

A meta-analysis of randomized, double-blind, placebo-controlled trials for the effects of garlic on serum lipid profiles

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Abstract

BACKGROUND: Inconsistent results were obtained for the lipid-regulating effects of garlic in clinical trials. With increasing interest in complementary medicine for hyperlipidemia, it is important to explore the real effects of garlic. This meta-analysis was performed to investigate the influence of garlic on serum lipid parameters.

RESULTS: A total of 26 studies were included into meta-analysis. Overall, garlic was superior to placebo in reducing serum total cholesterol (TC) and triglyceride (TG) levels. Compared with the placebo groups, serum TC and TG levels in the garlic group were reduced by 0.28 (95% CI, -0.45, -0.11) mmol L⁻¹ ($P = 0.001$) and 0.13 (95% CI, -0.20, -0.06) mmol L⁻¹ ($P < 0.001$), respectively. The effects of garlic were more striking in subjects with long-term intervention and higher baseline TC levels. Garlic powder and aged garlic extract were more effective in reducing serum TC levels, while garlic oil was more effective in lowering serum TG levels. In contrast, garlic did not influence other lipid parameters, including low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), apolipoprotein B, and TC/HDL-C ratio.

CONCLUSION: Garlic could reduce serum TC and TG levels, and garlic therapy should benefit patients with risk of cardiovascular diseases.

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Keywords: garlic; atherosclerosis; cardiovascular diseases; cholesterol; triglyceride

INTRODUCTION

Garlic (*Allium sativum*) has been used medicinally since antiquity, and today is still one of the top-selling herbal supplements.¹ The potential lipid-lowering effects of garlic make it to be a promising natural agent for the prevention of atherosclerosis. Unfortunately, not all studies, especially clinical trials, have provided consistent results.² Some studies demonstrated that garlic could reduce blood total cholesterol (TC) and triglyceride (TG) levels, while other studies contradicted these effects. The contradiction may be attributed to many factors, including the type and dose of garlic, duration of tests, and characteristics of the enrolled subjects.

Meta-analysis, a systematic and objective methodology for synthesizing research literature, can serve as a useful tool to analyze and disclose the true effects of garlic. Earlier meta-analyses strongly suggested that garlic was effective as a lipid-lowering agent. However, newer studies showed a smaller reduction,³⁻⁶ and two recently published works provided conflicting results.^{7,8} The reasons for the discrepancy may be associated with the incomprehensive literature search and the different inclusion criteria. Therefore, it is still necessary to explore the real effects of garlic on lipid parameters.

In the current meta-analysis, a systematic literature search was performed to identify randomized, double-blind, placebo-controlled clinical trials of garlic on serum lipid parameters. We make more stringent and prudential inclusion criteria

in order to explore the effects of garlic more accurately. Firstly, studies in which enrolled subjects suffered from diabetic mellitus^{9,10} were excluded, as diabetes mellitus can induce secondary hyperlipidemia and garlic was found to benefit diabetic treatments.¹¹⁻¹³ Studies with a gender difference between garlic and placebo groups¹⁴ were also excluded, as gender might serve as a confounding factor.¹⁵ In addition, only the first period data were included for crossover designed studies without wash-out time.¹⁶⁻¹⁸ The meta-analyses conducted by Warshafsky *et al.*³ and Stevinson *et al.*⁵ only analyzed the effects of garlic on serum TC levels, while TG, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were added in the studies by Silagy and Neil,⁴ Ackermann *et al.*,⁶ Khoo and Aziz,⁷ and Reinhart *et al.*⁸ In this meta-analysis, in addition to the above indices, we also analyzed the effects of garlic on apolipoprotein B (Apo-B) and the ratio of TC/HDL-C, as Apo-B

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Table 1. Characteristics of randomized, double-blind, placebo-controlled trials included in the meta-analysis

Study	Study design	Jadad score	Sex(M/F) Garlic/ Placebo	Age Garlic/ Placebo	Lipid criteria (Garlic/Placebo)				Type	Dose	Duration	Dropout rate	Dietary advice	Industrial funding
					TC (mmol L ⁻¹)	TG (mmol L ⁻¹)	LDL-C (mmol L ⁻¹)	HDL-C (mmol L ⁻¹)						
Bordia (1981) ⁴¹	Parallel	3	Not stated	54.7/53.0	7.68/7.24	1.94/2.03		GO	15 mg d ⁻¹	10 m	8.82%	Yes	No	
Plengvidhya et al. (1988) ¹⁸	Crossover	2	M/F: 14/16	49.2/50.0	6.88/7.62	3.55/4.47		others	700 mg d ⁻¹	2 m	0%	Yes	No	
Auer et al. (1990) ⁴⁰	Parallel	3	(11/13)/(10/13)	58/57	6.92/6.89	1.93/2.26		GP	600 mg d ⁻¹	12 w	0%	No	No	
Voreberg and Schneider (1990) ³⁹	Parallel	3	M/F: 17/23	Mean:50	7.60/7.44	2.35/2.18		GP	900 mg d ⁻¹	16 w	0%	No	No	
Phelps et al. (1993) ³⁶	Crossover	3	M/F: 5/5	32	4.55/4.50	0.89/0.85		GP	600 g d ⁻¹	2 w	0%	Yes	No	
Jain et al. (1993) ³⁷	Parallel	3	(11/9)/(8/14)	48/55	6.77/7.13	1.71/2.20		GP	900 mg d ⁻¹	12 w	0%	Yes	Yes	
Santos and Grunwald (1993) ³⁸	Parallel	3	(12/13)/(8/19)	53.0/51.1	6.92/7.05	1.65/1.80		GP	900 mg d ⁻¹	6m	13.33%	Yes	No	
Steiner et al. (1996) ¹⁷	Crossover	4	41(men)	32-68	6.36/6.28	2.44/2.39		AGE	7.2 g d ⁻¹	6 m	21.15%	Yes	No	
Neil et al. (1996) ³⁵	Parallel	5	(36/21)/(34/24)	53.0/52.6	6.96/6.99	-		GP	900 mg d ⁻¹	6 m	7.83%	Yes	No	
Adler and Holub (1997) ³⁴	Parallel	4	12/11(men)	45.9/45.4	6.54/6.46	1.98/1.95		GP	900 mg d ⁻¹	12 w	8%	no	No	
Isaacsohn et al. (1998) ³²	Parallel	4	(12/16)/(15/17)	58/57	7.1/6.4	1.9/1.8		GP	900 mg d ⁻¹	12 w	16%	Yes	Yes	
Berthold et al. (1998) ³³	Crossover	4	25(11/14)	58.3	7.53	1.45		GO	10 mg d ⁻¹	12 w	3.85%	Yes	No	
McCordle et al. (1998) ³¹	Parallel	5	(11/4)/(5/10)	13.9/14.1	7.06/6.66	1.14/1.38		GP	900 mg d ⁻¹	8 w	0%	Yes	No	
Superko and Krauss (2000) ³⁰	Parallel	2	Not stated	53	6.46/6.18	1.64/1.45		GP	900 mg d ⁻¹	12 w	0%	Yes	yes	
Kannar (2001) ²⁹	Parallel	4	(12/10)/(13/11)	52.6/57.4	7.4/7.1	1.8/2.3		GP	880 mg d ⁻¹	12 w	6.52%	Yes	yes	
Zhang et al. (2001) ²⁸	Parallel	3	27(men)	29.4/28.4	4.8/4.6	0.80/0.62		GO	12.3 mg d ⁻¹	16 w	16.7%	No	yes	
Zhang et al. (2001) ¹⁵	Parallel	3	(11/8)/(9/12)	24/29	4.8/4.9	1.19/0.96		GO	8.2 mg d ⁻¹	11 w	21.57%	Yes	yes	
Satitvipawee et al. (2003) ²⁶	Parallel	4	(23/47)/(25/41)	47/47	6.65/6.85	-		others	333 mg d ⁻¹	12 w	7.48%	Yes	No	
Peleg et al. (2003) ²⁷	Parallel	3	(8/10)/(9/12)	52.4/54.7	6.79/7.12	2.03/1.92		GP	22.4 mg alliin d ⁻¹	16 w	15.38%	Yes	No	
Tanamai et al. (2004) ¹⁶	Crossover	4	(15/30)/(18/37)	47/47	7.34/7.35	1.89/1.55		others	5 mg alliin d ⁻¹	3 m	13.79%	Yes	No	
Budoff et al. (2004) ²⁵	Parallel	3	(7/2)/(7/3)	61.4/58.5	4.55/5.14	1.59/1.50		AGE	4 ml d ⁻¹	12 m	17.39%	Yes	yes	
Gardner et al. (2007)(a) ²⁴	Parallel	5	22(27)/24(24)	49/49	5.84/5.89	1.10/1.38		others	4 g d ⁻¹	6 m	11.34%	No	No	
Gardner et al. (2007)(b) ²⁴	Parallel	5	22(25)/24(24)	50/49	5.87/5.89	1.29/1.38		GP	1.4 g d ⁻¹	6 m	11.58%	No	No	
Gardner et al. (2007)(c) ²⁴	Parallel	5	28(20)/24(24)	51/49	5.87/5.89	1.31/1.38		AGE	1.8 g d ⁻¹	6 m	11.46%	No	No	
Sobenin et al. (2008) ²³	Parallel	4	42 (men)	51.7/51.7	6.97/7.04	2.00/2.25		GP	600 mg d ⁻¹	12 w	0%	yes	No	
Sobenin et al. (2010) ⁴²	Parallel	5	(18/15)/(17/13)	56.7/56.3	6.96/6.53	1.83/1.44		GP	300 mg d ⁻¹	12 m	20.6%	No	No	

Garlic type: GO, garlic oil; GP, garlic powder; AGE, aged garlic extract; and others. Garlic brands: *Cardiomas*, Seven Seas, Hull, UK; *Kwai*, lichtwer Pharma GmbH, Berlin, Germany; *Tegra*, Hermes Arzneimittel GmbH, Munich, Germany; *Kyolic*, Wakunaga Nutritional Supplement, CA, USA; *Inodiel*, Arkopharma, France; *Garlicin*, Nature's Way Products Inc, Springville, Utah; *Kyolic-100*, Wakunaga of America Co, Mission Viejo, Calif; *AlliCor*, INAT-Farma, Russia.

and the TC/HDL-C ratio could serve as better predictors of atherosclerosis and cardiovascular diseases than TC or LDL-C.^{19,20} A series of subgroup analyses were also performed in order to reveal potential interference factors, including study design, type and dose of garlic, duration of intervention, initial TC and TG levels, dietary advice, receipt of industry funding, and gender. We believe that this meta-analysis provides novel and more accurate results than the literature for the effects of garlic on lipid parameters.

MATERIALS AND METHODS

Literature search

A systematically computerized literature search for the relevant papers published in English or Chinese covering the period from as early as possible to October 2011, from the databases including MEDLINE, ISI Web of Science, EMBASE, Cochrane databases, and China biology medical literature database, was conducted to identify the randomized, double-blind, placebo-controlled clinical trials of garlic on serum lipid parameters. We used the combination of one of the keywords about garlic including 'garlic', '*Allium sativum*', 'allicin' and 'organosulfur compounds', and one of the keywords including 'lipid', 'cholesterol', 'triglyceride', 'lipoprotein', 'hyperlipidemia', 'atherosclerosis' and 'cardiovascular diseases'. In addition, the reference lists of the published papers on clinical trials, review articles and meta-analyses were hand-searched for collection of other relevant studies.

Inclusion and exclusion criteria

A strict and prudential inclusion criterion was applied in this meta-analysis. Only randomized, double-blind, placebo-controlled clinical trials reporting the effects of garlic on serum TC, LDL-C, HDL-C, TG, Apo-B, or TC/HDL-C were eligible for analysis. Parallel or crossover studies utilized all forms, and doses of garlic products in both healthy and hypercholesterolemic subjects were included. For crossover studies without wash-out time only the first period data were included. Trials which used garlic in combination with other agents, and/or enrolled subjects suffering from diabetes mellitus, and/or enrolled subjects with gender difference between garlic and placebo groups, were also excluded for the reasons mentioned in the Introduction. All the studies were reviewed by two independent reviewers and the disagreement was resolved by discussion.

Data abstraction and quality assessment

Data were extracted according to the predefined criteria utilizing a standardized data abstraction form. The following information including author name, publication year, subject status (gender and age), sample size, type and dose of garlic, duration of the intervention, dropout rate, funding status and mean serum lipid levels, and the corresponding SD at the start and the end of intervention, were collected. Methodological assessment of the studies was by Jadad score.²¹ All the studies were reviewed by two independent reviewers and disagreement was resolved by discussion.

Data synthesis and analysis

Mean changes in lipid parameters from baseline of garlic and placebo groups were treated as continuous variables and entered into meta-analysis. For studies generally reporting data of the pre-intervention mean and SD and the post-intervention mean and SD, we calculated the SD of the net change by using a correlation

coefficient of 0.4, as suggested in a previous study.⁵ Heterogeneity among studies was assessed using the Q -test and I^2 statistic. The random-effect model was used as the pooling method when I^2 was $>50\%$; otherwise, the fixed-effect model was considered to be the appropriate choice.²²

Funnel plots and Egger's regression test were used to assess the potential publication bias. Sensitivity analysis was performed to evaluate the stability of the results by removing the studies in which the CI did not overlap the lines of the pooling results. Meta-regression was performed to find any association between serum lipid change and the following continuous variables including dosage, duration of intervention, gender (% men), initial TC and TG levels and dropout rate, and the following categorical variables including type of garlic, industry funding and dietary advice.

The study design (assessed by Jadad score), type of garlic, duration of intervention, initial lipid levels, gender, dietary advice, industry funding and dropout rate may influence the results; therefore, in addition to the comparison between all the garlic products versus placebo, we also performed the subgroup comparisons based on the above parameters.

Statistical analyses were performed using STATA version 9.2 (Stata Corporation, College Station, TX, USA). All reported probabilities (P -values) were two-sided, and <0.05 was considered statistically significant.

RESULTS

A total of 26 studies were included in this meta-analysis (Table 1).^{15–18,23–42} Twenty-two studies enrolled subjects of both gender, while four trials were restricted to men. Nine additional studies met the inclusion criteria,^{43–48} but were not included due to incomplete data for the statistical pooling (Table 2). Ten studies were excluded for several reasons, including that the enrolled subjects suffered from diabetes mellitus,^{9,10,14,49–51} concurrent use of lipid-lowering agents or immunosuppressive regimen,^{50,52,53} garlic administered with other components^{49,54} and gender difference between garlic and placebo groups.¹⁴

Twenty-one of the 26 included studies were parallel designed, while the other five were crossover studies. Most of the studies were well designed, and only two studies were assigned to lower Jadad score (2).^{18,30} Most studies enrolled patients with high TC and/or TG levels, while four studies enrolled subjects with normal lipid values. Garlic powder (GP), mainly *Kwai* brand with doses ranging from 600 to 900 mg d⁻¹, was the most utilized garlic product. Four studies used garlic oil (GO), while three studies used aged garlic extract (AGE). The duration of the intervention ranged from 2 weeks to 1 year. Nineteen of the 26 studies had a dropout rate lower than 15%, and volunteers in 18 studies received dietary advice. Eight of the 26 studies were at least partly industry funded. Twenty-three studies reported the effects on TC and TG levels, while 21, 22, four and seven studies investigated the effects of garlic on LDL-C, HDL-C, Apo-B and TC/HDL-C, respectively.

The effects of garlic on the levels of TC, TG, LDL-C, HDL-C, Apo-B and TC/HDL-C of all studies are shown in the Figs 1–6, respectively. Overall, garlic significantly reduced serum TC level by 0.28 (95% CI, $-0.45, -0.11$) mmol L⁻¹ compared to the placebo group ($P = 0.001$) (Fig. 1). There was a moderate degree of statistical heterogeneity among the studies ($I^2 = 64.2\%$), which was also illustrated by the chi-square test ($\chi^2 = 61.43$). When the two outliers,^{32,39} the CI of which did not overlap the line of the pooling result, were excluded, heterogeneity was much reduced ($I^2 = 10.5\%$), but the TC level was still significantly lowered (0.19 (95% CI,

Table 2. Randomized, double-blind, placebo-controlled trials lacking data for statistical pooling

Study	Study design	Jadad score	Sex(M/F) Garlic/ Placebo	Age(year) Garlic/ Placebo	Type	Dose	Duration	Dietary advice	Main effects
Luley et al. (1986) (a) ⁴⁸	Crossover	3	34	Not stated	Dried garlic	594 mg d ⁻¹	6 w	Not stated	No significant effects
Luley et al. (1986) (a) ⁴⁸	Crossover	3	51	Not stated	Dried garlic	1350 mg d ⁻¹	6 w	No stated	No significant effects
Kiesewetter et al. (1991) ⁴⁷	Parallel	3	18/42	23.8/24.2	GP	800 mg d ⁻¹	4 w	Not stated	No significant effects
Simons et al. (1995) ⁴⁶	Crossover	4	30	53.6	GP	900 mg d ⁻¹	12 w	Yes	No significant effects
Rahmani et al. (1999)(a) ⁴⁵	Parallel	2	-	30-70	GP	1.2-3.6 g d ⁻¹	12 w	Yes	Decreased TC levels
Rahmani et al. (1999)(b) ⁴⁵	Parallel	2	-	30-70	GP	1.2-3.6 g d ⁻¹	12 w	Yes	Decreased TC and LDL levels
Rahmani et al. (1999)(c) ⁴⁵	Parallel	2	-	30-70	GP	1.2-3.6 g d ⁻¹	12 w	Yes	No significant effects
Turner et al. (2004) ⁴⁴	Parallel	5	24/38	49.6/50.9	GP	920 mg d ⁻¹	12 w	Yes	Induced a near significant decrease of TG (12%)
van Doorn et al. (2006) ⁴³	Parallel	4	25/29	48.5/48.8	GP	2.1 g d ⁻¹	12 w	Not stated	No significant effects

Garlic brand: *Garlet*, Kowsar Pharmaceutical Co., Iran; *Futura Hvidløg Forte*, Dansk Droge, Ishøj, Denmark; *Kwai*, Lichtwer Pharma, Berlin, Germany; *Printanor*, INRA, Dijon, France.

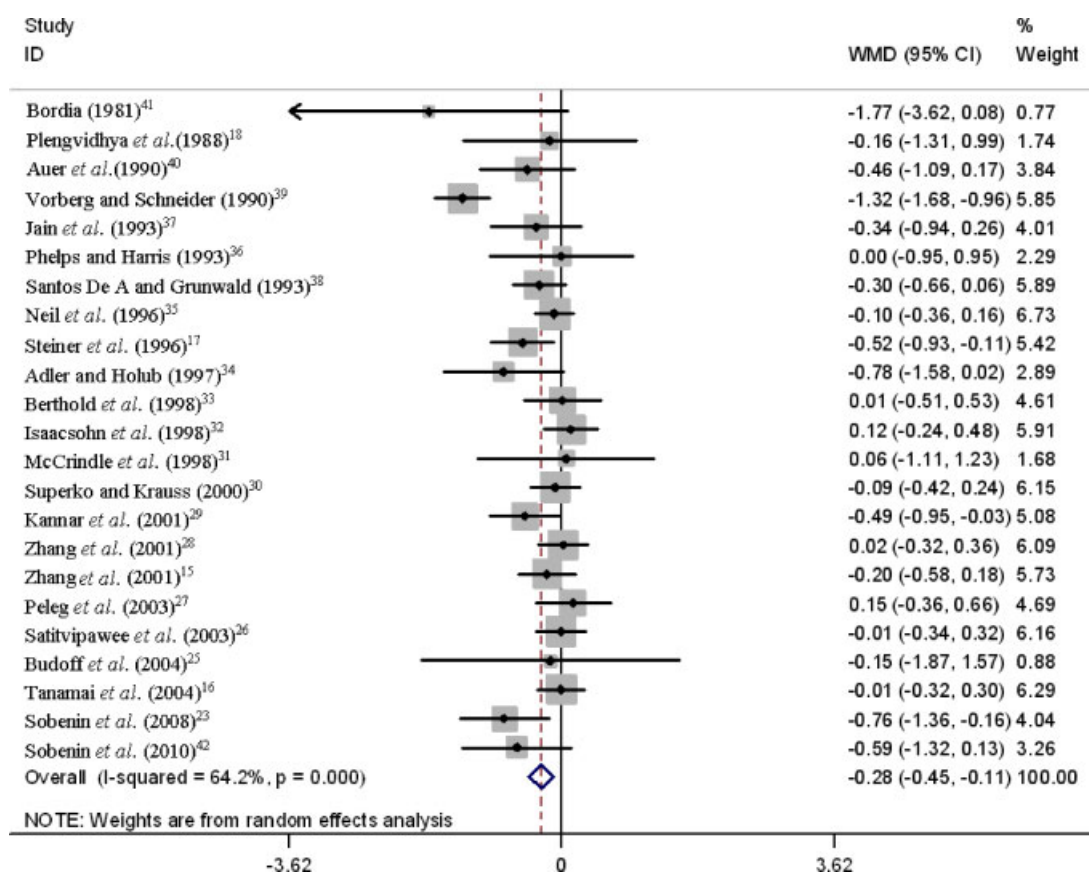


Figure 1. Forest plot results of the effects of garlic on serum TC levels (mmol L⁻¹). The black squares represent individual studies and the size of the square represents the weight given to each study in the meta-analysis. The diamond represents the pooled estimate and the horizontal line represents the 95% confidence interval.

-0.30, -0.08) mmol L⁻¹). Garlic also significantly lowered serum TG levels by 0.13 (95% CI, -0.20, -0.06) mmol L⁻¹, compared to placebo group (*P* < 0.001) (Fig. 2). When the two outliers were excluded,^{27,29} serum TG levels were reduced to a similar level (0.16 (95% CI, -0.23, -0.08) mmol L⁻¹), and the heterogeneity was further reduced (*I*² = 0%). Garlic therapy did not produce any significant influence on LDL-C (mean difference 0 mmol L⁻¹;

95% CI, -0.07 to 0.08 mmol L⁻¹), Apo-B level (mean difference -0.03 mg mL⁻¹; 95% CI, -0.13 to 0.08 mg mL⁻¹), TC/HDL-C ratio (mean difference -0.02; 95% CI, -0.11 to 0.08), and HDL-C level (mean difference 0.01 mmol L⁻¹; 95% CI, -0.02 to 0.03 mmol L⁻¹).

The potential publication bias was detected by funnel plots and Egger's regression test (Fig. 7). The results suggested no publication bias for the effects of garlic on the parameters,

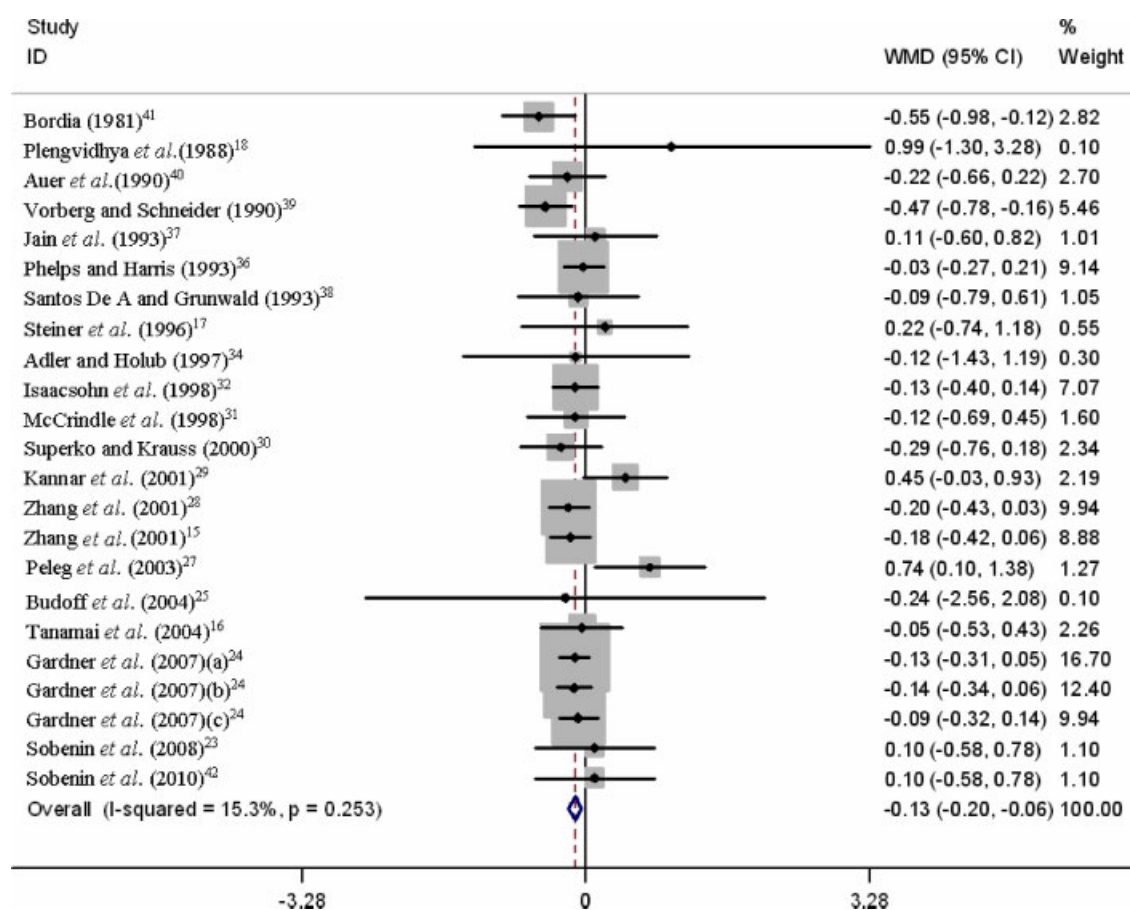


Figure 2. Forest plot results of the effects of garlic on serum TG levels (mmol L^{-1}). The black squares represent individual studies and the size of the square represents the weight given to each study in the meta-analysis. The diamond represents the pooled estimate and the horizontal line represents the 95% confidence interval.

including TC, TG, HDL-C, Apo-B and TC/HDL-C. However, Egger's test revealed that publication bias existed for the LDL-C ($P = 0.001$), which was also illustrated by Begg's test ($P = 0.009$). Meta-regression analysis did not find any significant association between serum blood lipid outcomes and the variables, including dose, duration of intervention, baseline TC/TG level and dietary control.

The results of the subgroup analyses are shown in Table 3. The effects of garlic on serum TC and TG levels were more striking in studies with long-term garlic intervention. The mean change of TC levels was -0.19 , -0.26 and $-0.41 \text{ mmol L}^{-1}$ for subgroups of 0–4 w, 4–12 w, and >12 w, respectively, while that of TG levels were -0.02 , -0.08 and $-0.16 \text{ mmol L}^{-1}$, respectively. GP and AGE were more effective in reducing serum TC levels, while GO were more effective in lowering serum TG levels. The effect of garlic on serum TC was found to be greater in subjects with higher baseline TC levels and in studies with lower dropout rate. The mean change of TC in ≤ 5.17 , 5.17 – 6.42 and $\geq 6.42 \text{ mmol L}^{-1}$ subgroups was -0.07 , -0.29 and $-0.32 \text{ mmol L}^{-1}$, respectively. Furthermore, the effects of garlic on serum TC and TG were more striking in studies without dietary intervention. No obvious difference in effects of garlic on LDL-C and HDL-C levels was found (Table 3).

DISCUSSION

This meta-analysis suggested that garlic could significantly reduce serum TC and TG levels compared to placebo. Compared to

the placebo group, serum TC and TG levels were lowered by 0.28 (95% CI, -0.45 , $-0.11 \text{ mmol L}^{-1}$) and 0.13 (95% CI, -0.20 , $-0.06 \text{ mmol L}^{-1}$), respectively. Other serum lipid parameters, including LDL-C, HDL-C, Apo-B and TC/HDL-C, were not significantly affected. The inconsistency between the change in TC/HDL-C ratio and the change in the single TC and HDL-C was not unexpected, as 23 studies and 22 studies, respectively, were included for TC and HDL-C analyses, whereas only six studies were included for statistical pooling of the TC/HDL-C ratio. A moderate degree of statistical heterogeneity existed among the studies pooled for TC analysis ($I^2 = 64.2\%$), which was markedly reduced when the two outlier trials were excluded ($I^2 = 10.5\%$). Mild to moderate degrees of statistical heterogeneity existed among the studies included for the analyses of TG, LDL-C, HDL-C, Apo-B and TC/HDL-C ($I^2 < 50\%$). Funnel plots and Egger's regression test showed possible publication bias for the LDL-C, but not for other parameters.

The 0.28 mmol L^{-1} reduction of serum TC and 0.13 mmol L^{-1} reduction of serum TG attributable to garlic were modest in size, and approximate to a 5.4% reduction in a patient with baseline TC level of 5 mmol L^{-1} and to a 6.5% reduction in a patient with baseline TG level of 2 mmol L^{-1} . Compared with the conventional methods for lipid-lowering, the estimated reduction of garlic obtained from this meta-analysis is unimpressive. Dietary interventions for 6 months have been shown to induce a similar decrease in TC levels of 5.3%.⁵⁵ Although Holzgartner *et al.* found

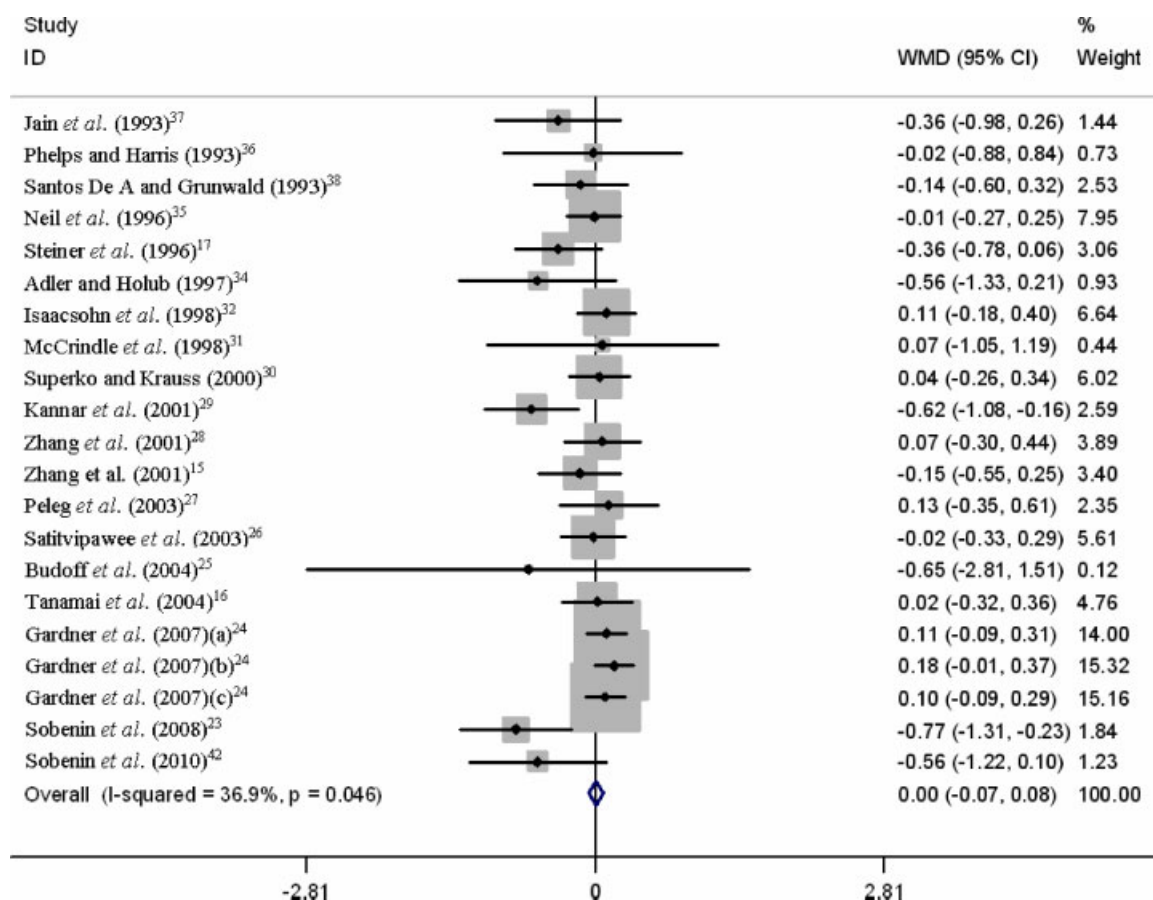


Figure 3. Forest plot results of the effects of garlic on serum LDL-C levels (mmol L^{-1}). The black squares represent individual studies and the size of the square represents the weight given to each study in the meta-analysis. The diamond represents the pooled estimate and the horizontal line represents the 95% confidence interval.

that the lipid-lowering ability of garlic was similar to that of bezafibrate after 12 weeks of treatment,⁵⁶ the effects of garlic were obviously inferior to prescription drugs such as statins and fibrates.

The results of the current meta-analysis on TC, TG, LDL-C and HDL-C were somewhat similar to those of Reinhart *et al.*, in which garlic was found to reduce TC (-0.19 ; 95% CI -0.33 , $-0.06 \text{ mmol L}^{-1}$) and TG (-0.11 ; 95% CI -0.19 , $-0.06 \text{ mmol L}^{-1}$), but did not affect levels of LDL-C and HDL-C. However, there were several differences between the two studies. The studies by Williams *et al.*,⁵² Mader,¹⁰ Macan *et al.*¹⁴ and Kiesewetter *et al.*⁵⁰ were included in the study by Reinhart *et al.*, but were excluded in the current study, as these studies enrolled subjects suffering from diabetes mellitus,^{10,50} taking lipid-lowering drugs,^{50,52} or gender difference between the garlic and placebo groups.¹⁴ We also added three studies^{23,24,42} omitted in Reinhart's review, but did not include four studies^{45,46,57,58} due to incomplete data for statistical pooling. In addition, this study analyzed the effects of garlic on Apo-B and TC/HDL-C ratio. Furthermore, we added several subgroup analyses based on gender, dropout rate, type of garlic products and industry funding. The results of the study by Khoo and Aziz⁷ were absolutely different from those of our study and the one by Reinhart *et al.* The incomprehensive literature search might be a reasonable explanation.

The lipid-lowering effects of garlic may be attributed to many factors. Garlic may inhibit 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR) directly,^{59–61} or indirectly by inhibition

of AMP-activated protein kinase (AMPK)^{15,62} and/or 4 α -methyl oxidase inhibition.⁶³ In addition to HMGCR, several other targets might be also be included. Garlic might suppress the activity of acyl-CoA:cholesterol acyltransferase (ACAT), which participates in cholesteryl ester formation, and stimulate cholesteryl ester hydrolase (CEH), which degrades cholesteryl esters.⁶⁴ Furthermore, human gastric lipase (HGL, an important enzyme in the digestion and absorption of dietary fats) and cholesteryl ester transfer protein (CETP, the key enzyme in the reverse cholesterol transport system that transports cholesterol from peripheral tissues to the liver) have also been demonstrated to be repressed by garlic.^{65,66} Lastly, garlic may influence the activity of fatty acid synthetase (FAS),⁶¹ and suppress the assembly and secretion of chylomicrons from the intestine to the blood circulation via inhibition of microsomal triglyceride transfer protein (MTP) gene expression.⁶⁷

There are several issues that need to be carefully scrutinized. The first point is the diversity in the production process for garlic products. GP is the most commonly used garlic product. The active substances of GP are believed to be remarkably similar to those found in raw, whole garlic cloves, and GP is usually standardized by alliin, the precursor of allicin and one of the principal active compounds in garlic.⁴⁴ Another two commonly used products, GO and AGE, have a very different composition. GO mainly contains lipid-soluble organosulfur compounds, while AGE is composed of water-soluble organosulfur compounds. Secondly, the truly active component of garlic accounting for the hypolipidemic effects is still unclear. GP is usually labeled by the release level of allicin.¹⁵

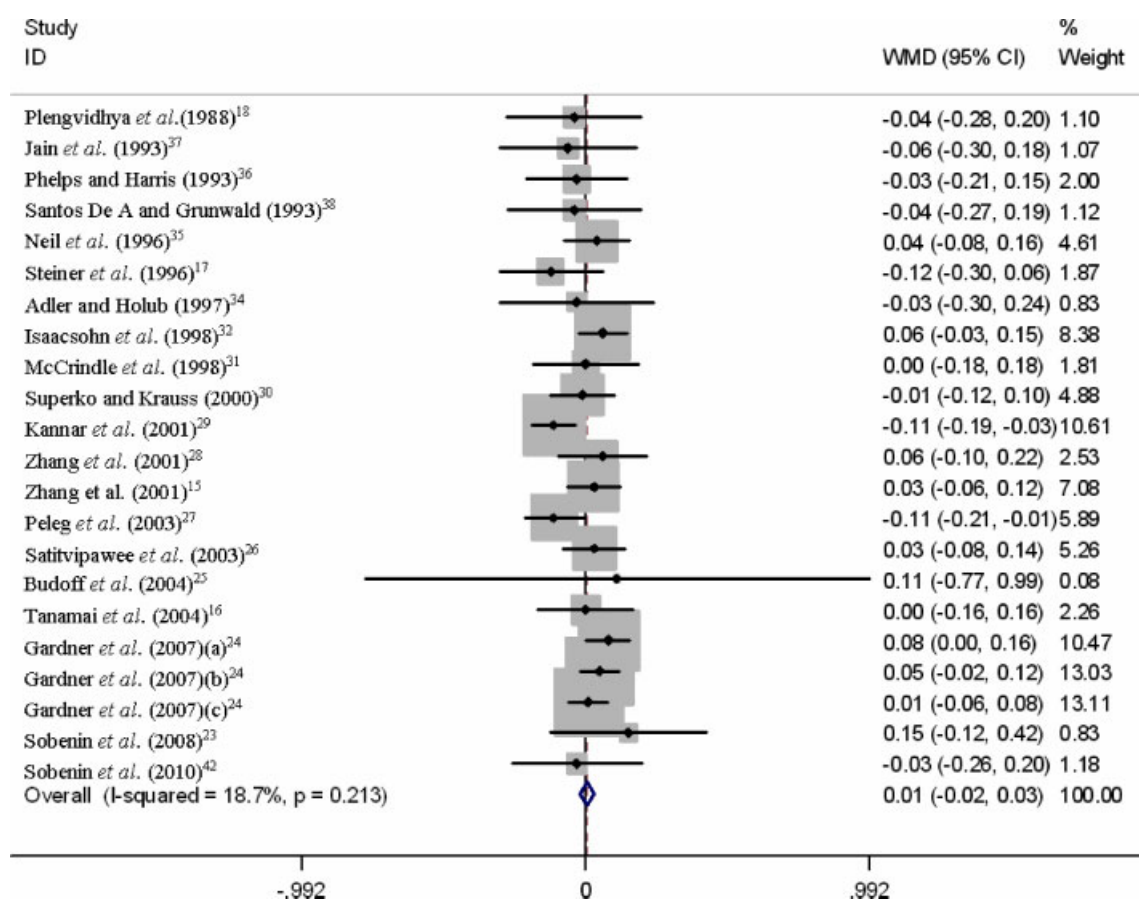


Figure 4. Forest plot results of the effects of garlic on serum HDL-C levels (mmol L^{-1}). The black squares represent individual studies and the size of the square represents the weight given to each study in the meta-analysis. The diamond represents the pooled estimate and the horizontal line represents the 95% confidence interval.

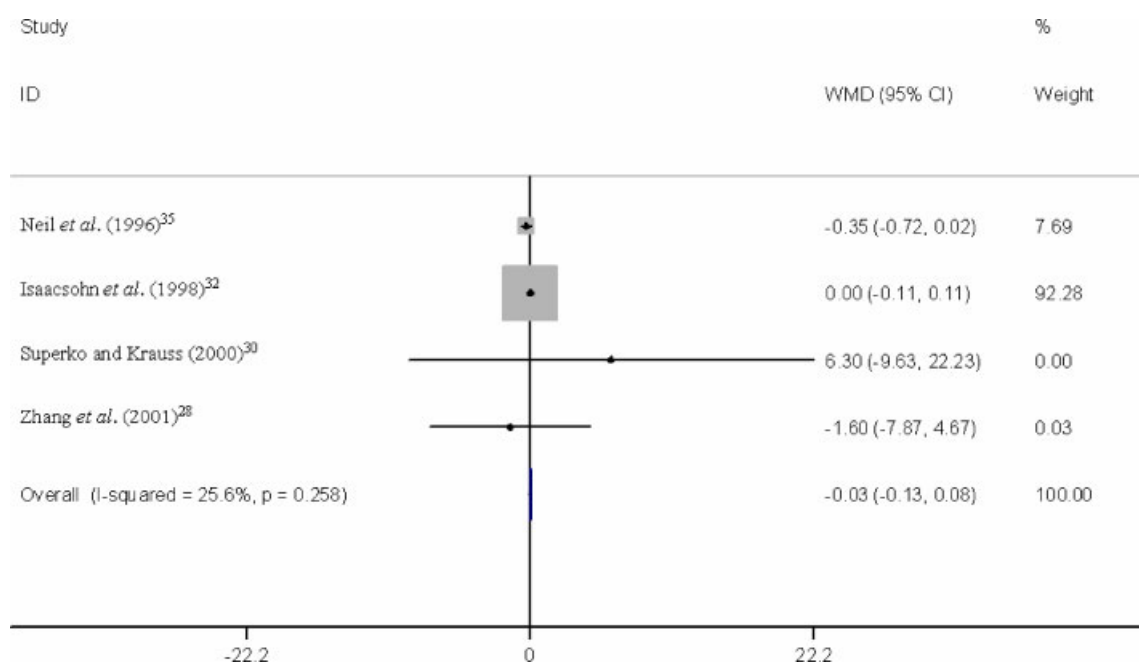


Figure 5. Forest plot results of the effects of garlic on Apo-B levels (mg mL^{-1}). The black squares represent individual studies and the size of the square represents the weight given to each study in the meta-analysis. The diamond represents the pooled estimate and the horizontal line represents the 95% confidence interval.

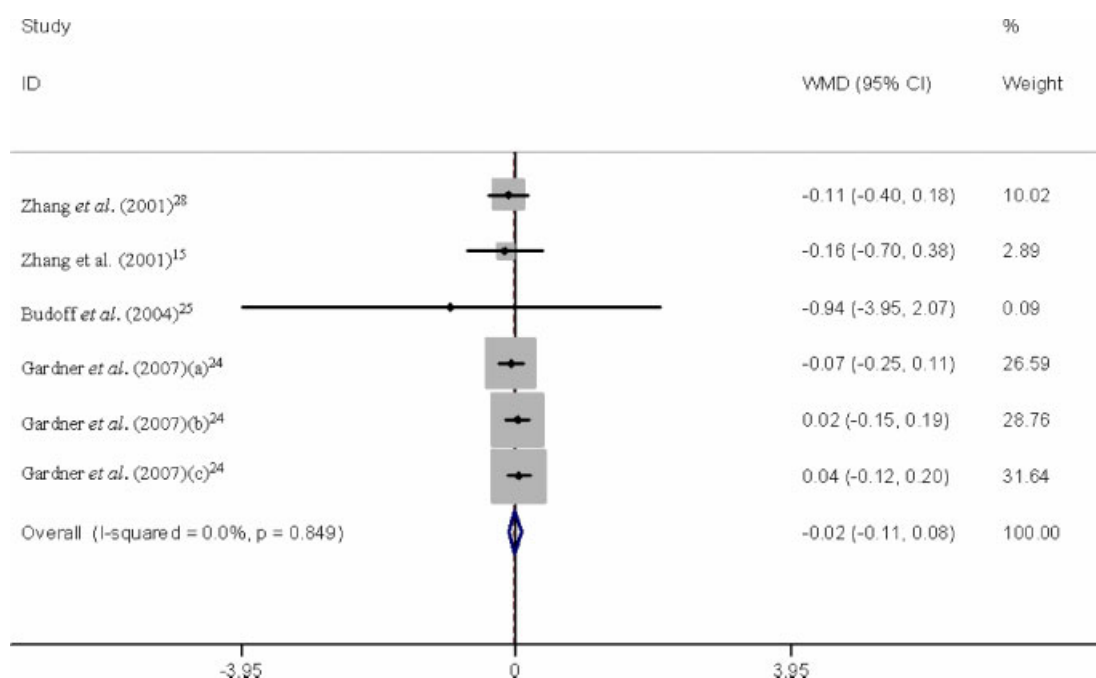


Figure 6. Forest plot results of the effects of garlic on TC/HDL-C. The black squares represent individual studies and the size of the square represents the weight given to each study in the meta-analysis. The diamond represents the pooled estimate and the horizontal line represents the 95% confidence interval.

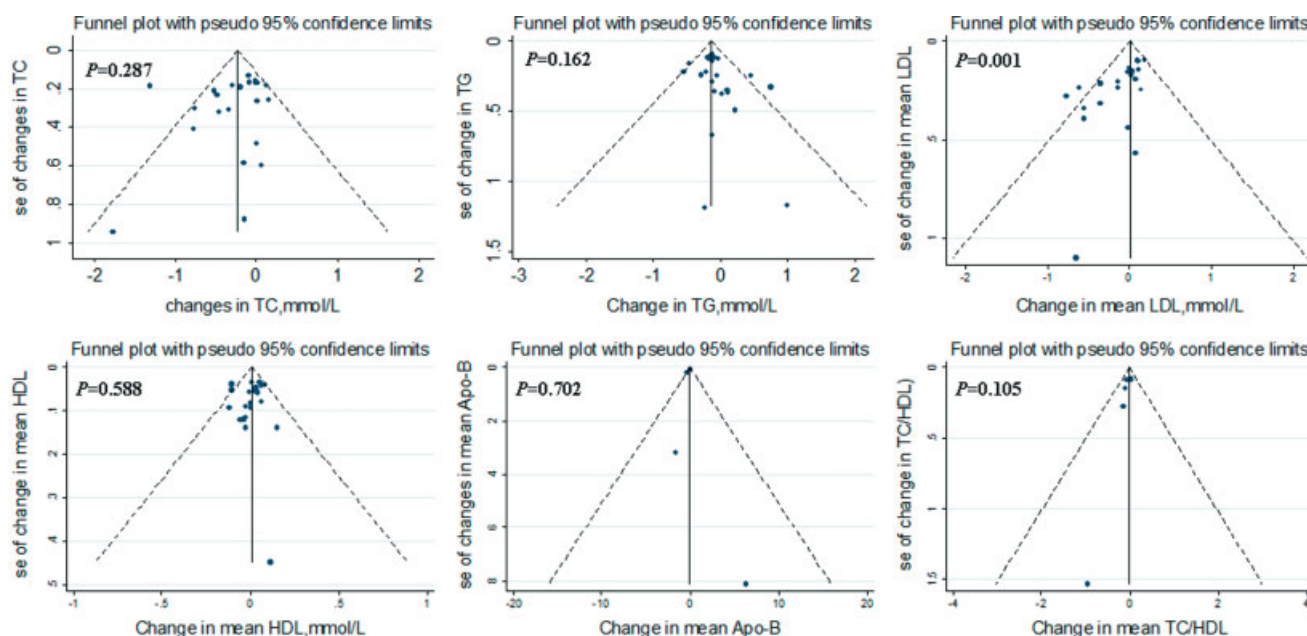


Figure 7. Funnel plots of studies included in meta-analysis on the effects of garlic on serum lipid parameters. The vertical line of funnel plot represents the pooled mean effects size, and the dotted line represents the 95% confidence interval. *P*-values are derived from Egger's test. The results show potential publication bias for LDL-C, but not for other parameters.

However, it is still uncertain whether allicin is the major active compound contributing to the hypolipidemic effects of garlic. One animal study showed that allicin decreased serum TC and LDL-C levels and increased HDL-C levels,⁶⁸ which was contradicted by the following study conducted by the same group.⁶⁹ In a well-designed clinical trial, Gardner *et al.* did not find any hypolipidemic effects²⁴ of Garlicin, a garlic product which can easily release allicin under gastrointestinal tract conditions defined by the United States Pharmacopeia (USP).⁷⁰ In fact, previous studies have revealed that

allicin serves as a transient compound that soon decomposes into many other volatile organosulfur components,^{70–72} and thus allicin might not be the genuine active compound of garlic from this point. Moreover, the relative ingredient content of whole garlic is affected by growth conditions such as soil composition. Owing to the different planting and processing procedures, garlic products usually differ in their composition and availability. As such, it may not be surprising to get different results with the same garlic preparation, let alone with different ones.

Table 3. Results of subgroup analysis (effect sizes and 95% confidence intervals)

		TC (mmol L ⁻¹)			TG (mmol L ⁻¹)			LDL (mmol L ⁻¹)			HDL (mmol L ⁻¹)		
		Effects size	95% CI	I ² (%)	Effects size	95% CI	I ² (%)	Effects size	95% CI	I ² (%)	Effects size	95% CI	I ² (%)
Jadad score	2	-0.10	-0.41, 0.22	0	-0.24	-0.70, 0.22	13	0.04	-0.26, 0.34	-	-0.02	-0.12, 0.09	0
	3	-0.36	-0.73, -0.00	77	-0.18	-0.29, -0.07	46	-0.06	-0.26, 0.13	0	-0.02	-0.08, 0.03	0
	4	-0.23	-0.46, -0.00	55	0.01	-0.18, 0.21	0	-0.25	-0.50, 0.01	62	-0.01	-0.09, 0.06	51
	5	-0.15	-0.39, 0.09	0	-0.12	-0.23, -0.01	0	0.09	-0.01, 0.19	3	0.04	0.00, 0.08	0
Duration	≤4 w	-0.19	-0.39, -0.00	5	-0.02	-0.17, 0.14	0	0.01	-0.22, 0.25	0	-0.04	-0.10, 0.01	0
	4–12 w	-0.26	-0.45, -0.08	63	-0.08	-0.19, 0.04	36	-0.09	-0.20, 0.02	36	-0.01	-0.05, 0.02	0
	>12 w	-0.41	-0.78, -0.05	81	-0.16	-0.25, -0.07	39	0.06	-0.03, 0.15	15	0.02	-0.02, 0.05	28
Type of garlic	GP	-0.36	-0.61, -0.11	73	-0.10	-0.20, 0.00	33	-0.13	-0.30, 0.05	53	-0.01	-0.04, 0.02	40
	AGE	-0.50	-0.90, -0.10	0	-0.08	-0.30, 0.15	0	-0.10	-0.49, 0.29	52	-0.01	-0.07, 0.06	0
	GO	-0.09	-0.31, 0.14	26	-0.24	-0.39, -0.08	16	-0.03	-0.31, 0.24	0	0.04	-0.04, 0.12	0
	Other	-0.02	-0.24, 0.21	0	-0.12	-0.28, 0.05	0	0.06	-0.09, 0.21	0	0.05	-0.01, 0.11	0
Baseline TC (mmol L ⁻¹)	≤5.17	-0.07	-0.31, 0.17	0	-0.14	-0.27, -0.00	0	-0.04	-0.30, 0.22	0	0.03	-0.05, 0.10	0
	5.17–6.42	-0.29	-0.71, 0.13	61	-0.13	-0.24, -0.02	0	0.09	-0.01, 0.19	26	0.03	-0.01, 0.07	26
	>6.42	-0.32	-0.55, -0.10	73	-0.13	-0.26, 0.00	44	-0.11	-0.23, 0.01	42	-0.02	-0.06, 0.01	28
Baseline TG (mmol L ⁻¹)	≤1.69	-0.10	-0.27, 0.08	0	-0.13	-0.22, -0.05	0	0.08	-0.01, 0.18	0	0.03	0.00, 0.07	0
	1.69–2.26	-0.21	-0.36, -0.06	48	-0.05	-0.21, 0.10	46	-0.22	-0.46, 0.03	56	-0.04	-0.09, 0.00	44
	≥2.26	-0.77	-1.46, -0.09	80	-0.39	-0.67, -0.10	37	-0.36	-0.78, 0.06	-	-0.09	-0.23, 0.05	0
Dropout rate (%)	≤10%	-0.39	-0.66, -0.12	72	-0.16	-0.29, -0.03	41	-0.15	-0.29, -0.00	43	-0.03	-0.07, 0.02	0
	>10%	-0.12	-0.25, 0.02	23	-0.12	-0.20, -0.03	0	0.06	-0.03, 0.15	5	0.02	-0.01, 0.06	24
Gender	Men	-0.44	-0.85, -0.03	63	-0.15	-0.36, 0.06	0	-0.35	-0.74, 0.03	58	0.01	-0.10, 0.11	14
	Both	-0.24	-0.44, -0.05	66	-0.13	-0.20, -0.05	26	0.04	-0.04, 0.11	12	0.01	-0.02, 0.03	28
Dietary control	Yes	-0.15	-0.25, -0.04	11	-0.07	-0.19, 0.04	27	-0.09	-0.19, 0.02	24	-0.02	-0.05, 0.01	16
	No	-0.62	-1.24, -0.01	86	-0.17	-0.26, -0.08	0	0.10	-0.01, 0.20	32	0.04	0.01, 0.08	0
Industry grant	Yes	-0.09	-0.22, 0.04	0	-0.10	-0.22, 0.03	50	-0.04	-0.16, 0.09	20	-0.02	-0.06, 0.02	47
	No	-0.42	-0.70, -0.15	71	-0.15	-0.24, -0.06	0	0.03	-0.07, 0.12	48	0.03	-0.01, 0.06	0

There are some strengths and limitations of this study. We make more strict inclusion criteria, and analyzed almost all the lipid parameters mentioned in the literature. A series of important subgroup analyses, which were not mentioned or only generally so in previous studies, were also performed. However, it should be noted that nine studies eligible for analyses were not included owing to incomplete data. As seven of these studies reported no difference between garlic and placebo groups, the effects of garlic on serum TC and TG might be reduced to a more modest level if all these studies were included. Another point which should be taken into account concerns the results about gender difference. The study by Zhang *et al.* suggested that women may benefit more than men from garlic treatment,¹⁵ while the current meta-analysis showed that the effects of garlic in men were greater than those in subjects of both gender (shown by the changes in TC and LDL-C). However, we must point out that only four studies were included in the analysis for men,^{17,23,28,34} while 17–18 studies were included for the groups of both genders. Therefore, the conclusion should be made with caution, and thus the influence of gender on garlic's effects warrants further studies.

CONCLUSIONS

This meta-analysis suggested that garlic was superior to placebo in reducing the serum TC and TG levels without influence on LDL-C, HDL-C, Apo-B, and TC/HDL-C ratio. Although the size of the effect is modest, garlic therapy should benefit patients with

risk of cardiovascular diseases, as garlic may also reduce blood pressure, decrease plasma viscosity, etc.⁷³ Future studies should be conducted to illustrate the active compounds in garlic responsible for the hypolipidemic effects, to explore the influence of gender on garlic's effects, and to compare the efficiency between garlic and regular lipid-lowering drugs such as statins and fibrates.

ACKNOWLEDGEMENTS

This work was funded by the Scientific and Technological Cooperation Project of Shandong Province (2008GG2NS02012), China Postdoctoral Science Foundation funded project (20100481253), Postdoctoral Science Foundation funded Project of Shandong Province (201002020), and Independent Innovation Foundation of Shandong University, IIFSDU (2010GN045).

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