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Safety of Garlic (*Allium Sativum*) and Turmeric (*Curcuma domestica*) Extract in Comparison with Simvastatin on Improving Lipid Profile in Dyslipidemia Patients

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Dyslipidemia is the major cause of atherosclerosis. A number of drugs that inhibit cholesterol synthesis has indicated to control lipid profile. However, these lipid lowering drugs are not free of side effect. Therefore a substance that less toxic and yet effective would be beneficial. Here we compared the anticholesterol effect of combination of garlic and turmeric extract, a herbal product, with a standard lipid lowering drug, simvastatin. Thirty nine people were recruited and randomized into two groups, Garlic-Turmeric (G-T) group (n = 19) received three times two capsules of garlic-turmeric extract (2.4 g day^{-1}) and simvastatin group (n = 20) received placebo and 5 mg simvastatin to blind the subjects from knowing what drugs they get, for 14 weeks. Garlic-turmeric extract could improve lipid profile comparable with simvastatin (p = 0.366). There were no adverse event related to garlic-turmeric administration, even there was improvement in liver function at the end of the study. In conclusion garlic-turmeric extract could improve lipid profile comparable to simvastatin with no significant adverse event.

Key words: Garlic, turmeric, dyslipidemia, adverse events

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INTRODUCTION

Dyslipidemia is a metabolic disorder characterized by increased concentrations of total cholesterol, Low-density Lipoprotein (LDL) or triglyceride, and/or decreased High-density Lipoprotein (HDL) (Pollex *et al*., 2008). The combination of hypertriglyceridemia, low HDL, presence of small LDL is the profile of atherogenic dyslipidemia. Atherosclerosis is a potential risk factor for Coronary Heart Disease (CHD) and other Cardiovascular Disease (CVD) including cerebrovascular disease. Elevation of LDL level is correlated to the increase of CHD risk (Vinik, 2005; Kumar and Singh, 2010). As estimated by WHO, CVD accounts for 29% of all deaths worldwide and CHD is the major cause of death related to CVD (Kumar and Singh, 2010). Therefore, many pharmacological interventions has been developed to improve lipid profile, such as 3-hydroxy 3-methylglutaryl coenzyme-A (HMG-CoA) reductase inhibitors (statins), bile acid binding sequestrans, fibrates and nicotinic acid but none are free from side effects (Ashraf *et al*., 2005; Pollex *et al*., 2008).

Statins are the most widely used antidyslipidemia with the mechanism of action to inhibit HMG-CoA reductase in the cholesterol biosynthesis pathway. Generally, statins are well-tolerated although it was reported that about 10% of patients experience muscle aches and smaller proportion of patients experience elevated serum creatine kinase and transaminases. Other antidyslipidemia agents also associated with various adverse effects. Therefore, new strategies in improving lipid profile with fewer side effects is a goal of current lipid lowering agent research development (Pollex *et al*., 2008).

The use of herbal medicines is more and more recognized since it is believed that natural substances may have fewer adverse effects than synthetic drugs. Garlic and turmeric has been claimed among other herbals to have positive effects against cardiovascular diseases (Ashraf *et al*., 2005; Seo *et al*. 2008). Our previous animal study has also found that combination of S-methyl cystein and curcuminoid, components of garlic and turmeric, respectively, has synergistic effect on regulating cholesterol homeostasis (Hasimun *et al*., 2011). The efficacy and safety of garlic-turmeric combination as antidyslipidemia agent has also been evaluated in type-2 diabetes mellitus patients with optimum therapeutic dose at 2.4 g daily (Sukandar *et al*., 2010b). Therefore, in this clinical trial we evaluated the safety profile of garlic and turmeric combination at the dose of 2.4 g day^{-1} as compared to a standard lipid lowering drug, simvastatin.

MATERIALS AND METHODS

This is a double blind, parallel, randomized control trial conducted in 14 weeks. The study protocol was approved by Ethics Committee on Research in Human, Hasan Sadikin Hospital, Bandung, Indonesia. Written informed consent was obtained from each patient before any procedure was performed. This clinical study was conducted according to Good Clinical Practice Procedure and in accordance with precepts established by the Declaration of Helsinki in 1974.

Subjects: Study subjects were male or female dyslipidemia patients, aged more than 35 years old, with total cholesterol >200 mg dL^{-1} or cholesterol LDL >130 mg dL^{-1} or triglyceride >200 mg dL^{-1} after two-week dietary period and had no history of antihyperlipidemia drug treatment. Patients who met exclusion criteria were excluded, i.e., patients with liver failure or kidney failure or bleeding history, pregnant/breastfeeding women and patients, who is on steroid or contraception drug treatment. Patients' characteristic was described in Table 1.

Study drugs preparation: The garlic-turmeric (G-T) preparation was 400 mg capsule containing 200 mg of turmeric (*Curcuma domestica*) ethanolic extract and 200 mg of garlic (*Allium sativum*) aqueous extract. Standard drug was 10 mg simvastatin (produced by Indofarma, Pte. Ltd., Indonesia).

Study design: Dyslipidemia patients according to the inclusion criteria were assigned in a two-week run-in phase. During run-in phase they were regularly performing diet and exercise and not allowing to take any lipid lowering drugs. After run-in phase, patients who still had dyslipidemia based on the inclusion criteria were divided into two treatment groups, i.e., garlic-turmeric (G-T) group and simvastatin group. Both groups received treatment for 12 weeks. The G-T group received the garlic-turmeric capsules at the dose of 2.4 g day^{-1}, consisted of three capsules twice a day (morning and evening) after meal. The simvastatin group received simvastatin 5 mg day^{-1} in combination with placebo capsules as follows: 3 placebo capsules in the morning, one 5 mg simvastatin capsule and 2 placebo capsules in the evening. Both study and standard drugs were prepared in similar capsules to blind the subjects and the investigator. All patients were scheduled for evaluation visits every 2 weeks during 12 weeks of treatment. On each visit, we evaluated their lipid profiles and also other related parameters.

Examination parameters: On each visit, we will performed examinations on lipid and supporting parameters (Fig. 1). The parameters including body weight, blood pressure, lipid profile (total cholesterol, HDL, LDL and triglyceride), blood glucose (fasting blood glucose, 2 h-postprandial (2HPP) blood glucose), HbA1c and fasting insulin, ECG,

Table 1: Demographic and baseline data of the patients (n = 39)

Parameter	G-T (n=19) (X±SEM)	Simvastatin (n = 20) (X±SEM)	p-value
Demography			
Age (year)	55.37±2.010	55.90±1.640	0.838
Weight (kg)	61.58±2.010	65.05±3.590	0.406
BMI (kg m^{-2})	25.10±0.720	26.77±1.260	0.261
Blood pressure			
Systole (mmHg)	132.89±4.700	121.00±3.600	0.051
Diastole (mmHg)	84.74±2.460	77.75±2.000	0.033*
Lipid profile			
Total cholesterol (mg dL^{-1})	251.21±7.680	246.35±7.160	0.646
HDL (mg dL^{-1})	49.79±2.550	47.70±2.980	0.599
LDL (mg dL^{-1})	163.42±9.330	162.95±6.230	0.966
Triglyceride (mg dL^{-1})	190.37±28.91	187.95±24.39	0.949
Hematology			
Hemoglobin (g dL^{-1})	14.14±0.280	13.89±0.280	0.517
Leukocyte ($10^3/mm^3$)	8.147±5510	7.14±44100	0.16
Thrombocyte ($10^3/mm^3$)	287.95±16.37	278.10±9.310	0.605
Hematocrite (%)	42.21±0.800	40.7±0.7700	0.182
Blood glucose			
Fasting glucose (mg dL^{-1})	112.89±7.640	165.40±22.48	0.037*
2-hour PP glucose (mg dL^{-1})	163.47±15.74	245.60±35.83	0.046*
HbA1c (%)	6.75±0.410	9.20±0.760	0.008*
Insulin (pmol L^{-1})	59.85±10.66	64.21±9.250	0.758
Blood coagulation function			
PT (sec)	12.61±0.120	13.07±0.300	0.173
APTT (sec)	30.76±0.780	29.44±0.640	0.194
INR	0.95±0.010	0.98±0.030	0.332
Liver function			
AST (U L^{-1})	21.50±0.990	21.77±1.300	0.074
ALT (U L^{-1})	19.20±1.670	23.88±2.120	0.058
Kidney function			
Ureum (mg dL^{-1})	23.74±1.910	27.35±1.470	0.140
Creatinine (mg dL^{-1})	0.92±0.060	0.81±0.040	0.185

Baseline data was measured in run-in phase, except blood coagulation parameters, liver function, kidney function, insulin and HbA1c which were measured on week 0. *Statistically significant difference at $p<0.05$

liver function (ALT and AST), kidney function (ureum and creatinine), hematology (hemoglobin, hematocrite, leucocyte, thrombocyte, Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) and International Normalized Ratio (INR) and routine urine screening. We also recorded any complaints or any other drugs taken during the study. Body Mass Index (BMI) was calculated from body weight divided by height^2 (kg m^{-2}). The profile of BMI of both G-T and simvastatin groups can be seen in Fig. 2.

Statistical analysis: We calculated the sample size using $\alpha = 0.05$ and power = 80%. From the calculation, the sample size in each group was about 20 subjects. Statistic tests were performed using general linear model repeated measure method to test the significancy of lipid profile changes between both groups and between its own group during the study. We performed independent t-test statistic test to compare demography and baseline data and chi square method to do proportion test. The analysis to evaluate the blood lipid profile and BMI profile changes from week to week during study was being done per protocol which is only using data from subjects that had finished the study according study protocol in order to describe the maximal potency of treatment effect. Analysis for laboratory parameters and adverse effects during study were done using intention to treat method in order to gain a better information about drug safety.

RESULTS

Fifty patients, who met inclusion criteria, were recruited and randomized (intention to treat/ITT). Eleven patients were withdrawed from the study before week 12 with various reasons; 3 patients from G-T group were withdrawed because not compliance or using corticosteroid; 8 patients from simvastatin group were withdrawed due to not compliance, weakness, unable to tolerate adverse events (myalgia), ALT level increased up to 3x normal level, or incomplete laboratory data. Thirty nine patients completed the study according to protocol (per protocol/PP), where 19 patients were in G-T group and 20 patients were in simvastatin group.

Patients' characteristics: Baseline and demographic data of evaluable patients was depicted in Table 1 and showed no significant difference between groups ($p>0.05$), except on blood glucose and systolic blood pressure parameters. Laboratory tests results described normal hematology profile, liver function, kidney function, insulin level and blood coagulation parameters and there was no significant difference in all those parameter between both

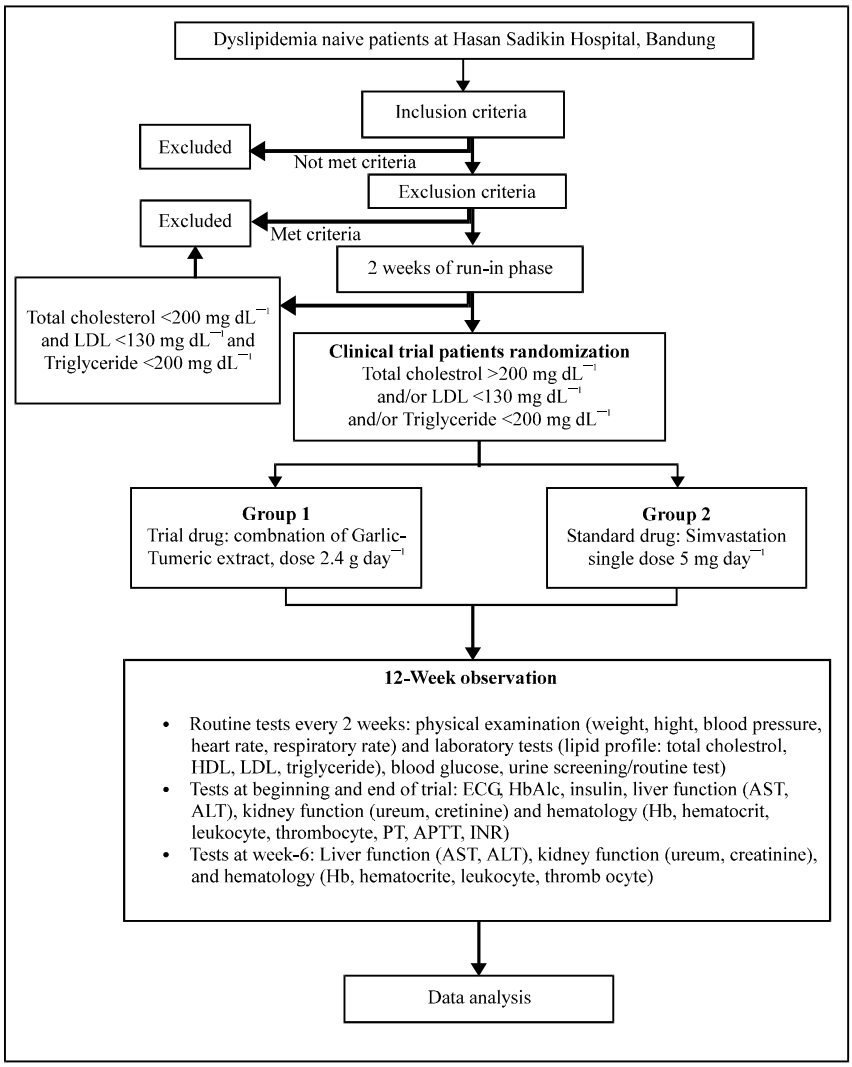

Fig. 1: Study scheme, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, PP: Post-prandial, ECG: Electrocardiogram, PT: Prothrombin time, APTT: Activated partial thromboplastin time, INR: International normalized ratio

groups. Different baseline data were observed in fasting blood glucose, 2 h postprandial blood glucose and HbA1c ($p<0.05$). Thess significant differences were due to a higher number of type-2 Diabetes Mellitus (DM) patients in simvastatin group than G-T group (14 vs. 6 patients, respectively, which may cause statistically significant diferrence in parameters related to glucose metabolism between both groups.

Lipid profile: The lipid profile were determined before and after treatment. There was a significant decrease of total cholesterol in each group but the decrease in simvastatin group was significantly greater than G-T group. The HDL levels in both groups slightly changed and there was an insignificant decrease in G-T group (Table 2). Even though simvastatin group had a statistically significant better result in lowering LDL than G-T group, the LDL

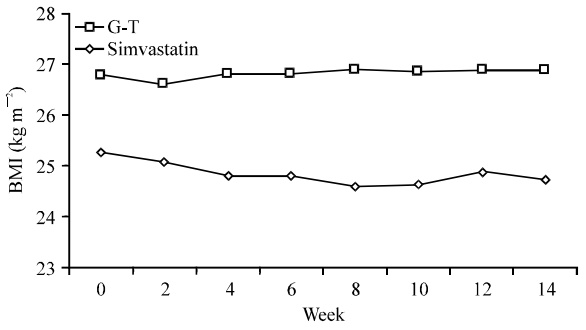

Fig. 2: Body mass index (BMI) profile

Table 2: Parameters observed before and after treatment (ITT patients)

Parameters	Treatment group	n	Before treatment (X±SEM)	After treatment (X±SEM)	p^a	p^b
Demography						
Weight (kg)	G-T	22	60.57±1.870	59.43±1.920	0.033*	0.306
	Simvastatin	28	62.75±2.840	62.75±2.650	1	
Systole (mmHg)	G-T	22	131.14±4.210	124.09±3.230	0.073	0.164
	Simvastatin	28	122.00±3.080	123.00±2.420	0.735	
Diastole (mmHg)	G-T	22	84.09±2.150	83.18±2.290	0.702	0.013*
	Simvastatin	28	77.96±1.630	78.43±1.460	0.799	
Hematology						
Hemoglobin (g dL^{-1})	G-T	20	14.03±0.290	13.95±0.290	0.775	0.373
	Simvastatin	26	18.80±4.740	14.05±0.430	0.331	
Leukocyte ($10^3/mm^3$)	G-T	20	8.06±0.530	7.61±0.500	0.202	0.202
	Simvastatin	26	7.22±0.350	6.94±0.430	0.440	
Platelet ($10^3/mm^3$)	G-T	20	290.00±15.67	278.75±14.63	0.275	0.164
	Simvastatin	26	267.50±9.310	253.81±13.10	0.247	
Hematocrite (%)	G-T	20	41.90±0.820	42.10±0.900	0.768	0.707
	Simvastatin	26	41.15±0.690	41.92±1.350	0.540	
Lipid parameter						
Total cholesterol	G-T	19	251.21±7.680	227.00±6.530	0.007	0.002
	Simvastatin	20	264.35±7.160	188.15±7.510	0.001	
LDL	G-T	19	163.42±9.330	144.74±7.060	0.044	0.003
	Simvastatin	20	162.95±6.230	108.35±6.040	<0.001	
HDL	G-T	19	49.79±2.550	48.89±1.860	0.673	0.899
	Simvastatin	20	47.70±2.980	50.00±3.280	0.322	
Triglyceride	G-T	19	190.37±28.91	167.00±20.53	0.303	0.61
	Simvastatin	20	187.95±24.39	149.15±14.49	0.575	
Diabetic parameters						
Fasting glucose (mg dL^{-1})	G-T	22	114.05±7.650	101.18±5.250	0.009*	0.007*
	Simvastatin	28	184.00±20.30	142.75±17.08	0.024*	
2-hour PP glucose (mg dL^{-1})	G-T	22	168.36±16.97	142.67±12.55	0.037*	0.024*
	Simvastatin	28	255.82±29.22	195.70±25.46	0.017*	
HbA1c (%)	G-T	19	6.75±0.410	6.23±0.150	0.087	0.006*
	Simvastatin	21	9.43±0.750	7.26±0.400	0.000*	
Insulin (pmol L^{-1})	G-T	19	59.85±10.66	50.28±9.550	0.173	0.482
	Simvastatin	20	63.37±9.210	65.47±11.15	0.825	
Blood coagulation parameters						
PT (sec)	G-T	19	12.61±0.120	12.86±0.330	0.523	0.806
	Simvastatin	21	12.92±0.300	12.42±0.140	0.088	
APTT (sec)	G-T	19	30.76±0.780	30.63±0.530	0.858	0.396
	Simvastatin	21	29.48±0.610	30.59±0.570	0.050*	
INR	G-T	19	0.95±0.010	0.96±0.030	0.684	0.587
	Simvastatin	21	0.96±0.030	0.92±0.010	0.090	
Kidney function						
Ureum (mg dL^{-1})	G-T	20	23.70±1.810	22.95±1.850	0.671	0.040*
	Simvastatin	26	27.38±1.140	26.65±1.280	0.654	
Creatinine (mg dL^{-1})	G-T	20	0.90±0.060	0.88±0.060	0.284	0.429
	Simvastatin	26	0.81±0.040	0.86±0.050	0.017*	
Liver function						
AST (U L^{-1})	G-T	20	21.50±0.990	18.35±0.950	0.026*	0.074
	Simvastatin	26	21.77±1.300	24.88±2.680	0.291	
ALT (U L^{-1})	G-T	20	19.20±1.670	16.10±0.960	0.081	0.058
	Simvastatin	26	23.88±2.120	31.92±7.850	0.268	

p^a: Intra-group p value, p^b: Inter-group p value, Baseline data is data on run-in phase, except blood coagulation function values (PT, APTT, INR), liver function (AST, ALT), insulin and HbA1c were data on week-0. *Statistically significant difference at $p<0.050$, The decrease of lipid level on Glibenclamide group was caused by simvastatin drug used by 12 out of 16 subjects

level in G-T group decreased significantly from 163.42 mg dL^{-1} before treatment to 144.74 mg dL^{-1} after treatment ($p = 0.044$ by student t-test). The improvement of triglyceride level in both groups was comparable (Table 2). Based on the overall lipid profiles, 68.42% patients in G-T group showed improvement and 85% in simvastatin group but the difference between them was not significant ($p = 0.366$) (Table 3).

Table 3: Overall lipid profile analysis

	G-T (n=19)		Simvastatin (n=20)	
Lipid profile analysis	n	%	n	%
Improve	13	68.42	17	85
No change	5	26.32	3	15
Worse	1	5.26	0	0
Inter-group p-value	0.366			

Body mass index (BMI) profile: Patients in G-T group showed a significant BMI decrease during the study

(p = 0.03), while simvastatin has failed to show favourable change on BMI even insignificant BMI increase was observed in Simvastatin group. However, the difference between both groups was not significant (Table 4). The BMI profile can be seen in Fig. 2.

Laboratory parameters: Laboratory parameters data was depicted in Table 2 Hematology tests including hemoglobin, hematocrite, leukocyte and platelets in both groups did not reveal any significant changes and were in normal range. The AST level was significantly decreased (21.5±0.99 to 18.35±0.96 U L^{-1}) in G-T group, while the ALT level also decreased but not statistically significant. In contrast, the AST and ALT levels increased although the increase was not statistically significant (p>0.05) and still in normal range. The kidney function parameters, ureum and creatinine, did not change significantly on G-T group, while in Simvastatin group creatinine level increased significantly (p = 0.017).

Table 4: Body mass index (BMI) profile during the study

	BMI (kg m^{-2})	
Week	G-T (n=19) (X±SEM)	Simvastatin (n=20) (X±SEM)
-2	25.26±0.71	26.77±1.26
0	25.07±0.72	26.61±1.23
2	24.78±0.74	26.81±1.20
4	24.79±0.71	26.82±1.19
6	24.60±0.71	26.90±1.18
8	24.66±0.70	26.83±1.13
10	24.87±0.72	26.88±1.15
12	24.73±0.72	26.87±1.15
Intra-group p-value	0.030*	0.747
Inter-group p-value	0.211	

*Statistically significant (p<0.05), #: Run-in phase

In this study, 20 out of 50 ITT patients are type 2 Diabetes Mellitus (DM) patients, 6 patients in G-T group and 14 patients in simvastatin group. Fasting blood glucose, 2 h postprandial blood glucose and HbA1C levels in Simvastatin group was significantly decreased since all DM patients in this group took oral antidiabetic drug. Patients in G-T group also showed improvement of blood glucose profile although the DM patients in this group did not take any antidiabetic drug (114.05±7.65 mg dL^{-1} before treatment to 101.18±5.25 mg dL^{-1} after treatment). The 2HPP blood glucose, fasting insulin and HbA1C levels in G-T group also decreased although it was not significant.

Other parameters: There was no signicant changes of systolic and diastolic blood pressure before and after treatment in G-T or simvastatin group. It was observed a decrease of systolic blood pressure in G-T group although it was not significant (p = 0.073). However, there was a significant difference of diastolic blood pressure between both groups (p = 0.013), which might be due to slightly decrease of diastolic blood pressure in G-T group and its slightly increase in simvastatin group (Table 2). After treatment, the body weight of patients in G-T group decreased significantly (p = 0.033), while it was not changed in simvastatin group (Table 2).

Adverse events: All adverse events reported by all subjects were listed in Table 5. It could be seen that the number of patients experiencing adverse events in simvastatin group was higher than G-T group (28 vs. 22

Table 5: Adverse events reported during the study

	G-T treatment (n = 22)		Simvastatin treatment (n = 28)	
Adverse events	No. (%)	Relationship to treatment	No. (%)	Relationship to treatment
Central nervous system	7(31.8)	Not related	9(32.1)	Possibly related
Musculoskeletal	16(72.7)	Not related	19(67.9)	Related
Gastrointestinal	8(36.4)	Not related	10(35.7)	Possibly related
Garlic breath	1(4.5)	Related	-	-
Burning sensation in esophagus	1(4.5)	Possibly related	-	-
Cough	-	-	3(10.7)	Not related
Flu-like syndrome	-	-	1(3.6)	Not related
Itchy	1(4.5)	Not related	1(3.6)	Not related
Dispnea (asthma)	-	-	1(3.6)	Not related
Polydipsia	-	-	4(14.3)	Not related
Polyuria	2(9.1)	Not related	5(17.9)	Not related
Drowsiness	1(4.5)	Not related	-	-
Chest pain	1(4.5)	Not related	-	-
Fever	-	-	1(3.6)	Not related
Tiredness	1(4.5)	Not related	4(14.3)	Possibly related
Blurred vision	-	-	3(10.7)	Possibly related
Urinary difficulty	1(4.5)	Not related	-	-
Hypoglycemia	-	-	1(3.6)	Not related
Palpitation	-	-	1(3.6)	Not related
Increased AST/ALT	-	-	2(7.1)	Possibly related

No.: Number of subjects

patients). The majority of adverse events in G-T group was related to gastrointestinal tract such as constipation, abdominal pain, flatulent, nausea, vomiting and increased appetite. The most frequent adverse event in simvastatin group was musculoskeletal complaints such as muscle cramps, muscle pain, muscle stiffnes. Concomitant drugs taken during the study were also recorded since subjects were allowed to take other drugs as long as they are known not influencing lipid metabolism. There was no drug interaction reported during the study by patients in G-T group taking analgesic (acetaminophen), anti-inflammation, ACE inhibitor, diuretics, vasodilators and vitamins.

DISCUSSION

Dyslipidemia is associated with an increased risk of Coronary Heart Disease (CHD). The most common forms of dyslipidemia are polygenic inherited with a strong lifestyle contribution. In addition, it may occur with other diseases such as hypothyroidism, chronic kidney disease and diabetes mellitus (Leon and Bronas, 2009). In addition to pharmacologic approach, lifestyle changes, consisting diet modification, physical exercise and weight management, are also important as nonpharmacologic management of dyslipidemia (Leon and Bronas, 2009; Stevinson *et al*., 2000). Potential health benefit of herbals for lowering lipid have been recently explored since none of lipid lowering drugs are free of adverse effects (Stevinson *et al*., 2000). The lipid-lowering effect of herbals, including garlic and turmeric, have been extensively investigated and reported in various preclinical studies (Sukandar *et al*., 2010a; Ashraf *et al*., 2005; Jang *et al*., 2008). The combination of garlic and turmeric extract was not harmful to the rat fetus (Sukandar *et al*., 2008).

The measurement of blood pressure, blood glucose and body weight is important because of their strong correlation with dyslipidemia (Moffatt and Stamford, 2006). Garlic is reported to have hypotension effect, however there was no signicant changes of systolic and diastolic blood pressure in G-T as well as simvastatin group. It is possibly caused by much lower dosage that we used in this study than the effective dosage for hypotension effect. Regarding the body weight, the average BMI in this study was in overweight category according to Asian standard ($\geq$23 kg m^{-2}) (WHO/IASO/IOTF, 2000). Obesity is often concomitantly found with hyperlipidemia and also one of the risk factors for coronary heart disease since increasing weight causing abdominal fat accumulation that may trigger atherogenic characteristic (Moffatt and Stamford, 2006). This study showed that G-T extract is better in lowering BMI than simvastatin, therefore it is quite potential in rendering the risk of coronary heart disease. The effect of garlic-turmeric extract on body weight is in accordance to our previous report (Sukandar *et al*., 2010b).

The G-T extract combination at the dose of 2.4 g day^{-1} have decreased total cholesterol and LDL levels significantly during study ($p = 0.039$ and 0.044), although those decreases in simvastatin group were greater than in G-T group. It is reported that garlic extract could inhibit cholesterol biosynthesis by inhibiting HMG Co-A reductase enzyme (Liu and Yeh, 2002; Barnes *et al*., 2007) and curcumin in turmeric could stimulate cholesterol convertion into bile acid that in turn increases cholesterol excretion (Braun and Cohen, 2007). Another plant which contains curcumin is *Curcuma xanthorrhiza* rhizome, its ehanol extract showed to decrease total blood cholesterol level in male Wistar rat and decreased LDL level significantly (Sukandar *et al*., 2012). The garlic and turmeric extract also decreased triglyceride in comparable fashion with simvastatin. Garlic contains S-allylcysteine, S-propylcysteine and S-ethylcysteine which have been known could inhibit triglyceride biosynthesis by reducing fatty acid synthesis through inhibition of fatty acid synthase enzyme and also by reducing NADPH in tissue (Barnes *et al*., 2007). Administration of G-T extract could improve lipid profile but life style improvement and regular exercise are still needed. Further studies should be done to reveal the G-T effect against lipoprotein density and size related to coronary heart disease risk.

In addition to dyslipidemia, type 2 diabetes mellitus is one of metabolic syndrome symptoms. High trygliceride level (>150 mg dL^{-1}) together with decreased HDL cholesterol indicated that there was insulin resistance since insulin resistance causes excessive carbohydrate, which in turn will increase triglyceride production (Moffatt and Stamford, 2006). In this study we observed that G-T extract could significantly improve diabetes mellitus parameters (fasting and 2 HPP blood glucose levels) ($p = 0.009$, $p = 0.037$, respectively). This results are consistent to our previous study (Sukandar *et al*., 2010b). Simvastatin could lower the diabetic parameters better than the G-T extract. This might be due to antihyperglycemic characteristic of the G-T extract that they alter the baseline glucose level in G-T group was lower than that in simvastatin group, therefore it may lead to a fewer alteration in the blood glucose levels. Madkor *et al*. (2011) has reported that a mixture containing garlic and turmeric did not significantly alter serum glucose level in healthy rats, thus it might be possible that the nearer glucose level to the normal level the lower antidiabetic effect of this G-T extract

(Madkor *et al*., 2011). The mechanism of antidiabetic effect of garlic might involve the allicin-derived organosulphur compounds, which sparing insulin from-SH inactivation by reacting with endogenous thiol containing molecules (Eidi *et al*., 2006; Madkor *et al*., 2011). While curcumin protected pancreatic β-cells from reactive oxygen species in diabetes (Madkor *et al*., 2011).

The G-T extract combination was better tolerated by patients during the study than simvastatin. The administration of G-T extract was safe against liver and kidney function. It even lowered the AST and ALT levels. An animal study has also shown that treatment of diabetic rats with garlic extract may reduce the activity of both enzymes in plasma (Eidi *et al*., 2006). Garlic and turmeric are known to have hepatoprotective effect (Braun and Cohen, 2007). In contrast, statin treatment showed hepatotoxic effect, which was indicated by increased hepatic transaminase enzymes up to three times normal value, although it was rarely occurred (Brunton *et al*., 2006).

Some of concomitant drugs taken in this study have potential interaction with G-T extract. However none drug interaction reaction was observed among subjects in the G-T group, unless one subjects who taken lisinopril for 12 weeks showed a decrease of blood pressure to normal range. We could not confirm whether the decrease of blood pressure was caused merely by lisinopril or the G-T extract also added the anti-hypertension effect to lisinopril. Blood coagulation parameters, such as Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) and International Normalized Ratio (INR), did not alter significantly in the G-T group, although it was reported that garlic extract has anti-platelets and fibrinolytic effect (Barnes *et al*., 2007) and curcumin also has antiplatelet effect (Braun and Cohen, 2007). In simvastatin group, PT and INR also did not change significantly but APTT level increased significantly ($p = 0.05$) although the value was still in normal range. It is known that simvastatin could lower platelet aggregation (Brunton *et al*., 2006). In this study, one subject in G-T group had a menstruation after a long time never had menstruation. The correlation between both AE with test drug is unconfirmed because there was only one report about garlic's utero-active effect in an *in vitro* research about uterine contraction (Barnes *et al*., 2007). Myopathy is main AE of simvastatin in this study and other AEs are nervous system complaint, gastrointestinal discomfort, increased AST and ALT, blurred vision and faint. All of those complaints were considered related with simvastatin based on previous reports (Aronson, 2005; Brunton *et al*., 2006).

CONCLUSION

This study demonstrated that the effect of garlic-turmeric extract was comparable to simvastatin on improving lipid profile in hyperlipidemic patients. The administration of garlic-turmeric was well-tolerated, no serious adverse event and no drug interaction observed.

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