

Antihyperlipidemia Effect of Saga Tree Leaf Ethanol Extract (*Adenanthera pavonina* L.) on Mencit (*Mus musculus*)

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ABSTRACT

There is no consensus on the optimal dosage and mechanism of action of saga leaf ethanol extract in lowering cholesterol levels in test animals; therefore, further research is needed to understand the effectiveness and optimal dose of this plant as a hyperlipidemia therapy. This study aims to determine the optimal dose of ethanol extract from the leaves of the saga tree (*Adenanthera pavonina* L.) in reducing cholesterol levels in hyperlipidemic mice. The study was conducted on 36 male mice that were acclimatized for 7 days and induced hyperlipidemia using Propylthiouracil. The test animals were divided into six treatment groups, including a negative control, a positive control, a drug control (simvastatin), and three treatment groups with extract doses of 14, 28, and 56 mg/20 g body weight (BW). Cholesterol levels were measured using the spectrophotometry method, and the data were analyzed using the ANOVA test. The results of the ANOVA test showed a significance value of 0.000 ($p < 0.05$), indicating a difference in cholesterol levels between groups. A dose of 56 mg/20 g BW showed the highest reduction in cholesterol levels of 57.87 mg/dL. It was concluded that the ethanol extract of the leaves of the saga tree was effective in reducing the cholesterol levels of hyperlipidemic mice at an optimal dose of 56 mg/20 g BW. These results show the potential of the extract as a natural antihyperlipidemia agent that can be developed into an alternative cholesterol-lowering therapy.

Keyword: *Adenanthera pavonina* L. leaves, Ethanol extract, Hyperlipidemia, Mice (*Mus musculus*)

1. INTRODUCTION

Natural resource processing in Indonesia has significant potential for profitability if managed effectively. One of the natural resources often considered wild is traditional plants, which can be used for medicinal purposes. Many plants have the potential to cure diseases, but the majority of medicinal plants around the world are still not well investigated for their medicinal activity. Research on the medicinal activity of plants is essential because it can support the development of new treatments and discoveries in the future, which can contribute to the improvement of public health more broadly (Rohini & Rajesh, 2019).

Lipids, which include fats, waxes, and sterols, play an important role in human life, where some types of lipoproteins, such as HDL, LDL, VLDL, and kilomicros, have functions strongly related to health (Jim, 2013). An imbalance in the amount of body fat can trigger the risk of

cardiovascular disease, stroke, and other health disorders (Hastuty, 2018). One disorder associated with increased fat levels is hyperlipidemia, characterized by elevated cholesterol, triglycerides, and LDL levels, as well as decreased HDL levels, which can contribute to the development of atherosclerosis and coronary heart disease (Nuralifah et al., 2020a). Previous research has shown that the use of pharmacological drugs, such as statins, resins, and fibrates, can lower cholesterol levels. However, these medications have side effects that can lead to other health problems (Wardani et al., 2020). On the other hand, non-pharmacological approaches such as regular exercise, a healthy diet, and a better lifestyle can also help lower cholesterol levels (Mulyani, 2020).

While various studies have shown the potential of traditional plants as a cholesterol-lowering factor, many of these studies have not thoroughly examined the effective dosage and long-term safety of using these plants. For example, a dose of 14 mg/20g of saga leaf ethanol extract can lower cholesterol by up to 25.33 mg/dL (Tengku Rahmadito Putra Samudra, 2023). Additionally, other studies have shown that higher doses may have a more effective outcome (Putri & Hastuti, 2015). However, there is no consensus regarding the optimal dosage and the more detailed mechanism of action of saga leaf ethanol extract in lowering cholesterol levels in test animals. Therefore, more research is still needed to understand the best dosage and effectiveness of the use of this plant for the treatment of hyperlipidemia.

This study aims to evaluate the effectiveness of the ethanol extract from the saga tree leaves in reducing cholesterol levels in mice with hypercholesterolemia. Researchers aim to determine the optimal dosage of ethanol extract from the saga tree leaves that yields the best results in lowering cholesterol levels. The results of this study are expected to make a significant contribution to the development of safe and effective herbal therapeutic alternatives for overcoming hyperlipidemia, as well as provide further insights into the potential of traditional plants as natural treatment solutions.

2. RESEARCH METHOD

Material

The materials used are saga leaves, 96% ethanol test animals (*Mus musculus*), cotton, tissue tablets simvastatin, alcohol for disinfectant, propyltiorsil, aquades, the tools used are spectrophotometers, 1 ml / 1 cc syringes, measuring flasks, stirring rods, analytical scales, mouse cage, *handscoons*, *beaker glass*, *sondes*, and scissors.

Extraction

A sample of 500 grams of saga leaf powder is put in a jar for the maceration process. Then, 2,500 ml of 96% ethanol solvent is added until the powder is completely submerged. The maceration container should be tightly closed and stored at room temperature for 3 times 24 hours with a sample and solvent ratio of 1:5, while stirring periodically. After that, filtrate is filtered, which is then evaporated to produce a thick extract. The viscous extracts were weighed using an analytical balance (Ngibad, 2019).

Test Animal Preparation

Male mice weighing 20-30 grams, aged 2-3 months, and totaling 36 animals were selected as test animals. Mice that will be treated need to be acclimatized for 7 days to adapt mice to environmental conditions by feeding CP-511 centrifus and drinking. The animals are kept in cages large enough to provide room for movement and prevent stress in the mice. The cage should be made of safe materials and will not injure mice. The husk is used to contain the urine and feces of mice, which must be cleaned regularly to prevent the spread of disease. The ventilation of the enclosure must have good air circulation to avoid excessive heat or moisture buildup. Easy access to drinking water must be provided, and food that suits the nutritional needs of mice is given, as much

as 5 grams for one meal. The cage should be equipped with a secure and sturdy cover to prevent accidents and escapes by mice (R. A. Nugroho, 2018).

Classification of Test Animal Groups

The mice used as test animals in this study numbered 36 and were divided into six groups. Each group consisted of 6 experimental animals with a body weight of 20 - 30 grams. The first group served as a control, consisting of 6 healthy mice that received no treatment. The second group served as a positive control, consisting of six healthy mice that received the drug propylthiouracil, which was weighed and suspended in an aqueous solution. The third group, with a dose of 14 mg/20 g body weight (BW), contained six healthy mice that received the saga tree leaf extract. The fourth group, with a dose of 28 mg/20 g BW, contained 6 healthy mice that were given the saga tree leaf extract. The fifth group, with a dose of 56 mg/20 g body weight (BW), was given a saga tree leaf extract. The sixth group functioned as a control for drug administration, containing six healthy mice that were given simvastatin (Puspita et al., 2021).

Treatment of Drug Administration of Propylthiouracil, Simvastatin, and Saga Tree Leaf Extract

Propylthiouracil was administered to mice in the positive control group, the drug control group, and the dosing group. The prepared drug propylthiouracil was administered to mice at a volume of 1 mL each using a syringe, and the treatment was conducted for 14 days until the cholesterol levels in the mice increased. Level measurements were performed after the mice had been fasted for 8-10 hours. Simvastatin was administered to mice in the drug group at a volume of 1 mL per day, using a probe, for 3 days. Meanwhile, the administration of the saga tree leaf extract was carried out on the dose groups, each of which contained six mice with doses of 14 mg/20 g body weight (BW), 28 mg/20 g BW, and 56 mg/20 g BW. Extracts that had been dissolved in 10 mL of aquades were given to mice at a volume of 1 mL per day using a probe for 3 days, and levels were measured to see a decrease in cholesterol levels in mice.

Hyperlipidemia Activity Testing

The test animals were acclimatized for 7 days for self-adjustment and divided into six groups. After acclimatization, the mice were fasted for 8-10 hours, then cholesterol levels were checked by taking blood samples from the caudal vein of the mice's tail. In the early stages, the blood cholesterol levels of mice are measured before the treatment is performed. After the pretest was carried out, on the 7th day, the positive group, the drug group, and the dose group were given hypercholesterolemia feed or PTU drugs until the 21st day or for 14 days. Before the cholesterol level check was carried out, the mice were fasted for 8-10 hours, and cholesterol levels were measured using a spectrophotometer to ensure an increase in cholesterol levels. The increase in cholesterol levels that occurred after PTU drug treatment was then followed by treatment in the Simvastatin drug group and the dose group, which was carried out from day 21 to day 24, or for 3 days. A re-examination of cholesterol levels on the 24th day was conducted to verify a decrease in cholesterol levels in mice that received drug and extract treatments. Blood samples were taken from the caudal vein of the tail of mice that were cut 0.2 cm long.

Measurement of Animal Cholesterol Levels Test

Cholesterol levels were measured using the CHOD-PAP method, which determines cholesterol levels after the hydrolysis and oxidation processes have been carried out. The indicator used is quinoneimine, which is formed from the reaction between hydrogen peroxide and 4-aminofenazon under the influence of phenol and peroxidase enzymes (Taurusita et al., 2017). The examination procedure begins with preparing the tools and materials, followed by sampling the test animals by gently massaging the tail of the mice and then disinfecting the tail. The tail of the mouse is cut 0.2 cm long, the blood is stored in a serum cup, and then centrifuged for 15 minutes at 3,000

rpm until a serum is formed. Reagents, standards, and serum samples are pipetted at predetermined doses, homogenized, and incubated for 10 minutes at a temperature of 20-25°C. The total cholesterol level is then measured using a spectrophotometer at a wavelength of 546 nm. Normal cholesterol values in mice range from 40 – 130 mg/dL (C. A. Nugroho et al., 2022).

Data Analysis

The data from the research were analyzed using *the Statistical Package for Social Science* (SPSS) computer program. The data obtained is entered into a table, then tested for normality and homogeneity (Shapiro-Wilk) to determine whether the data obtained is typically or abnormally distributed, as well as homogeneous or non-homogeneous. Normally distributed data were then tested using *the Analysis of Variance* (ANOVA) test, as the data consisted of more than two groups. In contrast, non-normally distributed data were tested using the *Wilcoxon Signed-Rank Test*.

3. RESULTS AND ANALYSIS

3.1 Extraction

Table 1 presents data on the yield of the leaf extract of the saga tree (*Adenanthera pavonina* L.) obtained through the extraction process using certain solvents. Yield refers to the percentage of extracts that are successfully obtained compared to the initial weight of the simplicia used in the extraction process. A total of 500 grams of saga tree leaf powder was used in the extraction process, resulting in 81.2 grams of thick extract. Based on calculations, the yield of the extracts obtained reached 16.24%. This figure illustrates the efficiency of the extraction process in extracting active compounds from the leaves of the saguaro tree.

Table 1. Yield of tree saga leaf extract

Simplisia	Powder Weight(g)	Extract Weight (g)	Rendemen (%)
Saga Tree Leaves	500	81,2	16,24

3.2 Test of Antihyperlipidemia Effect of Saga Tree Leaf Ethanol Extract

Table 2 presents the results of testing cholesterol levels in male mice given ethanol extracts from the leaves of the saga tree with three dose variations: 14 mg/20 g body weight (BW), 28 mg/20 g BW, and 56 mg/20 g BW. In addition, this study included a control group, consisting of a negative control (mice without treatment), a positive control (mice given a high-cholesterol diet without treatment), and a drug control (mice given cholesterol-lowering drugs). The negative control group had an average cholesterol level of 112.7 mg/dL, which was lower than that of the positive control (189.3 mg/dL), indicating the impact of a high-cholesterol diet. Control drugs (117.7 mg/dL) proved the effectiveness of lowering cholesterol. The administration of saga tree leaf extract lowered cholesterol levels along with the increase in dose, namely 168.8 mg/dL (14 mg/20 g BW), 161.2 mg/dL (28 mg/20 g BW), and 131.4 mg/dL (56 mg/20 g BW). The highest dose had the most significant deterrent effect, although it was still slightly above the drug's control.

Table 2. Cholesterol level test of male mice given ethanol extract of the saga tree leaves

Test Animals	Mice Cholesterol Level (mg/dL)					
	Negative Control	Positive Control	Drug Control	Dosis 1 (14 mg/20g BW)	Dosis 2 (28 mg/20g BW)	Dosis 3 (56 mg/20g BW)
1	120.9	191.2	130.6	169.6	162.1	128.7
2	125.5	189.3	128.5	176.9	161.5	136.4
3	102.4	196.5	120.6	167.2	147.9	122.3
4	99.3	194.7	117.5	173.8	171.8	146.1
5	116.8	183.7	96.2	158.9	181.3	152.7
6	111.5	180.4	112.5	166.4	142.7	102.4
Average	112.7	189.3	117.7	168.8	161.2	131.4

According to the results in Table 2, the average percentage of cholesterol levels in the positive control group increased by 76.57 mg/dL. The increase is caused by the addition of the drug propylthiouracil, which affects the body's lipid metabolism by interfering with the process of cholesterol formation, transport, and breakdown. The drug works by inhibiting specific enzymes in the thyroid gland that are involved in the production of thyroid hormones. Changes in thyroid gland function can affect the body's overall metabolism, including lipid metabolism, which may lead to an increase in cholesterol levels (Nuralifah et al., 2020b).

The control group showed an average reduction in cholesterol levels of 71.65 mg/dL, the most significant decrease among the group. Simvastatin is a type of drug that belongs to the statin group. This medication is prescribed to lower cholesterol levels by inhibiting the activity of the enzyme HMG-CoA reductase, which plays a crucial role in cholesterol production within the body. By inhibiting the activity of these enzymes, simvastatin can reduce cholesterol production in the liver as well as lower total cholesterol and LDL cholesterol levels. The administration of simvastatin in the drug control group aims to serve as a comparison to the dose treatment group in lowering lipid levels in hyperlipidemic mice (Nugraha et al., 2021).

Based on the normality test of cholesterol levels in hyperlipidemic mice, the results of the *Shapiro-Wilk* test yielded a significance value of > 0.05 . This indicates that the cholesterol level data in all treatment groups are normally distributed. Furthermore, the homogeneity test using the *Levene Test* showed a significance value of greater than 0.05, indicating that the variation in cholesterol level data was homogeneous across all groups. Furthermore, the ANOVA test on cholesterol levels yielded a significance value (*p-value*) of 0.000, indicating that the value is less than 0.05. This shows that the Zero Hypothesis (H_0) is rejected. Thus, it can be concluded that there is a difference in cholesterol levels between groups, which indicates the presence of antihyperlipidemia activity caused by the administration of ethanol extract of the leaves of the saga tree (*Adenanthera pavonina* L.).

Table 3. Reduction of mouse cholesterol levels (mg/dL) after administration of ethanol extract of the saga tree leaves

Treatment	Decreased Cholesterol Levels in Mice (mg/dl)
Simvastatin Drug Control	71.7
Dosis 1 (14 mg / 20 g BW)	20.5
Dosis 2 (28 mg / 20 g BW)	28.1
Dosis 3 (56 mg / 20 g BW)	57.9

Table 3 illustrates the reduction in cholesterol levels of mice after administration of the saga tree leaf ethanol extract in various doses, compared to the group receiving the drug control simvastatin. The control group given simvastatin experienced the highest reduction in cholesterol levels, which was 71.7 mg/dL. In contrast, the group that received the ethanol extract of the saga tree leaves showed a larger decrease, accompanied by an increase in dose. Dose 1 (14 mg/20 g BW) resulted in a reduction of 20.5 mg/dL, while dose 2 (28 mg/20 g BW) resulted in a decrease of 28.1 mg/dL. The highest dose, 56 mg/20 g BW, had the most significant effect among the extract group, with a decrease of 57.9 mg/dL, although it was still lower than that of simvastatin. Overall, this data pattern suggests that the ethanol extract of the saga tree leaves has the potential to lower cholesterol levels in a dose-dependent manner. However, its effectiveness is not yet comparable to that of simvastatin. Saponin, glycoside, and flavonoid compounds can reduce cholesterol deposits in the coronary heart wall as an anti-cholesterol as well as reduce the amount of total cholesterol by lowering the activity of HMG-CoA reductase, *Acyl-CoA cholesterol acyltransferase* (ACAT) enzyme, and the absorption of cholesterol in the digestive tract (Wang et al., 2015).

4. CONCLUSION

This study aims to determine the optimal dose of ethanol extract from the saga tree leaves that can achieve the best results in lowering cholesterol levels. The results showed that the optimal dose of ethanol extract from the leaves of the saga tree (*Adenanthera pavonina* L.) in reducing cholesterol levels in hyperlipidemic mice was 56 mg/20 g body weight (BW), resulting in a decrease of 57.87 mg/dL. The ethanol extract of the saga tree leaves has the potential to be a natural antihyperlipidemic agent, which could be developed as a cholesterol-lowering therapy. Further research is recommended to investigate its mechanism of action, effectiveness, and long-term safety.

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