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The Activity of Cordyline Terminalis's Leaf Extract as Antidiabetic in Obese Wistar Rats

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ABSTRACT

A high-fat diet can cause obesity and type 2 diabetes mellitus. This study aimed to observe the antioxidant compounds of Cordyline terminalis's leaf extract which have the ability to be in vitro antioxidant and antidiabetic. Phytochemical tests and IC 50 to dpph were carried out in vitro. The study was conducted in vivo using 24 female wistar rats, which were divided into 4 groups: control of normal rats, high fat diet in obese rats, extract 100 mg / kg bw and extract 200 mg / kg bw. After 30 days of research, blood samples were taken for examination of triglycerides, glucose, and free fatty acids. The results showed that methanol extract contained saponins, steroids, flavonoids, alkaloids and polyphenols. The methanol extract can reduce free radicals with IC_{50} 88.25 ppm. In vivo test results showed that there was a significant differences ($p < 0.05$) in the levels of TG, glucose and free fatty acids with the treatment of methanol extract (100 mg / kg bw and 200 mg / kg bw) compared to the high fat group. Based on the results of the study, it can be concluded that the methanol extract of andong leaves contained antioxidant compounds that act as antidiabetic in obese wistar rats.

Key words: *Antioxidants, Obesity, Cordyline Terminalis Leaf, Triglycerides, Free Fatty Acids, Glucose.*

INTRODUCTION

A high-fat diet and lack of activity are the causes of obesity [1-3]. The prevalence and complications of obesity continues to increase. Obesity is the result of excess fat accumulation that causes various degenerative diseases, such as type 2 diabetes mellitus, hypertension, dyslipidemia, insulin resistance, some cancers, atherosclerosis, coronary heart disease and arthritis [4-7]. Type 2 diabetes mellitus is an impact of obesity which can increase oxidative stress which accelerates atherosclerosis formation [8, 9]. Diabetes mellitus is as metabolic disorder which is resulted from defects in insulin scretion or insulin action and both can cause long-term damage and dysfunction in many organs. The patients with diabetes can spur heart, kidney disease, neurological or vascular, and blindness problems that can accelerate mortality [10, 11]. In the demand of preventing and treating diabetes mellitus, there are many synthetic drugs, but they retain many side effects. Natural medicine regards herbal drugs that have low/minimal side effects, are easy to use and inexpensive. The drugs to prevent and treat obesity by consuming natural medicines derived from plants should contain secondary metabolites or natural phytochemical namely polyphenols, flavonoids, steroids, tannins, triterpenes, alkaloids and saponins [12-15].

Natural medicines that can be used to prevent and reduce obesity and type 2 diabetes mellitus are the plants that contain secondary metabolites. All of these compounds are reported to have activities as antioxidants, hypoglycemia, anticancer, anti-inflammatory, antiepileptic, antipyretic, analgesic, antimicrobial and immunomodulatory [12, 15-17]. *Cordyline terminalis* Kunth is grown in Malaysia, Cameroon, India and Bali, and its leaf extracts contain alkaloids, amino acids, flavonoids, glycosides, phytosterols, saponins, tannins, triterpenoids, and steroids [17-19]. [20] and [21] reported that saponins of leaf and andong rhizomes had hypolipidemic activity in wistar rats with a high-cholesterol diet.

Based on the background above, the researchers intend to reveal the activity of methanol extract of *Cordyline terminalis* Kunth's leaves as an antioxidant and antidiabetic in obese wistar rats that have not been widely done; therefore, it is expected that with 100 mg / kg bw and 200 mg / kg bw, methanol extract of andong leaf can cause a decline: Lee obesity index, glucose, free fatty acids and blood triglycerides in obese wistar rats.

MATERIALS AND METHODS

Material used

Egg yolk duck, Lard, Leaf of Andong (Tampaksiring, Gianyar, Bali), Lipid kit profile for triglycerides (TG) (Sigma Diagnostic Ltd), and NaOH.

Collection and determination of plants

Andong leaves were collected from the Tampaksiring area, Gianyar, Bali, in January, determined by the Head of the Plant Conservation Center of the Botanical Garden 'Eka Karya' Bali-LIPI. The leaves obtained were then cleaned of dust and other dirt, and cut into small pieces then dried at room temperature in an open room to a moisture content of ±11%, then dried leaves were ground in a blender flask and filtered to 100 mesh fineness. Powder material was extracted by maceration [21].

Preliminary Phytochemicals Screening

One gram of methanol extracts of the leaves of *Cordyline terminalis* Kunth was subjected to preliminary phytochemicals screening following the methodology of Hossain and Nagooru, 2011 [17].

Andong Leaf Extraction

The powder of 0.5 kg was put into a 2.5-liter beaker, 2 liters of methanol were added and allowed to stand for 24 hours to extract all secondary metabolites in the sample. The mixture was filtered and the filtrate was collected. Maseration was repeated five times, until all the compounds that could be extracted with methanol, were completely extracted (methanol extract was tested by thin layer chromatography). The filtrate was collected, combined and evaporated [21].

Antioxidant of andong leaves of DPPH scavenging activity

The activity of DPPH scavenging of andong leaf extract was determined by the method of Pant, 2015 [16]. One meliliter of DPPH (0.135 mM) was mixed with 1 ml of different concentrations of andong (0-100 μg/ml). The reaction mixture was vortexed at room temperature for 30 minutes. Change in color from deep-violet to light-yellow was measured at 517 nm. The percentage inhibition of free radical DPPH was calculated from the following equation:

$$\%\,\text{inhibition} = -\frac{AControl - Atest}{AControl} \times 100$$

All the tests were carried out in triplicates. Though the activity is expressed as 50% inhibitory concentration, IC_{50} was calculated based on the percentage of DPPH radicals scavenged [17].

Animal Test

The study began with the selection of white female wistar rats that had been born with a weight of 150-200 g as much as 24. Eighteen rats were randomly assigned to be given a high-fat diet with the composition: 20% duck egg yolk, 20% lard, standard food Cp 550 60% (in the form of pellets) to obese rats (LOI > 0.3). Six of more rats were selected for negative control with a standard Cp 550 food only [22].

Determination of obesity was done using the Lee obesity index [23]. The rats were declared obese if the Lee obesity index was > 0.3 with a 4-week induction period. The test rats were divided into 4 treatment groups, namely the negative control group (normal rats) only given standard food (cp 550) and *ad libitum* drinking water. Treatment group 1 (positive control) is a group of obese rats without treatment. Treatment group 2 was the same as treatment group 1 with added andong leaf extract 100 mg / kg bw / d orally. Treatment group 3, the same as treatment group 1 with added andong leaf extract 200 mg / kg bw / d. Each group consisted of 6 rats and 30 days of treatment. For 30 days, the study were also carried out checking rats body weight and measuring the nasoanal length of rats.

After 30 days of treatment, the rats were fasted for 10 hours and post-test was examined by taking blood from the orbital sinus (eyes) using a 3 ml syringe. The collected blood was allowed to stay for 30 minutes at room temperature, then centrifuge at 1000 rpm for 10 minutes. The serum was separated and put into a bottle and then closed. The samples were then stored at 4^0 C, laboratory tests on TG, glucose and free fatty acids were carried out no later than 24 hours.

Analysis of Triglycerides, Glucose and Free Fatty Acids

TG testing was performed using TG diagnostic kit. Serum lipid profile was measured using a standard monograph [18, 21].

Measurement of free fatty acids with acid-base titrations

Acid-base titration or commonly referred to as asidi-alkalimetry titration is one method of titration that uses the principle of neutralization between acidic and alkaline solutions. The number of compounds titrated can be calculated from the volume and normality factor or molarity of titrant [24]. The Folch method is one of the extraction and purification methods used to measure lipid levels in the blood. In testing free fatty acids in the blood, the blood component was initially separated by centrifugation. The blood serum portion was then separated and dissolved by homogenizing the tissue in 2: 1 (v / v) chloroform-methanol solution. Furthermore, identification of free fatty acid levels can be done by acid-base titration method [25].

Measurement of Blood Glucose with Glucometer

Checking blood glucose levels is generally carried out in the laboratory with glucometer or glucose Point-of-Care Testing (POCT). This tool, according to Tonyushkina and Nichols, 2009 [26] is one of the most important advances in monitoring diabetes patients after the discovery of insulin. Glucometers generally use the glucose-oxidase biosensor method. Glucose in the capillary blood test will react with the glucose-oxidase enzyme that is on the test strip. The enzymatic reaction produces electrons that will be captured by the electrodes in the glucometer. The number of electrons captured is proportional to the level of glucose in the examination material [27].

Statistic analysis

Data analysis was done by a statistical system. Values are expressed by mean ± SD. The data results were analyzed by one-way ANOVA, and the value difference between treatment groups was determined by the least-significant-difference test (LSD) and Tamhane's test. Alpha 0.05 was used to determine statistically significant differences.

RESULTS AND DISCUSSION

Results

Phytochemical Test

The phytochemical test results on the extracts of andong leaf are presented in Table.1 as follows.

Table 1: Phytochemical Test Results of Andong Leaf Methanol Extract

No	Phytochemical Test	Reagent	Results	Description
1	Polyphenols	$FeCl_3$	Change color from light green to blackist green	Positive polyphenols
2	Flavonoids	Powder Mg and HCl	Change in color from light green to orange	Positive flavonoids
3	Saponins	HCl 1%	Froth does not disappear after HCl drops	Positive saponins
4	Alkaloids	Mayer	Brown precipitate is formed	Positive alkaloids
5	Steroids/Triterpenes	Anhydrous acetic acid and concentrated sulfuric acid	Change in light green to dark green	-Positive steroids -Positive Triterpenes

Antioxidant of Andong leaves extracts of DPPH scavenging activity

Based on the data in Figure 1 above, the intercept value was obtained as 0.383 and slope value as 16.20 so that the curve equation was y = 0.383x + 16.20 with a R^2 value of 0.995. The equation was used to determine IC_{50} (x) in methanol extract of andong leaf based on its absorbance. The results of IC_{50} measurements for DPPH scavenging on methanol extract are 88.25 ppm.

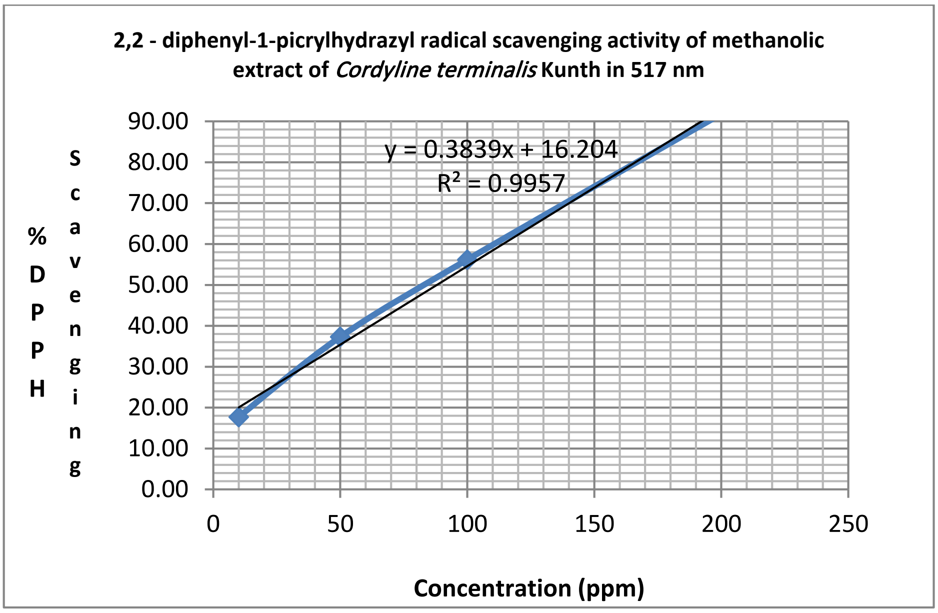

Figure 1. 2,2-diphenil—picrylhydrazyl radical scavenging activity of methanolic extract of Andong leaves

Experiment Diet Composition

The composition of the experimental diet is shown in Table 2. The 30-day treatment period, the body weight of the group of obese rats (including the high-fat diet group, the andong leaf extract group 100 mg / kg bw, and 200 mg / kg bw) was approximately 40% from the control group.

Table 2: Composition of Standard and High Fat Diets

Composition	Standard Diet % (cp 550)	High Fat Diet %
Water content	13	13
Protein	19-21	19-21
Fat	4	4
Fiber	6	6
Ash	8	8
Calcium	0.95	0.95
Phosphorus	0.70	0.70
Duck egg yolk	0	20
Lard	0	20

Try Animal Treatment

The rats that had been treated for 30 days were observed one day before blood was taken, ie before the rats were fasted for 12 hours. Body weight and the nasoanal length rats were measured to determine Lee obesity index (LOI) of each group. Rats were expressed as obese if Lee obesity index value was > 0.3 [23].

After being treated for 30 days, the rats were fasted for 12 hours then the blood of the rats was taken for blood glucose testing, free fatty acids, and triglycerides. The average value of the post test results of determining Lee obesity index, blood glucose, free fatty acids, and triglycerides can be seen in Table 3.

Table 3: Average Lee Obesity Index, Blood Glucose, Free Fatty Acids, and Triglycerides

Faktor	Control	HF	P100	P200
Lee Obesity Index	$0.294{\pm}0.005^{b,c,d}$	$0.357{\pm}0.004^{a,c,d}$	$0.235{\pm}0.007^{a,b,d}$	$0.215{\pm}0.018^{a,b,c}$
Glucose (mg/dl)	$79.800{\pm}4.324^{b,c,d}$	$149.000{\pm}9.695^{a,c,d}$	$91.210{\pm}2.588^{a,b}$	$90.520{\pm}3.647^{a,b}$
FFA (mmol/l)	$17.133{\pm}1.354^{b}$	$26.760{\pm}1.483^{a,c,d}$	$18.234{\pm}0.462^{b}$	$16.902{\pm}1.260^{b}$
Triglycerides (mg/dl)	$64.200{\pm}6.058^{b,c,d}$	$290.200{\pm}6.648^{a,c,d}$	$122.200{\pm}2.588^{a,b}$	$120.800{\pm}3.033^{a,b}$

The mean ± SD (n = 6) followed by a superscript in the same row shows a significant difference $p < 0.05$; treatment group 1 (HF = high fat), treatment group 2 (extract 100 mg / d), and treatment group 3 (extract 200 mg / d), compared with controls. TG (triglycerides); FFA (free fat acid).; ^{a} showed a significant difference from the control $p < 0.05$; [b] showed a significant difference from HF $p < 0.05$; [c] showed a significant difference from 100 mg / d $p < 0.05$; [d] showed a significant difference of 200 mg / d $p < 0.05$.

The post test results in Table 3 showed that the administration of methanol extract of andong leaf with a dose of 100 mg / d and 200 mg / d can reduce the Lee obesity index value compared to the high fat group.

Being overweight and obesity are defined as excess fat accumulation that can affect an individual's health. Obesity can trigger several diseases, one of which is type 2 diabetes mellitus which is a degenerative disease. Obesity can trigger pancreatic cell damage caused by oxidative stress. Oxidative stress is a state when the amount of free radicals in the body exceeds the body's ability to neutralize it. In conditions of oxidative stress, there is an increase in Reactive Oxygen Species (ROS) which will cause damage to the pancreatic, tissue or organ beta cells. One therapeutic approach in counteracting oxidative stress is with antioxidants [9, 28].

Rat Blood Glucose Levels

Glucose is a precursor for the synthesis of all other carbohydrates in the body, including glycogen for storage, ribose and deoxyribose in nucleic acids, galactose in milk lactose and glycolipids and in combination with proteins in glycoproteins and proteoglycans [29]. Glucose levels are influenced by several factors, one of which is the condition of obesity. Obesity is associated with insulin resistance which is characterized by excess blood sugar levels accompanied by hypertension, hypertliglycerides and low HDL, a condition called metabolic syndrome so that obesity sufferers are advised to control blood sugar levels regularly to prevent the occurrence of disease complications, especially referring to diabetes. The results of rat blood glucose levels after averaging are shown in Table 3.

Based on Table 3, it can be seen that there is a difference between negative control, positive control, and treatment groups, namely the treatment group had lower blood sugar compared to the positive control group and had higher blood glucose levels compared to the negative control group. The rats in the positive control group had blood sugar levels that exceeded normal levels of 50-135 mg / dl so that obese rats were declared to have hyperglycemia while the blood sugar levels of other rats were still within normal limits. This shows that the administration of methanol extract of good andong leaf with levels of 100 mg / d and 200 mg / d reduced blood glucose levels in obese rats.

Table 3 and Tamhane's test results showed that there were significant differences between the control group rats and the rats in the treatment group. The rats in the treatment group had blood sugar levels that tended to be lower than the high-fat group and approached blood sugar levels in the control group rats. The group of rats with the most significant differences were the groups of rats given extracts of 100 mg/d and 200 mg/d, in case of comparing the rats treated with 100 mg / d extract with the rat group treated with 200 mg/d extract, no significant difference is found ($p > 0.05$). The group of rats which were given 200 mg/d extract, had more significant difference compared to the group of rats given 100 mg/d extract of control group.

Free Fatty Acid Levels of Rats Blood

Free fatty acid levels are related to blood glucose production. In conditions of insulin resistance, lipase-sensitive hormones in adipose tissue will become active so that lipolysis of triglycerides in adipose tissue increases. This situation will produce excessive free fatty acids. Free fatty acids will enter the blood stream, some will be used as energy sources and some will be taken to the liver as triglyceride-forming raw materials. Free fatty acids reduce intake glucose in adipocytes and muscles and increase hepatic glucose excretion associated with insulin resistance which triggers type 2 DM (32). The results of determining free fatty acid levels are shown in Table 3.

Table 3 showed a group of high fat rats having high levels of free fatty acids more than the control group and extract treatment group 100 mg / d and 200 mg / d. While in the treatment group rats had free fatty acid levels that were close to the control rats. This shows that the administration of methanol extract of red andong leaf 100 mg / d and 200 mg / d reduced free fatty acid levels in obese rats.

There were significant differences between the groups treated with high fat groups. The group of rats fed with the methanol extract, had lower levels of free fatty acids then the high-fat group with a significant difference ($p < 0.05$). Decrease in free fatty acid levels that occurred in the rats given extracts both at doses of 100 mg / d and 200 mg / d, did not have significant differences indicating that the two doses had the same effectiveness in reducing levels of free fatty acids in the blood of obese rats.

Triglyceride levels

Triglycerides are a type of fat that is transported in the blood and stored in body fat tissue, normal levels in the blood of rats do not exceed 150 mg/dl. In certain conditions, such as diabetes mellitus, hyperlipidemia, obesity, and other congenital diseases, triglyceride levels can increase to more than 200 mg/dl, can even reach 500 mg/dl - 1000 mg/dl which is called hypertriglyceridemia. Triglycerides will be absorbed as free fatty acids while

cholesterol remains as cholesterol. In the small intestine free fatty acids will be changed again to triglycerides [29]. The results of determining free fatty acid levels are shown in Table 3.
Based on Table 3, the high-fat diet group had high triglyceride levels compared to the treatment group. This shows that methanol extract of red andong leaf can reduce triglyceride levels in the blood.
In Table 3 and Tamhane's test results, there were significant differences ($p < 0.05$) of triglyceride levels between the groups treated with high-fat groups. The group of rats that were given extracts at a dose of 100 mg / d and 200 mg / d did not show significant differences.

DISCUSSION

Based on the results of observations it is known that there is a relationship between obesity and an increase in blood sugar levels and free fatty acids accompanied by an increase in triglyceride levels in the blood. Obese sufferers experience abnormal fat metabolism resulting in an increase in plasma lipid fraction called hyperlipidemia. Lipids are stored in the body in the form of triglycerides. Triglycerides are formed in the liver from glycerol and fat derived from foods with insulin stimulation or excess calories due to excessive food intake [30]. Triglycerides with cholesterol form a chylomicron which is then described by the enzyme lipoprotein lipase forming free fatty acids and remnants chylomicrons. Free fatty acids then penetrate fat cells to be converted back to triglycerides as food reserves that can cause obesity [29]. Excess triglycerides in the blood will trigger the production of excess free fatty acids which will inhibit glucose intake in adipocytes and muscles so that the body experiences insulin resistance [31]. The relationship between obesity and increased free fatty acids and blood glucose can be seen in Table 3.
Under conditions of obesity and diabetes mellitus can increase oxidative stress so that appropriate therapy is needed. One therapeutic approach in overcoming obesity and hyperglycemia is by combining cholesterol-lowering drug therapy and lowering blood glucose. But with these therapies, it is not possible to prevent cell damage caused by free radicals. Therefore, additional antioxidants are needed for people with diabetes mellitus who are also obese [32]. The compounds that play a role in lowering cholesterol or lipids in the methanol extract of red andong leaf based on the analysis of phytochemical are saponins, tannins, steroids, polyphenolics, alkaloids and flavonoids [4, 12, 14]. While compounds that act as antihyperglycemia agents as well as antioxidants are flavonoids, tannins and phenols. Under conditions of obesity and diabetes mellitus can increase oxidative stress so that appropriate therapy is needed. One therapeutic approach in overcoming obesity and hyperglycemia is by combining cholesterol-lowering drug therapy and lowering blood glucose. But with these therapies, it is not possible to prevent cell damage caused by free radicals. Therefore, additional antioxidants are needed for people with diabetes mellitus who are also obese [32, 33]. The compounds that play a role in lowering cholesterol or lipids in the methanol extract of red andong leaf based on the analysis of phytochemical are saponins, tannins, steroids, phenolics, alkaloids and flavonoids. While compounds that act as antihyperglycemia agents as well as antioxidants are flavonoids, tannins and phenols.
Lakshmi (2012) [34] reported that steroid saponins from Chlorophytum nimonii can reduce total cholesterol, LDL cholesterol, triglycerides and raise HDL cholesterol significantly ($p < 0.01$). Intake of andong leaf saponins can reduce total cholesterol, LDL cholesterol, triglycerides, total bile acids and the ratio of total cholesterol / HDL cholesterol and increase HDL cholesterol with a significant difference ($p < 0.05$) compared to the treatment of high cholesterol. The intake of red andong leaf saponins not only binds cholesterol from food consumed, but also binds cholesterol derived from the liver which is secreted into the intestine with bile and subsequently discharged through feces. Saponins can also cause bile acid concentration and decreased plasma total cholesterol [20]. Saponin compounds found in red andong leaf (*Cordyline terminalis* Kunth) have been shown to reduce plasma cholesterol and blood plasma bile acids by the mechanism of action of saponins which can increase total cholesterol excretion and excretion of bile acids through feces and the ability of saponins in binding cholesterol to form saponin complexes cholesterol that has been tested *in vitro* [33].
In addition to saponins, flavonoid compounds also have activity as anti-hyperlipidemia. In the methanol extract of red andong leaf (*Cordyline terminalis* Kunth), it was found to contain high levels of flavonoids, polyphenols, and alkaloids. Based on the results of research by Ranti *et al*., (2013), it was proved that flavonoid extract from plant leaves Abelmoschus manihot was able to reduce cholesterol levels by 86.45% in wistar strain male rats [35]. According to Radhika *et al*. (2011) [36], flavonoid compounds have antihypercholesterolemia activity with the mechanism of action as reducing LDL in the body. Flavonoids can also increase LDL receptor density in the liver and bind apolipoprotein B. Flavonoids can reduce cholesterol levels in the blood by inhibiting the action of

the 3-hydroxy 3-methylglutaryl coenzyme A reductase (HMG Co-Areductase) enzyme. The function of HMG Co-A reductase is an enzyme to convert HMG Co-A to mevalonate to form cholesterol.

CONCLUSION

Based on the results of the research and discussion, the following conclusions are obtained.

1. Intake of methanol extract of andong leaf (*Cordyline temirminalis* Kunth) can reduce blood free fatty acid, glucose, and triglyserides levels in obese wistar rats.
2. The compounds that have the potential as antioxidants and antidiabetic in methanol extract of andong leaf which can reduce levels of Lee obesity index, free fatty acids, triglycerides and blood glucose in obese wistar rats were saponins, flavonoids, polyphenols, alkaloids, steroids and triterpenoids with IC 50 of DPPH is 88.25 ppm.

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