

EFFECT OF SOURSOP LEAF EXTRACT (*ANNONA MURICATA* L.) ON FASTING BLOOD GLUCOSE LEVELS IN ALLOXAN-INDUCED RATS

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ABSTRAK

Tanaman sirsak merupakan salah satu tanaman herbal yang dimanfaatkan masyarakat untuk mengatasi berbagai penyakit. Pemanfaatan tanaman sirsak banyak digunakan bagian daunnya saja. Salah satu manfaat daun sirsak adalah menurunkan kadar glukosa darah. Hal tersebut dikarenakan daun sirsak mengandung senyawa *flavonoid*, *tannin* dan *alkaloid*. Senyawa *flavonoid* memiliki efek hipoglikemik dan bertindak seperti insulin. Senyawa *tannin* mampu mengaktifasi enzim untuk memudahkan glukosa masuk ke dalam sel dan senyawa *alkaloid* dapat meregenerasi sel beta pankreas. Penelitian ini bertujuan untuk mengevaluasi efek hipoglikemik ekstrak daun sirsak pada tikus yang telah diinduksi aloksan. Penelitian ini adalah penelitian eksperimental pretest-posttest with control group design. Penelitian dilakukan pada tikus jantan putih Galur Wistar yang diberikan ekstrak daun sirsak dengan dosis 400mg/KgBW dan 800mg/KgBW selama 5 hari. Uji analisis yang digunakan adalah One-Way ANOVA. Dari penelitian yang dilakukan menunjukkan bahwa terdapat hubungan yang signifikan antara pemberian ekstrak daun sirsak terhadap kadar glukosa darah puasa pada kelompok intervensi dengan pemberian ekstrak daun sirsak dengan dosis 400mg/KgBW dan 800mg/KgBW dengan nilai $p = 0,000$ pada tikus yang diinduksi aloksan dengan perbedaan rata-rata kadar glukosa darah puasa pada kelompok K+ dengan P1 dan P2 yaitu 61,143 dan 82,000.

ABSTRACT

Effect of Soursop Leaf Extract (*Annona muricata* L.) on Fasting Blood Glucose Levels in Alloxan-Induced Rats. Soursop plant is one of the herbal plants used by the community to overcome various diseases. Soursop plant utilization is widely used for the leaves only. One of the benefits of soursop leaves is to reduce blood glucose levels. This is because soursop leaves contain *flavonoids*, *tannins*, and *alkaloid* compounds. *Flavonoid* compounds have hypoglycemic effects and act like insulin. *Tannin* compounds can activate enzymes to facilitate glucose entry into cells and *alkaloid* compounds can regenerate pancreatic beta cells. This study aims to evaluate the hypoglycemic effect of soursop leaf extract on rats that have been induced by alloxan. This study is a pretest-posttest experimental study with control group design. The study was conducted on white male Wistar rats given soursop leaf extract at a dose of 400mg/KgBW and 800mg/KgBW for 5 days. The analysis test used was One-Way ANOVA. From the research conducted shows that there is a significant relationship between the administration of soursop leaf extract on fasting blood glucose levels in the intervention group with the administration of soursop leaf extract at a dose of 400mg/KgBW and 800mg/KgBW with a value of $p = 0.000$ in rats induced alloxan with the mean difference in fasting blood glucose levels in the K + group with P1 and P2 is 61.143mg/dL and 82.000mg/dL.

INTRODUCTION

Along with the increase in technology in this century, people's daily activities have decreased. This condition, if left untreated, will have a negative impact on health, including diabetes mellitus. One of the characteristics of diabetes mellitus is hyperglycemia, which is an increase in blood glucose levels.¹ This disease occurs when the pancreas, which produces the hormone insulin, is no longer able to make the hormone, or the body is unable to process the insulin hormone.²

According to the International Diabetes Federation in 2021, there are about 537 million people living with diabetes aged 20-79 years. Around 2030, people living with diabetes will increase to 643 million, and by 2045, around 783 million.² Meanwhile, the increase in diabetes mellitus cases in 2018 was around 6.9 percent and became 8.5 percent in Indonesia.³

Examination of blood glucose levels in diabetes mellitus can be done in several ways, namely examination of fasting blood glucose levels, blood glucose levels during, blood glucose 2 hours postprandial, and HbA1C. The examination of fasting blood glucose levels and HbA1C can be used as a reference for the status of the patient's fasting blood glucose levels. Checking HbA1C and fasting blood glucose levels requires patients to always take care of themselves with good glucose management. However, the HbA1C test has a bias factor in that it cannot be performed on patients with anemia and a history of blood transfusion in the last 2-3 months. This makes the fasting blood glucose level check one of the important things to monitor the blood glucose level in the patient's body.^{4,5}

The high incidence of diabetes mellitus demands appropriate treatment. The current treatment for diabetes uses chemical pharmacotherapy. Recently, many researchers have examined the efficacy of herbal plants as a treatment therapy for diabetes mellitus. Herbal plants are pharmacotherapeutic treatments that are inherited from previous people and are easy to find and mix by yourself without a doctor's prescription. One of the plants that can reduce blood glucose levels is believed to be the soursop plant (*Annona muricata* L.).

The utilization of soursop plants can be used as an anti-diabetes, but what is used is the leaves. Soursop content related to blood glucose levels includes *flavonoids*, *tannins*, and *alkaloids*. *Flavonoid compounds in soursop leaves have a hypoglycemic effect that will slow the absorption of glucose by acting like insulin and stimulating insulin out.*⁶ *Tannin* compounds will facilitate glucose into cells by activating Mitogen-Activated Protein Kinase (MAPK). While *alkaloid* compounds can regenerate damaged pancreatic beta cells.⁷

Alloxan-induced rats given soursop leaf ethanol extract at doses of 200mg/Kg, 400mg/Kg, and 800mg/Kg for 5 days were able to reduce fasting blood glucose levels.⁸ Alloxan-induced white rats given soursop leaf ethanol extract at a dose of 400mg/KgBW and 800mg/KgBW for 5 days were able to reduce fasting blood glucose levels.⁹ From the above research, it was found that soursop leaf extract had an effect on lowering blood glucose levels in rats.

Therefore, researchers are interested in conducting deeper research to find out whether there is an effect of giving soursop leaf extract for 5 days on fasting blood glucose levels in rats that have been induced by alloxan.

METHODS

Type and Design of Research

This research is experimental research with a pretest-posttest control group design. The research was conducted in January-February 2024 at the Integrated Laboratory Animal Management Unit of the Pharmacology Section at the Faculty of Medicine, Muhammadiyah University of North Sumatera. In this study, the population was Wistar strain white male rats (*Rattus norvegicus* L.) aged 2-3 months with an average body weight of 200g. The research sample amounted to 28 rats.

Simplicia Preparation and Extraction Process of Soursop Leaf

Soursop leaves were taken from trees in the Terasjethi Home Garden, as much as 500g. Then wash thoroughly with water, drain, and dry for 2 days. The leaves were pulverized, and after becoming a simplisia powder, 100g was weighed for the maceration process. Then, 70% ethanol was added to a ratio of 1:10 for the maceration process. After 24 hours, the above process was repeated with the ratio being 1:5. The macerate was evaporated using a rotavapor at 40°C or using a water bath until a thick extract was found.¹⁰

Administration of Treatments to Experimental Animals

a. Distribution of treatment groups

The negative control group (K-) is only given standard food and is not induced by alloxan or given soursop leaf extract. The positive control group (K+) will be induced with alloxan on day 1 with a dose of 150mg/KgBW but not given soursop leaf extract. Treatment group 1 (P1) will be induced with alloxan on day 1 with a dose of 150mg/KgBW and given soursop leaf extract on day 5 with a dose of 400mg/KgBW for 5 consecutive days until day 9. Treatment group 2 (P2) will be induced with alloxan on day 1 with a dose of 150mg/KgBW and given soursop leaf extract on day 5 with a dose of 800mg/KgBW for 5 consecutive days until day 9. All groups will be checked for fasting blood glucose levels on day 0, day 4, and day 10.

b. Manufacture of diabetes in rats

Rats will be made diabetic by inducing or injecting alloxan solution intraperitoneally at a dose of 150mg/KgBW with a rat body weight of 200g. Alloxan will only be given once (single dose) as much as 2mL. The hyperglycemic effect will occur after 72 hours of alloxan induction.¹¹ Normal fasting blood glucose levels are 50-135 mg/dL.¹² Rats are said to be diabetic if the fasting blood glucose level is \geq 140mg/dL (\geq 7.8mmol/L).¹³

c. Blood glucose test

Blood was taken from the tail of rats that had been cleaned with alcohol. Blood was taken after the rats were fed for 8-12 hours with auto click and measured blood glucose levels using a glucometer.¹⁴ After that, the blood is placed on the glucose strip and then waits until the value comes out. Fasting blood glucose checks were carried out on day 0, day 4, and day 10.

d. Administration of soursop leaf extract

Soursop leaf extract in the treatment groups was given according to the dose, namely 1 mL for group P1 and 2 mL for group P2, orally using a disposable sonde once a day for 5 days for 5 days for 5 days.

Data Analysis

Data analysis will be carried out after the research data is collected. The data will be analyzed with the One-Way ANOVA test.

RESULTS

Fasting Blood Glucose Level of Rats on Day 0 (H0)

Table 1. Fasting Blood Glucose Level of Rats on Day 0 (H0)

Groups	n	Mean (mg/dL) ± SD
K- (Standard feeds)	7	96.43 ± 6.48
K+ (Alloxan 150mg/KgBW)	7	97.71 ± 11.64
P1 (Alloxan 150mg/KgBW) + Soursop leaf (400mg/KgBW)	7	94.43 ± 11.09
P2 (Alloxan 150mg/KgBW) + Soursop leaf (800mg/KgBW)	7	99.86 ± 6.2

Based on the results of the calculation of the average treatment group on H0, the highest average fasting blood sugar level was in group P2, which amounted to 99.86mg/dL ± 6.2. Meanwhile, the P1 group had the lowest average fasting blood glucose level of 94.43mg/dL ± 11.09.

Fasting Blood Glucose Level of Rats on Day 4 (H4)

Table 2. Fasting Blood Glucose Level of Rats on Day 4 (H4)

Groups	n	Mean (mg/dL) ± SD
K- (Standard feeds)	7	98.57 ± 5.19
K+ (Alloxan 150mg/KgBW)	7	163.86 ± 3.76
P1 (Alloxan 150mg/KgBW) + Soursop leaf (400mg/KgBW)	7	164.14 ± 9.86
P2 (Alloxan 150mg/KgBW) + Soursop leaf (800mg/KgBW)	7	175 ± 12.9

On H4, the highest average fasting blood glucose level was in the P2 group which amounted to 175mg/dL ± 12.9. Meanwhile, the K-group had the lowest average fasting blood glucose level of 98.57mg/dL, L ± 5.19.

Fasting Blood Glucose Level of Rats on Day 10 (H10)

Table 3. Fasting Blood Glucose Level of Rats on Day 10 (H10)

Groups	n	Mean (mg/dL) ± SD
K- (Standard feeds)	7	97.85 ± 5.43
K+ (Alloxan 150mg/KgBW)	7	163.71 ± 5.91
P1 (Alloxan 150mg/KgBW) + Soursop leaf (400mg/KgBW)	7	102.57 ± 6.29
P2 (Alloxan 150mg/KgBW) + Soursop leaf (800mg/KgBW)	7	81.71 ± 22.19

On H10, the highest average fasting blood glucose level was in the K+ group at 163.71mg/dL, ± 5.91. Meanwhile, the P2 group had the lowest average fasting blood glucose level of 81.71mg/dL ± 22.19.

In this study, it was found that the data were normally distributed, and homogeneity was met. Thus, the One-Way ANOVA test can be continued.

Table 4. Bivariate Analysis on Day 4 (H4)

Groups		Mean Difference (mg/dL)	p Value
K-	K+	-65.29	0.000
	P1	-65.57	0.000
	P2	-76.43	0.000
K+	P1	-0.29	1.000
	P2	-11.14	0.106
P1	P2	-10.86	0.120

Based on Table 4, it was found that on H4 the average fasting blood glucose level of the K- group was different from the other treatment groups ($p = 0.000$). Meanwhile, the K+ group did not differ from the P1 group ($p = 1.000$) and the P2 group ($p = 0.106$), and the average fasting blood glucose level of the P1 group did not differ from the P2 group ($p = 0.120$).

Table 5. Bivariate Analysis on Day 10 (H10)

Groups		Mean Difference (mg/dL)	P Value
K-	K+	-65.587	0.000
	P1	-4.714	0.467
	P2	16.143	0.323
K+	P1	61.143	0.000
	P2	82.000	0.000
P1	P2	20.857	0.166

Table 5 shows that there is an effect of soursop leaf extract administration at a dose of 400mg/KgBW and 800mg/KgBW compared to the untreated K+ group. However, the average fasting blood glucose level of the P1 group was not different from the P2 group ($p = 0.166$). This shows that the administration of soursop leaf extract at a dose of 400mg/KgBW and 800mg/KgBW does not have a significant difference.

Table 6. Phytochemical Test

Compound Test	Results	Interpretation
Flavonoids	+	Forms a yellow or orange or red color.
Tannins	+	Forms a brownish-green or bluish-black color.
Alkaloids	+	Mayer: White precipitate
		Dragendorf: Red precipitate

Based on Table 6, it is found that soursop leaves contain *flavonoids*, *tannins* and *alkaloids*.

DISCUSSION

Based on the results of the study, it was found that the administration of soursop leaf extract at a dose of 400mg/KgBW and 800mg/KgBW for 5 days had a significant effect on fasting blood glucose levels in white male Wistar rats induced by alloxan.

Table 3 shows that on H10, there is a difference in average fasting blood glucose levels between treatment groups. The average fasting blood glucose levels in groups K- (97.86mg/dL), K+ (163.71mg/dL), P1 (102.57mg/dL), and P2 (81.71mg/dL). The K+ group did not decrease because they were not given treatment to overcome hyperglycemia. While the P1 and P2 groups experienced

a decrease in fasting blood glucose levels because they were given soursop leaf extract at a dose of 400mg/KgBW and 800mg/KgBW. This is in line with research on rats induced by alloxan and given soursop leaf extract for 5 days showed that the average blood glucose levels at posttest were control group (103.96mg/dL), placebo (267.58mg/dL), glibenclamide (99.82mg/dL), 200mg/Kg extract (161.72mg/dL) 400mg/Kg extract (160.12mg/dL) and 800mg/Kg extract (97.26mg/dL). The average blood glucose levels in the glibenclamide, 200mg/Kg extract, 400mg/Kg extract and 800mg/Kg extract groups decreased due to the administration of glibenclamide and soursop leaf extract in the treatment groups.⁸

While research conducted by Pandaleke on rats induced by alloxan and given soursop leaf extract for 5 days showed that the average fasting blood glucose levels after administration of soursop leaf extract in group K- which was not given treatment (73.66mg/dL), K+ which was given metformin (109.66mg/dL), PS1 which was given soursop leaf extract as much as 400mg/KgBW (96.66mg/dL) and PS2 which was given soursop leaf extract as much as 800mg/KgBW (95mg/dL). The average fasting blood glucose level in the K+ group experienced the highest decrease due to metformin while PS1 and PS2 only experienced a slight decrease in average due to soursop leaf extract with a dose of 7.2mg and 14.4mg.⁹

Based on Table 5, it was found that the K+ group had a significant difference with the P1 and P2 groups with a p value = 0.000. This shows that there is an effect of soursop leaf extract administration at a dose of 400mg/KgBW and 800mg/KgBW compared to the K+ group, which was not given treatment to reduce blood glucose levels. The glibenclamide, 400mg/Kg and 800mg/Kg extract groups did not have significant differences. The group can reduce blood glucose levels after the treatment is given. However, the 200mg/Kg extract group did not decrease blood glucose levels.⁸ While research conducted by Pandaleke et al showed that the K+, PS1 and PS2 groups were not significantly different because the K+ group study was given treatment in the form of metformin and PS1 and PS2 were given soursop leaf extract at a dose of 7.2mg and 14.4mg as treatment to rats to reduce fasting blood glucose levels. It showed that the treatment of metformin and soursop leaf extract showed no significant difference in reducing fasting blood glucose levels.⁹

Based on Table 5, in groups P1 and P2, there is no significant difference with a p value = 0.166, with the dose of soursop leaf extract in group P1 is 400mg/KgBW, and group P2 is 800mg/KgBW. The average difference in fasting blood glucose levels on H10, which is after the administration of soursop leaf extract, between groups P1 and P2 is 20.857mg/dL. Although there was no significant average difference in the P1 and P2 groups, the highest decrease in fasting blood glucose levels occurred in the P2 group, which was 93.286mg/dL. However, the P1 group was also able to reduce fasting blood glucose levels of 61.571mg/dL, but not as good as the P2 group. This is in line with the research, which, when comparing the glibenclamide group, 400mg/Kg extract and 800mg/Kg extract, the 800mg/Kg extract was able to reduce blood glucose levels the most, with an average decrease of 50.72mg/dL. However, the decrease was not significantly different between the glibenclamide group and the 800mg/Kg extract.⁸ While the research of Pandaleke et al, when comparing the K+, PS1, and PS2 groups, the K+ given metformin was able to reduce fasting blood glucose levels the most with an average decrease of 29.67mg/dL. But the decrease was not significantly different between groups K +, PS1, and PS2.⁹

Soursop plant is an herbal plant that can reduce blood glucose levels. This is because the leaves of the soursop plant contain *flavonoids*, *tannins*, and *alkaloid* compounds. *Flavonoid* compounds have a hypoglycemic effect that will slow the absorption of glucose, act like insulin and stimulate insulin release, increase glucose uptake in peripheral tissues, and increase glucose

tolerance.⁶ *Tannin* compounds can activate Phosphoinositide, MAPK, or Mitogen-Activated Protein Kinase to increase glucose uptake so that glucose will be easier to enter the cell. *Alkaloid* compounds help increase insulin hormone production and can regenerate damaged pancreatic beta cells.⁷

The content contained in soursop leaves is proven to be able to act as a protector and help the recovery of pancreatic beta cells. Pancreatic beta cells are responsible for the recovery and release of insulin, a hormone that is important for the metabolic process of carbohydrates, fats, and proteins. The development of a chronic hyperglycemic state will become diabetes mellitus which occurs because insulin secretion or insulin use in the body is problematic. Soursop leaves have the potential to protect the pancreas from pancreatic islet damage by regenerating pancreatic cells, preserving pancreatic islet areas and cell proliferation, leading to a significant increase in insulin secretion that leads to normal blood glucose levels.¹⁵

CONCLUSION

From the research conducted, it was concluded that there was a relationship between the administration of soursop leaf extract on fasting blood glucose levels in white male Wistar rats induced by alloxan with a p value = 0.000. However, there was no difference in effect between the doses of soursop leaf extract 400mg/KgBW and 800mg/KgBW with a p value > 0.05. However, the largest decrease in average fasting blood glucose levels occurred at a dose of 800mg/KgBW.

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