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Effect of Giving Papaya Leaf Extract (*Carica Papaya L.*) on Changes in Fasting Blood Glucose in Male Wistar Rats (Rattus Norvegicus) Induced by Streptozotocin

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ABSTRACT

Background: Diabetes mellitus is a disease characterized by an increase in blood glucose levels due to decreased insulin production or decreased insulin action. Diabetes cases are described as a serious problem globally in the 21st century and cases are increasing worldwide. One type of plant that can be used as a medicine is papaya leaf (*Carica papaya L.*) which is known to contain several active compounds such as flavonoids, saponins, tannins, and alkaloids.

Objective: To determine the effect of papaya leaf extract (*Carica papaya L.*) on changes in fasting blood glucose levels of male Wistar rats with hyperglycemia conditions.

Methodology: This research is an experimental research Randomized Controlled Trial (RCT) with Pretest-Postest Group Design study design. This study used 35 male white rats which were divided into 5 groups. Group I (without treatment), group II (STZ-NA), group III (STZ-NA and Glimepiride), group IV (papaya leaf extract at a dose of 150mg/Kg), group V (papaya leaf extract at a dose of 200mg/Kg). The data obtained after the study will be tested for normality which is then continued with non-parametric tests using the Kruskal-Wallis and Mann-Whitney U tests, and an effect size test is carried out to determine how much effect is produced from the papaya leaf extract given.

Research Results: The administration of papaya leaf extract at a dose of 200mg/200grBody Weight in male Wistar rats in group 5 proved to reduce fasting blood glucose levels more significantly than the administration of glimepiride at a dose of 0.04 mg and papaya leaf extract at a dose of 150mg/Kg.

Conclusion: Administration of papaya leaf extract (*Carica papaya L.*) can reduce fasting blood glucose levels in diabetic model rats effectively at a dose of 200mg/Kg.

KEYWORDS: Carica Papaya L, Diabetes, Blood Glucose

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INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterised by elevated blood glucose levels associated with impaired metabolism of fats, carbohydrates and proteins as well as reduced insulin secretion, decreased insulin action or both (WHO, 2019). Diabetes cases are described as a serious health problem globally in the 21st century and cases are increasing worldwide (Marsha L. Tracey *et al*., 2016). Indonesia had one of the highest absolute prevalence worldwide in 2019 with 10.7 million people with diabetes and is expected to increase to 16.6 million by 2045 (Hidayat *et al*., 2022). Typical clinical symptoms of diabetes mellitus include eating a lot (*polyphagia*), drinking a lot (*polydipsia*), and frequent urination (*polyuria*). Diabetes management itself is carried out with the aim of eliminating complaints, signs of diabetes, preventing complications, and reducing mortality and morbidity (Fatimah, 2015). Pharmacological therapy is carried out to obtain good glucose levels balanced with non-pharmacological therapy (Chaudhury *et al*., 2017).

Glimepiride is a class of sulfonylureas that can reduce blood glucose levels. Glimepiride, like other sulfonylureas, can cause abdominal pain, vomiting and

diarrhoea and increase insulin secretion which can lead to hypoglycaemia (Trerattanavong & Tadi, 2023). Management using alternative medicine is an innovation in the development of anti-diabetic drugs without side effects. One of the plants that can be utilised as an anti-diabetic drug is papaya (Solikhah *et al*., 2020). Papaya leaf extract (*Carica Papaya L.*) contains several antioxidant compounds such as alkaloids, glycosides, tannins, saponins, and flavonoids (Singh *et al*., 2020). In the study of Isela Esther Juárez-Rojop and friends mentioned that oral administration of papaya leaf extract (*Carica Papaya L.*) can induce a significant decrease in glucose levels in diabetic rats (Juárez-Rojop *et al*., 2014).

The purpose of this study was to prove that papaya leaf extract has a hypoglycaemic effect on fasting blood glucose of male wistar rats induced with streptozotocin. This study analysed the effect of papaya leaf extract (*Carica Papaya L.*) at a dose of 150mg/Kg and 200mg/Kg on changes in fasting blood glucose levels in male Wistar rats.

RESEARCH METHODS

This study was conducted at the Surabaya University Faculty of Medicine Laboratory after obtaining an ethical eligibility letter from the Surabaya University ethics committee with number 348/KE/II/2024 on 28 February 2024. This study uses an experimental method conducted *Randomized Controlled Trial* (RCT) with pretest-posttest Group Design conducted on experimental animals, 35 rats. The criteria for rats in this study were male Wistar rats (Rattus Norvegicus) weighing between 200 to 250 grams, aged 2 to 3 months, had never been used as a research sample, healthy condition, active movement and no anatomical abnormalities.

The samples were divided into 5 groups that received various treatments, namely group I which is a normal group without treatment, group II which is a negative group with STZ-NA administration, group III is a positive control group given STZ-NA, group IV given STZ-NA and papaya leaf extract at a dose of 150mg/Kg, and group V given STZ-NA and papaya leaf extract at a dose of 200mg/Kg. Adaptation in experimental animals was carried out for fourteen days, on the fifteenth day groups II, III, IV, and V were given STZ at a dose of 65mg/Kg and NA at a dose of 230mg/Kg via intraperitoneal injection. Before being induced with STZ-NA, the blood glucose level was checked first, which was taken through the tail vein of the rat. Rats that have high blood sugar levels will not be given STZ-NA injection and are not included in the study. On the twenty-fifth day, papaya leaf extract was given at various doses to groups IV and V. Before the administration of papaya leaf extract on the twenty-fifth day, blood sugar levels were checked to determine any disturbances in pancreatic function, the administration of extracts was carried out until the thirty-eighth day.

At the end of the study (day thirty-eighth), termination or euthanasia was carried out using CO2 inhalation where the experimental animals would be put into an airtight container and then given CO2 gas so that the experimental animals would lose consciousness. Data processing and data analysis using SPSS software version 26. *Shapiro-Wilk* normality test was performed. The results of data analysis found that the data were not normally distributed, therefore the *Kruskal-Wallis* non-parametric test was carried out which was then continued with the *Mann-Whitney U* test and the *Effect Size* test.

RESULTS

The following (Table 1) is the ratio of fasting blood glucose (FBG) levels in each group

Table 1. ***Fasting Blood Glucose (FBG) Ratio in Each Group***

FBG	Group	Mean ± SD	Minimum	Maximum
1	I	95.86 ± 9.754	85	112
	II	98.00 ± 9.832	83	113
	III	100.86 ± 13.447	84	126
	IV	98.86 ± 9.263	87	116
	V	96.29 ± 13.035	82	119
2	I	95.57 ± 12.713	73	114
	II	339.57 ± 223.310	130	601
	III	352.57 ± 130.853	127	446
	IV	358.14 ± 157.599	141	601
	V	364.43 ± 216.244	142	601
3	I	90.14 ± 10.558	73	103
	II	252.00 ± 181.334	89	601
	III	308.43 ± 160.243	131	601
	IV	313.57 ± 117.460	154	460
	V	433.86 ± 225.831	108	601

Following in Table 2 are the results of data analysis for the normality test (*Saphiro-Wilk*) for each group.

Table 2: ***Normality Test Results***

FBG	Group I	Group II	Group III	Group IV	Group V
1	0,714	0,564	0,502	0,724	0,571
2	0,883	0,033	0,013	0,983	0,050
3	0,666	0,157	0,415	0,288	0,007

The results of the *Saphiro-Wilk* test obtained several results indicating that the test value was p> 0.05 and some data stated that p < 0.05 which means that there is inequality in the research group, so it is stated that the distribution in this study is not normal.

Table 3: ***Kruskal-Wallis Test Results***

Group	Results
I	0,488
II	0,004
III	0,001
IV	0,001
V	0,002

In Table 3, it can be seen that the results of the Kruskal-Wallis test obtained a p value> 0.05 in group I, which means that there is no difference in the fasting blood glucose test in group I. Kruskal-Wallis test results in groups II, III, IV, and V obtained p < 0.05 which means there is a difference in each fasting blood glucose level check that has been done.

Table 4: ***Mann-Whitney U Test Results Fasting Blood Glucose (FBG) 1 and 2***

Group	Results
I	0,848
II	0,002
III	0,002
IV	0,002
V	0,002

In Table 4, it can be seen that the results of the Mann-Whitney U test for fasting blood glucose 1 and 2 in group I showed p> 0.05, which means that there was no significant difference in the results of fasting blood glucose tests 1 and 2 that had been carried out. The results of the fasting blood glucose test 1 and 2 in groups II, III, IV, and V obtained the results of p < 0.05, which means that there is a significant difference in the results of fasting blood glucose tests 1 and 2.

Table 5: ***Mann-Whitney U Test Results Fasting Blood Glucose (FBG) 1 and 3***

Group	Results
I	0,276
II	0,018
III	0,002
IV	0,002
V	0,004

In Table 5, it can be seen that the results of the Mann-Whitney U test for fasting blood glucose 1 and 3 in group I showed p> 0.05, which means that there was no significant difference in the results of fasting blood glucose tests 1 and 3 that had been carried out. The results of the fasting blood glucose test 1 and 3 in groups II, III, IV, and V obtained the results of p < 0.05, which means that there is a significant difference in the results of fasting blood glucose tests 1 and 3.

Table 6: ***Mann-Whitney U Test Results Fasting Blood Glucose (FBG) 2 and 3***

Group	Results
I	0,336

II	0,480
III	0,338
IV	0,655
V	0,844

In Table 6, it can be seen that the results of the Mann-Whitney U test for fasting blood glucose 2 and 3 in groups I, II, III, IV, and V obtained p> 0.05, which means that there is no significant difference in the results of fasting blood glucose 2 and 3 that have been carried out.

Table 7: ***Effect Size Test Results***

Group	Results (Cohen's D formula)
I and II	1.021641
II and III	0.138093
II and IV	0.155376
II and V	0.327714
III and IV	0.018293
III and V	0.225226
IV and V	0.211056

Table 7 shows the comparison results of the Effect Size test between groups. In the comparison of groups I and II, there was a large effect in group II on the incidence of diabetes in experimental animals. In the comparison between groups II and III, the administration of glimepiride in group III could not have an effect on improving fasting blood glucoe. In the comparison between groups II and IV, the administration of the extract at a dose of 150mg/Kg in group IV could not have an effect on improving fasting blood glucose. In the comparison between groups II and V, the administration of extracts at a dose of 200mg/Kg in group V had the greatest effect which was classified as small on improving fasting blood glucose. In the comparison of groups III and IV can not provide an effect on the improvement of fasting blood glucose. In the comparison of groups III and V, group V can have a relatively small effect on improving fasting blood glucose. In the comparison of groups IV and V, the administration of extracts in group V can have a small effect on improving fasting blood glucose.

DISCUSSION

In Table 1, it can be seen that the fasting blood glucose ratio in each group is found to increase blood sugar levels or hyperglycaemia. The highest fasting blood glucose levels were found in groups II, IV, and V at the 2nd fasting blood glucose measurement after STZ-NA induction and in groups II, III, and V at the 3rd fasting blood glucose level examination which had a value of 601, with the lowest value in the treatment group found in group II with a value of 89 and followed by group V with a value of 108. In group II, the average FBG was 339.57 ± 223,310, group III with an average of 352.57 ± 130,853, group IV 358.14 ± 157,599, and group V 364.43 ± 216,244. This is also supported by the results of the second FBG examination in group I or the group not given STZ-NA induction which has an average value of 95.57 ± 12.713. This shows that STZ has a hyperglycaemic effect with a mechanism of action that induces inflammation of the pancreatic islets of Langerhans so that the destruction of pancreatic beta cells occurs, the hyperglycaemic effect appears in a few days later depending on the effect on GLUT-2 in rat pancreatic beta cells which will then stimulate the T cell activation pathway (Harijanto & Dewajanti, 2017). In this study, glimepiride was given at a dose of 0.04mg/200gr for 14 days, obtained an average FBG in group III of 308.43 ± 160.243 after glimepiride administration was carried out with an average value of 352.57 ± 130.853 before glimepiride was given and the Mann Whitney U test was calculated with the results of p = 0.338 and the Effect size test to determine how much effect glimepiride produced on rats given STZ-NA obtained the results of the effect size test with a value of 0.138093. All of these tests showed that there was no significant difference in the FBG levels of group III after being given glimepiride for 14 days.

The effect of papaya leaf extract administration in this study can be seen through the results of fasting blood glucose level tests that have been carried out in group IV and group V. It is known that the dose given to group IV is 150mg/Kg and in group V is 200mg/Kg. The results of the FBG level test that has been carried out show an average in group IV of 313.57 ± 117.460 with an average value when given STZ-NA of 358.14 ± 157.599, which is continued with the Mann Whitney U test with the results of group IV which is p=0.655 and the effect size test using the cohen's d formula which has a result of 0.155376. It can be concluded that the administration of papaya leaf extract at a dose of 150mg/Kg does not have good results to help reduce fasting glucose levels in rats that have been induced by STZ-NA. In group V, the results of the FBG test obtained an average of 433.86 ±

225.831 and had an average value of fasting glucose levels of 364.43 ± 216.244 when rats were given STZ-NA induction without giving papaya leaf extract, then continued the test using Mann Whitney U obtained the results of p = 0.844 and the effect size test using the cohen's d formula which had a result of 0.327714. It can be concluded that the administration of papaya leaf extract at a dose of 200mg/Kg has a small effect in helping to reduce fasting blood glucose levels in male Wistar rats that have been induced by STZ-NA. This is in accordance with previous research conducted by Ismukada, et al (2020) which said that the optimal dose of papaya leaf extract in helping to reduce blood glucose levels was 1000mg/Kg.

Previous literature has mentioned that carica papaya has bioactive compounds such as alkaloids, flavonoids, tannins, saponins, glycosides, and triterpenoids in phytochemical screening of etaol extract of carica papaya leaves (Roy *et al*., 2022). Papaya exhibits protective properties against diabetes-induced beta cell damage (Nyakundi & Yang, 2023).

CONCLUSION

It was found that Streptozotocin at a dose of 65mg/Kg can create a state of hyperglycaemia in rats. The administration of papaya leaf extract (*Carica Papaya L.*) has a hypoglycaemic effect that can reduce fasting blood glucose levels which can be seen in the results of the Effect Size test that papaya leaf extract (*Carica Papaya L.*) at a dose of 200mg/Kg is more effective in reducing fasting blood glucose levels than a dose of 150mg/Kg. In this study, histopathological examination of the pancreas organs of Wistar rats was not carried out. Suggestions for further research are histopathological examination of pancreatic organs from experimental animals so that it can be seen whether there is an improvement in pancreatic beta cell function by giving papaya leaf extract. Further research needs to be done related to the main active compounds in papaya leaf extract (*Carica Papaya L.*) in reducing or overcoming the condition of diabetes mellitus

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