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Antihyperlipidemic Effect of Ethanol Extract of *Lansau* a Traditional Medicine of Muna Ethnic, Indonesia

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Abstract: *Lansau* is a traditional herb medicine from Muna ethnic, Southeast Sulawesi, Indonesia, consisting of 44 medicinal plants. This study was performed to determine and evaluate the antihyperlipidemic effect of ethanol extract of *Lansau* in high cholesterol and propylthiouracil induced hyperlipidemic rats. The animal test Wistar strain were used and divided into six groups namely KN (Na. CMC 1%), K (-) (Na CMC 1% + MDLT), K (+) (simvastatin 0.40 mg/kg BW), LS I (*Lansau* ethanol extract 6.907 mg/kg BW), LS II (ethanol extract Lansau 13.814 mg/kg BW) and LS III (*Lansau* LS III ethanol extract 27.628 mg/kg BW. The results showed that ethanol extract of traditional Lansau medicine with dose LS I 6.907 mg/kg BW, LS II 27.628 mg/kg BW and LS III 27.628 mg/kg BW have significant activity as antihyperlipidemic (cholesterol and triglyceride) compared to negative control groups ($p < 0.05$) and showed the same activity with simvastatin in lowering total cholesterol and triglyceride levels ($p > 0.05$), which shows its potential as antihyperlipidemic herbal medicine.

Keywords: lansau; cholesterol; triglycerides; antihyperlipidemic; traditional medicine.

1. Introduction

Indonesia has a variety of plants that can serve potentially as a medicine. Until now, the people of Indonesia have many traditional uses of plants to cope with various types of diseases [1, 2]. The use of plants as medicine is generally only based on experience/inheritance without knowing the chemical content in detail. The plant, if further explored, has active chemical content which is useful for use in health, agriculture, and industry. The research and use of traditional medicine are currently being encouraged, especially for hyperlipidemia [3].

One of the richness of ethnomedicine in Indonesia is the use of traditional *Lansau* herbs typical of the Muna Ethnic in Southeast Sulawesi Province Indonesia in the treatment. *Lansau* has been long known by the Muna ethnic that consists of 44 kinds of plant material mixtures that are taken based on the beliefs and philosophical values embraced by the Muna ethnic community. Content and prayers from the physician to make the community treat *Lansau* as a cure for all the problems faced mainly related to the disease. *Lansau* by Muna ethnic community believed to treat all kinds of diseases, especially internal diseases. The diseases include hepatitis, heart disease, diabetes, cancer, liver, hypertension, diarrhea, cough, constipation, fever, rheumatic gout, cholesterol, ulcer, vaginal discharge, irregular menstruation, colitis, tumors, tonsillitis, impotence, joints, anemia, increase stamina, and lack

of appetite. Besides, treatment with herbs by the community is considered more economical than the formal treatment.

Hyperlipidemia is a condition in which elevated lipid levels in plasma include elevated triglycerides and total cholesterol, increased LDL (Low-Density Lipoprotein) and lowering HDL (High-Density Lipoprotein) [4]. This is one of the risk factors for atherosclerosis [5, 6]. Atherosclerosis is the process of thickening of blood vessel walls resulting in the narrowing and hardening of the arteries. Atherosclerosis is a risk factor of cardiovascular disease, especially postmenopausal woman, but under 50 years, man has a high risk [7]. About 56% of cardiovascular disease as a result of blood cholesterol and causes 4.6 million deaths every year [8]. Hyperlipidemia is influenced by daily food intake [9]. Efforts that can be used to lower cholesterol in the blood are diet, exercise, reduce consumption of foods containing high levels of fat with the consumption of medicine, either with synthetic medicine or utilizing medicinal plants.

One of the efforts in improving hyperlipidemia is the use of medicinal plants containing flavonoids and saponins. The flavonoid compounds can decrease the secretion of apo B in hepatocytes and also decrease the activity of HMG-CoA enzyme, while saponin has a role in lowering the absorption of cholesterol and increase excretion of bile acids, which is cholesterol secretion [10]. The analyses of the secondary metabolites of Lansau contains alkaloid compounds, tannins, flavonoids, saponins, and triterpenoids. Toxicity test with Brine shrimp lethality test (BSLT) used Artemia salina; Leach found that 27 are toxic ($LC_{50} < 1000$) from 44 plants of Lansau [11].

2. Materials and Methods

2.1. Preparation of Lansau Extracts.

The 44 of *Lansau* plant procured from Batalaiworu Village, Raha, Southeast Sulawesi Province, Indonesia. The plant is authenticated by the Indonesian Institute of Science (LIPI) Bogor, while pharmacognostic identification was made by the laboratory of pharmacy, Universitas Halu Oleo.

The plant extracts were rinsed and cleaned with water and dried by drying using a black cloth and then smoothed until a powder of Simplicia is obtained. *Lansau* is weighed 500 grams and put into a 50 ml round flask each. Then the *Lansau* medicinal plant is soaked using a 700 mL ethanol solvent. The solvent fluid is heated for evaporation, and the vapor is condensed by the cooling back, thus condensing into fluid molecules and falling back into the round bottom flask while extracting Simplicia. The separation of residue and filtrate is done by filtration. The filtrate was concentrated by evaporator using a rotary vacuum evaporator at a 40^{o}C until an ethanol extract was obtained.

2.2. Modeling of experimental animals.

Male Wistar albino rats aged 3 months with a bodyweight range from 200 – 300 g were obtained from the animal house of Surabaya city, Indonesia. They were housed at room temperature 25 - 30^{0}C, 12 h light/dark cycles.

Hyperlipidemia was induced with oral cholesterol pure of 3 days for 14 days, PTU 2.055 mg/200 gr BW ad libithium for 14 days and Eat High Fat Diet (MDLT) 10 kg contains 2 kg flour, 1 kg powder, 500-gram green flour, 1.5 kg, 1kg duck eggs, 1 kg quail egg, 1.5kg cattle fat, 500g of chicken liver and 1 kg butter are given for 14 days.

The experimental procedure and protocols employed were approved by the Institutional Ethics Committee Halu Oleo University number: 2123/UN.29.20/PPM/2017.

2.3. Experimental design.

Rats were grouped into six different groups (n = 4 in each group), i.e.:
Group I: The normal control group (hyperlipidemic rats + 1% CMC with standard feed)
Group II: The negative control group (hyperlipidemic rats + CMC and high-fat diet (MDTL)
Group III: Positive control group (hyperlipidemic rats + simvastatin 0.40 mg / 200kgBB)
Group IV: LS I dose (hyperlipidemia mice treated + Lansau extract 6.907 mg / kgBB)
Group V: LS II dose (hyperlipidemia rats treated + Lansau extract 13.814 mg / kgBB)
Group VI: LS III dose (hyperlipidemia rats treated + Lansau extract 27.628 mg / kg BB

2.4. Antihyperlipidemic test.

2.4.1. Cholesterol.

The blood is taken into a tube containing an anticoagulant (EDTA), then centrifuged for 10 minutes at a rate of 3000 rpm. A total of 3 µL serum blood in dropper pipette, added 300 µL SL cholesterol reagent, then incubated for 325 seconds and measured the level using a photometer with a wavelength of 500 nm (Elitech procedure).

2.4.2. Triglycerides.

The blood is taken into a tube containing an anticoagulant (EDTA), then centrifuged for 10 minutes at a rate of 3000 rpm. A total of 3 µL serum blood in dropper pipette, 300 µL of a new triglycerides SL mono reagent was incubated for 425 seconds and measured using a photometer with a wavelength of 500 nm (Elitech procedure).

2.5. Statistical Analysis.

The results were expressed as mean ± SD (standard deviation). Statistical significance ($p<0.05$) was performed by a one-way analysis of variance followed by LSD post hoc test.

3. Results and Discussion

From the measurement results, it was found that there was an increase in total cholesterol and triglyceride levels at day 14 compared with levels before modeling, as shown in Table 1. Normal levels of total cholesterol rats are 10-54 mg/dL, while normal levels of triglyceride rats are 200 mg/dL This finding indicated that the modeling of test animals performed successfully for 14 days with cholesterol levels reached 71.22 mg/dL and triglyceride levels reached 204.77 mg/dL.

Table 1. Cholesterol and triglyceride levels profile before and after induction.

Animal Groups	**n**	**Mean± SD**	***P***
Cholesterol level before modeling	24	39.16 ± 2.30	0,00
Cholesterol level after modeling		71.22 ± 16.53	
Triglycerides level before modeling	24	87.83 ± 6.75	0,00
Triglycerides level after induction		204.6 ± 71.92	

The result of the cholesterol profile shows that all groups have hyperlipidemic conditions before treatment. The negative control group showed elevated cholesterol levels on

the 7th day of treatment (70.33 mg/dL), and on the 14th-day treatment, there was a decrease of cholesterol level in the normal limit of 52.00 mg/dL. This can be expected because of the body's homeostatic process in animal testing that is the condition when the body tries to restore itself to a state of balance.

In the positive control group after administered simvastatin on 7th-day therapy was still hypercholesterolemia with the level of 58.33 mg/dL, and on the 14th day of cholesterol, positive control group therapy was within the normal limit (36.00 mg/dL).

The three groups of test doses (LS I, LS II, and LS III) after *Lansau* extract therapy on the 7th day still had hypercholesterolemia with consecutive levels of 69.67 mg/dL, 60.66 mg/dL, and 57.00 mg/dL. While on day 14, cholesterol level therapy for all three doses was within normal limits of 39.33 mg/dL, 40.67 mg/dL, and 39.57 mg/dL, respectively, as shown in Table 2.

Table 2. Cholesterol Levels Profile before and after therapy.

No	Groups	Mean (mg/dL) ± SD		
		Before therapy	Cholesterol levels after therapy 7th day	Cholesterol levels after therapy 14th day
1.	KN	40.66 ± 1.15	38.00 ± 2.00	40.33 ± 4.04
2.	K(-)	64.33 ± 14.36	70.33 ± 8.96	52.00 ± 20.07
3.	K(+)	85.33 ± 0.57	58.33 ± 7.63	36.00 ± 2.00
4.	LS I	78.66 ± 0.57	69.67 ± 6.81	39.33 ± 13.31
5.	LS II	76.00 ± 6.08	60.66 ± 9.07	40.67 ± 1.52
6.	LS III	82.33 ± 2.08	57.00 ± 5. 57	39.67 ± 11.01

Abbreviations: KN = normal control group (Na.CMC); K (-) = negative control group (Na.CMC + MDTL); K (+) = positive control group (simvastatin); LS I = *Lansau* ethanol extract I 6,907 mg/kg bw; LS II = *Lansau* ethanol extract 13,814 mg/kg bw; LS III = *Lansau* ethanol extract 27,628 mg/kg bw

To determine the potency of *Lansau* ethanol extract with antihyperlipidemic properties, the percentage ratio (Table 3) of total cholesterol decrease between the test dose group (LS I, LS II, and LS III) with a negative control group on the 7th day and 14th day of therapy. From the post hoc test, there was a significant difference ($p < 0.05$) between the three test dose groups (LS I, LS II, and LS III) to the negative control group on the 7th day and 14th day of therapy.

Table 3. Percent Level of cholesterol profile on the 7th day and 14th day of therapy.

No	Groups	Mean of Cholesterol Level Reduction ± SD	
		Therapy 7th day	Therapy 14th day
1	KN	6.55 ± -73.20	0.81 ± -250.00
2	K(-)	-9.32 ± -37.60	19.17 ± 39.76
3	K(+)	31.64 ± 1222.87*	57.81 ± -246.41*
4	LS I	11.44 ± 1078.98*	50.00 ± -2206.51*
5	LS II	20.17 ± -14.17*	46.49 ± 74.89*
6	LS III	30.76 ± -167.46*	51.82 ± -429.15*

Abbreviations: KN = normal control group (NaCMC); K (-) = Negative control group (Na.CMC + MDTL); K (+) = positive control group (simvastatin); LS I = *Lansau* Ethanol Extract I 6,907 mg/kg bw; LS II = *Lansau* ethanol extract 13,814 mg/kg bw; LS III = *Lansau* ethanol extract 27,628 mg/kg bw.
(*) = Significantly different $p < 0.05$ to negative control group;

The percentage decrease in cholesterol levels after giving the *Lansau* ethanol extract in all three dose test groups started to occur on the 7th day and 14th day of therapy. On the 7th day of therapy showed the LS III dose group had the highest percentage of 30.76% compared with LS II and LS I with the respective percentage decrease of 20,17% and 11,44%. The negative control group on the 7th day had a percentage decrease of -9.32%; the value showed an increase in total cholesterol levels. On the 14th day, therapy showed that LS III had the highest percentage of 51.82% compared to LS II and LS I, with the respective percentage decrease by 46.49% and 50.00%. The negative control group on day 14 had the lowest percentage of the

decline of 19.17%. There was a decrease in the percentage of cholesterol levels on the day 7 and 14 of therapy between the three test dose groups (LS I, LS II, and LS III) with the negative control group.

The above description of the triglyceride profile showed that first levels before therapy on negative control, positive control, and all three dose treatment groups (LS I, LS II, and LS III) showed hyperlipidemic conditions. In the negative control group, increased triglyceride levels on the 7th day of therapy, i.e. 256.67 mg / dL and 14th-day therapy, decreased triglyceride levels within normal limits of 166.63 mg / dL. This can be expected because of the body's homeostatic process in animal testing that is the condition when the body tries to restore itself to a state of balance.

In the positive control group after being given simvastatin medicine therapy on the 7th day, the therapy still had hypercholesterolemia with levels of 204.00 mg / dL, and on the 14th day, the positive cholesterol control group was within the normal limit of 97.67 mg / dL.

For the dose group of LS I and LS III tests (Table 4) after *Lansau* extract therapy on 7th day still had hypertriglyceridemia with consecutive levels of 209.00 mg /dL and 219.33 mg / dL and on the 14th day of therapy the cholesterol level for the third the dose group was within normal limits with consecutive levels of 94.33 mg/dL and 88.00 mg/dL. In the LS I dose test group on the 7th day and 14th-day therapy, there has been a decrease in triglyceride levels within normal limits with consecutive levels of 190.00 mg / dL and 90.00 mg/dL.

Table 4. Mean of triglyceride levels profile in the treatment group before and after therapy.

No	Groups	Mean (mg/dL) ± SD		
		First levels before therapy	Triglycerides levels after 7th day therapy	Triglycerides levels after 14th day therapy
1.	KN	76.00 ± 4.58	85.33 ± 4.50	83.67 ± 4.04
2.	K(-)	199.00 ± 91.82	256.67 ± 36.17	166.63 ± 68.22
3.	K(+)	267.33 ± 17.50	204.00 ± 7.21	97.67 ± 45.78
4.	LS I	231.66 ± 17.55	209.00 ± 19.69	94.33 ± 31.21
5.	LS II	242.00 ± 28.58	219.33 ± 14.01	88.00 ± 11.53
6.	LS III	211.66 ± 7.63	190.00 ± 15.00	90.00 ± 11.13

Abbreviations: KN = normal control group (NaCMC); K (-) = Negative control group (Na.CMC + MDTL); K (+) = positive control group (simvastatin); LS I = *Lansau* Ethanol Extract I 6,907 mg/kg bw; LS II = *Lansau* ethanol extract 13.814 mg/kg bw; LS III = *Lansau* ethanol extract 27.628 mg/kg bw

Table 5. The average profile percent decrease in triglyceride levels for the treatment group on the 7th day and the 14th day of therapy.

No	Groups	Average Percentage of triglyceride Reduction ± SD	
		Therapy 7th day	Therapy 14th day
1.	KN	-12.28 ± 1.60	-10.08 ± 11.80
2.	K(-)	-28.97 ± 60.60	17.92 ± 25.69
3.	K(+)	23.69 ± 58.79*	63.46 ± -161.60*
4.	LS I	9.78 ± -12.17	59.28 ± -77.6*
5.	LS II	9.36 ± 50.97	63.64 ± 59.65*
6.	LS III	10.23 ± 96.39	57.48 ± -45.80*

Abbreviations: KN = normal control group (NaCMC); K (-) = Negative control group (Na.CMC + MDTL); K (+) = positive control group (simvastatin); LS I = ethanol extract *Lansau* I 6,907 mg/kg bw; LS II = *Lansau* ethanol extract 13.814 mg/kg bw; LS III = *Lansau* ethanol extract 27,628 mg/kg bw
(*) significantly different p <0.05 to the negative control group

The potency of ethanol extract of *Lansau* as antihyperlipidemic, statistic test was done to determine the decrease of triglyceride level after giving the ethanol extract of *Lansau* at three groups of test dose (LS I, LS II and LS III) compared to a negative control group on the 7th day and 14th-day therapy (Table 5). On the 7th day of therapy, used *Kruskal wills* test was found to have significant differences (p <0.05). Furthermore, the analysis used the Mann Whitney test.

On the 14th day, a one-way ANOVA test was found to have a significant difference ($p < 0.05$). Furthermore, the analysis was performed by using a Post Hoc LSD test.

The results of Mann Whitney test analysis on the day 7 (LS I, LS II, LS III) showed no significant difference ($p > 0.05$), when compared with the negative control group with 3 test groups (LS I, LS II, LS III) there was no significant difference ($p > 0,05$). This shows the effect of ethanol extract therapy *Lansau* has not been maximal in lowering triglyceride levels in the mouse. On 7^{th} day therapy showed that the LS III dose group had the highest percentage of 10.23% compared to LS I and LS II with the respective percentage of decrease of 9.78% and 9.36%. The negative control group on the 7th day had a percent decrease of -28.97% of the value showed an increase in triglyceride levels. Results of LS post hoc test on 14^{th} day of the three therapeutic groups (LS I, LS II, and LS III) were significantly different ($p < 0.05$) when compared with the negative control group with 3 test groups (LS I, LS II, LS III) there was a significant difference ($p < 0.05$). On the 14th day of therapy showed LS II had the highest percentage of 63.64% decrease compared to LS I and LS III with the respective percentage of decrease of 59.28% and 57.48%. For the control group, negative on the 14^{th} day had the lowest percentage of decrease of 17.92%. There was a decrease in the percentage of triglyceride contents on the day 7 and 14 of therapy between the three test dose groups (LS I, LS II, and LS III) to the negative control group.

3.1. Effectiveness of Lansau ethanol extract.

To determine the effectiveness of ethanol extract of *Lansau* was measured based on differences in the decrease in total cholesterol and triglycerides in the three-dose test groups (LS I, LS II, and LS III) after treatment of positive control group. This research was conducted for measurement total cholesterol and triglyceride levels twice on the 7th day and the 14th day of therapy.

3.2. Cholesterol level.

Elevation of total cholesterol and triglycerides indicated of dyslipidemia with a low level of high-density lipoprotein (HDL) [12] and an elevated risk for coronary heart disease (CHD) [13]. The effectiveness of ethanol extract *Lansau* traditional medicine was valued based on an average percentage of total cholesterol reduction on all three test groups (LS I, LS II, and LS III) to the positive control group. Based on the ANOVA test result in the six treatment groups, there was a significant difference ($p < 0,05$). Based on LSD post hoc test result on the 7th day of LS, I group therapy there was a significant difference ($p < 0.05$) to LS II group and LS III group, compared to LS II group and LS III group there was no significant difference ($p > 0, 05$). In the simvastatin positive control group there was a significant difference ($p < 0.05$) in the LS I group did not show the same therapeutic effect with the simvastatin positive control group, compared with the LS II group and the LS III group there was no significant difference ($p < 0.05$). > 0.05) to the simvastatin positive control group, this showed the same therapeutic effect as the simvastatin positive control group.

On the 14th day of *Lansau* ethanol extract therapy in all three test dose groups (LS I, LS II, and LS III) there was no significant difference ($p > 0.05$). Compared between the three groups of test dose (LS I, LS II, and LS III) with the positive control group, there was no significant difference ($p > 0.05$) It was able to show the same therapeutic effect with positive simvastatin control. Statin used to prevent secondary cardiovascular disease like stroke caused by hyperlipidemia [14].

3.3. Triglycerides level.

Increased levels of triglycerides is also a risk factor for nephropathic diabetes in addition to dyslipidemia [15–17]. Hypertriglicerides can induce the reactive oxygen species (ROS) and cause oxidative stress in hyperlipidemia with the reduced antioxidant system [18],[19]. Evaluation of ethanol extract of traditional medicine of *Lansau* was valued based on the average percentage of decreased triglyceride levels in 3 test groups (LS I, LS II, LS III) to the positive control. Based on the results of the *Kruskal Walls* test in the six treatment groups showed a significant difference ($p < 0.05$). Based on the test results of Mann Whitney test on 7 the day of therapy, the effect of decreasing triglyceride levels among the three doses of test group (LS I, LS II, LS III) was no significant difference ($p > 0.05$) compared to the three dosage groups test (LS I, LS II, LS III) to the simvastatin positive control group showed a significant difference ($p < 0.05$). This has not shown the same therapeutic effect as the positive control group; it is suspected that the chemical compounds in the extract have not been able to reduce triglyceride levels on the 7th day of therapy.

ANOVA analysis test results on the 14th day showed a significant difference ($p < 0,05$). In the result of LSD post hoc test analysis between 3 test groups (LS I, LS II, LS III), there was no significant difference ($p > 0,05$). In the simvastatin positive control group compared with the three-dose test groups (LS I, LS II, and LS III), there was no significant difference ($p > 0.05$). These three groups of test doses (LS I, LS II, and LS III) were able to show the same therapeutic effect as the simvastatin positive control group. Flavonoid content in *Lansau*, which has antioxidant activity, is thought to reduce triglyceride levels [20]. Eleusine indica (L.) Gaertn herbaceous one of the *Lansau* plants, has the effect of reducing lipid levels by not having a toxic effect [21].

4. Conclusions

Based on the results of the study can be concluded that *Lansau* ethanol extract at a dose of LS I 6.907 mg/kg BW, LS II 13.814 mg/kg BW and LS III 27.628 mg/kg BW have potency as antihyperlipidemic in white male rat Wistar strain based on the decrease of cholesterol and triglyceride levels. *Lansau* ethanol extract at the dose of LS I 6.907 mg/kg BW, LS II 13.814 mg/kg BW and LS III 27.628 mg/kg BW, there was no difference decrease of total cholesterol and triglyceride level to a positive control group with p-value ($p > 0.05$) in white rat male Wistar strain.

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Conflicts of Interest

The authors declare no conflict of interest.

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