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The Effect of Butterfly Pea Extract on Blood Glucose Levels in White Rats with Metabolic Syndrome Model

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ABSTRACT

Introduction: Metabolic syndrome is an accumulation of several disorders, one of which is hyperglycemia. *Clitoria ternatea* is a plant that contains lots of flavonoids and is known to reduce blood glucose levels in metabolic syndrome. This study aimed to determine the effect of butterfly pea extract (*Clitoria ternatea*) on blood glucose levels in white rats with metabolic syndrome models.
Methods: This research is an experimental study using animal models with pre and post-test control group design method. The number of samples was 30 male white rats which were divided into 5 groups: group 1–negative control group; group 2–positive control group; group 3, group 4, and group 5 were the metabolic syndrome group which was given *Clitoria ternatea* extract with doses of 100, 200, and 400 mg/kgBW, respectively for 28 days. Measurement of blood glucose levels for all groups was carried out on the 36th day as the pre-test and the 64th day as the post-test. Blood glucose levels were obtained through retroorbital venous blood which was analyzed with the Easy Touch blood glucose stick meter. One-way ANOVA was used to analyze data, followed by post-hoc LSD test, and paired T-test.
Results: The average post-test random blood glucose levels decreased by 135.16 mg/dl, 163.18 mg/dl, and 168.35 mg/dl. There was a significant difference ($p<0.05$) between the pre-test and post-test blood glucose levels along with the average blood glucose level amongst groups.
Conclusion: Butterfly pea (*Clitoria ternatea*) could decrease blood glucose levels and cause further decrease with higher doses.

Keywords: clitoria ternatea; blood glucose; metabolic syndrome

INTRODUCTION

Metabolic syndrome is a combination of conditions that raises the risk of cardiovascular disease, diabetes, and vascular and neurological consequences[1]. In Indonesia, the prevalence of metabolic syndrome is 21.66 %, with the highest prevalence in Jakarta and East Kalimantan[2]. One of the criteria for metabolic syndrome is a rise of 100 mg/dl in fasting blood glucose[3]. Consequently, metabolic syndrome is closely associated with blood sugar levels.

If left untreated for an extended period of time, hyperglycemia can cause damage to multiple organs, including the heart, eyes, nerves, kidneys, and blood vessels[4]. The incidence of hyperglycemia has substantially grown over the past two decades as a result of a decline in physical activity, an increase

in fat, and an aging population. The incidence of hyperglycemia is identical across men and women. Hyperglycemia is more prevalent in households with low to middle income[5]. Improper management of hyperglycemia might result in long-term problems. By regulating body weight and hyperglycemia, proper hyperglycemia management can minimize the risk of metabolic syndrome and stroke[6].

Widespread research has been conducted on medicinal plants containing natural antidiabetic compounds in an effort to reduce blood glucose levels. The aforementioned natural anti-diabetic compounds are terpenoids, phenolic acids, and flavonoids[7]. *Clitoria ternatea* extract containing flavonoids is one of the natural therapies for individuals with hyperglycemia[8].

Butterfly Pea (*Clitoria ternatea*) is composed of several chemical substances, including sugars, tannins, saponins, triterpenoids, flavonoids, phenols, flavonol glycosides, alkaloids, proteins, anthraquinones, and anthocyanins[8]. Using *Clitoria ternatea* leaf extract can enhance insulin levels in the body and decrease blood sugar levels. This is demonstrated by the results of a study done by experts at the Swiss German University (SGU). To induce hyperglycemia, rats were injected with alloxan for the sake of conducting experiments. The mice's blood sugar levels returned to normal after eight weeks of therapy with *Clitoria ternatea* leaf extract[9].

Several further research has examined the hypoglycemic effects of *Clitoria ternatea* on diabetic rats. However, research on butterfly pea's influence on metabolic syndrome rat models is relatively limited. This research was conducted to examine the effect of butterfly pea administration on blood glucose levels in rats with metabolic syndrome.

METHOD

This research implemented a laboratory experimental design with pre and post-test control group design research method, and then the sample was divided into multiple groups using Simple Random Sampling. This research was carried out in the lab at Gajah Mada University in Yogyakarta's Center for Food and Nutrition Studies. Subjects of the study were white rats (*Rattus Norvegicus*) that fulfilled the inclusion and exclusion criteria. The inclusion criteria for research subjects were male sex, age 2 months, body weight ± 200 grams, white rats in good condition, absence of anomalies, and vigorous activity. In the meanwhile, the exclusion criteria included rats that died during the trial, rats that sustained a weight reduction of >10%, and rats that had been utilized in previous research. The samples consisted of thirty white rats (*Rattus norvegicus)* calculated by Federer's formula. Using simple randomization, the sample was then divided into five groups. Group 1 - Negative control group, which consisted of white rats fed standard BR-2 pellets without High-Fat High-Fructose Diet (HFFD), Streptozotocin-Nicotinamide (STZ-NA), and butterfly pea extract. Group 2 – positive control group, which consists of white rats administered HFFD and STZ-NA. Group 3 – treatment group 1 consisted of white rats administered HFFD, STZ-NA, and 100 mg/kgBW of butterfly pea extract for 28 days. Group 4 – the treatment group 2, which included white rats that were administered HFFD, STZ-NA, and 200 mg/kgBW of butterfly pea extract for 28 days. Group 5 – treatment group 3, namely white rats that were administered HFFD, STZ-NA, and 400 mg/kgBW of butterfly pea extract for 28 days.

Butterfly Pea extract is prepared by dehydrating, mashing, and macerating (soaking) it in 96% ethanol for 48 hours at 50°C[10]. East Java's Ngawi is where the butterfly pea was harvested. In the lab of the Center for Food and Nutrition Studies at Gajah Mada University in Yogyakarta, butterfly pea extract was created. Using a stomach probe, butterfly pea extract will be administered orally. Arifah's prior study will be used to determine the dose[11], namely dose I (100 mg/kgBW), dose II (200 mg/kgBW), and dose III (400 mg/kgBW). The measuring device for the butterfly pea extract is a digital scale with milligram units. Ordinal scales are used for measurements. Glycemia, or random blood glucose level, refers to the carbohydrate component of blood glucose[12]. Before giving butterfly pea extract (Pretest)

and after giving butterfly pea extract (post-test), blood glucose levels were checked twice (post-test). Blood was drawn from the retroorbital vein in the eyes of white rats, and blood glucose levels were determined using a Blood Glucose Stick Meter Easy Touch; the results were expressed in mg/dl. The ratio is the unit of measurement utilized.

The collected data will be processed with Statistical Products And Service Solutions (SPSS) software. Because the number of samples is less than 50, the Shapiro-Wilk test will be used to examine the distribution of the Pretest and post-test blood glucose values for each study group[13]. If the distribution is normal and fits the conditions, the investigation will proceed using Oneway Anova with a significance level of $p < 0.05$. If there is a substantial difference between the treatment groups, a Post Hoc Test is conducted to determine the location of the significantly different groups. If the aforementioned prerequisites are not met, for instance if the data are not normally distributed, the data must first be converted. This research has been approved by the health research ethics committee of regional public hospital Dr. Moewardi (approval number: 891/VI/HREC/2022).

RESULTS

Research Result Data

To be diagnosed with metabolic syndrome, at least three of the following five conditions must be present: hyperglycemia (RBG ≥200 mg/dl), obesity (body weight increase by ≥20%), hypertension (systolic blood pressure ≥130 mmHg and/or diastolic ≥85 mmHg), decreased HDL levels (<40 mg/dl), and elevated triglyceride levels (>150 mg/dl). The rats in this study were given HFFD for 28 days, and on the 31st day, STZ-Na was used to create the condition known as metabolic syndrome. The following information was gathered following the course of treatment:

Table 1. Mean Random Blood Glucose (RBG) Levels Pretest and post-test

	Pretest RBG Level ± Std. Deviation	Post-test RBG Level ± Std. Deviation	Sig.
Group 1	77.35 ± 0.94	78.35 ± 0.83	0,001
Group 2	272.78 ± 4.57	274.14 ± 3.87	0,009
Group 3	271.10 ± 1.27	135.94 ± 4.02	0,000
Group 4	272.31 ± 2.68	109.13 ± 4.66	0,000
Group 5	270.43 ± 3.42	102.08 ± 3.76	0,000

After feeding HFFD and injecting STZ-Na (Pre-Test) and following administration of butterfly pea extract, blood glucose levels were measured (post-test). In Table 1, the pretest section shows an increase in blood glucose levels in group 2, group 3, group 4, and the comparison between group 1—a negative control group—given regular pellet feed BR-2 and group 5, which was fed HFFD. Due to hyperglycemia, which occurred when blood glucose levels in groups 2, 3, 4, and 5 of rats reached ≥ 200 mg/dl, this satisfies the criteria for the first metabolic syndrome. In Table 1, the post-test section demonstrates a reduction in blood glucose levels in Groups 3 and 4, and Group 5, which received butterfly pea extract therapy, was compared to groups 1, which served as the negative control group, and group 2, which served as the positive control group and witnessed a rise in blood sugar levels at any time.

Table 2 shows that there was an increase in body weight in all groups of white rats. Body weight increased in group 1 by 14.7%, in group 2 and group 3, by 23.3%, in group 4, by 23.2%, and in group 5, by 22.9%. The HFFD-fed group in groups 2, 3, 4, and 5 gained 20% more body weight than the

control group, qualifying them as obese and at risk for developing insulin resistance[14]. Therefore, obesity, one of the requirements for the second metabolic syndrome, has been satisfied

Table 2. Average White Rat Weight on Day 8 and Day 36 in grams

	Day 8	Day 36
Group 1	173.83 ± 5.04	199.33 ± 4.46
Group 2	173.17 ± 4.99	213.50 ± 4.93
Group 3	172.50 ± 4.72	212.67 ± 4.23
Group 4	174.33 ± 4.13	214.83 ± 5.04
Group 5	175.67 ± 3.32	215.83 ± 2.92

Table 3. Average Pretest Lipid Profile Level

	Triglyceride	HDL	LDL	Total cholesterol
G 1	3.46	1.81	2.30	2.33
G 2	2.58	1.63	1.56	3.99
G 3	2.36	1.63	1.56	3.07
G 4	1.98	1.29	1.86	3.03
G 5	3.13	1.98	1.90	3.55

The lipid profile of the rats in the HFFD 28-day feeding group (groups 2, 3, 4, and 5) differed from that of the negative control group (group 1), which received just conventional pellet BR-2 diet. This is shown in Table 3. The group with HFFD diet tended to have triglyceride levels >100 mg/dl, HDL levels <40 mg/dl, LDL levels >80 mg/dl, and total cholesterol >100 mg/dl.

Following the administration of butterfly pea extract and HFFD (pretest), HDL levels were measured (post-test). In comparison to group 1, which is the negative control group, Table 3 demonstrates a decline in HDL levels in groups 2, 3, 4, and 5, which is the group receiving HFFD feed. Given that the HDL levels in groups 2, 3, 4, and 5 had decreased by < 40 mg/dl, this fits the criteria for the third metabolic syndrome.

Based on the aforementioned results, groups 2, 3, 4, and 5 that received HFFD and STZ-Na injections had higher blood glucose levels, lower HDL levels, and higher body weights than group 1, or the group that received regular pellet feed BR-2. Therefore, it can be concluded that groups 2, 3, 4, and 5 of white rats had metabolic syndrome because they met three of the five criteria for the condition.

Table 4. Levene's Test Transformation Data Homogeneity Test Results

		Levene Statistic	Sig.
RBG *Pretest* after transformation	By Mean	1,491	0,235
	By Median	1,136	0,362

Since the homogeneity test indicates that the data are homogeneous, they will be analyzed using the Oneway Anova parametric test. The p-value in Table 5 indicates that there is a significant difference ($p < 0.05$) between the five groups blood glucose levels.

Table 5. Test Results Oneway Anova

		df	Sig.
Result *Pretest* (transformation)	*Between Groups*	4	0,000
	Within Groups	25	
Result *post-test*	*Between Groups*	4	0,000
	Within Groups	25	

Post-Hoc test pretest data (Figure 1) revealed a significant p-value ($p < 0.05$) between group 1 (negative control group) fed the regular pellet diet BR-2 *ad libitum* and group 2 (positive control group) and group 3-5 (group with HFFD feed and streptozotocin-nicotinamide injection). This demonstrates that HFFD feeding plus STZ-Na injections can dramatically increase blood glucose levels in rats relative to the untreated control group. Therefore, it is possible to conclude that the therapy of metabolic syndrome in white rats was effective.

From the results of the Post Hoc test (Figure 1), it was also determined that the p-value between groups 2, 3, 4, and 5 was not significant ($p > 0.05$). This indicates that there is no difference between the effects of HFFD feeding and STZ-Na injection on random blood glucose levels, as both groups showed a rise in blood glucose levels following the administration of therapy.

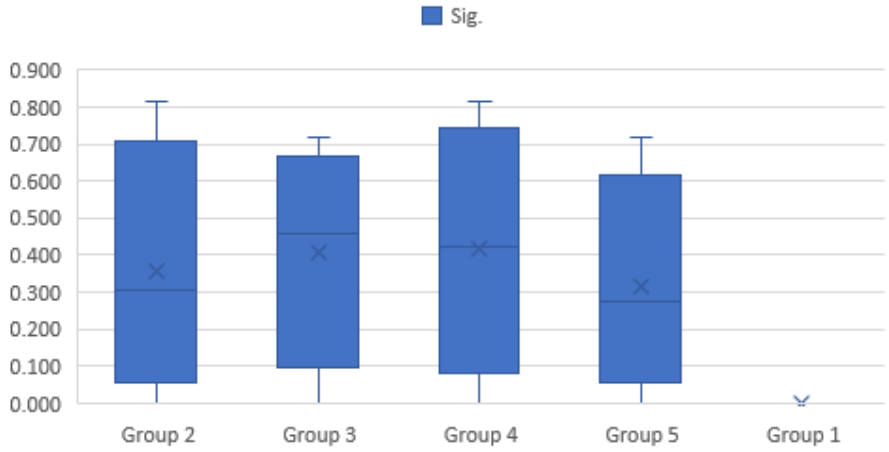

Figure 1. Post-Hoc Test Results of the Pretest group

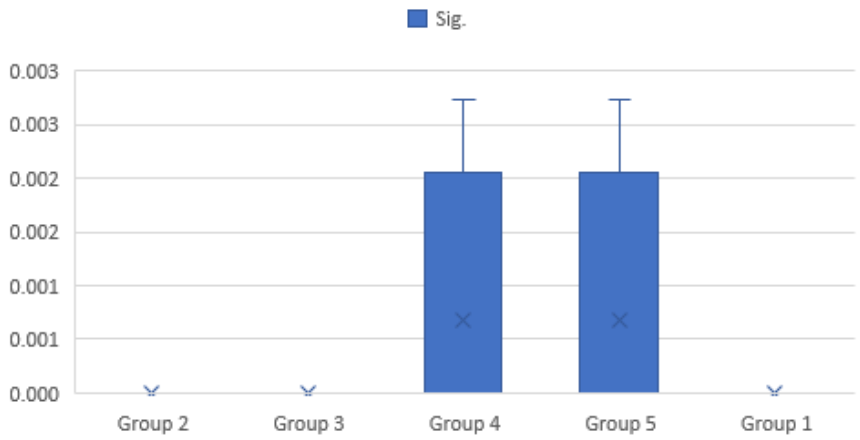

Figure 2. Post-Hoc Test Results of the post-test group

Based on Figure 2, it was found that between group 1 (negative control group), group 2 (positive control group), group 3 (group with butterfly pea extract treatment 100 mg/kgBW), group 4 (group with butterfly pea extract treatment 200 mg/kgBW), and group 5 (group with butterfly pea extract treatment 400 mg/kgBW) had significant differences because $p < 0.05$. Based on these findings, it can be said that administering butterfly pea extract at a dose of 100 mg/kgBW, 200 mg/kgBW, and 400 mg/kgBW can dramatically lower blood glucose levels in rats with metabolic syndrome models when compared to the negative control group and the positive control group that did not receive the butterfly pea extract.

The outcomes of the Pretest and post-test will be evaluated using a paired T-test after the Oneway Anova test and continuing with the Post-Hoc Test.

It may be inferred from Table 1 that there is a significant difference in blood glucose levels between the pretest and post-test groups in group 1, the negative control group with conventional pellet feed BR-2 ($p = 0.001$; $p < 0.05$). It can be inferred from group 2, the positive control group with High-Fat High-Fructose Diet meal and streptozotocin-nicotinamide injection, that there is a significant difference in blood glucose levels between the pretest and post-test groups ($p = 0.009$; Table 1). It may be inferred that there was a significant difference in blood glucose levels between pretest and post-test in groups 3, 4, and 5, namely the groups that was treated with butterfly pea extract, with a $p = 0.000$. The p-value of < 0.05 (Table 1) in groups 3, 4, and 5 indicates that the administration of butterfly pea extract has a significant effect on the post-test outcomes of blood glucose levels in white rats.

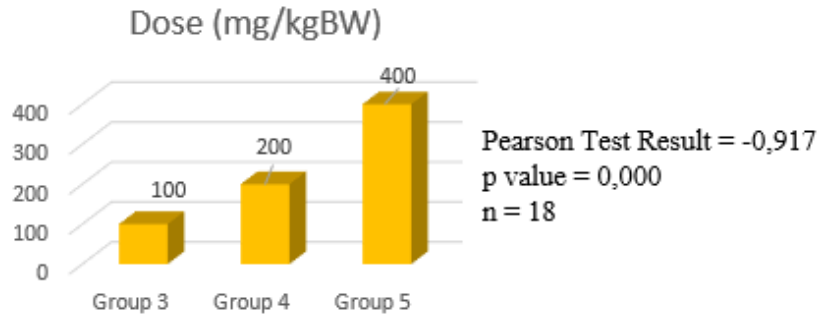

Figure 3. Pearson Test Results

The p-value of 0.000 in Figure 3 indicates that there is a strong link between *Clitoria ternatea* dose and blood glucose levels. The Pearson correlation coefficient indicates the strength of the link between *Clitoria ternatea* dose and blood glucose levels. A negative number denotes an inversely proportionate relationship between the two variables. There is a very high association between the dosage of *Clitoria ternatea* and blood glucose levels, as shown by the Pearson test findings (Figure 3), which got a value of -0.917 and fall within the range of 0.8-1. The two factors are negatively correlated, therefore the larger the dose of *Clitoria ternatea*, the lower the blood glucose levels in the white rats used as a model for the metabolic syndrome.

DISCUSSION

Using a High-Fat, High-Fructose Diet meal component in conjunction with an injection of streptozotocin-nicotinamide, the symptoms and indications of the human metabolic syndrome have been imitated in mice[15]. Streptozotocin is a glucose analogue that accumulates in pancreatic beta cells through the GLUT-2 transporter[16]. This caused the blood glucose level of the streptozotocin-treated group to exceed >200 mg/dl on day 36 of the pretest. According to Wolfenshon[17], normal rate rat blood glucose levels range between 50 - 135 mg/dl; therefore, hyperglycemia has occurred in groups 2, 3, 4, and 5. This variance in GDS levels was due to changes in the resistance level of the animals, namely

the ability of pancreatic beta cells to regenerate, which influenced the effect of streptozotocin administration.

The High-Fat High-Fructose Diet also caused the pretest value of total cholesterol to increase to >110 mg/dl, HDL levels to decline to <40 mg/dl, and the body weight of rats to increase by ≥20% of their baseline body weight. The results of the 36th day pretest of blood glucose levels, total cholesterol, HDL, and body weight show that the rats meet the criteria for metabolic syndrome[18]. However, a pretest triglyceride level <150 mg/dl may be the result of triglycerides generated by the liver and transported to peripheral tissues after VLDL has been digested by the enzyme lipoprotein lipase into LDL, which is high in cholesterol and low in triglycerides[19].

Group 1, the negative control group, which was fed only ordinary pellet BR-2 feed and was not treated, did not exhibit a reduction in blood glucose levels. Group 1 RBG levels were within the usual range of <200 mg/dl. In group 2, the positive control group, the average blood glucose levels increased because streptozotocin, which is toxic to pancreatic beta cells, was administered to the rats, resulting in hyperglycemia with RBG levels exceeding 200 mg/dl.

The butterfly pea extract reduced blood glucose levels in groups 3, 4, and 5 after administration (Table 1). This is likely due to the presence of flavonoid chemicals in butterfly pea, which can protect cells from hyperglycemic stress in a variety of ways. First, flavonoids were able to prevent a further reduction in NAD+ and NADH levels by inhibiting PARP-1 overactivation. In addition, flavonoids are able to reduce the harmful effects of oxidative stress due to their antioxidant characteristics. With this combination, flavonoids can protect cells from hyperglycemia-induced damage[20].

According to the results of this study, butterfly pea extract can lower blood sugar levels at doses of 100 mg/kg, 200 mg/kg, and 400 mg/kg. Blood sugar levels can be reduced by roughly 135.16 mg/dl, 163.18 mg/dl, and 168.35 mg/dl, respectively (Table 1). Based on these data, the results of this study are similar to the research conducted by Al-Snafi[21]. In this research, it was shown that *Clitoria ternatea* extract (200 and 400 mg/kgBW) effectively lowered blood glucose levels in streptozotocin-induced rats. A dose of 400 mg/kg produced a strong hypoglycemic impact, while a dose of 200 mg/kg also decreased glucose levels, but to a lesser extent. The results of the acute effect of methanol extract showed that doses of 200 and 400 mg/kg produced relatively similar effects, however at the initial 30-minute stage, the 200mg/kg dose resulted in a greater decrease in blood glucose levels. Long-term use of the extract at a dose of 200 mg/kg was significantly more effective at controlling blood glucose levels than usage at a dose of 400 mg/kg, according to subacute activity. Similarly, research conducted by Talpate revealed the same result[22]. In particular, *Clitoria ternatea* extract proved effective in lowering serum glucose levels in rats after streptozotocin induction. The doses utilized, 200 mg/kg and 400 mg/kg, are the same. Following the use of *Clitoria ternatea* extract for two weeks, According to the findings, a dose of 200 mg/kg can lower blood sugar levels to 153.6 mg/dl, while a dose of 400 mg/kg can do the same for 125.2 mg/dl. Daisy have also looked into how *Clitoria ternatea* extract affects blood sugar levels. Male Wistar rats' livers responded favorably to oral administration of *Clitoria ternatea* extract for 84 days by having higher glucokinase activity and lower glucose-6-phosphatase activity. In this research, it was discovered that *Clitoria ternatea* leaf and flower extracts at the same dose (400 mg/kgBW) were both effective, can dramatically lower blood glucose levels in Wistar rats produced by alloxan[23].

This research authors are consistent with several earlier research on the hypoglycemic impact of butterfly pea (*Clitoria ternatea*). For instance, research by Gunjan and Jana demonstrated that giving Wistar rats given alloxan-induced diabetes butterfly pea extract at a concentration of 100 mg/kgBW for 14 days helped lower blood glucose levels[24]. In previous research, *Clitoria ternatea*'s potential to reduce

blood sugar was also supported by Suganya who found the ethanolic extract of *Clitoria ternatea* has antihyperglycemic effects on yeast cells when glucose solution was added[25].

In this research, it can be concluded that the butterfly pea extract (*Clitoria ternatea*) at doses of 100 mg/kgBW, 200 mg/kgBW, and 400 mg/kgBW had an impact on lowering blood glucose levels in white rats with metabolic syndrome models. The reduction in blood glucose levels in male white rats is proportional to the amount of butterfly pea extract (*Clitoria ternatea*) administered.

Research Limitations

This research lacked the ability to define the ideal dose of butterfly pea extract for reducing blood glucose levels and was unable to determine the negative effects of butterfly pea extract on other organs due to the use of only three dose variations.

CONCLUSION

Based on the outcome of the research, it was determined that the extract of butterfly pea (*Clitoria ternatea*) had an influence on the blood glucose levels of white rats (*Rattus norvegicus*) metabolic syndrome model, specifically a hypoglycemic effect. The higher the dose of *Clitoria ternatea* extract used, the greater the decrease in blood glucose levels in male white rats with the tested dose limits is 100 mg/kgBW, 200 mg/kgBW, and 400 mg/kgBW.

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CONFLICT OF INTEREST

The authors reported no potential competing interests.

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