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Research Article
Evaluation of Antihyperglycemic Property from *Syzygium oleana* (Magnoliopsida: Myrtaceae) Pericarp

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Abstract

Background and Objective: Searching of type 2 diabetes drugs is moving forward due to the existing treatments considered less effective, high cost and contribute negative side effects on other organs. The searching for new drugs can be initiated from the ethnobotanical wisdom of a number of plants showing the effects of anti diabetes to treat type 2 diabetes. One of the plant used for the control of type 2 diabetes is *Syzygium oleana*. This study was to find out scientific evidence that the methanolic extract of *Syzygium oleana* pericarp has an antihyperglycemic property to manage type 2 diabetes. **Materials and Methods:** The secondary-metabolites' profile of methanolic extract of *S. oleana* pericarp was screened by phytochemical analysis methods, its antioxidant property was judged with DPPH scheme and linked to the ascorbic acid at the wavelength of 517 nm and its IC_{50} value was determined based on the Log dose inhibition curve. The paired samples t-test was used to determine the difference of blood glucose level of *Rattus norvegicus* before and after treatment by utilizing SPSS software version 24. The treated extract at 100 and 200 mg kg^{-1} b.wt., administered to the glucose-induced diabetic rat and compared to the metformin (65 mg kg^{-1} b.wt.). Histopathological investigations performed the evidence that the extract could improve pancreatic β-cells by depresses necrosis of pancreatic β-cells in the islet cells based on one way ANOVA ($p<0.05$). **Results:** (1) The methanolic extract of *S. oleana* pericarp exhibited antioxidant with IC_{50} value of 7.23 ppm compared to the ascorbic acid with IC_{50} value of 6.30 ppm, (2) The extract (100 and 200 mg kg^{-1} b.wt.) and metformin (65 mg kg^{-1} b.wt.) revealed to have antidiabetic effects in type 2 of glucose-induced diabetic rats. The dose of 200 mg kg^{-1} b.wt., showed the antidiabetic effect of 75.48% corresponding to 75.52% of the metformin ($p<0.05$) and (3) The extract showed a significant $p<0.05$ effect on reducing blood glucose level and improving granulation of pancreatic β-cells in the experimental rats. **Conclusion:** It was concluded that the methanol extract of *S. oleana* pericarp has an antihyperglycemic property.

Key words: *Syzygium oleana*, *Rattus norvegicus*, ethnobotany, antihyperglycemia, phytochemistry

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Governing type 2 diabetes for people with diabetes mellitus is generally done by taking synthetic antidiabetic drugs in addition to physical exercise or managing a healthy lifestyle[1]. The drugs are consumed by people with type 2 diabetes mellitus may have a negative impact on other body organs[2-4]. In addition, patients with type 2 diabetes have to spend more money to buy synthetic drugs for the rest of their lives[5]. Utilization of natural materials for handling and control of type 2 diabetes has been implemented in the diabetes community, especially in rural areas, due to low cost and fewer side effect[6,7]. One of the prospective plants to manage type 2 diabetes is *Syzygium oleana*.

Syzygium oleana (Magnoliopsida: Myrtaceae) is a type of ornamental plant due to the bright red beauty of its young leaves. Therefore, people grow this plant on yards, roadsides and park spaces in the office at both urban and village areas[8]. The plant can grow up until reach 5 m in height. This ornamental plant has a single lanceolate leaf sized ±6 cm in length and ±2 cm in width with the opposite position. The leaf varies its color from bright red to brown and then to green along with changes from young to old leaf[9]. This plant has a small flattened round shaped fruit. It is sweet and crimson when ripe. This plant is not uncommon used as an ornamental and shade plant. In fact, its fruit can be used to manage diabetes mellitus because it contains flavonoids and phenolics[10,11]. Numerous studies have proven that colored fruits contained flavonoids and phenolics can be used as an antioxidant[12-15]. An antioxidant has the ability to reduce a blood sugar level[16]. To the best the knowledge based on the electronic database searching, this is the first report of *S. oleana* pericarp published an antihyperglycemic property to type 2 diabetes.

MATERIALS AND METHODS

Materials: Drug, chemicals of analytical grade and kit were purchased commercially. The metformin (Glucophage, Detroit, USA) was used as the positive control of antihyperglycemic substance. The glucose monohydrate (Merck, Germany) was used to induce diabetes in rats. The Nesco Multicheck (Nesco Medlab, Indonesia) was used to check the blood glucose level.

Experimental animals: The adult rats were purchased from Pharmacology Laboratory of Veterinary Faculty of Syiah Kuala University, Banda Aceh, Indonesia.

Experimental laboratory: The phytochemical screening was carried out in the Marine Laboratory of Marine and Fisheries Faculty of Syiah Kuala University, Banda Aceh, Indonesia. The DPPH assay was run in the Chemistry Laboratory of Teacher Teaching and Education Faculty of Syiah Kuala University, Banda Aceh, Indonesia. The bioassay was conducted in the Pharmacology Laboratory of Veterinary Faculty of Syiah Kuala University, Banda Aceh, Indonesia.

Methods

Extraction of *S. oleana* pericarp: The *S. oleana* fruits were collected from the local areas of the Syiah Kuala University Campus (N 9°34' 5" E 95°22' 17"), Banda Aceh Municipality on January 10th, 2017. Then, this specimen was identified and authenticated by a plant taxonomist of Syiah Kuala University under code MM-010012017.

The ripe fruits (100 g, wet weight) were macerated with a liter of 76% ethanol at indoor temperature in lieu of 24 h. The filtrates were sieved through Whatman filter paper, then were evaporated to dryness. The residues were further separated based on their solubility in hexane, ethyl acetate and methanol solvents. The filtrate was vacuum evaporated at low temperature (40°C) until semisolid residue was obtained. The crude extract of each part was dried by placing in a vacuum desiccator (Duran®, Jakarta, Indonesia). The hexane, ethyl acetate and methanol extracts as much as 0.2, 11.4 and 23.3 g, respectively were stored in labeled bottles for the next activities.

Phytochemical analysis: The phytochemical screening of secondary metabolites of *S. oleana* pericarp was carried out using standard laboratory techniques[17]. The isoprenoids were analyzed through the Liebermann-Burchard's test[18], the alkaloids were analyzed via the Mayer's, the Wagner's and the Dragendorff's test[19], the saponin constituents were detected via the frothing test[19], the tannins were evaluated through the ferric chloride and the alkaline tests[19] and the flavonoid constituents were analyzed via the Shinoda's test[20].

Evaluation of antioxidant

DPPH assay: The antioxidant ability of methanol extract of *S. oleana* pericarp was measured by DPPH (2,2-diphenyl-1-picrylhydrazyl, $C_{18}H_{12}N_5O_6$) procedure[21]. The wavelength of 517 nm was fixed to measure absorbance by using UV-VIS double beam spectrophotometer (Analytik Jena SPEKOL 2000, Germany). The ascorbic acid was chosen as the standard of the antioxidant and the trial was arranged in triplicate. The Log dose inhibition curve was applied to decide an IC_{50} value of the extract.

Experimental protocol: This study used Wistar Fatty Rats (WFR) for model type 2 diabetes[22]. A dozen of the healthy adult rat (*Rattus norvegicus*, 200-250 g b.wt.) Wistar strain was adapted in cages[23]. Typical caging conditions were retained and supplied rat pellet diet and water *ad libitum* until the end of the experiment[24]. The adaptation period was executed in 7 days. On the 7th day, four groups of the rats set in three rats for each with the following criteria: The first group was determined as the negative control group, the second group was determined as the positive control group, the third and fourth groups were determined as the groups administrated the methanol extract of *S. oleana* pericarp with a dose of 100 and 200 mg kg^{-1} b.wt., respectively. Each rat in each group was taken its blood on the 7th day. This blood was marked as a pre-treatment blood and was excluded in statistical analysis. In order to generate diabetic rat, each rat in each group was injected with 1 mL of 50% w/v glucose monohydrate[25] via subcutaneous in peritoneum at the 8th and 11th days. On the 14th day, each rat blood was taken to determine the diabetic rat based on a criteria blood sugar level $\geq$200 mg dL^{-1}. This blood was collected as a diabetic blood and was marked as the blood obtained before treatment. From the 15th to 28th days at 10 am, all rats in the second, third and fourth groups were given the metformin in an amount of 65 mg kg^{-1} b.wt., the methanol extract of *S. oleana* pericarp with an amounts of 100 and 200 mg kg^{-1} b.wt., respectively. On the 29th day, all rats in each group were taken their blood. The blood was collected as a post-treatment blood and was marked as the blood obtained after treatment. The rat was sacrificed at the end of 29th day of treatment.

Histopathological studies: The pancreatic organ of sacrificed rat was performed. It was fixed in 10% formalin for a week and then histopathological investigations were performed[26]. The slices were stained with Hematoxylin Eosin (HE) and studied under DP12 Olympus binocular research microscope.

Data analysis: The percentage inhibition of antioxidant activity was designed through the Eq. 1:

$$\text{Inhibition (\%)} = \frac{A_0 - A_1}{A_0} \times 100 \quad (1)$$

where, A_0 was the absorbance of the ascorbic acid and A_1 was the absorbance of the extract[27].

The difference of blood glucose level was stated as an antidiabetic effect. The percentage of antidiabetic effect was calculated by the Eq. 2:

$$\text{Antidiabetic effect (\%)} = \frac{a - b}{a} \times 100 \quad (2)$$

where, a was blood glucose level of rat obtained before treatment and b was blood glucose level of rat obtained after treatment[28].

Statistical analysis: A paired samples t-test was performed using the SPSS software version 24 (IBM Corp., Armonk, New York, USA) to evaluate effect of methanolic extract of *S. oleana* pericarp on blood glucose level of glucose-induced diabetic rats. A one way ANOVA was performed using SAS software version 9.1.3 (SAS Institute Inc., Cary, NC, USA) to check effect of methanolic extract of *S. oleana* pericarp on granulation of β-cells. The Duncan's *post hoc* test was designated for comparing the treatments. The values were judged statistically significant difference when the $p<0.05$[29].

RESULTS

Phytochemical analysis and evaluation of antioxidant activity: Phytochemical screening of the methanolic extract of *S. oleana* pericarp showed that flavonoids and phenolics, isoprenoids and alkaloids and tannins were present in high, moderate and low concentrations respectively. The extract was evaluated for its antioxidant by DPPH method and showed an inhibition of 81.99% compared to ascorbic acid inhibition of 78.44% as displayed in Table 1.

Administration the extract to the glucose-induced diabetic rats: The paired samples t-test revealed that the methanolic extract of *S. oleana* pericarp reduced significantly blood glucose level ($p<0.05$) referenced to metformin as shown in Table 2.

Pancreatic histopathological observations: The one way ANOVA test showed that the methanolic extract of *S. oleana* pericarp significantly improve granulation of β-cells ($p<0.05$) as presented in Table 3 and the histopathological appearance through HE staining as displayed in Fig. 1.

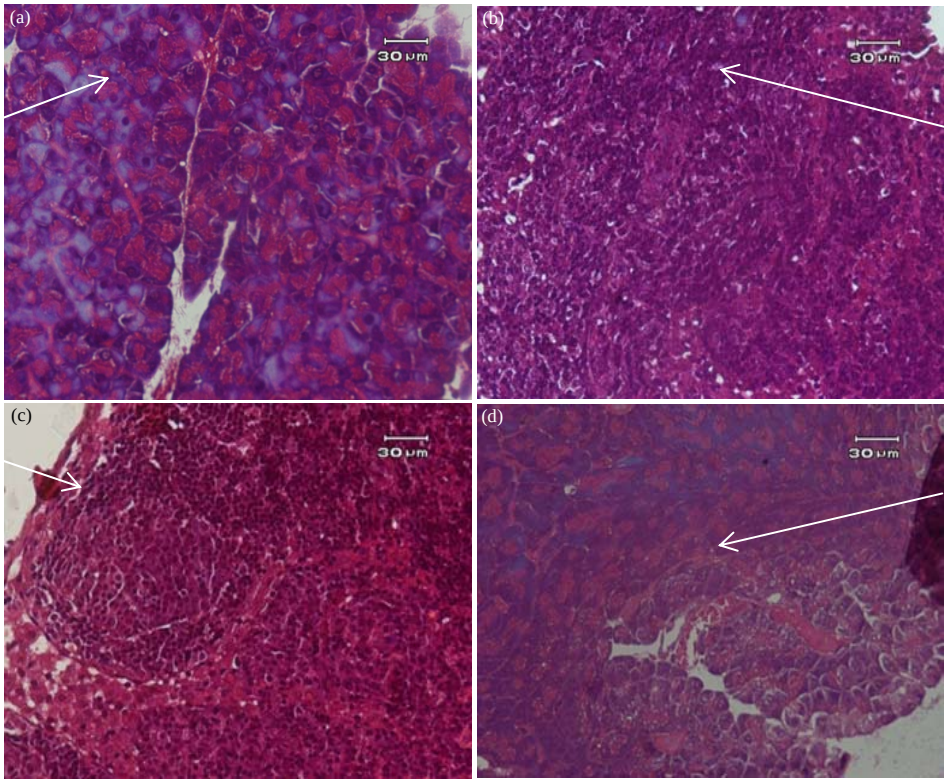

Fig. 1(a-d): Appearance of pancreatic β-cells in histopathologic observation was appointed by white arrow on (a) Negative control (b) Positive control, (c) Extract dose of 100 mg kg^{-1} b.wt. and (d) 200 mg kg^{-1} b.wt., treatments

Table 1: Absorbance and inhibition of the methanolic extract of *S. oleana* pericarp with reference ascorbic acid

Control (A)	Concentration (ppm)	Absorbance		Inhibition (%)		IC_{50} (ppm)	
		Ascorbic acid	*S. oleana*	Ascorbic acid	*S. oleana*	Ascorbic acid	*S. oleana*
0.422	2	0.389	0.397	7.82	5.92	6.30	7.23
	4	0.318	0.346	24.64	18.01		
	6	0.228	0.277	45.97	34.36		
	8	0.121	0.205	71.33	51.42		
	10	0.091	0.076	78.44	81.99		

Table 2: Effect of methanolic extract of *S. oleana* pericarp on blood glucose level of glucose-induced diabetic rats

Treatments	Blood glucose level (Mean±SD mg dL^{-1})			
	Pre-treatment blood	Diabetic blood	Post-treatment blood	Antidiabetic effect (%)
Negative control	117.00±0.00	413.67±4.04	459.00±39.00	-
Positive control (Metformin, 65 mg kg^{-1} b.wt.)	119.00±2.65	414.00±43.71*	101.33±1.53*	75.52
Extract dose of 100 mg kg^{-1} b.wt.	114.00±1.00	412.00±45.13*	101.67±1.53*	75.32
Extract dose of 200 mg kg^{-1} b.wt.	114.00±1.41	420.00±37.21*	103.00±0.82*	75.48

b.wt.: Body weight, *Paired samples t-test results showed significant differences ($p<0.05$) in blood glucose levels before (as diabetic blood) and after (as post-treatment blood) treatments

Table 3: Existing of granulated β-cells in the glucose-induced diabetic rats under various treatments

Treatments	Existing of granulated β-cells	
	Amount (cell)	Average (cell)
Negative control	801.00	267.00^{a**}
Positive control (Metformin, 65 mg kg^{-1} b.wt.)	654.00	218.00^{b**}
Extract dose of 100 mg kg^{-1} b.wt.	551.00	183.66^{b**}
Extract dose of 200 mg kg^{-1} b.wt.	732.00	244.00^{a**}

b.wt.: Body weight, Different letters indicated statistically significant differences (**) among the treatments ($p<0.05$, Duncan's *post hoc* following one way ANOVA)

DISCUSSION

The phytochemical screening revealed that the extract was very rich in flavonoid and phenolic compounds demonstrated an antioxidant property[30-32]. The result was confirmed by the antioxidant activity assay. The absorbance at 517 nm was displayed at 0.091 for the ascorbic acid and 0.076 for the extract and the IC_{50} values were calculated as 6.30 and 7.23 ppm for ascorbic acid and the extract respectively as shown in Table 1. It could be interpreted that the methanolic extract of *S. oleana* pericarp revealed decreasing absorbance and increasing IC_{50} values in connection to concentration attributable to the ability of the extract to capture more free radicals produced by DPPH[33,34].

Blood glucose levels in type 2 diabetic rats after treatment for 14 days reduced successively (Table 2) as well as the treatment of metformin ($p<0.05$). The antidiabetic effects of the extract and metformin experienced insulin resistance[35].

Histologic observation of pancreatic islets in negative control treatment showed normal arrangement of β-cells in solid state and no visible swelling occurs in cells. It pointed that the cells were in healthy and normal performances (Fig. 1). Increasing number of granulated β-cells (Table 3) is characterized by the increasing size of the islets. In this study, small sized islets indicated areas of necrosis due to glucose injection were present. Necrosis occurred in pancreas β-cells are thought to be due to depolarization of pancreas β-cell membranes facilitating the destruction of pancreatic β-cells that increasing blood glucose levels. In one way ANOVA test exhibited that the dose treatment effect was significant ($F(3,11) = 10.15$, $p = 0.0042$) to improve granulation of β-cells on the glucose-induced diabetic rats. Consequently, the 200 mg kg^{-1} b.wt., was endorsed dose to apply due to the dose was significantly different to the metformin as stated by Duncan's *post hoc* test result in Table 3.

Histopathology of pancreatic islets showed an improvement in the granulation of β-cells due to presumed methanolic extract of *S. oleana* pericarp reduced blood glucose level by affecting pancreatic islets[36]. Presumed the blood glucose reducing effect of methanolic extract of *S. oleana* pericarp due to the presence of flavonoids and phenolics which improved islet histology. The administration of flavonoid and phenolic compounds could capture free radicals and reduce oxidative stress[7,37]. The compounds can improve and increase the catalase enzyme reducing the number of Reactive Oxygen Species (ROS) so it can help restore cell integrity and increase the viability of a cell[38]. The better appearance of pancreatic histological structures was presumably due to the flavonoid and phenolic compounds contained in the methanolic extract of *S. oleana* pericarp capable to binding and reducing the amount of ROS causing necrosis in the pancreas β-cells[6]. In addition, the destruction of the pancreas β-cells causes impaired glucose metabolism resulting in increased blood glucose levels[39,40]. The impairment of Langerhans pancreatic β-cell caused interruption of insulin synthesis. Insulin plays an important role in the regulation of the blood glucose. Hence, insulin deficiency causes hyperglycemia[41].

A number of studies related to antioxidants and antidiabetic medicinal plants of the genus *Syzygium* have been published, i.e., *S. cumini*[42-48], *S. jambos*[49], *S. densiflorum*[50], *S. calophyllifolium*[51], *S. aromaticum*[52], *S. samarangense*, *S. malaccense*[53], *S. fruticosum*[54] and *S. guineense*[55]. However, the publication of anti diabetes from *S. oleana* so far could not be traced. This study demonstrated evidence that was in line with the antioxidant and antidiabetic findings of the genus *Syzygium* in previous studies. Thus, the information provided from this study became the most recent finding in the genus.

CONCLUSION

The methanolic extract of *S. oleana* pericarp has been confirmed to have the antioxidant and antidiabetic effects in type 2 of glucose-induced diabetic rats. The extract showed a significant improve in granulation of β-cells which affects the decrease in blood glucose level. This improvement could be due to flavonoids and phenolic compounds presented in the extract.

SIGNIFICANCE STATEMENT

This study discovered the methanolic extract of *S. oleana* pericarp had antidiabetic effects in type 2 of glucose-induced diabetic rats. This investigation will facilitate the researcher to obtain a novel drug for type 2 diabetes that many researchers are searching. Therefore, a new drug clinically effective to handle type 2 diabetes may be arrived at following time.

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