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A Comparison antidiabetic activity of water and ethanol extraction of *Muntingia calabura L* leaves against male mice

Perbandingan aktivitas antidiabetes ekstrak air dan etanol *Muntingia calabura L Folium* terhadap mencit jantan

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Abstract

Muntingia calabura L is an Indonesian herbal plant known as kersen which has the ability to reduce blood sugar levels. *M. Calabura* has secondary metabolites, namely flavonoids, tannins, triterpenoids, saponins and polyphenols. This study aimed to compare the antidiabetic activities of water and ethanol extracts of *M. calabura* in male mice. In this study, *M. calabura* was extracted using the maceration method with 70% ethanol solvent (EEMC) and decoction of Kersen leaves (EDMC). Blood glucose levels were measured at intervals of 15, 30, 45, and 60 minutes using a glucometer after being induced by alloxan induction. Animals were divided into eight groups (positive group, negative group and EEMC group, and EDMC group with doses of 125, 250 and 500 mg/kg BW. The results of the investigation showed that the activity to reduce blood glucose levels during the interval time was significantly different compared to the negative group, and positive control was not significantly different compared to the EEMC 250 mg/kg BW and EDMC 500 mg/kg BW groups. The conclusion of this study was that the EEMC and EDMC groups had decreased blood glucose levels. EEMC 250mg/kg BW and EDMC 500 mg/kg BW groups showed comparable activity to the positive control.

Keywords: Muntingia calabura L, glucose, glucometer.

Abstrak

Muntingia calabura L merupakan tanaman herbal indonesia yang dikenal kersen memiliki aktivitas untuk menurunkan kadar gula darah, *M. calabura Folium* memiliki metabolit sekunder yaitu tanin, flavonoid, saponin, triterpenoid serta polifenol yang juga memiliki antioksidan tinggi. Tujuan penelitian untuk menentukan aktivitas antidiabetes dari dekok *M.Calabura* dan etanol dari *M. Calabura Folium* terhadap mencit yang diinduksi aloksan. Metode penelitian ini, daun kersen yang diekstraksi secara maserasi dengan etanol 70% dan dekoksi daun kersen (EDMC) dan pengukuran kadar glukosa darah dengan interval waktu menggunakan glucometer setelah diinduksi aloksan. Hewan percobaan dibagi menjadi 8 kelompok (kelompok positif, kelompok negatif serta kelompok EEMC (ekstrak etanol Mutingia calabura) dan kelompok EDMC (Ekstraksi Dekok Muntingia calabura) dengan dosis 125mg, 250mg dan 500mg/kg BB. Hasil pengujian menunjukkan adanya aktivitas dalam menurunkan kadar gula darah selama interval waktu yang ditentukan berbeda siginifikan dibandingkan dengan kelompok negatif sementar kontrol positif (glibenklamid) menunjukkan tidak berbeda signifikan dibandingkan dengan EEMC 250 mg/kg BB dan EDMC 500 mg/kg BB. Kesimpulan penelitian ini bahwa kelompok EEMC dan kelompok EDMC memiliki aktivitas antidiabetes. EEMC 250 mg/kg BB dan EDMC 500 mg/kg BB sebanding dengan glibenklamid kemampuannya menurunkan konsentrasi glukosa darah terhadap mencit jantan.

Kata Kunci : Muntingia calabura L, glukosa, glukometer.

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Introduction

The World Health Organization (WHO) stated that there is indications that more than 180 million people will experience diabetes worldwide and it is estimated that by 2023 the number of sufferers will increase two-fold [1]. The International Diabetes Federation predicts that 451 million people suffered from diabetes in 2017 worldwide, projected to reach 693 million in 2045 if no effective prevention methods are implemented. In 2019, it was reported that diabetes was the ninth leading cause of death, with an estimated 1.5 million deaths directly attributable to diabetes [2]. Diabetes mellitus is a disease in the form of a metabolic disorder indicated by high glucose concentrations in the blood or also called hyperglycemia caused by a lack of insulin for the body's needs, insulin resistance or both. Hyperglycemia is a condition that is often found in people with type 2 DM where the condition is stated when the blood glucose concentration exceeds 200mg/dL and the HbA1c value ≥ 6.5% [3,4]. Diabetes mellitus is a condition of increased blood sugar caused by an abnormal metabolic system in the body, which causes the pancreas to be unable to meet the body's insulin needs [5].

Medicinal plants are still very popular among people as an alternative to traditional medicine used to treat diseases suffered by people. Some of these traditional medicines have been tested for their activity in vitro, in vivo research and clinical trials on humans [6]. Recently, people were using various herbal medicine products on the market. The use of medicinal plants that were often used empirically to treat diabetes and have been reported to be efficacious based on previous research is *Muntingia calabura* L. *Muntingia calabura* L or medicinal plants in Indonesia which are better known as kersen where this plant was also reported to have activity as an antidiabetes, anti-inflammatory, antioxidant, antibacterial, analgesic and antihyperlipidemia [7]. *M. Calabura* leaves contain secondary metabolites consisting of tannins, flavonoids, saponins, triterpenoids and polyphenols which also have antioxidant activity [8]. Tannins and flavonoids are active components as antidiabetics and their role as antioxidants [9]. Flavonoids play a role in increasing insulin sensitivity by reducing damage to β cells in the pancreas through a chain reaction of peroxidation by Reactive Oxygen Species [10,11]. Kersen leaf extract was reported to have high antioxidant activity in previous studies [12,13] and polyphenol compounds can ward off free radicals and oxidative stress which is one of the causes of diabetes by inhibiting enzymes that have the task of breaking down carbohydrates into glucose [14].

According to previous research, the potential of the kersen plant can be used as a traditional medicine to overcome diabetes which is understood that the side effects are relatively small. This study was conducted to determine the comparison of the antidiabetic activity of EEMC and EDMC (*Muntingia calabura* L) on male mice induced by alloxan by observing blood glucose concentrations at intervals of every 15 minutes for 60 minutes using a glucometer.

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Experimental Section

Plant Determination

Muntingia calabura was obtained from the city of Sibolga-North Sumatra. Identification of the kersen plant (Muntingia calabura L.) was carried out at the Medanese Herbarium (MEDA) USU, Jl. Bioteknologi No.1 University of Sumatra Utara, Medan-Indonesia (1198/MEDA/2023).

Preparation of Ethanol Extract of Mutingia calabura leaves

Muntingia Calabura leaf simplicia powder as much as 500 grams was macerated with 70% ethanol solvent, left for 5 days while stirring occasionally. Then filtered to obtain macerate. Rinse the dregs with 70% ethanol as much as 250 mL. All the macerate was left protected from sunlight for 2 days, then poured to obtain a liquid extract which was then concentrated using a rotary evaporator at a temperature of not more than 50^{o}C to produce a thick extract [6].

Preparation of Muntingia calabura Leaf Decoction

500 grams of Kersen leaf powder (*Muntingia Calabura* L.) into a container, then add 2 L of distilled water. This solution was heated for 30 minutes with the temperature set at 90^{o}C and stirred. Then filtering was carried out, the liquid extract obtained was evaporated to obtain a thick extract.

Preparation of Experimental Animals

Male mice (*Mus musculus*) used as experimental animals with a body weight ranging from 20-30 grams at the age of 2-3 months in healthy condition. 24 mice were used which were then divided into 8 groups where each group consisted of 4 experimental animals.

Anti-diabetic testing of ethanol extract and decoction of Kersen leaves

The experimental animals were acclimatized for 1 week by being given food and drinking water ad libitum. Then the mice were induced with alloxan to create a hyperglycemic state in each group. Initial blood glucose levels were checked before induction as a reference for normal blood glucose levels. Alloxan was given by dissolving it with physiological NaCl first intraperitoneally as much as 1 mL with a dose of 150 mg/kg BW. On the third day after induction, blood glucose levels were checked to determine the condition of the mice with hyperglycemia. The experimental animals were grouped into 8 treatment groups whose weights had been determined. Treatment given orally is as follows:

I. Group I : Na-CMC 1% w/v Suspension (Negative control)
II. Group II : EEMC 125mg/kg BW
III. Group III : EEMC 250mg/kg BW
IV. Group IV : EEMC 500mg/kg BW
V. Group V : EDMC 125mg/kg BW
VI. Group VI : EDMC 250mg/kg BW
VII. Group VII : EDMC 500mg/kg BW
VIII. Group VII : Glibenkelamid 0,052 mg/kg BB (Positive control)

Observations were assessed after treatment was given, by measuring blood glucose levels every 15 minutes for 60 minutes. Blood glucose concentrations were examined in mice using a glucometer.

Data analysis

Data collection based on the results of observations of blood sugar levels in mice was carried out statistical analysis based on the One way analysis of variance (ANOVA) method using SPSS software version 27.

Results and Discussion

The extract obtained from the maceration process of 500 grams of Muntingia Calabura L simple powder using 70% ethanol solvent obtained 80 grams of extract (EEMC) with an extract yield percentage of

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20.5% while the extract produced from the decocting process obtained an extract (EDMC) of 98.90 grams with an extract yield percentage of 15.95%.

In the antidiabetic activity test induced by alloxan, the observed response was the blood sugar levels of mice at intervals of 15 minutes for 60 minutes where blood samples were taken by injuring the tip of the mouse's tail and then the blood sugar levels were measured using a glucometer for each experimental group.

Table 1. Average Data on Blood Sugar Level Decrease Based on Time Interval

Treatment	Decreased Blood Glucose Levels				
	T0	T15	T30	T45	T60
Na CMC 1%	217,33±2,52	211±3	207±4,36	198,33±1,53	192±2
Glibenklamid	299,33±40	262,67±28,11	156,33±54,59	94±20,42	57±16,64
EEMC 125	272±41,76	242,67±34,65	189±18,19	138±23,3	81±12,29
EEMC 250	218,33±20,21	182,33±20,82	142,33±29,26	90,33±16,92	67±10
EEMC 500	249±1	160±10	110±10	84,67±6,66	65,33±11,02
EDMC 125	225±22,91	192,33±12,58	118,33±10,41	93,33±5,86	59,33±15,63
EDMC 250	253,33±19,86	195±12,17	102,33±6,81	83±4,36	56±9,85
EDMC 500	250±28	188,33±21,5	138±39,59	81,33±15,7	49±11,53

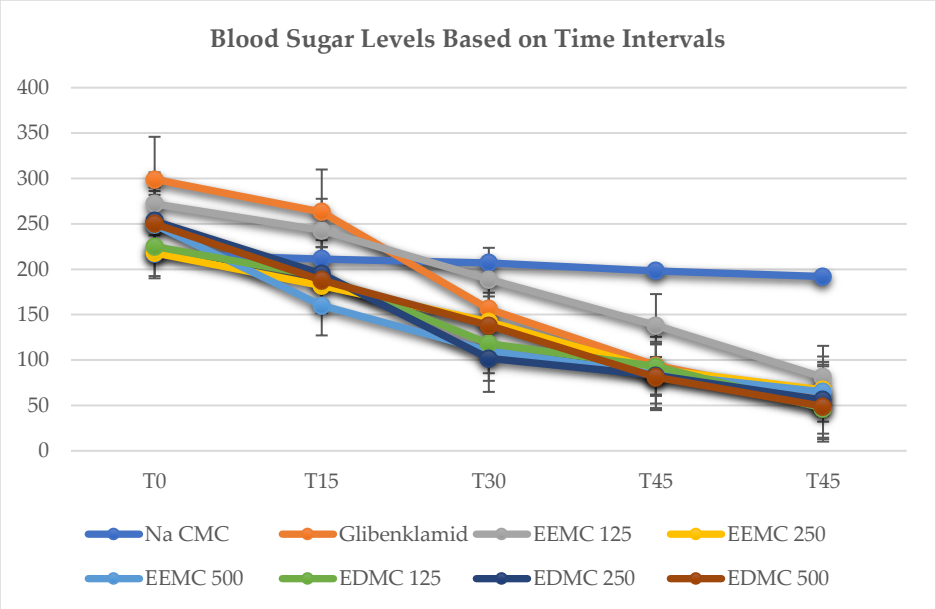

Figure 1. Activity data of Muntingia EEMC and EDMC ethanol extracts based on blood glucose concentration examination of mouse blood samples.

Based on observations in this study, it shows the average data of blood glucose levels in mice for each treatment group that was examined every 15 minutes for 60 minutes which can be shown in Figure 1. The results of the examination above explain that each dose in the EEMC group and the EDMC group, namely 125 mg / Kg, 250 mg / Kg BW and 500 mg / Kg BW, there was activity with a decrease in blood sugar levels in experimental animals compared to the negative control group (Na CMC 1%). According to observations based on the time interval, there was a decrease in blood sugar levels as time went on, while in the 1% Na CMC suspension, there was no significant decrease in blood sugar levels in experimental animals. However, the activity of the EEMC group and the EDMC group did not differ significantly compared to the Positive control group (glibenclamide) regarding the activity data in the form of a decrease in blood glucose concentration at each time interval in the EEMC 250 mg/Kg group and the EDMC 500 mg/Kg BW group, so from this data it

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can also be seen that EEMC250 mg/Kg BW has an activity that was comparable to the EDMC500 mg/Kg BW group based on a comparison with the activity given by the positive control group, which can cause blood glucose levels to decrease and is significantly different from the Na CMC suspension group.

The positive control group is a group whose treatment was given a drug that can lower blood glucose levels known as glibenclamide, where this drug is included in one of the sulfonylurea drugs used for treatment therapy for diabetes sufferers. Glibenclamide has a therapeutic effect for diabetes sufferers in lowering blood glucose levels which increase insulin secretion so that it meet the body's insulin needs. [15]. Apart from that, glibenclamide has a mechanism of action, namely triggering insulin secretion in the β cells in the Langerhans pancreas, so that interaction occurs in channels sensitive to potassium adenosine triphosphate in the β cell membrane which causes membrane depolarization and insulin entry occurs which ultimately activates insulin secretion which Next, it will bind glucose in the blood, causing blood glucose levels to return to normal conditions [16].

The decrease in blood glucose levels in EEMC and EDMC is caused by the presence of a group of plant compounds which are secondary metabolites. The group of secondary metabolite compounds contained in *Muntingia calabura* Folium are flavonoids (quercetin and kaempferol), tannins, saponins and polyphenols which have antioxidant activity [17,18]. Flavonoids have the function of regenerating pancreatic beta cells and have the activity of stimulating insulin secretion. [19]. It is reported that flavonoids have therapeutic effects for the treatment of diabetes sufferers by inhibiting glucose absorption and their ability to regulate enzyme secretion to assist in carbohydrate metabolism [20]. Polyphenols have a role as antioxidants which can capture free radicals that cause damage to pancreatic beta cells. Antioxidants have the ability to provide protection so that beta cells found in the islets of Langerhans remain normal, this can trigger the renewal of beta cells that are still in normal condition through the process of mitosis or the occurrence of endocrine proliferation and differentiation of ductal and ductular cells so that they form new islets. [17,21]. Tannin is known for its astringent function or is also called a chelator, where its function is to shrink the epithelial membrane in the small intestine. This process can inhibit the absorption of food essence so that sugar intake is inhibited and blood glucose levels are maintained so that they do not get too high [22].

Conclusions

The observational data from this study provide the conclusion that the EEMC 250 mg/Kg BW and EDMC 500 mg/Kg BW groups are comparable to glibenclamide in their activity in reducing blood glucose concentrations in male mice based on observations with time intervals.

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