 ± 9.18
DM	351 ± 215.65	525.67 ± 71.67	32.46 ± 41.81
DM+20	330.67 ± 103.37	288 ± 104.75	-12.91 ± 6.27*
DM+40	234.67 ± 34.43	142.67 ± 11.15	-64.54 ± 20.52*
DM+80	269 ± 18.36	136 ± 22.52	-102.55 ± 37.77*

Note: The sign (-) in the number indicates the percent decrease in blood glucose levels. Values are expressed as the mean ± STD; *= $P < 0.05$ vs Diabetic Group. Normal group (Rats without induced and treatment), DM (Rats Induced diabetes without treatment), DM+20 (Rats diabetes with treatment suruhan extract dose 20mg/kg BW), DM+40 (Rats diabetes with treatment suruhan extract dose 40mg/kg BW) and DM+80 (Rats diabetes with treatment suruhan extract dose 80mg/kg BW)

According to the results, the untreated control group experienced a decrease in body weight after 14 days, with statistical significance observed at a p -value of 0,000. The changes in body weight gain were in three dosage variations of suruhan leaf extract. In this study, the most effective dose of extract was 80 mg/kg BW. Food and water intake were elevated whereas the body weight significantly decreased in diabetic rats compared with normal control rats. This possibly occurs in diabetes where the body is unable to use glucose as an energy source due to a lack of insulin and an increase in body weight implying that the anabolic effect has overridden the catabolic (Al-Attar & Alsalmi, 2019).

Blood glucose levels

Blood glucose level is the main factor in producing diabetes in animal models. This study found blood glucose level of the 12 test animals that were induced by alloxan 150 mg/kg BW was recorded at >200 mg/dL after 72 hours. Similarly, in alloxan-induced rats, a study showed that rats had fasting blood glucose (FBG) >200mg/dL (Yuliani *et al.*, 2016). Rats having blood glucose levels of 220-250 mg/dL were considered diabetic (Rehman *et al.*, 2023). Table 2 presents fasting

blood glucose levels before and after treatment for 14 days. The group treatment with Suruhan leaves extract doses of 20 mg/BW, 40 mg/BW, and 80 mg/BW showed a significant decrease compared to the group DM control.

The study examined blood glucose levels within the control group and treatment group and observed which treatment with Suruhan extract significantly lowered blood glucose levels, resulting in a statistically significant result with a p -value = 0.007. The most effective dose to decrease blood glucose levels was found at an extract dose of 80 mg/kgBW. Several studies related to hypoglycemic activity have been carried out. Suruhan extract in three dose variations effectively reduces blood sugar levels (Salma *et al.*, 2013). Blood Glucose in the control group increases because Alloxan is a diabetogenic drug (Sheriff *et al.*, 2020). Treatment groups with Suruhan extract had been lowering blood glucose. It is probably phytochemicals, such as flavonoids that can improve insulin sensitivity (Bacanli *et al.*, 2019). Phytochemicals in ethanol extract of Suruhan such as flavonoids and triterpenoids are thought to be related to the effect antioxidants can

increase insulin expression and modulation of glucose transporter (Hidayati, 2021). On the other hand, suruhan extract has an α -amylase inhibitory activity that increases blood glucose levels (Men *et al.*, 2022).

Blood triglyceride level

The blood triglyceride levels of the test animals were measured at the end of the treatment period, precisely one day after the completion of the 14-day treatment regimen. There were significant differences in the average blood triglyceride levels among the 5 groups (Figure 1). The group with the highest average blood triglyceride level was the DM control group, with a value of 395.67 mg/dl. On the other hand, the group with the lowest average blood triglyceride level was the normal group, with a value of 127.67 mg/dl. In the treatment groups, the blood triglyceride levels were closest to normal in the group receiving dose 3, with an average of 143.33 mg/dl. A study reported total triglyceride normal levels in rats is 26-145 mg/dL (Mahdi *et al.*, 2020).

The graph depicts the blood triglyceride levels of the test animals in the 5 groups, where the highest blood triglyceride levels were found in the DM control group. Subsequently, the blood triglyceride levels of the test animals decrease sequentially in the groups of rats given doses of 20 mg/kg BW of the extract, 40 mg/kg BW of the extract, and 80 mg/kg BW of the extract. This indicates that as the dosage increases, the blood triglyceride levels in the test animals decrease. The most effective dose to decrease triglyceride levels was found at an extract dose of 80 mg/kg BW. Meanwhile, the

lowest blood triglyceride levels were observed in the normal group.

The hypothesis testing results for the blood triglyceride levels of the test animals in the five groups p-value of 0.000 or < 0.05 was obtained. Therefore, this data suggests a significant difference in blood triglyceride levels among the five groups.

Hypertriglyceridemia is exceedingly common in diabetes (Simha, 2020). Diabetes mellitus frequently results in hypertriglyceridemia which increases the risk of arteriosclerotic disease (Kane *et al.*, 2021). In Diabetic type 2 impaired glucose tolerance, the basic defect is postulated to be the loss of normal insulin sensitivity, leading to compensatory hyperinsulinemia and increased triglyceride secretion (Ye *et al.*, 2019). However, Plant extract administration in the animal diabetic model resulted in a reduction in blood glucose and triglyceride levels (Bacanli *et al.*, 2019; Khan *et al.*, 2019). Phytochemical content in extracts such as flavonoids lowers triglyceride levels and modulates lipid metabolism through the inhibition of fatty acid synthase (Luna-Castillo *et al.*, 2022). Other lipid metabolism-modulating effects of the extract are related to its ability to inhibit reactive oxygen species through the expression of antioxidants (Men *et al.*, 2022). In this study identification of flavonoid compounds in the leaf extract of the suruhan plant (*Peperomia pellucida* L. Kunth) was carried out. The test results were positive for containing flavonoids with the formation of an orange-yellow color (Rao *et al.*, 2016)

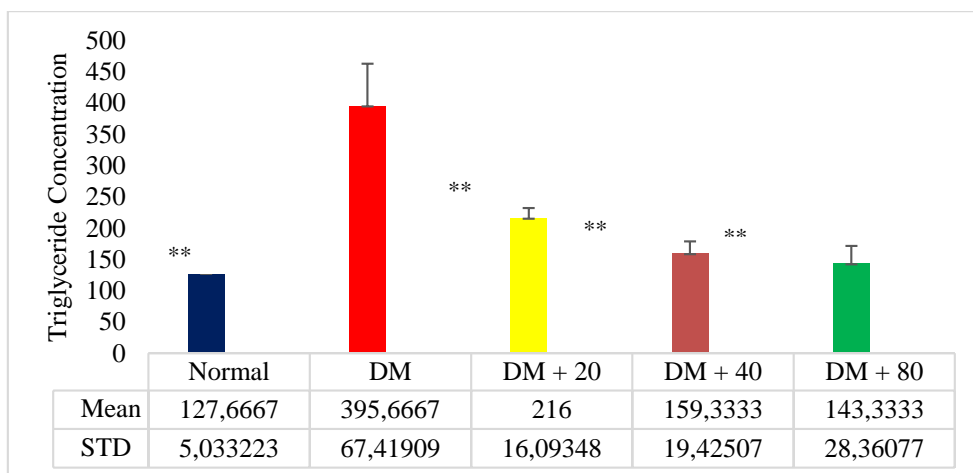


Figure 1. Blood triglyceride concentration of alloxan-induced diabetic rats treated with suruhan extract

Note: Each Value is presented as the mean ± standard deviation (STD); *Significant difference vs control group at P < 0.05, **highly significant difference vs the diabetic group at P < 0.01. Normal group (Rats without induced and treatment), DM (Rats Induced diabetes without treatment), DM+20 (Rats diabetes with treatment suruhan extract dose 20mg/kg BW), DM+40 (Rats diabetes with treatment suruhan extract dose 40mg/kg BW) and DM+80 (Rats diabetes with treatment suruhan extract dose 80mg/kg BW)

CONCLUSION

According to the findings of the conducted study the administration of Suruhan leaves extract (*Peperomia pellucida* L. Kunth) at doses of 20 mg/kg BW, 40 mg/kg BW, and 80 mg/kg BW over 14 days to diabetic rats induced with intraperitoneal alloxan at a dose of 150 mg/kg BW, resulted in a significant impact. This was characterized by a reduction in blood glucose levels and the achievement of normal blood triglyceride levels. The optimum dose for reducing blood glucose levels and achieving normal blood triglyceride levels was found to be at the 80 mg/kg BW dose. The higher the dosage used, the greater the average decrease in blood glucose and blood triglyceride levels in the test animals subjected to treatment for 14 days.

ETHICS STATEMENT

This research has obtained ethical approval from the Ethics Committee of the Faculty of Medicine, University of Indonesia - Dr. Cipto Mangunkusumo National Hospital, with the reference number 21-07-0792.

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AUTHOR CONTRIBUTIONS

Conceptualization, H.N.; Methodology, H.N.; Validation, H.D.M., H.N.; Formal Analysis, H.D.M., H.N.; Investigation, H.D.M.; Resources, H.D.M., N.R.H.; Data Curation, H.D.M.; Writing - Original Draft, H.D.M., N.R.H.; Writing - Review & Editing, H.N.; Visualization, H.N.; Supervision, H.N.; Project Administration, N.R.H.; Funding Acquisition, H.D.M., H.N.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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