Effectiveness of Kersen Leaf (Muntingia Calabura L.) Extract on Rats as an anti-Diabetic Agent.

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Abstract. Diabetes Mellitus (DM) is a chronic metabolic disease with many causes and is characterized by elevated blood sugar levels caused by failure of insulin secretion or insulin action. Many plant secondary metabolite compounds can be used as medicine. Kersen Leaves (Muntingia Calabura L.) have secondary metabolites that function as antioxidants and can produce the hormone insulin, which helps metabolize sugar. Therefore, this study investigated the effectiveness of Kersen Leaf in lowering blood glucose. This study uses a type of pure Experimental Research (True Experimental) and the design uses Pretest-Posttest Control Group Design. Then, the rats were grouped into 5 different groups, namely Group I (Negative Control), Group II (Positive Control), Group III (Kersen Leaf Extract 150 mg/kgBW/day), Group IV (Kersen Leaf Extract 300 mg/kgBW/day), Group V (Kersen Leaf Extract 600 mg/kgBW/day). Meanwhile, Kersen Leaves used in this study were extracted by maceration method using ethanol solvent. The results of this study showed that Kersen Leaf Ethanol Extract can significantly reduce blood sugar levels after 10 days to 15 days after administration of Kersen Leaf Ethanol Extract (P Value $< 0,05$). Thus, it can be concluded that Kersen Leaf Ethanol Extract can reduce blood sugar levels after 5 days of treatment.

Keywords: Diabetes Mellitus, Kersen Leaf, Ethanol, Alloxan and Wistar Rats.

1 Introduction

Diabetes Mellitus (DM) is often dubbed the mother of disease from hypertension, heart disease, blood vessels, stroke, kidney failure blindness and even death. Diabetes Mellitus (DM) is a chronic metabolic disease with multiple causes and is characterized by elevated blood sugar levels caused by failure of insulin secretion or insulin action [12].

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According to the World Health Organization (WHO) (2000), there are 150 million people worldwide suffering from DM, and this number will double by 2025. The International Diabetes Federation (2019) reported that 4,6 million people will die from Diabetes Mellitus (DM). The number of cases will continue to increase due to metabolic disorders caused by Diabetes Mellitus (DM) [14]. More than 400 plant species have been shown to have activity as traditional medicines. Products from plants are increasingly used in the manufacture of medicine, cosmetics, and nutraceuticals. The product can be used to treat long-term diseases such as hypertension, arthritis, diabetes mellitus, cancer, cough, medicine, memory loss and so on. The number of cases will continue to increase due to metabolic disorders causes by Diabetes Mellitus (DM) [9]. Plant products are usually available as tablets, capsules, powders or liquid extracts. Plant product can be consumed in both fresh and dried form [8]. Plants have many secondary metabolite compounds that can be used as drugs, for example, Kersen Leaves (Muntingia Calabura L.) [9]. Kersen Leaves (Muntingia Calabura L.) have secondary metabolites that are effective as anti-oxidants and can induce the hormone insulin, which helps metabolize sugar [12]. Research conducted by [9] with the title Effectiveness of Etanol Extract of Kersen Leaves (Muntingia Calabura L.) on Histological Profile of Hepar Diabetes Rats shows results that at concentrations of 200 mg and 400 mg significantly reduce blood glucose levels. Based on the above background, researchers want to conduct research related to the Effectiveness of Giving Kersen Leaf Extract (Muntingia Calabura L.) to Rats as Anti Diabetes with concentrations of 150 mg, 300 mg, 600 mg / kg/ BW/ day for 14 days.

2 Literature Review

Diabetes Mellitus (DM) is a metabolic disorder characterized by hyperglycemia [9], an increase in blood glucose levels caused by a failure of insulin secretion, insulin action, or both [4]. Chronic hyperglycemia can cause long-term damage, dysfunction, and failure of organs such as the eyes, kidneys, nerves, heart, and blood vessels. Because almost one-third of people with Diabetes Mellitus (DM) is called the silent killer. However, early signs of Diabetes Mellitus (DM), such as polydipsia, polyphagia, and polyuria, are early signs that the general public should be aware of [12].

Insulin is a hormone responsible for glucose metabolism through glycolysis and gluconeogenesis that occurs in hepatic cells [9]. Insulin also stimulates the liver to convert glucose into glycogen for storage in its cells; this improves blood sugar levels by accelerating the liver's release rate and regulating blood [5]. Insulin deficiency also causes Diabetes Mellitus (DM), which is usually caused by the destruction of a small or large portion of the Langerhans Island cells in the pancreas, which produce insulin [12].

There are four pathophysiologies of Diabetes Mellitus (DM):

1. **Type 1 Diabetes Mellitus**: This type of diabetes is rare, occurring in about 5%-10% of cases. It usually appears in childhood or early adulthood

and is caused by autoimmune-mediated destruction of pancreatic cells, leading to absolute insulin deficiency [15]. In addition to insulin deficiency, α-cells of Langerhans Island in patients with Type 1 Diabetes Mellitus (DM) also become abnormal. Normally, glucagon secretion is excessive due to hyperglycemia. One of the symptoms of this condition is the possibility of Type 1 Diabetes Mellitus (DM) patients experiencing diabetic ketoacidosis without insulin therapy [1]. The main problem in Type 1 Diabetes Mellitus (DM) is insulin secretion deficiency; patients who are not well-controlled can experience a decrease in the ability of target cells to respond to insulin therapy [7]. There is no treatment for Type 1 Diabetes Mellitus (DM), but good and effective metabolic control can maintain normal growth and prevent complications, allowing children to have a good quality of life. Components of good metabolic control include consistent insulin administration, dietary management, exercise, education, and close monitoring [1].

2. **Type 2 Diabetes Mellitus**: This is the most common type of diabetes, occurring in 90% of cases. It is characterized by a combination of insulin resistance and relative insulin deficiency [15]. Environmental influences and genetic factors are crucial for Type 2 Diabetes Mellitus (DM), including obesity, a high-fat, low-fiber diet, and sedentary lifestyle [7].
3. **Gestational Diabetes Mellitus**: This condition arises due to glucose intolerance during pregnancy and is usually temporary. Gestational Diabetes Mellitus (GDM) is known to occur in about 4%-5% of pregnant women and is usually found after the second trimester. Such risk can be reduced by strict metabolic control [7].
4. **Pre-Diabetes**: This condition occurs when blood sugar levels are higher than normal or between normal and diabetes but not high enough to be categorized as Type 2 Diabetes Mellitus (DM) [7]. Retinopathy, neuropathy, and nephropathy are examples of microvascular complications. Macrovascular complications include coronary heart disease, stroke, and peripheral vascular disease [15].

Symptoms indicating the possibility of Diabetes Mellitus (DM) include:

- Polyuria: frequent urination.
- Polydipsia: frequent thirst.
- Polyphagia: excessive hunger and eating.

Other complaints include blurred vision, impaired coordination or limb movement, tingling in the hands or feet, pruritus (severe itching), and unexplained weight loss [7].

Traditional medicine involves ingredients or herbs used for generations for treatment, such as plant materials, animal materials, mineral materials, galenic preparations, or their combinations. According to the Food and Drug Administration, medicinal plants are categorized into herbal medicine, standardized herbal medicines, and phytopharmaceuticals [7].

Kersen Leaves (*Muntingia calabura L.*) contain bioactive ingredients beneficial for health, including antiulcer, antipyretic, and anti-inflammatory properties [2]. Medicinal benefits include active substances like flavonoids, alkaloids,

saponins, tannins, and triterpenoids [9]. Additionally, Kersen Leaves can help maintain health due to their chemical composition, including primary and secondary metabolites and minerals. They can be processed into beverages to prevent diseases [6].

3 Methods

3.1 Preparation of Kersen Leaf (*Muntingia Calabura L.*) Simplisia

Before maceration, Kersen Leaves (*Muntingia Calabura L.*) were first sorted wet to separate the sample from impurities or other foreign materials. After the wet sorting process, the leaves were washed using clean and running water. The washing process required a high level of accuracy to remove impurities sticking to the leaves. The washed leaves were aerated in a room not exposed to direct sunlight, as this could damage the chemical content. Once air-dried, the leaves were placed in a cabinet dryer at 50°C for 24 hours to dry completely. Drying reduced the water content to prevent spoilage. The dried leaves were crushed into powder using a Miyako blender (1.5L) at a pulse speed of 265,000 rpm for fine particle size. The powdered simplisia was weighed, then stored in airtight plastic zip bags to maintain quality and prevent mold damage [9].

3.2 Kersen Leaf (*Muntingia Calabura L.*) Extraction

For liquid extract preparation, 500 grams of simplisia were weighed and mixed with 96% ethanol at a 1:10 ratio. The mixture was left for three days, after which it was filtered using filter paper. This process was repeated three times to obtain the liquid extract. The liquid extract was then concentrated using a rotary evaporator at 60°C. Finally, the concentrated extract was thickened using a water bath at 100°C [9].

3.3 Sample Testing of Kersen Leaf Extract (*Muntingia Calabura L.*)

Phytochemical tests were conducted on the extract to identify flavonoids, alkaloids, saponins, tannins, and triterpenoids-steroids.

1. Flavonoid Test 10 grams of the test sample were weighed and boiled with 6 mL of hot water for 5 minutes. The mixture was filtered under hot conditions, and 5 mL of filtrate was added to 0.1 gram of magnesium powder, 1 mL of concentrated hydrochloric acid, and 2 mL of amyl alcohol. The solution was shaken and allowed to separate. A red amyl alcohol layer indicated the presence of flavonoids [11].

2. Alkaloid Test 1 gram of extract was mixed with 96% ethanol, 4 drops of 2N HCl, and 6 mL of distilled water. After heating in a water bath for 2 minutes, the filtrate was divided into two parts. Mayer's reagent added to the first tube formed a white precipitate, indicating alkaloids. Dragendroff's reagent added to the second tube formed an orange to red-brown precipitate, also indicating alkaloids [3].

3. Saponins Test 0.5 grams of extract were mixed with 10 mL of hot water. After cooling, the mixture was shaken vigorously for 10 seconds. Persistent foam upon adding 2N HCl confirmed saponin presence [11].

4. Tannins Test 0.5 grams of extract were dissolved in 96% ethanol and mixed with 6 mL of hot water and 3 drops of $FeCl_3$. A white precipitate indicated the presence of tannins [3].

5. Triterpenoids-Steroid Test 0.5 grams of extract were dissolved in 96% ethanol and treated with Lieberman-Burchard reagent. A blue color indicated steroids, while a purple-red or brownish ring indicated triterpenoids [3].

3.4 Animal Preparation and Experimentation

Twenty-five 3-month-old male *Rattus norvegicus* rats with an initial body weight of 200–250 grams were used. Healthy rats were identified by active movements and were adapted for one week before the experiment. Under standard conditions (12-hour light/dark cycles), the rats were housed in polypropylene cages at 60–70% relative humidity. They were fed a pellet diet containing 12 grams of carbohydrates daily and had free access to water. Straw bedding was replaced every two days. Ethical approval was obtained from the Universitas Prima Indonesia Health Research Ethics Commission (Recommendation Number: 029/KEPK/UNPRI/V/2024, dated May 16, 2024) [9].

3.5 Preparation of Diabetic Mice

Alloxan was used to induce diabetes by damaging pancreatic beta cells. The body weight and fasting blood glucose levels of the rats were measured using a glucometer. Alloxan was dissolved in NaCl to achieve a pH of 4.5 [13]. Following [10], alloxan was administered intraperitoneally at a dose of 120 mg/kg BW using a 25G syringe. Fasting blood glucose levels were measured on days 5, 10, and 15. Rats with levels $> 126 mg/dL$ were considered diabetic [9].

3.6 Administration of Kersen Leaf (*Muntingia Calabura L.*) Extract

Kersen Leaf (*Muntingia Calabura L.*) extract was administered orally once daily for 14 days using a blunt-tip oral sonde. The extract was introduced into the

esophagus, and its effect on the rats was monitored. The rats were divided into five groups. Group 1 served as the negative control, consisting of normal rats fed a standard diet. Group 2, the positive control, consisted of rats given 1 mg/kg BW of glibenclamide daily, administered as 0.02 mL orally for 14 days. Group 3 consisted of rats given 150 mg/kg BW of Kersen Leaf extract daily, administered as 1.5 mL orally for 14 days. Group 4 consisted of rats given 300 mg/kg BW of Kersen Leaf extract daily, administered as 3 mL orally for 14 days. Finally, Group 5 consisted of rats given 600 mg/kg BW of Kersen Leaf extract daily, administered as 6 mL orally for 14 days [9].

Table 1. Division of Experimental Groups

Groups	Administration Dosage
Control (-)	Na CMC 0.5%
Control (+)	Glibenclamide 1mg/kgBW/day
Groups 1	Kersen Leaf (*Muntingia Calabura L.*) Extract 150mg/kgBW/day
Groups 2	Kersen Leaf (*Muntingia Calabura L.*) Extract 300mg/kgBW/day
Groups 3	Kersen Leaf (*Muntingia Calabura L.*) Extract 600mg/kgBW/day

3.7 Examination of Blood Sugar Levels in Rats

After 14 days the rats were given to each group. The examination was carried out on days 5, 10 and 15, only 3 times reduce the risk of bias in rats. Before measuring blood glucose levels, rats were fed for 6 hours. Then, each rat was observed using the glucometer strip test method. Data were obtained from the observation of glucometer results.

4 Discussion

4.1 Extract Characteristics

This study used Kersen Leaf (*Muntingia Calabura L.*) samples, and after the extraction process, the extracts with the following characteristics were obtained.

From the table data above, it can be seen that from 2000 grams of fresh Kersen Leaf (*Muntingia Calabura L.*), 500 grams of Kersen Leaf (*Muntingia Calabura L.*) *simplisia* powder was obtained. Then, the Kersen Leaf (*Muntingia Calabura L.*) *simplisia* powder was macerated using 8750 milliliters of ethanol solvent. After the Rotary Evaporator process, 107.97 grams of Kersen Leaf (*Muntingia Calabura L.*) extract was obtained. Based on these data, the yield value is 21%.

Table 2. Characteristics of Kersen Leaf (*Muntingia Calabura L.*) Extract

Characteristics	**Value**
Fresh *Simplisia* Weight (gr)	2000 gr
Dry *Simplisia* Powder Weight (gr)	500 gr
Solvent Volume (ml)	8750 ml
Extract Weight (gr)	107,97 gr
Yield (%)	21%

4.2 Phytochemical Screening

Kersen Leaf (Muntingia Calabura L.) Ethanol Extract was analyzed for phytochemical content through phytochemical screening and the results of the phytochemical screening can be seen in the following table.

Table 3. Phytochemical Screening Results of Kersen Leaf (*Muntingia Calabura L.*) Extract

Phytochemistry	**Method**	**Result**
Flavonoids	Powder mg + HCl 2N	(+)
Alkaloid	Mayer	(-)
	Dragendorff	(+)
Saponin	6 ml Aquadest	(+)
Tannin	3 drops $FeCl_3$	(+)
Triterpenoids	1 ml Chloroform + 2 ml H_2SO_4 + 1 ml Acetic Acid	(+)
Steroid	1 ml Chloroform + 1 ml H_2SO_4	(-)

From the table data above, it can be seen that Kersen Leaf (Muntingia Calabura L.) has phytochemical content in the form of Flavonoids, Alkaloids, Saponins, Tannins, and Triterpenoids.

4.3 Antidiabetic Test

This study evaluated the antidiabetic effect of EEDK (*Muntingia Calabura L.*) on male white rats induced with alloxan. Before treatment, rats were fed for approximately 8 hours, then given alloxan induction intraperitoneally, because alloxan can increase blood sugar levels quickly without damaging insulin-producing cells in the pancreas. Initial measurement of blood sugar levels (H_0) was done after

induction. Rats are said to experience hyperglycemia if their fasting blood sugar levels reach 126 mg/dL or higher.

The negative control group was given aquadest (K^-) as a comparison. The second group received glibenclamide, the third group received a combination of EEDK (*Muntingia Calabura L.*) 150 mg/kgBW, the fourth group EEDK (*Muntingia Calabura L.*) 300 mg/kgBW, and the fifth group received EEDK (*Muntingia Calabura L.*) 600 mg/kgBW. After the rats reached the condition of increased blood sugar levels, measurements of blood sugar levels were made on days 15, 20, 25, and 30.

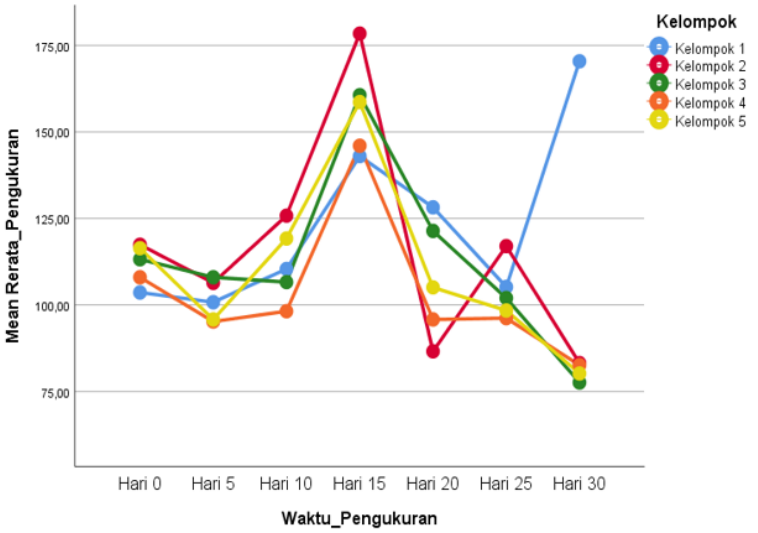

Fig. 1. Blood Sugar Reduction Chart

The average blood sugar levels in group 1 to group 5 showed an increase on Day 15, reaching > 126 mg/dL. However, in the next post test measurement, there was a decrease in blood sugar levels in group 2 to group 6. Conversely, the negative control group continued to experience an increase in blood sugar levels because they were not given any therapy, only given aquadest as a comparison. Furthermore, the percentage of increase and decrease as well as the graph of increase and decrease in blood sugar levels in each treatment with the aim of analyzing the percentage changes in various groups. The following is the complete data showing the percentage change of each group during the observed time period.

4.4 Data Analysis

Blood Sugar Level Evaluation Measurement of blood glucose levels was performed using a glucometer. Data from the measurement of blood glucose levels were analyzed using SPSS with significance based on the One Way ANOVA test ($P < 0.05$) followed by the Post Hoc LSD test. Based on the test results of blood glucose levels in hyperglycemic rats given various treatments, it was observed that the administration of EEDK can reduce glucose levels in hyperglycemic rats.

Table 4. Results of One-Way ANOVA Test and Post Hoc LSD between treatment groups

Measurement Time	Negative	Glibenclamide	Mean ± SD			p-value
			EEDK (*Muntingia calabura L.*) 150 mg/KgBW	EEDK (*Muntingia calabura L.*) 300 mg/KgBW	EEDK (*Muntingia calabura L.*) 600 mg/KgBW	
Day 0	103.60 ± 8.8	117.40 ± 12.3	113.20 ± 24.8	108.00 ± 10.7	116.40 ± 14.8	.589
Day 5	100.80 ± 7.3	106.40 ± 10.6	108.60 ± 22.9	95.20 ± 10.8	95.80 ± 11	.538
Day 10	110.40 ± 18.2	125.80 ± 22.5[a]	106.80 ± 8.5	98.20 ± 13.3[b]	119.20 ± 18.6	.130
Day 15	143 ± 23.8	178.40 ± 30.3	136.60 ± 16.2	124.60 ± 21.76	158.60 ± 34.8	.347
Day 20	128.20 ± 20.9[a,b,d,e]	86.60 ± 10.9[a,c,e]	160.60 ± 42.4[a,c]	95.80 ± 12.2[a]	118.80 ± 31.1[a,b,c,d]	.000
Day 25	105.20 ± 14.0	117 ± 40.2[a]	115.20 ± 30.8	92.20 ± 22.2[a]	118.40 ± 23.6[a]	.048
Day 30	170.40 ± 50.3[a,b,c,d,e]	83.20 ± 9.9[a]	77.60 ± 8.9[a]	82.80 ± 23.4[a]	114.10 ± 14.1[a]	.000

*EEDK = Ethanol Extract of Kersen Leaf (Muntingia Calabura L.)

Mean ± SD, P-Value of blood glucose levels at H0, H5, H10, H15, H20, H25 and H30 were determined based on the results of LSD post hoc non-parametic analysis of the results that showed significant results, namely in K1,K2, K3, K4, and K5. The result of post hoc non-parametric analysis. a significant difference to the Negative Group (P< 0.05); b significant difference to the Glibenclamid positive Group (P< 0.05); c significant difference to Treatment Group 1 EEDK (Muntingia Calabura L.) 150mg/kgBW (P< 0.05); d significant difference to Treatment Group 2 EEDK (Muntingia Calabura L.) 300mg/kgBW (P< 0.05); e significant difference to Treatments Group 3 EEDK (Muntingia Calabura L) 600mg/kgBW (P< 0.05).

Table 5. One-Way Anova and Post Hoc LSD test results between measurement times

Measurement Time	Negative	Glibenclamide	Mean±SD			p-value
			EEDK (*Muntingia calabura L.*) 150 mg/KgBW	EEDK (*Muntingia calabura L.*) 300 mg/KgBW	EEDK (*Muntingia calabura L.*) 600 mg/KgBW	
Day 0	103.60 ± 8.8[g]	117.40 ± 12.3[d,e,g]	113.20 ± 24.8[g,d]	108.00 ± 10.7[g,d]	116.40 ± 14.87[d,g]	,000
Day 5	100.80 ± 7.3[d,g]	106.40 ± 16.6[a,d]	108.00 ± 22.9[a,d]	95.20 ± 11[c,d]	95.80 ± 11.1[c,d]	,000
Day 10	110.40 ± 18.2[g]	125.80 ± 22.5[a,c,e]	106.80 ± 8.5[d]	98.20 ± 13.3[a,d]	119.20 ± 18.56[b,d,g]	,000
Day 15	143 ± 25.3[a,b]	178.40 ± 30.3[a,b,c,e,f,g]	146 ± 21.76[a,b,c,e]	124.60 ± 21.76[b,c]	158.60 ± 33.6[a,b,c,f,g]	,000
Day 20	128.20 ± 20.94[g]	86.60 ± 10.9[a,c,e,f]	142.40 ± 24.42[d,g]	95.80 ± 12.23[a,d]	118.80 ± 31.1[a,b,c,d]	,000
Day 25	105.20 ± 14.0[d,e,g]	117 ± 40.2[a,c,f,g]	115.20 ± 36.4[a,e,f,g]	92.20 ± 22.86[a,d]	98.40 ± 22.86[a,d]	,000
Day 30	170.40 ± 50.34[a,b,c,e,f]	83.20 ± 9.9[a,e,f]	77.60 ± 8.9[a,e,f]	82.80 ± 23.41[a,e,f]	80.30 ± 14.13[a,e,f]	,000

*EEDK = Ethanol Extract of Kersen Lead=f (Muntingia Calabura L.) Mean ± SD, P-Value of blood glucose levels at H0, H5, H10, H15, H20, H25 and H30 were determined based on the results of LSD post hoc non-parametric analysis of the results that showed significant results, namely at H0, H5, H10, H15, H20, H25 and H30. The results of non-parametric post hoc analysis. a significant difference to Day 0 ($P< 0.05$); b significant difference to Day 5 ($P< 0.05$); c significant difference to Day 10 ($P< 0.05$); d significant difference to Day 15 ($P< 0.05$); e significant difference to Day 20 ($P< 0.05$); f significant difference to Day 25 ($P< 0.05$); g significant difference to Day 30 ($P<0.05$).

5 Conclusion

Based on the research results above, it can be concluded that, Kersen Leaf (Muntingia Calabura L.) is effective in reducing glucose because it can be seen from the results and discussion on days 5 to 15 of the post test in group 2 to group 5 experiencing a decrease in blood glucose levels because it is below the fasting blood glucose level of 126 mg/dL. The optimal concentration of Kersen Leaf (Muntingia Calabura L.) 150 mg/kgBW, 300 mg/kgBW, and 600 mg/kgBW is the optimal level and effectiveness in reducing blood glucose levels because it does not exceed fasting blood glucose levels of 126 mg/dL and is not hypoglycemic at 70 mg/dL.

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