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THE EFFECT OF ANTLIONS EXTRACT TOWARDS BLOOD GLUCOSE LEVEL OF MALE SWISS MICE INDUCED BY STREPTOZOTOCIN

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ABSTRACT

Background: Diabetes mellitus is one of metabolic diseases characterized with hyperglycemia due to abnormal insulin secretion. The treatment of diabetes mellitus usually use the insulin injection and Oral Hypoglycemic Drugs (OHD). Antlions (*Myrmeleon sp)* is an animal that has potency to treat the diabetes mellitus. The sulfonylureas obtained from Antlions is a substance that stimulates insulin secretion in pancreatic beta cells. **Aim:** To analyse the effect of antlions extract on the blood glucose level of male swiss mice induced by streptozotocin. **Methods:** An experimental study with the pre and post test control group design, among 30 male swiss mice obtained from simple random sampling technique. The sample divided into 5 groups. The data obtained were analyzed using ANOVA test with a confidence level of 95%. **Results:** The administration of antlions extract could lower ($p<0.05$) blood glucose levels in male Swiss mice after 28 days of treatment. The administration of antlions extract with dose of 14 mg/kgBW and 56 mg/kgBW significantly lowered blood glucose levels in male Swiss mice as evidenced by $p=<0.001$ and $p=0.034$. Whereas the administration of antlions extract with a dose of 28 mg/kgBW was less significant in lowering blood glucose levels in male Swiss mice ($p=0.210$). **Conclusion:** The administration of 14 mg/kgBW antlions extract (*Myrmeleon sp*.) had the best effect on lowering blood glucose levels in male Swiss mice after 28 days of treatment.
Keywords: *antlions, blood glucose, diabetes mellitus*

INTRODUCTION

Diabetes Mellitus is a metabolic diseases characterized by hyperglycemia that occurs due to abnormal insulin secretion. Medical treatment of diabetes generally uses insulin injections and synthetic Oral Hypoglycemic Drugs (OHD). However, limited healthcare services in certain regions causes difficulties in obtaining those drugs.[1,2]

Regarding the issue of limited healthcare acccess in several areas, the treatment of diabetes mellitus can be shifted to traditional medicine which utilizes plants and animals that are efficacious in treating diabetes.[3] One of the animals that is believed to be efficacious for treating diabetes mellitus are antlions (*Myrmeleon sp*.). The body of antlions contains substances like sulfonylureas which are sulfanimide derivatives. Sulfonylureas stimulates insulin secretion in pancreatic beta cells where insulin functions in lowering blood glucose levels.[4]

A study conducted by Hamidah in 2016 shows that administration of ethanol antlions extract is more effective in lowering blood glucose level as compared to powdered antlions.[1] Other than that, a study conducted by Tyas in 2006 mentioned that administration of antlions juice with dose of 0.01 ml/ 200 g body weight of mice per day for 14 days can lower blood glucose levels in hyperglycemic mice ($p<0.05$).

Based on the explanation above, this study will examine the effect of antlions extract towards the blood glucose level of male Swiss mice induced with streptozotocin.

RESEARCH METHODS

This research is a study in the field of Biochemistry and Pharmacology with a laboratory experimental design, conducted using the Pretest-Posttest Control Group Design method. The sample used in this study are male Swiss mice, aged 2-4 months, body weight of 25-35 grams, in healthy conditions, normal blood glucose levels and with no anatomical or physiological abnormalities. Sampling was done using simple random sampling technique.

There were five treatment groups in this study, and each group used five male Swiss mice. Each groups adhere to the principle of 3R (Replacement, Reduction and Refinement). Negative control group (K1): mice given *ad libithum* drinking water, positive control group (K2): mice given *streptozotocin* dose of 200

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mg/kgBW intraperitoneally, treatment group 1 (P1): mice given *streptozotocin* dose of 200 mg/kgBW intraperitoneally and antlions extract of 14 mg/kgBW/day orally for 28 days, treatment group 2 (P2): mice given *streptozotocin* dose of 200 mg/kgBW intraperitoneally and antlions extract of 28 mg/kgBW/day orally for 28 days, treatment group 3 (P3): mice given *streptozotocin* dose of 200 mg/kgBW intraperitoneally and antlions extract of 56 mg/kgBW/day orally for 28 days.

The analysis data using Shapiro-Wilk normality test was performed. The analysis then continued, to see the effect of streptozocin injection on the blood glucose level, the Mann-Whitney U test were performed. To see the effect of administration of Antlions extract on the blood glucose level within time series, the Repeated ANOVA were used for the data that normally distributed, and the Friedman Test for the data is not normally distributed. To see the comparison of blood glucose levels on the day 28, the One Way ANOVA followed by Games Howell post-hoc analysis were used and the Kruskal-Wallis analysis continued with the Mann-Whitney test were used to compare the blood glucose levels on the day 21.

RESEARCH RESULTS

Research Sample Characteristics

The total number of samples in this study are 30 experimental animals which were male Swiss mice, divided into 5 groups where each groups consisted of 5 experimental animals and 1 reserve experimental animal. The average weight of the mice are included in table 1. This table shows that the average weight of the mice is 28.80 – 30.60 gram. And from the table, it can be proven that there is no weight difference found between those groups with p>0.05.

Table 1. Average weight of male swiss mice

Groups	Average weight±SD (gram)	P value
Group K1	29.60 ± 1.949	0.758*
Group K2	29.40 ± 2.191	0.607*
Group P1	30.60 ± 2.408	0.787*
Group P2	30.00 ± 2.739	0.833*
Group P3	28.80 ± 2.280	0.814*

Note: * Normal (p > 0.05); [£] Shapiro-wilk

Inferential Analysis

The Effect of Streptozotocin Injection towards the Blood Glucose Level of Male Swiss Mice

The result of the inferential analysis shows the blood glucose level on day-3 after the injection of streptozotocin in table 8, as follows:

Table 2. The analysis result of streptozotocin injection towards the blood glucose level

GD	K2	P1	P2	P3
Day 3 [a)]				
K1	0.009*	0.009*	0.009*	0.009*

Note: * Significant (p < 0.05); [a)] Mann-Whitney

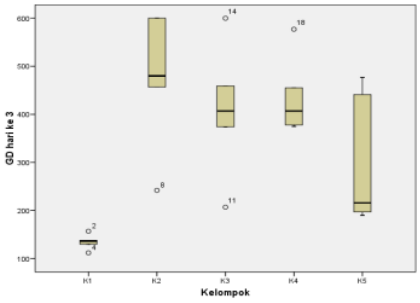

Figure 1. Streptozotocin injection towards blood glucose level

According to that table, it can be known that there is a significant difference in the average of blood glucose level between the negative control group (K1) and the positive control group (K2), treatment group 1 (P1), treatment group 2 (P2), treatment group 3 (P3) on the third day, meaning that the injection of streptozotocin dosed 200 mg/KgBW intraperitoneally had an effect towards the blood glucose level in male Swiss mice.

The Effect of Administration of Antlions Extract towards the Blood Glucose Level of Male Swiss Mice

The serial blood glucose level in each groups on day 3, day 21, and day 28 is included in table 3, as follows:

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Table 3. Analysis result of the administration of antlions extract towards blood glucose level on day 3, 21, and 28

GD	Day 3	Day 21	Day 28	p
K1	134.60 ± 16.18	112.20 ± 12.70	119,20 ± 19,10	0,006¶*
K2	475.80 ± 146.53	517.00 ± 129.30	546,00 ± 55,59	0,549†
P1	409.40 ± 142.31	600.00 ± 0.00	265,60 ± 32,25	<0,001¶*
P2	438.40 ± 83.87	519.00 ± 109.27	408,80 ± 216,74	0,210¶
P3	304.20 ± 142.20	376.80 ± 230.57	212,00 ± 158,53	0,015†*

Note: * Significant ($p < 0,05$); ¶ Repeated ANOVA; † Friedman

Based on that table, it can be known that there was a significant decrease of blood glucose level in the negative control group (K1), P1, and P3 from day 3 up to day 28. Meanwhile, there was no significant decrease of blood glucose level in the positive control group (K2) and P2.

Blood Glucose Level Comparation between Groups

The results of difference test of blood glucose level between groups injected by streptozotocin on day 21 and 28 is included in table 4 below:

Table 4. Comparation analysis result of blood glucose level between groups

GD	K2	P1	P2	P3
Day 21 [a)]				
K2	–	0.054	0.914	0.451
Day 28 [b)]				
K2	–	<0.001*	0.670	0.034*

Note: * Significant ($p < 0.05$); [a)] Mann-Whitney; [b)] Post Hoc Games-Howell

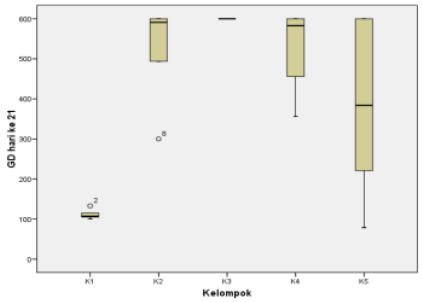

Figure 2. Blood glucose level comparation between groups on day 21

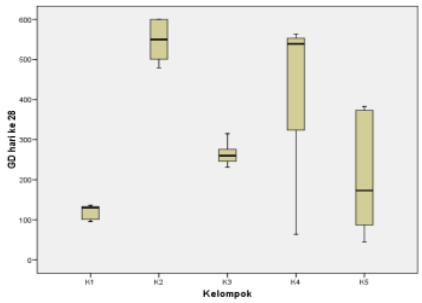

Figure 3. Blood glucose level comparation between groups on day 28

Based on table 5, it can be proven that on the 21st day there was no significant difference in blood glucose level between group K2 with all treatment groups (P1, P2, and P3). Meanwhile, on the 28th day there was a significant blood glucose level difference found between group K2 with P1 and P3, but now between K2 and P2.

Blood Glucose Comparation between Varying Doses in Treatment Group 1 (P2), Treatment Group 2 (P2), and Treatment Group 3 (P3) on Day 21 and Day 28

Table 5. Comparation Analysis Result of Blood Glucose Level between Treatment Groups

GD	K2	P1	P2	P3
Day 21 [a)]				
P1		-	0.054	0.054
P2			–	0.451
Day 28 [b)]				
P1		–	0.628	0.936
P2			–	0.518

Note: * Significant ($p < 0.05$); [a)] Mann-Whitney; [b)] Post Hoc Games-Howell

There was no significant difference found in the average blood glucose level between varying doses administration of antlions extract in treatment group 1 (P1), treatment group 2 (P2), and treatment group 3 (P3) on the 21st and 28th day proven by $p>0.05$.

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DISCUSSION

This study aimed to determine the effect of antlions extract 14 mg/kgBW, 28 mg/kgBW, and 56 mg/kgBW orally by the blood glucose level in male Swiss mice induced by streptozotocin. The blood glucose levels in normal mice ranged from 62.8 mg/dl - 176 mg/dl.[6] Based on the difference test between the negative control group (K1) which was only being fed, and the other groups (K2, P1, P2, P3) induced by streptozotocin 200 mg/kgBW, there was a significant increase of blood glucose level on day 3. This increase of blood glucose level in the male Swiss mice was caused by the induction of streptozotocin. Streptozotocin is an antibiotic synthesized from *Streptomycetes achromogenes*, widely used for inducing diabetes mellitus in experimental animals characterized by hyperglycemia after injection.[7] Streptozotocin has a cytotoxic effect on pancreatic β cells which is due to an increase in ROS, nitric oxide production, oxidative stress and mitochondrial dysfunction, thereby causing a decrease in insulin secretion and the increase of blood glucose level.[8]

The result of difference test, which was performed by comparing the positive control group (K2) and treatment group 1 (P1), showed that there was no decrease of blood glucose level on the 21st day proven by a value of 0.054. Whereas, there was a significant decrease on the 28th day proven by p value <0.00, meaning that the administration of 14 mg/kgBW antlions extract can cause the most significant decrease of blood glucose level on the 28th day as compared to the positive control group (K2). Meanwhile, the comparison between the positive control group (K2) and treatment group 2 (P2) did not show any significant decrease shown by p>0.05 on day 21 and 28, meaning that there was no significant decrease of blood glucose level in treatment group 2 (P2) administered with 28 mg/kgBW antlions extract on day 21 and 28. Comparison between the positive control group (K2) and treatment group 3 (P3) did not show any significant decrease of blood glucose level on the 21st day proven by p=0.451. While on the 28th day, there was a significant decrease of blood glucose level in male Swiss mice administered with 56 mg/kgBW antlions extract proven by p=0.034.

The comparison between varying doses in treatment group 1 (P1), treatment group 2 (P2), and treatment group 3 (P3) on the 21st and 28th day showed that there was no significant decrease in blood glucose level. This may be because blood glucose level correction hadn't took place yet, due to the spontaneous reversibility of pancreatic beta cells after being induced by streptozotocin. This is in line with a researched conducted by Zulkarnain (2013) that showed no correction on the average blood glucose level by the end of the 12th week post-induction of streptozotocin.[9] Meanwhile, a study conducted by Hartmann et al. showed that 70% of mice induced with low dose streptozotocin underwent blood glucose level correction and insulin secretion after 15 weeks. Based on a research by Prihatin Jekti, it can be known that the comparison between doses 2.5, 7.5 and 10 mg/kg are significant in lowering blood glucose level, but there was no significant differences between those doses.[10]

From this study, it can be known that treatment group 1 (P1) is the group that had the most significant decrease of blood glucose level on the 28th day seen from its p value <0.001, smaller than p value =0.0034 in treatment group 3 (P3). This result is in line with a research conducted by Tyas Kurniasih (2006) which showed that the administration of antions juice dosed 0.01 mg/200 g mice body weight can lower the blood glucose level in hyperglycemic mice (p<0.05). That dose was the smallest dose in her research.[5]

The result of another research done by Mufidah (2011) about the effect of antlions extract towards the lowering of blood glucose level in mice showed that 10 mg/kgBW antlions extract is effective in decreasing the blood glucose level in mice.[11] This is similar with a study by Prihatin Jekti et al (2019) which mentioned that mice being administered with antlions extract dosed 10 mg/kg can most significantly lower the blood glucose level.[12]

Meanwhile, in the results of this study, the administration of 28 mg/kgBW antlions extract (P2) in male Swiss mice did not cause any significant decrease in blood glucose level, and this may happen due to blunders during the administration of antlions extract through the feeding tube, thus resulting in defective intake of the extract.

Antlions contain sulfonylureas which is a substance that functions for expediting the pancreas

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in producing insulin. Sulfonylurea is the most commonly used Oral Hypoglycemic Drug (OHD), where this class of drugs has the main effect of increasing insulin secretion by pancreatic beta cells.[13] Sulfonylureas can hinder glycogenolysis and gluconeogenesis, as well as stimulate glycogenesis and the glycolytic pathway by regulating *phosphofructokinase-2* or *fructose2,6-biphosphatase* and *phosphoenolpyruvate carboxihase*. It can also decrease glucagon and the concentration of free fatty acid in the plasma, thus contributing towards insulin sensitivity in the body.[14,15] Sulfonylureas contained in antlions works in stimulating insulin secretion from granules of pancreatic Langerhans β cells. The stimulation done through interactions with ATP-sensitive K channels on the membrane of β cells which then cause membrane depolarization that will open the Ca cannal. With the opening of the Ca canal, Ca^{2+} ions will enter the β cells, stimulate insulin-filled granules and insulin secretion will occur with an amount equivalent to the C-peptides.[16]

CONCLUSION

The administration of antlions extract of 14 mg/kgBW and 56 mg/kgBW had an effect in lowering blood glucose levels in mice with diabetes mellitus on the 28th day, while the administration of antlions extract of 28 mg/kgBW had no significant effect in lowering blood glucose levels in mice with diabetes mellitus on the 28th day. In addition, the administration of antlions extract with a dose of 14 mg/kgBW had a better effect in lowering blood glucose levels as compared to administration of a dose of 28 mg/kgBW and 56 mg/kgBW in mice with diabetes mellitus.

SUGGESTION

Future studies are expected to conduct further research on the active substances contained in antlions extract both qualitatively and quantitatively so that the bioavailability can be verified along with the discovery of active substances that play the most role in lowering blood glucose levels. It is also recommended to conduct a research with longer period of time to determine the effectiveness of antlions extracts in lowering blood glucose levels.

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