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Research Article

Kersen (*Muntingia calabura* L.) Leaves Extract Increases GLUT 4 Concentration in Streptozotocin-Nicotinamide-Induced Male Rats

Ekstrak Daun Kersen (Muntingia calabura L.*) Meningkatkan Konsentrasi GLUT 4 pada Tikus Jantan yang Diinduksi Streptozotosin-Nikotinamida*

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ABSTRACT

Diabetes Mellitus (DM) is a group of metabolic diseases characterised by hyperglycaemia, resulting from abnormalities in insulin secretion, insulin action, or both. Kersen (*Muntingia calabura* L.) leaves contain bioactive compounds, namely flavonoids, tannins, terpenoids, saponins, and polyphenols, which exhibit antioxidants and anti-diabetics. Glucose transporter (GLUT) 4 is an insulin-responsive glucose transporter in muscle and adipose tissue. This study aimed to examine the effect of Kersen leaves extract on GLUT 4 concentration in male rats induced by Streptozotocin-Nicotinamide. Diabetic rats were induced by Streptozotocin 45 mg/kg BW-Nicotinamide 110 mg/kg BW intraperitoneally, and the extract was administered orally for 14 days. Blood glucose level was measured using the Glucose Oxidase-Phenol 4-Aminoantipyrine (GOD-PAP) method, and GLUT 4 activity was assessed using the ELISA method. Statistical results showed significant differences ($p<0.05$) at 200, 400, and 600 mg/kg BW doses on the glucose and GLUT 4 levels. The 600 mg/kg BW group dose showed the best result with a blood glucose level of 88.22±2.31 mg/dL and a GLUT 4 level of 37.21±0.81 ng/mL. These findings demonstrate that Kersen leaves ethanol extract effectively lowers blood glucose levels and enhances GLUT 4 activity, with the most effective dose being 600 mg/kg BW.

Keywords*:* Diabetes Mellitus, GLUT 4, Kersen Leaves

ABSTRAK

Diabetes Melitus (DM) merupakan kelompok penyakit metabolik yang ditandai dengan hiperglikemia, terjadi karena kelainan sekresi insulin, kerja insulin, ataupun keduanya. Daun Kersen (Muntingia calabura L.*) merupakan tanaman yang mengandung senyawa bioaktif, yaitu flavonoid, tanin, terpenoid, saponin, dan polifenol yang memliki aktivitas antioksidan dan anti-diabetes. GLUT 4 adalah transporter glukosa yang responsif terhadap insulin di otot dan jaringan adiposa. Tujuan penelitian ini untuk menguji pengaruh ekstrak daun Kersen terhadap konsentrasi GLUT 4 pada tikus jantan yang diinduksi Streptozotosin-Nikotinamida. Tikus diabetes diinduksi menggunakan Streptozotosin 45 mg/kg BB-Nikotinamida 110 mg/kg BB secara intraperitoneal, perlakuan ekstrak*

diberikan secara oral selama 14 hari. Pengukuran glukosa darah menggunakan metode Glukosa Oksidase Fenol 4-Aminoantipirin (GOD-PAP) dan metode ELISA untuk mengukur aktivitas GLUT 4. Hasil statistik menunjukkan perbedaan signifikan (p<0,05) pada dosis 200, 400, dan 600 mg/kg BB, dengan dosis terbaik untuk uji kadar glukosa darah adalah 600 mg/kg BB dengan rata-rata 88.22±2.31 mg/dL, dan uji aktivitas GLUT 4 dosis terbaik, yaitu 600 mg/kg BB dengan rata-rata 37.21±0.81 ng/mL. Ekstrak etanol daun Kersen telah terbukti efektif menurunkan kadar glukosa darah dan mampu meningkatkan konsentrasi GLUT 4 dengan dosis terbaik 600 mg/kg BB.

Kata Kunci: *Daun Kersen, Diabetes Melitus, GLUT 4*

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders characterised by hyperglycaemia, resulting from abnormalities in insulin secretion, insulin action, or both. DM is generally classified into two types: type 1 DM or Insulin Dependent Diabetes Mellitus (IDDM) and type 2 DM or Non-Insulin Dependent Diabetes Mellitus (NIDDM). Type 2 DM occurs due to inadequate insulin production by pancreatic β-cells or the development of insulin resistance (1). According to the International Diabetes Federation (IDF) data from 2021, the prevalence of DM in Indonesia was 10.6%. In Palembang, the prevalence of DM in 2019 was recorded at 71,031 cases, which increased to 172,044 in 2020, reaching 279,345 cases by 2021 (2).

The physiological process of glucose uptake into cells is regulated by insulin and the rate of glucose transport through specific plasma membrane-associated proteins known as Glucose Transporters (GLUT), one of which is GLUT 4. GLUT 4 is an insulin-responsive glucose transporter expressed in muscle and adipose tissues in humans and rodents. It is recognised as the primary glucose transporter that regulates insulin-stimulated glucose uptake, secreted by β-cells acting as glucose sensors (3). Phytochemical screening has shown that Kersen leaves (*Muntingia calabura* L.) contain flavonoid compounds. Several studies have reported that flavonoids exhibit antidiabetic activity and can enhance GLUT 4 translocation through the Phosphatidylinositol-3-kinase (PI3K)/Akt and AMP-activated protein kinase (AMPK) pathways. Previous research has demonstrated that Kersen Leaves Extract (KLE) at a dose of 400 mg/kg body weight (BW) possesses antidiabetic activity through mechanisms including enhancement of insulin secretion, regeneration of pancreatic β-cells, and improvement of insulin sensitivity (4). Another study also reported that administering KLE could reduce blood glucose levels in mice (*Mus musculus*) at 12 mg/20 g BW (5).

Pharmacological therapy for DM patients may include the use of biguanides, sulfonylureas, Dipeptidyl Peptidase-4 (DPP-4) inhibitors, Sodium-Glucose co-transporter-2 (SGLT2) inhibitors, Glucagon-like Peptide-1 (GLP-1) receptor agonists, dopamine-2 agonists, and Thiazolidinedione (TZD) class drugs (6). The TZD class, including pioglitazone and rosiglitazone, has positively correlated with increased GLUT 4 transcription. Kersen leaves are plants with bioactive compounds that may be used as medicinal agents. These leaves contain alkaloids, flavonoids, tannins, terpenoids, saponins, and phenolic compounds (7). The phenolic content exhibits antioxidant activity that may contribute to antidiabetic effects by protecting pancreatic β-cells from the toxic effects of free radicals produced during chronic hyperglycaemia conditions. Consequently, insulin levels can be maintained, helping regulate blood glucose within a normal range (8).

Despite these promising findings, molecular-level studies evaluating the effect of KLE on increasing GLUT 4 concentrations remain limited. Therefore, this study evaluated the activity of KLE on GLUT 4 concentration and its ability to reduce blood glucose levels in male rats induced with Streptozotocin-Nicotinamide (STZ-NA).

Materials and Methods

Materials

The Kersen leaves simplicia was obtained from Omah Djamoe Arroyan, Central Java, with a determination certificate number KM.04.02/2/332/2023. Pioglitazone, 70% ethanol, STZ-NA, sodium carboxymethylcellulose (CMC-Na), ketamine, Phosphate Buffered Saline (PBS), diluent buffer, and an ELISA kit (Fine Test, China) consisting of biotin-labelled antibody, SABC diluent buffer, 3′,5,5′-Tetramethylbenzidine (TMB) substrate, and stop solution. The experimental animals were 25 male Wistar rats aged 2-3 months, weighing 150-200 g. The rats were obtained from the Laboratory of the Centre for Food and Nutrition Studies breeding facility, Universitas Gadjah Mada, Yogyakarta.

Methods

1. Preparation of KLE

One kilogram of dried Kersen leaves powder was placed into a dark container, then 5 L of 70% ethanol (1:5 ratio) was added. The mixture was stored in a sealed container away from direct sunlight and stirred occasionally over 3 days until the solvent turned clear. Afterward, the mixture was filtered, and the remaining residue was remacerated with another 5 L of 70% ethanol. The extracts from both filtrations were combined and evaporated using a rotary evaporator (Eyela, Tokyo Rikakikai Co., LTD). The resulting concentrate was thickened using a water bath at approximately 50°C until a viscous paste-like texture was obtained.

2. Induction and Preparation of Animal Subjects

This study's research protocol for the diabetic intervention using KLE was reviewed and approved by the Health Research Ethics Committee (HREC) of the Faculty of Medicine, Muhammadiyah University of Surakarta, with the ethical clearance letter number 4800/A.2/KEPK-FKUMS/II/2023. Before induction, the animals' blood glucose levels were measured to assess their baseline glucose and plasma insulin levels. Induction was performed by injecting NA at a dose of 110 mg/kg BW intraperitoneally, followed by STZ injection at a dose of 45 mg/kg BW. The rats were divided into five groups, each consisting of five rats. Animals with fasting blood glucose levels greater than 180 mg/dL were included in the subsequent treatments and were housed for two weeks with free access to food and water. The animals were then orally administered daily doses of CMC-Na suspension, pioglitazone, or KLE for 14 days. The treatment groups were as follows: Group I (negative control) received 1% CMC-Na suspension, Group II (positive control) received 0.27 mg/kg BW pioglitazone, Group III received 200 mg/kg BW of KLE, Group IV received 400 mg/kg BW of KLE, and Group V received 600 mg/kg BW of KLE. On day 14, the blood samples and adipose tissue were collected.

3. Blood Glucose Measurement

Blood glucose levels were measured on days 0 (baseline), 2 post-STZ-NA induction, and 14 post-treatment. The blood glucose concentration was determined using the GOD-PAP method. Blood samples were collected from the retro-orbital plexus and centrifuged at 4.000 rpm for 10 minutes. The clear serum was then separated and analysed for blood glucose levels.

4. Adipose Tissue Isolation

The rats were anesthetised intraperitoneally with ketamine at 70 mg/kg BW. White adipose tissue was extracted via surgery from the abdominal wall, and 50 mg of retroperitoneal (visceral) adipose tissue was isolated and washed with 1% PBS. The tissue and PBS solution were centrifuged twice at 3.000 rpm for 20 minutes. After centrifugation, the pellet and supernatant were separated. The supernatant was collected for GLUT 4 measurement (9)

5. GLUT 4 Measurement

GLUT 4 concentration in the adipose tissue was determined using an ELISA kit. 100 µL of standards or samples were added to each well and incubated for 90 minutes at 37°C. After incubation, the solution was discarded and washed twice. Then, 100 µL of biotin-labelled antibody solution was added to each well and incubated for 60 minutes at 37°C, followed by washing the wells three times. Afterward, 100 µL of SABC work solution was added to each well and incubated for 30 minutes at 37°C, then the wells were washed five times. Next, 90 µL of TMB substrate solution was added and incubated

for 10-20 minutes at 37°C. The reaction was terminated by adding 50 µL of stop solution. Absorbance was measured at 450 nm using a microplate reader, and GLUT 4 concentration was calculated based on the standard curve.

Data Analysis

Statistical analysis was performed using SPSS 16.0 software. The diabetes induction in the rat model was confirmed by comparing the mean fasting blood glucose levels before and after STZ-NA induction. The data was tested for normality (Shapiro-Wilk test) and homogeneity (Levene's test). The normally distributed and homogeneous data were then tested with one-way ANOVA. Otherwise, the Kruskal-Wallis test was performed for non-normally distributed or heterogeneous data, followed by the Mann-Whitney test to determine differences between groups.

RESULTS

1. Extraction Results of Kersen Leaves

Following the concentration and weighing process, 152 g of KLE was obtained from 1 kg of dried Kersen leaves powder, yielding an extraction efficiency of 15.2%.

2. Results of Blood Glucose Levels Pre-Post Induction and Post-Treatment

Measurement of fasting blood glucose levels pre- and post-induction showed that each treatment group and the comparison group experienced an average increase in blood glucose levels after being induced with STZ-NA. The effectiveness of KLE on the rats' blood glucose levels was tested over 14 days by measuring blood glucose levels on the first day of treatment and then again on the 14th day to assess whether there was any reduction in blood glucose levels after KLE administration. The results showed that each treatment group experienced a reduction in blood glucose levels compared to the negative control (group I). The most pronounced reduction was observed in Group V (600 mg/kg BW), suggesting it was the most effective dose. Comparative data on glucose levels across the three measurement points are illustrated in **Figure 1**.

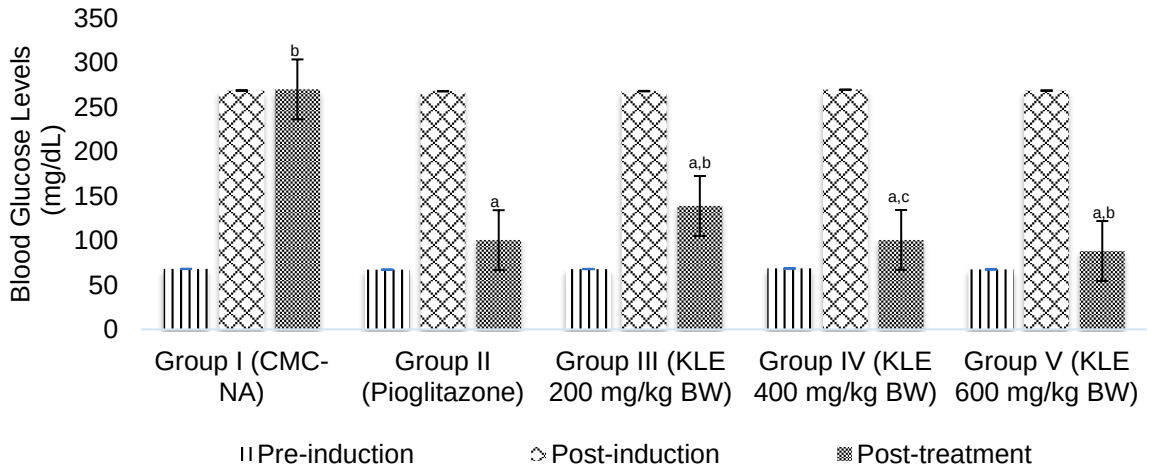

Figure 1. Comparison of blood glucose levels in rats pre- and post-STZ-NA induction, and after treatment with various doses of Kersen Leaves Extract (KLE), along with negative control, and positive control (a = significantly different from group I; b = significantly different from group II; c = no significant difference from group II)

Based on data presented in **Figure 1**, blood glucose levels post-induction with STZ-NA increased significantly following STZ-NA induction in all groups. The highest increase in blood glucose levels occurred in group IV. **Figure 1** also shows a reduction in glucose levels in group II and the treatment groups with all three doses. However, the group with the lowest reduction in blood glucose levels was group V, indicating that its effectiveness was better than that of group II, the positive control group. The next group to show a reduction in blood glucose levels was group IV, followed by group II. These two groups did not show significant differences, indicating that group IV had the same effectiveness as

group II. As the positive control group, pioglitazone, effectively lowers blood glucose levels, partly by increasing the body's response to insulin. When the blood glucose levels in the treatment groups approach or equal those of the positive control group, it can be concluded that the effectiveness of group IV is comparable to that of group II. The subsequent reduction in blood glucose levels was observed in group III. Group I, as the negative control, showed no decrease in blood glucose levels.

3. Effect of KLE on GLUT 4 Levels

The GLUT 4 levels were tested on the 14th day after treatment. The test aimed to assess whether KLE administration could enhance GLUT 4 concentration, which plays a crucial role in glucose uptake. Normality and homogeneity tests on the GLUT 4 levels showed that the data were normally distributed ($p>0.05$) but not homogeneous ($p<0.05$). Therefore, data analysis was performed using non-parametric tests, namely Kruskal-Wallis and Mann-Whitney tests. The statistical test results (**Table 2**) showed significant differences between groups I, II, and the treatment groups, as indicated by a $p<0.05$. The highest GLUT 4 concentration was observed in group V (37.21 ng/mL), better than pioglitazone (31.00 ng/mL), followed by group IV (30.02 ng/mL), and group III (17.59 ng/mL). These findings suggest that higher doses of KLE are associated with increased GLUT 4 expression, potentially enhancing glucose transport activity.

Table 2. Results of GLUT 4 Concentration Measurement After Administration of KLE, Negative Control, and Positive Control

Treatment Group	Average GLUT 4 Concentration (ng/mL)
Group I (CMC-NA 1%)	1.31 ± 0.14^{b}
Group II (Pioglitazone 0.27 mg/kg BW)	31.00 ± 0.54^{a}
Group III (KLE 200 mg/kg BW)	$17.59\pm0.38^{a,b}$
Group IV (KLE 400 mg/kg BW)	$30.02\pm0.15^{a,b}$
Group V (KLE 600 mg/kg BW)	$37.21\pm0.81^{a,b}$

Description: [a] = Significantly different from group I; [b] = Significantly different from group II

DISCUSSION

1. Extraction Results of Kersen Leaves

The extraction used the maceration method with 70% ethanol as the solvent. The maceration method was chosen for its simplicity, cost-effectiveness, and ease of execution without heating, thus preserving heat-sensitive compounds (10). Ethanol at 70% concentration is considered an ideal solvent for phytochemical extraction, as it effectively prevents microbial growth while extracting a wide range of bioactive compounds (11).

The extraction yield is the ratio of metabolites obtained after extraction to the weight of the sample used (12). The obtained KLE was 152 g, yielding 15.2%, compared to the previous findings by Uthia *et al.* (13) with 70% ethanol extract of Kersen leaves yielded 12.65%. The extract yield difference might be caused by the variety of particle size or the duration of extraction process (14).

2. Blood Glucose Levels Pre-Post Induction and Post-Treatment

The increase in blood glucose levels occurred due to STZ administration, which caused damage to the β-cells of the pancreas, leading to progressive weight loss, insulin deficiency, dyslipidaemia, and chronic hyperglycaemia (15). NA, a derivative of vitamin B3, protects the β-cells of the pancreas from the cytotoxicity of STZ (16). It aligns with research by Potarniche *et al.* (17), where NA could lighten the toxicity of STZ towards β-cells. STZ-NA administration induces hyperglycaemia by affecting the β-cells of the pancreas within 3 days or 72 hours, peaking on the 7th day after induction (9).

Figure 1 illustrates that the most significant reduction in blood glucose levels occurred in group V, which was more effective compared to group II. This result aligns with Varizza *et al.'s* study, which showed the dose-dependent result (18). This best activity in the highest dose group might be due to the active compounds in KLE, which affect the repairing of body cells (19). Research by Djarmi *et al.* showed that KLE was most effective in reducing blood glucose levels at a 70% concentration (20). According to Ahidin *et al*., the most effective dose of KLE in reducing blood glucose in mice was 12 mg/20 g BW (21). The reduction in blood glucose levels in the test animals is attributed to the active

metabolites in Kersen leaves, such as flavonoids, which help lower blood glucose by protecting pancreatic β-cells, improving insulin signalling, reducing oxidative stress and inflammation, activating the AMPK pathway, and inhibiting carbohydrate digestion and absorption (22). The primary compounds in Kersen leaves—flavonoids, tannins, and saponins—enhance biological mechanisms, acting as anti-diabetic agents by lowering blood glucose levels and increasing insulin levels in Wistar rats (23). Antioxidants such as flavonoids, saponins, and tannins have been reported to exhibit pharmacological activity in diabetes treatment (24). The findings from this study show that KLE at a dose of 600 mg/kg BW was more effective than the 400 mg/kg BW and 200 mg/kg BW doses in lowering blood glucose levels.

3. Effect of KLE on GLUT 4 Activity

GLUT 4 is a key glucose transporter predominantly expressed in muscle and adipose tissues. Impaired expression or translocation to the plasma membrane in type 2 DM patients can hinder glucose entry into cells for energy production. As a result, glucose fails to enter target tissues, such as muscle and adipose tissue, leading to elevated blood glucose levels (25). The GLUT 4 transporter mechanism occurs when insulin signals vesicles containing GLUT 4 to bind to the cell surface, causing the vesicles to fuse with the plasma membrane and allow glucose to enter the cell. When insulin secretion decreases, GLUT 4 is internalised from the plasma membrane into intracellular vesicles through endocytosis. The insulin suppresses hepatic glucose production and enhances glucose uptake by muscle and adipose tissues by increasing GLUT 4 translocation to the plasma membrane to maintain glucose homeostasis (26).

The increase in GLUT 4 concentration in adipose tissue following KLE administration is due to the flavonoid compounds, which enhance glucose uptake by stimulating GLUT 4 translocation to the cell membrane under basal and insulin-stimulated conditions (27). The antioxidant compounds in Kersen leaves, such as flavonoids, tannins, and saponins, exert anti-diabetic effects. This result is consistent with Yibing *et al.'s* research, which indicated that flavonoids could reduce hyperglycaemia, insulin resistance, and dyslipidaemia by activating the GLUT 4 pathway and regulating the expression of Peroxisome Proliferator-Activated Receptors Alpha (PPARα) and Gamma (PPARγ) in diabetes-induced mice, as well as increasing GLUT 4 translocation in vitro (28). Tannins have anti-diabetic effects by promoting cell recovery and reducing carbohydrate absorption by inhibiting α-amylase and α-glucosidase activity (29). Saponins modulate insulin signalling, inhibit α-glucosidase activity, and enhance GLUT 4 activity. Antioxidants reduce insulin resistance by increasing GLUT 4 expression in the skeletal muscle of obese animals (30).

Based on the GLUT 4 concentration measurement data in **Table 2**, the observed reduction in blood glucose levels and the corresponding increase in GLUT 4 concentration can be attributed to the antioxidant and anti-diabetic effects of the compounds in Kersen leaves. The increase in GLUT 4 concentration likely occurred as insulin levels returned to normal. However, the secondary metabolites responsible for the increase in GLUT 4 concentration remain unidentified.

CONCLUSION

This study concluded that the administration of 600 mg/kg BW of ethanol extract of Kersen leaves effectively lowers blood glucose levels and increases GLUT 4 concentration in rats induced with STZ-NA. Further research is needed to determine the levels of secondary metabolites in the ethanol extract of Kersen leaves.

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