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Efficacy of *Duku* Seed Extract on Reducing Levels of HbA1c in Diabetic Model Rat

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ABSTRACT

Background: Diabetes mellitus (DM) is a multisystem metabolic disease due to abnormal insulin secretion, work and insulin function, or both. Abnormalities in the secretion or work of insulin cause abnormalities in the metabolism of carbohydrates, fats and proteins. Phytochemical test of duku seeds showed that all extract fractions contained flavonoids and terpenoids, whereas acetone and residual fractions contained alkaloids and saponins. Most plants that contain bioactive compounds such as flavonoids, saponoid, saponins and triterpenoids have antioxidant activity and other mechanisms as substances that have the potential to cause hypoglycemic effects. The goal of this research was to determine the efficacy of duku seed extract (*Lansium domesticum Corr*) on decreasing HbA1c levels.
Method: In vivo, pre-and post-test design has been conduction at Animal House Faculty of Medicine, Sriwijaya University from November to December 2019. Twenty-four white rats weighing between 150-200g divided into 4 groups. Rats were acclimated for 7 days, after acclimation rats were induced with alloxan 160 mg / kg intraperitoneally. The first, second, third group were given duku seed extract 50, 100, and 150 mg / kg of duku seed extract, and the fourth group was given glimepiride 0.018ng / kg / day. All treatments were given orally for one week. The data obtained were analyzed by normality test, paired t test, ANOVA, and Post Hoc test by using STATA.
Results: The rats were homogen on weight and HbA1C. Treatment of 50 and 100 mg / kg duku seed extract in rats showed a significant difference (p = 0.05) on day 7. Blood HbA1C levels decreased by 14.87% in duku extract 50mg / kgbb, while in seed extract 100 mg / kg body weight HbA1C levels reduced by 9.45%.
Conclusion: The administration of duku seed extract (Lansium domesticum) in diabetic rats can reduce blood HbA1C levels.

Keywords: Duku seeds (L. Domesticum), alloxan, HbA1C, Diabetes Mellitus, in vivo study

INTRODUCTION

Diabetes mellitus (DM) is a multisystem metabolic disease due to abnormal insulin secretion, work and insulin function, or both. Abnormalities in the secretion or work of insulin cause abnormalities in the metabolism of carbohydrates, fats and proteins. The estimated prevalence of DM at the age of 20-79 years is 6.4% in 2010 and will increase to 7.7% by 2020. [1] Indonesia ranks 9th in the estimation of world DM epidemiology in 2010 with 7 million cases and will continue to rise to the 5th rank in 2030 with 20 million cases. [2]

Based on estimates from the *World Health Organization* (WHO), more than 80% of the population of developing countries depend on traditional medicines to overcome health problems. One plant of that has an antioxidant effect and is often used by Indonesian people in the treatment of diabetes is Mahogany (*Swietenia macrophilla King*). B mahogany iji

(*Swietenia macrophilla King*) has an antihyperglycemic effect. [3] In addition, *S. Mahagoni L. Jacq species* also shows potential as antidiabetic and antioxidative in diabetic rats. Mahogany is a plant from the *Meliaceace* family. The duku plant (*Lansium domesticum* Corr) is also a plant from the *Meliaceace* family. Therefore it is likely that duku seeds can be used as a diabetes medicine like mahogany seeds. [4]

The phytochemical test of duku seeds showed that all extract fractions contained flavonoids and terpenoids, while the acetone and residual fractions contained alkaloids and saponins. [5] Most of plants that contain bioactive compounds such as flavonoids, saponoid, saponins and triterpenoids have antioxidant activity and other mechanisms as substances that have the potential to cause hypoglycemic effects. Unfortunately, until now research on the potential hypoglycemic effect of duku seed extract has was few. Given the increasing epidemiological estimates of diabetes, the objective of this study was to evaluate conduct research on the potential hypoglycemic effect of duku seed extract in diabetic rats, as well as a manifestation of the preservation of medicinal plants sourced from the *local wisdom of the* people of South Sumatra. The goal of this research was to determine the efficacy of duku seed extract (*Lansium domesticum Corr*) on decreasing HbA1c levels.

METHODS

In vivo study has been conducted at Animal House Faculty of Medicine, Sriwijaya University form April 2019 to June 2019. There were 24 rats that fulfill the criteria inclusion. Criteria inclusion was rat adult male white mouse, age 3 months, body weight 150-160 grams, healthy physical condition (no defects or abnormalities).

The protocol of the study has been approved by Ethical Committee, Faculty of medicine, Moh. Hoesin Hospital, Sriwijaya University.

Materials and Tools

Seed duku (*Lansium domesticum* Corr), glimipiride from PT. Dexa Medica, male white wistar rats, 1% CMC solution, ethanol, alloxan, aquadest, standard feed in the form of pellets, ELISA kit HbA1c 1 set, alcohol *swabs* , handscoons, and tissues. K rat, mouse drinking bottles, gloves, sonde (oral needles), spool, analytical scales, bunsen lights, blenders, ovens, a set of distillation equipment, erlenmeyer flask, flacon bottle, *rotary evaporator*, mask, *blood glucose test meter* (Roche), *micropipet*, *microplate reader*, and *micocentrifuge tube*. Animal testing rat male Wistar strain 3 years old month with range for nothing body weight 200-25 0 grams.

Extract Seed Duku

Duku seeds that have been dried are weighed as much as 2 kg and cut into small pieces, mashed with a blender and sifted in sizes 80-100 mesh. Then filtering was done by maceration using ethanol and then the maceration results were evaporated by vacuum distillation and continued with a *rotary evaporator* until thick extracts were obtained.

Preparation and Treatment Animal Try

Rats were acclimatized indoors for 7 days before being treated. Rats were fasted for 8 hours (drinking is still given) then the rats were induced by alloxan at a dose of 160 mg / kg intraperitoneally. Then the mice were kept for 7 days and then their blood sugar levels were measured. Blood sugar levels of mice> 200 mg / dl were grouped as hyperglycemic mice. Hyperglycemic rats were grouped randomly into 5 groups. All groups of rats were given food and drink.

For make extract seed duku to be oral preparations, made solution in water with add NaCMC 1%. Treatment given for 7 days and respectively group given treatment *single dose*

Measurement HbA1c

Blood is taken from rats through the periorbita and put in a 0.5 ml EDTA tube. Then we send to Pathology Clinic

Laboratorium Moh. Hoesin Hospital Palembang.

Data Analysis

Data obtained from results observation that is analyzed in a manner statistics using the STATA version 15 program. Analysis beginning to test for normality and homogeneity test. If the data is normal and homogeneous ($p>0.05$), analysis next with *post-hoc* LSD. If the data is not normal or not homogeneous, analysis do with non parametric tests. Difference meaningful if significance less from level error α ($p <0.05$). [6]

RESULTS

Efficacy of Duku Seed Extract on Levels of HbA1C on Day 7 on each group

Table 1 . Comparison of HbA1C levels for each group on the 7th day

Treatment Group	HbA1C Before	HbA1C After	Difference in HbA1C Levels	*p value*
EBD 50mg / kgbb	9.48 ± 1.45	8.07 ± 2.1	1.41	0.0112
EBD 100mg / kgbb	11.1 ± 1.17	10.05 ± 1.32	1.05	0.0508
EBD 150mg / kgbb	12.86 ± 0.19	12.28 ± 1.21	0.58	0.3144
Glimepiride	12.45 ± 1.14	13.06 ± 1.39	0.61	0.2851

Paired t test, p = 0.05

Efficacy of Duku Seed to Blood HbA1C Levels Among Group

Table 2. Dosage Suitability Test of Duku-Glimepiride Seed Extract Group

Group	Treatment Group (n = 24)	*p value*
		Day 7
EBD 50mg / kgbb	EBD 100mg / kgbb	0.230
	EBD 150mg / kgbb	0.001
	Glimepiride	0,000
EBD 100mg / kgbb	EBD 50mg / kgbb	0.230
	EBD 150mg / kgbb	0.128
	Glimepiride	0.018
EBD 150mg / kgbb	EBD 50mg / kgbb	0.001
	EBD 100mg / kgbb	0.128
	Glimepiride	1,000
Glimepiride	EBD 50mg / kgbb	0,000
	EBD 100mg / kgbb	0.018
	EBD 150mg / kgbb	1,000

Independent t test, p = 0.05

DISCUSSION

Based on the results of data analysis it can be concluded that the hypothesis in this study was accepted, namely there was a significant difference in efficacy between duku seed extract and glimepiride in reducing the blood levels of HbA1C in rats *(Rattus novergicus)* diabetes induced by alloxan. Some theories that support the acceptance of these hypotheses will be explained in this section.

Alloxan compounds are toxic diabetogenic substances, especially in the pancreatic beta cells, when these substances are induced in test animals such as mice, these substances can damage the beta cells of the pancreas so that the animals try to become diabetic. Intraperitoneal alloxan induction in wistar rats did not cause a significant increase in blood glucose levels, this was caused by the regeneration of pancreatic beta cells after 12 days of administration of alloxan at 120 mg / kg. Whereas in money wistar rats injected with alloxan a dose of 140 mg / kg will experience an increase in blood glucose levels that return to normal within a few months. [7] Aloxan induced test with alloxan at a dose of 160 mg / kg was able to maintain blood glucose levels in mice in the range of 400 mg / dL for 3 months. [8]

In this study the dose of alloxan used was 160 mg / kg, carried out for 7 days in order to determine the effects of the test preparation in repairing damaged beta cells of the pancreas and stimulating cells that are still well functioning to produce insulin. The toxicity mechanism of alloxan begins with the entry of alloxan into the beta cells of the pancreas. Alloxan cytotoxic action is mediated by free radicals. The toxic action of alloxan in beta cells is initiated by free radicals formed by redox reactions. Alloxan and its reduction products, acidic acid, forms a redox cycle with superoxide radical formation. This radical undergoes dismutation into hydrogen peroxide. The hydroxyl radical with high reactivity is formed by the Fenton reaction. The action of free radicals with high stimulation increases the cytosolic calcium

concentration which causes rapid beta cell destruction. [9]

From the results of data analysis it can be concluded that the duku seed extract 50mg / kgbb was effective in reducing blood HbA1C levels in this study measured by HbA1C blood of diabetic test animals induced by alloxan. After treatment for 7 days duku seed extract with a dose of 50 mg / kg was more effective than the positive control of glimepiride. Futhermore with duku seed extract with a dose of 100mg / kgbb it was found to be more effective than positive control.

Glimepiride is a third generation sulfonylurea that has an advantage over the previous generation sulfonylureas. Glimepiride has two working mechanisms, namely repairing the secretion and work system of insulin. Pancreas glimepiride stimulates beta cells, while peripheral increases GLUT4 so that it can reduce blood glucose levels. Glimepiride increases serum adiponectin levels and decreases TNF-alpha, two things that are efficacious as insulin sensitizers. [10]

Glimepiride does not have an antioxidant effect where alloxan is used as diabetogenic ROS so that the pancreatic beta cells are damaged, therefore the action of glimepiride is not optimal.

After considering the assessment criteria that in clinical practice, the choice of oral therapy in patients with diabetes mellitus has the ability to control blood HbA1C levels and the safety of side effects and safety from the potential for hypoglycemia after therapy. Duku seed extract with a dose of 50 mg / kg is considered to have the potential to be developed. Natural duku-based seed extracts based on different ways of working can cause a holistic effect, which works on many target organs. [11]

Duku seed extract dose of 50mg / kgb showed the ability to reduce blood glucose levels through HbA1C levels on day 7 after treatment in diabetic rats giving a reduced percentage of HbA1C levels of blood that did not reach normal was considered safe from the potential for hypoglycemia. Giving duku seed extract for 7 days in test animals namely male wistar strain rats, equivalent to 187 days in humans. Tikus laboratory in a healthy state can live 2-3 years, one day rat age is equivalent to 26.7 human age days. [12]

The difference in effect on each dose of duku seed extract given needs to be observed, the indications that appear on the duku seed extract are small doses (50mg / kgbb) and moderate (100mg / kgbb) phytochemical compounds that contain the possibility of interacting synergistically to effect the decrease Blood HbA1C is quite significant. While large doses (150mg / kgbb) of the compounds contained are not all synergistic with the effects of partial agonists which have a insignificant effect on blood HbA1C levels. These made possible by increasing the dosage, increasing the concentration of the active substance dissolved. Although some of the active substances contained can suppress the increase in blood HbA1C levels, in large doses some of these substances may work antagonistically. The duku seed extract seems to have an inverted U-shaped dose curve which indicates that when the optimal dose is exceeded, then if the increased dose will reduce the positive effect of the duku seed extract. Possible substances contained in duku seed extract are a group of compounds of agonists or partial antagonists. Partial agonist or partial antagonist. Its nature is between *full agonist/ antagonist t*, that is, after the increase in receptor agonists may cause effects as well as antagonists. The affinity of a partial agonist for its receptor can be as large as a *full agonist*. However, the maximum effect of a partial agonist is smaller than a *full agonist*, because the situation of a *full agonist* allows carrying more active receptors than partial agonists. [13]

Studies of pharmacokinetic were needed in the future to explain that mechanism. Until now the pharmacokinetic aspects of an herbal preparation that

contains a class of antidiabetic compounds, such as those found in duku seed extract are still rare. In fact, the biological effects of a drug depending on drug action as measured by pharmacodynamics also depending on pharmacokinetic parameter.

Pharmacokinetic parameters are quantities that are derived mathematically from the levels of active drugs in the blood / urine / other biological fluids for a certain period of time, which describe the processes of absorption, distribution, metabolism, and excretion. [14]

CONCLUSION

Giving extract seed duku *(Lansium domesticum)* in diabetic model rats can bring down blood HbA1C levels.

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