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Pancreatic Histological Profile on the Efficacy of Extract of *Etlingera calophrys* (K. Schum) A.D. Poulsen Stem against Streptozotocin-Induced Diabetes in Diabetic Model Rats

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Abstract: Diabetes Mellitus (DM) is a metabolic disorder characterized by hyperglycemia that leads to oxidative stress. Antioxidant agents can be used to reduce oxidative stress. Olae (*Etlingera calophrys*) is one of the plants that exhibit antioxidant properties. Thus, this study aims to investigate the hypoglycemic and protective effect of Olae in the pancreatic of diabetic model rats. The anti-diabetic effect of Olae stems extracts conducted by measuring the blood glucose levels and histological examination of the pancreatic organ in diabetic model rats. All treatment groups with Olae stems extract decreased blood glucose levels compared to the negative control (p<0.05). The dose of 250 mg/kg BW provided higher activity than the 200; 150; and 100 mg/kg BW. Cell numbers of islets showed that Olae stems extract dose of 100; 150; 200; and 250 mg/kg BW increased, compared to normal and negative groups. In conclusion, Olae stems extract provides an anti-diabetic effect with a protective and repairing effect toward islets of Langerhans.

Keywords: Olae; *Etlingera calophrys* (K. Schum) A. D. Poulsen; antidiabetic; antioxidant.

1. Introduction

Diabetes Mellitus (DM) is a metabolic disorder of carbohydrate, fat, and protein resulting in a defect in insulin secretion, insulin sensitivity, or both. Hyperglycemia or increased blood glucose levels in circulation is characteristic of DM. [1]. WHO (World Health Organization) stated that 8.5% of adults (18 years and older) had diabetes in 2014, and was a direct cause of 1.6 million deaths in 2016 [2]. DM is a major problem worldwide and estimated around 424.9 million adults with DM [3].

Hyperglycemia in diabetic patients increases the production of mitochondrial reactive oxygen species (ROS), resulting in oxidative stress [4]. ROS is produced in many pathways, such as increased polyol pathway, increased formation of advanced end-products (AGEs), and protein kinase C (PKC) activation [5]. Oxidative stress causes apoptosis dysfunction and impairment in pancreatic β-cells, resulting in necrosis [6]. Besides, oxidative stress leads to multiorgan damage and triggers complications [7].

Antioxidant plays a vital role in the treatment of diabetes mellitus (DM). The antioxidant can neutralize free radicals, including ROS, and suppress oxidative stress during

hyperglycemia [8]. The terrestrial natural products become the source of antioxidants, such as plants of the genus Etlingera. The previous study conducted showed that several species from the genus Etlingera exhibit high antioxidant activity [9]. One of the genus Etlingera, *Etlingera elatior* (Jack) R.M Smith, has high antioxidant activity that suppresses oxidative stress and reduces blood glucose levels in the diabetic model rats [10,11].

Etlingera calophrys (K. Schum) A. D. Poulsen or locally in Southeast Sulawesi, known as Olae that exhibits high antioxidant activity from its stems [12]. Genus Etlingera contains flavonoids and tannins. Flavonoids are natural antioxidant agents that help DM complications involving oxidative stress such as neuropathy and renal and liver impairment [9]. On the other hand, tannins act as astringent on the surface of the small intestine's lining, thus inhibiting the absorption of glucose, resulting in decreased blood glucose levels.

Olae *(E. calophrys)* stems are suspected of having an antioxidant activity which can decrease blood glucose levels, due to distinct species in the same genus that usually provide similar activity such as *E. elatior* provides anti-diabetic activity [10,11]. Also, there are no studies reported yet the effect of Olae, primarily the stems in decreasing blood glucose levels. Thus, this study aims to investigate the effect of Olae or *E. calophrys* stems in decreasing blood glucose levels towards the diabetic model rats.

2. Materials and Methods

2.1. Plant collection, determination, and extraction.

A total of 20 kg of Olae (*Etlingera calophrys* (K. Schum) A. D. Poulsen) stems collected in Punggaluku, South Konawe, Southeast Sulawesi. The sample collected was determined in the Biological Laboratory of Faculty of Mathematics and Natural Science of Halu Oleo University. The collected sample was cleaned with running water, wetly sorted, and dried under sunlight obtained 1.5 Kg of powder.

Olae stems (1.5 Kg) were macerated using 96% ethanol (4.5 L) for 3 x 24 hours. The extract collected then concentrated using a rotary vacuum evaporator (50ºC) and obtained118.3 g concentrated extract (7.8%).

2.2. Extract characterization.

2.2.1. Solubility of extract.

Extract (5 g) was put in a volumetric flask and added 100 mL of water-saturated chloroform. The flask then was shaken for 6 hours and left for 18 hours. After that, the filtrate was evaporated on the pre-weighed evaporating dish at 105ºC until the weight is constant. Solubility extract in water is presented in percentage (%) [13].

2.2.2. Ethanol solubility of extract.

Extract (5 g) was put in a volumetric flask and added 100 mL of ethanol. The flask then was shaken for 6 hours and left for 18 hours. After that, the filtrate was evaporated on the pre-weighed evaporating dish at 105ºC until the weight is constant. Solubility extract in ethanol is presented in percentage [13].

2.2.3. Moisture content determination.

Extract (10 g) was put in a pre-weighed evaporating dish and heated at 105ºC for 5 hours and weighed until constant. Moisture content is stated in percentage (%) [13].

2.2.4. Ash content determination.

Extract (2 g) was put in pre-weighed closed silica-crucible. It was flamed (700-800ºC) until the charcoal ran out, then cooled down and followed by weighing the crucible [13].

2.3. Phytochemical screening.

The extract was chemically screened to detect alkaloids, flavonoids, tannins, saponins, quinines, and terpenoids. The reagents used to detect them were Mayer, Mg + HCl, HCl 2 N, FeCl3, Liebermann-Buchard, and NaOH 1 N, respectively [14].

2.4. Animals.

The animal used is male rats (*Rattus norvegicus*) that had been acclimatized for seven days in a controlled environment. They were fed with a regular diet at 08.00 and 17.00, and water *ad libitum.* Animals involved in this study were conducted under the ethical committee of Halu Oleo University (No. 737/UN29.20/PPM/2019).

2.5. Experimental design.

On day 8, animals were divided into seven groups (n=4): Group I, Group II, Group III, Group IV, Group V, Group VI, and Group VII. Group II-VII were starved overnight before induced with a streptozotocin (STZ) dose of 40 mg/mL intraperitoneally. Animals were returned in the cage and fed the regular diet and water *ad libitum.* On day 10, blood was collected to measure the glycemic status. On day 11, each group was treated for seven days, as follows:

Group I: non-induced group and 0.5% Na CMC (as normal control)
Group II: Metformin (as positive control)
Group III: 0.5% Na CMC (as negative control)
Group IV: *Etlingera caloprhrys* extract dose of 100 mg/kg BW
Group V: *Etlingera caloprhrys* extract dose of 150 mg/kg BW
Group VI: *Etlingera caloprhrys* extract dose of 200 mg/kg BW
Group VII: *Etlingera caloprhrys* extract dose of 100 mg/kg BW

On day 18, blood was drawn via a lateral vein (1 mL) and centrifuged for 10 minutes at 3000 rpm. Blood collected were combined with glucose reagent GOD FS (DiaSys®) and measured under photometer 5010_{v15+} (λ 546 nm).

The animals were sacrificed for harvesting pancreatic organ. The pancreatic organ was cleaned with 0.9% NaCl and fixated with 10% buffer neutral formalin (BNF) for 48 hours. The organ was then put in tissue cassette and dehydrated with an increased concentration of alcohol (70%, 80%, 90%, and 95%) and followed by clearing with using Xylol I and Xylol II and infiltrated with paraffin wax, thus forming blocks. The blocks were cut thickness of 4-5 µm with a microtome. The sections were put in object glass and incubated with an incubator (37ºC) for 24 hours. After that, sections were deparaffinated and rehydrated, followed by staining with hematoxylin and eosin (HE). Then, sections were examined and photographed by using a light microscope (magnification 400 x).

2.6. Statistical analysis.

Blood glucose levels were analyzed statistically using SPSS Statistics 20.0 (IBM Inc., USA). Data were analyzed by using One Way ANOVA, continued with post hoc LSD if data were normally distributed and were continued by Kruskal-Wallis if data were not normally distributed. The significant difference indicated with value $p<0.05$.

3. Results and Discussion

3.1. Extract characterization.

Olae (*Etlingera calophrys* (K.Schum) A. D. Poulsen) stems extract characterization aims to ensure the extract used in the study. The extract should meet the standards required. The result of the extract characterization is presented in Table 1.

Table 1. Characterization Extract of Olae (*Etlingera calophrys* (K.Schum) A. D. Poulsen) stems

	Standard	**Results**
Water Solubility of Extract	The higher the solubility level of the extract is good	26.7%
Ethanol Solubility of Extract	The higher the solubility level of the extract is good	38%
Moisture Content	≤10%	10%
Ash Content	≤7%	26.7%

Solubility extract in water and ethanol are conducted to determine the phytochemicals detected in solvents from the extract. Besides, it helps in choosing the right solvent [13]. Moisture content aims to determine the amount of water contained in the extracts. Excess amounts of water in extract accelerate the growth of microbes and decomposition [13]. Thus, the standard required for moisture content is less than 10% [13]. On the other hand, ash content conducted aims to determine the levels of inorganic minerals contained in the extract [13,14].

3.2. Phytochemical screening.

Phtochemical screening is conducted to determine phytochemicals contained in Olae (*Etlingera calophrys*) stems, thus provide the most likely compounds that playing roles in decreasing blood glucose levels [15,16]. Phytochemicals of Olae stems are presented in Table 2. According to results, Olae contains flavonoids, tannins, and terpenoids.

Table 2. Phytochemical Screening of *Etlingera calophrys.*

Phytochemical	**Result**
Alkaloids	-
Flavonoids	+
Saponins	-
Tannins	+
Terpenoids	+
Quinones	-
*+ = positive; - = negative	

3.3. Anti-diabetic effect of olae (Etlingera calophrys) stems to extract.

Anti-diabetic activity of Olae (*E. calophrys*) stems extract conducted to investigate the hypoglycemic effect of Olae stem extract in diabetic model rats. Rats were induced with the Streptozotocin (STZ) dose of 40 mg/mL, resulting in diabetic model rats. STZ is forming reactive free radicals that damage cell membranes, thus β-cell pancreatic disrupted in producing insulin [17,18].

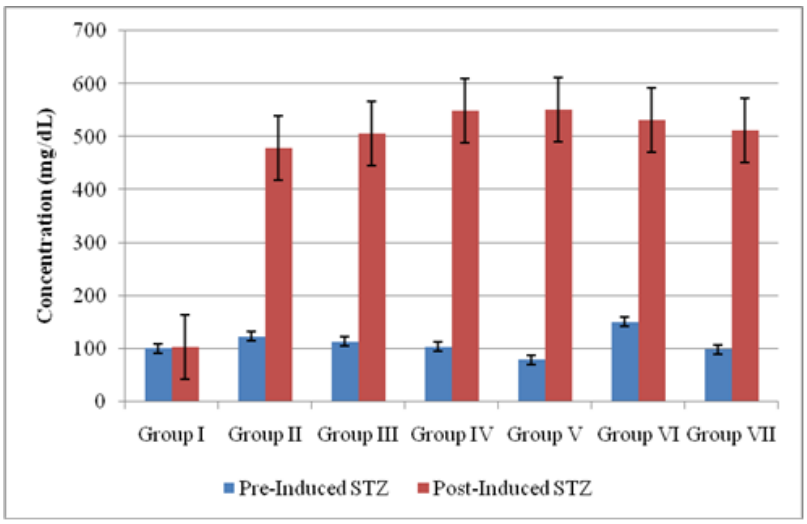

Figure 1. Effect of STZ (Streptozotocin) in Inducing Blood Glucose Levels of Rats in mean±SD.

The examination of blood glucose levels was conducted pre- and post-induction with STZ 40 mg/mL. All groups experienced increasing blood glucose levels post-induction, except group I or known as the normal group. Figure 1 is presenting the condition of rats.

Post-treatment in each group demonstrated decreased blood glucose levels of rats' post administrating with extract of Olae (*E. calophrys*) stems. Figure 2 is presenting the results.

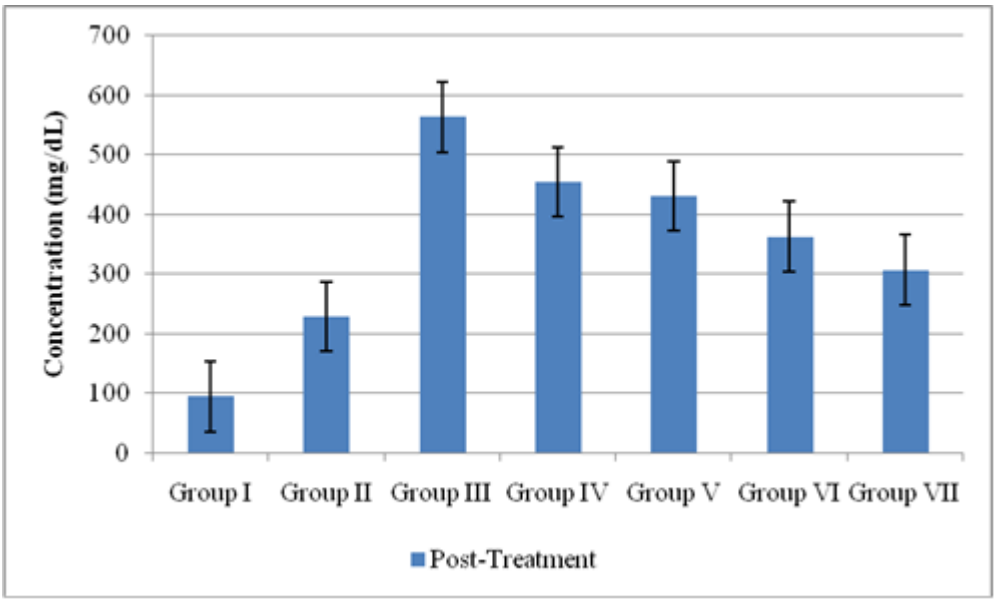

Figure 2. Effect of Olae Stems Extract in Decreasing Blood Glucose Levels of Rats in mean±SD (n=4). (Group I = normal control; group II = metformin dose of 500 mg/KgBW; group III = 0.5% Na CMC; Group IV = extract dose of 100 mg/KgBW; Group V = extract dose of 150 mg/KgBW; Group VI = extract dose of 200 mg/KgBW; Group VII = extract dose of 250 mg/KgBW.

The effect of Olae (*E. calophrys*) stems extract in decreasing blood glucose levels by comparing with group II (positive control) and Group III (negative control). All treatment groups (group IV-VII) demonstrate a significant decrease in blood glucose levels ($p<0.05$) compared to group II and Group III. Increasing dose of extract demonstrated better effect in decreasing blood glucose levels into 306.4 mg/dL (Group VII), 362.6 mg/dL (Group VI), 430.7 mg/dL (Group V), and 454.4 mg/dL (Group IV) compared to group III (563.4 mg/dL). Although, group II as the positive control (228.5 mg/dL) provided better decreased blood glucose levels compared to all treatment groups.

Both flavonoids and tannins are suspected of playing a vital role in decreasing blood glucose levels. Flavonoids have antioxidant properties, thus protect pancreatic cells from reactive oxygen species (ROS). Also, flavonoids have hypoglycemic activity by inhibiting the α amylase enzyme and α glucosidase enzyme, which plays a role in breaking down carbohydrates into monosaccharides, thereby being absorbed by the intestine [19-24]. Flavonoid also stimulates the insulin-dependent AMPK (adenosine monophosphate-activated protein kinase) pathway, which analog to metformin. Metformin is the positive control used in this study [25].

On the other hand, tannins stimulate glucose and fat metabolism by providing antioxidant and anti-diabetic properties [26]. Besides, it also functions as a preservative or chelating agent that shrinks the intestinal epithelial membrane, thereby reducing the absorption of food juice as a result of inhibiting glucose intake and followed by the reduced blood sugar levels [20,21,27].

3.4. Histology of pancreatic organ.

In diabetic model rats, there are morphological changes in pancreatic islets or islets of Langerhans, both of the number of cells and the shape islets cells [26]. The morphological change is involving necrosis and cell degeneration. Table 3 is presenting the number of islet cells**.**

Table 3. The number of islets cell in pancreatic organ of animals.

Group	Number of cells
Group I	653 cells
Group II	604 cells
Group III	208 cells
Group IV	404 cells
Group V	600 cells
Group VI	650 cells
Group VII	658 cells

According to the histology of pancreatic organ conducted, the group I as the normal control was only showing healthy cells. The number of cells of group I was 653 cells, caused by the group I was not induced with STZ. Histology of Group I is presented in Figure 3(a). Group III, as the negative control, showed morphological changes of islet cells, which shrink, decrease cell number, and necrosis. The number of cells of Group III dropped to 208 cells. Figure 3(c) is showing morphological changes in group III.

Group II, as the positive control, was a group induced with STZ and was treated with metformin (Figure 3(b). It showed some necrosis and loss of the nucleus; meanwhile, the number of cells was increased to 604 cells. Metformin has similar activity as antioxidants, thus prevent pancreatic β cell damage. Metformin captures or neutralizes the free radicals that repair tissue damage [22,25].

The group IV was induced with STZ and treated with Olae *(E. calophrys*) stems ethanol extract dose of 100 mg/kg BW. The group showed some necrosis and loss of the nucleus. The number of cells also increased to 404 cells. The histology of group IV is shown in Figure 3(d). Group V was induced with STZ and treated with the extract dose of 150 mg/kg BW was showing increasing number cells to 600 cells, yet still showing some necrosis and nucleus loss (Figure 3(e)).

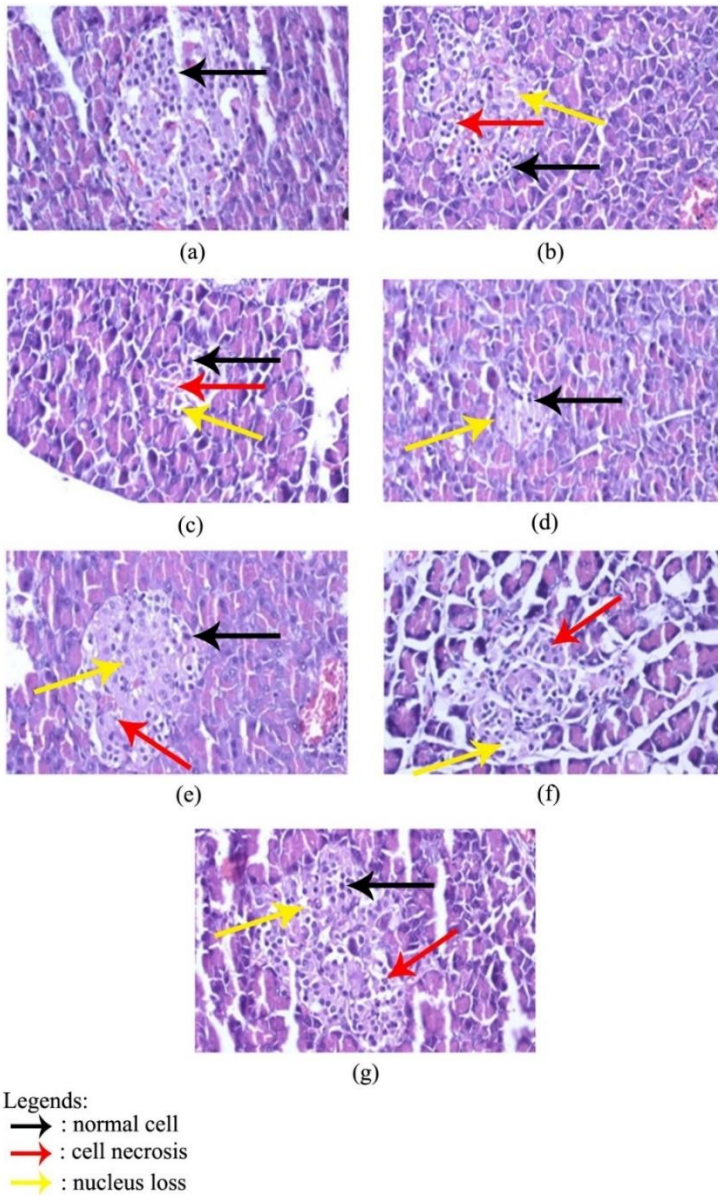

Figure 3. Histology of islets of langerhans of rat (a) Group I; (b) Group II; (c) Group III; (d) Group IV; (e) group V; (f) Group VI; (g) Group VII.

Group VI (extract dose of 200 mg/kg BW) and VII (250 mg/kg BW) showed increased numbers of cells into 650 cells and 658 cells, respectively. Both groups showed similar results with Group IV and Group V), which still showed some necrosis and nucleus loss. However, the increase in the number of cells shows the protective and repair effect of Olae (*E. calophrys*) stems to extract. Both flavonoids and tannins contained in the extract are suspected responsible for the protective and repair effect. They are considered as natural antioxidants. Flavonoids are possibly decreasing oxidative stress by decreasing H_2O_2-induced oxidative damage and preserving pancreatic β-cell integrity [28-32].

4. Conclusions

Despite flavonoids, tannins, and terpenoids are present in *Etlingera calophrys* (K.Schum) A.D. Poulsen, or Olae stems ethanol extract, only both flavonoids and tannins are suspected in providing anti-diabetic effect. The extract decreases blood glucose levels in diabetic model rats and increasing the β-cells regeneration of islets of Langerhans, proved by pancreatic organ histology.

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Conflicts of Interest

The authors declare no conflict of interest.

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