The Effect Of Giving Sambiloto Leaf Extract (*Andrographis Paniculata*) On Reducing Cholesterol Levels And Histopathological Picture Of The Liver Of Male Wistar White Rats

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ABSTRACT

Cholesterol is a lipophilic molecule that plays an important role in human life and does many things to help cells function properly.Cholesterol is needed by the body to build healthy body cells and produce hormones. However, the risk of heart disease and stroke increases with high cholesterol levels in the blood.

This study aims to prove, know and test the effect of administering sambiloto leaf extract.(Andrographis paniculata) on the decrease of cholesterol level and histopathology of liver of male white wistar rats. This research is an experimental research using pre-post test control group design. In this research, 24 male wistar rats were used as samples which were divided into 6 groups. Each group consists of 4 male wistar rats.

The results of the study showed that the extract of sambiloto leaves (Andrographis paniculata) proven effective in reducing cholesterol levels, body weight, andlow density lipoproteinswhite mouse (Rattus norvegicus) male Wistar strain fed with high fat feed. The results of phytochemical tests on sambiloto leaves (Andrographis Paniculata) conducted showed that there were secondary metabolite compounds in the extract of sambiloto leaves (Andrographis Paniculata) including flavonoids, alkaloids, saponins, steroidsand tannins. These compounds will eventually lower cholesterol levels,low density lipoproteinsand body weight in white mice (Rattus norvegicus) Wistar strain that has hypercholesterolemia.

Keywords: Cholesterol, Sambiloto leaves, Liver histopathology

INTRODUCTION

A lipophilic molecule, cholesterol is essential to human existence and performs a variety of tasks that support healthy cell function. As an illustration, cholesterol plays a crucial role in the structure and fluidity of the cell membrane (Yang ST, 2016). Despite being essential for many basic cell processes, cholesterol may be toxic to the body if blood levels are allowed to rise to dangerous levels. Patients with high cholesterol should receive extra attention when it comes to teaching them about the negative consequences of high cholesterol and how to lower their blood cholesterol levels.

Despite being essential for many basic cell processes, cholesterol may be toxic to the body if blood levels are allowed to rise to dangerous levels. Patients with high cholesterol should be informed about the negative consequences of high cholesterol as well as strategies for lowering blood cholesterol levels. Patients can reduce their cholesterol by changing their lifestyle to include more exercise, stopping smoking, and consuming more fibre and total calories while consuming less saturated and trans fats. If these behavioural modifications are not successful, cholesterol-lowering drugs should be utilised. a decrease in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL) (Yuliawati, 2021). This excessive fat accumulation can be caused by a number of factors. These factors are what will eventually cause someone to become obese (Piche, 2020). Cholesterol is needed by the body to build healthy body cells and produce hormones. However, the risk of heart disease and stroke increases with high cholesterol levels in the blood (Wahyuni FS, 2017).

A high-cholesterol diet may cause blood cholesterol levels to rise beyond the body's capacity to regulate them. According to Sastriamidjojo's idea, eating meals high in fat and cholesterol will raise LDL and total cholesterol levels (Sastromidjojo, 2000). Enough cholesterol will be present in the liver, which will also prevent LDL from being absorbed, which might raise total cholesterol levels. An rise in LDL levels in the blood is indirectly caused by high cholesterol levels (Revelation, 2011). Previous research conducted (Octomalioputri Biomechy, 2016) obtained the conclusion that the increase in LDL levels was seen significantly starting from the 10^{th} day of high cholesterol diet. However, among the treatment groups, there was no significant increase. The longer the high cholesterol diet was given, the less significant the increase was among the treatment groups (until the 30^{th} day of treatment). The administration of goat fat and quail eggs was found to accelerate the increase in LDL levels in the blood of mice.

Currently, there are many cholesterol-lowering drugs available in the market, both derived from natural and synthetic ingredients. However, the use of modern or synthetic drugs has side effects such as urinary retention with hyponatremia, gastrointestinal disorders, and others

(Krentz, 2005). So, the current tendency of society is to prefer natural medicines because natural medicines are believed to be safer, cheaper and the raw materials are easier to find in the community, compared to synthetic medicines (Muhtadi, 2013). This phenomenon is of particular concern among natural material researchers.

Sambiloto leaf plant (*Andrographis paniculata*) is a plant that has medicinal properties because it contains chemical compounds such as flavonoids, glycosides, saponins and tannins (Esha, 2019) these chemical compounds have various pharmacological activities, such as anti-inflammatory, analgesic, antibacterial and antioxidant (Princes, 2023). The extraordinary benefits of sambiloto leaves are not only useful in natural medicine, but also important in achieving a healthy and balanced lifestyle. By utilizing the power of sambiloto leaves, it can improve the quality of life and maintain body health in a natural and effective way. In Indonesia itself, herbs have been a hereditary heritage for treating various diseases, one of which is as an anti-cholesterol. Although there has been no research related to reducing cholesterol levels, researchers are interested in creating a research title using this chemical compound. The effect of giving sambiloto leaf extract (*Andrographis paniculata*) on the decrease in cholesterol levels and histopathological features of the liver of male wistar white rats.

LITERATURE REVIEW

Cholesterol is a fat that is naturally produced by the liver. This fat can also be found in foods that come from animals, such as meat and milk. In the body, cholesterol is needed to form healthy cells, produce a number of hormones, and produce vitamin D (Kurniadi, 2014). However, if the levels are too high, then it is dangerous for the body because it will cause various diseases and complications. In the blood, this compound is carried by proteins. The combination of the two is called lipoprotein. The two main types of lipoproteins are low-density lipoprotein (LDL) or bad cholesterol and high-density lipoprotein (HDL) or good cholesterol (Deora, 2022).

LDL's job is to transport cholesterol from the liver to cells that need it. However, if the amount exceeds the need, it can settle on the walls of the arteries causing disease. Meanwhile, HDL is responsible for transporting cholesterol back to the liver, as opposed to LDL. In the liver, this compound will be destroyed or excreted by the body through feces or waste. Cholesterol levels in the blood vary. Depending on whether you have a high or low risk of developing arterial disease. Meanwhile, examinations related to the levels or amount of cholesterol in the blood can be measured through a total cholesterol test (Listiyana, 2013).

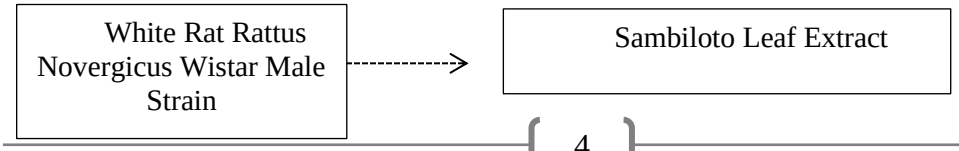
The liver is a chemical factory in the body whose function is to carry out a series of very complex tasks to keep the body in a healthy condition (Francis, 2021). The liver has many functions such as bile secretion, nutrient metabolism, metabolic detoxification and storage of minerals and vitamins. One of the functions of the liver is to break down cholesterol. If the liver is not functioning properly, it can cause cholesterol to build up in the body. Too much cholesterol can also trigger fat buildup in the liver area which increases the risk of chronic diseases, such as diabetes, stroke, and heart disease. The liver makes and produces cholesterol constantly. About 70% of the cholesterol in the blood comes from liver synthesis, and the rest comes from the food we eat. Steroid hormones are also made from cholesterol (Anies, 2015). The higher the cholesterol level, the longer the atherosclerosis process will last. Cholesterol plays an important role in the formation of atherosclerosis, according to a number of epidemiological, biochemical, and experimental studies. There is evidence that atherosclerosis is caused by high concentrations of LDL cholesterol in the blood (Kurniadi, 2014). When fat covers the muscle cells of the arteries, their elasticity decreases and their ability to control blood pressure decreases. As a result, a person can experience various diseases such as hypertension, arrhythmia, heart attack, and stroke, among others. There are several liver disorders that cause increased cholesterol.

This plant performs many pharmacological activities, and most of its health benefits and activities are related to its phytochemical constituents. According to phytochemical analysis, this plant has abundant sources of calcium, phosphorus, iron, potassium, vitamins A, and D, as well as essential amino acids, carbohydrates, and powerful antioxidant compounds such as flavonoids, ß-carotene, and vitamin C ((Esha, 2019).

Andrographolide, the main active compound of sambiloto leaves, functions as a medicine. Sambiloto leaves also have saponins, flavonoids, phenols, alkaloids, and tannins. One of the many chemical compounds found in sambiloto leaves is flavonoids, which function as growth hormones and enzyme inhibitors by forming complexes with proteins (Rahayu and Frasiska, 2019). One of the main bioactive ingredients of sambiloto leaves is andrographolide, a diterpenoid with a bitter taste that can increase appetite because it can increase salivary gland secretion, increase the production and amount of antibodies, and improve the immune system (A, 2010).

Referring to the conceptual framework, the hypothesis in this study is that there is an effect of giving sambiloto leaf extract (*Andrographis paniculata*) on reducing cholesterol levels and histopathological features of the liver of male Wistar strain white rats.

The conceptual framework in this study can be seen in Figure 1.



2

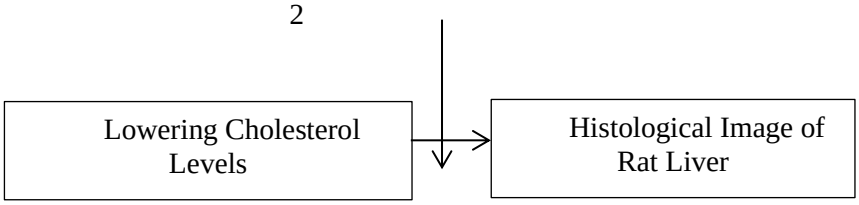


Figure 1 Conceptual Framework

METHODS

This research uses this type of research true experiment is an experimental study carried out in this study by controlling all external variables that can affect experimental activities. This study uses a pre-test and post-test group design to determine and analyze the effects before and after administration of sambiloto leaf extract (*Andrographis paniculata*.) in lowering cholesterol levels and how the histopathological picture of the liver in male wistar strain rats (*Rattus norvegicus*). The research period will take place from May to August 2024 at the Laboratory of the Department of Pharmacology and Therapeutics, Faculty of Medicine, University of North Sumatra. Ethical Clearance will be submitted to the Health Research Ethics Commission (KPEK) of Prima Indonesia University and is still in process.

The sample of this study was male wistar rats (*Rattus norvegicus*) aged 2 – 3 months and weighing 200 – 300 grams. In this study, 24 male wistar rats were used as samples which were divided into 6 groups. Each group contained 4 male wistar rats. The test animals were randomly grouped into six test groups. The variables in this study were:

a. Variable X (Free):	Giving sambiloto extract (*Andrographis paniculata)*
b. Variable Y (Bound):	Lowering Cholesterol Levels Histopathology of the Liver
c. Precondition Variables:	High cholesterol diet

Every day, the rats were given a diet heavy in fat and cholesterol. Quail egg yolk was used as the feed. This meal raises cholesterol levels exogenously. 14 days of high – fat, high-cholesterol diet were administered prior to beginning sambiloto leaf extract therapy. Serum was obtained from each test rat after 14 days of a high – cholesterol diet in order to verify that the rats had elevated cholesterol levels. Body weight and cholesterol levels were the metrics utilised to verify that the rats had elevated cholesterol level. After 14 days on a high-cholesterol diet, serum was taken from each test rat to be analysed for cholesterol levels in order to verify that the rats had elevated cholesterol levels. An rise in blood cholesterol levels

above normal is a sign of high cholesterol. Blood cholesterol levels in Wistar strain (*Rattus norvegicus*) white rats typically range between 10 and 54 mg/dL (Smith and Mangkoewidjojo 1998). When total cholesterol levels exceed 10 – 54 mg/dL, it is considered high cholesterol. After consuming a meal rich in fat and cholesterol and surviving the acclimatisation period, the test animals were randomly assigned to four groups, each with six mice. A waterproof marker was used to write the label on the tail of each mouse. The mice in the control group received nothing except distilled water. Mice in the treatment group received varying dosages of *Andrographis paniculata* leaf extract liquid. A study by Bann et al. (2023) found that 500 mg/kgBW of *Andrographis paniculata* leaf extract is an effective dosage for lowering cholesterol levels in male white rats (*Rattus norvegicus*). The researchers adapted the study and modified the dosage as follows: 1) Neutral Group (P – 0): Standard rat pellet feed + distilled water/day/head for 14 days, 2) negative control group (K^-), only given a high cholesterol diet, 3) positive control group (K^+), given a high cholesterol diet + Statin, 4) treatment group I (P – 1): High cholesterol diet + *Andrographis paniculata* with a dose of 100 mg/BW and given distilled water/day/head for 14 days, 5) treatment group II (P – 2): High cholesterol diet *Andrographis paniculata* leaves with a dose of 150 mg/BW and given distilled water/day/head for 14 days. 6) treatment group III (P-3) High cholesterol diet + *Andrographis paniculata* leaves with a dose of 200 mg/BW and given distilled water/day/head for 14 days. For histological examination, the fixed liver was cut and placed in a plastic specimen pot. Then, the preparation was stained with hematoxylin-eosin (HE) and viewed under a microscope at 400x magnification. Histopathological changes in mice were assessed using the Manja Roenigk scoring model as presented in the following table 1:

Table 1 Liver Histopathology Scoring

No.	Score	Level of Damage
1	1	Normal
2	2	Parenchymatous Degeneration
3	3	Hydropic degeneration
4	4	Necrosis

Scoring was then made from the data obtained from histopathological observations through microscopic examination. The data obtained from the study were tabulated, then analyzed on the changes found, and finally presented descriptively. Furthermore, the research data were analyzed using the Statistical Package for the Social Sciences (SPSS) 25.0 for Windows. To assess the normality of the data, the Shapiro Wilk test was used ($p > 0.05$). In addition, the significance between the trial groups was tested with One Way ANOVA or one-way analysis

of variance at a 95% confidence level. Further analysis or testing was carried out using the Post Hoc Test and LSD techniques.

RESULTS

The rats were fed a high-cholesterol diet every day. The feed given was quail egg yolk. This food exogenously increases cholesterol levels. High-fat, high-cholesterol food was given for 14 days before starting therapy with *Andrographis paniculata* leaf extract. During the treatment, there was a decrease in body weight. The control group 232 grams became 230 grams, negative control is 301 grams became is 250 grams, positive control is 308 grams became 235 grams, treatment 1 311 grams became 234 grams, treatment 2 318 grams became 230 grams and treatment 314 became 210 grams. In treatment 3 there was the highest weight loss of 104 grams. The results of the cholesterol tests on the test animals can be seen in table 2.

Table 2 Characteristics of Test Animals

Component	K	K-	K+	P1	P2	P3
Types of Rats	*Rattus norvegicus*white wistar strain					
Gender	Male					
General Conditions	White fur color, healthy and active					
Average Initial Body Weight	221gr	223gr	224gr	229gr	232gr	228gr
Average Body Weight After Being Given High Cholesterol Feed	232gr	301 gr	308 gr	311gr	318gr	314gr
Average Body Weight After Treatment	230 gr	250 gr	235 gr	234 gr	230 gr	210 gr

Making Sambiloto Leaf Extract (*Andrographis paniculata*)

The sambiloto plant that will be used is the leaves. Sambiloto leaves are dried at a temperature of 50 – 60°C and ground into a dry powder. The process of making sambiloto leaf extract uses the maceration technique. Dry sambiloto leaf powder is extracted using 96% ethanol then filtered and the filtrate is collected, the residue is then macerated again with the same method. The choice of this solvent is because ethanol is able to filter more active ingredients ranging from polar, semipolar and nonpolar. It is expected to produce the optimal amount of extract.

The ethanol content is evaporated using a rotary evaporator to obtain a thick extract. Extraction using the methanol solvent immersion method, then filtered and the filtrate is evaporated. The components of the secondary metabolites of the methanol extract of sambiloto leaves are determined by metabolite testing. Sambiloto is cultivated as herbal medicine, planted in pots, in yards, or gardens. Sambiloto leaves are often used as traditional medicine to cure burns, rheumatism, gout, lose weight, nosebleeds, kidney inflammation, intestinal inflammation, and cancer. However, the benefits of the sambiloto plant are not yet widely known by the Indonesian people. Sambiloto leaves contain saponins, tannins, flavonoids, alkaloids, and polyphenols with antioxidant properties (Souhoka et al., 2021). This is the reason researchers use sambiloto leaf extract (*Andrographis paniculata*) to lower cholesterol levels by looking at weight loss, LDL and HDL in mice fed high-fat feed. The following is a picture of the process of making sambiloto leaf extract (*Andrographis paniculata*) can be seen in Figure 2.

Figure 2 Manufacturing Process Sambiloto Leaf Extract (*Andrographis paniculata*)

The research data of the dose of binahong leaf extract used was the extract of sambiloto leaf extract (*Andrographis paniculata*) with a dose of 100 mg/BW a dose of 150 mg/BW and a dose of 2000 mg/BW and given aquades/day/head for 14 days. This dose was taken to see the effect of reducing cholesterol levels in white mice fed high cholesterol.

The next data is the phytochemical test on the extract of sambiloto leaves (*Andrographis paniculata*). The results of the phytochemical test conducted showed that there were secondary metabolite compounds contained in the extract of sambiloto leaves (*Andrographis paniculata*), the content is flavonoids, alkaloids, saponins, steroids, and tannins. These compounds will later reduce cholesterol levels, LDL and body weight in the blood serum of white rats (*Rattus norvegicus*) Wistar strain. The following are the screening results can be seen at Table 3.

Table 3 Phytochemical Tests

Secondary Metabolites	Results	Color
Alkaloid	+	Chocolate
Flavonoid	+	Red
Saponins	+	Foam does not disappear
Tannin	+	Green Blue
Steroids/Triterpenoids	+	Green
Glycosides	-	Purple brown

Description of Total Cholesterol Level

The second parameter to confirm that the test animals, mice, have high cholesterol levels, serum was collected from all mice for cholesterol levels after 14 days of high-fat and high-cholesterol feed, which is presented in the following table 4:

TABLE 4 TOTAL CHOLESTEROL LEVELS

No	Kel	Repetition	Initial Cholesterol Level (mg/dl)	Cholesterol levels after feeding (mg/dl)	Cholesterol levels after treatment (mg/dl)
1	Control	1	51.5	55.2	54.1
2		2	52	55	54.9
3		3	51.4	54.9	54.8
4		4	52.7	56	53.9
		Average	**51.9**	**55.275**	**54,425**
5	Negative Control	1	53.7	56.2	57.1
6		2	53.1	58.2	58.5
7		3	50.6	56.9	57.3
8		4	54.2	58.9	59
		Average	**52.9**	**57.55**	**57,975**
9		1	51.7	59.6	54.5

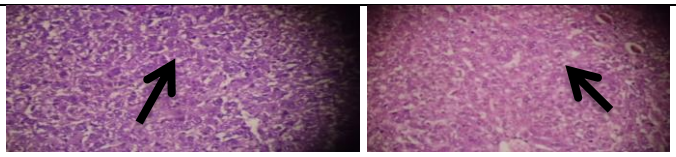
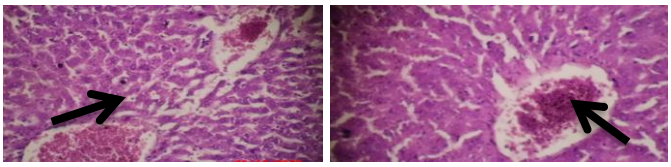
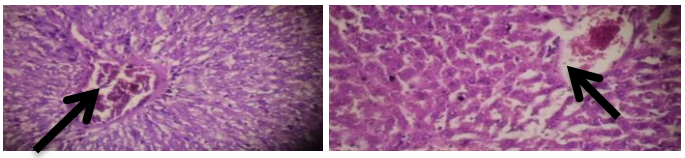
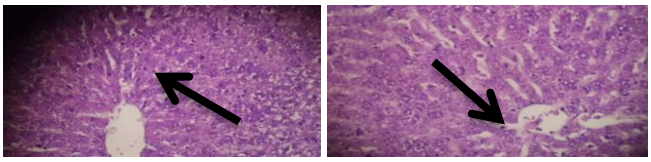
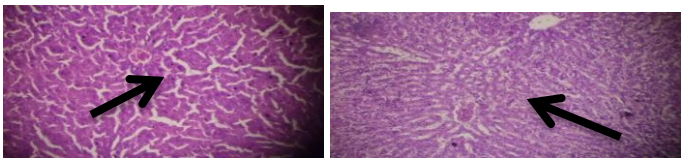
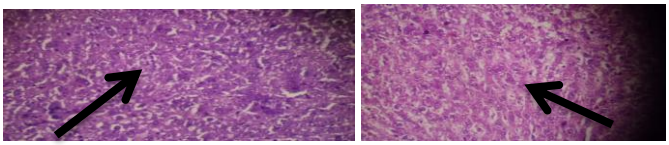
10	Positive Control	2	51	58.3	53.6
11		3	53.3	58.7	53.1
12		4	52.3	57.1	51.2
		Average	**52,075**	**58,425**	**53.1**
	Treatment 1	1	52.6	57.6	53
14		2	53.7	59.7	50
15		3	51.9	57.9	51.4
16		4	52.2	57.4	49.5
		Average	**52.6**	**58.15**	**50.9**
17	Treatment 2	1	51.9	59.4	49.3
18		2	52.4	59.6	50.1
19		3	53.8	59.1	47.5
20		4	52.6	58.9	47.1
		Average	**52,675**	**59.25**	**48.5**
21	Treatment 3	1	51.7	56.4	46.2
22		2	52.6	57.3	46.5
23		3	53.7	58.2	47.1
24		4	51.9	57.1	45.8
		Average	**52,475**	**57.25**	**46.4**

From the data above, it can be seen that the group given *Andrographis paniculata* leaf extract no longer experienced high cholesterol levels or hypercholesterolemia because the cholesterol levels were <54 mg/dl. Treatment group 1 had an average total cholesterol of 50.954 mg/dl, treatment group 2 had an average total cholesterol of 48.5 mg/dl and treatment group 3 had the highest cholesterol reduction, namely with an average cholesterol value of 46.4 mg/dl.

The following is a histological image of the liver tissue of each treatment group can be seen at tablet 5:

Table 5 Histopathological Description of Liver Tissue

No	Group	Histopathological Image of Liver Tissue

1	Control (Aquades)	 There are no changes in the histological structure of the liver (normal) which falls into score category 1.
2	Negative Control	 There is necrosis in the liver cells, so it falls into the score category 4 (visible necrosis).
3	Positive Control (Methmorphine)	 There is necrosis in the liver cells but it appears to be getting smaller so it falls into the score category 4 (visible necrosis).
4	Treatment 1 (200mg/KgBW)	 There is necrosis in the liver cells but it appears to have disappeared, so it falls into score category 3 (visible necrosis).
5	Treatment 2 (400mg/KgBW)	 Improvement of liver histological structure but still hydropic degeneration, so it is included in score category 2.
6	Treatment 3 (600mg/KgBW)	 The histological structure of the liver is seen to be close to the control group, so it falls into the score category 1.

Histopathological observations were conducted using a light microscope with 400x magnification. The purpose of this observation was to see the structure and morphology of cells, especially fibroblast cells in the liver of white rats fed high fat. The group fed peelet and

sambiloto leaf extract with a dose of 200 mg/BW, a dose of 400 mg/BW%, and finally a dose of 600 mg/BW.

DISCUSSION

According to the findings, the trial group that received leaf extract from *Andrographis paniculata* was able to lower their LDL levels in comparison to the group that received merely distilled water. This may happen as a result of the flavonoids, alkaloids, saponins, steroids, and tannins found in *Andrographis paniculata* leaf extract. Mice with excessive cholesterol can lose weight thanks to tannins' physiological effects, which include decreasing blood pressure, serum lipid levels, and demonstrating strong antioxidant capability (Kamarudin et al., 2021). Low – density lipoprotein (LDL) can be decreased by the bioactive substances tannin, flavonoids, alkaloids, and saponins (Kar et al., 2018).

The results of this study are in line with previous studies conducted by Satriyani and Rosyidah (2018), which revealed that sambiloto leaves (*Andrographis paniculata*) can affect the reduction of total cholesterol levels in hypercholesterolemic male white rats (*Rattus norvegicus*). Another similar study by Sianipar and Isnawati (2012) used sambiloto leaves (*Andrographis paniculata*) at a dose of 200 mg/day, the results showed that aloe vera juice can increase HDL levels and can significantly reduce LDL cholesterol levels. Furthermore, another factor that can also affect the results of this study is the number of samples used is less than previous studies, where in this study the samples used were only 20 white rats or 5 per group. The number of samples used will affect a study because the more samples used, the smaller the chance of generalization errors (Handayani, 2020). The number of samples used will affect a study because the more samples used, the smaller the chance of generalization errors (Handayani, 2020).

CONCLUSION

1. Sambiloto leaf extract (*Andrographis paniculata*) has been proven effective in reducing body weight and cholesterol levels in male white rats (*Rattus norvegicus*) of the Wistar strain that are fed high-fat feed.
2. After being treated with *Andrographis paniculata* leaf extract, the mice no longer experienced high cholesterol levels or hypercholesterolemia because the cholesterol levels were <54 mg/dl. Treatment group 3, with a dose of 200 mg//BW experienced the greatest decrease, namely from an initial level of 57.25 mg/dl to 46.4 mg/dl.
3. The results of phytochemical tests on sambiloto leaves (*Andrographis paniculata*) showed that there are secondary metabolite compounds in the extract of boinahong leaves

including flavonoids, alkaloids, saponins, steroids and tannins. These compounds will later reduce cholesterol levels, LDL and body weight in white rats (*Rattus norvegicus*) Wistar strain that experience hypercholesterolemia.

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