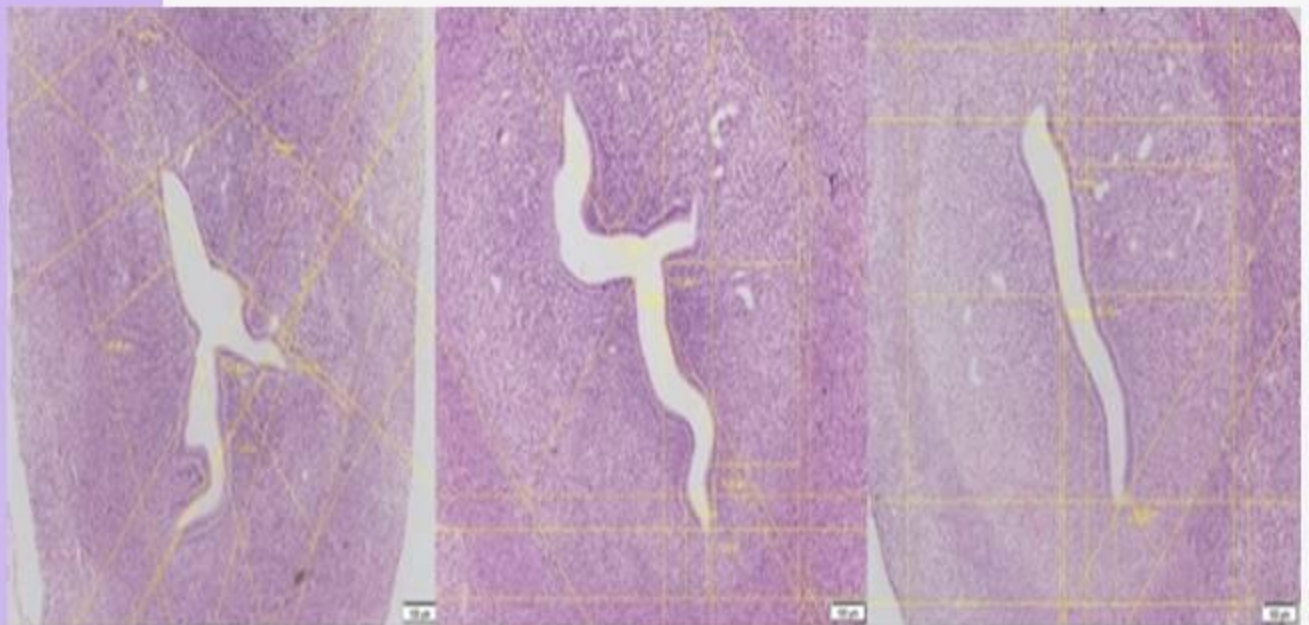


VOLUME 2 NO. 1 JUNE 2021

e-ISSN: 2746-4474

INDONESIAN ANDROLOGY AND BIOMEDICAL JOURNAL



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Effect of Kembang Bulan Leaf (*Tithonia diversifolia*) Ethanolic Extract to SGOT and SGPT Levels in Diabetic Rats (*Rattus norvegicus*)

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Received: April 2, 2021; Received in revised form: June 4, 2021;

Accepted: June 7, 2021; Available online: June 11, 2021

ABSTRACT

Introduction: Kembang Bulan (*Tithonia diversifolia*) is one of Indonesian traditional medicine that contains saponins, flavonoids, and, tannins and is predicted has a lowering effect on blood-glucose. Diabetes mellitus (DM) is a disease caused by insufficient insulin secretory by the pancreas or ineffective usage of insulin that produced by the body thus cause a hyperglycemia condition. Hyperglycemia can cause an increase in Reactive Oxygen Species which can cause free radicals. Free radicals can cause damage to liver cells.

Method: This was an experiment with *posttest control group design*. Samples were 40 rats, divided into five different groups (P1, P2, P3, P4 and P5). Each group were induced by multiple low doses STZ. P1 (give the extract of *Tithonia diversifolia* at a dose 50 mg/100 gr BB), P2 (give the extract of *Tithonia diversifolia* at a dose 150 mg/100 gr BB), and P3 (give the extract of *Tithonia diversifolia* at a dose 450 mg/100 gr BB), P4 was treated with metformin, P5 was not treated. After STZ induction and give the extract to diabetic rat model, the resulting liver cell damage will be measured using the SGOT and SGPT measurement methods.

Result: On the average results of SGOT levels in the five treatments, using the ANOVA test p value was 0.877 ($p > 0.05$) which means there were no significant differences. Furthermore, on the average results of SGPT levels in all five treatments, using the ANOVA test p value was 0.822 ($p > 0.05$) which means there were no significant differences. But from all results obtained P4 (given metformin) with the results closest to normal levels (SGOT: 197.5 ± 37.25 ; SGPT: 90.33 ± 29.36). From the treatment given *Tithonia diversifolia* extract obtained P1 (with a dose of 50 mg / 200gr BB) with the results closest to normal levels compared to P2 and P3.

Conclusion: The Extract of kembang Bulan Leaf (*Tithonia diversifolia*) obtained less significant results compared to the untreated group. However, there is no significant difference. And giving ethanol extract of the leaves of kembang Bulan (*Tithonia diversifolia*) at a dose of 50 mg / 100gr BB is the most effective way to reduce levels of SGOT and SGPT.

Keywords: Diabetes Mellitus, *Tithonia diversifolia*, Streptozotocin Induced, Rat, Transaminase Enzyme

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INTRODUCTION

Diabetes Mellitus (DM) is a disease caused by metabolic disorders. This disorder happened because the pancreas cannot produce insulin hormone. If the insulin hormone decreases, it can be ascertained that blood sugar levels in the body will increase.¹ In Indonesia, based on the prevalence of DM in 2013, Diabetes mellitus is a chronic disease that can cause death if the system is not managed correctly. The management system for diabetes mellitus includes the provision of therapy, both drug and non-drug therapy.²

There are many long-term complications of diabetes mellitus that can occur such as retinopathy with potential loss of vision, nephropathy that causes kidney failure, peripheral neuropathy with risk of foot ulcers, and autonomic neuropathy that causes gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. Diabetics have an increased incidence of cardiovascular atherosclerosis, peripheral arteries, and cerebrovascular disease.³ Type 2 diabetes mellitus can also be found in non-alcoholic fatty liver disease or NAFLD.⁴ The condition of hyperglycemia can cause the metabolic pathway of the polyol to be activated, glycation of proteins and glucose oxidation. These changes can accelerate the generation of reactive oxygen species (ROS) and result in increasing oxidative lipid modification, DNA and protein in various tissues. In other words, it can increase the formation of oxidative stress which can make an increase in lipid peroxidation and can affect the complications of diabetes mellitus.⁵

ROS (*Reactive Oxygen Species*) can increase the free radicals in the body. Free radicals can destroy tissue in the body, including liver cells.⁶ Liver is an organ which

can neutralize toxic substances that enter the body and is the target of increasing free radical concentration.⁷ SGOT and SGPT are transaminase enzymes which are produced by liver cells. Both of these enzymes can increase if there is damage to the cell.⁸

In therapeutic treatment, diabetes mellitus can be treated with metformin. Metformin is an oral hypoglycemic drug, an antidiabetic drug. Certainly, every drug, including metformin, has side effects such as nausea, vomiting, diarrhea, abdomen disorders, and anorexia. People who cannot tolerate these side effects will require an alternative drug for diabetes mellitus.⁹

Metformin has been used successfully since the 1950s as first line pharmacotherapy to treat people with type 2 diabetes. It is a biguanide that decreases blood glucose concentration by mechanisms different from those of insulin secretagogues, such as sulphonylureas, or exogenous insulin therapy. Metformin lowers, rather than increases, fasting plasma insulin concentrations and acts by enhancing insulin sensitivity, inducing greater peripheral uptake of glucose, and decreasing hepatic glucose output. By reducing hepatic glucose output it lowers blood glucose and insulin levels with minimal risk of hypoglycaemia, and when used as monotherapy can lower HbA1c by around 1.5%.¹⁰

Tithonia diversifolia or kembang bulan is one of the herbs that grow in Indonesia. ethanol extract of *Tithonia diversifolia* can reduce blood sugar concentration.¹¹ Based on the result of the phytochemical screening of the kembang bulan's ethanol extract, the screening results state that it contains Saponin, Tannin, and Flavonoids.¹²

METHODS

2.1 Design of the Study

The design of this study was carried out by experimental methods: Posttest only control group design while the selection of research objects for grouping and administering treatment using CRD (Complete Random Design) with 5 treatment groups:

P1 = Group of diabetic rats model which received the kembang bulan leaf extract therapy at a dose of 50 mg/100grBB.

P2 = Group of diabetic rats model which received the kembang bulan leaf extract therapy at a dose of 150 mg/100grBB.

P3 = Group of diabetic rats model which received kembang bulan leaf extract therapy at a dose of 450 mg/100grBB.

P4 = Group of diabetic rats model which received metformin therapy at a dose of 9 mg/200grBB.

P5 = Group of diabetic rats model which received no therapy (receive only a vehiculum).

2.2 Materials

The material used in the extraction process is the Kembang Bulan Plant (*Tithonia diversifolia*) which is obtained from the Balai Materia Medika, Batu. As thick as 300 grams and has undergone plant determination. The part of the plant taken is the leaves. The extraction process is done by maceration method.

The material used in the in vivo test is healthy experimental animal male rat (*Rattus norvegicus*) wistar strain which have never been used as experimental material. The age range 2-3 months with an average weight of 180 gr. The experimental animals were obtained from UGM Try Animal Unit.

Chemicals in this study include ether, 70% alcohol, Aquadestilata, carboxyl methyl

cellulose sodium, phosphate buffer saline, formaldehyde, Metformin, Streptozotocin, and Immunochemistry Kit.

2.3 Acclimatization

Acclimatization is a process of maintaining experimental animals (Wistar Rat) with the same conditions which aim of adjusting the environment, controlling the health and weight and homogenizing the food. Acclimatization is carried out for 1 week. If the experimental animals are sick, die, or lose more than 10% of weight, the animal will be excluded from the study.

2.4 Making kembang bulan leaf Ethanolic Extract (*Tithonia diversifolia*)

Kembang bulan leaves are dried at room temperature and may not be exposed to direct sunlight. Flower leaves are then powdered using a pollinating machine. The extraction process is carried out by weighing 300 grams of kembang bulan leaf powder, and then gradually soaked with 70% ethanol as much as 1 liter in a closed vessel. The soaking is often stirred and left for 24 hours. The immersion is filtered with a Buchner funnel. The filtrate obtained is evaporated by the ethanol content with rotavapour until it forms a paste. The paste form filtrate is ethanol extract of Kembang bulan leaves.

2.5 Diabetic Rat Model

The type of diabetes in the diabetic rat model for research is Diabetes Mellitus Type 2, to make this experimental model a low dose of STZ induction is required.¹³ The STZ dose is 150 mg/Kg BB. The STZ solution is made by diluting STZ with a citric solution according to the prescribed dose. STZ solution injected as much as 0.2 ml. The solution was made 20

minutes before induction. Rat fasted for 4 hours beforehand. Before induction begins to empty the stomach and reduce the risk of aspiration. Rat were injected with STZ solution according to intraperitoneal doses. Then they were given 10% sucrose solution and 10% dextrose throughout the first night after induction to avoid sudden hypoglycemic post. Significant hyperglycemia will occur two days after the induction. Blood sugar levels are calculated using a glucometer. Rat are declared DM if blood sugar levels ≥ 200 mg/dl.

2.6 Treatment

40 diabetic rats model were divided randomly into 5 groups. The first group (P1) was a group of diabetic rats model which was received ethanol extract of kembang bulan leaf at a dose of 50 mg/100gr BB. Group 2 (P2) received ethanol extract of kembang bulan leaf at a dose of 150 mg/100gr BB. Group 3 (P3) received ethanol extract of kembang bulan leaf at a dose of 450 mg/100gr BB. Group 4 (P4) received metformin at a dose of 9 mg/200gr BB. Group 2 (P2) did not get the vehiculum (aquadest and CMC Na 1%). Ethanol extract given to rat in the form of suspension. Suspensator used is carboxymethyl cellulose sodium (CMC Na) of 1%. Ethanol extract of leaves of Kembang Bulan and metformin are given once a day, for 14 days.

2.7 The Examination of SGOT and SGPT Levels

On day 15 diabetic rats model was dissected and blood was collected. Then the blood was centrifuged 3000 rpm for 15 minutes. Serum was taken to test the levels of SGOT and SGPT using a reagent kit and the results were seen through Pentra C 200 reader.¹⁴ The rats that have been sacrificed will be subjected to

histopathological examination of their organs and was part of other research.

2.8 Data Analysis

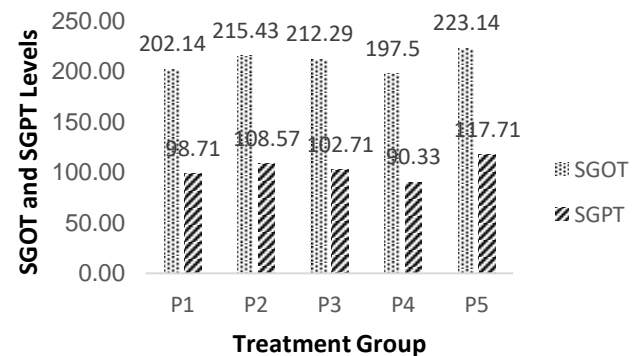
Data Test results of SGOT and SGPT levels were analyzed using ANOVA test ($\alpha = 0.05$) with the help of SPSS Statistics for Windows software and then described in the form of tables and graphs.

RESULTS

This research was conducted in August-October 2017 with the number of samples based on Federer's formula of 6 each group, but in practice 34 diabetic rats model were included in the study.

Picture 1. Average Result of SGOT and SGPT Levels

Source : research data, processed



The average SGOT level in the treatment group 1 was 202.14 ± 41.31 , in the treatment group 2 was 215.43 ± 43.22 , in the treatment group 3 was 212.29 ± 57.99 , in the treatment group 4 was 197.5 ± 37.25 , whereas in treatment 5 the average SGOT level was obtained at 223.14 ± 57.46 . From the results of the average SGOT levels, differences were

found between rat given kembang bulan leaf extract (in treatments 1,2 and 3), diabetic rats model given metformin and diabetic rats model which were not treated at all (in treatment 5). The results obtained shows that in diabetic rats model given extract kembang bulan leaves have a smaller average yield compared to non-treated diabetic rats model but were not better than ~~rat~~ diabetic rats model given metformin.

The average SGPT level in the treatment group 1 was 98.71 ± 44.17 , in the treatment group 2 was 108.57 ± 48.85 , in the treatment group 3 was 102.71 ± 39.75 , in the treatment group 4 (with given metformin dose of 9 mg / 200gr BB) was 90.33 ± 29.36 . In treatment 5, the average SGOT level was found to be 117.71 ± 47.77 . From the results of the average SGOT levels, differences were found between diabetic rats model given kembang bulan leaf extract (in treatments 1, 2 and 3), diabetic rats model given metformin and non-treated diabetic rats model (in treatment 5), the results obtained shows that rat given extract kembang bulan leaves have a smaller average yield compared to non-treated diabetic rats model but were not better than rat given metformin.

3.1 Normality Test

Table 1. Normality test using K-S sample

	p-value	Notes
SGOT	0,952	Normal
SGPT	0,153	Normal

Source : research data, processed

Based on the results of normality test using the K-S sample test (Kormogorov-Smirnov), SGOT and SGPT data have p value of more than 0.05 so it can be concluded that

the data in this study each had a normal distribution.

3.2 Homogeneity Test

Table 2. Homogeneity Test

	p-value	Notes
SGOT	0,909	Homogeneous
SGPT	0,404	Homogeneous

Source : research data, processed

Based on the result of homogeneity test, SGOT and SGPT data have p value of more than 0.05 so it can be concluded that the data in this study is homogeneous.

3.3 One Way Anova Test

Table 3. One Way Anova Test

	p-value	Notes
SGOT	0,877	No significant difference
SGPT	0,822	No significant difference

Source : research data, processed

Based on the results of test using the one-way ANOVA test to find out whether there are differences in the average SGOT and SGPT in the five treatments or not, it was obtained a p-value of 0.877 ($p > 0.05$) on SGOT data. Then it can be concluded that there are no significant differences between SGOT at all of treatment. P-value was obtained at 0.822 ($p > 0.05$) on SGPT data. Therefore, it can be concluded that there was no significant difference between SGPT at all of treatment.

DISCUSSION

4.1 The Effect of Kembang Bulan Leaf Ethanolic Extract to SGOT and SGPT Levels

From the one-way ANOVA test, it is known that the p value of SGOT is 0.877 and SGPT is 0.822 so that all treatments are not significantly different. Whereas between treatment 1,2, and 3, the lowest level was treatment 1 with a value of SGOT is 202.14 ± 41.31 , and SGPT is 98.71 ± 44.17 which was the closest to the normal value limit of SGOT levels.

Based on the average comparison between treatment 1,2 and 3, it can be concluded that the most effective dose to give effect is in treatment 1 with an extract dose of 50 mg / 100grBB.

There was a change in SGOT-SGPT levels with the distribution of kembang bulan leaf extract (*Tithonia diversifolia*) between the treatment of the 45th day and the 91st day. The p-value obtained with the overall t-test treatment group is on the 45th day p value >0.05 which means there is no significant difference and on the 91st day p value <0.05 which means there are significant differences.¹⁵

Kembang bulan leaf (*Tithonia diversifolia*) is a plant that has been used as an antidiabetic medicine. This plant contains compounds such as Flavonoids, Saponins, and Tannin.¹² The saponin content in kembang bulan leaf extract can increase insulin sensitivity by increasing adiponin, PPAR γ and GLUT-4 expression in adipose tissue. If the insulin sensitivity increased, insulin resistance will decrease. With the decline in insulin resistance, of course, hyperglycemia will not occur because glucose can enter the body as before. Saponin can also inhibit

gluconeogenesis by decreasing G6Pase expression in the liver where if the process of gluconeogenesis is inhibited, it can help reduce blood glucose levels.¹⁶ Tannin can also increase insulin sensitivity and increase glucose input into cells by mediating insulin signaling pathways in diabetes.¹⁷

Meanwhile, the kembang bulan leaf also has a hepatoprotective effect because it contains flavonoids.¹² Flavonoids are compounds that act as antioxidants. The flavonoids antioxidant mechanism is to directly capture ROS, prevent the regeneration of Reactive Oxygen Species (ROS) and indirectly increase the antioxidant activity of cellular antioxidant enzymes.¹⁸ Because of this antioxidant effect, liver damage can be inhibited, where liver damage caused by ROS can affect the increasing levels of SGOT and SGPT in the liver.¹⁹

4.2 The Effect of Metformin to SGOT and SGPT Levels

The average results of SGOT and SGPT levels in treatment group 4 were the least compared to the other treatment groups. However, based on the one-way Anova test, it is obtained that p value for SGOT is 0.877 ($p > 0.05$) and p value for SGPT is 0.822 ($p > 0.05$) which means that all treatments did not have a significant difference.

The effect of giving metformin to diabetics is to increase insulin sensitivity and fat oxidation.²⁰ In a study in 2014, it was stated that distribution of metformin to per oral 50 mg / 100gr BB in diabetic rats model were more effective in lowering blood glucose levels compared to the use of fragrant pandan leaf water extract.²¹

Before diabetic rats model were injected with STZ, average blood sugar level was

obtained before the metformin treatment was 400 mg/dl and after the treatment, the results of the average metformin level were 240 mg/dl. From the results above, it was found that there was a statistically significant decrease in blood sugar levels after 4 weeks of distribution, but it had better results compared to the group of diabetic rats model that were not given metformin.²²

4.3 The Influence of STZ to SGOT and SGPT Levels

In this study, the distribution of STZ injection in the formation of diabetic rats model showed an increase in blood sugar levels with an average of 406-600 mg/dl, compared to before the injection the average is 69 - 152 mg/dl. The results of STZ induction showed an increase in blood sugar levels with an average of 400-600 mg/dl, compared to before treatment with an average of 90-135 mg/dl.²³

The use of STZ by injection is to give the effect of hyperglycemia in diabetic rats model. The condition of diabetic rats model that experience prolonged hyperglycemia is also supported by the presence of NO- which is a free radical because of the formation of ROS (Reactive Oxygen Species). It is stimulated by Xantin Oxidase enzymes whose numbers increase due to STZ injection.²⁴ These conditions can cause DNA damage and changes in pancreatic β cell function as well as causing an increase in SGOT and SGPT enzymes levels. This increase shows that there is prolonged liver damage.⁶

CONCLUSION

Based on this research, it can be concluded that giving ethanol extract of the leaves of kembang Bulan (*Tithonia diversifolia*) obtained less significant results compared to the

untreated group. However, there is no significant difference. And giving ethanol extract of the leaves of kembang Bulan (*Tithonia diversifolia*) at a dose of 50 mg / 100gr BB is the most effective way to reduce levels of SGOT and SGPT.

CONFLICT OF INTEREST

The author stated there is no conflict of interest.

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