

Effect of Ethanol Extract of Jackfruit Leaves (*Artocarpus heterophyllus* Lamk.) in Reducing Blood Sugar Levels of Mice after Maltose Loading

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Abstract

Introduction: Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia due to reduced effectiveness of insulin, insulin secretion or a combination of both and there is a progressive change in the structure of pancreatic β cells. In 2015, adult mortality due to diabetes reached 10 million, ranking 7th highest in the world. Efforts to treat diabetes mellitus can be done by inhibiting the work of the enzyme α -glucosidase in the small intestine that works competitively with its substrate. Flavonoids are compounds that have the potential to inhibit α -amylase and α -glucosidase, tannins in extracts play a role in reducing blood glucose levels. Jackfruit leaves (*Artocarpus heterophyllus* Lamk.) contain flavonoid compounds, saponins, polyphenols and tannins which are often used as antidiabetic.

Objective: To find out the effect of ethanol extract of jackfruit leaves (*Artocarpus heterophyllus* Lamk.) in reducing blood sugar levels of mice after maltose loading. This study is a laboratory experimental study with randomized pre and post test control group design. Thirty male mice (*Mus musculus*. L) aged 3-4 months weighing 20-35 grams were randomly selected and divided into 5 groups consisting: negative control group, positive control group, EEDN 1.25% (125 mg/kgBB), EEDN 2.5% (250 mg/kgBB), and EEDN 5% (500 mg/kgBB). The extract was given first then after 10 minutes the whole group was burdened with maltose, measurements of blood sugar levels were done by measuring fasting KGD and KGD after loading of maltose at intervals of 30, 60, and 120 minutes.

Methods: The average value of KGD, normally distributed data ($p > 0.05$) ANOVA test was performed. Data not normally distributed ($p < 0.05$) was performed with a calc-wallis test. After calculating the value of the area under the curve (AUC), the data were normally distributed ($p > 0.05$) the least significance different (LSD) test was performed, the data were not normally distributed mann-whitney test was performed to see differences between groups. If $p < 0.05$, a significantly different result is obtained with a confidence level of 95%.

Results: The study showed that the treatment group (EEDN dose 125 mg/kgBB and EEDN dose 250 mg/kgBB) had an effect in reducing blood sugar levels which was marked by a significant difference with the negative control group at 120 minutes with a value ($p = 0.045$ and $p = 0.010$). But the treatment group (EEDN dose 125 mg/kgBB, EEDN dose 250 mg/kgBB and EEDN 500 mg/kgBB) were unable to inhibit the α -glucosidase enzyme seen from the absence of significant values between the negative control group and the treatment group at 30 minutes. The area under the curve (AUC) shows the AUC values respectively produced by the negative control group (272.917 ± 8.500), the positive control group (218.917 ± 12.091), EEDN 125 mg/kgBB (264.583 ± 74.714), EEDN 250 mg/kgBB (230.541 ± 48.817), and EEDN 500 mg/kgBB (315.667 ± 96.040). There was no significant difference between the negative control group and the EEDN treatment group with a dose of 125 mg/kgBB, EEDN dose 250 mg/kgBB, and EEDN 500mg/kgBB).

Conclusion: Ethanol extract of jackfruit leaves (*Artocarpus heterophyllus* Lamk.) Dose 125 mg/kgBB and EEDN dose 250 mg/kgBB able to reduce KGD of mice but unable to inhibit the α -glucosidase enzyme.

Suggestion: Research needs to be done for other mechanisms of ethanol extract of jackfruit leaves (*Artocarpus heterophyllus* Lamk.) in reducing blood sugar levels.

Keywords: *Artocarpus heterophyllus* Lamk., Blood Sugar Levels, Diabetes Mellitus, Maltose

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I. Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia due to reduced effectiveness of insulin, insulin secretion or a combination of both and there is a progressive change in the structure of pancreatic β cells (Prameswari & Widjanarko, 2014). Diabetes mellitus type 2 is one of the diseases with the most sufferers in the world. Based on data from the World Health Organization (WHO), there are around 220 million sufferers of the disease in the world and in 2040 diabetics are expected to increase 55% to

642 million. Although not contagious, diabetes mellitus can cause death. Based on the International Diabetes Federation (2015), in 2015 adult mortality due to diabetes reached 10 million with 7th highest rank in the world of the soul. The number of people with diabetes mellitus is dominated by patients with type II DM.

Type II diabetes mellitus is associated with postprandial hyperglycemia. Controlling postprandial glucose levels is one of the strategies in dealing with type II DM (Yuhao et al., 2005). α -glucosidase is an enzyme that plays a role in the breakdown of carbohydrates into glucose in the digestive tract (Subroto, 2006). This enzyme can increase blood sugar levels. So as to prevent the rise in blood sugar, we need an enzyme inhibitor α -glucosidase.

Carbohydrates that have been digested in the stomach enter the intestine and experience absorption. This absorption is facilitated by the presence of the glycoside bond-breaking enzyme, the α -glucosidase and α -amylase enzymes that are present at the brush border of intestinal cells (Katzung, 2002).

Efforts to treat diabetes mellitus can be done by inhibiting the work of the enzyme α -glucosidase in the small intestine that works competitively with its substrate, such as rootbosa (Kurniawan, 2010). The α -glucosidase enzyme inhibitors such as rootsbosa work by delaying the absorption of glucose in the intestine so as to prevent an increase in post-prandial blood sugar levels. Therefore, the α -glucosidase enzyme becomes one of the target enzymes for the treatment of type II diabetes mellitus.

However, many hypoglycemic agents have limitations, namely causing side effects and increasing diabetes complications. The main side effects of α -glucosidase inhibitors in the gastrointestinal include bloating, nausea, diarrhea, and flatulence. Natural α -glucosidase inhibitors derived from natural ingredients can be utilized as a therapeutic approach to treat postprandial hyperglycemia because it has low side effects and is more affordable than synthetic antihyperglycemic drugs (Sudha, 2011).

Tadera et al. (2006) have proven in vitro that flavonoids are compounds that have the potential to inhibit α -amylase and α -glucosidase. Research conducted by Mcdougall et al. (2003) also showed that phenolic compounds from some plants were able to inhibit the activity of the α -amylase enzyme and inhibit the α -glucosidase enzyme. The tannin compounds in extracts play a role in reducing blood glucose levels, presumably due to the presence of antioxidants which are natural antioxidant compounds in plants that can inhibit free radicals so as to reduce insulin resistance (Haryoto, et al., 2016). Based on research by Universty Research Colloquium in 2013, tannins can increase glucose uptake by translating GLUT-4 by modulating insulin signals through the PI3K pathway.

Plant sources that contain, flavonoids and phenolics that we often encounter and are easily obtained are jackfruit leaves. Jackfruit leaves are known to contain flavonoid compounds, saponins, polyphenols and tannins (Fitrianiingsih et al., 2014). Thus, the researchers wanted to see whether jackfruit leaf extract can reduce glucose levels by inhibiting the enzyme α -glucosidase as a medicinal plant to treat diabetes mellitus.

II. Objective and Methods

To find out the effect of ethanol extract of jackfruit leaves (*Artocarpus heterophyllus* Lamk.) in reducing blood sugar levels of mice after maltose loading.

The design of this research is laboratory experimental analytic using randomized pre and post test control group design as a research design.

This research was conducted in December 2019. The research was conducted after obtaining ethical clearance from the Ethics Committee of the Faculty of Mathematics and Natural Sciences (FMIPA), Universitas Sumatera Utara. The research site was conducted at the Pharmacology and Toxicology Laboratory, Faculty of Pharmacy, Universitas Sumatera Utara. The extract was obtained from the Laboratory of Pharmaceutical Biology, Faculty of Pharmacy, Universitas Sumatera Utara.

The study population was all male *Mus Musculus* L. mice in the Pharmacology and Toxicology Laboratory Unit, Faculty of Pharmacy, Universitas Sumatera Utara, Medan, Indonesia. The research sample was 30 male mice (*Mus Musculus* L.) from an affordable population that met the inclusion criteria.

This study is a laboratory experimental study with randomized pre and post test control group design. Thirty male mice (*Mus musculus*. L) aged 3-4 months weighing 20-35 grams were randomly selected and divided into 5 groups consisting: negative control group, positive control group, EEDN 1.25% (125 mg/kgBB), EEDN 2.5% (250 mg/kgBB), and EEDN 5% (500 mg/kgBB). The extract was given first then after 10 minutes the whole group was burdened with maltose, measurements of blood sugar levels were done by measuring fasting KGD and KGD after loading of maltose at intervals of 30, 60, and 120 minutes.

Data analysis was performed using SPSS. The first step is, observational data for blood sugar levels (KGD) of mice that have been tabulated are tested for normality distribution with the shapiro-wilk test. The data is normally distributed, that is, if the value (significance) $p > 0.05$, then it will be continued with the analysis of covarians (ANOVA) test, the true confidences of this test is 95%, so if $p < 0.05$, it can be concluded that there are differences meaningful. If it is not normally distributed, ie $p < 0.05$, it will be continued with the kruskal-wallis test. Observed data for tabulated area under the curve (AUC) values were tested for normality distribution with

the shapiro-wilk test. Data that is normally distributed, if the value (significance) $p > 0.05$, will continue with the least significance different (LSD) test. If the data are not normal in $p < 0.05$, it is continued with the mann-whitney test.

The average value of KGD, normally distributed data ($p > 0.05$) ANOVA test was performed. Data not normally distributed ($p < 0.05$) was performed with a calc-wallis test. After calculating the value of the area under the curve (AUC), the data were normally distributed ($p > 0.05$) the least significance different (LSD) test was performed, the data were not normally distributed mann-whitney test was performed to see differences between groups. If $p < 0.05$, a significantly different result is obtained with a confidence level of 95%.

III. Result

Research shows that the treatment group (EEDN dose 125 mg/kgBB and EEDN dose 250 mg/kgBB) has an effect in reducing blood sugar levels which is marked by a significant difference with the negative control group at 120 minutes with a value ($p = 0.045$ and $p = 0.010$).

Table 1. Comparison of KGD Value of the Control Group with the Ethanol Extract of Jackfruit Leaves Treatment in the 120th Minute

Group	EEDN 1,25%	EEDN 2,5%	EEDN5%
Aquadest	$p = 0,045^*$	$p = 0,010^*$	$p = 0,470$
Akarbosa	$p = 0,306$	$p = 0,095$	$p = 0,730$

Note: * = Significant

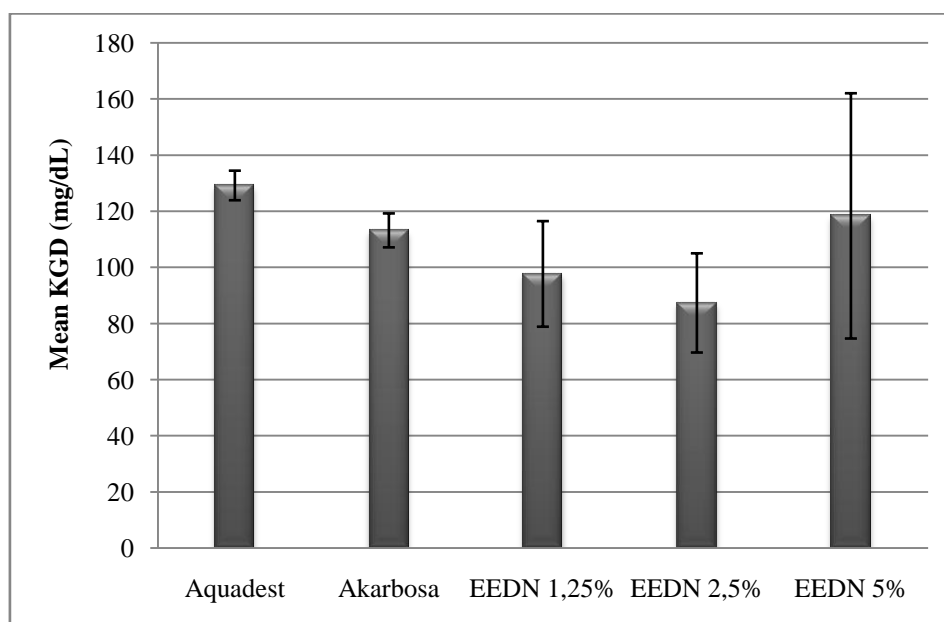


Figure 1. KGD Average Bar Diagram in the 120th Minute

At the 120th minute, when compared between the negative control group (aquadest) and the extract treatment group, it can be seen from Figure 1, the average KGD value of mice with EEDN treatment of 1.25% and EEDN of 2.5% lower compared to the control group negative with significant values ($p > p = 0.045$ and $p = 0.010$; $p < 0.05$).

If seen between the positive control group (akarbosa) and the treatment group of jackfruit leaf ethanol extract in Figure 1, the average values of EDN 1.25% KGD and 2.5% EEDN were lower than those in the positive control group with no significant difference values (Table 1). But for the average value of KGD the EEDN group was 5% higher than the positive control group with the difference value was not significant.

The treatment group (EEDN dose 125 mg/kgBB, EEDN dose 250 mg/kgBB and EEDN 500 mg/kgBB) were unable to inhibit the α -glucosidase enzyme as seen from the absence of significant values between the negative control group and the treatment group at 30 minutes. Area under the curve (AUC) shows the AUC value respectively produced by the negative control group (272,917±8,500), the positive control group (218,917±12,091), EEDN 125 mg/kgBB (264,583±74,714), EEDN 250 mg/kgBB (269,583±74,714), EEDN 250 mg/kgBB (264,583±74,714) 230,541±48,817), and EEDN 500mg/kgBB (315,667±96,040). There was no significant difference between the negative control group and the EEDN treatment group with a dose of 125 mg/kgBB, EEDN dose 250 mg/kgBB, and EEDN 500 mg/kgBB).

Table 2. Table of Area Under the Curve (AUC) of Blood Sugar Levels of Mice to Observation Times from the 0th Minute to the 120th Minute

Mice to	Aquadest	Akarbosa	EEDN 1,25%	EEDN 2,5%	EEDN 5%
1	264,5	234,75	220,75	248,5	353
2	277,75	210	230,75	250,5	489
3	280,5	230,25	211,5	198,75	281,75
4	265,75	210,5	390,5	307,75	215,75
5	283,25	222,75	211,5	208,25	294,5
6	265,75	205,25	322,5	169,5	260
Mean	272,917	218,917	264,583	230,541	315,667
SD	8,500	12,091	74,714	48,817	96,040

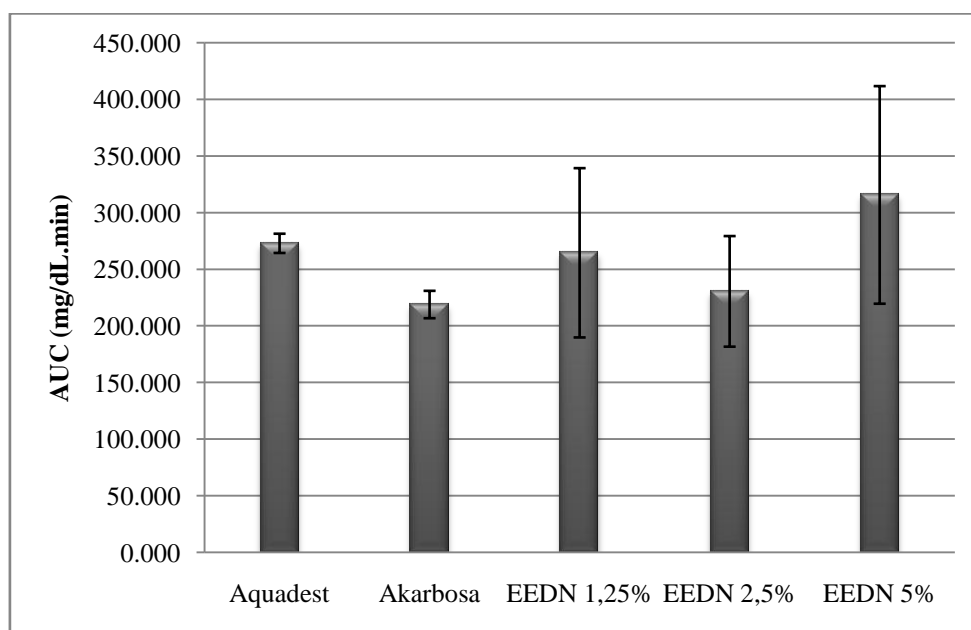


Figure 2. Total AUC histogram

Table 3. LSD Test Table of AUC0-120 Value Between Treatment Groups with 95% Confidence Level

Groups	Akarbosa	EEDN 1,25%	EEDN 2,5%	EEDN5%
Aquadest	p=0,094	p=0,791	p=0,185	p=0,181
Akarbosa		p=0,154	p=0,712	p=0,004*
EEDN 1,25%			p=0,284	p=0,112
EEDN 2,5%				p=0,011*

Note: * = Significant

The value of blood sugar level is used to calculate the area under the Area Under The Curve (AUC) curve of each treatment group to the time of observation, which shows the amount of changes in blood sugar levels over 120 minutes, due to the effect of treatment in each group.

From Figure 2., the negative control group (aquadest) has a higher AUC value compared to the EEDN group 1.25% and EEDN 2.5% but has an insignificant difference value ($p = 0.79$ and $p = 0.185$; $p > 0.05$) if seen from the AUC LSD test (Table 2). However it is different when compared to the 5% EEDN group which has a higher AUC value compared to the negative control group with a non-significant difference value ($p = 0.181$).

In Table 2 and Figure 2, when compared between the positive control group (roots) and the EEDN group, it can be seen that the AUC value of the positive control group is lower. And there is a significant difference between the positive control group and the 5% EEDN group ($p = 0.004$) can be seen in Table 3.

IV. Conclusion and Suggestion

Ethanol extract of jackfruit leaves (*Artocarpus heterophyllus* Lamk.) dose 125 mg/kgBB and 250 mg/kgBB dose influence in reducing blood sugar levels of mice given maltose loading.

Research needs to be done for other mechanisms of ethanol extract of jackfruit leaves (*Artocarpus heterophyllus* Lamk.) in reducing blood sugar levels.

References

- [1]. Fitrianiingsih, S.P., Aryanti, I., & Lestari, F. (2014). *Aktivitas Antihiperglukemia Ekstrak Daun Nangka (Artocarpus Heterophyllus Lamk.) dan DaunSirsak (Annona Muricata L.) Terhadap Mencit Jantan*. Indonesian Journal of Pharmaceutical Science and Technology, UniversitasIslam Bandung, 3 (2).
- [2]. Haryoto, Nurhardianti N., Sujono T.A., Suhendi A. & Muhtadi. 2016. *Antidiabetes Mellitus Ekstrak Etanol Kulit Batang Tumbuhan Sala (Cyanometra ramiflora L.) terhadap Tikus Jantan*.
- [3]. Katzung, B.G. (2002). *Farmakologi Dasar dan Klinik, Edisi III*. Penerbit Buku Kedokteran EGC.
- [4]. The International Diabetes Federation (IDF). (2015). *Diabetes Data*. www.idf.org.
- [5]. Kurniawan, I. (2010). *Diabetes Melitus Tipe 2 pada Usia Lanjut*. *Majalah Kedokteran Indonesia*. 60 (12): 576-584.
- [6]. McDougall, G., S. Faina, D. Patricia, S. Pauline, B. Alison & S. Derek. (2003). *Differ Polyphenolic Components of Soft Fruit Inhibit α -Amylase and α -Glucosidase*. Scottish Crop Research Institute. United Kingdom.
- [7]. Prameswari, O.M. & S.B. Widjanarko. (2014). *Uji Efek Ekstrak Air Daun Pandan Wangi terhadap Penurunan Kadar Glukosa Darah dan Histopatologi Tikus Diabetes Mellitus*. *Jurnal Pangan dan Agroindustri*. 2(2):16-27.
- [8]. Subroto. (2006). *Penatalaksanaan Diabetes*.
- [9]. Sudha, P., Zinjarde, S. S., Bhargava, S. Y., & Kumar, A. R. (2011). Potent α - amylase inhibitory activity of Indian Ayurvedic medicinal plants. *BMCComplementary and Alternative Medicine* 11:5, 2.
- [10]. Tadera, K., Y. Minami, K. Takamatsu and Matsuoka, T. 2006. Inhibition of α -Glucosidase and α -Amylase of Flavonoids. *Journal of NutritionalScience and Vitaminology*. 52:149-153.
- [11]. Yuhao, L., W. Suping, Kota, P. Bhavani, P. Gang, L. George Qin, Y. Yohji, &B.D. Roufogalis. (2005). *Punica granatum Flower Extract, a Potent Alpha-Glucosidase Inhibitor, Improves Postprandial Hyperglycemia in ZuckerDiabetic Fatty Rats*. *Journal of Ethnopharmacology*, 99(2): 239-244.

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