Anti-Diabetic Effect of Singi Fruit *(Dillenia serrata)* in Male Rats *(Rattus novergicus)* Induced with a High-Fat Diet

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Abstract. Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia that occurs due to defects in insulin secretion, insulin action, or both. Dyslipidemia is one of the risk factors for coronary heart disease and is often associated with diabetes mellitus. Statins are recommended by several guidelines as first-line treatment for lowering LDL levels and have been shown to be beneficial in primary and secondary prevention to reduce cardiovascular disease morbidity and mortality in high-risk patients. The usage of medications made from natural substances can be an alternative therapy that lessens the adverse effects brought on by the use of synthetic drugs. In vitro studies related to the potential of singi fruit (*D. serrata*) in inhibiting the activation of HMG CoA reductase and the presence of flavonoids as antioxidants that are protective against cell damage as well as insulin-producing and can increase insulin sensitivity This study used a quasi-experimental in vivo design with a pre- and posttest only control group design, with the independent variable being the feeding of singi fruit meat (*D. serrata*) and the dependent variable being blood glucose levels in male white rats of the Wistar strain (*Rattus novergicus),* which were divided into 4 groups, i.e the healthy rat group, High Fat diet (HFD) group, singi group, and simvastatin group. The results of this study revealed a significant effect on blood glucose levels in rats induced by a high-fat diet in groups: HFD group (0.017), *D. serrata* group (0.011), and simvastatin group (0.002), significant with a *p value* < 0.05, and significant differences between groups: healthy group, HFD group, *D. serrata* group, and simvastatin group with a *p value* 0.05).There was a significant effect of feeding singi fruit meat (*D. serrata*) on the blood glucose levels of rats induced with a high-fat diet.

Keywords: Anti-diabetic, Blood Glucose Level, *Dillenia serrata*, High Fat Diet.

1 Introduction

The shift of society from agricultural life to modern society has an impact on unhealthy modern lifestyles. The diet of today's people is switching to an instantly versatile diet high in fat, calories, and carbohydrates. Besides, the industrial revolution changed a person to do less physical activity because human power was replaced by machines [1],

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contributing to health problems including obesity, high cholesterol, and others as a result of the disruption of the body's metabolism.

Hypercholesterolemia is the most common form of dyslipidemia and is associated with an increased risk of cardiovascular disease with an increase in plasma low-density lipoprotein (LDL) cholesterol levels that rose to the 15th leading risk factor for death in 1990, reduced to 11th in 2007 and the 8th in 2019 [2]. According to the American Heart Association (AHA), hypercholesterolemia is the level of total and LDL cholesterol in the blood above normal levels. Hypercholesterolemia has a significant relationship with blood glucose levels [3]. Increased levels of fatty acids cause the pancreas to fail to provide enough insulin to cope with increased insulin requirements. This causes difficulties in eliminating fatty acid and lack of inhibition of glucose release in the liver that can lead to hyperglycaemia and hyperlipidemia [4]. In addition, insulin resistance will increase the lipolysis of stored fat reserves, thereby increasing free fatty acids in the blood. In patients with hypercholesterolemia, efforts can be made to reduce cholesterol by non-pharmacological means such as dietary adjustment, weight control, exercise, and pharmacological use of HMG-CoA reductase inhibitors (or statins) as first-line drugs [4,5].

Statin is a class of lipid-lowering drugs of the latest generation, with a mechanism that inhibits competitively the coenzyme HMG-CoA reductase, an enzyme that plays a role in the synthesis of cholesterol, especially in the liver. This inhibitor temporarily lowers the level of cellular cholesterol, which triggers the cell's signal cascade and ultimately activates the transcription factor sterol-regulating element binding protein (SREBP), which controls the expression of the gene that codes for the LDL receptor [5]. Statin is recommended by some guidelines as a first-line treatment for lowering LDL levels which has been shown to be beneficial in both primary and secondary prevention and decreasing morbidity and mortality of cardiovascular disease in patients at high risk [5]. Long-term statin use can have more serious adverse effects, such as an increased incidence of diabetes, neurological and neurocognitive consequences, hepatotoxicity, kidney damage, and other disorders. There is no commonly accepted definition of statin toxicity or intolerance at the moment. The incidence of statin intolerance is also being contested, owing to problems in detection and diagnosis [6].

Persuasive data from many randomized controlled trials and large long-term observational studies show a slight increase in the risk of developing new diabetes after statin initiation. Some meta-analyses of many statin trials as well as longitudinal population-based studies show that risk factors for diabetes in people treated with statins include the underlying risk of early diabetes (especially metabolic syndrome), the intensity of statin therapy, certain genetic properties that are independent of the risk of diabetes, and lifestyle factors. Limited data suggests that statins slightly aggravate hyperglycaemia and HbA1c levels in those suffering from DM or previously existing glucose intolerance. The precise mechanisms of diabetogenesis with statin therapy are unclear, but insulin sensitivity disruption and impaired β cell function through increased intracellular cholesterol absorption due to inhibition of intra-cell cholesterol synthesis by statins, as well as other mechanism, may be involved. In addition, statins are known to have anti-inflammatory effects, it is hypothesized that, under dismetabolic conditions, statines may have a pro-inflamatory effect through certain inflammatory induction. The risks and benefits for the onset of cardiovascular disease strongly support statin therapy in those at risk, despite the emergence of new diabetes. Compliance with lifestyle regimes is crucial in the prevention of new DM on statins [7].

As an alternative to reducing the side effects caused by the use of synthetic medicines, use of medicines derived from natural ingredients. Traditional medicines are considered safer than synthetics and are supported by the presence of back to nature issues in the prevention, promotion and rehabilitation efforts so that the usage of natural materials as raw materials is increasing [4,8]. The Singi plant (*Dillenia serrata*) is one of the endemic plants of Sulawesi that is found almost all over the region. Singi fruit is less in demand and not much benefited by society. Because of the sweet taste of the fruit. Besides, it is a seasonal fruit, similar in size to an orange, but known to have good medical value, so it is used by tribal communities and communities as a medicine [9]. The skin of this fruit is traditionally used by the community as a cure for fever and wounds, treating blood vomiting and treating swelling or inflammation. It contains citric acid, vitamin C and beta-carotene compounds. In addition, it contains secondary metabolic compound like alkaloid, flavonoid, saponins, polyphenols and triterpenoids [10,11]. In vitro research related to the potential of lily (*D. serrata)* in inhibiting the activation of HMG CoA reductase as well as the presence of flavonoid as an antioxidant substance that is protective against damage to β cells as an insulin producer and can increase insulin sensitivity, and the content of quercetin in inhibits GLUT2 intestinal mucosa so that it can reduce glucose absorption has been done but no animal trial related to benefits of the lily in lowering cholesterol and blood glucosa has not been done, so the researchers are interested to do research in vivo related to lily content and its effect on the blood sugar levels in rats given high-fat diet.

2 Methods

2.1 Materials

White male rat of a wistar rod (*Rattus novergicus*), aged 6-10 weeks, and weighing 150-250 grams, singi fruit (*D.serrata*), Simvastatin tablet, GOD-PAP (enzymatic photometric test) method using glucose FS reagents from Diasys, and high fat formula : 10% of beef fat, 20% of tar oil, and 20% of egg yolks.

2.2 Animals

The study was a quasi-experimental study of testing the anti-diabetic effects of *D. Serrata* meat in animal models of hypercholesterolemia in vivo. The study used a pre-post-test only control group design using a white male rat of a wistar rod (*Rattus novergicus*), aged 6-10 weeks, and weighing 150-250 grams. The animal trial was divided into four groups, i.e healthy rats (G1), high-fat diet rats (G2), high fat diets rats given *D. serrata*'s meat (G3), and high-fats diets simvastatin rats (G4).

2.3 Induction of a high fat diet

Induction of a high-fat diet is done by administering a high fat diet for 1-2 weeks with the following formula, (Gunawan, 2018) : Formula: 10% of beef fat, 20% of tar oil, and 20% of egg yolks mixed in 120 mL for each rats administrated orally. Blood collection in rats through the orbital vein, when the triglycemia levels are normal, total cholesterol is obtained >200 mg/dL, cholesterol LDL ≥ 190 mg/ dL and LDL < 40 mg/dl then the animal tries to declare hypercolesterolemia.

2.4 Treatment

Treatment of the animal was performed according to the respective group, G1 was administrated with standard feeding for 4 weeks, G2 was administrated with high-fat diet for 2 weeks continued standard feed for 2 weeks, G3 was administrated with a high-fatty diet for 2 weeks continuously with singi fruit for 2 weeks, and G4 was administrated with high-fat diets for 2 weeks continued simvastatin for 2 weeks.

2.5 Blood glucose measurement

Blood glucose and initial cholesterol levels were measured after a high-fat diet for 2 weeks, while final blood glucose levels were met after a four-week trial. The method used in determining blood glucose levels is the GOD-PAP (enzymatic photometric test) method using glucose FS reagents from Diasys.

2.6 Data analysis

White male rat of a wistar rod (*Rattus novergicus*), aged 6-10 weeks, and weighing 150-250 grams, singi fruit (*D.serrata*), Simvastatin tablet, GOD-PAP (enzymatic photometric test) method using glucose FS reagents from Diasys, and high fat formula : 10% of beef fat, 20% of tar oil, and 20% of egg yolks.

The differential increase in glucose levels in each treatment group was analyzed with the One Way ANOVA statistical test, and then continued with the Post Hoc Tests to compare between the groups. The one-way ANOVA test condition was with the same normality and the same data variance. The normality test used was the Shapiro Wilk test (normal criterion $p > 0.05$).

2.7 Ethical approval

The Health Researh Ethics Commission, Faculty of Medicine, Halu Oleo University, has issued a letter of ethical approval for this study with the following number : 026/UN29.17.1.3/ETIK/2022.

3 Results

Based on Table 1, the average weight of the rats increased after the induction of high-fat diets in all groups, but after the treatment of the HFD group, *D. serrata*, and simvastatin experienced weight loss. The normality test with the weight measurement data of rats (*Rattus novergicus*) before and after treatment assumes that the data is normally distributed by p>0,05. The results of the normality test of Shapiro-Wilk and the rate of measurements of the blood glucosis levels of rats (*Rattus Noervegicus*) prior to and following treatment can be seen in Table 1. The highest total cholesterol rate variance was observed in the elephant group from 379.1 ± 272.7 to 148.2 ± 17.02 with a ratio variance of -230.9 whereas the lowest was in the healthy rat group from 184.9 ± 91.9 to 156.5 ± 12.6 with the ratio difference of -28.4

Table 1. Characteristic of each groups

Treatment	n = 24 Pre-treatment (mean±SD)	Post-treatment (mean±SD)	Mean difference
Weight (grams)			
G1	175,67 ± 12	176,67 ± 4,4	+1
G2	198,17 ± 39	184,00 ± 17,5	-14,17
G3	199,67 ± 42	187,33 ± 31,3	-12,34
G4	194,33 ± 8	166,67 ± 9,6	-27,66
Glucose (g/dL)			
G1	156,19 ± 19,96	112,26 ± 24,29	-43,93
G2	152,17 ± 21,84	145,54 ± 33,70	-6,63
G3	196,27 ± 93,44	117,23 ± 10,70	-79,04
G4	116,35 ± 12,07	136,60 ± 12,95	+20,25
Cholesterol (g/dL)			
G1	173,3 ± 13,4	140,4 ± 24,2	-32,9
G2	251,7 ± 15,3	147,7 ± 14,7	-104
G3	379,1 ± 272,7	148,2 ± 17,02	-230,9
G4	184,9 ± 91,9	156,5 ± 12,6	-28,4

The results of the One Way Anova showed that the p-value analysis of blood glucose levels between groups was 0,000. This suggests that blood glucose levels between groups differ significantly ($p < 0.05$) (Table 2).

Table 2. Blood glucose difference between groups

Groups (n=6)	Mean of Glucose (mg/dL±SD)	*p-value*
G1	112,21 ± 24,23	

G2	138,37 ± 25,98	0.000*
G3	110,51 ± 11,69	
G4	136,60 ± 12,95	

Note: *Significant if p < 0,05.

Based on Table 3, the p-value analysis of the blood glucose ratio of healthy rats to the blood sugar ratio in the HFD group, the leopard group and the simvastatin group in sequence is as follows: 0,002 ($p<0.05$); 0,004 ($p <0.05$); and 0,000 ($p\leq0,05$). This indicates that the bloodglucose rate between the untreated group and leopards, non-treated groups and symvastatin groups is significantly the same ($P<0.05$).

Table 3. Comparison of glucose levels from different groups

Groups (n=24)		*p-value*
G1	G2	0,002
	G3	0,004
	G4	0,000
G2	G1	0,002
	G3	0,010
	G4	0,006
G3	G1	0,004
	G2	0,010
	G4	0,003
G4	G1	0,000
	G2	0,006
	G3	0,003

Note:**Post Hoc Test*, Significant if p < 0,05.

4 Discussion

Based on the results of the statistical trials showed that there was no significant difference between the *D. serrata* group and the symvastatin group, but from the data obtained there was a decrease in blood glucose levels in the group of *D. serrata* with a rate difference of -79,04 mg/dL, whereas in the groups of simvastatin there was an increasing in blood sugar levels of +20,25 mg / dL, so it could be concluded that the group can give a greater influence on the decreased blood glucosis levels than the simvastatine group. In addition, in the high-fat diet group, glucose levels decreased by -6.63 mg/dL. The drop in glucose is due to glycolysis. The initial phase of glucose conversion into energy metabolism in the body will take place anaerobically through a process called glycolysis. The essence of the whole glycolyse process is to convert glucosa into a final product of pyruvate, in addition to producing the final product as a pyruvate molecule, this glycolise process will also produce ATP molecules, the ATP that is formed then this will die by the body's cells as a basic component of the energy source [12]. This is in line with a study conducted by Garonzi et al., [13] that showed a decrease in glucose levels after the administration of high-fat and protein diets in patients with type 1 DM. In the study, patients with Type 1 DM were given foods high in fat and protein as well as low in fats and protein. In the results of the study for both groups experienced a decrease in glucose levels. In addition, the survey conducted by Eristamiani [14] showed that there was a difference in the average blood glucose value after activation, the occurrence of a decrease in glucosa in the rats occurred because the rats performed the activity as in general, it can also be supported by the occurrence of weight loss in rats given high fat feeding after the treatment.

The process of developing diseases such as cancer, diabetes, cardiovascular disease, Alzheimer's, and other degenerative diseases has been associated with oxidative stress accumulated in the human body. Flavonoids can lower blood glucose levels by their antioxidant ability. Flavonoids are protective against damage to pancreatic β cells as insulin producers and can increase insulin sensitivity [15]. Based on the phytochemical content, estimates of the total phenolic and flavonoid content in the methanol extract from the leopard's skin show a considerable amount of 5.92% phenolics and 2.34% flavanoids per gram of extract [15,16]. Flavonoids can be an antioxidant by capturing free radicals, so it is important inining the balance between oxidants and antioxidants in the body [17]. Based on its secondary metabolites, songi plants have the potential as an antagonists of free radicals. Free radicals are molecules that have one or more unpaired electrons. These unpairing electrons cause free radicals to become highly reactive compounds against the cells of the body by binding the electron molecule of the cell. Free radicals are normally produced by the body as a result of biochemical processes. Excessive free radicals can lead to degenerative diseases, such as heart disease, stroke, and cancer. An antioxidant is a compound that can delay or prevent oxidation by inhibiting the occurrence of oxidative chain reactions. The primary function of antioxidants is to neutralize free radicals, so the body is protected from a variety of degenerative diseases. Nowadays, antioxidants are widely used in the food industry. The most commonly used antioxidants are synthetic anti-oxidants, including butylated hydroxytoluene (BHT) and butyled hydroxyyanisole (BHA). The addition of synthetic antioxidants to food causes several health problems such as cancer, premature aging, rheumatoid arthritis and heart disease. For that reason, it is necessary to discover natural antioxidants from natural materials [18]. Flavonoids can inhibit FAS (Fatty Acid Synthase) by blocking acetyl-Coas and malonyl-coas, which are substrates of acyl-transferases that potentially inhibit genes that play a role in adipogenesis, thereby reducing the amount of adiposites [19].

Dillenia species with antibacterial and antifungal activities include *Dillenia indica, Dillenia papuana, pentagyna, sufruticosa*, and *sumatrana*. Extracts of these Plants were known to suppress the growth of both gram-positive and gram-negative bacteria. However, the extract showed weakness in inhibiting mushrooms such as *Aspergillus fumigatus, A. niger, Candida albicans, C. arriza,C. crusei, Penicillium sp., Rhizopusoryzae, Saccharomyces cerevisiae* and *Trichoderma viride*. Seven types of triterpenoids from the Dillenia plant have been shown to have antimicrobial effects [20]. Dillenia suffruticosa contains a secondary metabolite compound dominated by phenolic and flavonoid groups with a total Phenolic content (TPC) of 236.17±14.61 mg

EGA/g of extract and a total Flavonoidal Content (TFC) of 12.06±0.39 mg ER/g extract. The results also show that flavonoids have antidiabetic activity through their antioxidant functions. Ethanol extract has the ability to inhibit the enzymes α-glucosidase and free radicals. Antioxidants are able to bind free radicals so that they can reduce oxidative stress. Reduced Oxidative Stress can reduce insulin resistance and prevent the development of dysfunction and damage to pancreatic β cells.. *Dillenia philippinensis* has been shown to inhibit the growth of *Escherichia coli, Bacillus subtilis* and *Micrococcus luteusha* [20].

The fiber content (diatery fiber) in the fruit is to calm and smooth the metabolic processes of the body, so it is very well consumed by obese people. According to a study [21] that in the digestive tract fibers can bind bile salts (the end product of cholesterol) and then excreted together with stools. Thus, food fibers are able to reduce cholesterol levels in the blood plasma. When there is an increase in cholesterol excretion in the stool, it will lower the amount of colesterol that goes to the liver [22]. The data also showed that the *D. serrata* group and the healthy rat group differed significantly, which means that *D. serrata* groups had a decrease in blood glucose levels close to the healthy rats with a difference in the blood glucosis rate in the healthy rats group of -43.93 mg/dL, so it is expected that the decreases in blood sugar levels in the *D. serrata* group could be close to normal blood glucoma levels. In the results of the post-hoc test showed significant differences between the *D. serrata* group and the HFD group which means *D. serrata* has the potential to lower blood glucose levels, from the data obtained there was an increase in blood sugar levels in the symvastatin group with a difference of +20,25 mg/dL. The statin group is an effective and well tolerated drug to treat dyslipidemia. Statin is also known as a drug that is a powerful inhibitor of the inflammatory process. The mechanism of statins in causing the modulation of the immune response is complex, but it is said to be unrelated to its effect in lowering LDL cholesterol. The use of simvastatin is recommended to be modulated at low doses. Higher doses may be required if the patient has been taking the drug for more than a year. The side effects of statin use are myopathy, the most serious of which is rhabdomiolysis and can be harmful to the kidneys [23].

Some studies on the effects of statins on glucose metabolism are still controversial. Some have shown that simvastatin has insulin resistance effects, others have no effect on the work of insulin, besides, in other studies have identified symvastatin in glucose homoeostasis. This mechanism can be caused by different properties of statins. Water-soluble statins, such as rosuvastatain, are hepatocyte-specific and are not absorbed by pancreatic and adipose cells. Fat-solubile statins such as simvastatin enter extrahepatic cells easily and can suppress the synthesis of isoprenoid proteins, thereby lowering insulin levels [24].

Weight loss was observed in the HFD group after treatment, based on glucose data rats in HFD groups had an average fasting blood sugar level of 145 mg/dL which means the rats already had diabetes. According to the study [25] in patients with diabetes mellitus there is a problem in the effect of insulin in the metabolism of sugar into cells is not perfect so blood sugar remains high. The condition can be toxic and cause weakness and unhealthy as well as complications and other metabolic disorders. When the body is unable to obtain enough energy from sugar, the body will process other substances to be converted into energy like fat. The consumption or destruction of fat and protein leads to weight loss. Based on the analysis of the pair T test, there was a significant decrease in blood glucose levels in the group of *D. serrata*. Treatment of the trial animal for two weeks and a *D. serrata* dose of 60mg/kgBB was able to lower the blood sugar levels to normal (<126mg/dL)

5 Conclusion

There was an anti-diabetic potential of *D. serrata*'s meat (Dillenia serrata) in induced high-fat feed rats. Further researchers are expected to conduct a quantitative analysis of the secondary metabolic compounds of the *D. serrata* so that we can identify substances that can affect blood glucose levels and can conduct trials of the dose and duration of *D. serrata*'s administration in order to determine the optimal dosage and time that can lower the blood sugar levels.

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