

RESEARCH ARTICLES

Effectiveness of Fig Leaf Ethanol Extract (*Ficus carica L.*) As An Antidiabetes In Alloxan-Induced Diabetes Model in Rats

Muhammad Farhan Habibie¹, Dedi Ansyari²

¹Faculty of Medicine, Universitas Muhammadiyah Sumatera Utara, Jalan Gedung Arca No. 53, Medan 20217, Indonesia

²Department of Clinical Pathology, Fakultas Kedokteran, Universitas Muhammadiyah Sumatera Utara, Jalan Gedung Arca No. 53, Medan 20217, Indonesia

Corresponding Email: Muhammad.farhan2703@gmail.com

Abstract: Long-term use of diabetes mellitus medication can cause several complications, so other alternative treatments are needed that tend to have safer effects, such as herbal treatments using fig plants. Researchers feel the need to test with different doses and subjects to determine whether fig leaf extract (*Ficus carica L.*) is effective as an antidiabetic in alloxan-induced diabetic mouse models. This research uses a true experimental method with a pretest-posttest with control group design. Sampling used the simple random sampling method. The samples used were 36 male white rats (*Rattus norvegicus L.*), which were divided into 6 groups. Data will be analysed using the paired sample T test, one-way ANOVA test, and Post hoc test. The results showed that administering ethanol extract of fig leaves at doses of 200 mg/KgBW, 400 mg/KgBW, and 600 mg/KgBW had effectiveness as an antidiabetic in reducing fasting blood sugar levels in rats induced by alloxan ($p = 0.000$). However, only the ethanol extract group of fig leaves at a dose of 600 mg/kg bw (P3) had antidiabetic activity that was as effective as the drug glibenclamide ($p = 0.253$). Administration of ethanol extract of fig leaves (*Ficus carica L.*) has antidiabetic effectiveness in a rat model of alloxan-induced diabetes.

Keywords: Alloxan, diabetes mellitus, *Ficus carica l.*, tin

INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disorder caused by the pancreas not producing enough insulin or by the body experiencing insulin resistance, resulting in elevated blood glucose levels (hyperglycemia). The International Diabetes Federation (IDF) also predicts an increase in

the number of DM patients from 10.7 million to 13.7 million in 2030 2019 2030.¹ The World Health Organisation (WHO) has predicted that the number of type 2 DM patients in Indonesia will increase from 8.4 million in 2000 to 21.3 million in 2030.²

Glibenclamide is an oral antihyperglycemic drug from the

sulfonylurea class that primarily increases insulin secretion by pancreatic beta cells. This drug works by stimulating insulin secretion from granules in pancreatic beta cells by interacting with ATP-sensitive potassium channels, which causes depolarisation and the opening of voltage-gated calcium channels, allowing calcium ions to stimulate insulin secretion. Contraindications for the use of this drug include patients at high risk of hypoglycemia (the elderly, those with liver and kidney dysfunction), ketoacidosis, acute alcoholic intoxication, hypersensitivity, and severe liver and kidney disorders. Long-term use of this drug can cause obesity, decreased blood cell count, and slow liver damage.³ Therefore, alternative treatments are needed that are safer for long-term use, given that diabetes is a lifelong disease.

Indonesia is a country rich in natural resources, including flora and fauna. Various types of plants thrive, including those that can be used to treat various ailments. Fig plants (*Ficus carica L.*) are traditionally used as antimetabolites, cardiovascular, respiratory, antispasmodic, and anti-inflammatory drugs.⁴ Some compounds that have antidiabetic effects are flavonoids, tannins, saponins, alkaloids, and triterpenoids. These compounds play a role in controlling blood sugar levels in people with diabetes.⁵

Research using fig leaf extract with ethyl acetate solvent at doses of 250 mg/kgBW and 500 mg/kgBW showed a decrease in fasting blood sugar levels in

streptozotocin-induced mice.⁶ Other research also found that fig leaf extract at 5%, 10%, and 15% concentrations was effective in reducing blood glucose levels in alloxan-induced mice.⁷ In another study, ethanol extract of fig leaves (*Ficus carica L.*) at a dose of 840 mg/kgBW had a relatively similar effect to glibenclamide in alloxan-induced male mice.⁸

More research proving the antidiabetic effectiveness of fig leaf extract (*Ficus carica L.*) needs to be conducted, so researchers feel the need to test with different doses and subjects to determine whether fig leaf extract (*Ficus carica L.*) is effective as an antidiabetic in alloxan-induced diabetic mouse models.

METHOD

This research used a true experimental method with a pretest-posttest with a control group design, conducted from September to October 2023 at the Pharmacology Laboratory Animal Management Unit (UPHL), Muhammadiyah University of North Sumatra.

The sample size for this study was determined using the Federer formula, which obtained a minimum of 4 rats for each group, with two additional backup rats for each group, resulting in a total of 36 rats. In this study, 6 groups were divided into 6 groups using a simple random sampling technique: 1 healthy control group (KN), 1 positive control group (KP), a drug control group (KO), and 3 treatment groups (P1, P2, P3), divided as follows:

Table 1. Experiment on Rats in the Effects of Alloxan-Induced Diabetes

No	Group	Treatment	Amount
1	Group KN	rats that received no treatment	6
2	Group KP	rats that received only alloxan at 150 mg/kgBW	6
3	Group KO	rats that had been induced with alloxan and given glibenclamide at a dose of 5 mg/kgBW	6
4	Group P1	rats that had been induced with alloxan and given fig leaf extract (<i>F. carica L.</i>) at a dose of 200 mg/kgBW	6
5	Group P2	rats that had been induced with alloxan and given fig leaf extract (<i>F. carica L.</i>) at a dose of 400 mg/kgBW	6
6	Group P3	rats that had been induced with alloxan and given fig leaf extract (<i>F. carica L.</i>) at a dose of 600 mg/kgBW	6

Negative Control Group (KN): mice that were not treated. Positive Control Group (KP): mice that were only given alloxan at 150 mg/kgBW. Drug Control Group (KO): mice that had been induced with alloxan and given glibenclamide at a dose of 5 mg/kgBW. Extract Treatment Group 1 (P1): mice that had been induced with alloxan and given fig leaf extract (*F. carica L.*) at a dose of 200 mg/kgBW. Extract Treatment Group 2 (P2): mice that had been induced with alloxan and given fig leaf extract (*F. carica L.*) at a dose of 400 mg/kgBW. Extract Treatment Group 3 (P3): mice that had been induced with alloxan and given fig leaf

extract (*F. carica L.*) at a dose of 600 mg/kgBW.

Plant Determination Test. The plant determination test aims to determine and identify the authenticity of the plants used in the research, both from leaf morphological characteristics and from textbook references. The plant determination test was conducted in the Laboratory of the Faculty of Mathematics and Natural Sciences, University of North Sumatra.

Sampling. Leaf samples were randomly collected, selecting fresh, dark green, and clean leaves obtained from the Krajan area, Tamansari, Dringu District, Probolinggo Regency, East Java.

Preparation of Fig Leaf Simplex. The obtained fig leaves were then washed thoroughly with running water and dried in an oven at 55°C. The dried fig leaves were then ground and sieved using a 40-mesh sieve to obtain a fine powder.

Preparation of Fig Leaf Extract (*Ficus carica L.*). This extract was made from the dried powdered simplex using the maceration method. 500 grams of fig leaf powder was placed in a dark glass container and then soaked in 2000 mL of 70% ethanol. Soak for 3 days, stirring occasionally for 10 minutes each day for the first 6 hours, then let it sit for the remaining 18 hours. After 3 days of maceration, it can be separated by filtering, and filtrate 1 can be obtained. The remaining pulp in the bottle is soaked again in 625 mL of ethanol and filtered to produce filtrate 2. Combine filtrates 1 and 2. Then, distil to evaporate the ethanol in the solution

using a rotary evaporator until all the ethanol has evaporated, resulting in a thick fig leaf extract (*Ficus carica L.*) solution.⁸

Determining Per cent Yield. The per cent yield is obtained by weighing the extract, dividing it by the weight of the dry fig leaf powder and multiplying by 100%.

$$\% \text{ Yield} = \frac{\text{weight of fig leaves extract}}{\text{weight of gif leaves powder}} \times 100\%$$

Ethanol-Free Test. The concentrated extract is tested for ethanol-free status using an esterification test, which involves adding concentrated acetic acid and concentrated sulfuric acid to the extract. Compound Identification (Phytochemical Test). This test was conducted in the Biochemistry Laboratory of the Faculty of Medicine, University of Muhammadiyah North Sumatra.

Data Analysis. The blood sugar observation data obtained for each group were first tested for normal distribution using the Shapiro-Wilk test, followed by a Paired Sample T-Test to determine the difference in mean values before and after treatment. A one-way ANOVA was then performed, followed by a Post Hoc Test. All results are presented as mean \pm SD.

RESULT

This study has received approval from the Health Research Ethics Committee of the Faculty of Medicine, Muhammadiyah University of North Sumatra, No. 1037/KEPK/FKUMSU/2023, to use rats as research subjects. Three rats died during the

study. Two of the rats became ill due to fleas contaminated with animal feed, while one rat died as a result of the research procedure.

Plant Determination Results. The plant determination test was conducted at the Plant Systematics Laboratory of the Herbarium Medanense (MEDA), Faculty of Mathematics and Natural Sciences, University of North Sumatra. Based on the determination results, it was confirmed that the plant used in this study was the *Ficus carica L.* species.

Ethanol Extract of Fig Leaves (*Ficus carica L.*). 500 grams of the obtained fig leaf extract were weighed into a dark glass bottle and macerated with 2,000 mL of 70% ethanol for 3 days. The first filtrate was then filtered into a dark glass bottle, and the residue was re-macerated with 625 ml of 70% ethanol for 1 day. The entire filtrate was then concentrated using a rotary evaporator at 50 rpm at 45°C. This was followed by a thickening process using a heated stirrer on a petri dish at 45°C. This test was conducted in the Biochemistry Laboratory of the Faculty of Medicine, University of Muhammadiyah North Sumatra. The yield results were as follows:

Table 2. Percentage Yield of Fig Leaf Extract

Simplex	Simplex weight (g)	Extract Weight (g)	Percentage (%)
Fig leaves	500	34,27	6,85

Ethanol-Free Test Results. The obtained tin leaf extract was then tested for ethanol-free status using an ethanol esterification test. This test was conducted in

the Biochemistry Laboratory of the Faculty of Medicine, Muhammadiyah University of North Sumatra. Based on the results of the ethanol-free test, the tin leaf extract did not exhibit a distinctive ethanol odour.

Compound Identification Results (Phytochemical Test). The results of the phytochemical test on fig leaf extract (*Ficus carica* L.) can be seen in the table below:

Table 3. Results of Compound Identification (Phytochemical Test) of Fig Leaf Extract

Compound	Result	Conclusion
Flavonoid	The orange colour is formed.	+
Alkaloid	Orange sediment	+
Tanin	Greenish black colour	+
Saponin	Foam 2 – 5 cm high	+
Triterpenoid	Brownish ring	+

Normality Test. The results of the Shapiro normality test will be used to determine the testing method to be used. The results of the normality test are as follows:

Table 4. Normality Test Results

	Group	Sig. (p)
Fasting Blood Glucose Test (BGC) Before Alloxan Induction (Day 8)	KN	0,998
	KP	0,860
	KO	0,773
	P1	0,416
	P2	0,499
	P3	0,873
Fasting Blood Glucose Test (BGC) After Alloxan Induction (Day 11)	KN	0,468
	KP	0,891
	KO	0,997
	P1	0,894
	P2	0,630
	P3	0,973
	KN	0,625

Fasting Blood Glucose Test	KP	0,346
After Treatment (Day 21)	KO	0,512
	P1	0,859
	P2	0,994
	P3	0,689

Based on Table 4, the results of the normality test show that all data are normally distributed ($p > 0.05$), so that the Paired Sample T test and One-Way Anova test can be carried out.

Paired Sample T-Test. A paired samples t-test was used to determine whether there was a significant difference between mean blood sugar levels before and after treatment. The results were as follows:

Table 5. Comparison of Average Fasting Blood Sugar Levels Before and After Alloxan Induction

Group	Pretest Mean±SD	Posttest Mean±SD	Sig. (p)
KN	90,25±13,07*	93,75±6,65*	0,558
KP	89,75±17,74	290,25±42,93	0,004
KO	88,00±14,14	306,25±17,53	0,000
P1	85,25±5,73	299,50±26,33	0,001
P2	92,00±15,72	292±21,52	0,000
P3	98,75±13,12	308,75±10,53	0,000

Note: * = no treatment.

Based on the decision-making criteria in the Paired Samples T-Test, a p-value < 0.05 indicates a significant difference between the pretest and posttest results. Conversely, a p-value > 0.05 indicates no significant difference between the pretest and posttest results. Based on the test results above, a p-value > 0.05 was obtained in the KN group, indicating no significant difference between the pretest and posttest

results in the KN group, given that this group was not treated. Meanwhile, p-values < 0.05 were obtained in the KP, KO, P1, P2, and P3 groups, indicating a significant difference between the fasting blood sugar levels of the rats before and after alloxan induction.

A second Paired Sample T-Test was conducted to determine whether there was a significant difference between the average fasting blood sugar levels before and after treatment. The results are as follows:

Table 6. Comparison of Average Fasting Blood Sugar Levels Before and After Treatment

Group	Pretest Mean \pm SD	Posttest Mean \pm SD	Sig. (p)
KN	93,75 \pm 6,65*	96,75 \pm 14,81 *	0,673
KP	290,25 \pm 42,93 *	288,50 \pm 38,0 3*	0,806
KO	306,25 \pm 17,53	91,25 \pm 5,67	0,000
P1	299,50 \pm 26,33	135,50 \pm 7,32	0,002
P2	292,00 \pm 21,52	118,75 \pm 18,0 1	0,000
P3	308,75 \pm 10,53	101,00 \pm 5,29	0,000

Note: * = no treatment

Based on Table 6, a p-value of > 0.05 was obtained in the KN and KP groups, which can be concluded that there was no significant difference between the pretest and posttest results in these groups, considering that neither group was given treatment. In the KO, P1, P2, and P3 groups, a p-value of < 0.05 was obtained, so it can be concluded that there was a significant difference between the results of fasting blood sugar levels in rats before and after treatment.

Homogeneity Test. This test is used to determine whether each group has data

samples with the same variance. This test is performed as a decision-making criterion in determining the type of post-hoc test to be used if the One-Way ANOVA test results yield a p-value < 0.05 .

Table 7. Homogeneity Test Results

Group	Sig. (p)
Fasting Blood Glucose Test After Treatment	0,030

Based on Table 7, the homogeneity test results show a p-value < 0.05 , thus concluding that the fasting blood glucose group data after treatment are not homogeneous. Therefore, if a post-hoc test is conducted, the Games-Howell method should be used.

One-Way Anova Test. This test was used to determine whether there were differences in the average data for each group. The results of this test are as follows:

Table 8. One-Way ANOVA Test Results

Kelompok	Sig. (p)
Fasting Blood Glucose Test After Treatment	0,000

Based on Table 8, the results of the One-Way Anova test showed a p-value < 0.05 , thus concluding that there was a significant difference in the average fasting blood glucose reduction between each group.

Howell's Games Post Hoc Test. The Howell's Games Post Hoc Test aims to determine which groups show significant differences.

Table 9. Comparison of Average Decrease in Fasting Blood Glucose Levels After Treatment in Each Group

Kelompok	KN	KP	KO	P1	P2	P3
KN		0,005	0,973*	0,044	0,281*	0,990*
KP	0,005		0,008	0,016	0,010	0,010
KO	0,973*	0,008		0,001	0,035	0,253*
P1	0,044	0,016	0,001		0,215	0,003
P2	0,281	0,010	0,035	0,215*		0,157*
P3	0,990*	0,010	0,253*	0,003	0,157*	

Note: * = $p > 0.05$

Based on Table 9, the Negative Control (KN) group, compared to the Drug Control (KO) group, showed a p-value of 0.973, which indicates that the Drug Control (NC) group did not have a significant difference in the average reduction in fasting blood glucose compared to the Negative Control (KN) group. A comparison between the Negative Control group and the Extract 2 group also showed a p-value of 0.281, indicating that the Extract 2 group did not have a significant difference in the average reduction in fasting blood glucose compared to the Negative Control (KN) group. A comparison between the Negative Control (KN) group and the Extract 3 (P3) group also showed a p-value of 0.990, indicating that the Extract 3 (P3) group also did not have a significant difference in the average reduction in fasting blood glucose compared

to the Negative Control (KN) group. The comparison between Extract 1 (P1) and Extract 2 (P2) showed a p-value of 0.215, indicating that there was no significant difference in the average reduction in fasting blood sugar levels in the two groups.

However, a comparison between the Drug Control (KO) and Extract 1 (P1) groups showed a p-value of 0.001, indicating a significant difference in the average reduction in fasting blood sugar levels between the Drug Control (KO) and Extract 1 (P1) groups. Therefore, the reduction in fasting blood sugar levels at a dose of 200 mg/kgBW of fig leaf ethanol extract was not as effective as the administration of glibenclamide. A comparison between the Drug Control (KO) and Extract 2 (P2) groups showed a p-value of 0.035, indicating that the Drug Control (KO) and Extract 2 (P2) groups also had a significant difference

in the average reduction in fasting blood sugar levels, indicating that the reduction in fasting blood sugar levels at a dose of 400 mg/kgBW of fig leaf ethanol extract was not as effective as the administration of glibenclamide.

In the Drug Control (KO) group with the Extract 3 (P3) group, the p-value showed 0.253, so it can be concluded that the Drug Control (KO) group with the Extract 3 (P3) group did not have a significant difference in the average decrease in fasting blood glucose. Thus, it can be concluded that the decrease in fasting blood glucose at a dose of 600 mg/kg BW of fig leaf ethanol extract has the same effectiveness as the administration of a dose of glibenclamide.

DISCUSSION

Based on the results of this study, there is an effect of administering fig leaf ethanol extract on the fasting BCG of rats that have been induced by alloxan. This can be seen through the measurement of fasting BCG in each group. The administration of alloxan aims to damage pancreatic beta cells in rats, thereby reducing or stopping insulin secretion.⁹ The results of the average fasting BCG test before and after alloxan induction in this study using the paired sample T test showed a p value < 0.05, which can be concluded that there is a significant difference in the average fasting blood glucose before and after alloxan induction.

The results of the one-way ANOVA test in each group after being given treatment showed a significant difference in the

average decrease in fasting blood glucose in rats given three different doses of fig leaf ethanol extract, with a p-value = 0.000 ($p < 0.05$). Thus, it can be concluded that fig leaf ethanol extract has effectiveness as an antidiabetic in alloxan-induced rats. This is in line with research conducted by Irudayaraj *et al.* that the administration of fig leaf extract using ethyl acetate solvent at doses of 250 mg/KgBW and 500 mg/KgBW has effectiveness in reducing fasting blood sugar levels in streptozotocin-induced rats.⁶ Another study conducted by Nur Aisyah *et al.* also showed that the administration of fig leaf ethanol extract with concentrations of 5%, 10%, and 15% has effectiveness as an antidiabetic in reducing fasting blood sugar levels in alloxan-induced mice.⁷ Similar research conducted by Dita with different doses also showed that the administration of fig leaf ethanol extract with doses of 210 mg/KgBW, 420 mg/KgBW, and 840 mg/KgBW also has effectiveness as an antidiabetic in reducing fasting blood sugar levels in alloxan-induced mice.⁸

Of the three different doses, the fig leaf ethanol extract group with a dose of 600 mg/kg BW showed the greatest average decrease in fasting blood glucose, namely 101 mg/dl. Based on the results of statistical tests, it was found that the fig leaf ethanol extract group with a dose of 600 mg/kg bw (P3) had the same effectiveness as the Drug Control group (KO) with a p-value = 0.253 ($p > 0.05$). This is in line with research conducted by Dita, which stated that the fig leaf ethanol extract group with a dose of 840

mg/kg bw was better at lowering blood sugar levels and had the same effectiveness as glibenclamide. This is because the compounds that play a role in lowering blood sugar levels in mice are much more abundant in higher doses of fig leaf ethanol extract.⁸

The flavonoid content found in fig leaf extract functions as an antioxidant that can neutralise free radical reactions caused by alloxan induction. This compound is also believed to have the ability to regenerate pancreatic beta cells, which can increase production and restore insulin sensitivity needed to lower blood sugar levels.¹⁰ Tannin and saponin compounds can also neutralise free radicals, such as flavonoid compounds. In addition, these two compounds also play a role in inhibiting the adipogenesis process, inhibiting the process of glucose absorption in the intestine.¹¹ Saponin compounds are also believed to be able to regenerate pancreatic cells, thereby increasing insulin secretion and inhibiting the activity of the α -glucosidase enzyme, thereby reducing the process of glucose absorption in the intestine.¹² Alkaloid compounds found in fig leaf extract also have a role in regenerating pancreatic beta cells, increasing glucose transport in the blood, inhibiting glucose absorption in the intestine, and stimulating the process of glycogen synthesis.¹³ Triterpenoid compounds also play a role in stimulating GLUT-4 translocation, which causes an increase in the uptake process and use of glucose by muscles. In addition, this compound can inhibit the production of

TNF- α caused by alloxan.¹³ Compounds such as flavonoids, alkaloids, tannins, saponins, and triterpenoids contained in the ethanol extract of fig leaves have their own working mechanisms, such as preventing free radical reactions against pancreatic beta cells due to ROS reactions in the body, secreting insulin, increasing glucose uptake in the blood, and inhibiting glucose absorption in the small intestine^{14,15}

From the results above, it can be concluded that the three groups given fig leaf ethanol extract at doses of 200 mg/KgBW, 400 mg/KgBW, and 600 mg/KgBW were equally effective as antidiabetics in reducing fasting blood sugar levels in alloxan-induced rats. However, only the fig leaf ethanol extract group at a dose of 600 mg/kg bw (P3) had antidiabetic activity as effective as glibenclamide. The higher content of antidiabetic substances such as flavonoids, alkaloids, tannins, saponins, and triterpenoids in the ethanol leaf extract group at a dose of 600 mg/kg bw also had a greater effect in reducing fasting blood sugar levels in rats.

CONCLUSION

Based on the results of a study on the effectiveness of fig leaf ethanol extract (*Ficus carica L.*) as an antidiabetic agent in a rat model of alloxan-induced diabetes, it can be concluded that the fig leaf ethanol extract (*Ficus carica L.*) has antidiabetic activity in a rat model of alloxan-induced diabetes.

Based on the results of this study, the fig leaf ethanol extract contains antidiabetic substances such as flavonoids, alkaloids, tannins, saponins, and triterpenoids after phytochemical testing.

Based on these results, the fig leaf ethanol extract at a dose of 600 mg/kgBW was the most effective dose and had the same activity as glibenclamide in reducing fasting blood sugar levels in alloxan-induced rats.

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The limitations of this study are that the yield results are below the standard value (<10%) and the method of taking blood from rats uses a simple method, which increases the possibility of rats experiencing stress during the blood collection process.

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