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# EFFECT OF ADMINISTRATION OF BINAHONG LEAF ETHANOL EXTRACT ON REDUCING BLOOD SUGAR LEVELS IN TYPE 2 DIABETES MELLITUS MODEL RAT

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**ABSTRACT**

**Background**. Type 2 diabetes mellitus (T2DM) is characterized by elevated levels of blood glucose. Binahong leaves contain various metabolites such as flavonoids which are known to have antidiabetic effects. The research aims to determine the effect of administering ethanol extract of Anredera cordifolia (Ten.) Steenis leaves on reducing blood sugar levels in T2DM rats.
**Methods**. This study is a true experimental in vivo with a pre-post test control group design. This study used 30 rats consisting of 6 groups: normal control, negative control, positive control (metformin), ethanol extract of binahong leaves dose 25 mg/kgBW, ethanol extract of binahong leaves dose 50 mg/kgBW, and ethanol extract of binahong leaves dose 100 mg/kgBW. The treatment group was induced by HFD for 14 days and injected with streptozotocin 30 mg/kgBW followed by ethanol extract of binahong leaves for 14 days. Rat blood sugar levels were evaluated 7 and 14 days after administration of binahong leaf ethanol extract. Data analysis used parametric and Wilcoxon non-parametric statistical tests.
**Results**. Ethanol extract of binahong leaves doses of 25 mg/kgBB, 50 mg/kgBW, and 100 mg/kgBB affected reduced blood glucose significantly.
**Conclusion**. Ethanol extract from binahong leaves can reduce the blood glucose in T2DM rats significantly.

**Keyword:** Diabetes Mellitus, Hyperglycemia, Binahong Leaf Extract, Flavonoid, Streptozotocin

**ABSTRAK**

***Latar belakang**. Diabetes mellitus tipe 2 (DMT2) ditandai dengan peningkatan kadar glukosa darah. Daun binahong mengandung berbagai metabolit seperti flavonoid yang diketahui memiliki efek antidiabetes. Penelitian ini bertujuan untuk mengetahui efek pemberian ekstrak Anredera cordifolia (Ten.) Steenis etanol Anredera cordifolia terhadap penurunan kadar gula darah pada tikus T2DM.*
***Metode**. Studi ini adalah eksperimental in vivo dengan desain kelompok kontrol pre-post test. Penelitian ini menggunakan 30 ekor tikus yang terdiri dari 6 kelompok: kontrol normal, kontrol negatif, kontrol positif (metformin), ekstrak etanol daun binahong dosis 25 mg/kgBW, ekstrak etanol daun binahong dosis 50 mg/kgBW, dan ekstrak etanol daun binahong dosis 100 mg/kgBW. Kelompok perlakuan diinduksi oleh HFD selama 14 hari dan disuntik dengan streptozotocin 30 mg/kgBW diikuti dengan ekstrak etanol daun binahong selama 14 hari. Kadar*

*gula darah tikus dievaluasi 7 dan 14 hari setelah pemberian ekstrak etanol daun binahong. Analisis data menggunakan uji statistik non-parametrik dan Wilcoxon.*
***Hasil**. Ekstrak etanol daun binahong dosis 25 mg/kgBB, 50 mg/kgBW, dan 100 mg/kgBB mempengaruhi penurunan glukosa darah secara signifikan.*
***Kesimpulan.** Ekstrak etanol dari daun binahong dapat menurunkan glukosa darah pada tikus DMT2 secara signifikan.*

***Keyword:** Diabetes Mellitus, Hiperglikemia, Ekstrak Daun Binahong, Flavonoid, Streptozotocin*

## 1. Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by high blood sugar levels due to impaired insulin production or insulin action [1]. Diabetes can be classified into the following general categories: 1, Type 1 diabetes (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood). 2, Type 2 diabetes (due to a non-autoimmune progressive loss of adequate β-cell insulin secretion frequently on the background of insulin resistance and metabolic syndrome). 3, Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation). 4, Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not overt diabetes before gestation) [2]. The most common is type 2 diabetes. Lifestyle changes play a critical role in the incidence of T2DM, such as consuming high-fat foods. Diabetes remains a substantial public health issue. Type 2 diabetes, which makes up the bulk of diabetes cases, is largely preventable and, in some cases, potentially reversible if identified and managed early in the disease course. However, all evidence indicates that diabetes prevalence is increasing worldwide, primarily due to a rise in obesity caused by multiple factors. Preventing and controlling type 2 diabetes remains an ongoing challenge. It is essential to better understand disparities in risk factor profiles and diabetes burden across populations, to inform strategies to successfully control diabetes risk factors within the context of multiple and complex drivers [3]. An estimated 573 million people were living with diabetes in 2021, which would increase to 643 million in 2045. Diabetes is one of the leading causes of death and disability worldwide and affects people regardless of country, age group, or sex. Using the most recent evidentiary and analytical framework from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), we produced location-specific, age-specific, and sex-specific estimates of diabetes prevalence and burden from 1990 to 2021, the proportion of type 1 and type 2 diabetes in 2021, the proportion of the type 2 diabetes burden attributable to selected risk factors, and projections of diabetes prevalence through 2050 [4]. The majority of diabetes incidence occurs in low- and middle-income countries. Indonesia ranked fifth in the world for the number of DM patients, which reached 19.5 million people [5]. Synthetic drugs often cause side effects. Because of this, herbal medicine has begun to be developed [6]. People believe herbal medicine has milder side effects than modern medicines.

Worldwide, plant-based traditional medicines are the most commonly used form of treatment for a range of health problems. Studies reported that 80% of people in developing countries depend on traditional medicines as the primary remedy for various ailments. These traditional medicines play an important role in primary health care in many developing countries. Tanzania is among the countries where the majority of the population depends on traditional medicines for the management of their health problems, including diabetes [7]. Binahong plant is one of the medicinal plants that has been widely used to cure various kinds of diseases. The binahong plant is well known to the Indonesian people and is often used in traditional medicine, for weight loss [8]. The other research reported that giving boiled leaves of binahong as much as 155 g/kgBB for 14 days can decrease fasting blood glucose levels in adult women [9]. Based on the analyses conducted, it can be concluded that the administration of A. cordifolia leaf extract decreased glucose levels in HFD T2DM rats by regulating fatty acid and amino acid metabolism. A dose of 50 mg/kg BW A. cordifolia leaf extract elicited a better effect than other dosages or glibenclamide. Binahong leaves contain flavonoids, saponins, alkaloids, polyphenols, and monosaccharides [10]. Currently, research indicates that certain natural flavonoids can reduce blood sugar levels via inhibition of the α-glucosidase enzyme involved in hydrolyzing carbohydrates into glucose [11]. The α-glucosidase inhibitors reduce postprandial hyperglycemia [12]. The study was done in DM but did not use the method of high-fat diet animal study but a high carbohydrate diet. The study aims to know the effectiveness of ethanol extract binahong leaves in reducing blood glucose levels in type 2 DM rats induced by a high-fat diet and streptozotocin injection [13].

## 2. Methods

### 2.1. Animal Models

The research sample use male white Wistar rats, aged 6-8 weeks, body weight 150-200 g, kept in separate cages. Rats obtained from Pharmacology Laboratory, Faculty of Medicine, Universitas Sumatera Utara. The treatment of rats started by adapting rats for 7 days in a cage, a standardized 12/12 h light/dark cycle. During the adaptation period, rats were given food and water ad libitum. The research was conducted at the Pharmacology Laboratory, Faculty of Medicine, Universitas Sumatera Utara, with the approval of Law No. 765/KEPK/USU/2023 ethics committee of experimental animals.

### 2.2. Research Design

This study was a laboratory experiment with only a post-test control group design. In this study 30 male white rats. Rats were randomly selected and then divided into 6 groups: high-fat diet group (K1), high-fat diet and STZ group (K2), high-fat diet, STZ, and metformin (K 3), high-fat diet, STZ and ethanol extract of binahong leaves 25 mg/kgBW (K4), high-fat diet, STZ and ethanol extract of binahong leaves 50 mg/kgBW (K5), high-fat diet, STZ and ethanol extract of binahong leaves 100 mg/kgBW (K6).
Each group consisted of 5 rats. At the beginning of treatment, the body weight, abdominal circumference, and blood glucose levels of rats were measured. We measured the body weight and abdominal circumference every week. We measured blood glucose levels every 2 weeks.

### 2.3. Composition of High Fat Diet

High high-fat diet is made with the composition of 300 grams of pork fat and 200 grams of duck egg yolks in 100 mL of aquadest. The high-fat diet was given as much as 1 ml/200 gBW to rats every day for 2 weeks [13].

### 2.4. Induction of Diabetes Mellitus Type 2 by HFD Feeding and Streptozotocin

All groups (1-6) received a high-fat diet for 2 weeks. On the 15th day, STZ was administered intraperitoneally (30 mg/kgBW) to groups of diabetic rats (3-6). After 3 days of induction with STZ, blood glucose was measured to confirm the establishment of diabetes. Rats having blood glucose levels>200 mg/dl were considered diabetic. Rat blood was taken from the tail tip of the rats. The tail was cleaned with 70% alcohol, and then blood glucose levels were determined using a glucometer Easy Touch.

### 2.5. Statistical Analysis

Data from all experimental groups were gathered and analyzed by SPSS software. Data were analyzed using parametric statistical analysis and non-parametric statistical analysis to determine significant differences between the treatment group and the control group with a p-value <0.05 chosen as the significance level.

## 3. Results

In this study, all groups of rats were given a high-fat diet for 2 weeks. On the 14$^{th}$ day, we found that a high-fat diet gained weight in rats significantly ($p<0.05$), as shown in Table 1.

**Table 1**: The body weight (BW) of the group before and after induction of a high-fat diet (grams)

| Group | BW Before Induction | BW After Induction | p-value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| K1 | 151.2 ± 13.6 | 171.00 ± 10.8 | 0.022 |
| K2 | 153.0 ± 25.8 | 173.00 ± 16.5 | 0.016 |
| K3 | 147.2 ± 10.7 | 177.00 ± 8.5 | 0.000 |
| K4 | 158.8 ± 28.1 | 186.40 ± 19.4 | 0.004 |
| K5 | 154.4 ± 14.4 | 181.80 ± 11.3 | 0.000 |
| K6 | 160.0 ± 26.2 | 187.80 ± 18.6 | 0.002 |

In this study, we also found that a high-fat diet for 2 weeks increased abdominal circumference in all groups. There was a significant difference ($p<0.05$) in the addition of abdominal circumference in groups 1, 2, 4, and 5. On the other hand, in groups 3 and 6 there was no significant difference ($p> 0.05$). Data can be seen in Table 2.

**Table 2**: The abdominal circumference (AC) of the group before and after induction of a high-fat diet (cm)

| Group | AC Before Induction | AC After Induction | p-value |
|---|---|---|---|
| | Median | Median | |
| K1 | 12.5 (12 – 13.5) | 13.5 (13 –15) | 0.042 |
| K2 | 12 (12 – 13.5) | 14 (13 – 15) | 0.039 |
| K3 | 12.5 (11.5 – 13) | 13.5 (12.5 –15) | 0.066 |
| K4 | 13 (12 – 14) | 14.5 (13.5 –16) | 0.042 |
| K5 | 13 (12 – 13) | 14 (13 – 14.5) | 0.039 |
| K6 | 13.5 (11.5 – 14) | 14 (13 – 15) | 0.063 |

In this study, Wistar rats were fed a high-fat diet for 2 weeks followed by an injection of 30 mg/kg BW streptozotocin to induce type 2 diabetes mellitus. Rats having blood glucose levels>200 mg/dl were considered diabetic. In diabetic rats, metformin (group 3) and ethanol extract binahong (groups 4, 5, and 6) were orally given for 2 weeks. Its effect on blood glucose was determined after 14 days of administration. There was a significant difference in blood sugar levels ($p<0.05$) in groups 3, 4, 5, and 6 mice after the administration of metformin and extract of binahong leaves, as shown in Table 3.

**Table 3**: The blood sugar levels (BSL) of the group before and after administration of metformin and binahong extract (mg/dl)

| Kelompok | BSL Before Treatment | BSL After Treatment | p-value |
|---|---|---|---|
| | Median | Median | |
| K1 | 105 (83 – 124) | 119 (111 – 142) | 0.138 |
| K2 | 339 (297 – 348) | 310 (0 – 465) | 0.500 |
| K3 | 211 (207 – 297) | 164 (142 – 223) | 0.043 |
| P1 | 334 (203 – 510) | 72 (0 – 408) | 0.043 |
| P2 | 430 (368 – 483) | 0 (0 – 402) | 0.043 |
| P3 | 325 (256 – 492) | 119 (0 – 183) | 0.043 |

## 4. Discussions

In this study, Wistar rats were fed a high-fat diet followed by an injection of streptozotocin to generate a rat model of type 2 DM. This induction procedure refers to previous research which stated that the combination of a high-fat diet with STZ injection was successful in creating hyperglycemia in experimental animals that resemble type 2 DM in humans [14].

All groups were given a high-fat diet for 2 weeks to induce obesity. Obesity is a risk factor for type 2 DM [15]. Rats were considered as obesity if there was body weight gain >20% of their initial body weight [14]. This study showed an increase in body weight in all groups of mice after being given a high-fat diet for 2 weeks. The increase in body weight in the rat groups was the result of an energy imbalance between calories consumed and calories expended. Long-term high-fat diet consumption can reduce the physical activity of experimental animals [16].

This research also proves that giving a high-fat diet for 2 weeks can increase the abdominal circumference of mice. Excessive high-fat diets cause fat accumulation around the abdomen, resulting in increased abdominal circumference [17]. In another study, a high-fat diet for 9 weeks could increase the abdominal circumference of rats The increase in abdominal circumference was the result of enlarged liver and excessive fat accumulation in the liver [18].

After all groups of rats (1-6) showed weight gain (obese). Then, groups of diabetic rats (3-6) received multiple low-dose streptozotocin at a dose of 30 mg/kgBW. Multiple injections because some rats did not respond to the first streptozotocin injection [19]. A lower dose of STZ produces less ROS [20]. ROS plays a role in damage to pancreatic beta cells [21]. The rats' lack of response to the first STZ injection probably occurred because the endogenous antioxidants in the mice's bodies were still able to neutralize free radicals so that ongoing beta-cell damage did not occur [22]. Rats are declared diabetic if the BSL is ~200 mg/dl. Increased blood glucose levels occur due to damage to pancreatic beta cells which are no longer able to secrete insulin [23].

Next, a group of diabetic mice were given metformin and ethanol extract from binahong leaves for 14 days [24]. In this study, metformin was used as a comparative therapy because metformin is the first-line drug in the treatment of T2DM [25]. Previous research reported that oral administration of metformin at a dose of 50 mg/kgBW could reduce BSL in a rat model of STZ-induced DM. Metformin works by increasing insulin sensitivity [26]. However, metformin does not have a direct effect on the pancreas, so pancreatic beta cells are still damaged due to oxidative stress [27]. This is different from the ethanol extract of binahong leaves, which is believed to have the ability to regenerate damaged beta cells [28].

This research showed that there was a decrease in blood sugar levels in both the metformin group and the binahong leaf ethanol extract group. Previous research stated that giving ethanol extract from binahong leaves for 21 days was able to reduce BSL in T2DM rats.

This research showed that giving ethanol extract from binahong leaves for 14 days can reduce blood sugar levels in T2DM rats. This decrease in Blood Sugar levels (BSL) is thought to be related to the flavonoid compounds contained in the extract [3],[29]. Flavonoids act as antioxidants that can neutralize ROS produced by diabetogenic agents, so that damage to pancreatic beta cells can be prevented [29]. Apart from that, flavonoids also can repair beta cell damage [30]. Previous research has proven that steeping binahong leaves for 14 days can regenerate STZ-induced beta cell damage in mice. Apart from that, the quercetin compound contained in the extract also plays a role in reducing BSL [31]. Quercetin has a mechanism of action like metformin [32]. Quercetin activates adenosine monophosphate-activated protein kinase (AMPK) resulting in increased translocation of GLUT4 to the plasma membrane of skeletal muscle cells so that glucose uptake by the cells increases [33]. In addition, AMPK activation will reduce the expression of glucose 6-phosphatase (G6Pase), an enzyme that is important in the gluconeogenesis process. Decreased G6Pase expression suppresses glucose production resulting in a decrease in Blood Sugar Levels. (BSL) [34]-[35]

## 5. Conclusions

Based on the analyses conducted, it can be concluded that administration of ethanol extract of binahong leaves at doses of 25, 50, and 100 mg/kgBW decreased blood glucose levels in Type 2 DM Wistar rats induced by a high-fat diet and streptozotocin.

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## Conflict of Interest

The authors declare no conflict of interest.

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