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Antidiabetic Potential Screening of Ulin Fruit Extract (*Eusideroxylon zwageri*) Against Streptozotocin-Induced Diabetic Rats

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Abstract

Empirical evidence of complementary medicine from one community in Kalimantan often uses Ulin fruit (*Eusideroxylon zwageri*) for medical therapy or as herbal drinks by people with diabetes mellitus. This research aims to identify the antidiabetic compound of Ulin fruit extract against Streptozotocin (STZ) induced diabetic rats. Extraction was performed by maceration method using 96% ethanol, phytochemical test of extracts, extract toxicity test on mice (50 mg/BW to 200 mg/BW), test antidiabetic extract in diabetic rats induced by STZ as much as 70 mg/kgBW with each extract dose of 150, 300, and 600 mg given for 14 days, positive control is Glibenclamide 0.25 mg/kg/day, and the negative control is CMC 1%. Phytochemical test results showed that the extract of Ulin contains alkaloids, tannins, flavonoids, phenolics, terpenoids, and steroids. Ulin fruit extract was not toxic to rats at 50, 150, and 200 mg for three days. Based on the *Mann-Whitney* test, there was an effect of giving the extract on changes in the average body weight and body temperature of rats during three days of administration ($p = 0.000$). The results showed novelty that the extract of Ulin fruit affected reducing blood glucose levels in diabetic rats during 14 days of administration ($p=0.000$).

Keywords: Antidiabetic, *Eusideroxylon zwageri*, flavonoids, streprozotocin, diabetic rats

Skrining Potensi Antidiabetes Ekstrak Buah Ulin (*Eusideroxylon zwageri*) Terhadap Tikus Diabetes yang Diinduksi Streptozotocin

Abstrak

Bukti empiris pengobatan tradisional salah satu masyarakat di Kalimantan sering menggunakan buah ulin (*Eusideroxylon zwageri*) untuk terapi medis atau sebagai minuman herbal oleh penderita diabetes mellitus. Penelitian ini bertujuan untuk mengidentifikasi senyawa antidiabetes ekstrak buah ulin terhadap tikus diabetes yang diinduksi Streptozotocin (STZ). Ekstraksi dengan metode maserasi menggunakan etanol 96%, uji fitokimia ekstrak, uji toksisitas ekstrak terhadap tikus (50mg/BB sampai dengan 200mg/BB), uji antidiabetes ekstrak pada tikus diabetik yang diinduksi STZ sebanyak 70 mg/kgBB dengan masing-masing dosis esktrak yaitu 150, 300, dan 600 mg yang diberikan selama 14 hari, kontrol positif Glibenclamide 0,25 mg/kg/hari dan kontrol negatif CMC 1%. Hasil uji fitokimia menunjukkan bahwa ekstrak buah ulin mengandung alkaloid, tanin, flavonoid, fenolat, terpenoid, dan steroid. Ekstrak buah ulin tidak bersifat toksik pada tikus pada dosis 50, 150, dan 200 mg selama pemberian 3 hari. Berdasarkan uji *Mann-Whitney*, terdapat pengaruh pemberian ekstrak terhadap perubahan rerata berat badan dan suhu badan tikus selama pemberian 3 hari ($p=0,000$). Hasil uji menunjukkan kebaruan bahwa ekstrak buah ulin berpengaruh terhadap penurunan kadar glukosa darah tikus diabetes selama pemberian 14 hari ($p=0,000$).

Kata Kunci: Antidiabetes, *Eusideroxylon zwageri*, flavonoid, streprozotocin, tikus diabetes

1. Introduction

Diabetes mellitus (DM) is a global health problem and has been increasing rapidly in both developed and developing countries. The International Diabetes Federation (IDF) estimates that around 415 million adults had diabetes in 2015, and the number of adults with DM in the world could increase to 642 million by 2040.[1] DM is a serious chronic and complex metabolic disorder of several etiologies with profound consequences, both acute and chronic. It is a metabolic disorder characterized by high blood glucose, high insulin production, high insulin resistance and glucose or insulin intolerance. There are two main forms of diabetes, insulin dependent diabetes mellitus (type 1 diabetes mellitus, T1DM) and non-insulin dependent diabetes mellitus (type 2 diabetes mellitus, T2DM).[2]

The World Health Organization (WHO) has also estimated that nearly 422 million people were affected with T2DM worldwide in 2014 and the condition will double by 2030. The prevalence of diabetes mellitus in Indonesia is 2.1%. The highest prevalence of diabetes mellitus is at age >15 years. The highest prevalence of diabetes mellitus is Central Sulawesi (3.7%), North Sulawesi (3.6%) and South Sulawesi (3.4%). While the lowest was in Lampung Province (0.8%), then Bengkulu and West Kalimantan (1%) and Central Kalimantan (1.5%), and South Kalimantan (1%).[3]

Many active fractions from plants with medicinal properties have been isolated and about 50% of pharmaceutical drugs are directly or indirectly derived from plants. Due to some limitations associated with the use of existing synthetic antidiabetic drugs, the search for newer antidiabetic drugs from natural sources continues. For centuries, many plants have been considered as basic sources of potent antidiabetic drugs. In developing countries, in particular, medicinal plants are used to treat diabetes. Natural products, especially those of plant origin, are the main source for finding promising prime candidates and play an important role in drug development programs.[4]

Pandit's research results stated that *Ficus religiosa* bark extract showed significant antilipidperoxidative effect on the pancreas of Streptozotoxin-induced diabetic rats, *Ficus religiosa* bark extract had significant antidiabetic activity.[5] In addition, the bark extract (70% ethanol) from the V*atairea macrocarpa* plant showed that long-term use of the *V. macrocarpa* bark extract could be helpful in treating diabetic conditions.[6] The discovery of new drugs for diabetes mellitus is still being carried out and research is still ongoing in the scientific community around the world to evaluate the antidiabetic activity of raw materials or isolated natural products without side effects.

Ulin fruit is a fruit that grows on the Ulin Tree (*Eusideroxylon zwageri*) is widely used by the people of West and South Kalimantan as a herbal medicine to treat diabetes mellitus and heart disease, and empirical evidence from the people in West Kalimantan that Ulin fruit is often consumed by people with diabetes mellitus and heart disease and is proven to be effective. lowers blood sugar levels and also improves heart performance. Departing from this empirical evidence, researchers want to dig deeper into the potential of phytochemical compounds from Ulin fruit as antidiabetic. The purpose of this study was to identify the antidiabetic compound of ulin fruit extract (*Eusideroxylon zwageri*) against Streptozotocin (STZ) induced diabetic rats.

2. Materials and methods

2.1. Tools and materials

Ulin fruit used was taken from the Amuntai Tropical Forest with the specimen number 01 BU. Ulin fruit extract, 96% ethanol, wistar rats, salt, glucose, and streptozotocin. The tools used in this study were a socket, shaker, test tube, measuring flask, measuring cup, beaker, funnel, autoclave, volumetric pipette, and evaporator.

2.2. Methods

2.2.1 Ulin Fruit Extraction Method

Ulin fruits were extracted with solvents such as ethanol, methanol, hexane, petroleum ether using soxhlet apparatus. 20 g of sample was extracted using 200 mL of the above

mentioned solvent for 6 hours. Using a rotary evaporator, the solvent evaporates under reduced pressure at 55°C. The extract was prepared by dissolving 20 g of sample in 200 mL of water and incubated overnight in a shaker at 37°C. The dry extract was used for further studies.

2.2.2 Phytochemical Analysis

Extract of Ulin Fruit were tested for the presence of active compound such as alkaloid, flavonoids, steroids, triterpenoids, phenolic, saponins, and tannins.

2.2.3 Acute Toxicity Studies

Acute oral toxicity studies were carried out according to the guidelines established by the OECD. The starting dose was chosen to be 200 mg/kg and finally the 500 mg/kg dose was evaluated for toxicity.

2.2.4 Evaluation of Antidiabetic Ulin Fruit Extract

Rats were induced by intraperitoneal injection of Steptozotoxin (STZ) at a dose of 70 mg/kg body weight, dissolved in 0.1M cold citrate buffer (pH = 4.5).

2.2.5 Chronic Rat Treatment Model

Rats were divided into three groups each (n = 2). Group 1 served as control and untreated diabetes control, respectively. Group 2 served as the standard and was treated with 0.25 mg/kg/day of glibenclamide (Sun Pharmaceuticals Ltd.). Group 3 was given Ulin fruit extract at 500 mg/kg orally/ day for 14 days. Blood glucose levels were measured on days 1, 7, and 14.

2.2.6 Statistical analysis

The data obtained were expressed as mean ± mean standard error for the toxicity test and for antidiabetics determined by Kruskal Wallis and followed by the *Mann-Whitney* test.

3. Result

3.1. Phytochemical Analysis

Table 1 shows the screening results of phytochemical compounds from whole Ulin fruit extract (*Eusideroxylon zwageri*).

3.2. Acute Toxicity Studies

3.2.1 Weight

Based on Table 2 shows that the dose of ironwood extract (*Eusideroxylon zwageri*) 150 mg has an effect on changes in the average body weight of wistar rats with p value = 0.000.

Based on Table 3 shows that the incubation period of 48 hours and 72 hours in the administration of ironwood extract to diabetic rats there was a significant difference with p value = 0.001.

3.2.2 Body temperature

Based on Table 4, it shows that the administration of concentrations (50, 100, 150, and 200 mg) dose of Ulin fruit extract has an effect on changes in the average body temperature of rats given for 3 days.

Based on Table 5 shows that the incubation time of 24 hours and 48 hours has a significant difference (p = 0.004) to changes in the average body temperature of rats, 48 hours and 72 hours has a significant difference (p = 0.042) to changes in the average body

Table 1. Screening Results of Phytochemical Compounds from Whole Ulin Fruit Extract (*Eusideroxylon zwageri*)

No.	Active Compounds from Whole Ulin Fruit Extract	Information
1	Alkaloids	Positive
2	Flavonoids	Positive
2	Steroids	Positive
4	Triterpenoids	Positive
5	Phenolic	Positive
6	Saponins	Positive
7	Tannins	Positive

Table 2. Average Body Weight of Rats when Given Ulin Fruit Extract (*Eusideroxylon zwageri*) with Dosage 50, 100, 150, and 200 mg for 3 Days

Treatment	Extract Concentration	Mean ± SD	P
Control (CMC 0.1)	50 mg	-0.77 ± 2.83	0.999
	100mg	4.66 ± 2.83	0.477
	150mg	17.55* ± 2.83	0.000
	200mg	3.44 ± 2.83	0.742
50 mg	Control	0.77 ± 2.83	0.999
	100mg	5.44 ± 2.83	0.323
	150mg	18.33* ± 2.83	0.000
	200mg	4.22 ± 2.83	0.574
100 mg	Control	-4.66 ± 2.83	0.477
	50mg	-5.44 ± 2.83	0.323
	150mg	12.88* ± 2.83	0.000
	200mg	-1.22 ± 2.83	0.992
150 mg	Control	-17.55 ± 2.83	0.000
	50mg	-18.33* ± 2.83	0.000
	100mg	-12.88* ± 2.83	0.000
	200mg	-14.11 ± 2.83	0.000
200 mg	Control	-3.44 ± 2.83	0.742
	50mg	-4.22 ± 2.83	0.574
	100mg	1.22 ± 2.83	0.992
	150mg	14.11* ± 2.83	0.000

temperature of rats.

3.3. Antidiabetic from Ulin Fruit Extract (*Eusideroxylon zwageri*)

From the results of the data obtained for 14 days of administration of Ulin fruit extract (*Eusideroxylon zwageri*) with concentrations of 150 mg, 300 mg, and 600 mg, it can be seen from Table 6 that blood glucose levels in rats decreased, which previously increased blood glucose levels in test animals. after being given a Steptozotocin compound intravenously. From the three concentrations, we can see that it is able to reduce blood sugar levels in rats. The results of statistical analysis with *Mann Whitney* showed that the duration of administration of Ulin fruit extract (*Eusideroxylon zwageri*) had an effect on decreasing blood glucose levels of diabetic wistar rats (p=0.000).

4. Discussion

Based on phytochemicals screening of Ulin fruit extract (*Eusideroxylon zwageri*), produced seven phytochemicals, namely Alkaloids, Flavonoids, Steroids,

Table 3. Effect of Ulin Fruit Extract Concentration (*Eusideroxylon zwageri*) on Changes in Rat Body Weight Based on Incubation Duration for 72 Hours

Incubation period	Time	Mean ± SD	P
24 hours	48 hours	4.6 ± 2.19	0.097
	72 hours	-4.3 ± 2.19	0.132
48 hours	24 hours	-4.6 ± 2.19	0.097
	72 hours	-9.0* ± 2.19	0.001
72 hours	24 hours	4.3 ± 2.19	0.132
	48 hours	9.0* ± 2.19	0.001

Table 4. Average Body Temperature of Rats when Given Ulin Fruit Extract (*Eusideroxylon zwageri*) with Dosage 50, 100, 150, and 200 mg for 3 Days

Treatment	Extract Concentration	Mean ± SD	P
Control (CMC 0.1)	50 mg	-0.25 ± 0.09	0.132
	100mg	-0.15 ± 0.07	0.356
	150mg	0.12 ± 0.08	0.600
	200mg	0.17 ± 0.08	0.314
50 mg	Control	0.25 ± 0.09	0.132
	100mg	0.10 ± 0.07	0.707
	150mg	0.38* ± 0.08	0.007
	200mg	0.42* ± 0.08	0.003
100 mg	Control	0.15 ± 0.07	0.356
	50mg	-0.10 ± 0.07	0.707
	150mg	0.28* ± 0.06	0.010
	200mg	0.32* ± 0.06	0.002
150 mg	Control	-0.12 ± 0.08	0.600
	50mg	-0.38* ± 0.08	0.007
	100mg	-0.28* ± 0.06	0.010
	200mg	0.04 ± 0.07	0.973
200 mg	Control	-0.17 ± 0.08	0.314
	50mg	-0.42* ± 0.08	0.003
	100mg	-0.32* ± 0.06	0.002
	150mg	-0.04 ± 0.07	0.973

Triterpenoids, Phenolics, Saponins, and Tannins. A phytochemical screening test is helpful for early detection of active compounds and as an early picture in starting drug search and development, especially for antidiabetic. Due to the presence of seven phytochemicals in Ulin fruit extract (*Eusideroxylon zwageri*), it can be used as an initial screening to see antidiabetic activity in diabetic rats induced by streptozotocin.

One of the natural compounds as antidiabetic producers is flavonoids.[7] Flavonoids are an important class of natural products; in particular, they belong to a class of plant secondary metabolites having a polyphenolic structure, found abundantly in certain fruits, vegetables and beverages. They have various beneficial biochemical and antioxidant effects associated with various diseases such as cancer, Alzheimer's disease (AD), atherosclerosis, diabetes, and others.[8]

Based on the other research, apigenin plays an antidiabetic role[9] mainly through signalling pathways that work in small islets and peripheral tissues. For example, apigenin may protect-cell function by inhibiting

Table 5. Effect of Ulin Fruit Extract (*Eusideroxylon zwageri*) on Changes in Body Temperature of Rats Based on Incubation Time for 72 hours

Incubation period	Time	Mean ± SD	P
24 hours	48 hours	-0.23* ± 0.05	0.004
	72 hours	-0.07 ± 0.05	0.411
48 hours	24 hours	0.23* ± 0.05	0.004
	72 hours	0.16* ± 0.05	0.042
72 hours	24 hours	0.07 ± 0.05	0.411
	48 hours	-0.16* ± 0.05	0.042

inflammatory signalling pathways, further suggesting that inflammatory signalling pathways may be a novel therapy. Target the antidiabetic effect of apigenin, which needs further investigation. Apigenin can also increase peripheral insulin sensitivity and promote insulin resistance and abnormal lipid metabolism, which is achieved mainly through modulation of AMPK activity and related gene expression and miRNA regulation.[10]

Secondary metabolites (phytochemicals) and other chemical constituents of medicinal plants explain their medicinal value. For example, saponins have hypotensive and cardio depressant properties.[11] The presence of saponins in whole Ulin fruit extract may play a role in its cardioprotective potential.[12] Based on research Bhandary *et al.* stated that three different extracts of whole fruit (*Punicia granatum*) were found to contain Triterpenoids, Steroids, Glycosides, Saponins, Alkaloids, Flavonoids, Tannins, Carbohydrates & Vitamin C.[13]

This study was conducted to evaluate the toxicity of Ulin fruit extract and its effect on STZ-induced diabetic rats. The results indicated that no signs of toxicity from the Ulin fruit extract that was given, starting from a dose of 50 mg/bb to a dose of 200 mg/bb rats. It can be seen from the average body weight of rats and the body temperature of rats, which are stable and there is no decrease, and there is no morbidity or injury in rats. In testing the antidiabetic activity of Ulin fruit extract on rats, it showed that when induced with STZ, rats blood glucose levels were 200mg/dL for all treatments (this indicates diabetes). After being given the extract on the first day, there was still an increase in rat blood glucose levels. On the seventh day, there was a decrease in the rats blood glucose levels until the 14th day. The rats blood glucose levels decreased and were stable, and they did not experience diabetes anymore. Provides evidence that Ulin fruit extract may contain hypoglycemic compounds. Phytochemical compounds of Ulin fruit extract have shown the presence of tannins, flavonoids known for their hypoglycemic activity.[14] Plants can exert their action by increasing the proliferation or renewal of islet cells after destruction by streptozotocin. It was amplified by the strong immunostaining of mouse islet cells treated with plant extracts.[15]

It is known that streptozotocin acts by damaging cells;[16] so that plant extracts can act in these conditions by increasing peripheral glucose uptake. In streptozotocin-induced diabetic mice, the reduction was moderate but significant. Reported that glibenclamide was ineffective when it destroyed cells.[17] In our study, glibenclamide induced a significant decrease in blood glucose levels in streptozotocin-induced diabetic rats exhibiting partial destruction of pancreatic cells. This is in line with the results of previous studies as revealed by Alotaibi *et al*. According to Alotaibi *et al*., the effect of gilbenclamide on

Table 6. Antidiabetic Activity of Ulin Fruit Extract Against Streptozotoxin-induced Diabetic Rats

Treatment	Blood Glucose (mg/dL)					P
	Before Induced STZ	After Induced STZ	Day 1	Day 7	Day 14	
Negative control	92	200	250	496	403	0.000*
Positive control	74	200	113	78	85	
150 mg Extract Ulin Fruits	77.5	200	354.5	100	73	
300 mg Extract Ulin Fruits	62.5	200	246.5	99	86	
600 mg Extract Ulin Fruits	70	200	315	88	88.5	

**Mann Whitney* Test

lowering glucose levels in serum was induced by NA-STZ induced diabetic rats.[18]

Streptozotocin induces an increase in triglycerides, total cholesterol, LDL-cholesterol, atherogenic index and lowers HDL cholesterol. Hypertriglyceridemia and hypercholesterolemia are the main factors of diabetes involved in developing atherosclerosis and coronary heart disease, which is a secondary complication of diabetes,[19] However, in our study, we have not tested cholesterol levels. We also believe due to the phytochemical studies was done previously.[20] The phytochemical test showed the presence of alkaloid compounds in which these compounds function to overcome arrhythmias,[21] also contain flavonoid compounds that prevent heart disease.[22]

These results prove the hypothesis that plant extracts have antidiabetic activity as in the study[23] rats induced by diabetes showed a significant decrease in blood glucose and triglycerides ($p < 0.05$) after being given the ethanolic extract of *Sphagnelicola trilobata* flowers for 14 days. In addition, Florence *et al*. showed that the *Annona muricata* plant had antidiabetic against STZ-induced diabetic rats during 28 days of administration.[24] Based on the other study, *Carissa carandas* Linn. fruit extract showed that the methanol extract and its ethyl acetate soluble fraction significantly reduced the increase in blood glucose levels by 48% ($p < 0.001$) and 64.5% ($p < 0.001$).[25]

5. Conclusion

Ulin fruit extract can be used as an antidiabetic drug because it is not toxic, it is proven in the results that the extract is safe to use starting at doses of 50 mg - 200 mg. Ulin fruit extract also had antidiabetic against STZ-induced diabetic rats during 14 days of administration with doses of 150 mg, 300 mg, and 600 mg. Based on statistical analysis with *Mann Whitney* showed that there were significant differences in each dose of Ulin fruit extract in reducing blood glucose levels in diabetic rats (P=0.000).

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