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# Effect of palm sap (*Arenga pinnata*) on blood glucose levels of mice (*Mus musculus*) alloxan-induced diabetic

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**Abstract.** *Liputo SM, Lamondo D, Solang M. 2021. Effect of palm sap (*Arenga pinnata*) on blood glucose levels of mice (*Mus musculus*) alloxan-induced diabetic. Asian J Nat Prod Biochem 20: 11-15.* This study aims to determine the effect of palm sap (*Arenga pinnata* (Wurmb) Merr.) in reducing blood glucose levels in alloxan-induced diabetic mice (*Mus musculus* Linnaeus, 1758). Twenty-five mice aged 2-3 months were grouped into a negative control group, a positive control group and a palm sap group (0.2 mL, 0.4 mL, and 0.6 mL). The result showed that the palm sap with a dose of 0.4 mL was the most significant in reducing blood glucose levels. This study concluded that the administration of palm sap affected decreasing blood glucose levels ($p < 0.05$).

**Keywords:** Alloxan, blood glucose, mice, palm sap

## INTRODUCTION

Diabetes is one of the fastest-growing health emergencies compared to other diseases. Diabetes mellitus is a condition in metabolism defect that features hyperglycemia symptoms, which require constant medical care. DM can cause many acute and seriously chronic complications, such as diabetic ketoacidosis, nonketotic hyperosmolar coma, cardiovascular disease, chronic kidney failure, foot ulcers and damage to the eyes. Based on data from the International Diabetes Federation (IDF), in 2019, people with diabetes reached 465 million adults in the world and it is predicted that in 2045 700 million adults will suffer from this disease or an increase of 51% in 2045 (IDF 2019).

As a developing country, Indonesia has experienced an increase in diabetes mellitus cases. Diabetes affected 7.7 million adults (20-79 years old) in 2013 and 10.7 million adults in 2019. (IDF 2019). According to National Health Survey(Riskesdas) (2018), the number of DM sufferers aged 15 years has increased by 2% compared to 2013. Gorontalo is one of the provinces in the country with the highest number of people with diabetes. Based on Riskesdas (2018), the prevalence of diabetes mellitus in Gorontalo has increased to 2.4 percent which only 1.5% in 2013.

Synthetic chemicals and traditional medicines are effective treatments for DM (Diabetes Mellitus) patients. One of the synthetic drug classes that are most often used to treat DM is glibenclamide because it is widely marketed and the price is affordable. However, glibenclamide has side effects, such as nausea, constipation, dizziness, tremors, and hypoglycemia (Putra et al. 2017). Therefore, as stated by WHO (2004), traditional medicine is used as self-medication or alternative treatment, particularly for chronic diseases such as diabetes and endocrine disorders. Additionally, although WHO recommends traditional medicine, scientific research is still needed to determine the truth of its efficacy, for example, palm sap (*Arenga pinnata* (Wurmb) Merr.).

Aren is one type of palm plant that is almost spread throughout Indonesia. Almost all parts of this plant can be utilized and used for various needs, both from parts of plant organs (roots, stems, leaves, fruit, etc.), as well as their production (sap, starch/flour) (Lempang 2012; Gunawan et al. 2017). According to Kandowangko et al. (2011), palm sap (*A. pinnata*) has long been utilized as an antidiabetic medicine by the people of Gorontalo, Indonesia. This plant contains water, minerals, carbohydrates, fats, proteins (Ismail et al. 2020), vitamin C (Choong et al. 2016), phenolic and amino acids (Kurniawan et al. 2018). Palm sap (*A. pinnata*) has several pharmacological, including a diuretic, anti-tuberculosis and anti-fatigue. In addition, vitamins can help prevent insulin resistance due to Reactive Oxygen Species (ROS) that damage pancreatic cells (Fitriani et al. 2018). Furthermore, given their antioxidant and antihyperglycemic properties, phenolics aid in the reduction of blood glucose in people with diabetes by preventing excessive oxidation and maintaining insulin content in pancreatic cells, binding free radicals and removing them from the body through the excretory system (Wisudanti 2016). Thus, the content of palm sap (*A. pinnata*) has great potential in treating DM.

Palm sap was applied to experimental animals in the form of male mice (*Mus musculus* Linnaeus, 1758). The mice used were normal mice induced with diabetogenic agents. The use of mice as experimental animals is because mice have a high sensitivity compared to other experimental animals to blood glucose tests, male mice are not influenced by hormonal factors such as female mice. In addition, mice have genes similar to humans (Rudiawan

2016). Therefore, before being given palm sap, the mice were first induced with a diabetogenic agent.

Alloxan, a well-known diabetogenic agent, is widely used to induce type 2 diabetes in animals. In addition, alloxan-induced diabetes mellitus serves as a pathological bio model for testing a substance with supposed antioxidant activities. Alloxan can increase blood glucose in mice within 2 x 24 hours without causing death (Rudiawan 2016).

## MATERIALS AND METHODS

### Research design

This study employed a post-test control group design, i.e., the effect of treatment, by comparing the treatment group with the control group after being given the action. The experimental design used was a randomized design (CRD) with five treatment groups consisting of two control groups and three groups of palm sap (0.2 mL, 0.4 mL, 0.6 mL).

### Sampling and preparation

Palm sap is obtained from the community in Dulamayo, Bone Bolango District, Gorontalo, Indonesia. Male mice (M. musculus) aged 2-3 months were involved as test animals. Alloxan was chosen as the diabetogenic agent since it is the most extensively used chemical for producing diabetes in test animals. Glibenclamide as standard hypoglycemic medication and aquades is utilized as drinking water for mice since it is mineral-free, ensuring that the fall in blood glucose levels is not due to minerals in the water.

### Group of test animals

Mice were divided into five treatment groups, those are K- = negative control group only given aquadest and feed, K+ = positive control group given glibenclamide 0.013 mg/20 g mice BW, K+ = positive control group given glibenclamide 0.013 mg/20 g mice BW, K+ = positive control group given glibenclamide 0.013 mg/20 g mice BW, K+ = positive control group given glibenclamide 0.013 mg/20 g mice BW, K P1 = Treatment 1, palm sap was given at a dose of 0.2 mL/20 g BW mice, P2 = Treatment 2, palm sap was given at a dose of 0.4 mL/20 g BW mice, and P3 = Treatment 3, given palm at a dose of 0.6 mL/20 g BW rats.

### Research procedure

*Test animals preparation (acclimatization)*

Mice were acclimatized for seven days to adapt to the new environment and were given water and food ad libitum.

*Alloxan treatment to mice*

Alloxan was induced subcutaneously at 100 mg/kg BW dosage after acclimation. Fasting blood glucose (FBG) levels were measured on the third day following alloxan induction. Before measurement, mice fasted for 10 hours. This study employed mice with FBG >126 mg/dL.

*Test materials provision*

On the 4th day, glibenclamide and palm sap were given for three days in a row according to the group, and the dose was determined after alloxan was induced. Next, GCU was used to measure fasting blood glucose levels on day 6, and the mice were fasted for 10 hours before being measured.

### Data analysis

The research data were analyzed using SPSS (Statistical Products and Services Solutions) version 25. Normality was assessed using the Shapiro-Wilk method ($p>0.05$), and homogeneity was determined using the Levene method ($p>0.05$) and proceeded with the one-way ANOVA test. If there is a significant difference, it would be continued with Duncan's test to see the difference between the treatment groups.

## RESULTS AND DISCUSSION

### Results

A total of 25 mice (*M. musculus*) were given three different doses of palm sap (0.2 mL, 0.4 mL, and 0.6 mL) and glibenclamide and distilled water as positive and negative controls, respectively. A total of 3 blood draws were performed to measure blood glucose levels (mg/dL). A post hoc test revealed no significant difference between groups ($p<0.05$) before alloxan induction towards the mice. This is supported by the fact that all groups experienced the same condition. The measurement results of FBG were also within the limits of normal FBG (<126 mg/dL), which shows that there is no hyperglycemic activity in the mice before the administration of any substance. After the third day of alloxan administration, all groups' FBG showed a hyperglycemic condition, and there was no significant difference. FBG increased significantly ($p<0.05$) after alloxan administration to mice compared to before administration. After giving palm sap, hyperglycemia was shown in all of the groups following the decreasing FBG of mice. GDP levels were lower in the palm sap (*A. pinnata*) group (P1, P2, and P3) than in the control group (K- and K+). The data of glucose measurement results can be seen in Table 1 and Figure 1.

Based on the results, the percentage of the palm sap group with a dose of 0.4 mL was more influential in lowering fasting blood glucose in mice after alloxan was induced. An ANOVA statistical test was used to measure if there was a significant effect on each group, and normality and homogeneity checks were performed before the implementation. Based on the normality test results using the Shapiro-Wilk test, the p-value is 0.05, which means the research data is normally distributed. Furthermore, based on the homogeneity test using the Levene test, a p-value of 0.05 was obtained, which means that the fasting blood glucose of mice was homogeneous. Bearing this in mind, the requirements in the ANOVA test are met.

**Table 1.** Average fasting blood glucose (FBG) levels before and after treatment

| Group | Before administration of alloxan ±SD | After administration of alloxan ±SD | After administration of palm sap ±SD | Decrease in FBG after giving palm sap (%) |
|---|---|---|---|---|
| K- (Without Treatment) | 86.20 ± 3,52[1,a] | 139.80 ± 3,59[2,a] | 112.80 ± 3,38[3,a] | 19% |
| K+ (Glibenclamide) | 85.20 ± 4,64[1,a] | 139.60 ± 5.05[2,a] | 101.00 ± 2.07[3,a] | 28% |
| P1 (Palm Sap 0.2 mL) | 81.40 ± 4,92[1,a] | 133.40 ± 3,76[2,a] | 84. ± 5.07[1,b] | 37% |
| P2 (Palm Sap 0.4 mL) | 82.20 ± 5,28[1,a] | 141.80± 5,81[2,a] | 64.00 ± 5.32[3,c] | 55% |
| P3 (Palm Sap 0.6 mL) | 81.80 ± 2.17[1,a] | 134.40 ± 4,79[2,a] | 78.40 ± 3.26[1,b] | 42% |

Note: Group K- (negative control): alloxan + aquadest, K+ (positive control): alloxan + glibenclamide, P1 (treatment 1): alloxan + palm sap 0.2 mL, P2 (treatment 2): alloxan + palm sap 0.4 mL, P3 ( treatment 3): alloxan + palm sap 0.6 mL. The different superscript letters within the same column were significantly different at $P < 0.05$. The different superscript numbers within the same row were significantly different at $P < 0.05$

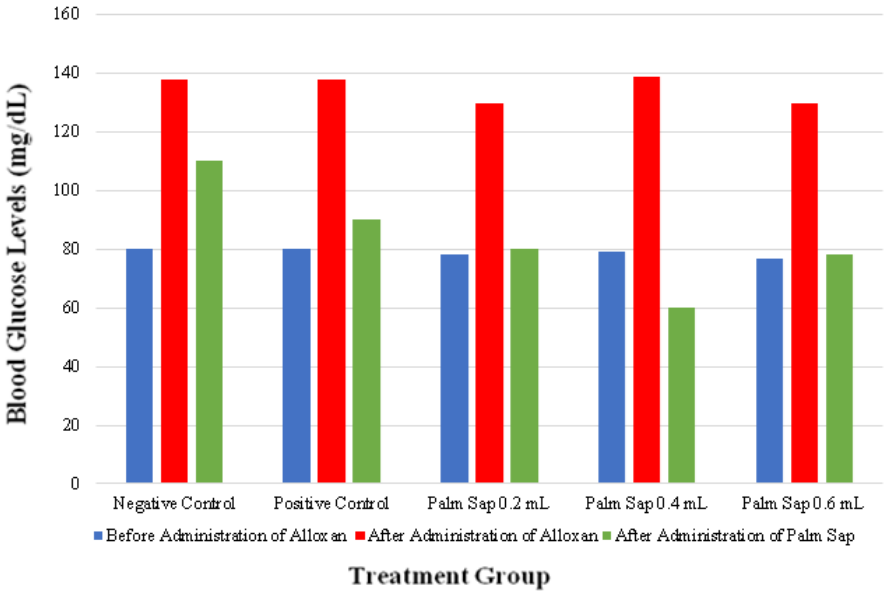


**Figure 1.** Average fasting blood glucose (FBG) levels in mice before and after treatment

Based on the One Way ANOVA statistical analysis results, there was an effect of giving palm sap on reducing fasting blood glucose in mice with a significant value = 0. 00 = 0.05. To see the difference in each treatment entails Duncan's test. The results of Duncan's analysis showed that the K- group was not significantly different from K+ but significantly different from the P1, P2, and P3 groups. The P1 group was significantly different from the K-, K+, and P2 groups but not significantly different from the P3 group. The P2 group was significantly different from the K-, K+ and P1 groups (Table 1).

The normality test utilizing the Shapiro-Wilk test yielded a p-value of 0.05, indicating that the research data is normally distributed (Appendix 2). Furthermore, the p-value of 0.05 was achieved based on the Levene test's homogeneity test, indicating that the fasting blood glucose of mice was homogeneous (Appendix 2). By this, the ANOVA test's conditions are met. According to the results of a One Way ANOVA statistical analysis, there was an effect of feeding palm sap on reducing fasting blood glucose in mice, with a value of sig = 0. 00 = 0.05. Then, I continued Duncan's test to see how each treatment differed. Duncan's study revealed that the K- group did not differ significantly from the K+ group, but did differ considerably from the P1, P2, and P3 groups. The P1 group differed considerably from the K-, K+, and P2 groups, but not from the P3 group. The P2 group differed significantly from the K-, K+, and P1 groups (Table 1).

## Discussion

The measurement of fasting blood glucose (GDP) before alloxan was given, all mice were in normal condition (70-100 mg/dL). However, after alloxan was induced, the levels of FBG in mice experienced hyperglycemia (>126 mg/dL). This result proves that alloxan can produce experimental diabetic conditions in test animals. Alloxan is a widely used chemical to induce diabetes in test animals.

Toxicity produced by alloxan occurs due to the formation of free radicals (superoxide radicals and hydroxyl radicals). Free radical activity causes an increase in cytosolic calcium concentration resulting in pancreatic-

cell necrosis. A decrease follows this damage in insulin secretion, which results in the reaction of glycogenesis and reduced glucose transport in cells. In addition, glycogenolysis becomes uncontrolled, resulting in increased blood glucose in the body (Yusni et al. 2017). Meanwhile, according to Sari et al. (2020), alloxan is a toxic glucose analog that selectively destroys insulin-producing pancreatic cells.

In this study, the K- group was the alloxan induction group but was not given any treatment. The K- group, before being induced with alloxan had fasting blood glucose of 86.20±3.52 mg/dL (normal), after alloxan was induced, fasting blood glucose increased to139.80±3.59 mg/dL (hyperglycemia), then there was a decrease in fasting blood glucose by 19%. This decrease is caused by the body's defense efforts to ward off free radicals. In addition, it is because mice's body has endogenous antioxidants such as catalase, superoxide dismutase (SOD), glutathione peroxidase, and glutathione S-transferase (Pratama and Busman 2020).

The K+ group in this study was the group that was given glibenclamide. The K+ group, before being induced with alloxan had a fasting blood glucose of 85.2±4.64 mg/dL (normal). After alloxan was induced, fasting blood glucose increased to 139.60±5.05 mg/dL (hyperglycemia). Yet, after giving glibenclamide, fasting blood glucose decreased by 28%.

Glibenclamide was administered to the K+ group in this study. Before being induced with alloxan, the K+ group had a fasting blood glucose of 85.24.64 mg/dL (normal), fasting blood glucose climbed to 139.605.05mg/dL (hyperglycemia), and fasting blood glucose was reduced by 28% after being given glibenclamide.

Based on the results of the One Way ANOVA test, the most significant group in reducing fasting blood glucose in mice was the palm sap group with a dose of 0.4 mL (P2) and 0.6 mL (P3), but based on the calculation of the percentage of the palm sap group with a dose of 0.4 mL (P2) which most influential with a decrease of 55%. This decrease was higher than the glibenclamide (K+) group of 28%, 0.2 mL of palm juice (P2) 37% and 0.6 mL of palm juice (P3) 42%. This study is by research conducted by Swastini et al. (2018), which found that the administration of palm sap reduces fasting blood glucose in male rats induced by alloxan.

The decrease in fasting blood glucose in the palm sap group is thought to be influenced by the compounds contained in palm sap which can prevent the oxidation of pancreatic -cells caused by alloxan induction so that the damage can be controlled. The compounds contained in palm sap are minerals, protein (Ismail et al. 2020), vitamin C (Lempang and Mangopang 2012), triterpenoids, flavonoids, saponins, and alkaloids (Putri et al. 2020).

Protein aids in the regulation of high fasting blood glucose in the body. Based on Gannon et al. (2003), protein can increase insulin concentration. According to Prastari et al. (2017), protein plays a role in inhibiting the work of the -glucosidase enzyme in breaking down carbohydrates into glucose, allowing fasting blood glucose to be managed.

Phenolics play a role in lowering fasting blood glucose by damaging the lipid oxidation structure by donating hydrogen atoms (Bahman et al. 2019). In addition, phenolic inhibits enzymes involved in carbohydrate metabolism processes such as -amylase and -glucosidase. Inhibition of this enzyme slows the breakdown of disaccharides into simple glucose so that the body absorbs glucose is reduced (Oboh and Ademosun 2011). The phenolic groups found in palm sap are triterpenoids, flavonoids, saponins, and alkaloids (Putri et al. 2020).

Triterpenoids work as antidiabetics by causing an increase in AMP-activated protein kinase (AMPK) in muscle cells, which enhances glucose consumption in muscle cells and lowers blood glucose. Triterpenoids also help reduce pancreatic-cell damage by delaying the synthesis of TNF- (Tumor Necrosis Factor-alpha) produced by ROS activity (Putra 2013). In insulin-resistant cells, triterpenoids accelerate glucose metabolism and can lower fasting blood glucose in vivo (Hu et al. 2014).

Flavonoids are antioxidants that can inhibit pancreatic cell damage by neutralizing free radicals (Parwata et al. 2018). In addition, flavonoids stop the peroxidation process by inhibiting enzymes that produce superoxide anions and decreasing alkoxyl and peroxyl radicals (Yuslianti 2017). Furthermore, flavonoids act directly on pancreatic -cells, activating the cAMP signal cascade to boost insulin production, triggered by glucose (Hikmah et al. 2016), preventing glucose absorption in the gut (Parwata et al. 2018).

Alkaloids have therapeutic effects and are antidiabetic since these compounds have the potential to interact with various proteins involved in glucose homeostasis (Rasouli et al. 2020). Alkaloids act as antidiabetic, both in extracts and isolated molecules. It inhibited the glucosidase enzyme, deactivated DPP-IV (Dipeptidyl Peptidase-4), improved insulin sensitivity, and reduced oxidative stress (Ajebli et al. 2021)

Vitamin C helps repair damaged cells and insulin resistance and inflexible blood vessels associated with diabetes (Aprila et al. 2015). Vitamin C is a group of micronutrients that plays a role as an antioxidant in human plasma and functions as an electron donor or electron reducing agent, which allows it to serve as an antioxidant. According to Maha (2013), Vitamin C can lower fasting blood glucose, which can provide primary and secondary protection against oxidative damage to lipids and lipoproteins and improve the negative effects of DM.

Aprila et al. (2015) stated that magnesium simplifies glucose transport into cells, cofactors various enzymes involved in the glucose oxidation process, and helps to increase insulin sensitivity and avoids insulin resistance (Larsson and Wolk 2007). In addition, intracellular magnesium deficiency can reduce the action of tyrosine kinase on insulin receptors (Mulatsih 2020).

In conclusion, the administration of palm sap (*A. pinnata*) can lower fasting blood glucose in mice (*M. musculus*) with alloxan-induced diabetes. Palm sap (*A. pinnata*) 0.4 mL was the most significant in lowering the mice’s fasting blood glucose.

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