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Effect of Ethanol Extract *Elaeocarpus grandiflorus* Leaf on Lipid Profile of Hyperlipidemic Rats

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Abstract
The purpose of the study was to examine the effect of *Elaeocarpus grandiflorus* leaf extract on the lipid profile of hyperlipidemic rats. A randomized post-test control group design was conducted on 4 groups of hyperlipidemic rats. The control group was given a high-fat diet only, while the experimental groups were given a high-fat diet and extract in doses of 200 mg/kgBW (P1), 400 mg/kgBW (P2), and 800 mg/kgBW (P3). The high-fat diet was administered on days 1-14, and the extract was given orally on days 8-14. HDL, LDL, and triglyceride (TG) levels were measured on day 15. The means for LDL were 22.98 mg/dL (control), 16.76 mg/dL (P1), 13.87 mg/dL (P2), and 16.64 mg/dL (P3). The means for HDL were 51.60 mg/dL (control), 48.20 mg/dL (P1), 48.20 mg/dL (P2), and 57.00 mg/dL (P3). Triglyceride levels were 227.36 mg/dL (control), 173.86 mg/dL (P1), 155.63 mg/dL (P2), and 148.63 mg/dL (P3). Although the means of HDL increased and the means of LDL and TG decreased, the statistical analysis showed no significant difference between the control and experimental groups. The study concluded that *E. grandiflorus* at doses of 100, 200, and 400 mg/kgBW did not significantly impact the lipid profile.
Keywords: *E. grandiflorus*; hyperlipidemic; HDL; LDL

Introduction

Hyperlipidemia is a condition that describes high levels of lipids in the blood and is characterized by high levels of total blood cholesterol, triglycerides, and low-density lipoprotein (LDL) and low levels of high-density lipoprotein (HDL) [1]. Hyperlipidemia can be caused by a high fat intake, especially saturated fat. Saturated fat can increase blood cholesterol levels by 15–25%. In addition, high-fat food intake results in increased lipogenesis activity and the formation of free fatty acid (FFA), which results in increased blood triglyceride levels [2], [3].

Increased blood cholesterol and triglyceride levels lead to plaque formation in blood vessels, or atherosclerosis [4],[5]. Atherosclerosis is the cause of coronary heart disease, carotid artery disease, and peripheral artery disease and is the leading cause of morbidity and mortality in the world.

Plant bioactive compounds can be used as antihyperlipidemic agents. Many studies have been conducted to prove that bioactive compounds in plants can affect blood lipid profiles. *E. grandiflorus* leaves are one of the plants that contain many bioactive compounds. Most of the compounds contained in *E. grandiflorus* suspension are flavonoids consisting of 32 compounds, including kaempferol, epicatechin, quercetin, vitexin, naringin, orientin, and procyanidin groups [6].

Flavonoids are phenolic substances that show considerable biological activity. Flavonoid class compounds show various effects that can prevent the development of atherosclerosis and diseases such as hypercholesterolemia, hypertension and obesity that cause cardiovascular disease. Flavonoids of the quercetin, kaempferol, myricetin, and naringenin groups have various biological functions such as antioxidant, antithrombotic, anti-inflammatory, antiatherogenic, anti-atherosclerotic and cardioprotective effects [7],[8].

Previous research shows that flavonoid compounds in plants can reduce blood cholesterol levels by inhibiting cholesterol synthesis through the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, and that flavonoid compounds can also reduce blood triglyceride levels by increasing

the enzyme lipoprotein lipase (LPL) through PPAR (peroxisome proliferator activated enzyme) activation [9].

Other research shows that flavonoids can prevent LDL oxidation and increase LDL receptor expression so that cholesterol levels decrease [10]. Other studies have also shown that flavonoids of the quercetin group can reduce triglyceride levels through increased transport and oxidation-ß fatty acids through the PPAR pathway [11]. The research aims to examine the antihyperlipidemic effect of *E. grandiflorus* extract in rat by looking at its effect on HDL, LDL and triglyceride levels.

Materials and methods

This study is an experimental study with a randomized posttest only control group research design using 20 rats divided into 4 groups, namely 1 control group and 3 treatment groups. In the treatment group, rats were given varying doses of ethanol extract from *E. grandiflorus* leaves (200 mg/kg), 400 mg/kg, and 800 mg/kg) to determine the effect of *E. grandiflorus* leaf extract on LDL levels, HDL levels, and triglyceride levels. Maintenance and treatment of test animals were carried out at the Biology Animal Cage, FMIPA UNNES. Examination of triglyceride, LDL, and HDL levels was carried out at the Semarang City Regional Health Laboratory.

Animal testing and ethical clearance

This study was designed randomized post test control groups. The experimental animal study has obtained an ethical permit issued by the Health Research Ethics Committee (KEPK) of Semarang State University with number 295/KEPK/EC/2023.

High-fat diet preparation

The high-fat feed consists of a mixture of pork oil and duck egg yolk with a ratio of 50% pork oil and 50% duck egg yolk [12]. The high-fat feedstock is made by mixing 300 ml of pork oil with 300 ml of raw duck egg yolk and stirring until homogeneous. The composition of the feed mixture was placed in one container.

Research procedure

This study used hyperlipidemic Wistar female rats. The rats an age of 2–3 months and a weight of 100–200 grams were obtained from the Biology Laboratory of FMIPA UNNES. A total of 20 white rats were divided into 4 test groups, namely 1 control group and 3 treatment groups (P1, P2, and P3), with each group consisting of 5 rats. Rats in all groups were made hyperlipidemic by receiving high-fat feed consisting of pork oil and egg yolk orally for 14 days. On the 8th day, rats in groups P1, P2, and P3 were added to the ethanol extract of *E. grandiflorus* leaves at varying doses of 200, 400, and 800 mg/kg BW. This administration is done orally using a gastric sonde for 7 days. On the 15th day, blood was taken using a microhematocrit tube in the orbital sinus. The blood was then centrifuged to form blood serum.

Total cholesterol, LDL, HDL and triglyceride

LDL cholesterol levels were measured using the indirect method using the Friedewald formula. The Friedewald formula is a calculation of LDL levels that uses total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (HDL) levels. The Friedewald calculation is not applicable if the triglyceride level is > 400 mg/dL. Total cholesterol levels and HDL levels were measured using the enzymatic cholesterol oxidase-aminophenazone (CHODPAP) photometric assay method expressed in mg/dL. Triglyceride levels were examined using a spectrophotometer with the Colorimetric Enzymatic Test GPO-PAP method, expressed in mg/dL. LDL, HDL, and triglyceride levels were analyzed at the Semarang City Health Laboratory.

Data analysis

The data obtained were analyzed statistically using SPSS. Data normality was tested with the Shapiro-Wilk test, and data homogeneity was tested with the Levene test. Normally distributed and

homogeneous data were analyzed by a one-way ANOVA test. Data that were not normally distributed and homogeneous were analyzed using the Kruskal-Wallis non-parametric test.

Results and discussion

All treatment groups are still in a state of hyperlipidemia (>54 mg/dL). Normality and homogeneity tests of total cholesterol levels showed a distribution of data that was not normally distributed and homogeneous, so the analysis was carried out using the Kruskal-Wallis. While the LDL, HDL and triglyceride were analyzed by ANOVA. The average total cholesterol level after feeding a high-fat diet and ethanol extract of *E. grandiflorus* leaves was lower than the control group except group P3. The results of measuring the average levels of cholesterol, LDL, HDL, and triglycerides in the blood of rats after feeding a high-fat diet and ethanol extract of *E. grandiflorus* leaves are presented in **Tables 1** and **2**.

Table 1: Mean of LDL and HDL levels (mg/dL) of hyperlipidemia rats treated with *E. grandiflorus* leaf extract.

Group	Mean LDL Level ± STD	Asym p.Sig	Mean HDL Level ± STD	Asym p.Sig
K	2.98 ± 9.72	0,521^{ns}	51,60**±**8,385	0.603^{ns}
P1	16.76 ± 8.13		48.20 ± 5.26	
P2	13.87 ± 8.39		48.20 ± 6.22	
P3	16.64 ± 12.13		57.00 ± 14.11	

Table 2: Mean of total cholesterol and triglyceride levels (mg/dL) of hyperlipidemia rats was treated with *E. grandiflorus* leaf extract.

Group	Mean Cholesterol Levels ± STD	Asym p.Sig	Mean Triglyceride Levels ± STD	Asym p.Sig
K	74.10 ± 13.33	0.448	227.36 ± 62.93	0.330
P1	70.09 ± 10.88		173.86 ± 51.50	
P2	66.62 ± 8.44		155.63 ± 69.28	
P3	79.77 ± 1.69		148.63 ± 95.92	

E. grandiflorus contains the most abundant flavonoid compounds with more than 50% components, including kaempferol, quercetin, procyanidin, luteolin, and naringin groups [6]. Flavonoids have a variety of pharmacological activities, one of which is antioxidants. Antioxidants are known to inhibit the formation of atherosclerosis and can reduce cholesterol levels in the blood [13].

Flavonoids act as inhibitors of the enzyme HMG-CoA reductase so that cholesterol synthesis decreases. When cholesterol is transported from the intestine to the liver, HMG-CoA reductase will convert acetyl-CoA into mevalonate, and cholesterol synthesis will be inhibited [14]. Inhibited cholesterol synthesis will result in a decrease in cholesterol levels in the blood. A decrease in blood cholesterol levels will increase LDL receptor expression in the cell membrane [15]. As a result, the level of LDL cholesterol in the blood circulation will be reduced.

Flavonoid compounds as antioxidants can reduce cholesterol levels by inhibiting cholesterol absorption in the intestine. Flavonoids will increase the reaction of bile acid formation from cholesterol to be excreted through faeces [16]. In absorbing cholesterol in the intestine, flavonoids will inhibit the activity of pancreatic lipase enzyme performance in hydrolyzing triglycerides into free fatty acids [17]. Inhibition of the pancreatic lipase enzyme will result in a decreased amount of free fatty acids in the liver.

Besides flavonoids, kaempferol is one of the flavanols that has pharmacological activities such as antioxidant, anti-inflammatory, anticancer, antimicrobial, neuroprotective, antidiabetic, analgesic, and antiallergic activities. Kaempferol will increase LDL receptors in the liver so that cholesterol-LDL clearance becomes faster [18]. Increased LDL receptors will result in decreased LDL-cholesterol levels. Another study also mentioned that kaempferol compounds directly bind and activate LXR-β to reduce glucose and increase the concentration of high-density lipoprotein (HDL) cholesterol. Activation of LXR-β will increase bile acid excretion through faeces [19].

Another content of *E. grandiflorus* is quercetin. The role of quercetin as an antioxidant can prevent LDL oxidation by binding free radicals [20]. One hydrogen atom on quercetin will be given to the active peroxide compound (ROO) to form a non-reactive end product. The formation of non-reactive radical compounds causes total cholesterol levels to decrease because LDL is not oxidized. Quercetin also regulates cholesterol metabolism by increasing bile acid excretion, lowering blood cholesterol levels [21].

In theory, the content of *E. grandiflorus* leaf compounds such as flavonoids, kaempferol and quercetin can reduce cholesterol levels and LDL and increase HDL. In this study after giving ethanol extract of *E. grandiflorus* leaves. rats were still in hyperlipidemia. Meanwhile, LDL and HDL levels did not decrease or increase and were still in the range of normal levels. In rats, the normal limit of LDL levels is 2-27 mg/dL and 35-85 mg/dL for HDL levels [22]. This can be caused by a less high dose of extracts or less time given to test animals, so the effect is still insignificant on cholesterol, LDL, and HDL levels.

The normal limit for triglyceride levels is <150 mg/dl. If the triglyceride level is > 150 mg / dl, it is said to be hypertriglyceridemia [23]. Based on table 2. The highest triglyceride levels were in the control group and the lowest in the P3 group. The high value of triglyceride levels in the control group was due to the provision of high-fat feed which was not followed by the provision of ethanol extract of *E. grandiflorus* leaves. High-fat intake can cause triglyceride levels in the blood due to increased fatty acid synthesis in the liver.

The lowest mean triglyceride levels were in the P3 group given ethanol extract of *E. grandiflorus* leaves at a dose of 800 mg/KgBB. Giving ethanol extract of *E. grandiflorus* leaves at a dose of 800 mg/KgBB is expected to reduce blood triglyceride levels to within the normal threshold. This is because ethanol extract of *E. grandiflorus* leaves contains bioactive compounds that can reduce blood triglyceride levels.

E. grandiflorus leaves contain flavonoid compounds, including kaempferol, quercetin, rutin, and orientin [6]. According to previous research, quercetin can reduce blood triglyceride levels by inducing browning of animal white fat tissue, which can increase fatty acid absorption. In addition, quercetin can also reduce lipolysis from fat tissue [24],[25]. Routine compounds can reduce Very Low-Density Lipoprotein (VLDL) and cholesterol in the blood, followed by increased LPL enzymes [26]. Orientin compounds can reduce fatty acid accumulation and triglyceride levels by inhibiting the expression of several genes involved in fatty acid and triglyceride synthesis [27].

The results of other studies also mention that kaempferol compounds can increase the regulation of Liver Peroxisome Proliferator-Activated α (PPAR- α)[28]. PPAR activation causes modification of gene transcription, resulting in an increase in Lipoprotein Lipase (LPL) enzyme activity. PPAR ligands can downregulate the expression of the Apolipoprotein C3 (APO-C3) gene, which is an LPL inhibitor, and increase the expression of the Apolipoprotein A5 (APO-A5) and Apolipoprotein C2 (APO-C2) genes, which are LPL enzyme activators [29],[9]. PPAR activation also increases fatty acid oxidation in the liver, which causes a decrease in VLDL levels. This leads to decreased blood triglyceride levels due to increased hydrolysis of VLDL and TG chylomicrons by the enzyme Lipoprotein Lipase [11].

The results of One Way Anova statistical analysis of triglyceride levels showed no significant differences between groups. However, the mean triglyceride levels in the treatment group that received ethanol extract of *E. grandiflorus* leaves had lower mean triglyceride levels than the control group. This study is an initial study using *E. grandiflorus* extract; in other studies with different plants, the use of higher doses and longer administration times showed a significant reduction in blood triglyceride levels. The absence of significant differences between groups may be due to stress in the test animals,

inappropriateness in giving the dose of extract to the test animals, giving a dose of extract that is not high enough or not giving the extract to the test animals for a long time.

Conclusion

E. grandiflorus extract contains many bioactive components that have the potential to regulate hyperlipidemic conditions. However, administration of *E. grandiflorus* extracts up to a dose of 800 mg/KgBW did not significantly affect LDL and HDL levels of hyperlipidemia rats. The effect on triglyceride levels was also not significant, although there was a trend towards decreasing levels. Further research needs to be carried out by adding the time of administration of the extract and increasing the dose of extract used to show significant results.

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