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The Antihyperglycemic Effects of Glibenclamide and Matoa Leaves Extract (*Pometia pinnata* J.R. Forst & G. Forst) On Alloxan-Induced Rats

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Abstract

Glibenclamide (GLI) oral treatment for diabetes mellitus has adverse effects such as hypoglycemia and weight gain. A synergistic effect achieved through the combination of natural constituents provides an alternative method for reducing adverse effects. The effect of giving matoa leaves to prevent an increase in blood glucose in the induction of large doses of glucose. The aim of this study was to investigate the contribution of 50% ethanol extract of matoa leaves (EEDM) to to reduce the side effect of weight gain and hypoglycemic at the administration of GLI in alloxan induced rats. A total of 20 rats were divided into 4 groups, namely normal control (NC), negative control, GLI 5 mg/KgBW group, and the combination of GLI 5 mg/KgBW and EEDM 100 mg/KgBW. Fasting Blood Glucose data (FBG), body weight, and urine analysis for 15 days of treatment were measured. The results show the ability of the GLI-EEDM combination to lower FBG more effective and can withstand the hypoglycemic effects of GLI, in addition to improving the secretion of glucose in the urine.

***Keywords**: Alloxan, Antidiabetic, Glibenclamide, Matoa Leaves*

INTRODUCTION

Glibenclamide (GLI) is an oral sulfonylurea (SU) that has the ability to stimulate insulin secretion from the β-cells in Langerhans islets located in the pancreas. Interactions with K^+ ion channels that are sensitive to ATP in the cell membrane cause depolarization of the membrane that allows Ca^{2+} ions to enter the cell, stimulating insulin-secreting granules (Fridlyand *et al*., 2013).

Many patients with type 2 diabetes treated with antidiabetic SU show long-term insulin secretory failure and the administration of GLI may result in weight gain and hypoglycemic adverse effects (PERKENI, 2021) which increases the risk factor of pancreatic *β*-cells necrosis, consequently diminishes Langerhans islets (Remedi and Nichols, 2008).

The damage to *β* cells in the pancreas can be prevented by antioxidant supplementation from herbs. So this combination will synergize in optimizing therapy and reducing the side effects of oral antidiabetic drugs (Iswahyudi *et al*., 2018). Matoa leaves (*Pometia pinnata* J.R. Forst & G. Forst) has several compounds including the saponin, phenols, flavonoids, tannins, polyphenols, alkaloids, coumarins, terpenoids (Maryam *et al*., 2020). The contents of the flavonoid compounds have strong antioxidant activity,can be used as the human body's defense system against free radicals (Widowati *et al*., 2015). *Quercetin-3-O-rhamnoside* flavonoid compound contained in matoa leaves (Suedee *et al*., 2013).

Quercetin are participates in various biological processes, including maintaining glucose balance: enhancing insulin sensitivity and secretion, promoting glucose utilization in peripheral tissues; inhibiting the absorption of glucose in the intestines (Al-Ishaq *et al*., 2019). The contents of the saponins have also been shown to have anti-obesity properties. The potential anti obesity may be partially due to the inhibitory influence of the absorption of lipids in digesting ratslles within the intestines (Suzuki *et al*., 2021). The utilization GLI and Matoa leaves is anticipated to reduce of the blood glucose levels and counteract the

adverse effects weight gain and hypoglycemic usage of GLI.

RESEARCH METHODOLOGY

Materials

The materials used matoa leaves from Surakarta District, alloxan (Sigma Aldrich), Glibenclamide (Indofarma), saline solution (WIDA®), Analytical Balance (OHAUS 214®), Rotary Evaporator (HeidollphL® 4000) Glassware (Pyrex®), Spectrophotometer UV (Star Dust MC 15), CMC Na (Sigma Aldrich®), Glucose GOD FS (DiaSys®), reagent kit (DiaSys®), Urine Reagen Strip (Verify®). Ethanol, Aquadest, Lactose, Aerosil, HCl 0.9%.

Animal Test

Twenty (20) rats with wistar strain aged 2-3 months, weighing 150 -200 g, are active and physically conditioned with bright red eyes and spotless white feathers. The animals were acclimated for one week to prevent stress. The experimental animals are housed in expansive enclosures that permit unrestricted movement. In addition to being provided with pellet feed in the morning and afternoon, they were also watered ad libitum. Animal confinement is maintained through sanitation and subsequent cleansing with the clean and running water. The experimental animals were housed in a room maintained at a temperature of 25 ± 1°C, with 12 hours dark cycle lighting and 12 hours lighting (Putri *et al*., 2019).

Extraction

Extraction Raw materials from matoa leaves as much as 500 grams of leaves were gathered, and the color of the leaves was green, the sheets were thick, the bones were hard in one piece. Determination of plants carried out in Biology Laboratory of University of Setia Budi Surakarta with number 008/A.E-I/LAB.BIO/I/2019. A total of 155 grams of dried of matoa leaves are soaked with 50% ethanol as much as 1.5 L for 2 x 24 hours with intermittent mixing. The liquid extract is bound with a rotary evaporator continued with water-bath of 60°C, 12 hours. The dry extract was obtained by adding lactose: aerosil (3:2), making it a powder with a 70:30 ratio.

Flavonoid Test

Extract (2 mL; 0.5 g/5 mL) added sufficient Mg powder, drip HCl concentrated 2-4 drops. A positive reaction is shown by change color to red, yellow or orange (Utoro *et al*., 2022).

Test Preparations

GLI 5 mg/KgBW and EEDM 100 mg/KgBW preparations are prepared in CMC Na 0,5% and administered orally 1 mL/200 gBW.

Animal Modeling Diabetes Melitus Test

A total of 20 fasted rats 12-18 hours were induced with 125 mg/KgBW alloxan doses intraperitone-ally and 2-6 hours were given 2 mL of 20% glucose orally. Blood glucose levels are determined on the 5th day, If blood glucose levels ranging from 200 to 600 mg/dL are observed in rats, it indicates that they are experiencing hyperglycemia. (Sasongko *et al*., 2020; Sintowati *et al*., 2021). The animals which indicated hyperglycemia were grouped into groups II-IV (n=5) and subsequently given the following treatment: Group I rats with normal Fasting Blood Glucose (FBG) are were administered 0.5% with carboxymethyl cellulose sodium (CMC Na) solution (normal control (NC). Group II received CMC Na 0.5% (control negative (Neg-C). Group III received dosage of GLI 5 mg/KgBW. Group IV received GLI 5 mg/KgBW and combined with EEDM 100 mg/KgBW. Levels of Fasting Blood Glucose data (FBG) were assessed on day 0 (baseline), induced, day 5, day 10, and day 15 of treatment.

Determination of Blood Glucose Levels

Blood samples taken through the conjunctival capillary veins of the eye are centrifugated at a speed of 5000 rpm for 10 minutes until the serum is obtained and stored in the freezer (-21℃). Aquadest, standard of glucose and serum taken as much as 5 µL placed on a different cuvette added reagent kit Glucose GOD FS 500 µL, incubated at a temperature of 37℃ for 10 minutes and absorbance read with visible photometer at wavelength of 546 nm (Chaianantakul *et al*., 2018).

Data Analysis

Data analysis was conducted on 4 groups using IBM SPSS Statistic Version 23 For Windows with One Way ANOVA parametric test to see significant differences between groups and continued with Post Hoc LSD. An independent t-test was carried out to compare data from 2 groups, namely treatment control group I and treatment control 2. Analysis of changes in body weight and blood glucose levels was analyzed with paired t-tests and urine analysis was performed manually.

RESULT AND DISCUSSION

Extraction of matoa leaves with maceration will attract the active compounds contained in simplicia. The extraction was done using 50% ethanol to obtain the content of flavonoid compounds (Sidoretno *et al*., 2018). Ethanol will enter the cell walls and the cell cavity, causing imbalance because of the difference in concentration between the solution inside and outside the cell (Handoyo, 2020; Putri *et al*., 2023). The result extraction obtained a yield of 31.5% (**Table 1**).

Table 1. Yield of 50% Matoa Leaves Ethanol Extract (EEDM)

Items	Parameters
Sample	Matoa leaves
Wet fresh matoa leaves (g)	500
Dry simplicia (g)	155
Dry Extract Results (g)	16.95
Yield (%w/w)	31.5
Water Content (%)	5.32
Flavonoid	orange color (positive)

The use 50% ethanol matoa leaves based on the solubility of a substance on the use of ethanol above 70% can lead to a decrease in the levels of flavonoid compounds. The water content test results showed 5.32%, the extracted substance satisfies the dry extract criterion of 10% or less (Kemenkes RI, 2017).

Alloxan-induced wistar rats will have hyperglycemia, which manifests as blood sugar levels greater than 200 mg/dL, weight loss, and the presence of glucose in urine and specific weight of urine greater than 1 (>1). Although the hyperglycemia condition up to day 15 is still high, there are no protein levels in the urine, hence nephropathy has not occurred. Administration of GLI 5 mg/KgBW and EEDM 100 mg/KgBW has significant differences in the blood sugar levels. GLI lowered Fasting Blood Glucose data (FBG) on day 15 by an average of 131±24.21 mg/dL and combination of GLI and EEDM by 66.4±7.40 mg/dL (**Table 2**).

The modelling of diabetic rats in this investigation accomplished by intraperitoneal induction 125 mg/KgBW of alloxan, resulting in Wrats developing type 2 diabetes mellitus (Oshkondali *et al*., 2019). Diabetogenic administration can cause animals to develop of diabetes mellitus (DM type-2) with damage pancreatic β cells and is characterized by presence of hyperglycemia (Suarsana *et al*., 2010). In addition, alloxan also inhibits the process of glucokinase in metabolic process (Terayama *et al*., 2017), but this substance can be a hypoglycemic phase which generally occurs 4 to 8 hours after induction which results in seizures, then it is necessary giving 20% glucose orally (Prihanti *et al*., 2020). Alloxan administration was carried out in groups II-IV with an increase in blood glucose levels up to day 10 and a decrease after day 15 (**Table 2**). During hyperglycemia, glucose is also found in the urine, this is because the body will occur homeostasis for blood sugar levels by the removing excess blood glucose produced through urine (El-Sakhawy *et al*., 2023). On day 10, there is still glucose in the urine of group III, but not in group IV. This is because urine tests may detect glucose levels up to 180 mg/dL (Lestari *et al*., 2021).

The study by examined the impact of combining GLI and EEDM on blood glucose levels. It was found group GLI 5 mg/KgBW experienced a significant decrease of 21.15% in blood glucose levels daily, while group GLI 5 + EEDM 100 mg/KgBW experienced a decrease of 13.00% in blood glucose levels

Table 2. Body Weight (g), Fasting Blood Glucose Levels (mg/dL), Glucose in Urine, Protein in Urine, and Specific Gravity of Urine

Parameters	Group	Baseline	Induced	Day-5	Day-10	Day-15	% daily changes
Body Weight (g)	NC	168.8±18.24	170.2±16.24	170.4±12.66	177.0±10.07	182.0±10.93	(+)7.81
	Neg-C	165.0±14.00	157.0±13.45	151.0±11.55	142.8±16.21	165.2±10.31	(+)0.12
	GLI 5	170.4±13.03	163.6±10.21	170.4±11.67	174.6±13.68	175.8±17.44	(+)3.17
	GLI 5+EEDM 100	167.0±12.98	163.2±13.16	157.4±8.37	161.9±6.95	162.4±7.33	(-)2.75
Fasting Blood Glucose (FBG) (mg/dL)	NC	90.4±14.40	87.2±10.23	88.4±13.45	95.4±16.67	99.2±20.56	(+)9.73
	Neg-C	79.8±20.23	251.2±21.90	366.0±53.15	416.6±68.22	312±59.23	(+)24.20
	GLI 5	75.6±12.11	448.2±54.76	267.2±37.20*	194±28.28*,#	131±24.21*	(-)21.15
	GLI 5+EEDM 100	79.0±15.36	261.8±26.78	129.4±23.39*	91.6±3.64*,#	66.4±7.4*	(-)13.00
Glucose in urine	NC	-	-	-	-	-	
	Neg-C	-	+	++	+	+	
	GLI 5	-	++	+	±	-	
	GLI 5+EEDM 100	-	++	±	-	-	
Protein in urine	NC	-	-	-	-	-	
	Neg-C	-	-	-	-	-	
	GLI 5	-	-	-	-	-	
	GLI 5+EEDM 100	-	-	-	-	-	
Specific gravity of urine	NC	1.020	1.010	1.010	1.020	1.020	
	Neg-C	1.010	1.025	1.030	1.030	1.030	
	GLI 5	1.020	1.025	1.030	1.030	1.020	
	GLI 5+EEDM 100	1.020	1.020	1.030	1.025	1.020	

*:significant with Neg-Control (p<0.05), #:Significant difference between GLI group and GLI+EEDM (p<0.05)

daily (p<0.05). The combination of GLI 5 + EEDM 100 mg/KgBW can reduce risk of hypoglycemia from the average percentage of daily reduction in fasting blood glucose levels (13%) compared to single GLI (21.15%).

The weight body loss experienced by hyperglycemic compensated for decreased glucose transport to cells (Pournaghi *et al*., 2012). Weight gain also occurred in groups III and IV (**Table 2**) but was still within the normal range of less than 10 grams per week (Rizma *et al*., 2021) and not yet included in the category of susceptible to insulin resistance because weight gain does not exceed are more than 20% (Votruba and Jensen, 2011).

The specific gravity of urine has a normal range of 1,005-1,030, and in this study there was an increase in the specific gravity value of test animals with diabetes (Musaidah *et al*., 2018). Increased specific gravity values in diabetes mellitus affect the increase in glucose levels (Brunzel, 2013). Protein in urine is not found in all groups, this because urine protein will be identified in diabetes with a duration of diabetes type-2 are more than 10 years (Abdelhafiz, 2020; Wirawan *et al*., 2022).

GLI is an oral antidiabetic drug that can reduce insulin secretion by stimulating insulin secretion in the pancreas (Maliangkay *et al*., 2018; Sutrisna *et al*., 2018). While matoa leaves (*Pometia pinnata* J.R. Forst & G. Forst) contain flavonoids form of Quercetin-3-O-rhamnoside (Suedee *et al*., 2013).

The content of flavonoid compounds in matoa has the potential as an antioxidant and antidiabetic with the ability to inhibit free radicals causing the inhibitory power of the α-amylase enzyme is also greater so that it can reduce blood glucose levels (Wulandari *et al*., 2021). In addition, the formation of Reactive oxygen species (ROS) lipid peroxidation which can cause apoptosis and necroptosis so that β cells can produce insulin normally (Ghorbani *et al*., 2019).

Based on the results of reducing blood glucose levels, the combination of GLI and

EEDM can reduce blood glucose levels with a synergistic effect. Studies that have been conducted and observed the combined use of GLI and EEDM is more effective in lowering glucose in blood and urine than the use of a single GLI, but still needs further research on the mechanism of side effects on the kidneys and liver and safety in long-term use.

CONCLUSIONS

The administration of GLI 5 mg/KgBW in combination with EEDM 50% at a dose of 100 mg/KgBW is more efficacious in reducing blood glucose levels and has a greater ability to counteract hypoglycemia effects compared use of GLI alone can cause adverse effect of weight gain. Additionally, this combination treatment enhances glucose excretion in urine.

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