The Efficacy of Cholesterol-lowering Action and Side Effects of Garlic Enteric Coated Tablets in Man

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The present study aimed at investigating the cholesterol-lowering and side effects of garlic enteric coated tablets in comparison with placebo tablets. The study is a randomized double-blinded crossover design involving 116 volunteers. However, 16 of them did not complete the study. The remaining 100 volunteers were divided into two groups: 45 were in the trial group and the remaining 55 in the control group. The volunteers in the trial group were asked to take garlic tablets in the first three months, placebo in the second three months and discontinue all tablets in the last three months, while the volunteers in the control group started with three months of placebo followed by three months of garlic tablets and ended up with three months of tablets discontinuity. The results showed that there were no significant differences in the total serum cholesterol levels between the two groups at the end of three months or six months of the study. Side effects included headache, itching and complaints of garlic smell. No serious side effects relating to liver, kidney functions or hematologic side effects were detected.

Keywords : *Garlic, Cholesterol-lowering agent, Hyperlipidemia*

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Hyperlipidaemia is an important risk factor of coronary artery diseases which often lead to myocardial infarction and heart failure[1,2]. It has been shown that control of total serum cholesterol levels can reduce the incidence and mortality from coronary artery disease[2,3]. The control of serum cholesterol level is recognized as a primary prevention of the coronary artery disease and an attribute to less financial loss and an improved quality of life for the patients. Exercise and a diet with minimal saturated lipid will help the patients to increase their serum HDL and lower triglyceride levels[5,6]. Cholesterol lowering medications are prescribed either for patients with high risks of coronary artery disease which include obesity, hypertension, diabetes and smoking habits. Lipiding-lowering drugs used for treating high-risk persons includes 3-hydroxy - 3 methyl glutaryl coenzyme A reductase inhibitors (statins), bile acid sequestrants, fibrates and nicotinates[2]. Most of these agents have side effects[2] and are expensive. From previous studies on the effectiveness of garlic, a traditional herb used widely in Thailand, it has been reported that garlic with its active principle agent, Allicin, can reduce the levels of serum cholesterol, triglyceride and LDL[8-15]. In terms of the mechanism of action, it reduces cholesterol synthesis, inhibits fatty acid synthesis and platelet aggregation, and prevents thrombosis. Allicin has also been used for treating and preventing cardiovascular diseases. With regards to the effectiveness of garlic, there have been several studies on cholesterol-lowering effect conducted in Thailand and overseas. The findings from these reports were, however, inconsistent. Some studies show benefit[9,10,14,15] while the others found the opposite[16-19]. The earlier studies examined a variety of garlic dosages. Of these studies, some were conducted either with a small number of subjects or were uncontrolled-studies. The present study aimed at exploring the effectiveness of enteric coated tablets of garlic extract on the cholesterol-lowering effect in Thai patients. The garlic tablets used in this study were manufactured in Thailand. Each tablet contained 5000 micrograms, 1.5% of Allicin.

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Material and Method

The study was conducted with an experimental double-blinded crossover design in which

neither the volunteers nor the researchers knew who were given garlic until the study was completed. The volunteers who met the following inclusion criteria were enrolled in the study: aged 35 years and over, serum cholesterol levels greater than 250 gm/dl, no other complications including hepatic, kidney, heart, cerebrovascular diseases, and not on antihypertensive drugs. The study volunteers were all given advice on dietary control and physical exercises. All had been informed about the study procedures and were involved in the study with the volunteers' consent.

The study volunteers were randomly assigned to the trial or control group. In terms of study design, all of the volunteers participated over a period of 9 months. The volunteers in the trial group (group 1) followed through with three consecutive regimens of three months each: taking garlic tablets, taking placebo and discontinuing the tablets. The volunteers in the control group (group 2) had three different consecutive regimens: started with three months of placebo followed by three months garlic tablets and ended up with three months tablet discontinuity. Placebo tablets looked and tasted like the garlic preparation but contained no active ingredient.

To examine the effect of garlic on serum lipid levels in volunteers with high serum lipid, the volunteers were required to take blood tests for serum cholesterol, triglyceride and HDL levels monthly over a nine-month period. Blood sugar, liver, kidney functions and complete blood counts were tested monthly and the volunteers were asked about any side effects. The study would terminate when complications occurred which required urgent treatment, when adverse drug reactions were observed, or when the volunteers could not comply with the procedures specified.

Statistical analysis of the differences between the control and trial group were conducted by means of t-test, ANOVA, Least Significance Difference LSD and the relationship between variables was determined by using chi-square test.

Results

Among the 116 eligible volunteers, 16 dropped out of the study. Of these 16, one developed itching, one had headache and 14 could not be followed up for blood testing throughout the study. There were 100 remaining volunteers. Demographic details concerning the volunteers are provided in Table 1.

Group I (Trial group):

The total of 45 volunteers in this group, were 33.3% in males and 66.7% in females as well as the average age of the group was 47.02 years. For the serum levels of cholesterol, triglyceride, LDL and HDL, the group had baseline averages of 283.84, 167.09, 187.67 and 62.69 mg% respectively.

Table 1. Demographic characteristics of the subjects in both group 1 and group 2

Characteristics	Group 1 (N = 45)	Group 2 (N = 55)	Statistic Significance
Gender			
• Male	15 (33.3%)	18 (32.7%)	NS
• Female	30 (66.7%)	37 (67.3%)	NS
Age (years)	47.02±6.96	47.03±6.7	NS
Cholesterol (mg%)	283.84±23.48	284.27±28.44	NS
HDL (mg %)	62.69±15.25	66.16±16.85	NS
Triglyceride (mg%)	167.09±124.79	137.22±71.59	NS
LDL (mg%)	187.67±30.13	190.65±31.98	NS

(mean ± SD)
Group 1 = Trial group
Group 2 = Control group

Group II (Control group):

The total of 55 volunteers were in this group. The group consisted of 32.7% males, 67.3% females with an average age of 47.03 years. In terms of serum cholesterol, triglyceride, LDL and HDL levels, the group had baseline averages of 284.27, 137.22, 190.65 and 66.16 mg% respectively.

Cholesterol levels

During the study over 9 months, cholesterol levels were carefully monitored in both the trial and control groups. Within each group, cholesterol levels either at the 3rd, or 6th, or 9th month differed from its own group's baseline (ANOVA; group 1 *p* value = 0.005; group 2 *p* value = 0.036), as shown in Table 2. But there were no significant differences between cholesterol levels among the volunteers in group 1 and group 2 at the end of the 3rd, 6th and the 9th months (Table 3). By using ANOVA and LSD for further analysis, it was found that there were no significant differences of cholesterol levels among those at 3rd, 6th, and 9th months within each group although there was decreasing trend of this laboratory outcome. Therefore, the findings suggested that cholesterol levels were not influenced by garlic tablets. Since the significant difference of the cholesterol levels at the 3rd and 6th months between group 1 and group 2 were not found, the findings could not be interpreted in the way that the cholesterol levels were attributable to

Table 2. Laboratory outcomes of patients in both group 1 and 2 at the baseline, 3rd, 6th and 9th months and the significant differences of these laboratory levels within each group

	At baseline Group 1 = 45 Group 2 = 55	At the 3rd month	At the 6th month	At the 9th month	Significant difference within each group (by using ANOVA)	The months which differed from the others
Cholesterol					*p* value	
Gr 1	283.84±23.48	266.18±29.46	260.24±30.14	259.50±30.03	0.005	▪ 0 vs 3,6,9
Gr 2	284.27±28.44	266.82±29.84	265.05±27.22	268.64±32.94	0.036	▪ 0 vs3,6,9
Triglyceride						
Gr 1	167.09±124.8	154.04±106.92	164.29±160.45	142.73±84.04	0.964	
Gr 2	137.22±71.59	128.35±63.66	130.13±71.93	127.87±81.36	0.968	
HDL						
Gr 1	62.69±15.25	57.47±12.08	57.27±10.44	55.13±11.77	0.225	
Gr 2	66.16±16.85	61.04±14.50	60.78±14.38	59.82±12.63	0.266	
LDL						
Gr 1	187.67±30.13	177.89±29.35	170.18±37.76	179.84±37.79	P >0.05	
Gr 2	190.65±31.98	180.13±30.1	178.27±26.31	184.35±35.04	P >0.05	

the garlic tablets. In other words, it is likely that the decreasing trend of the cholesterol levels either at the 3rd, or 6th, or 9th from its baseline could be caused by other factors, and not by the garlic tablets. This was also confirmed by chi-square test when the correlation between taking garlic tablets and the ability to lower cholesterol levels was not found ($p > 0.05$), as shown in Table 4.

Table 3. The comparison of means between group 1 and 2 by using Student's t-test at95% confidence

	Group 1 N=45	Group 2 N=55	student t-test
Age	47.02±6.96	47.04±6.7	NS
HDL			
Baseline	62.69±15.25	66.16±16.85	0.287
3 rd month	57.47±12.08	61.04±14.50	0.190
6th month	57.27±10.44	60.78±14.38	0.161
9th month	55.13±11.77	59.82±12.63	0.060
LDL			
Baseline	187.67±30.13	190.65±31.98	NS
3rd month	177.89±29.35	180.13±30.1	NS
6th month	170.18±37.76	178.27±26.31	NS
9th month	179.84±37.79	184.35±35.04	NS
Cholesterol			
Baseline	283.84±23.48	284.27±28.44	0.936
3rd month	266.18±29.46	266.82±29.84	0.915
6th month	260.24±30.14	265.05±27.22	0.404
9th month	259.50±30.03	268.64±32.94	0.155
Triglyceride			
Baseline	167.09±124.79	137.22±71.59	0.158
3rd month	154.04±106.92	128.35±63.66	0.140
6th month	164.29±160.45	130.13±71.93	0.160
9th month	142.73±84.04	127.87±81.36	0.373

The levels of Triglyceride, HDL, and LDL

It was also found in the present study that the serum levels of triglyceride, HDL and LDL at baseline and at the end of the 3rd, 6th and 9th months in each group did not differ from one another (ANOVA; p value > 0.05 in both group 1 and 2) (Table 2). When the significant differences of these laboratory levels between group 1 and 2 were tested, no significant difference was found either at the baseline, or the 3rd, or 6th or 9th month (Student t-test, $p>0.05$) (Table 3). These findings suggested that garlic tablets had no effect on these laboratory values (Table 3 and 4).

There were no significant differences in the measured parameters such as SGOT, BUN, Cr, FBS levels between the trial and control groups.

The most frequent side effects were unpleasant garlic odor and increased appetite. One volunteer had pruritus, one had severe headache, which resulted in the discontinuation of his medication. There were, however, no serious renal, hepatic and hematological side effects. In general, garlic tablets were well tolerated.

Discussion

The present study was conducted by using a double blinded randomised crossover design. One hundred and sixteen volunteers who met the entry criteria were randomly recruited. However, of these 116 volunteers, 16 could not participate throughout

Table 4. Testing for relationship between garlic taking and the ability in improving hyperlipidemia by using chi-square test

	Have taken garlic	Have not taken garlic	Statistical significance p value
Cholesterol			
• The number of patients with improved laboratory results	81	149	0.21
• The number of patients either with unimproved or with unchanged laboratory outcomes	19	51	

Remark: The number of patients in the categories of either have taken or have not taken garlic tablets were obtained by the following design

	3rd month	6th month	9th month
Patients who have taken garlic tablets	Group 1	Group 2	-
Patients who have not taken garlic tablets	Group 2	Group 1	Group 1+Group 2

the entire research period and were excluded from the study. The remaining 100 volunteers were assigned to either the control or trial group. The volunteers in both groups were also given information/educational intervention from the physicians and gave informed consent. There was no significant difference between the control and trial group in the variables studied, such as age, the levels of serum cholesterol, triglyceride, LDL and HDL. None of the volunteers had either diabetic, hypertension, hepatic or renal diseases. All of the volunteers in both groups were educated on diet control and doing exercises. Therefore, it could be considered that there were similarities between the volunteers assigned to each group. In the present study, it was revealed that the cholesterol and LDL levels of the volunteers in both the control and trial groups, decreased from the baselines. But when compared to the control and trial group, it was found that means of these laboratory results of the two groups did not differ significantly. The findings suggest that there is little room for certainty in cholesterol and LDL lowering by using garlic tablets. Therefore, garlic tablets were no better than placebo in lowering serum cholesterol and LDL levels. Perhaps, volunteers may feel obliged to comply with the physicians' instruction on diet control and doing exercise rather than on the effect of garlic tablets alone.

In a review of the published literature, the correlation between garlic intake and its lipid lowering effect was inconsistent. However, the findings of the present study were similar to the ones reported by Simons in 1995[16] and Issacsohn in 1998[17], in which 300 mg of Kwai or Garlic powder was given to the subjects 3 times daily. Also, the studies of Berthold in 1997[18] and Gardner in 2001[19] found similar negative results by using garlic oil in former study and 500-1000 mg of garlic powder daily in the latter one.

Conversely, some previous studies showed favorable outcomes of garlic. For example, the study of Vorberg in 1990[9] used 900 mg garlic powder per day and found that among 40 subjects involved, garlic could lower cholesterol and triglyceride levels. Another study of Jain in 1993[14], in which 300 mg of garlic powder was given 3 times daily for 12 weeks, found favorable results: LDL could be decreased by 11%, while triglyceride and HDL remained unchanged. Also Steiner in 1996[10] found that 7.2 gm of aged garlic extract per day for 6 months could lower cholesterol and LDL by 6.1% and 4% respectively. Similarly, the research carried out by Adler in 1997[15] demonstrated consistent outcomes as the 3 studies mentioned above. In his study, 50 subjects were given 900 mg of Kwai for 12 weeks and found that it could lower both cholesterol and LDL levels. The reported mechanisms include reduced hepatic 3-hydroxy-3-methyl glutaryl coenzyme A reductase activity and increased bile acid excretion[13].

In Thailand, there have been several studies relating to effectiveness of garlic. Several favorable outcome researches emerged for the effectiveness of garlic in its ability in cholesterol lowering. For example, in 1987 the study conducted by Nitiyanant et al[20] was designed to determine the effectiveness of garlic dried powder extract. They found that garlic could contribute to cholesterol lowering. Also, the study of Sitprija in 1987[21] and of Plengvidhya in 1988[22] showed the trend in cholesterol and triglyceride lowering together with HDL increasing by using spray dried garlic preparation. But unfortunately, there was no significant difference found between control and trial groups which could be attributable to the insufficient number of subjects in the study.

The findings of present study by using enteric coated tablets of garlic consisting of 500 mg of Allicin seem to be a contrast to those of other previous studies conducted in Thailand. Even where the trend

of lipid lowering was observed, the effectiveness of the garlic enteric coated tablets in lipid lowering was consistent between control and trial groups. That is, no significant differences of lipid levels between control and trial groups were found although the decreasing trend of lipid levels over time could be observed. A possible explanation for this finding could be that strict diet control and exercise among the subjects in both groups in early period of the study could influence and contribute to decreased lipid levels. This explanation is supported by several previous studies which reported that diet control could lower cholesterol level by 5.3% after receiving 6 months intervention. In terms of doing exercise, it has been reported that aerobic exercise could increase serum HDL levels, together with a decrease in triglyceride level, while it has no effect on cholesterol level. Also, it was found in previous studies that low intensity endurance exercise could decrease LDL levels together with an increase in HDL levels significantly[6].

As regards the commonest complaint relating to garlic preparation, the unpleasant smell of garlic was the most common complaint. Minor side effects of garlic, such as itching and headache, were observed, while no other serious side effects were detected.

Conclusion

Garlic enteric coated tablets consisting of 5000 micrograms of Allicin, used in this study did not contribute to either lowering serum cholesterol and triglyceride levels or increasing HDL levels. Therefore, further study is needed, especially in determining whether the higher strength of garlic could influence lipid levels and in investigating if other enteric coated tablet preparations could contribute to better stability of garlic components. Since it has been reported that garlic could have a similar mechanism as statin in lowering and regulating cholesterol and fatty acid levels, taking it in the evening would be preferred. Further study on an appropriate regimen including appropriate doses and time for taking medication should also be considered.

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การศึกษาเปรียบเทียบประสิทธิผลและผลข้างเคียงของกระเทียมเคลือบแบบ Enteric coated กับ Placebo ในการลดโคเลสเตอรอล

ใยวรรณ ธนะมัย, ศรชัย วีรมโนมัย, นิศา อินทรโกเศศ

การวิจัยนี้เพื่อศึกษาประสิทธิผลและผลข้างเคียงของกระเทียม ในการลดโคเลสเตอรอล เป็นการศึกษาแบบ Randomised double blinded crossover study โดยมีอาสาสมัคร 116 คน 16 คน ไม่สามารถร่วมจนจบโครงการได้ เหลืออาสาสมัคร 100 คน แบ่งเป็นกลุ่มทดลอง 45 คน กลุ่มควบคุม 55 คน โดยกลุ่มทดลองได้รับกระเทียม 3 เดือน และยาหลอก 3 เดือน และหยุดยาต่อไปอีก 3 เดือน ในขณะที่กลุ่มควบคุมได้รับยาหลอกก่อน 3 เดือน ต่อด้วยกระเทียม 3 เดือน และหยุดยาต่ออีก 3 เดือนเช่นกัน ปรากฏว่าระดับโคเลสเตอรอลในเดือนที่ 3 และเดือนที่ 6 ในกลุ่มทดลอง และกลุ่มควบคุมไม่แตกต่างกัน แสดงว่ากระเทียมไม่มีผลในการลดโคเลสเตอรอล สำหรับผลข้างเคียงที่พบคือ มีกลิ่นกระเทียม คันตามตัว ปวดศีรษะ ไม่พบผลข้างเคียงที่รุนแรงอื่น ๆ ไม่ว่าจะเป็นผลข้างเคียงของตับ ไต ตลอดจนเม็ดเลือด