Garlic for Treating Hypercholesterolemia

A Meta-Analysis of Randomized Clinical Trials

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Purpose: **To investigate the effect of garlic on total cholesterol level in persons with elevated levels by conducting a meta-analysis of randomized, double-blind, placebo-controlled trials.**

Data Sources: **Systematic literature searches were conducted on the MEDLINE, EMBASE, BIOSIS, Cochrane Library, AMED, and CISCOM databases. Manufacturers of commercial garlic preparations and experts in the field were asked about published or unpublished trials.**

Study Selection: **Selected trials were required to state that they were randomized, double-blind, and placebo-controlled; use garlic monopreparations; include persons with mean total cholesterol levels of at least 5.17 mmol/L (200 mg/dL); and report total cholesterol level as an end point. There were no language restrictions.**

Data Extraction: **Two reviewers, blinded to key identifiers of each paper, independently extracted data in a standardized manner and assessed methodologic quality by using the Jadad scale. Discrepancies were settled through discussion.**

Data Synthesis: **In the 13 trials included in the meta-analysis, garlic reduced total cholesterol level from baseline significantly more than placebo ($P < 0.01$); the weighted mean difference was −0.41 mmol/L (95% CI, −0.66 to −0.15 mmol/L) (−15.7 mg/dL [CI, −25.6 to −5.7 mg/dL]). Six diet-controlled trials with the highest scores for methodologic quality revealed a nonsignificant difference between garlic and placebo groups; the weighted mean difference was −0.11 mmol/L (CI, −0.30 to 0.08 mmol/L) (−4.3 mg/dL [CI, −11.7 to 3.1 mg/dL]).**

Conclusions: **The available data suggest that garlic is superior to placebo in reducing total cholesterol levels. However, the size of the effect is modest, and the robustness of the effect is debatable. The use of garlic for hypercholesterolemia is therefore of questionable value.**

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In all cultures, increased serum total cholesterol levels are directly associated with an increased risk for coronary heart disease (1); 5.17 mmol/L (200 mg/dL) has been identified as the point at which strategies for reducing levels should be considered (2, 3). Nonpharmacologic interventions consisting largely of diet modification and increased physical activity are the first-line approach for both primary and secondary prevention of coronary heart disease (4). Lipid-lowering drugs used for treating high-risk persons include 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), bile acid sequestrants, fibrates, and nicotinates (3). None of these pharmacologic options are free of adverse effects (3), and some have been associated with potential carcinogenicity (5). A harmless yet effective therapy for lowering cholesterol levels would therefore be of considerable interest.

The lipid-lowering effects of garlic (*Allium sativum*) have been demonstrated in animal experiments (6), and garlic's efficacy in lowering cholesterol levels in humans has been the subject of randomized clinical trials. A meta-analysis of the effect of garlic on total serum cholesterol level (7) found a significant reduction in total cholesterol levels of 0.59 mmol/L (22.8 mg/dL), which was equivalent to a decrease of approximately 9% compared with placebo. This figure was based on four statistically homogeneous trials that included 324 participants. A subsequent meta-analysis (8) assessing 952 persons from 16 trials reached a similar conclusion, reporting a reduction of 0.77 mmol/L (29.7 mg/dL); this represented a 12% average decrease in total cholesterol level. When these authors later reanalyzed the data, including the results of their own trial of 115 persons (9), the overall reduction in total cholesterol level had diminished to 0.65 mmol/L (25.1 mg/dL); however, it remained significantly greater than that seen with placebo. Because several additional trials have since been published, we decided to reevaluate the totality of available data. We used rigorous criteria to select studies for statistical pooling in an attempt to determine the specific effect of garlic on total serum cholesterol level in persons with elevated levels.

Methods

We performed systematic searches on the MEDLINE, EMBASE, BIOSIS, AMED, Cochrane Library, and CISCOM databases. The search terms used were *garlic*, Allium sativum, and *Knoblauch* (the German term for *A. sativum*). Each database was searched from its inception

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until November 1998. We asked manufacturers of garlic preparations and experts in the field about any published or unpublished trials, and we searched the bibliographies of all papers for further studies. There were no language restrictions. Selected studies were required to state that they were randomized, double-blind, and placebo-controlled; use garlic monopreparations; include patients with a mean total cholesterol level of at least 5.17 mmol/L (200 mg/dL); and report total cholesterol level as an end point.

Reviewers were blinded to the authors, institutions, addresses, and publication details of each paper. Data were extracted in a systematic manner according to predefined criteria. When information was insufficient for statistical pooling, the authors of the study and manufacturers were approached in an attempt to obtain more details. Methodologic quality was assessed by the Jadad scale, which quantifies the likelihood of bias inherent in trials on the basis of their description of randomization, blinding, and withdrawals (10). Two of the authors extracted data and evaluated methodologic quality independently, and discrepancies were resolved through discussion.

The mean change in total cholesterol level compared with baseline was defined as the common end point and was used to assess the differences between the garlic and placebo groups. Weighted means and 95% CIs intervals were calculated by using standard meta-analysis software (RevMan 3.01, Update Software Ltd., Oxford, United Kingdom), which uses the inverse of the variance to assign a weight to the mean of the within-study treatment effect. Most studies, however, did not report enough information to allow us to directly calculate the variance of the preintervention to postintervention change. Studies generally reported data on the preintervention mean and standard deviation and the postintervention mean and standard deviation, but not the standard deviation of the change. It has been suggested that the variance of the change can be imputed by assuming a correlation of 0.4 between preintervention and postintervention values (11). This assumption and the reported values were used to impute the variance of the change, which was then used to assign a weight to the mean of the within-study treatment effect. Summary estimates of the treatment effect were calculated by using a random-effects model.

The chi-square test for homogeneity was performed to determine whether the distribution of the results was compatible with the assumption that intertrial differences were attributable to chance variation alone. Calculations were made in traditional units (mg/dL), and a factor of 0.0259 was used to convert the resulting figures to SI units (mmol/L). Publication bias was assessed by using a funnel plot, whereby effect estimates of the common outcome measure were plotted against trial sample size. The funnel plot was examined visually and tested for symmetry by using a regression method developed by Egger and colleagues (12).

Results

Our search revealed 39 trials in the literature; no unpublished studies were identified. Thirteen of these trials met the inclusion criteria (9, 13–24) and provided data suitable for statistical pooling. Twenty-one trials were excluded because they were not placebo-controlled (25–33), were not randomized (34, 35), were not double-blind (36–38), did not test a monopreparation (39, 40), did not report total cholesterol level (41–43), or reported a mean baseline total cholesterol level less than 5.17 mmol/L (200 mg/dL) (44, 45). Five other trials reported in four papers (46–49) met the inclusion criteria, but data necessary for statistical pooling could not be obtained. Although these studies could not be included in the meta-analysis, they are presented in **Table 1**.

Key data from the 13 included trials are presented in **Table 2**. A total of 796 persons were involved. Baseline values (mean ± SD) in the garlic groups ranged from 5.78 ± 1.06 mmol/L (223 ± 41 mg/dL) to 7.72 ± 3.37 mmol/L (298 ± 130 mg/dL). In the placebo groups, the baseline values ranged from 5.62 ± 0.70 mmol/L (217 ± 27 mg/dL) to 7.64 ± 1.55 mmol/L (295 ± 60 mg/dL).

The results of the meta-analysis are displayed in **Figure 1**. Ten trials report mean differences that favor garlic over placebo. Three trials show 95% CIs that do not overlap the line of zero effect indicating significant differences. Meta-analysis of all trials indicated a significant difference ($P < 0.01$) in the reduction of total cholesterol level from baseline in favor of garlic compared with placebo; the weighted mean difference was −0.41 mmol/L (95% CI, −0.66 to −0.15 mmol/L) (−15.7 mg/dL [CI, −25.6 to −5.7 mg/dL]). This is equivalent to a 5.8% reduction in total cholesterol levels from baseline due to garlic.

The chi-square test for homogeneity indicated a degree of heterogeneity (chi-square = 36.76). A graphical display identified one outlier (15); if this outlier was removed, homogeneity could be demonstrated across the remaining trials (chi-square = 16.33). Pooling the data for only the

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Table 1. **Randomized, Double-Blind, Placebo-Controlled Trials That Lacked Data for Statistical Pooling**

Study (Reference)	Year	Design	Diagnosis	Lipid Criteria	Randomly Assigned Patients/ Analyzed Patients	Type of Extract	Daily Dose	Duration	Jadad Score	Control of Lifestyle Factors	Main Result
					n/n		*mg*	*wk*			
Luley et al. (46)	1986	Crossover	Hyperlipoproteinemia	Not specified	34/34	Powder	540	6	3	None	Garlic no different from placebo
Luley et al. (46)	1986	Crossover	Hyperlipoproteinemia	Not specified	51/51	Powder	1340	6	3	None	Garlic no different from placebo
Kiesewetter et al. (47)	1991	Parallel	Thrombocyte aggregation	Not specified	60/not stated	Standardized powder (Kwai)*	800	4	3	None	Garlic no different from placebo
Simons et al. (48)	1995	Crossover	Hypercholesterolemia	Total cholesterol level 6.0–7.8 mmol/L (230–300 mg/dL)	31/28	Standardized powder (Kwai)*	900	12	4	Dietary advice	Garlic no different from placebo
Steiner et al. (49)	1996	Crossover	Hypercholesterolemia	Total cholesterol level 5.7–7.5 mmol/L (220–290 mg/dL)	56/41	Aged (AGE)†	7200	24	4	Dietary advice	Garlic reduced total cholesterol level more than placebo

* Lichtwer Pharma GmbH, Berlin, Germany.
† Wakunaga of America, Mission Viejo, California.

12 homogeneous trials resulted in a slightly smaller reduction in cholesterol level; the weighted mean difference was −0.30 mmol/L (CI, −0.48 to −0.11 mmol/L) (−11.4 mg/dL [CI, −18.6 to −4.2 mg/dL]), representing an improvement of 4.3%.

We produced a funnel plot of all trials included in the meta-analysis, plotting the mean difference against trial sample size (**Figure 2**). Visual inspection indicated a reasonably symmetrical funnel plot. Studies with smaller sample sizes were distributed around the overall weighted mean difference of the total cholesterol reduction, whereas larger studies more closely resembled this overall weighted estimate. Symmetry of the funnel plot was confirmed by a regression test (12) of all trials ($P > 0.2$).

Two sensitivity analyses were conducted to test the robustness of the results of the overall analysis. The first sensitivity analysis involved five trials with similar methodologic features. All five used the same garlic preparation standardized to 1.3% alliin, the main ingredient of garlic (Kwai, Lichtwer Pharma GmbH, Berlin, Germany), at the same dose of 900 mg over a treatment period of 3 to 6 months, and all controlled for dietary factors (9, 18, 19, 21, 23). Meta-analysis of these data revealed a weighted mean difference of −0.19 mmol/L (CI, −0.39 to 0.01 mmol/L) (−7.3 mg/dL [CI, −15.0 to 0.3 mg/dL]), indicating no significant difference in the reduction of total cholesterol level in persons receiving garlic compared with placebo (**Figure 1**). The second sensitivity analysis involved only the six diet-controlled trials with the highest scores (4 or 5 points on the Jadad scale) for methodologic quality (9, 20–24). Meta-analysis of these data showed no significant difference between garlic and placebo; the weighted mean difference was −0.11 mmol/L (CI, −0.30 to 0.08 mmol/L) (−4.3 mg/dL [CI, −11.7 to 3.1 mg/dL]) (**Figure 1**).

Our meta-analysis focused on the effect of garlic on total cholesterol level. However, because five of the trials (9, 13, 18, 19, 21) also presented other lipid data, they were analyzed to provide an indication of the effect on garlic on high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels. The results indicated a nonsignificant difference in the reduction of LDL cholesterol levels between garlic and placebo and a nonsignificant difference in the increase of HDL cholesterol between garlic and placebo. The weighted mean differences were −0.17 mmol/L (CI, −0.35 to 0.01 mmol/L) (−6.6 mg/L [CI, −13.5 to 0.4 mg/dL]) and 0.07 mmol/L (CI, −0.10 to 0.2 mmol/L) (2.7 mg/dL [CI, −3.9 to 8.9 mg/dL]), respectively. Ten of the 13 trials provided information on adverse events (**Table 2**); gastrointestinal symptoms and garlic breath were reported most frequently.

Discussion

The results of our meta-analysis suggest that compared with placebo, garlic reduces total cholesterol levels in per-

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sons whose levels are elevated. Our findings corroborate the results of previous meta-analyses but suggest that the magnitude of the therapeutic effect may be considerably smaller than previously reported.

Overall, the reduction of total cholesterol level was −0.41 mmol/L (CI, −0.66 to −0.15 mmol/L) (−15.7 mg/dL [CI, −25.6 to −5.7 mg/dL]) for garlic compared with placebo. Although this reduction is smaller than the reduction of −0.59 mmol/L (CI, −0.74 to −0.44 mmol/L) (22.8 mg/dL [CI, −28.6 to −17.0 mg/dL]) reported by Warshafsky and colleagues (7), a small overlap of the CIs indicates some consistency in the two results. The reduction of total cholesterol level shown here, however, is markedly less than that of −0.77 mmol/L (CI, −0.89 to −0.65 mmol/L) (−29.7 mg/dL [CI, −34.4 to −25.1 mg/dL]) reported by Silagy and Neil (8). This is partly because the two analyses used different eligibility criteria and were therefore based on disparate data sets. As well as introducing 5 new trials (19–23), our meta-analysis excluded 9 of the 16 trials in the analyses by Silagy and Neil (8) and Neil and coworkers (9). These papers included trials that were not blinded or placebo-controlled and involved volunteers with normal cholesterol levels. Our meta-analysis was therefore intended to provide a more precise indication of the specific value of garlic in lowering total cholesterol level in persons with hypercholesterolemia.

There was a degree of heterogeneity in our analysis of 13 trials, as indicated by a chi-square test. This could be attributed to a single trial (15). When this trial was excluded from the calculations, the effect of garlic was decreased but remained superior to that of placebo. Although there may be an element of uncertainty about the preciseness of the overall estimate, it is clear for cholesterol level attributable to garlic is approximately 4% to 6%.

Compared with conventional methods of lipid lowering, the estimated reduction for garlic is unimpressive. Dietary interventions have been shown to decrease total cholesterol level by 5.3% after 6 months compared with no treatment (50). Systematic reviews of randomized clinical trials of statin drugs (51, 52) have reported reductions in total cholesterol level from baseline between 17% and 32%, compared with 0.6% for placebo. Of interest, the only randomized clinical trial (33) comparing garlic with a conventional lipid-lowering agent reported no significant difference in the reduction of lipid values between garlic (25.3%) and bezafibrate (27.2%) after 12 weeks of treatment in 98 patients. This finding has yet to be independently confirmed.

Because we tried to locate trials that were suitable for statistical pooling, only 13 trials could be included in our meta-analysis. Five other trials from four papers met the inclusion criteria but could not be analyzed because they lacked data necessary for statistical pooling, and attempts to obtain the information from the authors were unsuccessful. It is noteworthy that four of these studies suggested no superiority of garlic over placebo.

Although systematic efforts were made to find all studies on the subject, some may not have been discovered. Several forms of publication and location bias exist (53), including the tendency for negative trials to remain unpublished (54), for positive findings to be published in English-language journals (55), and for major medical databases not to index some European journals (56). There is also evidence that positive findings may be overrepresented in complementary medicine journals (57) and that these journals favor positive conclusions at the expense of methodologic quality (58). Therefore, it is possible that treatment effects have been exaggerated. The search strategy for our review involved several databases, including those with a focus on the European and U.S. literature, as well as manual searching and contact with experts and manufacturers. Moreover, it was not restricted in terms of publication language. Overall, this should have reduced the effects of database and English-language bias. Furthermore, data were extracted and quality was assessed under blinded conditions to avoid bias at this stage. The result of the funnel plot suggested that efforts to minimize the effects of publication bias were successful.

Only randomized, double-blind, placebo-controlled trials were included in this investigation. Nonetheless, the extent of methodologic rigor varied among studies. Six trials scored a maximum of 5 points on the quality assessment (9, 17, 20, 22–24), but another had a score as low as 2 points (14). Only six trials described their randomization method, and although trials had to be double-blind to be included, only one study actually reported checking the success of blinding (21). Approximately two thirds of participants in each group correctly identified the intervention that they were receiving. This may point to unblinding due to the detection of garlic odor; 20% of the garlic group reported odor compared with none of the placebo group. Several other trials also reported greater detection of garlic odor in the active treatment group (9, 17, 23), including

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Table 2. **Randomized, Double-Blind, Placebo-Controlled Trials of the Effect of Garlic on Total Cholesterol***

Study (Reference)	Year	Design	Diagnosis	Lipid Criteria	Randomly Assigned Patients/Analyzed Patients	Type of Extract†	Daily Dose	Duration	Jadad Score
					n/n			*wk*	
Bordia (13)	1981	Parallel	Coronary heart disease	TCL 6.5–9.1 mmol/L (250–350 mg/dL)	68/62	Essential oil	0.25 mg/kg body mass	20	3
Plengvidhya et al. (14)	1988	Parallel‡	Hyperlipoproteinemia	Not specified	30/30	Spray-dried powder	700 mg	8	2
Vorberg and Schneider (15)	1990	Parallel	Hypercholesterolemia	TCL 6.0–9.1 mmol/L (230–350 mg/dL)	40/40	Standardized powder (Kwai)	900 mg	16	3
Auer et al. (16)	1990	Parallel	Hypertension	Not specified	47/47	Standardized powder (Kwai)	600 mg	12	3
Mader (17)	1990	Parallel	Hyperlipoproteinemia	TCL 5.2–7.8 mmol/L (200–300 mg/dL)	261/221	Standardized powder (Kwai)	800 mg	16	5
De A Santos and Grünwald (18)	1993	Parallel	Hypercholesterolemia	TCL > 6.5 mmol/L (250 mg/dL)	60/52	Standardized powder (Kwai)	900 mg	24	3
Jain et al. (19)	1993	Parallel	Hypercholesterolemia	TCL ≥ 6.0 mmol/L (230 mg/dL)	42/42	Standardized powder (Kwai)	900 mg	12	3
Saradeth et al. (20)	1994	Parallel	Normal	Not specified	68/52	Standardized powder (Kwai)	600 mg	15	5
Neil et al. (9)	1996	Parallel	Hypercholesterolemia	TCL 6.0–8.5 mmol/L (230–330 mg/dL)	115/115	Standardized powder (Kwai)	900 mg	24	5
Adler and Holub (21)	1997	Parallel	Hypercholesterolemia	TCL > 5.2 mmol/L (200 mg/dL)	25/23	Standardized powder (Kwai)	900 mg	12	4
McCrindle et al. (22)	1998	Parallel	Familial hyperlipidemia in children	TCL > 4.8 mmol/L (185 mg/dL)	30/30	Standardized powder (Kwai)	900 mg	8	5
Isaacsohn et al. (23)	1998	Parallel	Hypercholesterolemia	LDL ≤ 4.1 mmol/L (160 mg/dL) and triglyceride level ≤ 4.0 mmol/L (350 mg/dL)	50/42	Standardized powder (Kwai)	900 mg	12	5
Berthold et al. (24)	1998	Crossover	Hypercholesterolemia	TCL 6.2–9.0 mmol/L (240–348 mg/dL) and triglyceride level < 3.0 mmol/L (265 mg/dL)	25/25	Steam-distilled oil	10 mg	12	5

* LDL = low-density lipoprotein cholesterol level; TCL = total cholesterol level.
† Kwai is manufactured by Lichtwer Pharma GmbH, Berlin, Germany.
‡ Trial was conducted with crossover design, but groups were analyzed separately; therefore, only data from the first part of the trial were used in the calculation.
§ Did not specify the intervention group in which symptoms occurred.

two that attempted to reduce the risk for unblinding by flavoring the placebo capsules with garlic (9, 23). Since the numbers of participants reporting garlic odor varied noticeably across studies despite the fact that many studies used the same preparation, the disparate figures may depend on whether patients were specifically questioned about odor or were merely expected to spontaneously report it. The effect of unblinding on trial results is hard to determine, but if participants believe that they are assigned to a potentially beneficial intervention (for example, garlic), they may alter their behavior (for example, diet or exercise) and thereby confound the findings of the trial. Furthermore, empirical research suggests that trials that are not double-blind or that have inadequately concealed treatment allocation yield larger estimates of treatment effects (59). It is therefore possible that a degree of unblinding inherent in many, if not all, garlic studies may have led to an exaggeration of the effects attributed to garlic.

All trials used predefined inclusion and exclusion criteria for selecting patients, and all trials excluded patients

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Table 2. **Continued**

Control of Lifestyle Factors	Mean ± SD Change in TCL from Baseline with Garlic	Mean ± SD Change in TCL from Baseline with Placebo	Mean Difference between Groups [95% CI]	Adverse Events Reported for Garlic	Adverse Events Reported for Placebo
	← *mmol/L (mg/dL)* →				
Maintenance of usual diet/ work	−1.82 ± 3.16 (−70.4 ± 122.2)	0.06 ± 3.40 (2.3 ± 131.1)	−1.88 [−3.52 to −0.24] (−72.7 [−136.1 to −9.3])	Diarrhea (n = 1), epigastric distress (n = 3)§	
Dietary advice	−0.83 ± 1.56 (−32.0 ± 60.4)	−0.67 ± 1.65 (−26.0 ± 63.6)	−0.16 [−1.31 to 0.99] (−6.0 [−50.4 to 38.4])	Not stated	Not stated
None	−1.59 ± 0.69 (−61.5 ± 26.7)	−0.28 ± 0.66 (−10.9 ± 25.5)	−1.31 [−1.73 to −0.89] (−50.6 [−66.8 to −34.4])	Not stated	Not stated
None	−0.98 ± 1.00 (−38.0 ± 38.8)	−0.54 ± 1.18 (−21.0 ± 45.7)	−0.44 [−1.07 to 0.19] (−17.0 [−41.3 to 7.3])	Odor (n = 3)§	
None	−0.81 ± 1.00 (−31.2 ± 38.8)	−0.18 ± 1.18 (−7.0 ± 45.7)	−0.63 [−0.92 to −0.34] (−24.2 [35.4 to −13.1])	Gastrointestinal symptoms (n = 1), odor (n = 30)	Gastrointestinal symptoms (n = 2), allergy (n = 1), odor (n = 12)
Dietary advice	−0.61 ± 0.64 (−23.6 ± 24.7)	−0.31 ± 0.68 (−12.0 ± 26.1)	−0.30 [−0.66 to 0.06] (−11.6 [−25.4 to 2.2])	Flatulance and aftertaste (n = 1)	None
Maintenance of usual diet/ activity	−0.39 ± 1.07 (−15.0 ± 41.3)	−0.05 ± 0.90 (−2.0 ± 34.8)	−0.34 [−0.94 to 0.26] (−13.0 [−36.2 to 10.2])	Odor and belching (n = 1)	Abdominal symptoms (n = 2), minor rash (n = 1), increased bleeding (n = 1)
Maintenance of usual diet/ lifestyle	−0.22 ± 1.14 (−8.4 ± 44.1)	0.03 ± 0.77 (1.3 ± 29.6)	−0.25 [−0.78 to 0.28] (−9.7 [−30.3 to 10.9])	Not stated	Not stated
Dietary advice	−0.05 ± 0.68 (−1.9 ± 26.4)	0.05 ± 0.74 (1.9 ± 28.6)	−0.10 [−0.36 to 0.16] (−3.8 [−13.9 to 6.3])	Abdominal symptoms (n = 4), odor (n = 19)	Abdominal symptoms (n = 2), odor (n = 5), myocardial infarction (n = 1)
Maintenance of usual diet	−0.75 ± 0.91 (−29.0 ± 35.3)	0.03 ± 1.05 (1.1 ± 40.4)	−0.78 [−1.59 to 0.03] (−30.1 [−61.2 to 1.0])	Odor (20% of participants)	None
Dietary advice	0.08 ± 1.77 (3.0 ± 68.5)	0.08 ± 1.50 (3.0 ± 57.8)	0.00 [−1.18 to 1.18] (0.0 [−45.4 to 45.4])	Headache and upset stomach (31% of participants)	Headache and upset stomach (36% of participants)
Dietary advice	0.13 ± 1.09 (5.0 ± 42.2)	0.00 ± 0.76 (0.0 ± 29.4)	0.13 [−0.43 to 0.69] (5.0 [−16.7 to 26.7])	Abdominal symptoms (n = 2), odor (n = 5), intestinal obstruction (n = 1)	Epigastric burning (n = 1), myocardial infarction (n = 1), chest pain (n = 1)
Maintenance of usual diet	−0.04 ± 0.89 (−1.5 ± 34.5)	−0.05 ± 0.97 (−2.1 ± 37.6)	0.02 [−0.5 to 0.53] (0.6 [−19.4 to 20.6])	Abdominal symptoms, odor (a few participants)	Abdominal symptoms, odor (a few participants)

receiving hypolipidemic drugs. However, other important confounding factors were not controlled for in some studies. For example, in five trials (9, 14, 18, 22, 23), patients were given dietary advice. Five other trials (13, 19–21, 24) instructed patients not to change their normal diets, and the remaining three trials (15–17) were not diet-controlled. Six studies (13, 19, 21–24) attempted to monitor patients' dietary intake with diaries or questioning or assessed body weight. Physical activity was monitored in only two trials (19, 22), and only six studies (9, 19, 21–24) assessed compliance with the treatment regimen. All but one of these trials (9) reported satisfactory compliance, and none found any difference between the groups in diet or lifestyle factors. Dropout rates ranged from 6% to 13% where stated. Several studies had small sample sizes, and only four (9, 17, 22, 23) reported a power calculation. Only one trial (9) analyzed the data on an intention-to-treat basis. Methodologic weaknesses are likely to detract from the validity of trial results and to inflate the effect size of an intervention (60). This point is supported in our paper by the result of the sensitivity analysis of studies with the highest methodologic quality.

In addition to methodologic limitations, concerns have been raised regarding the content of the preparations

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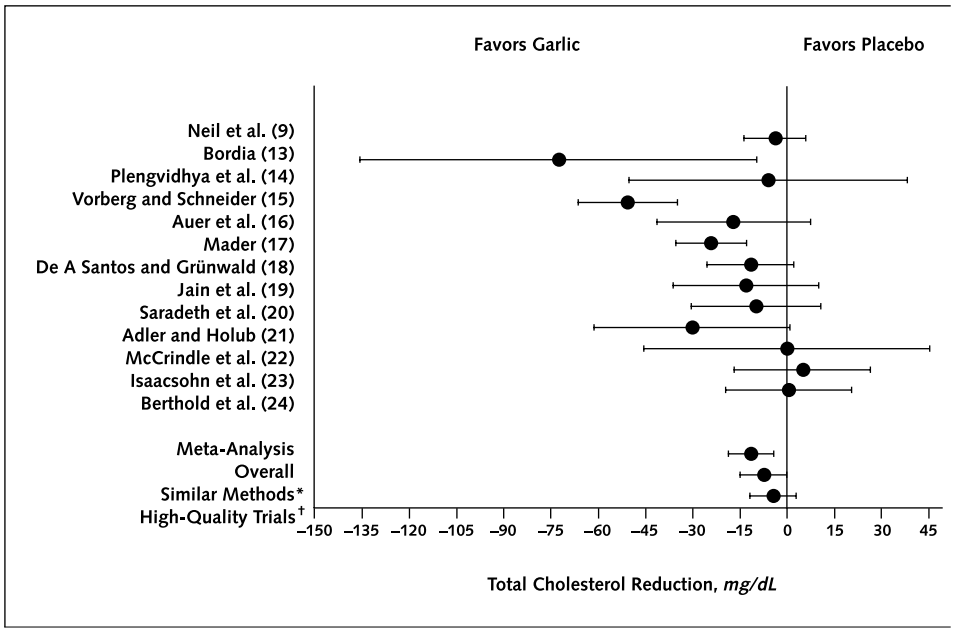
Figure 1. **Mean differences and 95% CIs of randomized, double-blind, placebo-controlled trials of the effect of garlic on total cholesterol.**



The vertical line represents the absence of difference between garlic and placebo. Trials to the left of the line favor garlic, and trials to the right favor placebo. To convert mg/dL to mmol/L, multiply by 0.0259. *Diet-controlled trials that used same garlic preparation and dosage (Kwai [Lichtwer Pharma GmbH, Berlin, Germany], 900 mg/d for 3 to 6 months) (9, 18, 19, 21, 23). †Diet-controlled trials that scored 4 or 5 points on the Jadad scale (9, 20–24).

used in some trials. Kwai was used in 10 of the 13 trials, 4 of which were published after 1995. According to one expert (61), inefficiency and inconsistency in the in vivo production of allicin from the alliin contained in Kwai tablets may explain recent negative findings in clinical trials with this preparation. Effective allicin yields for different lots of Kwai tablets indicated incomplete allicin formation in lots manufactured from 1995 to 1997 compared with those manufactured from 1989 to 1992. Whether these data can account for negative results in clinical trials is uncertain. Other preparations have also yielded negative findings (14, 24, 46), and the relevance of allicin for the lipid-lowering properties of garlic is not clear. The sulfur-containing compound alliin is broken down by the enzyme alliinase and converted to allicin when the bulb is crushed. Allicin in turn is degraded into ajoene and several polysulfides, which are responsible for the distinctive smell of garlic. Commercial preparations of garlic are usually standardized according to alliin content, but the active ingredients and mechanism of action remain unknown.

Ten of the 13 included trials used the same standardized garlic powder (Kwai). The other trials used garlic oil or spray-dried garlic. Aged extracts, raw or cooked garlic, and other standardized products have also been tested in clinical studies. Because the existence and quantities of certain constituents may vary with the type of preparation (62), it is not ideal to include all studies in one analysis. Well-designed placebo-controlled trials comparing the efficacy of different types of garlic preparations at similar doses would help determine whether garlic has a specific effect on cholesterol levels and would provide clues to its active ingredients.

Not all authors provided precise diagnostic criteria for inclusion of patients in trials, yet this is important for an accurate interpretation of results. In the trial by McCrindle and colleagues (22), the sample consisted of children with familial hypercholesterolemia. Since it is particularly difficult to decrease cholesterol levels in persons with this genetic defect, comparisons with the results of trials in a different patient group are problematic.

Changes in HDL and LDL cholesterol as well as total cholesterol levels should be investigated in clinical trials of garlic. Our meta-analysis concentrated on total cholesterol, but an additional analysis of lipid data from a small number of trials revealed a slight reduction in LDL cholesterol level and a slight increase in HDL cholesterol level in the

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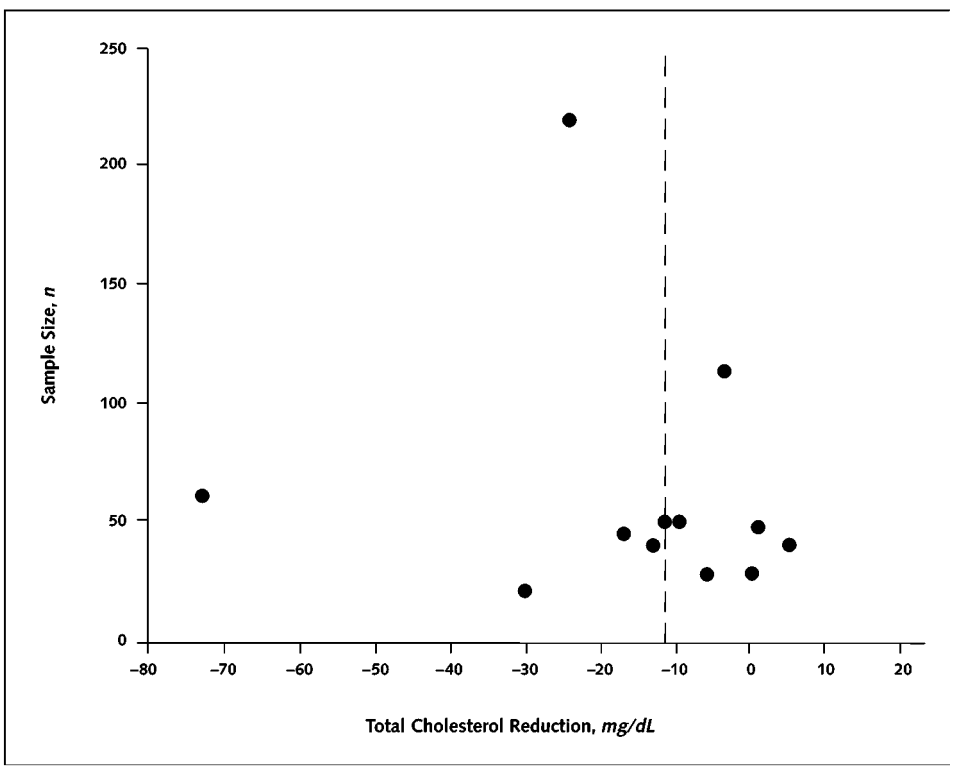
garlic group, neither of which was significantly different from the effect of placebo. The lack of statistical power in these analyses prevents interpretation of these results.

Few adverse events were reported in the trials, and few differences were seen between garlic and placebo groups in the number and nature of adverse events. Gastrointestinal symptoms were the most common problems reported besides garlic breath and body odor. On the basis of this information, garlic seems to be a relatively harmless intervention.

None of these trials directly addressed the clinical implications of lowering plasma lipid levels through administration of garlic. Although modification of risk factors does not necessarily translate into clinical benefits, such as lower incidence of coronary heart disease, it is important to note that garlic may have other protective effects with regard to cardiovascular disease (for example, reduced blood pressure, platelet inhibition, and increased blood flow) that are independent of changes in cholesterol level (63). The longest treatment period of any trial included in our paper was 10 months (13), and most were of a much shorter duration. Large-scale, long-term studies are needed to provide useful data on any association between garlic consumption and important clinical outcomes. One attempt to do this reported a deceleration of atherosclerotic plaque formation after 4 years of garlic administration compared with placebo in 152 patients who had atherosclerotic risk factors (64). Although this study had an encouraging outcome, many methodologic limitations cast doubt on the validity of its findings (65).

Our results suggest that garlic is superior to placebo in reducing elevated total cholesterol levels. However, the size of the effect is modest, and the robustness of the effect is debatable. The implication for clinical practice, therefore, is that garlic use is not an efficient way to decrease total serum cholesterol level. Patients expressing interest in taking garlic for this reason should be advised that according to current evidence, any specific effect is small and may not be clinically meaningful.

Figure 2. **Funnel plot of mean difference in total cholesterol level against sample size in randomized, double-blind, placebo-controlled trials of garlic.**



The broken line represents the combined result of all trials. To convert mg/dL to mmol/L, multiply by 0.0259.

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