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Clinical Study of Turmeric (*Curcuma longa* L.) and Garlic (*Allium sativum* L.) Extracts as Antihyperglycemic and Antihyperlipidemic Agent in Type-2 Diabetes-Dyslipidemia Patients

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Abstract: Turmeric (*Curcuma longa* L.) and garlic (*Allium sativum* Lin.) are known as traditional drugs that can cure several diseases such as dyslipidemia and diabetes. Many studies on individual usages of garlic and turmeric have been done previously. Present preclinical study showed that combination of both substances gave a better result compared to their individual usage. This research was aimed to evaluate the efficacy and safety of turmeric and garlic extracts combination as antihyperglycemic and antihyperlipidemic agents for type-2 diabetes-dyslipidemia. Three doses were evaluated: 1.2, 1.6 and 2.4 g, daily. It was found that the garlic-curcuma combination could reduce plasma glucose level and HbA1C as well as improve the lipid profile. Among those 3 dosages, the dose of 2.4 g decreased fasting glucose level, 2 h postprandial glucose level, HbA1C, total cholesterol, low density lipoprotein, triglyceride and body mass index more than the two other dosages. This dose level also increased high density lipoprotein higher than the other two dosages. There was no significant adverse event observed during the study. The treatment also showed no side effect on kidney and liver functions as well as the blood composition of all subjects.

Key words: Garlic, turmeric, antihyperglycemic, antihyperlipidemic, efficacy, body mass index

INTRODUCTION

There is a growing prevalence of type-2 diabetes mellitus. Approximately 197 million people worldwide have impaired glucose tolerance. Diabetes is rapidly emerging as a global health problem which could reach pandemic levels by 2030. The number of worldwide diabetes cases is projected to increase from 171 million in 2000 to 366 million in 2030. The noticeable increase will be observed in developing countries (Hossain *et al*., 2007). The prevalence of type-2 diabetes mellitus varies widely among various race and ethnic groups. In Indonesia, the prevalence of type-2 diabetes mellitus was 14.7% in urban area and 7.2% in rural area. While type 2 diabetes mellitus has been usually affected individuals older than 40 years, it is being recognized that the incidence and prevalence are increasing at an alarming rate in younger person, particularly in obese children (Hossain *et al*., 2007).

Insulin resistance and insulin deficiency could lead to changes in plasma lipoprotein in patients with diabetes. The most common pattern of dyslipidemia in diabetes characterized by high serum triglyceride levels, low serum High Density Lipoprotein (HDL) cholesterol levels and increased concentration of serum Low Density Lipoprotein (LDL) cholesterol. Dyslipidemia in diabetes contributes to higher risk of atherosclerosis and hypertension; and subsequently to cardiovascular disease. Diabetes-related changes in plasma lipid concentrations are amenable to intervention (Eckel, 2008; Mooradian, 2009).

Herbal compounds have been proven to be beneficial in the treatment of various diseases, such as diabetes, cardiovascular disease, cancer, infection, etc. Among others, turmeric (*Curcuma longa* L.) and garlic (*Allium sativum* L.) have been used as traditional medicine for different diseases, including diabetes and hyperlipidemia. Both have shown multiple biological activities which are attributed to the reduction of risk factors of cardiovascular disease, hypoglycemic action, hypolipidemic action, antimicrobial effect and antioxidant effect (Thomson *et al*., 2007; Banerjee and Maulik, 2002; Ashraf *et al*., 2005a; Itokawa *et al*., 2008; Kuroda *et al*., 2005).

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Garlic (*Allium sativum*) contains alliin and other sulphur compounds. When garlic cloves are crushed or disrupted, allinase enzyme, present in garlic will be activated and acts on alliin to produce allicin. Allicin has been proven to be the principal bioactive compound in garlic (Banerjee and Maulik, 2002; Ashraf *et al*., 2005a). Turmeric, the rhizome of *Curcuma longa*, is used as spice and also as medicine to treat inflammation and sprains in some Asian countries. Curcuminoid is the main component in *Curcuma* species and is responsible for their major biological effects. Curcumin, the major component in curcuminoid, possesses the wide range of pharmacological effects including anti-inflammatory effects, anti-oxidant activity, anti-cancer effects, reduction of blood cholesterol level, lowering blood glucose level and other biological effects (Itokawa *et al*., 2008; Kuroda *et al*., 2005; Maheshwari *et al*., 2006).

Our animal study showed that combination of both substances gives a better result compared to their individual usage. Ashraf *et al*. (2005b) also showed that garlic and turmeric combination are potent vasorelaxants and could reduce the atherogenic properties of cholesterol. In the present study, the efficacy and safety of turmeric and garlic extracts combination as hypoglycemic and hypolipidemic agents in type-2 diabetes-dyslipidemia patients were evaluated.

MATERIALS AND METHODS

A double-blind, randomized study was conducted from May 2006 until September 2007. The study protocol was approved by Ethics Committee on Research in Human, Hasan Sadikin Hospital (HSH), Bandung, Indonesia on March 17th, 2006. Written informed consent was obtained from each patient before any procedure performed.

Subjects: Patients aged from 35 to 70 years with type-2 diabetes mellitus and dyslipidemia of either sex, who had failed to comply with diet therapies, were recruited from HSH. The inclusion criteria for diabetes was indicated by fasting glucose levels >126 mg dL^{-1} and 2 h post-prandial (2HPP) glucose levels >200 mg dL^{-1}, while the dyslipidemia was based on National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) indicated by total blood cholesterol >200 mg dL^{-1} and either LDL levels > 130 mg dL^{-1} or HDL levels <40 mg dL^{-1} or triglyceride levels >150 mg dL^{-1}. Patients with type 1 diabetes mellitus, significant renal or hepatic dysfunction, coronary heart disease, ulcus diabetic, or have been treated with other anti-cholesterol or anti-diabetes agents (according to patients' reports from HSH medical records), were excluded. Women, who were under hormone contraception, pregnant or lactating, were also excluded; the enrolment chart is shown in Fig. 1.

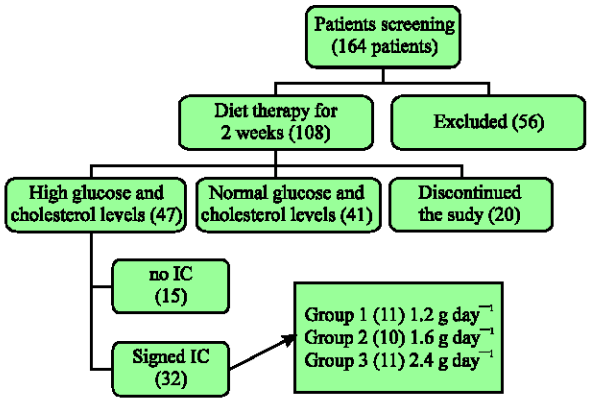

Fig. 1: Patient's enrolment chart

Preparation of study drugs: The capsules of study drugs contained 200 mg of turmeric ethanolic extract and 200 mg of garlic aqueous extract. The study drugs were produced by Pharmacy Installation of Indonesian Air Force.

Study design: Patients were instructed to do a diet and exercise for 2 weeks before the treatment. These activities then had to be done regularly during the study. Demographic information, daily habits, such as cigarette smoking and alcohol consumption, medical history and Body Mass Index (BMI) were recorded at the first visit. After two weeks, patients were screened again for the blood glucose level and lipid profiles based on the criteria.

Patients who failed to improve their blood glucose and lipid status after two weeks were then randomly grouped into different dosages of study drugs, i.e., group A with 1.2 g, group B: 1.6 g, or group C: 2.4 g daily for 12 weeks. Group A received 2 Allium-Curcuma (A-C) capsules + 1 placebo capsule in the morning and 1 A-C capsule + 2 placebo capsules in the evening orally. Group B received 2 A-C capsules + 1 placebo capsules in the morning and in the evening and group C received 2 times of 3 A-C capsules in the morning and in the evening.

Patients were scheduled for a regular visit, every two weeks, for three months to collect blood glucose and lipid profile data as well as the blood pressure and body weight data. A control card was given to each patient and had to be presented during visit. Patients were also asked about any adverse effects, dosage acceptance, diet obedience and any concomitant medication taken during the study in every visit.

Measurement of blood glucose, lipid profile and other haematological parameters: Blood lipids (total cholesterol, LDL, HDL and triglycerides), glucose level, were assessed at each visit. Overnight fasting blood sample was used for blood glucose and lipid profile tests. Test results from the first visit were used for screening to determine whether the subject met the inclusion criteria. The second test results were used as the baseline data. The liver function (AST, ALT), kidney function (urea, creatinine) and haematology tests were performed at the beginning, middle and end of the study to determine the safety of the drug. All the clinical tests were done in the Hasan Sadikin Hospital Laboratory.

Data analysis: The data were analyzed using a computer software package (SPSS version 14.0). Analysis of Variance (ANOVA) was used to compare the changes in parameters of interest between 3 dosage groups during the study. The significance level was set at 5%.

RESULTS AND DISCUSSION

Thirty two patients were met the inclusion criteria and were willing to follow the study. They were randomized into group A (n = 11), group B (n = 10) and group C (n = 11). The average age of group A, B and C were not statistically different. The average of fasting blood glucose level, 2HPP glucose level and HbA1c of the three groups were met the requirement of diabetes criteria. Dyslipidemia in all three groups was concluded from the average of total cholesterol, LDL, triglyceride and HDL levels. All groups showed obesity based on body mass index value. All patients were accompanied by other diseases such as hypertension, peptic ulcer, rheumatoid, or osteoporosis. Baseline characteristics of each group are shown in Table 1.

After treated with combination of garlic and turmeric for 12 weeks, group A, B and C showed a decrease of fasting glucose level by 18, 11 and 20%, respectively. However, these decreases were not statistically significant. There were insignificant decrease of 2HPP glucose for group A and B, whereas group C showed a significant decrease by 22.68% (p = 0.032). Table 2 recorded the weekly changes of fasting and 2HPP glucose levels for each group. There was a decrease of HbA1c after 12 weeks of treatment in group A, while group B showed an increase but both were statistically not

Table 1: Baseline characteristic of group A, B and C

Baseline characteristics	Groups A (1.2 g daily (n = 11))	B (1.6 g daily (n = 10))	C (2.4 g daily (n = 11))	p-value between groups
Sex				
Men	1	1	3	0.421
Women	10	9	8	
Age (years)	59.29 (6.820)	54.44 (4.360)	54.50 (8.400)	0.292
Fasting glucose (mg dL^{-1})	177.64 (52.13)	177.20 (45.04)	175.09 (51.03)	0.992
2 h postprandial (mg dL^{-1})	235.80 (87.96)	249.44 (65.55)	266.27 (60.06)	0.629
Insulin (IU mL^{-1})	8.36 (4.730)	8.20 (7.390)	7.90 (5.290)	0.931
HbA1C (%)	10.06 (3.040)	9.60 (1.690)	11.48 (1.470)	0.213
Total cholesterol (mg dL^{-1})	229.09 (33.77)	228.50 (44.67)	217.45 (38.20)	0.738
LDL (mg dL^{-1})	148.91 (28.19)	148.20 (38.13)	137.82 (38.58)	0.716
HDL (mg dL^{-1})	48.00 (10.74)	48.00 (7.500)	46.45 (9.070)	0.905
Triglyceride (mg dL^{-1})	161.00 (96.14)	161.70 (59.80)	165.73 (58.20)	0.987
BMI (kg m^{-2})	25.53 (3.260)	27.59 (4.830)	29.17 (3.460)	0.344

±SD values are in the brackets

Table 2: Mean of fasting and 2HPP plasma glucose levels of group A, B and C

	Fasting glucose (mg dL^{-1})						2HPP glucose (mg dL^{-1})					
Weeks	Group A	p-value	Group B	p-value	Group C	p-value	Group A	p-value	Group B	p-value	Group C	p-value
W0	177.6 (52.1)		177.2 (45.0)		175.1 (51.0)		235.8 (87.9)		249.4 (65.5)		266.3 (60.1)	
W2	156.2 (47.6)	0.359	158.4 (41.7)	0.311	162.8 (39.5)	0.598	210.1 (71.1)	0.427	256 (57.7)	0.816	268.7 (45.4)	0.923
W4	151.4 (54.4)	0.289	165.2 (36.3)	0.504	164.5 (48.3)	0.651	207.7 (67.6)	0.408	247.3 (49.6)	0.940	239.5 (57.3)	0.294
W6	151.6 (62.5)	0.291	170 (41.7)	0.696	145.1 (59.5)	0.211	184.6 (60.3)	0.135	228.3 (55.6)	0.454	225.4 (50.3)	0.120
W8	138.8 (59.0)	0.118	164 (43.4)	0.488	158.2 (61.1)	0.492	201.2 (69.6)	0.310	223.5 (57.3)	0.373	211.7 (90.6)	0.045*
W10	139.5 (52.9)	0.137	155.5 (36.1)	0.229	150.3 (64.0)	0.315	200.5 (75.9)	0.315	232.2 (58.5)	0.530	222 (61.0)	0.102
W12	146 (52.7)	0.234	157.1 (34.4)	0.278	139.4 (57.9)	0.162	212.1 (78.9)	0.516	222.2 (69.3)	0.335	205.9 (39.3)	0.032*

*Statistically significant ($p<0.05$), SD values are in the bracket. p-value: Significant difference of blood glucose level in each observation week compared to week 0

Table 3: Lipid profiles of intention to treat (ITT) group A, B and C

Weeks	Group A (n = 11)	p-value	Group B (n = 10)	p-value	Group C (n = 11)	p-value
Total cholesterol (mg dL^{-1})						
W0	229.1 (33.8)		228.5 (44.7)		217.5 (38.2)	
W2	237.7 (42.1)	0.210	230.2 (40.9)	0.868	225.9 (24.4)	0.429
W4	232.6 (39.6)	0.873	236.0 (40.3)	0.526	226.7 (27.1)	0.126
W6	222.8 (33.3)	0.208	244.9 (41.0)	0.212	222.2 (38.9)	0.935
W8	224.2 (43.3)	0.373	239.4 (44.7)	0.488	224.3 (39.6)	0.663
W10	242.3 (30.2)	0.949	228.6 (23.3)	0.992	231.4 (37.5)	0.279
W12	244.4 (31.7)	0.711	230.1 (22.6)	0.881	227.3 (40.8)	0.919
LDL (mg dL^{-1})						
W0	148.9 (28.2)		148.2 (38.1)		137.8 (38.6)	
W2	150.2 (42.4)	0.891	141.0 (48.6)	0.652	147.5 (22.8)	0.353
W4	146.2 (39.2)	0.615	158.1 (35.5)	0.307	147.7 (28.2)	0.106
W6	141.0 (32.3)	0.172	156.1 (33.3)	0.456	147.2 (33.0)	0.623
W8	135.1 (36.9)	0.150	153.2 (41.1)	0.760	149.9 (33.6)	0.333
W10	158.1 (24.5)	0.986	148.7 (23.5)	0.963	151.3 (33.5)	0.382
W12	159.0 (31.0)	0.650	149.3 (30.0)	0.945	148.1 (36.3)	0.969
HDL (mg dL^{-1})						
W0	48.0 (10.7)		48.0 (7.5)		46.5 (9.1)	
W2	51.6 (9.8)	0.074	47.6 (6.2)	0.735	45.4 (6.7)	0.667
W4	49.1 (12.2)	0.778	46.3 (8.3)	0.519	47.3 (9.0)	0.602
W6	49.8 (15.8)	0.690	50.2 (9.5)	0.202	45.7 (7.6)	0.821
W8	51.2 (11.7)	0.432	48.1 (9.2)	0.936	45.3 (8.6)	0.745
W10	51.0 (10.1)	0.083	48.5 (8.2)	0.859	49.0 (5.2)	0.286
W12	54.3 (12.9)	0.116	48.2 (8.1)	0.962	48.8 (4.4)	0.549
Triglyceride (mg dL^{-1})						
W0	161.0 (96.1)		161.7 (59.8)		165.7 (58.2)	
W2	197.9 (195.1)	0.351	199.1 (122.0)	0.302	162.9 (70.4)	0.838
W4	186.1 (107.9)	0.510	157.6 (43.0)	0.634	160.0 (57.4)	0.691
W6	165.7 (83.4)	0.670	192.9 (67.8)	0.619	146.3 (40.1)	0.211
W8	189.0 (94.2)	0.457	184.6 (72.9)	0.364	151.3 (63.5)	0.532
W10	203.8 (122.1)	0.255	178.3 (73.6)	0.264	156.7 (52.2)	0.719
W12	168.4 (94.9)	0.164	166.7 (80.4)	0.164	151.0 (44.3)	0.529

±SD values are in the bracket, p-value: Significant difference of lipid levels in each observation week compared to week 0

significant. A significant decrease of HbA1c was found in group C with average decrease of 2.77% from baseline ($p = 0.025$).

Table 3 showed the change of lipid profile before and after therapy for the Intent To Treat (ITT) patients, In the ITT analysis and the lipid profile showed no significant changes. Then we analysed the effect of this compound on subjects that had baseline of total cholesterol >200 mg dL^{-1}, or LDL >150 mg dL^{-1}, or HDL <50 mg dL^{-1}, or triglyceride >200 mg dL^{-1} (Table 4). It was found that at week-8, subgroup A showed significant decrease of total cholesterol. The LDL levels decreased in the three groups but the decreases were not significant. HDL level in subgroup A and C increased significantly in week 10 and 12, respectively. Triglyceride levels showed a tendency to decrease in subgroups A and C, but they were not significant. The BMI in group A, B and C decreased by 2.6, 2.7 and 4.3%, respectively and statistically significant (Table 5).

This study supported the result of earlier study on garlic and turmeric as anti-diabetic and anti-hyperlipidemic. Both garlic and turmeric alone showed antidiabetic and antihyperlipidemic (Thomson *et al*., 2007; Ashraf *et al*., 2005a; Kuroda *et al*., 2005; Jang *et al*., 2008).

The action mechanism of turmeric as anti-diabetic could be explained that reported beneficial effects of curcumin on the liver of diabetic animals. An important enzyme that converts glucose into glycogen was higher in the diabetic mice treated with curcumin compared to the control mice. This enzyme was thought to inhibit the post-meal rise of glucose level. The anti-inflammatory and anti-oxidant properties of turmeric also have been proposed to lessen insulin resistance and prevent type-2 diabetes in mice model by dampening the inflammatory response caused by obesity. It was also found that dietary curcumin could increase the expression of adiponectin, which in turn will improve insulin sensitivity in insulin resistance animal models (Weisberg *et al*., 2008). Curcumin also suppressed hepatic glucose production by activating AMP kinase and inhibiting glucose-6-phosphatase and phosphoenolpyruvate carboxykinase (Fujiwara *et al*., 2008).

Anti-diabetic activity of garlic supported by Eidi *et al*. (2006) using animal study. They found that garlic extract could bring serum glucose toward normal values. Garlic extract was found to be even more effective than glibenclamide. This hypoglycemic effect

Table 4: Subgroup analysis of lipid profiles in group A, B and C with total cholesterol >200 mg dL^{-1}, or LDL >150 mg dL^{-1}, or HDL <50 mg dL^{-1}, or triglyceride >150 mg dL^{-1}

Weeks	Group A (n = 7)	p-value	Group B (n = 7)	p-value	Group C (n = 7)	p-value
Total cholesterol (mg dL^{-1})						
W0	248.0 (24.7)		246.1 (31.6)		234.1 (35.0)	
W2	255.4 (36.0)	0.294	236.9 (44.7)	0.540	227.9 (25.0)	0.648
W4	231.1 (39.9)	0.245	242.3 (46.3)	0.752	233.9 (27.6)	0.965
W6	229.4 (39.4)	0.061	249.0 (44.8)	0.839	231.3 (43.7)	0.832
W8	223.6 (43.9)	0.037*	249.9 (42.3)	0.821	234.7 (38.3)	0.936
W10	242.4 (28.5)	0.394	234.6 (23.0)	0.229	241.6 (36.1)	0.494
W12	244.4 (31.7)	0.711	229.6 (25.9)	0.115	236.7 (33.2)	0.833
	Group A (n = 6)	p-value	Group B (n = 4)	p-value	Group C (n = 3)	p-value
LDL (mg dL^{-1})						
W0	169.2 (11.5)		184.5 (19.5)		180.7 (41.0)	
W2	183.8 (22.0)	0.182	159.3 (68.4)	0.481	168.0 (23.3)	0.664
W4	165.2 (28.9)	0.720	190.0 (27.9)	0.735	182.0 (22.1)	0.928
W6	157.5 (20.5)	0.104	183.8 (32.0)	0.972	183.0 (20.7)	0.895
W8	147.0 (38.8)	0.150	175.5 (54.9)	0.788	184.7 (36.5)	0.761
W10	163.0 (26.7)	0.425	160.0 (20.9)	0.194	182.7 (34.3)	0.900
W12	164.3 (30.2)	0.667	169.5 (16.0)	0.308	164.7 (46.5)	0.653
	Group A (n = 5)	p-value	Group B (n = 5)	p-value	Group C (n = 6)	p-value
HDL (mg dL^{-1})						
W0	40.4 (7.1)		42.8 (4.7)		42.5 (4.8)	
W2	46.2 (8.7)	0.170	44.2 (5.6)	0.706	42.9 (6.7)	0.882
W4	40.4 (7.4)	1.000	43.5 (8.3)	0.908	43.6 (4.8)	0.457
W6	39.4 (8.7)	0.828	44.8 (6.2)	0.743	42.9 (5.3)	0.530
W8	44.6 (7.5)	0.349	46.8 (9.9)	0.281	42.6 (6.8)	0.363
W10	47.2 (3.9)	0.010*	46.3 (9.4)	0.565	47.3 (4.2)	0.073
W12	49.6 (11.4)	0.229	44.6 (4.9)	0.514	48.7 (4.8)	0.002*
	Group A (n = 3)	p value	Group B (n =2)	p-value	Group C (n = 3)	p-value
Triglyceride (mg dL^{-1})						
W0	293.0 (82.1)		235.5 (26.2)		237.3 (32.3)	
W2	401.3 (318.4)	0.516	321.5 (239.7)	0.670	209.0 (98.6)	0.553
W4	293.0 (96.1)	0.583	203.0 (12.7)	0.181	197.3 (88.9)	0.454
W6	260.0 (84.4)	0.339	282.5 (31.8)	0.054	158.3 (55.5)	0.127
W8	287.7 (89.6)	0.359	280.0 (58.0)	0.298	190.7 (64.8)	0.432
W10	305.7 (150.2)	0.656	269.5 (67.2)	0.450	166.3 (37.9)	0.107
W12	240.7 (70.0)	0.417	263.0 (127.3)	0.766	164.0 (30.5)	0.072

*Statistical significant ($p<0.05$). ±SD values are in the bracket. p-value: Significant difference of lipid levels in each observation week compared to week 0

Table 5: Mean of BMI (Body Mass Index) of group A, B and C

Weeks	Group A	p-value	Group B	p-value	Group C	p-value
W0	25.53 (3.26)		27.50 (4.83)		29.17 (3.46)	
W2	25.45 (3.10)	0.692	27.47 (4.82)	0.363	28.03 (4.59)	0.115
W4	24.95 (3.26)	0.023*	27.22 (4.71)	0.106	28.45 (3.18)	0.042*
W6	25.12 (3.46)	0.084	26.96 (4.81)	0.002*	28.07 (3.28)	0.089
W8	25.08 (3.15)	0.027*	26.76 (4.81)	0.022*	28.07 (3.58)	0.054
W10	24.86 (3.21)	0.058	26.87 (4.62)	0.065	28.00 (3.58)	0.024*
W12	24.86 (3.21)	0.058	26.77 (4.52)	0.048*	27.93 (3.56)	0.021*

*Statistically significant ($p<0.05$). ±SD values are in brackets. p value: Significant difference of BMI in each observation week compared to week 0

was attributed mainly to allicin compound of garlic (Chang and Johnson, 1980). Though the exact mechanisms of garlic as hypoglycemic agent is still not clear several mechanisms have been suggested (Jain and Vyas, 1975; Patumraj *et al*., 2000; Banerjee and Maulik, 2002). Garlic may potentiate insulin effect on plasma by increasing secretion of insulin from beta cells pancreas or its release from bound insulin (Jain and Vyas, 1975). Allicin, the principal bioactive compounds in garlic extract, showed *in vitro* anti-oxidant and free radical scavenging effects, which may contribute to its beneficial effect in diabetes (Lau, 2001; Orekhov and Grunwald, 1997; Thomson *et al*., 2007).

In this study, treatment of garlic and turmeric combination for 12 weeks improved the blood glucose profile. Fasting blood glucose levels in 3 groups were decreased where the lowest was found in group C. The 2HPP plasma glucose level decreased in three groups, but only significant for group C. The level of 2HPP glucose is determined by the insulin capacity to increase the glucose intake into the tissues and also depends on tissue's sensitivity to insulin.

Turmeric and garlic could contribute to the improvement of HbA1c level in diabetic patients. The HbA1c test is used to evaluate the glucose control and effect of the treatment within the last 8-12 weeks. The

HbA1c test is a simple test because it does not require the patient to fast and also is not influenced by acute change of insulin or short term lifestyle changes, such as exercise and diet (Saudek *et al*., 2008). An increase of HbA1c level may contribute to the increase of diabetic complication incidence. It was also suggested that HbA1c level is a marker of pathological process related to elevated glucose levels that contribute to vascular disease risk (Selvin *et al*., 2005). A 1% increase in HbA1c was associated with 12% increased of heart failure (Iribarren *et al*., 2001). An *in vitro* study has demonstrated that curcumin may inhibit glycosylation of hemoglobin in high glucose concentration (Jain *et al*., 2006). The hypoglycemic and anti-oxidant effects of garlic and turmeric were also associated with lower blood glucose level and glycated hemoglobin (Jang *et al*., 2008). Turmeric and garlic combination were potential as anti-diabetic in lowering glucose and HbA1c levels and therefore they can decrease the risk factor of heart failure.

Diabetes is directly or indirectly associated with alterations in lipid profile. Evidences suggested that insulin resistance contributes in the development of dyslipidemia. Insulin resistance initiates the conditions of high triglyceride level, low HDL level and high small dense LDL level (Mooradian, 2009).

Garlic has been proposed to have direct anti-atherogenic (preventive) and anti-atherosclerotic (causing regression) effects at the artery wall (Orekhov and Grunwald, 1997). The possible mechanisms of garlic as lipid lowering agent are its inhibitory effect on hepatic activities of lipogenic and cholesterogenic enzymes such as malic enzyme, fatty acid synthase, glucose-6 phosphate dehydrogenase and 3-hydroxy-3-methyl-glutaryl-CoA (HMG CoA) reductase (Yeh and Liu, 2001). It was also suggested that garlic lowers serum lipids by delaying lipid absorption from gastrointestinal tract and diminishing LDL cholesterol synthesis in the liver (Afkhami-Ardekani *et al*., 2006). In an animal study, garlic supplement could significantly decrease total cholesterol, triglyceride, LDL and VLDL serum levels (Prasad *et al*., 2009).

Turmeric has also been shown to lower total cholesterol, triglyceride and LDL levels. The possible mechanisms have been proposed regarding anti-dyslipidemia effect of turmeric, i.e., increasing cholesterol catabolism by increasing hepatic cholesterol-7a-hydroxylase activity (Babu and Srinivasan, 1997), inhibiting cholesterol synthesis by inhibiting HMG CoA reductase (Jang *et al*., 2008). Curcumin was also found to increase LDL receptor (LXR), which plays a role in elimination of LDL from blood (Peschel *et al*., 2007) and to inhibit dietary cholesterol absorption (Arafa, 2005). In summary, we concluded that garlic and turmeric involved in regulation of lipid profile.

Garlic and turmeric combination contributed to improve lipid profile in diabetic-dyslipidemic patients. Increasing dose of turmeric and garlic combination increased HDL level. The LDL level showed no change in ITT group A, B and C. However, we observed a decrease of LDL in subgroup A, B and C among subjects with baseline LDL level >150 mg dL^{-1}. The triglyceride level was also relatively similar in ITT group A, B and C. Among the three groups, group C showed the most consistent improvement of LDL, HDL and triglyceride levels. However, the improvement has not yet reached normal level and some were not statistically significant. The effect of turmeric and garlic combination was more effective for more severe dyslipidemia patients but this finding required further investigations using more samples. Based on this result in lipid profile of diabetic-dyslipidemic patients, turmeric and garlic is a potent combination to increase HDL level.

Present results that turmeric and garlic improved lipid profile supported by others (Orekhov and Grunwald, 1997; Lau, 2001; Hussain, 2002; Yeh and Liu, 2001; Weisberg *et al*., 2008). Several studies contradicted this result. Superko and Krauss (2000) showed that garlic powder supplementation for 12 weeks had no significant effect on plasma lipids and lipoprotein. It has been reported that hypocholesterolemic effect occurs only after long term dietary administration of garlic i.e., 6 months (Lau *et al*., 1987). Ashraf *et al*. (2005a) have observed that the onset of hypolipidemic effect was evident at 6th week and become more progressive and greater with time. Therefore, the modest improvement of serum lipids in our study may be due to the short term of treatment. This was supported by Duda *et al*. (2008) that reported the increased HDL level after short-term garlic supplementation.

In this study, the body mass index significantly decreased in all groups ($p<0.05$). This is in agreement with animal study that showed that dietary curcumin was associated with significantly less body weight and less body fat when compared to the control group. The curcumin-enriched diet significantly reduced the weight of Diet-Induced Obesity (DIO) mice by 2 weeks (Weisberg *et al*., 2008). It was also suggested that hypolipidemic effect of curcumin could be also valuable for the prevention of high-fat induced obesity (Arafa, 2005). Curcumin is known to decrease ATP biosynthesis resulted in an increase of AMP: ATP ratio and then activation of 5'-AMP kinase (AMPK). Activated AMPK would inhibit the synthesis of fatty acid and cholesterol which explains the anti-obesity effect of curcumin (Lim *et al*., 2009).

Adverse events were recorded during therapy every two weeks. Administration of extract combination up to 2.4 g daily did not cause any serious adverse events. The administration of the three levels of dosages for three

months decreased the level of AST and ALT, ureum and creatinin, which were still within the normal limits (data not shown). These results were in agreement with previous study that administration of curcumin decreased of AST, ALT and creatinin levels (Arafa, 2005; Nwozo *et al*., 2009). In this study, the administration of garlic and turmeric combination up to 2.4 g daily was found to be safe and well tolerated. Our teratogenicity study in mice showed that the combination of turmeric and garlic extract of 1000 mg kg^{-1} b.wt. each, which is equivalent to 11.20 g of each extract in human, was safe to fetus of mice (Sukandar *et al*., 2008).

Combination of turmeric and garlic extracts showed a better antidyslipidemia and antidiabetes effect compared to its single usage. We suspected that the side effects from garlic usage could be attenuated by turmeric. For example, gastrointestinal disorder caused by garlic usage was compensated by turmeric which has been proved to improve gastrointestinal disorder in irritable bowel syndrome (Bundy *et al*., 2004; Coon and Ernst, 2002). According to Tiwari and Rao (2002), there is advantage of polyherbal over monoherbal therapy. Polyherbal therapy may have synergistic, potentiative, agonist/antagonist pharmacological effect within themselves that produce therapeutic efficacy with minimum side effects (Eyong *et al*., 2008). Turmeric also stabilizes the allicin in garlic extract towards chemical degrade and furthermore reduces the bad odor from garlic caused by its sulfuric compound.

CONCLUSIONS

The results of this study showed that administration of garlic and turmeric combination decreased the plasma glucose levels and improved the lipid profiles of type-2 diabetic-dyslipidemic patients. It also significantly decreased the BMI. The safety data also showed that 3 months administration of the extract combination for all dosage levels were safe and well tolerated.

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REFERENCES

Afkhami-Ardekani, M., A.R. Kamali-Ardekani and A. Shojaoddiny-Ardekani, 2006. Effects of garlic on serum lipids and blood glucose of type 2 diabetic patients. Int. J. Diab. Dev. Countries, 26: 86-88.

Arafa, H.M., 2005. Curcumin attenuates diet induced hypercholesterolemia in rats. Med. Sci. Monit., 11: 228-234.

Ashraf, M.Z., M.E. Hussain and M. Fahim, 2005. Antiatherosclerotic effects of dietary supplementations of garlic and turmeric: Restoration of endothelial function in rats. Life Sci., 77: 837-857.

Ashraf, R., K. Aamir, A.R. Shaikh and T. Ahmed, 2005. Effects of garlic on dyslipidemia in patients with type 2 diabetes mellitus. J. Ayub. Med. Coll. Abbottabad, 17: 60-64.

Babu, P.S. and K. Srinivasan, 1997. Hypolipidemic action of curcumin, the active principle of turmeric (*Curcuma longa*) in streptozotocin induced diabetic rats. Mol. Cell. Biochem., 166: 169-175.

Banerjee, S.K. and S.K. Maulik, 2002. Effect of garlic on cardiovascular disorders: A review. Nutr. J., 1: 1-14.

Bundy, R., A.F. Walker, R.W. Middleton and J. Booth, 2004. Turmeric extract may improve irritable bowel syndrome symptomology in otherwise healthy adults: A pilot study. J. Alter. Complement. Med., 10: 1015-1018.

Chang, M.L.W. and M.A. Johnson, 1980. Effect of garlic on carbohydrate metabolism and lipid synthesis in rats. J. Nutr., 110: 931-936.

Coon, J.T. and E. Ernst, 2002. Systematic review: Herbal medicinal products for non-ulcer dyspepsia. Aliment. Pharmacol. Ther., 16: 1689-1699.

Duda, G., J. Suliburska and D. Pupek-Musialik, 2008. Effects of short-term garlic supplementation on lipid metabolism and antioxidant status in hypertensive adults. Pharmacol. Reports, 60: 163-170.

Eckel, R.H., 2008. Diabetic dyslipidemia and cardiovascular risk. Curr. Diab. Rep., 8: 421-423.

Eidi, A., M. Eidi and E. Esmaeili, 2006. Antidiabetic effect of garlic (*Allium sativum* L.) in normal and streptozotocin-induced diabetic rats. Phytomedicine, 13: 624-629.

Eyong, E.U., G.E. Egbung, I.J. Atangwho and P.E. Ebong, 2008. The antidiabetic efficacy of combined extracts from two continental plants: *Azadirachta indica* (A. Juss) (Neem) and *Vernonia amygdalina* (Del.) (African Bitter Leaf). Am. J. Biochem. Biotehcnol., 4: 239-244.

Fujiwara, H., M. Hosokawa, X. Zhou, S. Fujimoto and K. Fukuda *et al*., 2008. Curcumin inhibits glucose production in isolated mice hepatocytes. Diabetes Res. Clin. Pract., 80: 185-190.

Hossain, P., B. Kawar and M. El-Nahas, 2007. Obesity and diabetes in the developing world-A growing challenge. New Engl. J. Med., 356: 213-215.

Hussain, H.E.M.A., 2002. Hypoglycemic, hypolipidemic and antioxidant properties of combination of curcumin from *curcuma longa* Linn. and partially purified product from *abroma augusta*, Linn. in streptozotocin induced diabetes. Indian J. Clin. Biochem., 17: 33-43.

Iribarren, C., A.J. Karter, A.S. Go, A. Ferrara, J.Y. Liu, S. Sidney and J.V. Selby, 2001. Glycemic control and heart failure among adult patients with diabetes. Circulation, 103: 2668-2673.

Itokawa, H., Q. Shi, T. Akiyama, S.L. Morris-Natschke and K.H. Lee, 2008. Recent advances in the investigation of curcuminoids. Chin. Med., 3: 11-11.

Jain, R.C. and C.R. Vyas, 1975. Garlic in alloxan-induced diabetic rabbits. Am. J. Clin. Nutr., 28: 684-685.

Jain, S.K., J. Rains and K. Jones, 2006. Effect of curcumin on protein glycosylation, lipid peroxidation, and oxygen radical generation in human red blood cells exposed to high glucose levels. Free. Radic. Biol. Med., 41: 92-96.

Jang, E.M., M.S. Choi, U.J. Jung, M.J. Kim and H.J. Kim *et al*., 2008. Beneficial effects of curcumin on hyperlipidemia and insulin resistance in high-fat-fed hamster. Metab. Clin. Exp., 57: 1576-1583.

Kuroda, M., Y. Mimaki, T. Nishiyama, T. Mae and H. Kishida *et al*., 2005. Hypoglycemic effects of turmeric (*Curcuma longa* L. Rhizomes) on genetically diabetic KK-Ay mice. Biol. Pharm. Bull., 28: 937-939.

Lau, B.H., 2001. Suppression of LDL oxidation by garlic. J. Nutr., 131: 985S-988S.

Lau, B.H.S., F. Lam and R. Wang-Cheng, 1987. Effect of an odor-modified garlic preparation on blood lipids. Nutr. Res., 7: 139-149.

Lim, H.W., H.Y. Lim and K.P. Wong, 2009. Uncoupling of oxidative phosphorylation by curcumin: Implication of its cellular mechanism of action. Biochem. Biophys. Res. Com., 389: 187-192.

Maheshwari, R.K., A.K. Singh, J. Gaddipati and R.C. Srimal, 2006. Multiple biological activities of curcumin: A short review. Life Sci., 78: 2081-2087.

Mooradian, A.D., 2009. Dyslipidemia in type 2 diabetes mellitus. Nat. Clin. Pract. Endocrin. Metab., 5: 150-159.

Nwozo, S., O. Adaramoye and E. Ajaiyeoba, 2009. Oral administration of extract from Curcuma longa lowers blood glucose and attenuates alloxan-induced hyperlipidemia in diabetic rabbits. Pak. J. Nutr., 8: 625-628.

Orekhov, A.N. and J. Grunwald, 1997. Effects of garlic on atherosclerosis. Nutrition, 13: 656-663.

Patumraj, S., S. Tewit, S. Amatyakul, A. Jariyapongskul, S. Maneesri, V. Kasantikul and D. Shepro, 2000. Comparative effects of garlic and aspirin on diabetic cardiovascular complications. Drug Deliv., 7: 91-96.

Peschel, D., R. Koerting and N. Nass, 2007. Curcumin induces changes in expression of genes involved in cholesterol homeostasis. J. Nutr. Biochem., 18: 113-119.

Prasad, R., M.K. Rose, M. Virmani, S.L. Garg and J.P. Puri, 2009. Lipid profile of chicken (*Gallus domesticus*) in response to dietary supplementation of garlic (*Allium sativum*). Int. J. Poult. Sci., 8: 270-276.

Saudek, C.D., W.H. Herman, D.B. Sacks, R.M. Bergenstal, D. Edelman and M.B. Davidson, 2008. A new look at screening and diagnosing diabetes mellitus. J. Clin. Endocrinol. Metab., 93: 2447-2453.

Selvin, E., J. Coresh, S.H. Golden, F.L. Brancati, A.R. Folsom and M.W. Steffes, 2005. Glycemic control and coronary heart disease risk in persons with and without diabetes. Arch. Int. Med., 165: 1910-1916.

Sukandar, E.Y., I. Fidrianny and A.N. Garmana, 2008. Effect of garlic and turmeric extracts on Swiss-Webster mice fetus. J. Kedokt. Maranatha., 8: 36-44.

Superko, H.R. and R.M. Krauss, 2000. Garlic powder, effect on plasma lipids, postprandial lipemia, low-density lipoprotein particle size, high-density lipoprotein subclass distribution and lipoprotein (a). J. Am. Coll. Cardiol., 35: 321-326.

Thomson, M., Z.M. Al-Amin, K.K. Al-Qattan, L.H. Shaban and M. Ali, 2007. Anti-diabetic and hypolipidaemic properties of garlic (*Allium sativum*) in stereptozotocin- induced diabetic rats. Int. J. Diabetes Metabol., 15: 108-115.

Tiwari, A.K. and J. Madhusudana-Rao, 2002. Diabetes mellitus and multiple therapeutic approaches of phytochemicals: Present status and future prospects. Curr. Sci., 83: 30-38.

Weisberg, S.P., R. Leibel and D.V. Tortoriello, 2008. Dietary curcumin significantly improves obesity-associated inflammation and diabetes in mouse models of diabesity. Endocrinology, 149: 3549-3558.

Yeh, Y.Y. and L. Liu, 2001. Cholesterol-lowering effect of garlic extracts and organosulfur compounds: Human and animal studies. J. Nutr., 131: 989S-993S.