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Antihypercholesterolemic Effect of Combination of *Guazuma ulmifolia* Lamk. Leaves and *Curcuma xanthorrhiza* Roxb. Rhizomes Extract in Wistar Rats

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Abstract: *Guazuma ulmifolia* Lamk. (mutamba) and *Curcuma xanthorrhiza* Roxb. (java turmeric) has been used traditionally as slimming agent and for treating various diseases including hypercholesterolemia. In this study, the effect of aqueous extract of mutamba leaves in combination with ethanol extract of java turmeric has been determined on lipid blood level of Wistar rats compared to each extract alone in hyperlipidemic induced rats. Thirty male rats weighing 180-200 g were divided into six groups receiving mutamba extract, java turmeric extract, simvastatin as a reference of antihyperlipidemic drug, combination of mutamba and java turmeric at two different doses and one control group. The extract was given daily for 14 days at the same time as the administration of propylthiouracil and food high in cholesterol content to induce hyperlipidemia. The serum levels of total cholesterol, triglyceride, HDL and LDL were measured after 3, 7 and 14 days of treatment. The result were analyzed statistically using ANOVA. The results indicated that combination of aqueous extract of mutamba leaves at a dose of 25 mg kg^{-1} b.wt. and ethanol extract of Java turmeric rhizome at a dose of 12.5 mg kg^{-1} b.wt. decreased total cholesterol and LDL level significantly compared to control group ($p = 0.004$) after 7 days of treatments. Aqueous extract of mutamba leaves at a dose of 50 mg kg^{-1} b.wt. did not show any significant effect while ethanol extract of java turmeric rhizome at a dose of 25 mg kg^{-1} b.wt. decreased only LDL level significantly.

Key words: *Guazuma ulmifolia*, *Curcuma xanthorrhiza*, antihyperlipidemic, mutamba, java turmeric

INTRODUCTION

Cardiovascular diseases especially coronary heart disease is a very common disease found in the world and one of a main disease that cause death. One of factors that can stimulate cardiovascular disorders is dyslipidemic. Dyslipidemia is lipid metabolism failure characterized by an elevated total cholesterol, low density lipoprotein (LDL) cholesterol, or triglycerides; a low high density lipoprotein (HDL) cholesterol; or a combination of these abnormalities (Dipiro *et al*., 2008).

Indonesian medicinal plant java turmeric, the rhizome of *Curcuma xanthorrhiza*, was used traditionally for treating various diseases (Kasahara and Hemmi, 1995). Wientarsih *et al*. (2002) proved that java turmeric lowered cholesterol concentration, HDL and LDL by increasing fat excretion via the bile into feces and HMGCo-A reductase inhibition in rabbit. Their study also proved the decreased of triglyceride concentration. *Curcuma xanthorrhiza* extract showed to inhibit human cytochrome P450 enzyme activities especially CYP2D6 with IC 50 value of 215.3±71.6 μg mL^{-1} (Hanapi *et al*., 2010). An other study showed that curcumin as the active compounds of *Curcuma xanthorrhiza* inhibited the activity of cytochrome P450 on toad liver (Abdel-Latif and Sadek, 1999).

Curcuminoids are the main component in *Curcuma* species especially *Curcuma longa* (turmeric) and *Curcuma xanthorrhiza* (java turmeric), the curcuminoid is responsible for their major biological effects. Curcumin, predominantly contained in curcuminoids, has a wide range of pharmacological effects including reduction of blood cholesterol and glucose levels and other medicinal effects (Kuroda *et al*., 2005; Maheshwari *et al*., 2006; Itokawa *et al*., 2008). Curcumin showed to have beneficial effects in preventing hyperglycemia induced by streptozotocin. In addition to hyperglycemia, other parameters induced by streptozotocin were HbA1c (glycosylated haemoglobin in red blood cells), AST and ALT. Curcumin can change the parameters to near normal value (Hussein and Abu-Zinadah, 2010). Another study that was consistent with this study had shown that curcumin reduced gluconeogenesis in hepatocytes and showed antioxidant activity *in vitro* (Sivabalan and Anuradha, 2010).

In addition to the above effects, curcumin also found to be active for helminth infection. Curcumin at a dose of

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20 mg kg^{-1} b.wt. showed activity against *Schistosoma mansoni* by reducing the development of *Schistosoma mansoni* cercariae into worm form in mice, the number of *Schistosoma mansoni* worm was reduced in mice treated with curcumin compared to control untreated mice (El-Sherbiny *et al*., 2006).

Our previous animal study showed that curcuminoid contained in turmeric and in combination with S-methyl cysteine reduced total cholesterol in serum and liver. The mechanism of action of curcuminoid alone and in combination with S-methyl cysteine in lowering cholesterol level was inhibiting cholesterol absorption and biosynthesis (Hasimun *et al*., 2011). A study by Sovia *et al*. (2011) also revealed that curcuminoid decreased blood glucose level by repairing the damage pancreatic β-cells in alloxan-induced diabetic mice. Turmeric extract and in combination with garlic extract has been proven in rats as antihyperlipidemic and antidiabetic agent (Sukandar *et al*., 2010a) and the effect of this combination has been proven clinically (Sukandar *et al*., 2010b).

Another researcher studied the effect of java turmeric in rats given a cholesterol-free diet, java turmeric decreased the concentrations of serum triglycerides and phospholipids and liver cholesterol and increased serum HDL-cholesterol and apo A-I. Java turmeric contains the active substance other than curcuminoids that can alter fat metabolism and lipoproteins (Yasni *et al*., 1993). Yasni *et al*. (1994) also proved that α-curcumene is one of the active substance which has the effect of lowering triglycerides in mice by suppressing the synthesis of fatty acids. Sukisamrarn *et al*. (1994) found phenolic diarylheptanoids from java turmeric rhizome.

The leaves of *Guazuma ulmifolia* Lamk. (mutamba) has been used in Indonesian traditional medicine for treating obesity, diarrhea, cough and abdominal pain (Kasahara and Hemmi, 1995). Pizana *et al*. (2010) reported that mutamba had an antifungal activity, the aqueous extract inhibited the mycelia growth of *Fusarium oxysporum* f. sp. *gadioli* (Massey). Aqueous extract of mutamba showed antidiabetic effect by stimulating uptake of glucose in insulin sensitive and resistant adipocytes (Alonso-Castro and Salazar-Oliva, 2008). Bark of mutamba contained of procyanidin B2, B5, C1 and epicatechin and the compounds used as chemical marker for quality control analysis of mutamba were procyanidin B2 and epicatechin (Lopes *et al*., 2012). Research result of Magos *et al*. (2008) showed that procyanidins fraction of mutamba produced an intense and long lasting antihypertension and vasorelaxing effect in rats.

Our previous research showed that mutamba water extract at a dose of 50 mg kg^{-1} b.wt. lowered the total cholesterol and LDL-cholesterol significantly compared to control group (Sukandar, 2009).

Both java turmeric and mutamba had activity in lowering blood cholesterol level therefore, the both extracts were combined in order to increase antihyperlipidemic effect. In this study, antihyperlipidemic effect of each extract and its combination has been tested in hyperlipidemic endogenous and exogenous-induced Wistar rats.

MATERIALS AND METHODS

Animal: Male Wistar rats aged 12 weeks, weighing 180- 200 g, were kept under usual management conditions in conventional animal house of School of Pharmacy, Bandung Institute of Technology. Rats were fed with standard laboratory diet and water *ad libitum*.

Plants material: Water extract of mutamba leaves, ethanol extract of java turmeric rhizome, simvastatin, tragacanth, propylthiouracil, ethanol, aquadest, animal food high in fat contain, reagents of cholesterol, HDL, LDL and triglyceride.

Apparatus: Rat balance, oral gavage for rat, centrifuge, spectrophotometer (Clinicon 4010 Mannheim GMBH), freeze drier, rotary vacuum evaporator.

Experimental procedure: This study was conducted according to Guide for the Care and Use of Laboratory Animals, Institute for Laboratory Animal Research, National Research Council Washington, DC: The National Academies Press, 1996. This study was done from September 2008 to July 2009 at School of Pharmacy, Bandung Institute of Technology.

Preparation of water extract of jati belanda leaves: Dried crude drugs of jati belanda were boiled for 30 min and filtered. Extract was then dried using freeze drier until concentrated extract of 8.42% achieved.

Preparation of ethanol extract of temulawak rhizome: Dried crude drugs of temulawak rhizome were macerated for 4×24 h. Extracts were collected and evaporated using rotary vacuum evaporator until concentrated extract of 26.15% achieved.

Preparation of material for hypercholesterolemia induction: Cholesterol of Wistar rats was induced exogenously using cholesterol-rich food and endogenously using 0.01% propylthiouracil.

Antihyperlipidemic test of combination of water extract of mutamba leaves and ethanol extract of java turmeric rhizome: Animals were divided into 6 groups, each group consist of 5 rats. They were control group received vehicle, groups treated with simvastatin 3.6 mg kg^{-1} b.wt., one group treated with mutamba extract at a dose of 50 mg kg^{-1} b.wt., one group treated with java turmeric at a dose of 25 mg kg^{-1} b.wt. and two groups treated with combination of mutamba 50 mg kg^{-1} b.wt.-java turmeric 25 and b.wt.-12,5 mg kg^{-1} b.wt., respectively. Induction process of hyperlipidemia was at the same time with the administration of test substance. Blood lipid level were measured on day 3, 7 and 14 after treatment.

Measurement of blood lipid concentration: Measurements were done using enzymatic method with specific reagent for total cholesterol, HDL and triglyceride. Adsorptions were then measured using UV spectrophotometer at the wavelength 546 nm. While LDL concentration was calculated using formula LDL = total cholesterol-HDL-(triglyceride/5).

Statistical analysis: The result were analyzed statistically using one-way ANOVA. Values of $p<0.05$ were taken as significant.

RESULTS AND DISCUSSION

Phytochemical screening showed that mutamba leaves contain alkaloid, flavonoid, tannin and steroid/triterpenoid while java turmeric rhizomes contain quinone, flavonoid and steroid/triterpenoid. Dried mutamba leaves have water contents of 7%, total ash content of 12.49% and water dissolved extract content of 19.35%. Dried java turmeric rhizome have water contents of 6%, total ash content of 5.34% and ethanol dissolved extract content of 6.7%. Aqueous extract of mutamba has water content of 8% and of java turmeric of 2.5 %.

Mutamba aqueous extract at a dose of 50 mg kg^{-1} b.wt. and java turmeric extract at a dose of 25 mg kg^{-1} b.wt. lowered cholesterol level by 27.28±25.33 and 57.72±45.31 mg dL^{-1}, respectively but not significant statistically while combination of both extracts at half dose each could lower cholesterol level significantly. Combination of aqueous extract of mutamba at a dose of 25 mg kg^{-1} b.wt. and ethanol extract of java turmeric at a dose of 12.5 mg kg^{-1} b.wt. (combination 1, combination of half dose each) were able to decrease total cholesterol significantly on day-7 after treatment ($p = 0.006$) as well as combination the extract of 50 and 25 mg kg^{-1} b.wt. (combination 2, combination of 1 dose each) ($p = 0.030$). The decrease of total cholesterol at combination 1 was bigger than that of combination 2 i.e., 89.28±37.54 mg dL^{-1} vs. 66.46±41.03 mg dL^{-1}. It was shown that antihyperlipidemic effect of combination 1 was better than that of combination 2. This observation can be seen in Table 1. The decrease of cholesterol level by mutamba 50 mg kg^{-1} b.wt. in this study differed from the previous study showing that mutamba with dose of 50 mg kg^{-1} b.wt. lowered total cholesterol and LDL level in rats significantly (Sukandar, 2009). The different effect may be caused by different harvest season of mutamba which correlated with the content of active components.

Active substance that lowered cholesterol level from java turmeric is well known namely curcumin (Kuroda *et al*., 2005; Maheshwari *et al*., 2006; Itokawa *et al*., 2008; Wientarsih *et al*., 2002; Hasimun *et al*., 2011) and active substance from mutamba is procyamidin (Magos *et al*., 2008. Beside as antihyperlipidemia, both curcumin and mutamba showed also antidiabetic (Sovia *et al*., 2011; Sivabalan and Anuradha, 2010; Hussein and Abu-Zinadah, 2010; Alonso-Castro and Salazar-Oliva, 2008), so it can be used for treating both diseases at once. In the previous clinical study, combination of turmeric and garlic showed beneficial effect to treat patients who suffered from diabetes and hyperlipidemia simultaneously (Sukandar *et al*., 2010b).

Triglyceride and HDL level were not influenced significantly in all groups. Java turmeric, combination 1 and combination 2 decreased HDL level by 0.88±5.92 and 3.16±1.64, respectively after 14 days, but this change was not significant statistically. These results were in line with the research of Wientarsih *et al*. (2002) who found that java turmeric lowered cholesterol including HDL concentration. The data can be seen in Table 3.

Table 1: Decrease of total blood cholesterol concentration after treatment

	Total cholesterol					
Treated groups	Δ1 (mg dL^{-1})	p	Δ2 (mg dL^{-1})	p	Δ3 (mg dL^{-1})	p
Control	33.83±11.78	-	3.05±24.55	-	14.70±19.19	-
Simvastatin 3.6 mg kg^{-1} b.wt.	46.10±21.96	0.351	(55.46±22.89)*	0.013	29.02±24.42	0.371
M 50 mg kg^{-1} b.wt.	18.88±29.53	0.377	27.28±25.33	0.192	12.32±22.91	0.873
JT 25 mg kg^{-1} b.wt.	32.56±47.29	0.960	57.72±45.31	0.068	50.98±47.82	0.200
M 25 - JT 12.5 mg kg^{-1} b.wt.	83.58±49.05	0.091	(89.28±37.54)*	0.006	76.70±50.54	0.050
M50-JT 25 mg kg^{-1} b.wt.	70.12±45.83	0.171	(66.46±41.03)*	0.030	55.62±34.17	0.071

Δ1: Difference of total cholesterol concentration on day 3 after treatment, Δ2: Difference of total cholesterol on day 7 after treatment, Δ3: Difference of total cholesterol on day 14 after treatment, p: Significantly level compared to control, M: Mutamba, JT: Java turmeric, ( )*: Significantly different to control ($p<0.05$), (-): Show increasing of total cholesterol concentration

Table 2: Decrease of blood triglyceride concentration after treatment

	Triglyceride					
Treated groups	Δ1 (mg dL^{-1})	p	Δ2 (mg dL^{-1})	p	Δ3 (mg dL^{-1})	p
Control	8.40±52.28	-	-14.03±31.08	-	14.98±35.04	-
Simvastatin 3.6 mg kg^{-1} b.wt.	-4.24±17.62	0.624	-16.94±34.56	0.899	-20.34±15.69	0.081
M 50 mg kg^{-1} b.wt.	13.28±22.32	0.854	-13.24±40.82	0.976	-1.06±24.13	0.442
JT 25 mg kg^{-1} b.wt.	-3.38±16.18	0.644	-27.40±58.54	0.695	(-61.42±43.44)*	0.025
M 25-JT 12.5 mg kg^{-1} b.wt.	4.58±40.64	0.905	-10.70±52.96	0.915	-11.68±53.10	0.419
M50-JT 25 mg kg^{-1} b.wt.	16.10±19.66	0.792	-9.08±58.15	0.886	-3.85±52.70	0.574

Δ1: Difference of triglyceride concentration on day 3 after treatment, Δ2: Difference of triglyceride concentration on day 7 after treatment, Δ3: Difference of triglyceride concentration on day 14 after treatment, p: Significantly level compared to control, M: Mutamba, JT Java turmeric, ( )*: Significantly different to control (p<0.05), (-): Show increasing of triglyceride concentration

Table 3: Change of blood HDL concentration after treatment

	HDL					
Treated groups	Δ1 (mg dL^{-1})	p	Δ2 (mg dL^{-1})	p	Δ3 (mg dL^{-1})	p
Control	-4.18±10.33	-	-6.05±12.28	-	-2.38±5.49	-
Simvastatin 3.6 mg kg^{-1} b.wt.	3.80±10.50	0.292	-4.60±3.73	0.807	3.34±2.37	0.072
M 50 mg kg^{-1} b.wt.	8.60±8.36	0.079	2.92±9.67	0.259	7.12±8.19	0.089
JT 25 mg kg^{-1} b.wt.	2.70±2.99	0.194	-1.16±4.41	0.430	-0.94±2.97	0.629
M 25-JT 12.5 mg kg^{-1} b.wt.	-1.94±4.95	0.679	-2.22±6.84	0.569	-0.88±5.92	0.709
M50-JT 25 mg kg^{-1} b.wt.	-2.90±2.00	0.792	-3.04±1.12	0.596	-3.16±1.64	0.767

Δ1: Difference of lipid concentration on day 3 after treatment, Δ2: Difference of lipid concentration on day 7 after treatment, Δ3: Difference of lipid concentration on day 14 after treatment, p: Significantly level compared to control, M: Mutamba, JT: Java turmeric, ( )*: Significantly different to control (p<0.05), (-): Show decreasing of HDL concentration

Table 4: Decreasing of blood LDL concentration after treatment of 3, 7 and 14 days

	LDL					
Treated groups	Δ1 (mg dL^{-1})	p	Δ2 (mg dL^{-1})	p	Δ3 (mg dL^{-1})	p
Control	17.29±19.10	-	-19.89±19.60	-	-5.51±25.62	-
Simvastatin 3.6 mg kg^{-1} b.wt.	48.09±29,26	0.114	(48.51±24.57)*	0.003	30.75±28.20	0.087
M 50 mg kg^{-1} b.wt.	21.82±28.76	0.795	(29.85±16.36)*	0.004	16.65±20.11	0.188
JT 25 mg kg^{-1} b.wt.	35.94±49.39	0.503	(63.47±17.76)*	0.000	(62.32±52.83)*	0.045
M 25-JT 12.5 mg kg^{-1} b.wt.	(80.72±48.49)*	0,045	(89.2±34.74)*	0,001	(78.16±46.95)*	0.016
M 50-JT 25 mg kg^{-1} b.wt.	55.23±44.96	0.171	(48.83±8.25)*	0.001	(48.02±32.73)*	0.042

Δ1: Difference of lipid concentration on day 3 after treatment, Δ2: Difference of lipid concentration on day 7 after treatment, Δ3: Difference of lipid concentration on day 14 after treatment, p: Significantly level compared to control, M: Mutamba, JT: Java turmeric, ( )*: Significantly different to control (p<0.05), (-): Show increasing of LDL concentration

According to Yasni *et al.* (1994), java turmeric could lower triglyceride level in diabetic rat, this effect was also seen in this study at a dose of 25 mg kg^{-1} b.wt. after 14 days with the TG decrease of 61.42±43.44 mg dL^{-1} (p = 0.025). Combination 1 showed T G decrease o f 11.68±53. 10 mg dL^{-1} and combination 2 showed TG decrease of 3.85± 52.70, this results were not significantly different compared to control group, possibly it caused by a large standard deviation due to individual variation of rat, the data can be seen in Table 2.

Dominant effect of java turmeric-mutamba combination was the ability to lower LDL level. LDL level of rats which was given dose combination 1 showed the LDL decrease of 80.72±48.49 mg dL^{-1} on day-3, 89.2±34.74 mg dL^{-1} on day-7 and 78.16 ±46.95 mg dL^{-1} on day-14 with p value of 0.045, 0.001 and 0.016, respectively compared to control group (Table 4).

Combination 1 showed reduction of LDL level significantly different compared to mutamba leaves extract

Table 5: Significancy (p value) of extract combination compared to single extract effect

		Δ1		Δ2		Δ3	
		M50	JT25	M50	JT25	M50	JT25
Lipid	Group	(mg kg^{-1} b.wt.)					
Chol.	M25-JT 12.5	(0.035)*	0.133	(0.016)*	0.265	(0.032)*	0.432
	M 50-JT 25	0.069	0.238	0.107	0.757	(0.046)*	0.864
TG	M25-JT 12.5	0.686	0.695	0.934	0.649	0.695	0.144
	M 50-JT 25	0.849	0.146	0.903	0.654	0.918	0.115
HDL	M25-JT 12.5	0.052	0.111	0.361	0.778	0.115	0.984
	M 50-JT 25	0.057	0.058	0.209	0.383	0.055	0.182
LDL	M25-JT 12.5	(0.048)*	0.186	(0.009)*	0.179	(0.027)*	0.630
	M 50-JT 25	0.216	0.564	0.074	0.175	0.118	0.052

Δ1: Difference of lipid concentration on day 3 after treatment, Δ2: Difference of lipid concentration on day 7 after treatment, Δ3: Difference of lipid concentration on day 14 after treatment, M: Mutamba, JT: Java turmeric ( )*: Significantly different compared to single extract (p<0.05)

(p = 0.048 at day 3, p = 0.009 at day 7 and p = 0.027 at 2 (Table 5). Explanation of why the higher dose showed a lower effect, it may correlate with the constituents of the extract. Whole extract contains many compounds, the effect of active component at a higher dose may be

antagonized by other compounds that has an opposite effect and lead to reduce the antihypercholesterolemic effect.

Curcumin as active component of java turmeric inhibits cytochrome P450 (CYP2D6) in human liver (Hanapi *et al*., 2010), so that we can predict an interaction between curcumin and another drug that metabolized by this enzyme.

Combination of java turmeric and mutamba extract was not found in the literature, this combination demonstrated prospectively to be developed as a herbal medicine for hypercholesterolemia.

CONCLUSION

Combination of water extract of mutamba leaves at a dose of 25 mg kg^{-1} b.wt. and ethanol extract of java turmeric rhizome at a dose of 12.5 mg kg^{-1} b.wt. decreased total blood cholesterol level of male Wistar rat and decreased LDL level significantly compared to control group and to mutamba extract at a dose of 50 mg kg^{-1} b.wt. ($p<0.05$).

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