Original Research

Hypocholesterolemic Effect of an Enteric-Coated Garlic Supplement

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Key words: garlic supplement, allicin, enteric coating, hypercholesterolemia, lipid profile, food intake

Objective: To evaluate the hypocholesterolemic effect of an enteric-coated garlic supplement standardized for allicin-releasing potential in mild to moderate hypercholesterolemic patients.

Methods: A double-blind randomized, placebo-controlled intervention study was conducted in 46 hypercholesterolemic subjects who had failed or were not compliant with drug therapy. Each subject was given dietary counseling to lower fat intake and enteric-coated Australian garlic powder tablets with 9.6 mg allicin-releasing potential or matching placebo tablets.

Results: After 12 weeks, the garlic supplement group (n=22) had a significant reduction in total cholesterol (TC, −0.36 mmol/L, −4.2%) and LDL-cholesterol (LDL-C, −0.44 mmol/L, −6.6%) while the placebo group (n=24) had a non-significant increase in TC (0.13 mmol/L, 2.0%) and LDL-C (0.18 mmol/L, 3.7%). HDL-cholesterol was significantly increased in the placebo group (0.09 mmol/L, 9.1%), compared to the garlic group (−0.02 mmol/L, −0.9%), and no significant difference in triglycerides or in LDL/HDL ratio was observed between groups.

Conclusions: The study demonstrates that enteric-coated garlic powder supplements with 9.6 mg allicin-releasing potential may have value in mild to moderate hypercholesterolemic patients when combined with a low fat diet. Taken with other evidence, the efficacy of garlic for lipoprotein metabolism might require allicin bioavailability to be enhanced through the use of, for example, an enteric-coated dose form. If this is the case, the possibility remains that greater hypocholesterolemic efficacy may be evident at a higher allicin dose. Also noteworthy in this study was a small reduction in energy intake with garlic compared with placebo, attributable to reduction in fat, carbohydrate and alcohol intakes. This may also have contributed to the effects on blood lipids. This study suggests that garlic supplementation has a cholesterol-lowering effect, which may be mediated by direct action of a biologically active compound or compounds and in part through the effect on food and nutrient intake.

INTRODUCTION

Over 40 clinical trials have been conducted to determine the lipid-lowering effects of fresh garlic (*Allium sativum*) and garlic supplements [1]. Pooling of data in two meta-analyses indicates that reduction of both serum cholesterol (9% to 12%) and triglycerides (13.4%) [1–3] may be expected after at least four weeks of treatment, but even in rigorously conducted studies, inconsistent lipid-lowering results have been reported [4–7]. This may have arisen because of methodological shortcomings [2,3,6,8] such as inappropriate methods of randomization, lack of dietary run in period, short duration, failure to undertake intention to treat analysis and inadequate statistical power. More recent studies however suggest that the incomplete *in vivo* release of allicin may be partly responsible for the inconsistent results [9].

Allicin has been proposed as the active compound produced by garlic [10–13] responsible for health promotion and hypocholesterolemic benefits [1,14–15]. Nevertheless, it does not circulate long in blood due to extensive metabolism [16–19], and forms an active metabolite or metabolites which have not yet been identified [18,20]. While other sulfur-based compounds are proposed to be active [21–22], their role in lowering

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elevated plasma lipids is untested, so it seems "for now the beneficial effects attributed to garlic are best obtained from fresh garlic" [10] or garlic powder [1]. Fresh and powdered garlic is also representative of historic use and health promotion supported by epidemiological evidence [23–24].

Formulation of garlic supplements could also be a critical factor, as chemical conversion of alliin to allicin is dependent upon the alliinase enzyme which is inhibited in acidic conditions [11,25]. It is suggested that this could be overcome with use of an enteric-coated dose form that optimizes *in vivo* allicin release [9]. In the present study, we evaluated the hypocholesterolemic effect of an enteric-coated garlic supplement standardized for allicin releasing potential in mild to moderate hypercholesterolemic subjects. This garlic supplement was prepared in the form of tablets from Australian-based freeze-dried garlic powder and was not commercially available at the time of the clinical trial.

SUBJECTS AND METHODS

Study Design

A double-blind, randomized, placebo-controlled intervention study was conducted using a well-characterized enteric-coated garlic powder supplement in mild to moderate hypercholesterolemic subjects. Upon recruitment, subjects entered a dietary run-in period (one to two weeks), then attended the clinic every four weeks for the following 12 weeks. Changes to blood lipids (LDL, triglycerides, HDL, LDLC/HDLC ratio) were assessed at each visit and the completion of the study. The study protocol was approved by the Monash University Standing Ethics Committee on Research in Humans. Written informed consent was obtained from each subject before any study-specific procedure was performed.

Subjects

Volunteers who had failed to comply with previous lipid-lowering therapies (% in each category) were recruited by local newspaper advertisements and word of mouth. Subjects were eligible for the study if their screening blood cholesterol was in the range of 6.5 to 9.0 mmol/L. The exclusion criteria included having significant renal or hepatic disease, a heart condition, uncontrolled endocrine disease, diabetes mellitus or gastrointestinal disease interfering with drug absorption, undergoing other therapies for high cholesterol or anticoagulant therapy, presence of alcohol or drug abuse or any known adverse reaction to HMG-CoA reductase inhibitors. Women of childbearing age not practicing an adequate method of contraception, pregnant and lactating women were also excluded. If subjects showed any significant disease or condition, including emotional disorders which in the opinion of the investigator could alter the course of the study or the patient's ability to participate in the study, they were also excluded.

Run-In Phase

All subjects were required to have a one- or two-week run-in period before the commencement of clinical intervention. At Visit 1, each subject was given dietary advice and encouraged to follow the Australian National Heart Foundation guidelines, i.e. no more than 30% of total energy intake be derived from dietary fat, 10% from polyunsaturated fat and 6% from saturated fat, throughout the study. A specific request was also made not to consume any garlic supplement during the study period.

Clinical Intervention

Subjects were randomly assigned to receive garlic supplement or placebo over a 12-week study period, and fasting blood samples were taken for lipid assessments. Every four weeks, subjects were given a total of 116 tablets and asked to return the remaining tablets at the next visit. Subjects in the garlic group consumed four enteric-coated garlic tablets daily with meals, two in the morning and two in the evening. Each garlic tablet contained 220 mg of garlic powder (equivalent to approximately 2.6 g fresh garlic) standardized to produce 2.4 mg allicin *in vitro*. The four tablets therefore produced 9.6 mg (1.09%) allicin per day. The placebo group received four tablets containing lactose. As the garlic and lactose tablets were slightly different in color and odor, all tablets were individually packed in foil to ensure they were indistinguishable to both investigators and subjects, who remained blinded throughout the study. Both garlic and placebo tablets were manufactured by Pharmaction Pty Ltd in Melbourne, Australia, and were compliant to the United States Pharmacopeia guidelines in terms of dissolution and disintegration [26].

All clinic visits were organized at Visit 2 for the entire study and a printed appointment schedule provided informing the subject of preparation required for each visit, including fasting for blood measurements. At each visit subjects were asked to comment on acceptability of the regimen, side effects, adherence to dietary recommendations and change in concomitant medications. Compliance to the medication was assessed at each visit throughout the study by counting the number of tablets remaining in the dispensing unit returned at each visit.

Fasting blood samples were analyzed for total cholesterol, triglycerides, HDL and LDL cholesterol. The measurement taken at Visit 1 was used to determine eligibility, and at Visit 2 as the baseline value. Liver function tests and full blood examination were undertaken before and after the clinical intervention, as indicators of toxicity or adverse effects. All biochemical measurements were performed at the Department of Clinical Biochemistry, Monash Medical Centre, Melbourne, Australia.

Demographic information, cigarette smoking, alcohol consumption and medical history were recorded at Visits 1 and 2. Adverse events and concomitant medications were recorded and documented throughout the study. Information on food was

collected using a seven-day food diary method at study entry and exit. A software package DIET/1 (Xyris, Queensland, Australia) with the Australian Food Composition Table (NUTTAB95, Canberra, ACT, Australia) was used to obtain data on nutrient intake.

Data Analysis

A Statistical Analysis System computer program version 6.12 (SAS Institute Inc, Cary, NC) was used to perform all the statistical analyses. Analyses of variance (ANOVA) and covariance (ANCOVA) were used, without and with adjustments for confounding factors, for comparisons between the placebo and garlic groups at different time points and the changes in parameters of interest from the baseline and study exit. The significance level was set at 5%.

RESULTS

Subjects were similar between treatment groups with respect to age, lipid profile and the proportion of gender, cigarette smoking and alcohol consumption status (Table 1). Of 46 subjects entering the study, a total of 43 completed the 12-week intervention trial. Three subjects voluntarily withdrew from the study, two men because of lack of interest and one woman because of heartburn, later diagnosed to be caused by a gastric ulcer. Reported side effects or complaints including increased bowel movement, flatulence and bloating were not different between groups, except for garlic breath odor reported by 18 of 20 subjects (90%) randomized to the garlic (which was noticed either by themselves or by a close associate), while none of the 23 subjects randomized to placebo reported this. It is, however, important to note that, despite being reported, the breath odor did not cause withdrawal of subjects from the study. All samples were handled, coded and blinded to questionnaire information.

Compliance to the Clinical Intervention

The tablet counting method, which was used to monitor compliance of subjects to the clinical intervention in the present study, showed that, overall, 97% of the subjects were 100% compliant, indicating that, despite the odor associated with the garlic tablets, the dose regimen was acceptable to study subjects.

Serum Lipid Profile and Its Changes over the Study Period

Blood lipid profile was monitored throughout the study and changes reported in Table 2. At the end of the 12-week intervention period, it was found that changes in TC, HDL-C, LDL-C and triglycerides were significantly different between the garlic and placebo groups. The mean total cholesterol concentration dropped in the garlic group by 0.36 mmol/L, compared to an increase recorded in the placebo group (0.13 mmol/L). Similarly, LDL-C was also reduced in the garlic group by 0.44 mmol/L, while the placebo group had an increase of 0.18 mmol/L. Surprisingly, HDL-C was significantly increased in the placebo group (0.09 mmol/L), compared to the minimal reduction in the garlic group (0.02 mmol/L). The changes in triglycerides were observed to be 0.16 mmol/L for the garlic group and −0.29 mmol/L for the placebo. No significant differences in the change between groups for LDL-C/HDL-C ratio were observed (Table 2).

Nutrient Intake and Changes during the Intervention

Dietary advice, with emphasis on a low-fat diet, was given and encouraged throughout the study. Many subjects reported being already aware of and compliant to "low fat" dietary guidelines (Table 3). The estimation of nutrient intake using a seven-day food diary method suggests that at study entry over 60% of the subjects had less than 30% of energy intake from fat

Table 1. Characteristics of Subjects at Registration (Visit 1)

Parameters	Placebo		Garlic	
	n		n	
Male:Female Ratio	24	13:11	22	12:10
Smoker (%)	24	0	22	14
Regular drinker (%)	24	33	22	36
		Mean ± SD		Mean ± SD
Age (years)	24	57.4 ± 9.0	22	52.6 ± 10.4
Weight (kg)	24	80.5 ± 20.9	22	69.4 ± 10.4
Height (cm)	24	167.8 ± 9.4	22	168.4 ± 10.2
Body mass index (kg/m^2)	24	28.4 ± 6.3	22	24.5 ± 2.6
Total cholesterol (mmol/L)	24	7.6 ± 0.9	22	7.5 ± 0.8
Triglycerides (mmol/L)	24	2.2 ± 1.6	22	2.0 ± 1.3
HDL cholesterol (mmol/L)	24	1.35 ± 0.49	22	1.34 ± 0.34
LDL cholesterol (mmol/L)	23	5.3 ± 0.9	20	5.3 ± 0.9
LDL/HDL cholesterol ratio	23	4.30 ± 1.76	20	4.13 ± 1.34

No significant differences between the treatment groups in age, weight, height, body mass index and blood lipids (*t* test).

Table 2. Change in Lipid Values after 12 Weeks' Supplementation

	Placebo		Garlic	
	n	Mean±SD	n	Mean±SD
At Study Entry (Visit 2)				
Total cholesterol (mmol/L)	24	7.1 ± 0.9	22	7.4 ± 1.1
Triglycerides (mmol/L)	24	2.3 ± 2.4	22	1.8 ± 1.0
HDL cholesterol (mmol/L)	24	1.26 ± 0.47	22	1.33 ± 0.39
LDL cholesterol (mmol/L)	23	4.9 ± 0.9	21	5.4 ± 1.1
LDL/HDL cholesterol ratio	23	4.36 ± 2.04	21	4.31 ± 1.48
Change in Lipid Profile after Supplementation				
Total cholesterol (mmol/L)	23	0.13 ± 0.58	20	−0.36 ± 0.89[a]
Triglycerides (mmol/L)	23	−0.29 ± 0.98	20	0.16 ± 0.62
HDL cholesterol (mmol/L)	23	0.09 ± 0.11	20	−0.02 ± 0.14[a]
LDL cholesterol (mmol/L)	22	0.18 ± 0.45	19	−0.44 ± 0.93[a]
LDL/HDL cholesterol ratio	22	−0.18 ± 0.62	19	−0.30 ± 0.82

[a] Denotes significant differences from placebo (*t* test, $p<0.05$).

(Table 4). However, only 36% of the study population followed the guidelines with respect to saturated and polyunsaturated fat.

Compared with the placebo group, garlic-group subjects significantly reduced their intake of fat (monounsaturated and polyunsaturated fat), carbohydrate and alcohol, resulting in a reduction in energy intake, which may have contributed to the reduction in serum lipids. The amount of garlic, onions and leeks consumed by subjects at study entry and exit were compared, but no significant changes or differences were observed between the study groups (data not shown).

Fig. 1 shows that after controlling for changes in dietary protein, fat, carbohydrate and alcohol intakes during the study period, subjects receiving garlic tablets had a reduction in TC by 0.4 mmol/L, HDL-C by 0.03 mmol/L and LDL-C by 0.6 mmol/L. In contrast, the placebo had an increase in TC, HDL-C and LDL-C (0.2, 0.08 and 0.3 mmol/L, respectively).

Table 3. Number of Subjects Compliant with the Australian Dietary Guidelines at Visits 2 and 5

	Placebo (n=21)	Garlic (n=20)
At Visit 2		
Condition 1	16 (76.2%)	12 (60.0%)
Condition 2	9 (42.9%)	9 (45.0%)
Condition 3	4 (19.1%)	3 (15.0%)
At Visit 5		
Condition 1	14 (66.7%)	9 (45.0%)
Condition 2	8 (38.1%)	7 (35.0%)
Condition 3	3 (14.3%)	4 (20.0%)

Condition 1: % energy from fat no more than 30%.

Condition 2: Condition 1+% energy from saturated fat no more than 6% and from polyunsaturated fat no more than 10%.

Condition 3: Condition 2+alcohol consumption no more than 40 g/d for men or 20 g/d for women.

Table 4. Daily Nutrient Intake at Study Entry and Changes during the Study Period

Parameters	Placebo (n=21) Mean±SD	Garlic (n=20) Mean±SD
At Randomisation (Visit 2)		
Total food intake (g/d)	2187 ± 371	2418 ± 901
Energy (MJ/d)	7.4 ± 1.5	8.6 ± 2.4
Protein (g/d)	88 ± 18	89 ± 18
Fat (g/d)	52 ± 14	65 ± 19[a]
Carbohydrate (g/d)	219 ± 50	247 ± 73
Alcohol (g/d)	13 ± 14	21 ± 30
% Energy from protein	20 ± 4	18 ± 3[a]
% Energy from fat	26 ± 4	29 ± 6
% Energy from carbohydrate	49 ± 5	48 ± 8
% Energy from alcohol	5 ± 5	6 ± 7
Dietary cholesterol (mg/d)	209 ± 91	233 ± 88
SFAs (g/d)	18 ± 7	24 ± 9
MUFAs (g/d)	19 ± 5	23 ± 7
PUFAs (g/d)	10 ± 3	12 ± 3
Dietary fiber (g/d)	26 ± 5	25 ± 8
Changes from Visits 2 to 5		
Total food intake (g/d)	−46 ± 296	−188 ± 300
Energy (MJ/d)	0.4 ± 1.5	−0.9 ± 1.0[a]
Protein (g/d)	4 ± 20	−5 ± 17
Fat (g/d)	9 ± 20	−4 ± 16[a]
Carbohydrate (g/d)	−1 ± 42	−31 ± 41[a]
Alcohol (g/d)	−1 ± 6	−6 ± 11[a]
% Energy from protein	0 ± 2	0 ± 3
% Energy from fat	2 ± 4	2 ± 7
% Energy from carbohydrate	−2 ± 4	−1 ± 8
% Energy from alcohol	0 ± 2	−1 ± 3
Dietary cholesterol (mg/d)	44 ± 110	−25 ± 116
SFAs (g/d)	3 ± 8	−1 ± 7
MUFAs (g/d)	4 ± 8	−1 ± 6[a]
PUFAs (g/d)	1 ± 3	−1 ± 3[a]
Dietary fiber (g/d)	−1 ± 6	−2 ± 6

[a] Denotes significant differences from placebo (ANOVA, $p<0.05$).

SFAs=saturated fatty acids, MUFAs=monounsaturated fatty acids, PUFAs=polyunsaturated fatty acids.

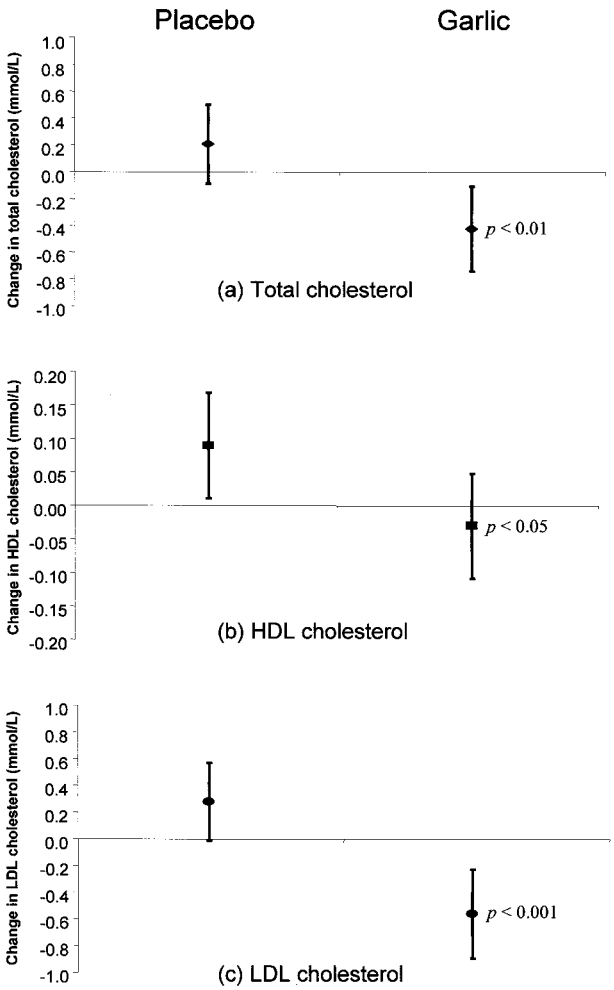

Fig. 1. 95% confidence interval of changes in serum cholesterol, adjusted for changes in dietary protein, fat, carbohydrate, and alcohol intake, after the 12-week study period, with significant differences between the placebo and garlic groups (ANCOVA).

DISCUSSION

Cholesterol-Lowering Effect of Garlic Supplementation

It is suggested that 'quality assessment' of previous trials has been generally poor due to problems in trial design, the manner of reporting cholesterol entry levels, inappropriate randomization, under reporting of garlic odor, inadequate assessment of dietary behavior and reporting of body weight during the trial [2,6]. In the present study, a cross-over design was not considered an option, because of the difficulty in blinding subjects and investigators from the garlic odor. It seems that the odor of the tablets is difficult to avoid completely, as the odor was still noticed even with use of an enteric-coated tablet. It appears, however, that, despite the odor, tablets used in the present study were well tolerated and did not require withdrawal of any subject from the clinical trial.

Although some garlic extracts may produce reductions in cholesterol, trials using dried garlic powder have recorded the most significant and consistent benefits [1], which may be dose dependent [27]. Garlic powder can contain up to 75% non-digestible carbohydrate [28–30] which has not been reported in garlic extracts and may be associated with bowel changes reported in other studies [5]. While it has been reported that larger quantities of indigestible carbohydrates can lower serum cholesterol [31–34], it is difficult to determine the role of this fraction from the data presented. Despite this, it still seems advisable to consume fresh garlic or carefully dried garlic powder of known quality, in preference to garlic extracts [10], as garlic powder is more reflective of historic use, best replicates fresh garlic—supplying both known/unknown phytochemical compounds and is supported by epidemiological evidence [23–24].

The result that consumption of enteric-coated garlic supplements, standardized to produce 9.6 mg allicin, significantly decreased TC and LDL-C, is in agreement with the meta-analysis of Silagy *et al*. [2] and Warshafsky *et al*. [3]. The 4% reduction in TC and 7% reduction of LDL-C were, however, lower than previously reported values, but significant in that the change was additional to dietary intervention and in subjects who had failed or were non-compliant with cholesterol-lowering drug therapy. Triglycerides remained unchanged by the treatment medication while HDL-C decreased. Other studies have, however, reported significant reduction of triglycerides and increase in HDL-C using garlic, but have not used a dietary run-in period, except for Holzgartner *et al*., who demonstrated an increase in HDL-C [35]. These findings vary from the results of similar studies previously published that nonenteric-coated garlic powder preparations with 0.6% (5.4 mg) allicin yield produced no demonstrable reduction in serum lipids [4–7].

Since it was observed that the garlic group had a significant reduction in serum cholesterol, after changes in energy and fat intake were adjusted for, compared to the placebo group, it is likely that the cholesterol-lowering effect is attributed to the garlic supplementation for 12 weeks. The ability to demonstrate a hypocholesterolemic effect of the garlic powder supplement in the present study, while some other studies failed [4–7], may be attributed to the high allicin yield and enteric-coated dose form of the garlic powder supplement used. Whether this effect was mediated by a direct metabolic action of allicin or other organosulfur compound(s) (or their metabolites) or how and to what extent they operate through food and nutrient intake is not resolved by this study.

Garlic Supplement Phytochemical Content

Allicin accounts for approximately 70% of total thiosulfinates produced [1] when the pro-drugs alliin, isoalliin and methiin interact with alliinase after mature garlic bulbs are crushed or garlic powder is mixed in water [11]. Allinase is pH sensitive and activity optimal in an alkaline environment [25].

Dietary supplements unable to produce allicin are associated with a lack of blood cholesterol-lowering efficacy [36–38], so maximization of allicin yield seems a key component in relationship to lowering elevated blood cholesterol levels. Our study utilized Australian-based freeze-dried garlic powder, believed to be a potent source in terms of allicin releasing potential. Allicin yield of the garlic supplement used in the present study was 9.6 mg/d (4 tablets @ 1.09% × 220 mg), which was higher than 5.4 mg/d (3 tablets @ 0.6% × 300 mg) of tablets used in other studies where no demonstrable reduction in serum lipids was reported [5–7].

Dose Forms of Garlic Supplements

An enteric-coated tablet was used in the present study, to protect alliinase required for the conversion of alliin to allicin, which could be deactivated in the acidic environment of the stomach. Use of enteric-coated garlic supplements is therefore warranted when effective release of the full allicin releasing potential, which is suggested to be a predictor of clinical effectiveness [9]. To our knowledge, this study is the first to use an enteric-coated garlic powder supplement to evaluate any hypocholesterolemic effect. The enteric coating complied with USP dissolution and disintegration guidelines [26], which combined with the higher allicin yield may account for reductions in total and LDL-C reported in this study. That our findings concur with those of Alder and Holub [39] and Holzgartner *et al*. [35], however, may not be explained by the type of dose form used. It is difficult to be certain that this is the case, as information on formulation pharmaceutics of tablets used in other studies is limited.

Effect of Dietary Intervention on Serum Lipids

During the run-in period, an average reduction in TC (from 7.6 to 7.1 mmol/L) and LDL-C (from 5.3 to 4.9 mmol/L) was observed in the study population, especially the placebo group, despite many subjects' reporting themselves already aware of and compliant to the Australian National Heart Foundation guidelines. Similar drops in cholesterol as a result of dietary intervention have previously been reported in a survey of 16 controlled studies on the efficacy of dietary recommendations [40]. It is noted that no difference was observed in TC or LDL-C at registration (Visit 1) or before randomization (Visit 2), between the garlic and placebo groups. As similar dietary advice was given to all subjects by the same dietitian who was blinded to the treatment groups, it is likely that the failure to observe a reduction in TC in the garlic group during the run-in period happened by chance.

Possible Effect of Garlic on Food and Nutrient Intakes

This 12-week intervention study has shown for the first time that garlic tablets could have interfered with satiety and influenced food choices, resulting in a reduction in energy and dietary fat intake. To date, only few studies on the hypocholesterolemic effect of garlic provided dietary counseling or imposed dietary restrictions as part of the study design [1], let alone investigated the effect of garlic on food or nutrient intakes. Results of animal studies suggest that garlic may have an effect on the central nervous system. The concentration of labeled allicin metabolites at several organ sites including the vertebral column has been demonstrated in an animal whole body autoradiographic study after oral administration of allicin [17]. It is therefore possible that satiety may change with garlic intake and operate through a central mechanism, and, in turn, this may have mediated the lipid-lowering action of garlic. It is intriguing to consider what mechanism(s) by which organosulfur and non-sulfur compounds in garlic might operate on food intake and/or lipid metabolism. It remains possible that non-sulfur compounds in garlic remained to be identified along with their biological activity.

In conclusion, the present study has demonstrated the hypocholesterolemic effect of a garlic supplement. It is suggested that such effect is dependent upon adequate production of allicin, which was maximized by using high allicin-producing garlic powder and an enteric-coated tablet. Whether the hypocholesterolemic effect increases in a dose-dependent manner with allicin yield has yet to be determined and awaits further research. Moreover, our study raises the possibility that bioavailable allicin-standardized garlic may have useful biological effects through effects on food and nutrient intake.

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