REVIEW ARTICLE

Garlic Shows Promise for Improving Some Cardiovascular Risk Factors

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Objectives: To summarize the effects of garlic on several cardiovascular-related factors and to note its adverse effects.

Methods: English and non-English citations were identified from 11 electronic databases, references, manufacturers, and experts from January 1966 through February 2000 (depending on the database searched). Reports of cardiovascular-related effects were limited to randomized controlled trials lasting at least 4 weeks. Reports of adverse effects were not limited by study design. From 1798 pertinent records, 45 randomized trials and 73 additional studies reporting adverse events were identified. Two physicians abstracted outcomes and assessed adequacy of randomization, blinding, and handling of dropouts. Standardized mean differences of lipid outcomes from placebo-controlled trials were adjusted for baseline differences and pooled using random effects methods.

Results: Compared with placebo, garlic preparations may lead to small reductions in the total cholesterol level at 1 month (range of average pooled reductions, 0.03-0.45 mmol/L [1.2-17.3 mg/dL]) and at 3 months (range of average pooled reductions 0.32-0.66 mmol/L [12.4-25.4 mg/dL]), but not at 6 months. Changes in low-density lipoprotein levels and triglyceride levels paralleled total cholesterol level results; no statistically significant changes in high-density lipoprotein levels were observed. Trials also reported significant reductions in platelet aggregation and mixed effects on blood pressure outcomes. No effects on glycemic-related outcomes were found. Proven adverse effects included malodorous breath and body odor. Other unproven effects included flatulence, esophageal and abdominal pain, allergic reactions, and bleeding.

Conclusions: Trials suggest possible small short-term benefits of garlic on some lipid and antiplatelet factors, insignificant effects on blood pressure, and no effect on glucose levels. Conclusions regarding clinical significance are limited by the marginal quality and short duration of many trials and by the unpredictable release and inadequate definition of active constituents in study preparations.

Arch Intern Med. 2001;161:813-824

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AMERICAN CONSUMER use of complementary and alternative medicine is escalating rapidly. Out-of-pocket expenditures for herbal therapies are estimated at more than $5 billion per year in the United States alone.[1] Garlic (*Allium sativum*) is clearly one of the most popular herbal remedies worldwide today. Animal studies suggest that garlic has potential antilipidemic, antihypertensive, antiglycemic, antithrombotic, and antiatherogenic properties.[2-7] Although some small studies in humans corroborate the findings of animal studies, the results are often conflicting.[5,8-14] Several previous reviews summarize trials in humans, but they cite different original studies, emphasize single cardiovascular factors (eg, lipid levels or hypertension only), and provide variable attention to specific garlic preparations and constituents.[15-21]

Inabilities to blind subjects to the smell and taste of garlic as well as unpredictability in the release of potential active ingredients have limited clinical applicability of prior trial results. Some investigators have simply conducted nonblinded trials with various odor-containing garlic preparations. Others have used "odor-free" commercial preparations, such as dehydrated tablets (eg, Kwai, Lichtwer Pharmaceuticals, Berlin, Germany; Sapec, Lichtwer Pharmaceuticals; Pure-Gar Deodorized Garlic, Essentially Pure Ingredients, Chatsworth, Calif) and "aged garlic extract" (eg, Kyolic, Wakunage of America, Mission Viejo, Calif), or have instead compared garlic with matching odor- or taste-containing placebos. Dehydrated preparations are used most commonly and reportedly contain most constituents found naturally in whole garlic. Many

dehydrated preparations are further "standardized" according to particular constituents, most commonly to the compound S-allyl cysteine–S-oxide (alliin). Standardization to alliin is believed to provide a greater potential for liberation of the thiosulfinate compound allicin, which is produced enzymatically from alliin following hydration. Allicin has been shown in animal models to have significant antilipidemic potential.[22,23] Alternatively, aged garlic extract (Kyolic) is based on the content of S-allyl cysteine, as it is reportedly prepared by allowing more volatile compounds found in chopped garlic (eg, allicin) to slowly evaporate in the presence of aqueous alcohol. Throughout the remainder of this review, "standardized" will refer to commercial garlic preparations that are marketed by their potential to liberate a weight-based percentage of allicin after human consumption.

This systematic review will carefully scrutinize the internal validity of trials using oral garlic preparations, focus on the importance of differences among various preparations, and comprehensively summarize multiple reported cardiovascular-related effects and potential adverse effects of various oral garlic preparations.

MATERIALS AND METHODS

DATA SOURCES

English and non-English citations were identified from 11 electronic databases, references of pertinent articles, symposia, manufacturers, and experts. Electronic databases, including AMED, CISCOM, the Cochrane Library, EMBASE, MEDLINE, and NAPRALERT, were searched from January 1996 through July 1999 (depending on the database) using the following terms: "2-propenesulfenic acid," "aglio," "ajo," "ajoene," "alisat," "allicin," "alliinase," "*Allium sativum*," "allyl mercaptan," "diallyl disulphide," "diallyl sulfide," "diallyl sulphide," "dipropyl disulphide," "dipropyl sulphide," "garlic," "garlic extract," "garlic oil," "knoblauch," Kwai, Kyolic, "S-allyl cysteine," "thioallyl derivative," "thiosulfinates," and "vinyl dithiin." This search was updated on PubMed in February 2000.

STUDY SELECTION

Reports of effects on cardiovascular outcomes were limited to randomized controlled human trials, lasting at least 4 weeks, and comparing garlic with placebo, no garlic, or another active agent. Reports of adverse effects included any human study that identified adverse clinical symptoms or events associated with garlic exposure. From 1798 possible pertinent records, 2 independent reviewers (C.D.M. and V.A.L.) identified 45 randomized trials and 73 additional studies reporting adverse effects. One additional trial, available only in abstract form, was not reviewed.[24]

DATA EXTRACTION

Two independent physicians (R.T.A. and C.D.M.) abstracted data from trials, and one physician (L.M.) abstracted studies of adverse effects. Original authors were contacted and requested to provide information when data were unreported. No formal reliability tests of abstractions were conducted; disagreements were resolved by consensus (R.T.A., C.D.M., and L.A.).

DATA SYNTHESIS

Placebo-controlled randomized trials with lipid level outcomes were quantitatively pooled because (1) multiple small to moderate-sized studies with lipid level outcomes were available, (2) similar control groups were used, and (3) lipid level outcomes were measured using similar parameters at similar follow-up times. Standardized mean differences, adjusted for baseline differences, were used as the effect size measure rather than mean differences.[25,26] Effect sizes calculated as mean differences can be variably influenced by underlying population values when studies exhibit substantial heterogeneity at baseline; greater absolute effects are more likely, for example, to occur among patients with high baseline cholesterol levels than among those with lower baseline cholesterol levels.[26] We tried to identify outlier studies with Galbraith plots, a standard χ^2 test, and funnel plots. Studies were considered outliers if the χ^2 test was $P<.10$ and/or if they fell outside of the Galbraith or funnel plot.

Data were pooled using a random effects estimate both with and without studies that were identified as outliers.[27] (Results presented in the text are without outliers, while figures give results of both analyses.) Subgroup analyses were conducted for trials that (1) used similar dried standardized preparations of garlic, (2) enrolled subjects with hypercholesterolemia, and (3) used double-blind designs. A study that evaluated a garlic and fish oil combination was not pooled because of possible independent effects of fish oil on lipid levels. Effect sizes were converted to clinical laboratory units using the following weighted average pooled SDs: total cholesterol level, 1.05 mmol/L (40.8 mg/dL); low-density lipoprotein cholesterol level (LDL-C), 0.75 mmol/L (29.1 mg/dL); high-density lipoprotein cholesterol level (HDL-C), 0.29 mmol/L (11.4 mg/dL); and triglyceride levels, 0.97 mmol/L (85.9 mg/dL).

RESULTS

OVERVIEW OF TRIAL QUALITY

Randomized trials were published in scientific journals (n=37), symposia proceedings (n=5), a book chapter (n=1), a thesis (n=1), and an abstract (n=1; full report was obtained from the corresponding author). Details of randomization procedures were scant. Whether 2 trials were actually randomized was unclear; attempts to contact the original authors for clarification were unsuccessful.[28,29] Equivalencies between randomized groups for baseline lipid levels, blood pressure, body mass, diet, or activity levels were reported in 16 trials.[21,30-44]

Of 34 trials with double-blind designs, only one, which used an odor-free dehydrated tablet, assessed adequacy of blinding through direct questioning. Blinding was reportedly not successful.[33] Eight trials reported adverse effects clearly

attributable to garlic (ie, body odor, breath, or taste) that occurred significantly more frequently in garlic-treated subjects than in those receiving placebo; all of these trials used standardized dehydrated tablets.[21,33,39,40,43,45-47] Four trials specifically used a placebo with garlic odor or taste.[30,35,48,49] One of these, which involved a nonstandardized dehydrated preparation, reported that an insignificant number of subjects correctly guessed their assignment.[30]

Four trials had dropout rates that were 20% or greater.[40,43,50,51] Five excluded subjects from the statistical analysis due to insufficient compliance, protocol violations, or missed visits,[34,38-41] and 3 reported rates of compliance that were less than 80%.[21,50,52] Only 6 specifically conducted intention-to-treat analyses or reported no dropouts.[21,34,37,53,54]

INTERVENTION AND CONTROL GROUPS

Twenty-two studies evaluated dehydrated garlic preparations that were standardized to an alliin content of 1.3% of the weight of active powder within each tablet (**Table 1**).* Other preparations were standardized to a minimum release of 0.3% allicin,[62] and 4.6 mg of alliin per tablet.[45] The remainder used various nonstandardized preparations alone,† or in combination with either fish oil, hawthorn, soya lecithin, gingko biloba, or other lesser ingredients.[35,37,41,67,68] Compliance of preparations with gastrointestinal dissolution standards were rarely reported.[46]

Placebos were used as control comparisons except for a no-garlic control,[65] an antilipidemic agent,[34] an antihypertensive agent,[59] and a head-to-head comparison of 2 different garlic preparations.[57] Ten studies specified low-fat, low-cholesterol, high-fiber diets.‡ Other studies defined no specific dietary measures and generally allowed usual diets. Seven trials reported no changes in diet during follow-up,[30,33,42,44,47,49,52] 15 reported no changes in body mass,§ and 2 reported no changes in physical activity.[30,52] Trials used various lipid measurement protocols; a few clearly followed current suggested guidelines.[21,30,42,44,45,58]

References 9, 21, 32-34, 38-40, 43, 44, 46, 47, 51, 52, 54-61.

†*References 28-33, 36, 42, 48-50, 53, 57, 63-66.*

‡*References 21, 34, 44, 45, 47, 50, 52, 56, 58, 62.*

§*References 9, 30, 33-35, 38, 42, 44, 47, 49-52, 56, 58.*

TRIAL OUTCOMES

Antilipidemic Effects

Meta-analyses of placebo-controlled trials that reported total cholesterol level outcomes at 4 to 6 weeks, 8 to 12 weeks, and 20 to 24 weeks are shown in the **Figure**. Combining all studies regardless of garlic preparation showed that compared with placebo the total cholesterol level was reduced on average by 0.19 mmol/L (7.2 mg/dL) (95% confidence interval [CI], 0.03-0.34 mmol/L [1.2-13.15 mg/dL]) after 4 to 6 weeks of therapy (n=14) and 0.44 mmol/L (17.1 mg/dL) (95% CI, 0.32-0.57 mmol/L [12.37-22.04 mg/dL]) after 8 to 12 weeks (n=24). Studies evaluating standardized dehydrated garlic preparations revealed average reductions of 0.26 mmol/L (10.2 mg/dL) (95% CI, 0.08-0.45 mmol/L [3.09-17.40 mg/dL]) after 4 to 6 weeks (n=8) and 0.50 mmol/L (19.2 mg/dL) (95% CI, 0.34-0.66 mmol/L [13.15-25.52 mg/dL]) after 8 to 12 weeks (n=12). Average reductions after 20 to 24 weeks of treatment were not statistically significant (all garlic preparations [n=6]: 0.03 mmol/L (1.2 mg/dL) 95% CI, −0.21 to 0.28 mmol/L (−8.12 to 10.83 mg/dL); standardized dehydrated garlic preparations only [n=3]: 0.07 mmol/L (2.8 mg/dL) (95% CI, −0.22 to 0.37 mmol/L (−8.51 to 14.31 mg/dL).

At 8 to 12 weeks, average triglyceride level reductions from placebo-controlled trials, regardless of garlic preparation type (n=17), were 0.21 mmol/L (19.1 mg/dL) (95% CI, 0.09-0.34 mmol/L [3.48-13.15 mg/dL]); average reductions among trials evaluating standardized dehydrated garlic tablets (n=13) were 0.24 mmol/L (21.1 mg/dL) (95% CI, 0.09-0.38 mmol/L [3.48-14.69 mg/dL]). At 8 to 12 weeks, average LDL-C level reductions across all garlic preparation types (n=13) were 0.16 mmol/L (6.2 mg/dL) (95% CI, 0.02-0.30 mmol/L [0.77-11.6 mg/dL]), and standardized dehydrated garlic tablets alone (n=10) were 0.17 mmol/L (6.7 mg/dL) (95% CI, 0-0.34 mmol/L [0-13.15 mg/dL]). At 8 to 12 weeks the average HDL-C level *reduction* from all garlic preparations combined (n=14) was 0.02 mmol/L (0.9 mg/dL) (95% CI, −0.03 to 0.07 mmol/L [−1.2 to 2.70 mg/dL]), whereas reduction from standardized dehydrated garlic preparations (n=10) was 0.01 mmol/L (0.2 mg/dL) (95% CI, −0.05 to 0.06 mmol/L [−1.93 to 2.32 mg/dL]). Analyses limited to trials with only subjects with hyperlipidemia or that used double-blind methods did not vary significantly from those presented earlier.

The only head-to-head trial compared a standardized dehydrated preparation (Kwai) to garlic oil (Hoefels Original Garlic Oil with Rutin; Seven Seas Limited, Marfleet Hull, England). This unblinded trial found a statistically significant reduction in LDL-C level, but not total cholesterol or HDL-C level, favoring the dehydrated preparation after 4 months of therapy.[57] The one trial that compared a commercial antilipidemic agent (bezafibrate) with a garlic preparation (Kwai) found no differences in lipid level outcomes after 3 months of therapy.[34]

Antihypertensive Effects

Of 30 trials measuring blood pressure outcomes, 23 reported results from placebo comparisons (3 did not report results[29,39,43]; 4 used nonplacebo controls[34,57,59,60]). Three trials focused on subjects with hypertension and studied blood pressure as the primary outcome.[55,59,60] Seven clearly excluded use of additional antihypertensive agents.[32,33,47,55-57,67] Although several trials reported significant reductions in blood pressure among subjects given garlic (within group comparisons), only 3 demonstrated statistically significant reductions in diastolic blood pressure (range, 2%-7%),[33,54,55] and 1 in systolic blood pressure (approximately 3%)[33] between persons given garlic and those given placebo. These data were not pooled because about

Table 1. All Randomized Trials With Serum Lipid Endpoints of 4 Weeks or Longer Comparing Garlic to Placebo or Other Therapy

Source, y	Sample Size (N)	% of Male Subjects	Mean Age (Range), y	Recruitment Setting	Characteristics of Subjects*	Randomization Process†
Adler and Holub,[33] 1997	25	100	46	Unclear	Hyperlipidemia	Unclear
Auer et al,[55] 1990	47	45	58	11 General practices	Hypertension; 45% of the subjects had a total cholesterol level >6.46 mmol/L	Unclear
Barrie et al,[48] 1987	20	Unclear	26	Student volunteers	All previously healthy; total cholesterol levels ranged from 3.36-6.98 mmol/L	Unclear
Berthold et al,[49] 1998	26	54	58	Community volunteers	Hyperlipidemia	Probably adequate
Bordia et al,[64] 1981	25	100	55	Unclear	Known coronary artery disease; hyperlipidemia	Unclear
Bordia,[29] 1989	432	Unclear	Not given	Unclear	History of myocardial infarction	Unclear (potentially inadequate)
Bordia et al,[28] 1998	60	Unclear	Not given	Unclear	History of myocardial infarction	Unclear (potentially inadequate)
Buhshan et al,[65] 1979	25	100	(18-35)	Unclear	Hyperlipidemia	Unclear
Chutani and Bordia,[66] 1981	30	Unclear	50	Unclear	Ischemic heart disease	Unclear
Czerny and Samochowiec,[67] 1996	100	65	55	Unclear	Hyperlipidemia; atherosclerotic disease; and hypertensive	Unclear
Gardner et al,[30] 1999	53	51	52	Unclear	Hyperlipidemia	Unclear
Holzgartner et al,[34] 1992	98	39	57	5 General practices	Hyperlipoproteinemia types Ia, IIb, or IV; 35% of the subjects had hypertension	Probably adequate
Isaacsohn et al,[58] 1998	50	54	58	Specialty clinic	Hyperlipidemia	Probably adequate
Jain et al,[9] 1993	42	45	52	Community volunteers	Hyperlipidemia	Unclear
Kandziora,[60] 1988	40	Unclear	(43-65)	Unclear	Hypertension; hyperlipidemia	Unclear
Kandziora,[59] 1988	40	83	56	Unclear	Hypertension; hyperlipidemia	Unclear
Kannar,[45] 1998	46	54	(30-74)	Community volunteers	Hyperlipidemia; no diabetes mellitus	Adequate
Kenzelmann and Kade,[35] 1993	46	33	43	Volunteers and 4 general practices	Hyperlipidemia	Probably adequate
Kiesewetter et al,[32] 1991	60	30	24	Volunteers	Elevated spontaneous platelet aggregation	Unclear
Kiesewetter et al,[40] 1993	80	67	60	Unclear	Peripheral vascular disease; hyperlipidemia	Unclear
Koscielny et al,[43] 1999	280	71	60	Unclear	Asymptomatic advanced atherosclerosis; hyperlipidemia; and 38% of the subjects had hypertension	Unclear
Lash et al,[62] 1998	35	49	45	Unclear	Hyperlipidemia; all after renal transplantation	Unclear
Lau et al,[36] 1987‖						
1	32	56	52	Community or clinic volunteers	Hyperlipidemia; 44% of the subjects were vegetarians	Unclear
2	14	56	26	Community or clinic volunteers	Normolipidemia; 57% of the subjects were vegetarian	Unclear

Intervention (Daily Garlic Dosage)‡	Control Group	Double-blind Study	Endpoints§					Trial Length, wk	% of Dropouts per Group
			Clinical Symptoms	Lipid Levels	Blood Pressure	Glucose Level	Thrombotic State		
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X	X			12	Garlic treated, 8; placebo, 8
Dehydrated tablet: Kwai (600 mg)	Placebo	Yes		X	X	X		12	Unclear
Oil macerate (18 mg)	Placebo	Yes		X	X		X	4‖	Unclear
Garlic distillate: Tegra (5 mg)	Placebo	Yes		X				12‖	Pooled, 4
Garlic ether extract (0.25 mg/kg of body weight)	Placebo	Yes		X				43	Pooled, 9
Garlic ether extract (6-10 g)	Habitual coronary therapy	Unclear	X	X	X			156	Unclear
Garlic ether extract (1 g)	Placebo	Unclear		X		X	X	13	Unclear
Raw garlic (10 g)	No garlic treatment	No		X				8	Unclear
Raw or fried garlic	No garlic treatment	No					X	4	Unclear
A combination of oil macerate, soya lectin, hawthorn oil, and wheat germ (400 mg)	Placebo	Yes	X	X	X	X	X	16	Unclear
Dehydrated tablet: (500 mg and 1000 mg)	Placebo	Yes		X	X			12	Garlic treated, 4; placebo, 0
Dehydrated tablet: Kwai (900 mg)	Antilipidemic	Yes		X	X			12	0 (4% Excluded for protocol violations)
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X	X			12	Garlic treated, 14; Placebo, 18
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X	X	X		12	Unclear
Dehydrated tablet: Kwai (600 mg)	Placebo	Yes		X	X	X		12	Unclear
Dehydrated tablet: Kwai (600 mg)	Antihypertensive	Single		X	X	X		12	Unclear
Dehydrated tablet: Garlic 100 (880 mg)	Placebo	Yes		X	X			12	Garlic treated, 9; placebo, 4
Dehydrated tablet with ginkoba extract: Allium Plus (200 mg)	Placebo	Yes		X				8	Garlic treated, 4; placebo, 9
Dehydrated tablet: Kwai (800 mg)	Placebo	Yes		X	X	X	X	4	Unclear
Dehydrated tablet: Kwai (800 mg)	Placebo	Yes	X	X	X		X	12	Garlic treated, 20; placebo, 20
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X	X	X	X	208	Garlic treated, 40; placebo (at 6 mo), 21
Dehydrated tablet: Pure-Gar (1360 mg)	Placebo	Unclear		X				12	Unclear
Aged garlic extract: Kyolic (4 mL of extract = 1000 mg)	Placebo	Unclear		X				26	Garlic treated, 6; placebo, 25
Aged garlic extract: Kyolic (4 mL of extract = 1000 mg)	Placebo	Unclear		X				26	Unclear

(Continued)

Table 1. All Randomized Trials With Serum Lipid Endpoints of 4 Weeks or Longer Comparing Garlic to Placebo or Other Ther apy (cont)

Source, y	Sample Size (N)	% of Male Subjects	Mean Age (Range), y	Recruitment Setting	Characteristics of Subjects*	Randomization Process†
Luley et al,[53] 1986‖						
1	34	Unclear	Not given	Unclear	Hyperlipoproteinemia types IIa, IIb, or IV	Unclear
2	51	Unclear	Not given	Unclear	Hyperlipoproteinemia types IIa, IIb, or IV	Unclear
Lutomski,[41] 1984	102	49	52	Unclear	Nonspecific functional complaints; 44% of the subjects had hypertension and normolipidemia	Unclear
Mader,[39] 1990	261	44	59	Community clinic	Hyperlipidemia; 47% of the subjects had hypertension	Probably adequate
Mansell et al,[46] 1996	60	77	63	Unclear	All subjects had type 2 diabetes mellitus	Unclear
McCrindle et al,[52] 1998	31	52	14	Specialty clinic	Hyperlipidemia; family history of high lipid levels; and early coronary artery disease	Probably adequate
Melvin,[51] 1996	34	47	54	Volunteers	Hyperlipidemia	Unclear
Morcos,[68] 1997	40	58	53	Community clinic volunteers	Hyperlipidemia	Unclear
Neil et al,[21] 1996	115	61	53	Community clinic	Hyperlipidemia; obesity	Adequate
Plengvidhya et al,[63] 1988	30	47	49	Unclear	Hyperlipidemia	Unclear
Rotzsch et al,[61] 1992	24	42	37	Unclear	HDL-C2 level: <0.26 mmol/L, men; <0.39 mmol/L, women	Unclear
Santos and Grunwald,[56] 1993	60	39	52	Community clinic	Hyperlipidemia	Unclear
Santos and Jones,[57] 1995	80	35	57	Single specialist practice	Hyperlipidemia	Unclear
Saradeth et al,[38] 1994	72	31	39	Community volunteers	Hyperlipidemia	Unclear
Simons et al,[47] 1995	31	53	54	Community volunteers	Hyperlipidemia	Unclear
Sitprija et al,[31] 1987	40	33	50	Outpatient clinic	All subjects had diabetes mellitus without complications	Unclear
Steiner,[50,69] 1996	52	100	(32-68)	Unclear	Hyperlipidemia	Unclear
Superko and Krauss,[44] 2000	50	Unclear	53	Unclear	Hyperlipidemia	Unclear
Ventura et al,[37] 1990	40	38	59	Community volunteers	Hyperlipidemia; peripheral vascular disease	Unclear
Vorberg and Schneider,[54] 1990	40	43	50	Community clinic	Hyperlipidemia	Unclear
Yeh et al,[42] 1997	34	100	48	Collegiate community	Hyperlipidemia	Unclear

**To convert the total cholesterol high-density lipoprotein cholesterol-subfraction 2 (HDL-C2) levels to milligrams per deciliters, multiply by 0.02586.*

†The randomization process was classified as follows: unclear, probably adequate, and adequate. Unclear indicates that the process was not described in significant enough detail to ensure adequacy. Probably adequate indicates the use of sealed envelopes but not sequentially numbered or opaque; list of random numbers read by someone enrolling the subject into the trial (open list); description suggests adequate concealment but other features such as markedly different characteristics among intervention and control groups are suspicious. Adequate indicates centralized randomization by telephone; randomization scheme controlled by pharmacy; numbered or coded identical containers administered sequentially; on-site computer system that can only be accessed after entering the characteristics of an enrollee; and sequentially numbered, sealed, and opaque envelopes.

‡The manufacturers of the garlic products mentioned in this column are as follows: Kwai, Lichtwer Pharmaceuticals, Berlin, Germany; Tegra, Hermes Pharmaceuticals, Munich, Germany; Garlic 100, Cotter Foods, Melbourne, Australia; Allium-Plus, Zeller AG, Romanshorn, Switzerland; Pure-Gar Deodorized Garlic, Essentially Pure Ingredients, Chatsworth, Clif; Kyolic, Wakunaga of America, Mission Viejo, Calif; Ilja Rogoff Garlic Tablets with Rutin, Woelm Pharmaceuticals GmbH & Company, Eschwege, Germany; LipoGuard, Viva America Incorporated, Costa Mesa, Calif; and Fitoaglio, Farmaceutici Procemsa, Torino, Italy.

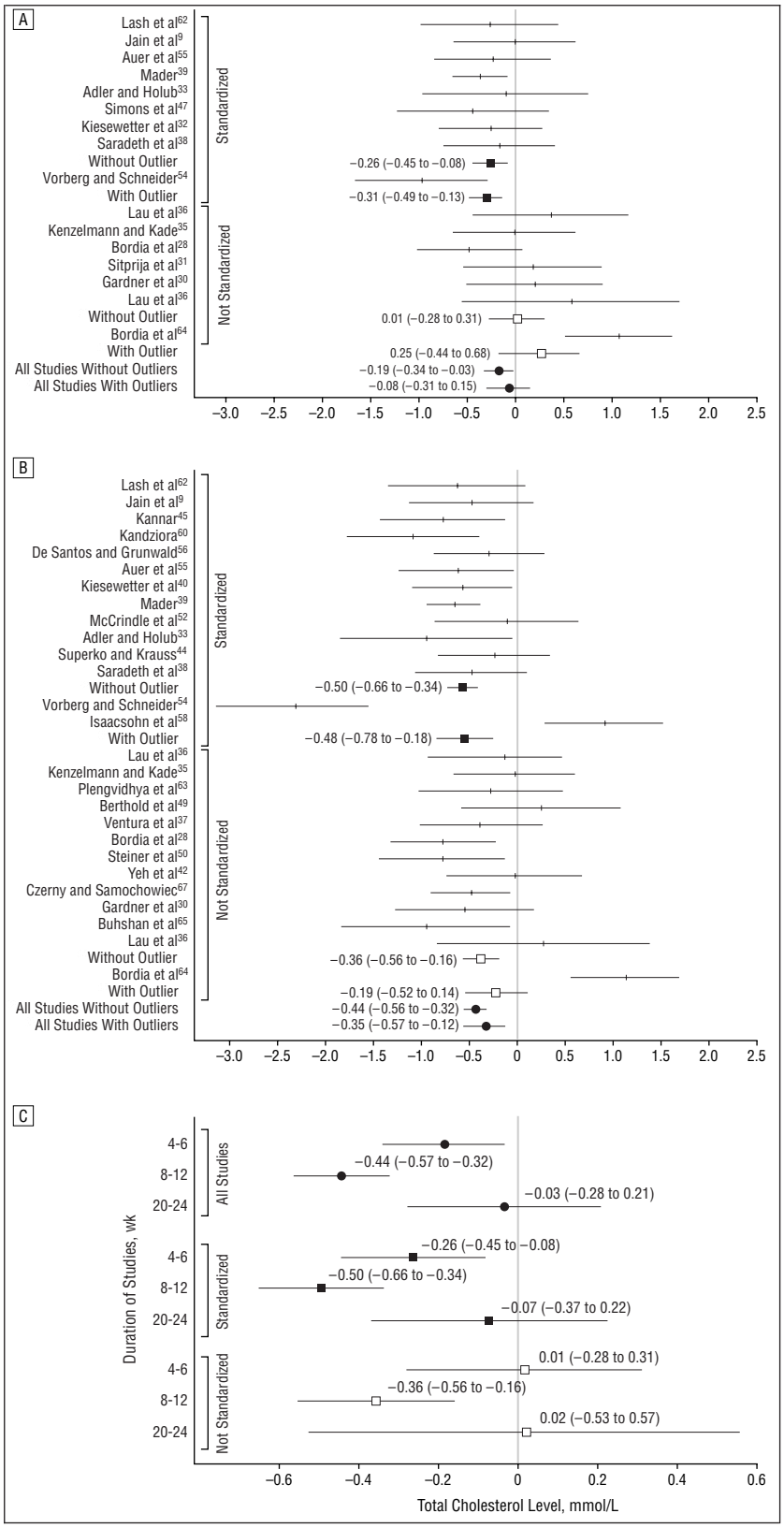
§*An* X *indicates that that particular outcome was reported by the original authors.*

‖*Publication contained 2 distinctly different studies presented in a single publication; therefore, the same reference has been assigned.*

¶*This was a crossover study.*

#These were clearly stated to not be commercial tablets.

Intervention (Daily Garlic Dosage)‡	Control Group	Double-Blind Study	Endpoints§					Trial Length, wk	% of Dropouts per Group
			Clinical Symptoms	Lipid Levels	Blood Pressure	Glucose Level	Thrombotic State		
Dehydrated tablet (594 mg)	Placebo	Yes		X	X	X		6‖	0
Dehydrated tablet (1350 mg)	Placebo	Yes		X	X	X	X	6‖	0
Dehydrated tablet/other: Ilja Rogoff Garlic Tablets with Rutin (300 mg)	Placebo	Yes		X	X			12	Pooled, 5 (15% excluded for protocol violations)
Dehydrated tablet: Kwai (800 mg)	Placebo	Yes		X	X			16	Garlic treated, 4; placebo, 7 (10% excluded for protocol violations)
Dehydrated tablet: Kwai (900 mg)	Placebo	Unclear		X	X	X		12	Unclear
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X	X		X	8	Pooled, 3
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X				4¶	Pooled, 44 (excluded for protocol violations)
Dehydrated tablet with fish oil: LipoGuard (1200 mg)	Placebo	Single		X				4¶	Unclear
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X				24	Pooled, 8
Dehydrated tablet (700 mg)#	Placebo	Yes		X				6¶	Unclear
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X				6	Unclear
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X	X			24	Garlic treated, 17; placebo, 10
Dehydrated tablet: Kwai (600 mg)	Garlic oil: Hoefels Original Garlic Oil (1.98 mg/d)	No		X	X			16	Tablet treated, 10; oil treated, 15
Dehydrated tablet: Kwai (600 mg)	Placebo	Yes		X	X			15	Garlic treated, 1; placebo, 4 (22% excluded for incomplete data)
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X	X			12¶	Pooled, 6
Dehydrated tablet (700 mg)#	Placebo	Yes		X		X		4	Garlic treated, 15; placebo, 20
Aged garlic extract: Kyolic (7200 mg)	Placebo	Yes		X	X			26¶	21 (cumulative)
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X	X			12	Unclear
Dehydrated tablet, hawthorn, and other: Fitoaglio (450 mg)	Placebo	Yes		X	X			8	0
Dehydrated tablet: Kwai (900 mg)	Placebo	Yes		X	X			16	0
Aged garlic extract: Kyolic (7200 mg)	Placebo	Yes		X	X			22	Pooled, 6



Forest plot of studies with total cholesterol level results at 4 to 6 weeks (A) and at 8 to 12 weeks (B). C, Forest plot of pooled results of total cholesterol level findings at different periods. All Forest plot levels are measured in millimoles per liter. To calculate the conventional units of milligram per deciliter for the total cholesterol levels multiply by the conversion factor of 38.67. The numbers in parentheses indicate 95% confidence intervals for the pooled standarzied mean differences (in millimoles per liter). The minus signs indicate that these levels were reduced relative to pacebo changes over the intervention period. Solid squares indicate those studies using standardized preparations; open squares, those studies using nonstandardized preparations; and solid circles, all preparations together.

half of the studies did not present numerical data that could be used in a quantitative analysis, multiple different methods of blood pressure measurement were used, and few studies had a priori hypotheses related to blood pressure.

Antiglycemic Effects

Twelve trials assessed the effect of garlic on the serum glucose level.* Two studied adults with diabetes mellitus and considered serum glucose level as a primary outcome.[31,46] Only one 4-week trial, conducted in nondiabetic persons, reported a statistically significantly greater reduction in the serum glucose level with standardized dehydrated garlic tablets (Kwai) compared with placebo.[32] No statistically significant effects were reported for glycosylated hemoglobin,[46] serum insulin and C-peptide levels,[46] and responsiveness of serum insulin levels to an oral glucose challenge.[31]

Antithrombotic Effects

Ten trials assessed the effectiveness of garlic on potential prothrombotic risk factors.† Of 6 of these 10 trials measuring effects on spontaneous platelet aggregation, 5 provided results[32,40,48,67,69]; 4 of these 10 trials, all prohibiting intake of additional antiplatelet medications, reported modest but significant decreases in platelet aggregation with garlic treatment compared with placebo,[32,40,48,67] and the other reported significant decreases in epinephrine-induced, but not adenosine diphosphate–induced, platelet aggregation.[69] Mixed effects on fibrinolytic activity[28,53,66] and plasma viscosity were reported, while no trials assessing serum fibrinogen levels[28,32,52,53] or serum homocysteine levels[52] reported significant results.

Effects on Cardiovascular Morbidity and Mortality

Clinical trial data for cardiovascular morbidity outcomes are limited. Two trials assessed improve-

**References 9, 28, 31, 32, 43, 46, 53, 55, 59, 60, 67.*

†References 28, 32, 40, 43, 48, 52, 53, 66, 67, 69.

Table 2. Summary of Adverse Effects

Adverse Effect	Type of Garlic Exposure	Level of Evidence
Breath or body odor	Oral use of standardized dehydrated tablet	Randomized controlled trials
Skin manifestations: contact dermatitis, ulcerus necrotic lesions; and blisters, bullae, and vesicles	Oral use for 1 case of contact dermatitis; topical use for the remaining lesions	Case series and multiple case reports with resolution of lesions after discontinuation of garlic treatment; no rechallenge tests
Allergic manifestations: asthma, rhinitis, conjunctivitis, urticaria, and anaphylaxis; angioedema	Oral use for 1 case of asthma and rhinitis; garlic dust inhalation for the remaining cases	Case series and multiple case reports with resolution of symptoms after discontinuation of garlic treatment; positive rechallenge test results for asthma
Cardiovascular dysfunction: myocardial infarction	Oral use	1 Case report
Coagulation dysfunction: postoperative bleeding, spontaneous spinal epidural hematoma, increased International Normalized Ratio, clotting time prolongation, and failure of platelet aggregation test	Oral use	Case reports
Gastrointestinal tract dysfunction: small-intestine obstruction, epigastric and esophageal pain, and flatulence; hematemesis and hematochezia	Oral use	Case reports and case series
Other: Meniere disease	Oral use	Case report

ment in pain-free walking distance in subjects with lower extremity peripheral vascular disease treated with garlic vs placebo.[40,67] Although the authors of one trial reported significant increases in the walking distance with standardized dehydrated tablets (Kwai), there was a 20% dropout rate with no intention-to-treat analysis, significant disparities in the reporting of a garlic taste between garlic-treated and placebo groups that suggested possible inadequate blinding, and a reanalysis using baseline walking distances from the time of randomization rather than during a run-in phase no longer yielded significant results.[40] The second trial reported statistically significant increases in pain-free walking but used a garlic oil macerate–soya lecithin–hawthorn oil–wheat germ oil combination, making it difficult to assess the independent effect of garlic on this end point.[67]

One 3-year trial assessing reinfarction rates in 432 patients with evidence of a prior myocardial infarction reported 11 deaths and 15 reinfarctions in 222 subjects randomized to a garlic extract (0.1 g/kg per day for body mass) and 20 deaths and 22 reinfarctions in the 210 placebo recipients.[29] Although the author reported significant differences, reanalysis of between-group comparisons using a χ^2 test revealed no statistically significant differences in total mortality ($P=.07$) or myocardial infarction ($P=.13$). The trial was not published in peer-reviewed literature, and details of randomization processes, blinding, and handling of dropouts could not be obtained despite attempts to contact the original author.

Original authors of a placebo-controlled trial with standardized dehydrated tablets (Kwai) involving 280 subjects have reported statistically significant ($P<.001$) regression in atherosclerotic plaque volume over 48 months.[43] As of February 2000, the authenticity of this trial was under investigation owing to concerns regarding the validity of the ultrasound images accompanying the published text, unsuccessful randomization procedures, an unusually high (46%) unequal dropout rate, and inappropriate analyses.[70]

Adverse Effects

Approximately half of the trials reported adverse effects. Of those reporting adverse effects, 8 reported significantly greater numbers of subjects assigned garlic treatment had malodorous breath or body odor (as perceived by themselves or others) compared with subjects assigned placebo.[21,33,39,40,43,45-47] The other trials that reported adverse effects stated that persons assigned to dehydrated garlic tablets self-reported malodorous breath or body odor, abdominal pain, fullness, anorexia, or flatulence, but had too few numbers to statistically compare differences between groups. In addition to the trials, 73 further studies were found that addressed adverse effects (**Table 2**). Most (97%) were case reports or small case series. Reported adverse effects of garlic ingestion (dietary and supplements) were dermatitis, rhinitis, Meniere disease, asthma, myocardial infarction, bleeding, epidural hematoma, increased International Normalized Ratio in persons taking warfarin sodium, small-intestine obstruction, esophageal and abdominal pain, and flatulence. The frequency of adverse effects and whether they varied by particular preparations were not studied.

COMMENT

Although inconclusive, randomized controlled trial data are compatible with the hypothesis that garlic supplementation may produce mild short-term benefits on the levels of total cholesterol, triglycerides, and LDL-C, and on platelet aggregation. Several small short-term trials show mixed, but never large, effects of garlic on blood pressure outcomes, and no effects on glycemic-related outcomes. Given the overall marginal quality of many trials with respect to adequacy of randomization and blinding, as well as an inadequate definition of the specific biologically active garlic constituents in tested preparations, these results have limited clinical applicability. Although multiple adverse effects of garlic ingestion have been

reported, causality is established only for malodorous breath and body odor. The most serious potential adverse effect that has been cited is spontaneous epidural bleeding. The expected frequency of adverse effects, whether they are "dose-related," and whether they are specific to or occur more commonly with particular garlic preparations than others are unclear.

Few trials clearly reported error-free randomization procedures. Blinding of subjects was impossible in many trials that evaluated odor-producing preparations, and several double-blind trials that used odor-free coated preparations still reported adverse effects discernable to subjects that were clearly attributable to garlic. The inability to adequately blind subjects may have led to systematic overestimation or underestimation of garlic's effects. For example, it is possible that true putative health benefits of ingesting garlic are attributable to the presence, concentration, and form of its many sulfur-containing compounds. These sulfur-containing compounds generate the unique taste and odor of garlic. Studies of garlic treatment that successfully blind subjects to group assignments may be using garlic products that not only have undetectable taste and odor but that also have low levels of active sulfur-containing compounds. If benefits are tied to sulfur-containing compounds, such studies might underestimate them.

Concealment of random allocation from investigators, blinding of subjects, and proper handling of missing data are the only quality variables that have been empirically shown to affect trial outcomes.[71] Because of unclear adequacy of double-blinding techniques and because very few trials performed intention-to-treat analyses or reported no dropouts, distinguishing higher-quality trials was infeasible for performing sensitivity analyses. These methodological limitations affect the clinical relevance of even statistically significant results and further limit the use of attempting to rationalize the significance of trends in the pooled data analyses.

Several issues related to the intrinsic qualities of garlic further complicate interpretation of current human studies. First, there is no universal consensus regarding exactly which constituents of garlic have major effects on particular cardiovascular risk factors in vivo and by what mechanism these effects are achieved. Second, the relative ingredient content of whole garlic is affected by growth conditions such as soil composition. Finally, variation in the methods of preparing particular garlic preparations results in significant differences in final composition. For instance, crushing or cutting whole garlic commingles the ingredient alliin with an enzyme, alliinase, resulting in liberation of allicin, which is believed by most garlic researchers to be the major ingredient responsible for potential antilipidemic effects. The herbal industry is unable to guarantee allicin content within tablets because of limitations in the stability of this compound. Most allicin-based preparations are, therefore, designed to generate allicin enzymatically from alliin after ingestion. Although commercial tablets are standardized to fixed amounts of alliin and allinase with the intention of maximizing allicin production after consumption, allinase quickly denatures at low gastric pHs. Maximal allicin release, therefore, depends not only on high alliin concentration and alliinase activity in the tablet, but also protection of allinase from gastric acid pH followed by rapid tablet dissolution in enteric pH. Despite the addition of tablet coatings to prevent premature dissolution, most preparations have not been systematically tested against *US Pharmacopeia* methods for compliance with enteric-coating standards. Notably, differential liberation of allicin from otherwise identical standardized dehydrated garlic tablets, produced by the same manufacturer but in differen batches, has been demonstrated.[72] This variability in allicin liberation, despite standardization, has recently been suggested to correlate with variability in antilipidemic effects among many recent trials using particular standardized dehydrated garlic tablet preparations.[73]

Additionally, although several trials reported equivalent baseline body mass, diet, or activity level between groups, few assessed whether these factors remained matched throughout the trial intervention. The presence of confounding effects is supported by several trials that reported significant,[39,40] or a trend toward significant,* benefit from placebo administration alone. Even accounting for regression to the mean, some investigators argue such effects are more likely attributable to unanticipated cointerventions or poor control for bias than true placebo effects.[74-76] Several trials used volunteer subjects who may potentially be seeking lifestyle modifications for poor baseline dietary and activity habits. Studying such populations could increase the perception of beneficial short-term effects simply as a result of drift toward a more average lifestyle during the intervention period—an effect that may be greater in a motivated group that is aware of receiving a presumably beneficial study medication.[74,75]

Pooled analyses of trials do show reductions in the total cholesterol level at 4 to 6 weeks with trends toward further reductions at 8 to 12 weeks, although this trend did not persist at 20 to 24 weeks. Despite several possible explanations for these trends, the marginal statistical significance of observed short-term benefits and the generalized methodological shortcomings of trials make further conjecture unwarranted. Pooled analyses also suggest that standardized dehydrated preparations may result in greater mean short-term (4-12 weeks) cholesterol level reductions than other preparations, but this difference is neither clinically (approximately 0.12-0.26 mmol/L [5-10 mg/dL]) nor statistically ($P>.10$) significant. Absence of a significant disparity between preparations believed to contain distinctly different ingredients might generally suggest that there is a common active constituent among all preparations or that reported results are actually due to something other than garlic itself, such as an unmeasured lifestyle modification. Alternatively, it is also possible that the expected differences in ingredient availability after ingestion were minimized by in-

**References 9, 28, 36, 37, 48, 51, 54-56, 58, 59, 63, 68.*

advertent selection of particular preparations that have been shown to have substantially limited capabilities of liberating allicin under gastrointestinal conditions.

Studies with significant results, written in English, or funded by pharmaceutical companies historically have been more likely to be published.[77] Of 45 randomized trials in our analysis, 36 (80%) were published in peer-reviewed journals, 38 (84%) were published in the English language only, and 35 (78%) were sponsored, to some degree, by herbal manufacturers. Although we believe our search was comprehensive, and significant efforts were made to retrieve unreported data from investigators, the potential for missing data and publication bias in our review is still real.

CONCLUSIONS

One of the most readily apparent problems with human research about the effects of garlic treatment is inadequate definition of biologically active constituents and predictable availability of these constituents after ingestion. Delineating major active ingredients and their mechanisms of action are essential before conducting more trials. Although studies in humans report promising potential lipid-lowering and antithrombotic benefits, they are limited by unclear randomization procedures, short durations, and unclear adequacy of blinding to treatment administration and outcome assessments. Further studies with similar design features are useless. Rather, a few well-designed trials of longer duration are warranted. Such trials should detail a clear and unbiased recruitment and selection process, a clearly adequate randomization procedure, and assessment of the successfulness of blinding techniques. Additional emphasis on controlling cointerventions that can affect outcomes, clearly defining the constituents and dissolution properties of garlic preparations being studied, and using intention-to-treat analyses are also necessary.

Accepted for publication November 1, 2000.

This study was prepared by the San Antonio Evidence-based Practice Center under contract 290-97-0012, task order 3, to the Agency for Healthcare Research and Quality (formerly the Agency for Health Care Policy and Research), Rockville, Md.

Presented as an abstract at the Complementary and Alternative Medicine in Cardiovascular, Lung, and Blood Research, National Heart, Lung, and Blood Institute Campus, Bethesda, Md, June 12-13, 2000, and the Evidence-based Complementary Medicine Congress, Munich, Germany, April 8, 2000.

We are indebted to the following persons for their contributions to this project: Eric Block, PhD, for input regarding the chemistry of garlic; Paul Heidenreich, MD, MS, for expert cardiological advice; Christine Aguilar, MD, MPH, Mark Loveland, and David Mullins for help in abstracting data; Andrew Vickers, MD, and Molly Harris, MLS, MA, for conducting the literature searches; and Jennifer Arterburn, MTSC, for assisting with technical writing.

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