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Research Article

Antihyperlipidemia activity of sungkai (*Peronema canescens*) leaves extract in albino rats *Rattus noverticus* (Wistar strain) with propylthiouracil-induced hyperlipidemia

Ulfa Pratiwi[1], Muharni Muharni[2]*, Ferlinahayati Ferlinahayati[2], Heni Yohandini[2] and Suheryanto Suheryanto[2]

[1]*Master Program of Chemistry Faculty of Mathematics and Natural Sciences, University of Sriwijaya, Indralaya, Ogan Ilir, South Sumatra, 30662 Indonesia*

[2]*Department of Chemistry, Faculty of Mathematics and Natural Sciences, University of Sriwijaya, Indralaya, Ogan Ilir, South Sumatra, 30662 Indonesia*

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ABSTRACT

Peronema canescens has traditionally been used by the community of Musi Banyuasin, South Sumatera, Indonesia, to treat hypertension. One of the triggers for hypertension is high levels of blood cholesterol. The *in vivo* research on the anti-hyperlipidemia activity of the ethanol extract *P. canescens* leaves in albino rats *Rattus noverticus* (Wistar strain) with propylthiouracil-induced hyperlipidemia was done. The animal test was separated into six groups: normal group, negative group, positive group (simvastatin), and three treatment groups with extract doses of 100, 200, and 400 mg/kgBW. The hyperlipidemia parameter was determined using the photometric enzymatic method. The ethanol extract of *P. canescens* leaves provided the highest anti-hyperlipidemia activity at 400 mg/kgBW with decreased total cholesterol percentage of 64.82%, LDL of 44.31%, triglyceride 69.00% and increased HDL of 76.89%. *P. canescens* extract can lower hyperlipidemia with the effective dose (ED_{50}) at 162.12 mg/kgBW. Our results indicated that *P. canescens* could be used in hyperlipidemia treatment, but further in vivo testing is required.

Keywords: Anti-hyperlipidemia, leaf extract, *Peronema canescens*, propylthiouracil, *in vivo*

INTRODUCTION

Hyperlipidemia is a condition marked by high levels of fats or lipids in the blood, such as cholesterol and triglycerides. This condition is common when too much non-HDL and LDL cholesterol are in the blood, thereby increasing fat deposits in the arteries. The high cholesterol in the blood causes narrowing and stiffness in the walls of the blood vessels, which in turn can cause atherosclerosis, leading to an increase in blood pressure, blockage of the heart arteries, and risk of heart disease (Nelson, 2013). Hyperlipidemia condition generally not accompanied by any specific symptoms. Synthetic drugs such as simvastatin, atorvastatin, rosuvastatin, fluvastatin, and pitavastatin, are being used to lower cholesterol; however, the use of synthetic drugs can cause side effects such as allergies, muscle pain, skin rashes, autoimmune disease, and liver damage (Thompson *et al*., 2016; Alexandre *et al*., 2020). Therefore, alternatives such

*Corresponding author e-mail: muharnikimia@unsri.ac.id

as natural herbal compounds are necessary to reduce cholesterol levels. Several medicinal plants have been reported to have hypolipidemic activity, such as *Averrhoa carambola, Trixis angustifolia,* and *Hibiscus sabdariffa* (Aladaileh *et al*., 2019; Salazar-Gómez *et al*., 2019; Umoren *et al*., 2020). Furthermore, sungkai (*Peronema canescens*) leaves have been used as a traditional medicine for fever, malaria, toothache, and ringworms. In contrast, the boiled water of the bark of *P. canescens* was used as medicine for smallpox (Yani *et al*., 2014). It is a traditional medicine used in West Java to treat malaria (Hidayat *et al*., 2021) and in South Sumatra, particularly by the Musi Banyuasin ethnic group, for the treatment of hypertension and hypercholesterolemia. *P. canescens* is a tropical plant often found in tropical rain forests and belongs to the Lamiaceae family and was spread in Thailand, Malaysia, and Indonesia (Wiart, 2006).

The methanol extract of *P. canencens* leaves has been reported to contain alkaloids, terpenoids, steroids, flavonoids, and tannin (Sitepu, 2020). In plants, steroids, triterpenoids and phenolic compounds have a proportion of lowering cholesterol levels (Kopylov *et al*., 2021; Prado *et al*., 2019). Furthermore, flavonoid compounds are also reported to reduce cholesterol levels in the blood (AL-Ishaq *et al*., 2019). Muharni *et al*. (2021) reported that the triterpenoid betulinic acid compound from the extracted *P. canescens* leaves showed anti-cholesterol activity with IC_{50} values of 60.53 µg/mL. The extract of ethanol of *P. canescens* leaves showed anti-cholesterol activity, whereas the anti-cholesterol activity of the ethyl acetate fraction was higher than that of the n-hexane and methanol fractions. The anti-cholesterol activity of *P. canescens* leaves shows its potential as a natural source of anti-cholesterol agents. This aim of this study was to analyze the potential of ethanol extract of *P. canescens* leaves as anti-hyperlipidemia treatment.

MATERIALS AND METHODS

Leaves of *P. canescens* were collected from the Musi Banyuasin Regency of South Sumatra, Indonesia in January 2021. The plant was identified as *Peronema canescens* Jack at the Herbarium Bogoriense, Research Center for Biology, Indonesian Institute of Sciences in Bogor, Indonesia with registration number B-134/IV/D1-01/1/2021. The rats used as test animals weighing 150-250 g were obtained from the BioScience Research Laboratory, Palembang City. The experiments were performed after accepting an approval letter from the ethical clearance committee of Ahmad Dahlan University, Number: 022109039. The animals tested were acclimatized for seven days.

Extraction

The fresh *P. canescens* leaves (1 kg) were macerated with 96% ethanol (5L). Leaves were allowed to stand for 48 hours and filtered to obtain the filtrate and residue. The residue was extracted again with three repetitions. The filtrate was concentrated using a rotary evaporator at a temperature of 60ºC to obtain crude extract.

In vivo anti-hyperlipidemia

The tested animals were acclimatized for seven days with standard food and drink before treatment. On the eighth day, each rat's body weight, total cholesterol, triglyceride, LDL (low-density lipoprotein), and HDL (high-density lipoprotein) levels were determined. The animals were randomly divided into six groups: a normal group, a positive control group, a negative control group, and three treatment groups at doses of 100, 200, and 400 mg/kgBW. Each group consisted of five male rats. The animal test was induced with a solution of propylthiouracil (PTU) and high-fat foods consisting of egg yolk, cooking oil, and butter. The normal control group was given standard foods (Demjan *et al*., 2020). This induction was carried out for 14 days. On day 15, rat blood was taken to determine the rats' total cholesterol, triglyceride, HDL, and LDL levels. The rats in the condition of hyperlipidemia were given treatment: group 1 (normal) and group 2 (negative) were given Na CMC (carboxymethyl cellulose sodium) solution of 1%, group 3 (positive) was given a simvastatin solution at a dose of 0.193 mg/200gBW, group 4, 5, and 6 were given the ethanol extract of *P. canescens* leaves at doses of 100, 200, and 400 mg/kgBW respectively. The dosage was given orally for 14 days. On day 30, rat blood was taken to determine the total cholesterol, triglyceride, HDL, and LDL levels using a UV-Vis spectrophotometer using a biosystem analyzer (Aberare *et al*., 2021; Sheu *et al*., 2013). The body weight of the rats was measured before and after induction and after extract treatment (Siahaan *et al*., 2020).

Analysis data

Analysis of the measurements of data was recorded in triplicate. Data are provided as mean ± SD. Data were analyzed statistically using ANOVA (α 0.05), followed by the Duncan New Multiple Range Test (DNMRT) at 0.05. The Effective dose (ED_{50}) was determined using Microsoft Excel.

RESULTS AND DISCUSSION

Antihyperlipidemic activity ethanol extract of *P. canescens* was done using albino rats of the Wistar strain. Before treatment, each test animal had its levels of cholesterol, LDL, triglycerides, and HDL values measured. Table 1 shows that all test animals had cholesterol levels in the range of 45.92 ± 4.45 to 68.26 ± 15.64 mg/dL and were still within normal limits (37–85 mg/dL) (Giknis and Clifford, 2008). Induction of a high-fat diet and PTU (propylthiouracil) food was given orally once a day for 14 days in all test animals except the normal group. On day 15, total cholesterol levels were measured again. The results obtained from the examination showed an increase in total cholesterol levels in rats induced by a high-fat diet and PTU, with a range from 45.92 ± 4.45 - 68.26 ± 15.64 mg/dL to 157.35 ± 11.02 - 173.75 ± 4.53 mg/dL (Table 1). These data indicate that after induction, the rats were already in a state of cholesterol above normal (>85 mg/dL). Rats are hypercholesterolemic if they have cholesterol levels above 155 mg/dL. It can be concluded that all groups of test animals were in a state of hypercholesterolemia. Induction of PTU can inhibit thyroid cells in rats, so thyroid hormone production was inhibited and causes rats to experience hyperthyroidism which affects lipoprotein metabolism, increasing cholesterol levels (Singh *et al*., 2020).

Furthermore, the extract was given at various doses for 14 days, and on the 30th day, cholesterol levels were tested again. Table 1 shows that the most significant decrease in the average total cholesterol level was evident in the positive control group, from 173.75 ± 4.53 to 69.12 ± 4.47 mg/dL. The treatment in the positive control group was given a simvastatin solution compared to the extract suspension. Simvastatin works by inhibiting HMG-CoA reductase as catalyzing cholesterol biosynthesis. Simvastatin is the drug of choice for lowering blood lipid levels. Treatment group III also significantly decreased the average total cholesterol level. Statistical analysis tests showed that all treatments could reduce total cholesterol levels significantly ($p < 0.05$); however, the magnitude of the decrease is low compared to the positive control groups treatment simvastatin, as the group showed no significant difference ($p > 0.05$) with the normal group. The extracts can significantly reduce total cholesterol levels, indicating that *P. canescens* leaves contain secondary metabolites that can reduce hyperlipidemia levels.

The average decrease in total cholesterol levels was determined by the percentage value of the reduction of total cholesterol levels to determine the ED_{50} value (Harini and Astirin, 2010). The ED_{50} value was determined based on a regression linear equation between the percent of lowering total cholesterol and dose. An effective dose of 50 is required to achieve a therapeutic effect of 50% in experimental animals. The ED_{50} value decreased total cholesterol by 334.07 mg/kg BW (Table 2).

Table 1: Total cholesterol of animals test before induction, after induction and after treatment

Groups	Choleterol level (mg/dL) Means ±SD		
	After aclimatitation (day -0)	After Induction (day-15)	After treatment (day-30)
Normal	68.26 ± 15.64	70.89 ± 14.45^{a}	72.29 ± 13.54^{a}
Control (-)	60.56 ± 2.25	162.37 ± 7.11^{b}	161.85 ± 4.03^{b}
Control (+)	63.21 ± 4.93	173.75 ± 4.53^{c}	69.12 ± 4.47^{a}
Dose 100 mg/kgBW	45.92 ± 4.45	170.74 ± 8.94^{c}	159.59 ± 8.80^{d}
Dose 200 mg/kgBW	50.71 ± 10.00	157.35 ± 11.02^{d}	138.24 ± 6.04^{e}
Dose 400 mg/kgBW	57.78 ± 5.26	169.87 ± 6.98^{c}	97.21 ± 8.28^{f}

The data were presented as mean ± SD; n=3; Number followed by the same superscript indicated a non-significantly difference according to the Duncan New Multiple Range Test (DNMRT) at 0.05

Table 2: Percentage decrease in total cholesterol

Groups	Decrease in total cholesterol (%)	ED_{50} (mg/kg BW)
Dose 100 mg/kgBW	8.90	334.07
Dose 200 mg/kgBW	17.80	
Dose 400 mg/kgBW	64.82	

Table 4: Percentage decrease in LDL

Groups	Decrease in LDL (%)	ED_{50} (mg/kgBW)
Dose 100 mg/kgBW	15.21	431.11
Dose 200 mg/kgBW	38.79	
Dose 400 mg/kgBW	44.31	

Administration of PTU solutions and high-fat diet foods also increases LDL levels significantly. Normal LDL levels in rats are 7 to 27.2 mg/dL (Giknis and Clifford, 2008). Table 3 shows the average increase in LDL values to be within the range of 33.11 ± 1.86 mg/dL - 36.07 ± 0.20 mg/dL (Table 3). The treatment was given for 14 days, and then the LDL value of the test animals was measured again.

After induction, the control and treatment groups showed a significant increase in LDL levels ($p > 0.05$) compared to the normal group (Table 3). LDL levels after the administration of simvastatin were significantly reduced ($p < 0.05$). Simvastatin can reduce the amount of LDL and inhibit cholesterol biosynthesis in the liver (Peter *et al*., 2019). In the positive control group, the administration of *P. canescens* leaf ethanol extract at a dose of 400 mg/kgBw also showed significant results suggesting that it could reduce LDL. All treatment groups could reduce LDL significantly ($p < 0.05$), although the magnitude of the decrease did not exceed the positive control group given simvastatin. The results indicate that the ED_{50} LDL of the ethanol extract of sungkai leaves was 431.11 mg/kg BW (Table 4).

Normal levels of triglycerides in rats range from 20-114 mg/dL. The animal test group, after being induced, showed a significant increase ($p < 0.05$) in triglyceride levels. Only a 1% Na CMC solution was given in the normal group. The increase in triglyceride levels was caused by the provision of foods containing high fat, such as duck egg yolk, resulting in fat accumulation in the blood of the test animals. Giving PTU also raises the rate of lipid catabolism in the body (Yu *et al*., 2019). The simvastatin treatment given to the positive control group revealed a decrease in triglyceride levels. Giving ethanol extract of sungkai leaf bark for all treatment doses of 100, 200, and 400 mg/kgBW can also reduce triglyceride levels. The statistical analysis showed that the positive control group and all treatments experienced significantly reduced triglyceride ($p < 0.05$). Furthermore, the percent value of the decrease in triglyceride levels was calculated (Table 5). The ED_{50} was determined to base on the linear regression, and obtained the ED_{50} of reduction in triglycerides was 257.48 mg/kgBW (Table 6).

The measurement of HDL levels was also carried out in this study. HDL is a protective lipoprotein that reduces the risk of coronary heart disease (Kosmas *et al*., 2018). Its protective effect is due to the transport of cholesterol from the periphery; it has to be metabolized in the liver and inhibits oxidative modification of LDL via paraoxonase,

Table 3: Analysis of LDL levels before and after induction and after treatment

Groups	LDL Level (mg/dL) Means ±SD		
	After aclimatitation (day -0)	After Induction (day-15)	After treatment (day-30)
Normal	9.26 ± 1.36	12.65 ± 2.48^{a}	10.20 ± 0.88^{a}
Control (-)	11.39 ± 1.49	34.35 ± 1.45^{b}	34.31 ± 2.42^{b}
Control (+)	9.35 ± 0.28	35.02 ± 2.53^{b}	17.21 ± 2.71^{c}
Dose 100 mg/kgBW	9.18 ± 1.72	33.11 ± 1.86^{b}	29.46 ± 2.62^{d}
Dose 200 mg/kgBW	10.81 ± 2.67	36.07 ± 0.20^{b}	26.25 ± 1.66^{e}
Dose 400 mg/kgBW	8.82 ± 0.47	34.30 ± 0.33^{b}	23.01 ± 1.17^{f}

The data were presented as mean ± SD; n=3; Number followed by the same superscript indicated a non-significantly difference according to the Duncan New Multiple Range Test (DNMRT) at 0.05

Table 5: Analysis of triglyseride levels before and after induction and after treatment

Groups	Trigliserida Level (mg/dL) Means ± SD		
	After aclimatitation (day -0)	**After Induction (day-15)**	**After treatment (day-30)**
Normal	113.36 ± 9.56	117.33 ± 27.37[a]	99.63 ± 7.14[f]
Control (-)	116.47 ± 11.03	149.48 ± 30.93[b]	147.66 ± 30.66[b]
Control (+)	85.84 ± 25.00	167.78 ± 19.23[c]	105.00 ± 3.14[g]
Dose 100 mg/kgBW	94.65 ± 14.02	151.07 ± 4.87[b]	139.57 ± 3.95[h]
Dose 200 mg/kgBW	107.22 ± 8.49	179.14 ± 1.75[d]	143.37 ± 6.96i
Dose 400 mg/kgBW	107.58 ± 5.25	161.81 ± 7.64[e]	124.39 ± 7.66[j]

The data were presented as mean ± SD; n=3; Number followed by the same superscript indicated a non- significantly difference according to the Duncan New Multiple Range Test (DNMRT) at 0.05

Table 6: Percentage decrease trygliceride of animals test

Groups	Decrease in triglyceride (%)	ED_{50} (mg/kgBW)
Dose 100 mg/kgBW	20.38	257.48
Dose 200 mg/kgBW	49.76	
Dose 400 mg/kgBW	69.00	

an antioxidant protein associated with HDL. Normal HDL in rats is 35 to 85 mg/dL (Giknis and Clifford, 2008). After acclimatization, HDL levels were in the normal range (Table 7) with an average value of 37.69 ± 6.44 - 40.27 ± 11.50 mg/dL.

Administration of PTU and a high-fat diet led to a significant decrease in HDL levels ($p<0.05$) compared after acclimatization. Low levels of HDL can increase the risk of coronary heart disease (Landmesser and Hazen, 2018). The average decrease in HDL levels after induction had the lowest average value of 27.50 ± 1.36 mg/dL. After treatment, it was seen that there was an increase in HDL values in the group of test animals that were treated with extracts for all treatment doses. Administration of a simvastatin solution also showed an increase in HDL levels. The statistical analysis tests showed that the administration of *P. canescens* leaf ethanol extract could significantly increase HDL levels in the blood ($p<0.05$). Furthermore, the ED_{50} value for HDL levels was calculated and obtained ED_{50} HDL was 162.12 mg/kgBW (Table 8).

The ethanol extract of *P. canescens* leaves can reduce total cholesterol, triglycerides, and LDL and significantly increase HDL levels. The decreasing levels are greatest in dose III, 400 mg/kgBW. *P. canescens* leaves on the

Tabel 8: Percentage increased of HDL levels

Groups	Increase in HDL (%)	ED_{50} (mg/kgBW)
Dose 100 mg/kgBW	30.97	162.12
Dose 200 mg/kgBW	71.05	
Dose 400 mg/kgBW	76.86	

Table 7: Analysis of HDL levels before and after induction and after treatment

Groups	HDL level (mg/dL) Means ±SD		
	After aclimatitation (day -0)	**After Induction (day-15)**	**After treatment (day-30)**
Normal	40.27 ± 11.50	35.82 ± 4.84[a]	33.58 ± 3.46[a]
Control (-)	37.69 ± 6.44	27.50 ± 11.36[b]	65.31 ± 67.38[e]
Controll (+)	39.17 ± 2.04	27.64 ± 1.84[b]	38.90 ± 4.01[d]
Dose 100 mg/kgBW	38.97 ± 2.92	34.10 ± 3.75[a]	49.66 ± 7.51[c]
Dose 200 mg/kgBW	39.48 ± 4.22	33.64 ± 2.63[a]	41.86 ± 2.37[d]
Dose 400 mg/kgBW	38.46 ± 1.00	32.58 ± 1.15[a]	40.23 ± 1.55[d]

The data were presented as mean ± SD; n=3; Number followed by the same superscript indicated a non-significantly difference according to the Duncan New Multiple Range Test (DNMRT) at 0.05

Table 9: Body weight of rats before and after induction and after extract treatment

Groups	Before induction (g)	After induction (g)	After treatment (g)
Normal	187.33 ± 2.52[a]	204.67 ± 6.81[d]	210.67 ± 7.37[e]
Control (-)	199.33 ± 4.04[b]	215.33 ± 5.51[e]	226.67 ± 9.07[g]
Controll (+)	182.00 ± 5.57[c]	191.33 ± 8.14[f]	184.00 ± 7.21[c]
Dose 100 mg/kgBW	187.67 ± 7.77[a]	193.33± 11.72[f]	185.67 ± 6.03[c]
Dose 200 mg/kgBW	183.67 ± 13.87[c]	199.67 ± 11.02[b]	191.33 ± 8.08[f]
Dose 400 mg/kgBW	198.00 ± 13.53[b]	206.33 ± 13.05[d]	200.33 ± 4.04[b]

The data were presented as mean ± SD; n=3; Number followed by the same superscript indicated a non-significantly difference according to the Duncan New Multiple Range Test (DNMRT) at 0.05

phytochemical test showed that the extract contained flavonoid, steroid, triterpenoid, and phenolic compounds. The leaves of *P. canescens* have been reported to contain a compound of betulonic acid (Muharni *et al*., 2021). Flavonoids can reduce total cholesterol levels by reducing the activity of the HMG-CoA reductase enzyme or increasing bile acid excretion, decreasing the activity of the Acyl-CoA cholesterol acyltransferase enzyme and potentially reducing cholesterol absorption in the gastrointestinal tract. Flavonoids are natural antioxidants that can affect cholesterol and LDL metabolism. Additionally, flavonoids can increase the ability of LDL to bind to its receptors to decrease levels of LDL (Ciumarnean *et al*., 2020). The mechanism flavonoids employ to lower triglyceride levels is inhibiting the accumulation of free fatty acids in the liver and stimulating thermogenesis by increasing fat burning during resting conditions. The decrease in triglycerides was caused by flavonoids being able to inhibit the absorption of exogenous fat from a diet high in cholesterol and fat (Wang *et al*., 2019). According to Medina-Vera *et al.* (2021), antioxidant compounds can increase HDL levels. Phenolic compounds have antioxidant activity to reduce LDL and total cholesterol levels; additionally, they can reduce the cholesterol esterification process so that cholesterol ester and triglyceride levels decrease in the blood. The compound sitosterol glycosides work by inhibiting cholesterol absorption of cholesterol in the gastrointestinal tract. *P. canescens* leaves also contain steroid and triterpenoid compounds. Steroids can reduce cholesterol absorption in the gastrointestinal tract and increase its excretion in bile. Steroids have a structure similar to cholesterol; therefore, steroids can partially replace the role of cholesterol in the absorption of cholesterol called mixed micelles. This causes cholesterol absorption in the intestine to decrease so that the formation of very-low density lipoproteins (VLDL) will be inhibited, and the formation of chylomicrons will be disrupted (Packard *et al*., 2020).

Data in Table 9 showed a significant difference ($p<0.05$) in the increase in body weight of the test animals after induction with PTU and high-fat diet food. After being given simvastatin treatment in the positive control group, the extract administration in treatment groups I, II, and III showed a significant reduction in body weight. The statistical analysis also showed a significant difference in body weight after induction and treatment ($p<0.05$). This indicates that the content of flavonoids, steroids, and phenolics in the ethanol extract of P. *canescens* causes a decrease in the body weight of the test animals

CONCLUSION

The ethanol extracts of *P. canescens* leaves had an antihyperlipidemic activity with reduced total cholesterol, triglyceride, LDL levels, and increased HDL levels in male rats with effective doses (ED_{50}) at 162.12 mg/kg BW. *P. canescens* can be used in hyperlipidemia treatment.

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Conflicts of interest

There is no conflict of interest in this work.

REFERENCES

Aberare OL, Okuonghae P, Mukoro N, Dirisu JO, Osazuwa F, Odigie E and Omoregie (2011). Triglycerides, total cholesterol, high density lipoprotein cholesterol and low density lipoprotein cholesterol in rats exposed to premium motor spirit fumes. *N. Am. J. Med. Sci.,* 3(6): 277–280.

Aladaileh SH, Saghir SAM, Murugesu K, Sadikun A, Ahmad A, Kaur G, Mahmoud AM and Murugaiyah V (2019). Antihyperlipidemic and antioxidant effects of *Averrhoa Carambola* extract in high-fat diet-fed rats. *Biomedicines*, 7(3): 72.

Alexandre J, Carmo H, Carvalho F and Silva JP (2020). Synthetic cannabinoids and their impact on neurodevelopmental processes. *Addict. Biol*., 25(2): e12824.

AL-Ishaq RK, Abotaleb M, Kubatka P, Kajo K and Büsselberg D (2019). Flavonoids and their anti-diabetic effects: Cellular mechanisms and effects to improve blood sugar levels. *Biomoecules*, 9(9): 430-465.

Cao NT, Nguyen NA, Park CM, Cha GS, Park KD and Yun CH (2021). A novel statin compound from monacolin J produced using CYP102A1-catalyzed regioselective C-hydroxylation. *Pharmaceuticals,* 14(10): 981-995.

Ciumarnean L, Milaciu MV, Runcan O,Vesa CC Andreea LRAL, Negrean V, Perne MG, Donca VI, Alexescu TG, Para L and Dogar, G (2020). The effects of flavonoids in cardiovascular diseases. *Molecules*, 25(18): 4320.

Demján V, Kiss T, Siska A, Márton RSMR, Sarkozy M, Imre FI, Dezso CD and Csont T (2020). Effect of *Stellaria media* tea on lipid profile in rats. *J. Evidence-Based Complementary Altern. Med.,* 2020: Article ID 5109328: 1-7.

Giknis ML and Clifford CB (2008). Clinical laboratory parameters for Crl: Wl (Han). Charles River Laboratories International, Canada, pp 1-17.

Harini M and Astirin OP (2010). Blood cholesterol levels of hypercholesterolemic rat (*Rattus norvegicus*) after VCO treatment. *Bioscience*, 1(2): 53-58.

Hidayat S, Zuhud EAM, Widyatmoko D and Bahruni (2021). The commercial potential of forest trees as medicinal and health ingredients, *Biodiversitas*, 22(7): 2795-2804.

Kopylov AT, Malsagova KA, Stepanov AA and Kaysheva AL (2021). Diversity of plant sterols metabolism: The impact on human health, sport, and accumulation of contaminating sterols. *Nutrients*, 13(5): 1623-1653.

Kosmas CE, Martinez I, Sourlas A, Bouza KV, Campos FN, Torres V, Montan PD and Guzman E (2018). High-density lipoprotein (HDL) functionality and its relevance to atherosclerotic cardiovascular disease. *Drugs in Context*, 7: 212525.

Landmesser U and Hazen S (2018). HDL-cholesterol, genetics, and coronary artery disease: the myth of the good cholesterol. *Eur. Heart. J.*, 39(23): 2179-2182.

Medina-Vera I, Gomez-de-Regil L, Gutierrez-Solis AL, Lugo R, Guevara-Cruz M, Pedraza-Chaverri J and Avila-Nava, A (2021). Dietary strategies by foods with antioxidant effect on nutritional management of dyslipidemias: A systematic review. *Antioxidants*, 10(2): 225-234.

Muharni M, Ferlinahayati F, Yohandini H and Riyanti, F and Pakpahan NAP (2021). The anti-cholesterol activity of betulinic acid and stigmasterol isolated from the leaves of sungkai (*Paronema canescens* Jack). *Int. J. App. Pharm*., 13(2): 198-203.

Nelson RH (2013). Hyperlipidemia as a risk factor for cardiovascular disease. *Prim. Care Clinic in Office Practice*, 40(1):195–211.

Packard CJ, Boren J and Taskinen MR (2020). Causes and consequences of hypertriglyceridemia. *Front. Endocrinol*., 11: 252-267.

Peter PTM, Maciej Banach MD (2019). Statins: Then and now. *Methodist Debakey Cardiovasc. J*., 15(1): 23–31.

Prado ASL, Shen Y, Ardoin R, Osorio LF, Cardona J, Xu Z and Prinyawiwatkul W (2019). Effects of different solvents on total phenolic and total anthocyanin contents of *Clitoria ternatea* L. petal and their anti-cholesterol oxidation capabilities. *Int. J. Food Sci. Tech*., 54(2): 424-431.

Salazar-Gomez A, Sanchez-Chavez AC, Zepeda-Vallejo G, Chamorro-Cevallos G, Garduno-Siciliano L and Vargas-Diaz E (2019). Hypolipidemic effect of *Trixis angustifolia* aqueous extract on triton WR-1339- and high-fat diet-induced hyperlipidemic mice. *Nat. Prod. Com.*, 14(7): 1–6.

Sheu MJ, Hsieh YY, Hsiu LC, Chang CCD and Hsi WC (2013). Antihyperlipidemic and antioxidant effects of C-phycocyanin in golden syrian hamsters fed with a hypercholesterolemic diet. *J. Tradit. Complement Med.,* 3(1): 41–47.

Siahaan JM, Illyas S, Lindarto D and Nainggola M (2020). The effect of ethanol and ethyl acetate fraction of chayote fruit (*Sechium edule* Jacq. Swartz) on the oxidative stress and insulin resistance of male white rat model type 2 diabetes mellitus, *Maced. J. Med. Sci*., 8(A): 962-969.

Singh S, Panda V, Sudhamani S and Dande, P (2020). Protective effect of a polyherbal bioactive fraction in propylthiouracil-induced thyroid toxicity in ratsby modulation of the hypothalamic–pituitary–thyroid and hypothalamic–pituitary–adrenal axes. *Toxico. Rep.*, 7(1): 730-742.

Sitepu N (2020). *In vitro* test of antibacterial ethanol extract, *n*-hexane fraction and ethyl acetate fraction of sungkai leaf (*Peronema canescens*) against *Salmonella typhi*. *Asian J. Pharm. Res. Dev*., 8(3): 57-60.

Thompson PD, Panza G, Zaleski A and Taylor, B (2016). Statin-associated side effects. *J. Am .Coll. Cardiol*., 67: 2395-2410.

Umoren EB, Ekpenyong JF, Oyama OE and Obembe AO (2020). The hypolipidemic effect of aqueous extract of *Hibiscus sabdariffa* on paracetamol-induced hepatotoxicity in albino Wistar rats. *Eur. J. Med. Plants*., 31(7): 54-60.

Wang M, Xiao FL, Mao YJ, Ying LL, Zhou B and Li Y (2019). Quercetin decreases the triglyceride content through the PPAR signalling pathway in primary hepatocytes of broiler chickens, *Biotechnol. Biotechnol. Equip*., 33(1): 1000-1010.

Wiart C (2006). Medicinal plants of Asia and the pacific. Boca Raton: CRC Press Taylor & Francis Group. United States of America. pp 336.

Yani AP and Putranto MH (2014). Examination of the sungkai's young leaf extract (*Peronema canescens*) as an antipiretic, immunity, antiplasmodium and teratogenity in mice (*Mus muculus*). *Int. J. Sci. Eng.*, 7(1): 30-34.

Yu Z, Mao C, Fu X and Ma M (2019). High density lipoprotein from egg yolk (EYHDL) improves dyslipidemia by mediating fatty acids metabolism in high fat diet-induced obese mice. *Food Sci. of Anim. Resour.*, 39(2): 179–196.