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ANTIHYPERLIPIDEMIC ACTIVITY OF *PLECTRANTHUS SCUTELLARIOIDES* ON NORMAL AND PROPYLTHIOURACIL INDUCED HYPERLIPIDEMIC RATS

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A B S T R A C T

The present study investigated the antihyperlipidemic activity of *Plectranthus scutellarioides* on normal and propylthiouracil induced hiperlipidemic rats. *Plectranthus scutellarioides* leaves were extracted with ethanol 70% by macerator apparatus. Propylthiouracil and a high-fat diet were used to induced hyperlipidemic rats and followed by oral administration of simvastatin 1 mg/kg, PSE 400 mg/kg, PSE 500 mg/kg and PSE 600 mg/kg for two weeks. Total cholesterol, triglycerides, and HDL cholesterol were measured and also calculated by formula LDL cholesterol, VLDL cholesterol, atherogenic index and coronary risk index. The result showed that PSE 600 mg/kg had better activity to decrease total cholesterol. PSE 500 mg/kg showed better activity to decrease triglycerides, VLDL cholesterol and LDL cholesterol. PSE 400 mg/kg showed better activity to increase HDL cholesterol. Therefore, *Plectranthus scutellarioides* extract dose 400 mg/kg, 500 mg/kg and 600 mg/kg have antihyperlipidemic activity with decreasing total cholesterol, triglycerides, LDL cholesterol, VLDL cholesterol and increasing HDL cholesterol.

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INTRODUCTION

Hyperlipidemia characterized by an increase in total cholesterol, triglycerides, VLDL, LDL and also a decrease in HDL cholesterol. Hyperlipidemia is a risk factor for atherosclerosis. Long-term atherosclerosis can lead to heart disease and stroke (Nelson, 2013). The World Health Organization states that in 2012, stroke is the highest cause of death in Indonesia causing the death of 328,500 people (WHO, 2012).

Synthetic drugs is one way to reduce hyperlipidemia. However, the use of this synthetic drug has many side effects. The use of herbal medicine has grown rapidly in the world because it can be an alternative in patients who have tolerance to synthesis drugs and also its use in the long run is relatively safer than synthesis drugs (Kaliora, *et al*., 2006).

Leaves of *Plectranthus scutellarioides* are widely grown in Indonesia, purple in color, belonging to the Lamiaceae which is a shrub ornamental plant and grows in the lowlands to an altitude of 1,300 m above sea level (Kloppenburgh and Versteegh, 2006). Through chemotaxonomic approach, it can be seen the possibility of compounds contained in a plant based on kinship in plant systematics. This is because the biosynthesis of chemical compounds occurs through identical biosynthetic pathways. Ethanol extract *Plectranthus amboinicus* (Lamiaceae) of 200 mg/kg and 400 mg/kg was reported to have significantly antihyperglycemia and antihyperlipidemia activity in alloxan-induced rats (Viswanathaswamy *et al.*, 2011). Based on the above explanation, the present study investigated the antihyperlipidemic activity of *Plectranthus scutellarioides* on normal and propylthiouracil induced hyperlipidemic rats.

MATERIALS AND METHODS

Material

Leaves of *Plectranthus scutellarioides* which has been dried obtained from Indonesian Spices and Medicinal Crops Research Institute, Bogor, West Java in October 2016. Wistar male white rats with 2-3 months and had 170-200 gram in weight, were taken from D' Wistar, Bandung, West Java. Other materials used are 70% ethanol, aquadest, ethil acetate, n-hexane, Dragendorff reagent, Mayer reagent, Liebermann-Burchard reagent, propylthiouracil, simvastatin, pulvis gummi arabicum (PGA), Total Cholesterol Kit, Triglycerides Kit, HDL-Cholesterol Kit from Biolabo.

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Apparatus

Macerators, Evaporators, Waterbath, Blood Collection Tube No Additive, Centrifuge (Hettich) and Visible Spectrophotometer (Thermo Genesys).

Research Story

Plectranthus scutellarioides leaves were determined in *Herbarium Bandungense*, School of Life Science and Technology, Bandung Institute of Technology, with the document number 4394/I1.CO2.2/PL/2016. The research was agreed by the Health Research Ethics Committee of Faculty of Medicine of Padjadjaran University, with the document number 548/UN6.C.10/PN/2017.

Preparation of Extract

Plectranthus scutellarioides leaves were extracted with ethanol 70% by macerator apparatus, then kept 3x24 hours by changing ethanol every 24 hours. Liquid extract was then separated by using flannel cloth and the filtrate was concentrated by evaporator. The concentrated extract further will be referred as *Plectranthus scutellarioides* extract (PSE).

Phytochemical screening of Plecranthus scutellarioides extract

The *Plecranthus scutellarioides* extract was qualitatively tested for the presence of secondary metabolite in extract by using phytochemical screening.

Protocols

All wistar male white rats were acclimated for 10 days before the experiment. All rats were divided into following six groups with each group containing five rats.

- Group I-Normal group in which the rats were daily administered vehicle PGA2% for 14 days
- Group II-Hyperlipidemic group in which the rats were daily administered propylthiouracil 2 mg/kg and high-fat diet for 14 days
- Group III-Positive group in which the rats were daily administered propylthiouracil 2 mg/kg, high-fat diet and simvastatin 1mg/kg for 14 days
- Group IV-Test group in which the rats were daily administered propylthiouracil 2 mg/kg, high-fat diet and PSE 400 mg/kg for 14 days
- Group V-Test group in which the rats were daily administered propylthiouracil 2 mg/kg, high-fat diet and PSE 500 mg/kg for 14 days
- Group VI-Test group in which the rats were daily administered propylthiouracil 2 mg/kg, high-fat diet and PSE 600 mg/kg for 14 days

High-fat diet made in the form of emulsions, all the ingredients are mixed and stirred until homogeneous and made freshly every day. High-fat diet were given 2 mL/200gram by oral to induce hyperlipidemic. High-fat diet is made with a total volume of 100 ml;egg yolk 80 gram, glucose 65% 15 gram, cow fat 5 gram. Propylthiouracil 2 mg/kg bw were suspended in a vehicle PGA 2% orally to induce hyperlipidemia. Simvastatin and PES were suspended in a vehicle PGA 2% by oral. Propylthiouracil and high-fat diet were administered daily at relatively the same time. Simvastatin and PSE were given to test group one hour after induced hyperlipidemic. At the end of experimental study, rats were fasted for 12-14 hours and then ether anesthesia. The blood was collected by intracardial with syringe 3 mL and put into vacutainer. Vacutainer contains blood centrifuged for 10 minutes with 3.000 rpm. The blood separated into serum and plasma. Serum was transferred into Eppendorf tube and then stored in the refrigerator 20^0C before analyzed (Ochani, *et al*., 2009; Soemardji, *et al*., 2016; Safitri *et al*., 2016).

Estimation of Serum Lipid Profile

Serum of total cholesterol, triglycerides and HDL cholesterol were estimated using kit Biolabo. VLDL cholesterol and LDL cholesterol was calculated.

$$\text{VLDL cholesterol} = \frac{\text{Triglycerides}}{5}$$

$$\text{LDL cholesterol} = \text{Total cholesterol} - \frac{\text{Triglycerides}}{5} - \text{HDL cholesterol}$$

$$\text{Atherogenid Index (AI)} = \frac{\text{LDL cholesterol}}{\text{HDL cholesterol}}$$

$$\text{Coronary Risk Index (CRI)} = \frac{\text{Total cholesterol}}{\text{HDL cholesterol}}$$

Statistical Analysis

The result was analyzed using Statistical Package for the Social Sciences 21 by one way ANOVA followed by Tukey's multiple comparion test. The P value <0.05 was set for statistical significant.

RESULT

Table 1 Rendemen Extract of *Pelctranthus scutellarioides*

Dry leaves	Concentrated Extract	Rendemen Extract
3200 gram	604.860 gram	18.901%

Table 2 Phytochemical screening of *Plecranthus scutellarioides*

Secondary metabolite	Dry leaves	Concentrated Extract
Alkaloid	+	+
Polyphenols	+	+
Tannin	+	+
Flavonoid	+	+
Kuinon	-	-
Saponin	+	+
Monoterpenoid/Sesquiterpenoid	-	-
Steroid/Triterpenoid	-	-

+ : Detected - : Undetected

DISCUSSION

Phytochemical screening of *Plecranthus scutellarioides* showed the presence of alkaloid, polyphenols, tannin, flavonoid and saponin. Some researchers reported that polyphenols, tannin, flavonoid and saponin has a hypolipidemic effect. Flavonoid and polyphenols can decrease LDL cholesterol, VLDL cholesterol, triglycerides and increase HDL cholesterol (Rajasekaran *et al*., 2013).

Table 3 Effect of *Plectranthus scutellarioides* Extract on Serum Lipid Profile in Normal and Hyperlipidemic Rats (Mean±SEM)

Groups	Total Cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL Cholesterol (mg/dl)	LDL Cholesterol (mg/dl)	VLDL Cholesterol (mg/dl)
Normal	84.503±3.244[b]	80.833±2.826[b]	43.031±0.846	25.305±2.774[b]	16.167±0.565[b]
Hyperlipidemic	134.940±3.395[a]	132.500±2.764[a]	35.394±2.553	73.046±5.487[a]	26.500±0.553[a]
Positive	87.947±2.863[b]	75.417±7.523[b]	45.002±1.654[b]	27.862±3.228[b]	15.083±1.505[b]
PSE 400 mg/kg	95.046±4.484[b]	120.370±5.586[a]	46.613±1.634[b]	24.360±5.965[b]	24.074±1.117[a]
PSE 500 mg/kg	90.225±4.333[b]	98.889±3.445[b]	44.886±2.068[b]	25.562±4.862[b]	19.778±0.689[b]
PSE 600 mg/kg	88.848±1.734[b]	112.963±6.599[a]	41.073±3.042	25.182±4.155[b]	22.593±1.320[a]

a: Significantly different compared with normal rats (p<0,05)
b: Significantly different compared with hyperlipidemic rats (p<0,05)

Table 4 Effect of *Plectranthus scutellarioides* extract on atherogenic index and coronary risk index in normal and hyperlipidemic Rats (Mean±SEM)

Groups	Atherogenic Index	Coronary Risk Index
Normal	0.589±0.065[b]	1.965±0.073[b]
Hyperlipidemic	2.137±0.282[a]	3.898±0.316[a]
Positive	0.630±0.091[b]	1.971±0.125[b]
PSE 400 mg/kg	0.535±0.140[b]	2.052±0.131[b]
PSE 500 mg/kg	0.579±0.116[b]	2.025±0.122[b]
PSE 600 mg/kg	0.657±0.148[b]	2.221±0.199[b]

a: Significantly different compared with normal rats (p<0,05)
b: Significantly different compared with hyperlipidemic rats (p<0,05)

Flavonid and polyphenols can inhibit HMG-CoA reductase enzyme and could prevent formation of free radicals thus has a hypolipidemic effect (Safitri, *et al*., 2016). Saponin could prevent formation of micelles with cholesterol in the small intestine thus the absorption of cholesterol in the intestine becomes inhibited. Therefore, the liver produce more bile from cholesterol (Bogoriani, *et al*., 2015).

Propylthiouracil can inhibit thyroid hormone synthesis and inhibit cholesterol metabolism so as to increase cholesterol levels. It has been reported that propylthiouracil orally can increase triglycerides and total cholesterol total for 2 weeks (Soemardji *et al*., 2016). Propylthiouracil is used as an endogenous induction and the high-fat diet is used as an exogenous induction. Simvastatin orally to positive group was used to compare an antihyperlipidemic effect. Simvastatin can reduce production of cholesterol by inhibiting enzyme that catalyzes metabolism of cholesterol. The enzyme is HMG-CoA reductase (AHFS, 2011). Simvastatin is metabolized at the liver by CYP3A4, 95% bound to plasma proteins, excreted in urine (13%) and feces (60%) and half life 0.5-3 hours (Martindale The Complete Drug Reference, 2009). In this experiment, total cholesterol were measured in all groups showed that there is a treatment effect in each group. Data showed that all group have significantly different compared with hyperlipidemic rats. Simvastatin 1 mg/kg, PSE 400 mg/kg, PSE 500 mg/kg, and PSE 600 mg/kg could decrease total cholesterol in the blood.

Triglycerides are another component in measuring blood lipid profiles. Triglycerides measured in all groups showed that there is a treatment effect in each group. Hyperlipidemic group, PSE 400 mg/kg group and PSE 600 mg/kg group have significantly different compared with normal rats. Data showed that normal group, positive group and PSE 500 mg/kg group have significantly different compared with hyperlipidemic rats. Therefore, simvastatin 1 mg/kg and PSE 500 mg/kg proved to be more effective in decreasing triglycerides levels in the blood.

HDL cholesterol or so called "good cholesterol" plays a role in reducing the risk of coronary heart disease. The measured HDL cholesterol is expected to have a high value. Positive group, PSE 400 mg/kg group and PSE 500 mg/kg group have significantly different compared with hyperlipidemic rats. However, HDL cholesterol of PSE 400 mg/kg group is higher than that of the positive group. This is because PSE contains quercetin compounds that have antioxidant properties (Moektiwardoyo, 2010). In addition, PSE also contains anthocyanin compounds that can increasing HDL cholesterol (Zhu *et al*., 2014).

LDL cholesterol or commonly called "bad cholesterol" is expected to have a low value. All group have significantly different compared with hyperlipidemic rats. However, LDL cholesterol of PSE 400 mg/kg group is lower than that of the positive group. This is because PSE contains quercetin compounds that can prevent the oxidation process of Low Density Lipoprotein (LDL) by catching free radicals and chelating transition metal ions (Paramawati, 2016).

VLDL cholesterol was calculated using the formula shows that hyperlipidemic group, PSE 400 mg/kg group and PSE 600 mg/kg group have significantly different compared with normal rats. Data showed that normal group, positive group and PSE 500 mg/kg group have significantly different compared with hyperlipidemic rats. Simvastatin 1 mg/kg and PSE 500 mg/kg can decreasing VLDL cholesterol levels in the blood.

The results of the calculation of atherogenic index and coronary risk index showed that there is a treatment effect in each group. Data showed that all group have significantly different compared with hyperlipidemic rats. Atherogenic index shows the index of atherosclerosis. Atherogenic index in PSE 400 mg/kg group and PSE 500 mg/kg group showed better results than normal group and positive group. This is due to the influence of higher HDL cholesterol and lower cholesterol LDL than normal group and positive group. Therefore, PSE can prevent the formation of atherosclerosis. Coronary risk index shows the risk index of coronary heart disease. Coronary risk index in the positive group and PSE 500 mg/kg is more effective than PSE 400 mg/kg group and PSE 600 mg/kg group.

CONCLUSION

Plectranthus scutellarioides extract dose 400 mg/kg, 500 mg/kg and 600 mg/kg have antihyperlipidemic activity with decreasing total cholesterol, triglycerides, LDL cholesterol, VLDL cholesterol and increasing HDL cholesterol. PSE 600 mg/kg showed better activity to decrease total cholesterol. PSE 500 mg/kg showed better activity to decrease triglycerides, VLDL cholesterol and LDL cholesterol. PSE 400 mg/kg showed better activity to increase HDL cholesterol.

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