

Effect of Raw Garlic vs Commercial Garlic Supplements on Plasma Lipid Concentrations in Adults With Moderate Hypercholesterolemia

A Randomized Clinical Trial

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Background: Garlic is widely promoted as a cholesterol-lowering agent, but efficacy studies have produced conflicting results. Garlic supplements differ in bioavailability of key phytochemicals. We evaluated the effect of raw garlic and 2 commonly used garlic supplements on cholesterol concentrations in adults with moderate hypercholesterolemia.

Methods: In this parallel-design trial, 192 adults with low-density lipoprotein cholesterol (LDL-C) concentrations of 130 to 190 mg/dL (3.36-4.91 mmol/L) were randomly assigned to 1 of the following 4 treatment arms: raw garlic, powdered garlic supplement, aged garlic extract supplement, or placebo. Garlic product doses equivalent to an average-sized garlic clove were consumed 6 d/wk for 6 months. The primary study outcome was LDL-C concentration. Fasting plasma lipid concentrations were assessed monthly. Extensive chemical characterization of study materials was conducted throughout the trial.

Results: Retention was 87% to 90% in all 4 treatment arms, and chemical stability of study materials was high throughout the trial. There were no statistically significant effects

of the 3 forms of garlic on LDL-C concentrations. The 6-month mean (SD) changes in LDL-C concentrations were +0.4 (19.3) mg/dL (+0.01 [0.50] mmol/L), +3.2 (17.2) mg/dL (+0.08 [0.44] mmol/L), +0.2 (17.8) mg/dL (+0.005 [0.46] mmol/L), and -3.9 (16.5) mg/dL (-0.10 [0.43] mmol/L) for raw garlic, powdered supplement, aged extract supplement, and placebo, respectively. There were no statistically significant effects on high-density lipoprotein cholesterol, triglyceride levels, or total cholesterol-high-density lipoprotein cholesterol ratio.

Conclusions: None of the forms of garlic used in this study, including raw garlic, when given at an approximate dose of a 4-g clove per day, 6 d/wk for 6 months, had statistically or clinically significant effects on LDL-C or other plasma lipid concentrations in adults with moderate hypercholesterolemia.

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GARLIC (*ALLIUM SATIVUM*) has been used medicinally since antiquity. Garlic supplements, many of which seek to package the benefits of raw garlic in more palatable forms,¹⁻⁵ are promoted as cholesterol-lowering agents and are among the

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top-selling herbal supplements.^{6,7} Crushing garlic triggers the formation of allicin through action of alliinase enzymes on the stable precursor alliin, and allicin inhibits cholesterol synthesis in vitro.^{8,9} Despite promising in vitro studies and a strong plausibility of effect demonstrated in more than 110 animal studies,¹⁰ the clinical trial evidence supporting a hypocholesterol-

emic effect of various forms of garlic is highly inconsistent.¹¹⁻¹⁹ A strong criticism of these trials has been that the bioavailability of the important sulfur-containing constituents differs significantly between raw garlic and the specific garlic supplement formulations.^{19,22} The objective of the current study was to compare the effect of raw garlic and of 2 garlic supplements with distinctly different formulations on the plasma lipid concentrations of adults with moderate hypercholesterolemia for 6 months.

METHODS

STUDY PARTICIPANTS

Participants were recruited from the local community primarily through media advertisements. Adults aged 30 to 65 years were invited to enroll if they had a fasting plasma low-density lipoprotein cholesterol (LDL-C) concen-

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tration of 130 to 190 mg/dL (3.36-4.91 mmol/L), a triglyceride level less than 250 mg/dL (<2.82 mmol/L), and body mass index (calculated as weight in kilograms divided by height in meters squared) of 19 to 30. Exclusion criteria included the following: self-reported pregnancy, lactation, current smoking, prevalent heart disease, cancer, renal disorder, or diabetes mellitus, and use of lipid or antihypertensive medications. All study participants provided written informed consent, and the study was approved annually by the Stanford University Human Subjects Committee.

GARLIC PRODUCTS AND PLACEBO

Garlic was provided in 3 forms: raw garlic (California Early; Christopher Ranch, Gilroy, Calif) and 2 commercial tablet formulations, Garlicin (Nature's Way Products Inc, Springville, Utah) and Kyolic-100 (Wakunaga of America Co, Mission Viejo, Calif). Raw garlic was selected as an important arm because of the scarcity of available data about raw garlic and because it would be free of potential losses in natural garlic activity that could arise in the processing and manufacture of garlic supplements. Garlicin was selected to represent powdered garlic supplements. It is the only brand that has been shown in bioavailability studies to release allicin at a level equivalent to that in crushed raw garlic.^{21,23} Kyolic was selected because it is one of the most popular brands on the market,²⁴ it is a very different type of product (aged) from the powdered supplements, and it is the only brand other than powdered supplements that has more than one clinical trial published about its lipid-lowering effects.^{25,26}

Each garlic product or placebo was consumed 6 d/wk (1 day off per week to increase long-term adherence) for 6 months, as follows: 4.0 g of blended raw garlic (an average-sized clove crushed in a blender; hereafter, raw garlic), 4 Garlicin tablets (twice the recommended dose), 6 Kyolic tablets (1½-3 times the recommended dose), or 4 or 6 placebo tablets. The raw garlic dose had an allicin content similar to the allicin yield of the Garlicin dose, and both had a dry garlic matter content slightly less than the Kyolic dose. Individually packaged aliquots of raw garlic were frozen at -80°C. When distributed, raw garlic aliquots were thawed, mixed with condiments, and served in sandwiches, as detailed elsewhere.²⁷ Single lot numbers of Garlicin and Kyolic were obtained for the entire study. Placebo tablets were similar in composition and appearance to Garlicin tablets but with cellulose replacing the garlic powder. Other details of procurement, product preparation, repackaging, storage, and distribution of the garlic products are described elsewhere.²⁷

Before study initiation and at 3, 6, 12, 18, and 24 months during the study, 14 sulfur and 2 nonsulfur compounds were measured in all 3 garlic products, as described elsewhere.²⁷ The content and potential of allyl thiosulfates (mainly allicin) for raw garlic and Garlicin, respectively, were nearly identical. Substantial qualitative and quantitative differences were found between Kyolic aged extract tablets and raw garlic and Garlicin, as a result of the aging and extraction procedures. Raw garlic thiosulfinate content was stable at 4°C for 3 days when mixed with condiments used in study sandwiches. Allyl thiosulfinate content in raw garlic stored at -80°C and the ability of Garlicin tablets stored at 4°C to produce thiosulfates on hydration were unchanged after 2 years. S-Allylcysteine content in Kyolic tablets stored at room temperature was stable for 1 year but declined by 12% at 2 years; the storage temperature was, therefore, changed to 4°C. Dissolution formation and release of allicin from Garlicin tablets, under simulated gastrointestinal tract conditions defined by the *United States Pharmacopeia*, were found to be equal to their potential to produce allicin in water.²³ Complete in vivo formation of allicin from Garlicin tablets was verified by finding a similar area under the curve for the exhaled allicin metabolite allyl methyl sulfide, in comparison with consuming raw garlic, in which allicin is fully present before consumption.²³

STUDY SANDWICHES

Sandwiches were included in the study design to incorporate raw garlic in a palatable form. All sandwiches were prepared by and distributed through the General Clinical Research Center. Participants were instructed to heat the sandwich bread or filling as desired, but not the condiment because it contained the raw garlic (for those randomized to the raw garlic group) and heat causes allicin loss. Twelve types of sandwiches were served to provide dietary variety. Sandwiches were designed to contain approximately 375 kcal (mean±SD, 373±21 kcal), with no more than 10% of energy from saturated fat. Because the sandwiches themselves could affect blood lipid levels, identical sandwiches were provided to all participants. Participants not randomized to the raw garlic group received placebo sandwiches, without garlic mixed into the condiments. The characteristic strong taste of garlic made blinding impossible; rather, the intent of providing all 4 groups with study sandwiches was for these to have a similar effect on the overall diets of all participants.

CONDUCT OF THE STUDY

Participants were instructed to avoid choosing foods known to contain garlic and to minimize intake of raw onions and chives because these contain some of the sulfur compounds found in garlic. The first 2 weeks of the protocol was a run-in phase during which participants consumed daily study sandwiches after picking them up during the scheduled twice-weekly General Clinical Research Center pickups. No study tablets were provided during the run-in phase. Participants who found the protocol acceptable were randomly assigned to the full 26-week protocol. Those in the raw garlic group received placebo tablets and raw garlic mixed in sandwich condiments. Those in the Garlicin, Kyolic, and placebo groups received their specific study tablets and sandwiches without garlic. Randomization was done by a research assistant drawing assignments from an opaque envelope in blocks of 24 (ie, 6 per treatment arm) without replacement until all 24 allocations were assigned, then beginning again. In both the raw garlic and placebo groups, equal numbers of participants were randomized to receive 4 and 6 placebo tablets per day. Investigators were blinded to treatment assignment until all plasma lipid analyses were completed.

Blood samples were collected in EDTA-coated tubes after participants had fasted overnight for 12 hours or longer. Samples were centrifuged, aliquoted, and frozen at -80°C within 2 hours of collection. The protocol included 11 blood samples, as follows: 1 to determine eligibility, 1 at initiation of the 2-week run-in phase, 2 within 1 week before randomization, 5 at monthly intervals from month 1 to month 5, and 2 within 1 week of the last week of the intervention. All 11 plasma samples for a single participant were analyzed at the same time, once a participant completed the protocol, to minimize interassay variation.

ASSESSMENT OF ADHERENCE AND BLINDING

Participants completed and returned weekly logs indicating the number of sandwiches consumed and any missed. Adherence to the study regimen was determined by tablet count from returned bottles. Each participant was asked on concluding their participation whether they believed they had received garlic or placebo sandwiches and garlic or placebo tablets.

ASSESSMENT OF PLASMA LIPID CONCENTRATIONS

Plasma total cholesterol and triglyceride concentrations (free glycerol blank subtracted) were measured enzymatically

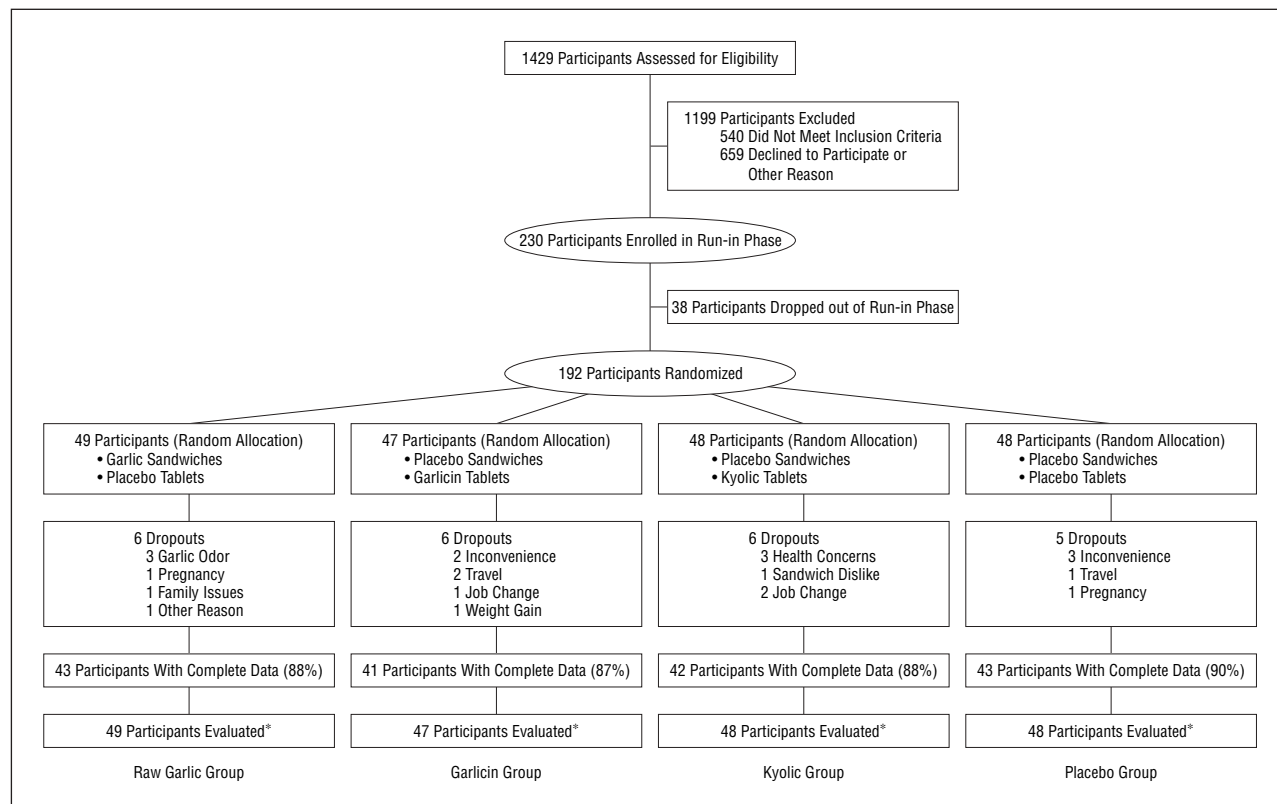


Figure 1. Flowchart of participant screening, enrollment, withdrawal, and protocol completion. Asterisk indicates those with partial or missing data included in analyses using the mixed procedure (PROC MIX, SAS 9.1 Service Pack 3; SAS Institute, Cary, NC).

using methods established by the Stanford Clinical Chemistry Laboratory.^{28,29} High-density lipoprotein cholesterol was measured by liquid selective detergent followed by enzymatic determination of cholesterol.³⁰ Low-density lipoprotein cholesterol (LDL-C) was calculated according to the method of Friedewald et al.³¹ Lipid assays were monitored by the Lipid Standardization Program of the Centers for Disease Control and Prevention and were consistently within specified limits (monthly coefficients of variation were all $\leq 3.1\%$). Laboratory staff conducting these analyses were blinded to treatment assignment.

ASSESSMENT OF POTENTIAL CONFOUNDERS OF DIET, PHYSICAL ACTIVITY, AND WEIGHT

Dietary intake was assessed by review of 3-day food records collected at the start of the run-in phase, at randomization, at mid-study, and at the end of the study, and were analyzed using Food Processor software (version 8.4; ESHA Research, Salem, Ore). Physical activity was assessed at randomization, at midstudy, and at the end of the study using the Baecke Activity Questionnaire.³² Weight was measured at the General Clinical Research Center on a standardized scale at randomization, at midstudy, and at the end of the study.

STATISTICAL ANALYSIS

The primary hypothesis was that garlic would lower LDL-C compared with placebo during 6 months of treatment. A secondary hypothesis was that the effect might differ by type of garlic product and be greatest for raw garlic. The minimal clinically significant between-group difference in LDL-C change selected was 10 mg/dL (0.03 mmol/L), and a 20-mg/dL (0.52-mmol/L) SD of LDL-C change was projected based on previ-

ous trials in similar study populations. Thus, the study was powered for a moderate effect size of $d = .5$.³³ With 4 treatment groups and 45 participants in each group, the study had 80% power to detect a 10-mg/dL (0.3-mmol/L) difference between groups. Descriptive statistics using means and standard deviations were determined for participant baseline characteristics. For lipid variables, the 2 prerandomization and 2 end-study assessments were averaged. Repeated measures taken over time were assessed using random effects regression models.³⁴ Comparisons between the 4 treatments at the 7 postrandomization times (end of run-in phase, months 1-5, and end of the study) and the interaction between treatment and time were modeled as fixed effects, with participants treated as a repeated measure with a first-order autoregressive covariance structure using the mixed procedure (PROC MIX) in SAS 9.1.3 Service Pack 3 (SAS Institute Inc, Cary, NC). In secondary analyses, percent lipid changes from the end of the run-in phase were tested for group differences by analysis of variance among those participants with end of the run-in phase and 6-month data. In addition, gender, baseline weight, and physical activity were considered additional covariates, but they did not change the findings of the primary analysis. The same analytical approaches were used in post hoc analyses to test for differences between groups among the subset of participants with LDL-C concentrations above the median at the end of the run-in phase.

RESULTS

STUDY PARTICIPANTS

Participant enrollment began in November 2002, and the study ended in June 2005. **Figure 1** shows participant flow; **Table 1** gives baseline characteristics.

Table 1. Baseline Characteristics*

| Characteristic | Raw Garlic Group (n = 49) | Garlicin Group (n = 47) | Kyolic Group (n = 48) | Placebo Group (n = 48) |
|---|------------------------------|----------------------------|--------------------------|---------------------------|
| Demographic data | | | | |
| Age, y | 49 ± 9 | 50 ± 8 | 51 ± 10 | 49 ± 9 |
| Gender, F/M | 27/22 | 25/22 | 20/28 | 24/24 |
| BMI† | 25 ± 3 | 26 ± 4 | 25 ± 3 | 25 ± 3 |
| Educational achievement, y | 16.5 ± 2.0 | 16.2 ± 2.8 | 16.8 ± 1.4 | 17.0 ± 1.6 |
| Race/ethnicity, No. | | | | |
| Non-Hispanic white | 36 | 31 | 32 | 31 |
| Non-Hispanic black | 2 | 2 | 1 | 0 |
| Non-Hispanic Asian | 9 | 10 | 10 | 7 |
| Hispanic | 1 | 3 | 1 | 2 |
| Other or not disclosed | 1 | 1 | 4 | 8 |
| Lipid and lipoprotein concentration, mg/dL‡ | | | | |
| Total cholesterol | 226 ± 18 | 227 ± 16 | 227 ± 20 | 228 ± 21 |
| LDL-C | 151 ± 15 | 149 ± 14 | 152 ± 15 | 150 ± 14 |
| HDL-C | 58 ± 15 | 55 ± 12 | 53 ± 11 | 54 ± 14 |
| Triglycerides | 97 ± 44 | 114 ± 44 | 116 ± 46 | 122 ± 54 |
| Total cholesterol–HDL-C ratio | 4.1 ± 0.9 | 4.3 ± 0.8 | 4.5 ± 0.8 | 4.4 ± 0.9 |
| Dietary intake per day† | | | | |
| Calories, kcal | 1925 ± 563 | 1879 ± 735 | 2161 ± 729 | 2111 ± 575 |
| Carbohydrate, % | 49 ± 10 | 51 ± 11 | 48 ± 12 | 49 ± 10 |
| Protein, % | 17 ± 4 | 17 ± 4 | 17 ± 3 | 18 ± 4 |
| Fat, % | 32 ± 8 | 31 ± 9 | 33 ± 11 | 31 ± 9 |
| Saturated fat, g | 21 ± 10 | 20 ± 11 | 25 ± 14 | 23 ± 11 |
| Cholesterol, mg | 250 ± 158 | 217 ± 161 | 248 ± 138 | 258 ± 129 |
| Fiber, g | 21 ± 9 | 21 ± 8 | 24 ± 12 | 23 ± 8 |
| Physical activity score†§ | | | | |
| Work index | 2.3 ± 0.5 | 2.4 ± 0.6 | 2.4 ± 0.7 | 2.3 ± 0.5 |
| Sport index | 3.0 ± 0.7 | 3.0 ± 0.5 | 3.0 ± 0.8 | 3.1 ± 0.9 |
| Leisure time index | 2.9 ± 0.7 | 2.7 ± 0.7 | 2.7 ± 0.8 | 2.8 ± 0.7 |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.02586; triglycerides to millimoles per liter, multiply by 0.01129.

*Data are given as mean ± SD unless otherwise indicated.

†Determined at the end of the 2-week run-in phase, at randomization.

‡Determined at screening for eligibility.

§Based on ARIC (Atherosclerosis Risk in Community) study, Baecke Activity Questionnaire, and 5-point Likert Scale questions (1, sedentary; 5, vigorously active).

STABILITY OF POTENTIAL CONFOUNDERS

No significant between-group differences were found during the study for changes in physical activity, weight, or dietary intake of saturated fat, fiber, or calories (all $P \geq .10$).

ADHERENCE AND BLINDING

The mean adherence to tablet consumption was 91% to 94% among the 4 treatment arms ($P = .60$). At least 80% adherence was achieved by 82%, 94%, 90%, and 88% of the raw garlic, Garlicin, Kyolic, and placebo groups, respectively ($P = .30$). Adherence to sandwich consumption was 96% to 97% for all 4 treatment arms ($P = .60$); 100% of participants consumed at least 80% of the study sandwiches.

As anticipated, only a few participants incorrectly identified (3%) or were uncertain about (7%) whether they received raw garlic. Overall, approximately 55% correctly identified whether they received garlic vs placebo supplements and approximately 35% did not venture a guess; there was no difference across groups in the proportion guessing correctly ($P = .30$).

EFFECT OF GARLIC ON PLASMA LIPID CONCENTRATIONS

Of the 192 participants randomized, 169 completed the full 6-month protocol, 19 discontinued participation between 1 and 5 months, and 4 discontinued before 1 month. All available data at each time point from the 192 randomized participants were used in the intention-to-treat analysis by the PROC MIX procedure (SAS Institute Inc).

There were no statistically significant differences by treatment group for any of the fasting plasma lipid concentrations (**Table 2**). Net 6-month changes (ie, disregarding data for months 1-5 and for those who did not complete the protocol) are shown in **Figure 2**; 95% confidence interval data for these net changes are given in Table 2.

There was a 9% decrease in mean (SD) LDL-C concentrations overall between screening (150 ± 15 mg/dL [3.88 ± 0.39 mmol/L]) and the start of the 2-week run-in phase (138 ± 21 mg/dL [3.57 ± 0.54 mmol/L]), presumably attributable to regression to the mean. At post hoc analysis, participants were divided into those with LDL-C concentrations below and above the median at the end

Table 2. Lipid Results by Group and Time Point*

| Variable | Raw Garlic Group (n = 49†) | Garlicin Group (n = 47†) | Kyolic Group (n = 48†) | Placebo Group (n = 48†) | Group × Time P Value‡ |
|--------------------------------------|-------------------------------|-----------------------------|---------------------------|----------------------------|--------------------------|
| LDL-C, mg/dL | | | | | |
| End of run-in phase | 142 ± 22 | 134 ± 19 | 136 ± 20 | 139 ± 22 | .54 |
| Month 1 | 146 ± 19 | 138 ± 26 | 139 ± 27 | 134 ± 26 | |
| Month 2 | 142 ± 22 | 134 ± 22 | 135 ± 20 | 136 ± 22 | |
| Month 3 | 140 ± 20 | 135 ± 23 | 140 ± 24 | 137 ± 24 | |
| Month 4 | 141 ± 21 | 135 ± 23 | 136 ± 23 | 138 ± 23 | |
| Month 5 | 140 ± 21 | 134 ± 25 | 133 ± 24 | 133 ± 23 | |
| End of study | 142 ± 22 | 137 ± 25 | 137 ± 22 | 133 ± 21 | |
| 6-mo Net change, mean (95% CI)§ | 0.4 (-5.5 to 6.4) | 3.2 (-2.2 to 8.7) | 0.2 (-5.3 to 5.7) | -3.9 (-9.0 to 1.2) | |
| HDL-C, mg/dL | | | | | |
| End of run-in phase | 55 ± 13 | 53 ± 11 | 51 ± 9 | 52 ± 14 | .47 |
| Month 1 | 56 ± 13 | 52 ± 13 | 51 ± 10 | 51 ± 13 | |
| Month 2 | 56 ± 14 | 53 ± 13 | 51 ± 9 | 51 ± 12 | |
| Month 3 | 57 ± 14 | 52 ± 12 | 51 ± 9 | 52 ± 13 | |
| Month 4 | 56 ± 14 | 53 ± 12 | 51 ± 9 | 52 ± 12 | |
| Month 5 | 57 ± 14 | 51 ± 12 | 50 ± 10 | 53 ± 14 | |
| End of study | 58 ± 14 | 53 ± 12 | 51 ± 9 | 52 ± 13 | |
| 6-mo Net change, mean (95% CI)§ | 2.3 (0.4 to 4.2) | 1.0 (-0.3 to 2.4) | -0.3 (-1.6 to 1.0) | -0.8 (-3.2 to 1.6) | |
| Triglycerides, mg/dL | | | | | |
| End of run-in phase | 98 ± 48 | 122 ± 55 | 126 ± 54 | 126 ± 63 | .88 |
| Month 1 | 110 ± 82 | 125 ± 71 | 137 ± 116 | 141 ± 78 | |
| Month 2 | 107 ± 70 | 122 ± 65 | 129 ± 54 | 138 ± 82 | |
| Month 3 | 94 ± 53 | 126 ± 63 | 121 ± 59 | 135 ± 81 | |
| Month 4 | 102 ± 56 | 129 ± 63 | 134 ± 73 | 144 ± 89 | |
| Month 5 | 105 ± 50 | 134 ± 69 | 141 ± 69 | 136 ± 82 | |
| End of study | 95 ± 49 | 120 ± 49 | 119 ± 72 | 134 ± 74 | |
| 6-mo Net change, mean (95% CI)§ | -5.2 (-14.6 to 4.2) | -6.6 (-19.9 to 6.7) | -2.0 (-18.2 to 14.1) | 6.4 (-6.4 to 19.2) | |
| Total cholesterol-HDL-C ratio | | | | | |
| End of run-in phase | 4.1 ± 0.9 | 4.2 ± 0.8 | 4.2 ± 0.7 | 4.4 ± 1.1 | .89 |
| Month 1 | 4.2 ± 1.0 | 4.3 ± 0.9 | 4.4 ± 1.0 | 4.4 ± 1.1 | |
| Month 2 | 4.1 ± 1.1 | 4.2 ± 0.8 | 4.2 ± 0.7 | 4.3 ± 1.0 | |
| Month 3 | 4.0 ± 1.0 | 4.2 ± 0.8 | 4.3 ± 0.8 | 4.4 ± 1.1 | |
| Month 4 | 4.1 ± 1.0 | 4.2 ± 0.8 | 4.3 ± 0.7 | 4.4 ± 1.2 | |
| Month 5 | 4.0 ± 1.0 | 4.3 ± 0.9 | 4.3 ± 0.7 | 4.3 ± 1.2 | |
| End of study | 4.0 ± 1.0 | 4.2 ± 0.8 | 4.2 ± 0.8 | 4.3 ± 1.0 | |
| 6-mo Net change, mean (95% CI)§ | -0.11 (-0.26 to 0.03) | -0.02 (-0.16 to 0.11) | 0.0 (-0.13 to 0.12) | -0.04 (-0.15 to 0.08) | |

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.02586; triglycerides to millimoles per liter, multiply by 0.01129.

*Data are given as mean ± SD unless otherwise indicated.

†Sample sizes decreased from the end of the run-in phase with time because of dropouts and missed blood sampling. For the end of the run-in phase, months 1 through 5, and the end of the study (month 6), respective sample sizes were as follows: raw garlic group: n = 49, 47, 46, 46, 45, 41, 43; Garlicin group: n = 47, 43, 43, 41, 41, 41; Kyolic group: n = 48, 47, 45, 46, 43, 42, 42; and placebo group: n = 48, 48, 46, 46, 42, 41, 43.

‡Statistical testing was done using the PROC MIX procedure (SAS 9.1 Service Pack 3; SAS Institute, Cary, NC) with all available data at each time point.

§Data for the 169 participants with end of run-in phase and 6-month data.

of the run-in phase (138.5 mg/dL [3.58 mmol/L]) to explore the possibility of a clinically significant effect among those with more elevated LDL-C concentrations. There were no significant differences by group among the subset with LDL-C concentrations above the median (**Table 3**).

ADVERSE EVENTS

No serious adverse events occurred. There were rare reports of individual symptoms possibly linked to study materials, including rash, heartburn, and mouth ulcers in 1 participant each. Bad body and breath odor were reported “often” or “almost always” by 28 participants (57%) in the raw garlic group and by 1 participant in the Kyolic group, but by no participants in the Garlicin or placebo

groups. Flatulence attributed to study materials was reported “often” or “almost always” by 3 participants in the raw garlic group, 4 participants each in the Garlicin and Kyolic groups, and 1 participant in the placebo group. All other symptom reports were even less frequent.

COMMENT

This study compared the effects on plasma lipid concentrations of raw garlic and 2 types of commercial garlic supplements. The garlic products, all extensively characterized chemically, had neither a statistically detectable effect nor a clinically relevant effect on plasma lipid concentrations in adults with moderate hypercholesterolemia.

The plausibility of a cholesterol-lowering effect of garlic in human beings is supported by significant positive effects in approximately 85% of more than 110 animal studies that examined the effects of allicin-derived garlic oils, crushed raw garlic, and garlic powder on serum lipid concentration.¹⁰ Furthermore, clinical trials conducted before 1995 with garlic powder tablets at doses of 0.6 to 1.2 g suggested a modest beneficial effect of garlic on lipid concentration in adults with substantial hypercholesterolemia, but these trials were criticized for serious design and conduct limitations.^{14,16} Trials conducted after 1995 with similar doses consistently reported no significant effects on plasma lipid concentrations in similar populations.^{13,14,18,35-37} Notably, almost all commercial garlic supplements, especially those used in post-1995 trials, yield unexpectedly low amounts of the putative garlic active agent allicin under physiologically relevant dissolution conditions.^{20,21} Therefore, the effectiveness of garlic and garlic supplements has remained ambiguous.

The most common type of garlic supplement consumed contains dried, pulverized cloves. Garlicin is a dried garlic product that was chosen for this trial because it releases sufficiently high amounts of allicin *in vivo*²³ and under simulated gastrointestinal conditions²¹ to represent the allicin produced by a similar weight of raw garlic. The consumed dose of garlic powder (1.4 g) from Gar-

licin (twice the label-recommended dose) and the allicin potential (15 mg) at this dose were considerably greater than used in previous clinical trials with other commercial powder supplements,^{20,23,27} including the brands used in trials reporting significant effects on serum lipid concentrations. Hence, this trial was better positioned than previous clinical trials to find a cholesterol-lowering effect from a garlic powder supplement.

Kyolic aged garlic extract powder at a dose of 7.2 g daily for 6 months was used in 2 controlled clinical trials for effects on serum lipid concentrations. The first trial included subjects with a mean baseline LDL-C concentration of 160 mg/dL (4.14 mmol/L) and reported a 4.0% to 4.6% decrease in LDL-C.²⁵ The second trial included subjects with a mean baseline LDL-C concentration of 170 mg/dL (4.40 mmol/L) and reported a 10% decrease in LDL-C.²⁶ The discrepancy between our results and those of these earlier trials seems to be related, not to the initial LDL-C values, which were nearly as high for the subset of participants with LDL-C concentrations above the median at the end of the run-in phase (152 mg/dL [3.93 mmol/L]; Table 3), but more likely to the 4-fold lower dose (1.8 g) used in our study. The dose of aged extract used in our study was chosen to provide a similar amount of dry garlic matter (1.8 g) as found in the dose of raw garlic (1.5 g), and is still 1½ to 3 times the recommended dose of 0.6 to 1.2 g for Kyolic aged garlic extract powder.

First among the strengths of this trial is the extensive chemical characterization of the study products before and throughout the study.³⁸ The composition of Garlicin is similar to that of raw garlic, both of which are very different from Kyolic. The major garlic components in raw garlic, Garlicin, and Kyolic were stable throughout the trial. A second important strength of this trial is the inclusion of raw garlic as one of the treatment arms. If there were problems with bioavailability of active ingredients from commercial supplement formulations, raw garlic should be superior. A third strength of this trial is its 6-month duration, with monthly blood sampling, allowing us to test the suggestion that garlic might exert a moderate but transient cholesterol-lowering effect.¹¹ No short-term or longer-term effects were observed. Finally, the sample size of the current trial was substantially larger than almost all previous trials and was designed to detect even modest effects on plasma lipid concentrations, which were not observed.

The results of this trial should not be generalized to other populations or health effects. Garlic might lower

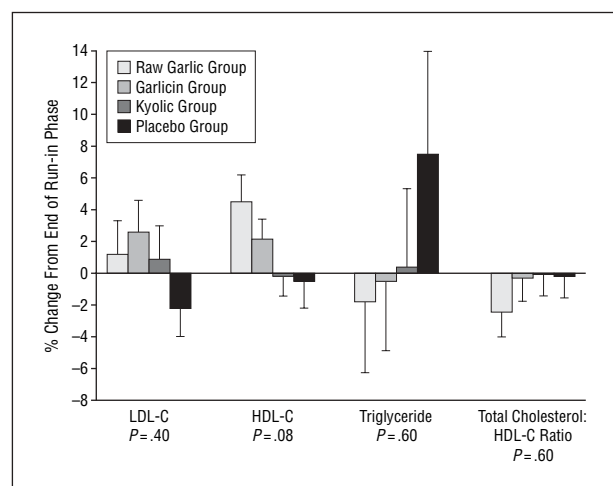


Figure 2. Six-month percent change (mean and SE) relative to the end of the run-in phase in participants with available data. The raw garlic group consisted of 43 participants; the Garlicin group, 41; the Kyolic group, 42; and the placebo group, 43. No significant treatment differences were detected by analysis of variance. HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 3. Values in the Subset of Participants With LDL-C Concentrations Above the Median at the End of the Run-in Phase Who Completed the 6-Month Protocol*

| Variable | Raw Garlic Group (n = 26) | Garlicin Group (n = 20) | Kyolic Group (n = 25) | Placebo Group (n = 24) | P Value† |
|---------------------|---------------------------|-------------------------|-----------------------|------------------------|----------|
| End of run-in phase | 157.9 ± 15.4 | 151.0 ± 10.5 | 151.9 ± 7.0 | 156.4 ± 16.7 | |
| 6-mo Change | -5.4 ± 17.9 | +1.8 ± 20.1 | -5.2 ± 18.2 | -9.7 ± 16.9 | .29 |

Abbreviation: LDL-C, low-density lipoprotein cholesterol.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.02586.

*Data are given as mean ± SD, expressed in milligrams per deciliter.

†Analysis of variance for differences in change between groups.

LDL in specific subpopulations, such as those with higher LDL concentrations, or may have other beneficial health effects. Also, we studied only one dosage level, and effects might emerge at higher doses, if tolerated.

Based on our results and those of other recent trials, physicians can advise patients with moderately elevated LDL-C concentrations that garlic supplements or dietary garlic in reasonable doses are unlikely to produce lipid benefits. While garlic may have other health effects, such as increased fibrinolysis, decreased atherosclerosis, or anticarcinogenic properties,³⁹⁻⁴⁴ we would argue that these possible effects also should be scrutinized in large, carefully designed trials with chemically defined garlic products.

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Author Contributions: Dr Gardner had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Gardner, Lawson, Block, Balise, and Kraemer. Acquisition of data: Gardner and Chatterjee. Analysis and interpretation of data: Gardner, Lawson, Block, Kiazand, Balise, and Kraemer. Drafting of the manuscript: Gardner, Lawson, Chatterjee, Kiazand, and Kraemer. Critical revision of the manuscript for important intellectual content: Gardner, Lawson, Block, Kiazand, Balise, and Kraemer. Statistical analysis: Gardner, Balise, and Kraemer. Obtained funding: Gardner and Lawson. Administrative, technical, and material support: Block. Study supervision: Gardner and Chatterjee.

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Correction

Error in Financial Disclosure. In the Editorial by de Lemos titled "The Latest and Greatest New Biomarkers: Which Ones Should We Measure for Risk Prediction in Our Practice?" published in the December 11/25 issue of the ARCHIVES (2006;166:2428-2430), an error occurred in the Financial Disclosure on page 2429. The disclosure should have read as follows: Dr de Lemos has received grant support from Biosite (current) and Roche (>24 months previously); has received speaker honoraria from Biosite for educational programs; and is a consultant to Bayer Diagnostics, Biosite, and Inverness.