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Pharmacokinetic Profile and Antihyperlipidemic Effectiveness of Nanoemulsion and Ethanol Extract of Parang Romang (*Boehmeria virgata*) Leaves

(*Profil Farmakokinetik dan Efektifitas Antihiperlipidemia Sediaan Nanoemulsi dan Ekstrak Etanol Daun Parang Romang (Boehmeria virgata)*)

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ABSTRACT

Background: Parang romang (*Boehmeria virgata*) has an antihyperlipidemic effect, but the use of herbs commonly has limitations with poor solubility in water, causing failure in the clinical phase due to low bioavailability. Bioavailability can be increased by nanotechnologies, one of them is nanoemulsion**. Objectives:** This study aimed to determine the pharmacokinetic profile and effectiveness of antihyperlipidemic activity of nanoemulsion preparation and ethanol extract of parang romang leaves. **Methods:** Pharmacokinetic study was done with 10 rats that each given 100 mg/kg BW of nanoemulsion and ethanol extract from parang romang leaves. The blood was taken at 0.5; 1; 1.5; 2; 2.5; 3; 3.5; 4 hours to measure tmax, Cpmax, and AUC. Study of antihyperlipidemic was done with 30 rats divided into 5 groups with normal control group I given Na CMC suspension, group II negative control given high fat feed + streptozotocin, group III positive control given high fat feed + streptozotocin and simvastatin 0.9 mg/ kg BW, group IV given high fat feed + streptozotocin + ethanol extract of parang romang leaves 100 mg/kg BW and group V given high fat feed + streptozotocin + nanoemulsion of ethanol extract of parang romang 100 mg/kg BW. The blood was then taken on day 0,14,21, 28 and 35. **Results:** The results of the pharmacokinetic profile test showed that the values of tmax, Cpmax, and AUC for nanoemulsions and extract were respectively; 0.5 hours, 96.68 g/ml and 297.57 and 1-hour, 15.44 g/ml and 93.53. The statistical results obtained a significant value ($P < 0,05$) which showed a significant effect between nanoemulsion and ethanol extract of parang romang to reduce cholesterol levels **Conclusions:** There are differences in pharmacokinetic profile and antihyperlipidemic effectiveness between nanoemulsion preparations and ethanol extracts from parang romang leaves.

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ABSTRAK

Latar Belakang: Ekstrak etanol parang romang memiliki efek antihiperlipidemia, akan tetapi penggunaan bahan alam pada umumnya memiliki keterbatasan yaitu kelarutan yang buruk di dalam air sehingga menyebabkan terjadi kegagalan pada fase klinik disebabkan rendahnya bioavailabilitas. Bioavailabilitas dapat ditingkatkan dengan teknologi nano salah satunya adalah nanoemulsi. Tujuan: untuk menentukan profil farmakokinetik dan efektifitas antihiperlipidemia dari sediaan nanoemulsi dan ekstrak etanol dari daun parang romang. Bahan dan Metode: Studi farmakokinetik dengan 10 ekor tikus masing-masing diberikan 100 mg/kgBB nanoemulsi dan ekstrak etanol dari daun parang romang lalu diambil darahnya jam ke 0,5; 1; 1,5; 2; 2,5; 3; 3,5; 4. Studi perbandingan antihiperlipidemia dengan tikus 25 ekor dibagi menjadi 5 kelompok yaitu kelompok I kontrol normal yang diberikan suspensi Na CMC, kelompok II Kontrol negatif yang diberikan pakan tinggi lemak+streptozotocin, kelompok III kontrol positif diberikan pakan tinggi lemak + streptozotocin & simvastatin 0,9 mg/KgBB, kelompok IV diberikan pakan tinggi lemak+ streptozotocin + ekstrak etanol daun parang romang 100 mg/kgBB dan kelompok V yang diberikan pakan tinggi lemak+ streptozotocin + nanoemulsi 100 mg/kgBB. Selanjutnya dilakukan pengambilan darah pada hari ke 0, 14 dan hari ke- 21,28 dan 35. Hasil: Profil farmakokinetik diperoleh nilai tmax, Cpmax, dan AUC untuk nanoemulsi dan ekstrak berturut-turut adalah 0,5 jam; 96,68 g/ml dan 297,57 dan 1 jam, 15,44 g/ml dan 93,53. Hasil uji statistik efektifitas antihiperlipidemia diperoleh nilai yang signifikan ($p<0,05$) yang menunjukkan perbedaan signifikan antara ekstrak dan nanoemulsi menurunkan kadar kolesterol Kesimpulan: Terdapat perbedaan profil farmakokinetik dan efektifitas antihiperlipidemia antara sediaan nanoemulsi dan ekstrak etanol dari daun parang romang.

Kata kunci: Profil Farmakokinetik, Antihiperlipidemia, Efektivitas, Nanoemulsi, Ekstrak Etanol, Daun Parang Romang.

INTRODUCTION

The increasing people interest in the use of herbal medicines has made many researchers compete to find alternative medicines that are easy, cheap, safe, and effective. One of the herbal plants that have antihyperglycemic and antihyperlipidemic effects is the parang romang (*Boehmeria virgata*) (Magfirah, 2018). Parang romang (*Boehmeria virgata*) contains secondary metabolites in the form of alkaloids, terpenoids, phenolics, and flavonoids. Research conducted by Rusdi (2017) showed that the ethanol extract of Parang Romang stems at a dose of 50 mg/kg BW, 100 mg/kg BW, 150 mg/kg BW, and 200 mg/kg BW, had a greater hypoglycemic effect when compared with negative control (Na-CMC 1%) and the effect was significantly different from glibenclamide tablets 0.017 mg/kg BW. A study conducted by Paramitha (2017) showed that the ethanolic extract of the roots of Parang Romang (*Boehmeria virgata* (Forst.) Guill) can reduce cholesterol levels with a dose of 14 mg/20 g which is the best effect in lowering cholesterol in mice (*Mus musculus*).

The use of natural ingredients has limitations, including failure in the clinical phase due to the low dissolution rate causing low bioavailability (Chaturvedi et al., 2011). Since drugs are generally absorbed from the gastrointestinal tract by passive diffusion mechanisms, poorly soluble drugs are a problem in the pharmaceutical industry, and the dissolution rate of drugs determines their bioavailability. One of the methods developed to increase the bioavailability is nanoemulsion, which is a mixture of oil solution, surfactant, and co-surfactant with active substances to form an oil-in-water (w/o) emulsion that when in contact with gastrointestinal fluids will form an emulsion that occurs spontaneously, therefore the drug

dissolves with a small particle size leading to the increasing of the effective surface area for absorption that can increase the concentration of the active substance in plasma to produce an optimal therapeutic effect (K. Gurpret & SK Singh, 2018). This study aims to determine the pharmacokinetic profile and effectiveness of nanoemulsion and ethanol extract of parang romang leaves in diabetic hypercholesterolemic white rats.

MATERIAL AND METHODS

Materials

Parang romang (*Boehmeria virgata*) plant was taken in Ojoloboku village, Moncongloe district, Gowa regency, South Sulawesi province. The plants was identified at UPT. Sulawesi Biological Resources Tadulako University. Male white rats wistar strain were obtained from Palu City, Central Sulawesi. Distilled water, alcohol 96 % (Merck), aluminum foil, hydrochloric acid (Merck), iron (III) chloride (Merck), citrate buffered saline (Merck), Henskun (Sensi), cotton, label paper, filter paper, egg yolk, Pig lard, Olive oil (Bertolli), Na-CMC (Merck), Standard feed (composition of corn, soybean meal, wheat pollard, coconut meal, fish meal, meat meal, rice flour, tapioca, coconut oil, and fish oil premix), Propylthiouracil (Kimia Farma), Propylene glycol (Merck), Streptozotocin (Bioworld USA), Simvastatin (Kimia Farma), and Tween 80 (Merck).

Methods

Extraction

Parang romang (*Boehmeria virgata*) leaves (800 grams) were extracted using maceration with 96% ethanol solvent for 3 days. The extract was filtered using filter paper and the obtained filtrate was then concentrated using a rotary vacuum evaporator at a temperature of 60ºC and evaporated using a water bath to obtain the concentrated extract (Magfirah & Utami, 2021).

Preparation of Animal

The in vivo study was carried out according to protocol guidelines approved by the ethics committee of Tadulako University with code of ethics number 6621/UN.28.1.30/KL/2020. 40 Wistar rats were adapted for two weeks in the laboratory and adequately housed at ambient temperature and given standard feed and drinking. The test animals were 40 male white rats (*Rattus norvegicus*), divided into 7 groups consisting of a normal control group, a negative control group, a positive control group, ethanol extract of parang romang treatment group at a dose of 100 mg/Kg BW, nanoemulsion of parang romang ethanol extract dose of 100 mg/Kg BW and 2 animal groups for pharmacokinetic testing.

Preparation of high fat feed

The high fat feed used is lard and quail egg yolk. The feed is prepared in the following way: the lard was melted by heating until the lard becomes oil in a ratio of 50% each. The yolk and egg white was separated and mixed with yolk and the melting lard until homogeneous. This feed was given orally for 14 days (Tandi *et al*, 2019).

Preparation of streptozotocin solution

Streptozotocin was weighed as much as 0.32 grams and then dissolved using citrate-buffered saline at pH 4.5 and then induced in test animal's male white rats via intraperitoneal. The dose of streptozotocin is 30 mg/kg BW (Tandi *et al*, 2019).

Preparation of suspension Na CMC 0.5%

A total of 0.5 grams of sodium carboxymethyl cellulose (Na CMC) was weighed, sprinkled on a mortar containing 10 ml of heated distilled water, allowed to stand for 15 minutes until a clear mass was obtained, and stirred until uniform. The NaCMC solution was transferred to a 100 mL volumetric flask and added to volume 100 ml with distilled water (Tandi *et al*, 2019).

Preparation of Propylthiouracil Suspension (PTU)

One tablet of propylthiouracil 100 mg was crushed in a mortar and then the propylthiouracil powder was put into a volumetric flask and distilled water was added. The mixture was shaken until homogeneous, and the volume was made up to 100 mL (Tandi *et al*, 2019).

Preparation of nanoemulsion of ethanol extract of parang romang leaves

Ethanol extract of 0.10 gr of parang romang leaves was added to 100 mL of carrier components (Tween 80, propylene glycol, and olive oil) according to the optimization results. Then homogenized for 30 minutes on a magnetic stirrer, sonicated for 15 minutes, and conditioned for 10 minutes in a 45°C water bath. The resulting mixture was left at room temperature for 24 hours (Magfirah & Utami, 2021).

Preparation of ethanol extract of parang romang suspension

Parang romang leaf extract was weighed to make a test suspension with each 0.2 gram (100 mg/kg BW). To each extract, 0.5% Na CMC was added and the volume was made up to 25 ml with distilled water and then shaken until homogeneous (Tandi *et al*, 2019).

Preparation of simvastatin suspension

Simvastatin tablets of 10 mg were crushed, then weighed to the equivalent of 1.8 mg and then put into a mortar by adding 0.5% Na CMC suspension while grinding until homogeneous. The mixture was put into a 25 ml volumetric flask, then added 0.5% Na CMC suspension (Tandi *et al*, 2019)

Pharmacokinetics profile test

The testing of pharmacokinetic profiles was carried out with 2 treatments. The first treatment was the treatment in experimental animals by administration of ethanol extract of parang romang leaves at a dose of 100 mg/kg BW. The second treatment was the treatment in experimental animals by administering nanoemulsion of ethanol extract of parang romang leaves at 100 mg/kg BW. Blood sampling in all three treatments was carried out by testing animals' blood drawn from rats' marginal veins as much as 1- 2 ml with a span of 0 hours; 0.5 hours; 1 hour; 1.5 hours; 2 hours; 4 hours (Aswinda et al. 2015). The blood was then put into a polytube that has been given 2 drops of heparin, then vortex and centrifuged at a speed of 3000 rpm for 10 minutes, and added 1 ml of 20% TCA solution. The mixture was then centrifuged and supernatant was taken. After that, the levels were measured by using spectrophotometry (Aswinda et al. 2015). The obtained nanoemulsion and ethanol extract from parang romang leaves concentration was used to measure the bioavailability parameters of tmax, Cpmax, and AUC.

Antihyperlipidemic effect test

The initial total cholesterol level was measured using the spectrophotometric method. The rats were adapted for 14 days and before taking blood, the rats fasted for 16 hours. After measuring the initial total of cholesterol level, in the same-day group, rats were given standard feed and drinking water. Groups II, III, IV, V, and VI were given a high fat feed orally and drinking water in the form of Propylthiouracil (PTU) suspension. This treatment lasted for 14 days, then cholesterol levels were measured again. On the same day, rats were induced by streptozotocin 30 mg/kg BW. Wistar rats have hypercholesterolemia if cholesterol levels are >130 mg/dL. Total cholesterol levels were measured again after treatment. Group I and group II (normal control and negative control) were given Na CMC suspension, group III (positive control) was given simvastatin suspension, and groups IV and V were given ethanol extract and nanoemulsion preparation of parang romang ethanol extract at a dose of 100 mg/kg BW. After giving treatment to each group, the cholesterol levels of rats were measured again at day 14 and day 21. The measurement data of total cholesterol levels before and after treatment were recorded and analyzed (Tandi *et al*, 2019).

Data collection and analysis

The data obtained in the form of profile data for total cholesterol levels were analyzed for normality and homogeneity of the data to see the distribution of the data being normally distributed/homogeneous. If the data is normally distributed and statistically homogeneous, it is continued using the one-way ANOVA test, at the 95% confidence level. The Post hoc Least Significant Difference (LSD) test was choosen as a further test to see if there was a significant difference between treatments.

RESULTS AND DISCUSSION

Parang romang plants are empirically used by the community as medicinal plants for antihyperglycemic, antihyperlipidemic, and anti-cancer. However, its use is still simple and has limitations in solubility that cause the low bioavailability. The methods of nanoemulsions aims to increase the drug solubility. The identification result proves that the plants used in the study are species of Urticaceae. The results of the extraction carried out by maceration and the percentage yield of the obtained extract was 5.31%. The optimization results were carried out on 14 formulas resulting from a simple lattice obtained from 3 (three) formulas that did not separate after 24 hours of storage with a concentration of 100 mg of ethanol extract in 70 ml of tween 80/20, 27 ml of propylene glycol and 3 ml of olive oil. This study aims to determine the pharmacokinetic profile and effectiveness of ethanolic extract of parang romang leaves and nanoemulsion of ethanolic extract of parang romang leaves in reducing total cholesterol levels in male hypercholesterolemic diabetic rats.

Study of the pharmacokinetic profile of rats strain wistar given nanoemulsion preparation and ethanol extract from parang romang leaves at 0.5; 1; 1.5; 2; 2.5; 3; 3.5; and 4 hours was measured using spectrophotometry. The pharmacokinetic profile nanoemulsion preparation and ethanol extract from parang romang leaves can be seen in table 1.

Table 1. Pharmacokinetic profile of nanoemulsion and ethanol extract of parang romang leaves

Sample	Pharmacokinetic Profile		
	Tmax (hour)	Cp Max (µg/ml)	AUC
Nanoemulsion ethanol extract Parang romang leaves	0,5 ±0	96,68±0,116	297,57±0,192
Ethanol extract Parang romang leaves	1±0	15,44±0,004	93,62±0,126

The pharmacokinetic profile describes the kinetics, absorption, distribution, and elimination of the drug. The pharmacokinetic profile study used two treatment groups of rats, where group 1 was given ethanol extract of parang romang leaves and group 2 was given nanoemulsion from ethanol extract of parang romang leaves with a dose of 100 mg/kg BW. The maximum peak time (Tmax) describes the time required to reach the maximum concentration (Cpmax) and indicates the process of absorption of drug compounds (Sun *et al* 2019). The results of the study show that the maximum peak time of the group given the ethanol extract of parang romang leaves was 1 hour and the nanoemulsion were 0.5 hours. This shows that the time required by the nanoemulsion is better than that of the extract. At the time of the maximum peak, the maximum concentration of the active compound in the plasma was also obtained. The maximum concentration in plasma is related to the dose, absorption, and elimination of a drug. The results of this study showed that the maximum concentration of active compounds in plasma for ethanol extract of parang romang leaves was 15,44±0,004 g/ml and for nanoemulsion was 96,68±0,116 g/ml (Table 1). The area under curve (AUC) value reflects the total amount of drug that reaches the systemic circulation. The results of the area under curve (AUC) study for the group given ethanol extract of parang romang leaves was 93,62±0,126 hour/ml and nanoemulsion was 297,57±0,192 hour/ml (Table 1). This shows that the concentration of the active compound in the nanoemulsion dosage form reaches the systemic circulation is more than the extract, so that the availability of the drug in the target cells is maximized, therefore it can deliver the drug better to smaller units in the body. Resistance is due to the body's physiological barrier so that it can be targeted, reduce toxicity, and increase the efficiency of drug distribution whose data increase the bioavailability of drugs with low absorption (Magfirah, *et al* 2021).

The measurement of cholesterol levels on days 0, 14, 21, 28, and 35 use the CHOD-PAP method. The principle of this method is that cholesterol, in the form of esters, is hydrolyzed by cholesterol esterase enzyme. Cholesterol will be oxidized to produce hydrogen peroxide. This compound will then convert 4-aminoantiripine and phenol with cement catalase peroxide enzyme rock into colored quiomin and its intensity can be measured photometrically. The results of cholesterol level measurements can be seen in Table 2

Table 2. Total cholesterol levels of ethanol extract and nanoemulsion of parang romang leaves

Average ± SD Total Blood Cholesterol (mg/dL)					
Days	**Normal control**	**Negative control**	**Positive control**	**Parang romang leaf ethanol extract**	**Parang romang leaf ethanol extract nanoemulsion**
0	26,66±3,7a	25,15±6,7a	20,85±0,9a	23,49±3,5a	19,73±2,6a
14	33,48±7,1a	238,48±15,8b	232,29±19,3b	228,05±12,53 b	245,06±3,23b
21	37,33±11,15a	50,34±11,4b	284,11±57,8 b	258,01±7,4 b	263,91±6,8b
28	37,62±6,6a	264,02±7,5b	50,96 ±6,5a	139,55±6,3 b	48,59±1,9 a
35	42,66±2,1a	278,84±8,1b	40±2,3a	51,5±1,2 a	36,14±4,3 a

*same letter (P > 0.05) = its not significantly different; unequal letters (P < 0.05) = significantly different

This antihyperlipidemic study was carried out for 35 days, starting with feeding a high fat feed for 14 days and giving streptozotocin induction on day 14. Measurement results of cholesterol levels can be seen in table 2. The results of measuring cholesterol levels in all rats on day 0 obtained a range of 19.73±2.6 - 26.66±3.7 where the normal value of cholesterol levels in white rats is 10-50 mg/dl. One way ANOVA statistical test results on day 0 obtained a p-value > 0.05 which indicates that all rats have the same cholesterol levels and are normal. After induction of high fat feed in the treatment group negative control, positive control, ethanol extract of parang romang leaves dose 100 mg/kg BW, and nanoemulsion dose 100 mg/kg BW for 14 days and then continued with streptozotocin induction, total cholesterol level increased from average to 250.34±11.48 - 284.11±57.8. Statistical test results obtained a p-value <0.05, which means there is a difference in cholesterol levels between rats induced with high fat feed (positive control, negative control, and dose group with rats that were not induced (normal group). This shows the induction of high fat feed consisting of quail egg yolk and lard melting can increase the blood cholesterol levels, where quail eggs are a high source of cholesterol (844 mg/dl), while lard fat contains palmitic acid, stearic acid, oleic acid, and linoleic acid. Lard fat has a higher cholesterol content than other animal oils. This causes an increase in fat accumulation in the liver which can increase the amount of acetyl Co-A in liver cells to produce cholesterol so that cholesterol levels increase. In addition, high fat feed in the form of melting lard contains 25% of saturated fat that increases the amount of acetyl-CoA in liver cells to produce cholesterol (Tanggu et.al, 2021).

The results of measuring total cholesterol levels on day 21, the statistical of one way Anova shows p-value<0.05 (p = 0.000) indicating that there were significant differences in all groups of test animals, so it was continued with a post hoc test of least significant difference (LSD) to see the significant differences between treatment groups. The results of the post hoc LSD test showed a significant difference between normal controls and all treatment groups. The increase in cholesterol levels is caused

by the effect of streptozotocin administration. This is because streptozotocin can interfere with insulin secretion. Giving streptozotocin causes free radicals that can increase the reactive oxygen which has an important role in the destruction of pancreatic cells. Damage to pancreatic cells caused by impaired insulin secretion causes a decrease in insulin production which will result in impaired fat metabolism resulting in an increase in triglycerides (TG) and cholesterol (Kintoko *et al*, 2018).

The results of measuring total cholesterol levels on day 28, after two weeks of administration of the nanoemulsion preparation and ethanol extract from parang romang in the dose group, a significant reduction in cholesterol levels was obtained in the nanoemulsion group and the positive control with an average of 48.59 ± 1.9 and 50.96 ± 6.5 while the extract also decreased the cholesterol levels but it did not reach the normal levels, namely 139.55±6.3 (the normal value of cholesterol levels in white rats is 10-50 mg/dl). The ethanol extract of parang romang leaves (*Boehmeria virgata* L) contains alkaloid compounds that can prevent the increasing of total cholesterol, triglycerides, low density lipoprotein (LDL), significantly increase high density lipoprotein (HDL) and can also reduce cholesterol levels. Flavonoid compounds work by inhibiting cholesterol synthesis through HMG CoA reductase inhibitors, reducing acyl-CoA cholesterol acyltransferase (ACAT) enzyme activity, and reducing cholesterol absorption in the digestive tract (Diarti et al, 2018). Statistical test results obtained a p-value <0.05, which means that there was a difference in cholesterol levels between rats given simvastatin (positive control) and the dose group given extract suspension and nanoemulsion, respectively, with rats that were not induced (normal group) and which were not given the extract (negative control). The positive control was not significantly different from the parang romang ethanol extract nanoemulsion (p-value>0,05). This shows that the administration of nanoemulsion of parang romang leaves has almost the same effect as the administration of simvastatin as a positive control on reducing cholesterol levels. The positive control group and the parang romang ethanol extract nanoemulsion were significantly different from the ethanol extract of parang romang leaves (p-value<0,05). This shows that the nanoemulsion effect of parang romang is faster in lowering cholesterol levels than the ethanol extract of parang romang. This is because the nanoemulsion can improve the absorption of ethanol extract of parang romang so that it can increase its bioavailability (K. Gurpret & SK Singh, 2018).

Measurement of cholesterol levels on the 35th day after administration nanoemulsion preparation and ethanol extract from parang romang in the dose group obtained a significant reduction in cholesterol levels in the nanoemulsion group and positive control with an average of 36.14±4.3 and 40±2.5 while the extract group also experienced a decrease in cholesterol levels 51.5±1.2. The ethanol extract of parang romang leaves (*Boehmeria virgata* L) contains tannin compounds that can react with mucous enzymes and intestinal epithelial cells. The enzyme binds to tannins, causing the enzyme to settle on the surface of the intestine so that the absorption of foods containing fat will be inhibited. Saponin

compounds can form complex bonds with cholesterol from food. These complex bonds cannot be dissolved in the intestine so cholesterol cannot be absorbed, and cholesterol can excretion the digestive tract. This can cause cholesterol in the body to be reduced (Lovianie, et al 2019). Statistical test results obtained from the normal control group differ significantly between the negative control group and extract ethanol of parang romang (p-value <0.05) but it was not significantly different from the positive control and nanoemulsion of parang romang leaves (p-value >0,05). This indicates that the effect of extract ethanol of parang romang leaves in decreasing the total cholesterol levels was not close to normal control, while positive control and nanoemulsion of parang romang leaves had an effect on reducing blood cholesterol levels in male white rats (*Rattus norvegicus*) which was close to normal control. The negative control group was significantly different from all treatment groups. This is expected because Na CMC used as a carrier does not affect blood cholesterol levels (Edi kamal, 2019). The positive control group was significantly different from the negative control and ethanol extract of parang romang leaves (p-value<0,05) but not significantly different from the normal control group and the nanoemulsion of ethanol extract of parang romang (p-value>0,05). This indicated that the administration of simvastatin as a positive control and nanoemulsion of ethanol extract of parang romang affected to reduce the total cholesterol levels which were close to normal control.

CONCLUSION

The results of the pharmacokinetic profile of nanoemulsion preparations show the values of Tmax, Cpmax, and AUC are 0.5 hours; 96.17 g/ml and 297.57, while the ethanol extract of parang romang leaves are 1 hour, 15.44 g/ml and 93.53. The results of statistical tests on the effectiveness of antihyperlipidemic obtained (p-value <0.05) showed a significant effect between nanoemulsion preparations and extract ethanol of parang romang leaves in reducing cholesterol levels.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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