

Garlic Lowers Blood Pressure in Hypertensive Individuals, Regulates Serum Cholesterol, and Stimulates Immunity: An Updated Meta-analysis and Review^{1,2}

Karin Ried*

National Institute of Integrative Medicine, Melbourne, Australia

Abstract

Background: Garlic has been shown to have cardiovascular protective and immunomodulatory properties.

Objectives: We updated a previous meta-analysis on the effect of garlic on blood pressure and reviewed the effect of garlic on cholesterol and immunity.

Methods: We searched the Medline database for randomized controlled trials (RCTs) published between 1955 and December 2013 on the effect of garlic preparations on blood pressure. In addition, we reviewed the effect of garlic on cholesterol and immunity.

Results: Our updated meta-analysis on the effect of garlic on blood pressure, which included 20 trials with 970 participants, showed a mean \pm SE decrease in systolic blood pressure (SBP) of 5.1 ± 2.2 mm Hg ($P < 0.001$) and a mean \pm SE decrease in diastolic blood pressure (DBP) of 2.5 ± 1.6 mm Hg ($P < 0.002$) compared with placebo. Subgroup analysis of trials in hypertensive subjects (SBP/DBP $\geq 140/90$ mm Hg) at baseline revealed a larger significant reduction in SBP of 8.7 ± 2.2 mm Hg ($P < 0.001$; $n = 10$) and in DBP of 6.1 ± 1.3 mm Hg ($P < 0.001$; $n = 6$). A previously published meta-analysis on the effect of garlic on blood lipids, which included 39 primary RCTs and 2300 adults treated for a minimum of 2 wk, suggested garlic to be effective in reducing total and LDL cholesterol by 10% if taken for >2 mo by individuals with slightly elevated concentrations [e.g., total cholesterol >200 mg/dL (>5.5 mmol/L)]. Garlic has immunomodulating effects by increasing macrophage activity, natural killer cells, and the production of T and B cells. Clinical trials have shown garlic to significantly reduce the number, duration, and severity of upper respiratory infections.

Conclusions: Our review suggests that garlic supplements have the potential to lower blood pressure in hypertensive individuals, to regulate slightly elevated cholesterol concentrations, and to stimulate the immune system. Garlic supplements are highly tolerated and may be considered as a complementary treatment option for hypertension, slightly elevated cholesterol, and stimulation of immunity. Future long-term trials are needed to elucidate the effect of garlic on cardiovascular morbidity and mortality. *J Nutr* 2016;146(Suppl):389S–96S.

Keywords: garlic, hypertension, cholesterol, immunity, meta-analysis

Introduction

Traditionally, garlic has a long history as a remedy for improving strength, reducing fatigue, and increasing immunity both in prevention and treatment of infectious diseases and gastrointestinal function (1). In modern times, garlic has also been linked to improved cardiovascular health, including blood pressure, cholesterol, and other cardiovascular markers (2, 3). We updated our previously published meta-analysis on the effect of garlic on blood pressure (2) with the inclusion of several more recent trials, reviewed our meta-analysis on the effect of garlic on cholesterol, and summarized the effect of garlic on the immune system.

Effect of garlic on blood pressure. High blood pressure is an important risk factor for cardiovascular disease and is attributed to an estimated 70% of heart attacks, strokes, and chronic heart failure, leading to 37% of cardiovascular deaths in Western countries and 13.5% globally (4, 5).³ Epidemiologic studies describe a continuous association between blood pressure and cardiovascular disease risk, suggesting a reduction in high systolic blood pressure (SBP; >140 mm Hg) by 20 mm Hg and a reduction in high diastolic blood pressure (DBP; >90 mm Hg) by 10 mm Hg to be associated with a 50% risk reduction in developing cardiovascular disease (6). Hypertension affects $\sim 30\%$ of adults in Western countries, with 68 million adults

in the United States alone (7). Although management of blood pressure in family practice has increased in the past 20 y, a large proportion of adults (23%) have uncontrolled blood pressure (7, 8), 9% have untreated blood pressure, and half of those treated do not achieve optimal control (7, 9).

Current medical treatment of hypertension. Approximately 40% of hypertensive patients can achieve the target blood pressure of <140/90 mm Hg with monotherapy, independent of the type of antihypertensive medication used. Approximately 40% require combination therapy with 2 agents, and 20% need to take ≥ 3 antihypertensive medications to achieve blood pressure control (10). In Australia, for example, the most commonly prescribed class of antihypertensive medications (56%) are angiotensin-converting enzyme inhibitors, followed by angiotensin II receptor antagonists (27%), calcium channel blockers, diuretics, and β -blockers (11). Adverse reactions from antihypertensive medications may occur in a significant number of patients and are more likely when multiple drugs are prescribed (12). Adverse reactions include fatigue, dizziness, cough, headache, myalgia, angioedema, renal impairment, gastrointestinal upset, and hyperglycemia (12).

Garlic supplements have shown promise in lowering blood pressure in several meta-analyses (2, 13, 14), and the blood pressure-lowering action of garlic is biologically plausible. Garlic contains a number of active sulfur compounds (15) that have been reported to modulate endothelium-relaxing and -constricting factors, leading to blood pressure reduction. Specifically, garlic has been shown to stimulate the production of NO and hydrogen sulphide (H_2S), both gasotransmitters leading to vasorelaxation (16–18). In addition, others reported that garlic

reduced the production of the vasoconstricting factors endothelin 1 and angiotensin II (19, 20). This meta-analysis and review updates our previously published meta-analyses on the effect of garlic on blood pressure with the inclusion of recent trials.

Methods

We included trials selected in previous meta-analyses by Silagy and Neil (13), Reinhart et al. (14), and Ried et al. (2) and extended the search by using the search terms “garlic” and “hypertension” or “blood pressure” in Medline for published trials between 2008 and 2013. We included studies with placebo control groups, that used garlic-only supplements, and that reported mean SBP and/or DBP and SDs (Table 1).

Changes in mean SBP or DBP in garlic and control groups before and after intervention were entered into the meta-analysis by using a random-effects model in Review Manager, version 5.2 (21). In addition, we performed a subgroup meta-analysis of trials in hypertensive subjects at the start of treatment (mean SBP ≥ 140 mm Hg or mean DBP ≥ 90 mm Hg) and a subgroup analysis of trials in normotensive subjects at the start of treatment (mean SBP <140 mm Hg or mean DBP <90 mm Hg).

Results

Meta-analysis

A total of 20 trials in >900 participants were identified as meeting the inclusion criteria (22–41), including 5 recent trials (37–41) that were not included in previous meta-analyses (2, 13, 14). Two trials (39, 41) included hypertensive and normotensive participants in the garlic and placebo groups. We undertook a meta-analysis that included all patients as well as a subgroup meta-analysis by baseline blood pressure (hypertensive or normotensive at baseline). Two trials (38, 40) featured 4-group, parallel, randomized controlled trials, with 3 active garlic groups of different dosages and a placebo group. In the main meta-analysis, we included only one active group compared with placebo from each of the 2 trials: the Allicor (INAT-Farma, Moscow, Russia) 400-mg group (38) and the garlic 2-capsule group (40). In addition, we tested the other active garlic groups of the 2 trials in sensitivity analysis.

Meta-analyses of all 20 trials (25 trial arms) suggested that garlic supplements significantly lower SBP by a mean (\pm SE) difference of 5.1 ± 2.2 mm Hg ($P < 0.001$; $n = 19$) and DBP by a mean difference of 2.6 ± 1.6 mm Hg ($P < 0.001$; $n = 20$) (Figures 1 and 2). Subgroup meta-analysis of trials and trial arms involving hypertensive participants revealed a larger significant reduction in SBP (mean difference for SBP_{hypertensive}: -8.6 ± 2.2 mm Hg; $P < 0.001$; $n = 10$) and DBP (mean difference for DBP_{hypertensive}: -6.1 ± 1.3 mm Hg; $P < 0.001$; $n = 6$) (Figures 3 and 4). In contrast, subgroup meta-analyses of trials involving participants with blood pressure in the prehypertensive and normal range at baseline (SBP/DBP <140/90 mm Hg) did not reveal a significant effect (mean difference for SBP_{normotensive}: -1.5 ± 1.9 mm Hg; $n = 11$; mean difference for DBP_{normotensive}: -0.4 ± 1.2 mm Hg; $n = 14$).

The majority of trials included in the meta-analysis used standard garlic powder (GP) supplements ($n = 13$), 5 trials used aged garlic extract (AGE), 1 trial used garlic oil (GO), and 1 trial used an egg yolk-enriched GP. Results of subgroup analysis by type of garlic were similar between GP ($n = 13$) and AGE ($n = 5$) (Table 2). In addition, we conducted sensitivity analyses excluding the trial by Nakasone et al. (41), because this trial used a modified GP, and the influence of the egg yolk on blood pressure cannot be ruled out. These and other sensitivity analyses that used alternate

¹ Published in a supplement to *The Journal of Nutrition*. Presented at the conference “2014 International Garlic Symposium: Role of Garlic in Cardiovascular Disease Prevention, Metabolic Syndrome, and Immunology,” held 4–6 March 2014 at St. Regis Monarch Beach Resort in Dana Point, CA. This supplement is dedicated to our colleague and friend John A. Milner. His dedication to good science and his voice for nutrition are remembered and sorely missed. The symposium was sponsored by the University of California, Los Angeles School of Medicine and the University of Florida and co-sponsored by the American Botanical Council; the American Herbal Products Association; the ASN; the Japanese Society for Food Factors; the Japan Society for Bioscience, Biotechnology, and Agrochemistry; the Japan Society of Nutrition and Food Science; and the Natural Products Association. The symposium was supported by Agencias Motta S.A.; Bionam; Eco-Nutraceuticals; Healthy U 2000 Ltd.; Magna; Mannavita Byba; MaxiPharma; Medica Nord A.S.; Nature’s Farm Pte. Ltd.; Nature Valley W.L.L.; Organic Health Ltd.; Oy Valoravinto Ab; Purity Life Health Products L.P.; PT Nutriprima Jayasakti; Vitaco Health Ltd.; Vitae Natural Nutrition; Sanofi Consumer Health Care; Wakunaga of America Co., Ltd.; and Wakunaga of America Co., Ltd. The Chair of the conference and Scientific Program Coordinator for the supplement publication was Matthew J. Budoff, Harbor-UCLA Medical Center, Torrance, CA. Scientific Program Coordinator disclosures: MJ Budoff has been awarded research grants from Wakunaga of America Co., Ltd., and received an honorarium for serving as Chair of the conference. Vice-Chair and Supplement Coordinator for the supplement publication was Susan S. Percival, University of Florida, Gainesville, FL. Supplement Coordinator disclosures: SS Percival has been awarded research grants from Wakunaga of America Co., Ltd., and received an honorarium for serving as Vice-Chair of the conference. Publication costs for this supplement were defrayed in part by the payment of page charges. This publication must therefore be hereby marked “advertisement” in accordance with 18 USC section 1734 solely to indicate this fact. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors or the publisher, Editor, or Editorial Board of *The Journal of Nutrition*.

² Author disclosures: K. Ried, no conflicts of interest. K. Ried received travel sponsorship from Wakunaga of America Co. Ltd. to attend the 2014 International Garlic Symposium.

³ To whom correspondence should be addressed. E-mail: karinried@niim.com.au.

⁴ Abbreviations used: AGE, aged garlic extract; ASA, allium sativum agglutinin; DBP, diastolic blood pressure; GO, garlic oil; GP, garlic powder; SBP, systolic blood pressure.

TABLE 1 Characteristics of trials included in the meta-analysis of the effect of garlic on blood pressure¹

Authors, year (reference)	Garlic/control <i>n</i>	Study design	Garlic type	Brand ²	Dosage, mg/d	Dosage of active ingredient, mg/d	Duration, wk	Baseline mean SBP/DBP, mm Hg	
								Garlic	Control
Kandziora, 1988 (22)	20/20	p	GP	Kwai	600	7.8, alliin	12	174/99	175/98
Auer et al., 1990 (23)	24/23	p	GP	Kwai	600	7.8, alliin	12	171/102	161/97
Vorberg and Schneider, 1990 (24)	20/20	p	GP	Kwai	900	11.7, alliin	16	144.5/91	144/88
Holzgartner et al., 1992 (25)	47/47	p	GP	Kwai	900	11.7, alliin	12	143/83	141/82
Jain et al., 1993 (26)	20/22	p	GP	Kwai	900	11.7, alliin	12	129/82	128/83
DeASantos and Gruenwald, 1993 (27)	25/27	p	GP	Kwai	900	11.7, alliin	24	143/89	144/89
Kiesewetter et al., 1993 (28)	32/32	p	GP	Kwai	800	10.4, alliin	12	NR/85	NR/83
Saradeth et al., 1994 (29)	31/37	p	GP	Kwai	600	7.8, alliin	15	125/81	125/82
Simons et al., 1995 (30)	28/28	c	GP	Kwai	900	11.7, alliin	12	127/80	127/80
Steiner et al., 1996 (31)	41/41	p	AGE	Kyolic	2400	NR	23	134/84	134/85
Adler and Holub, 1997 (32)	12/11	p	GP	Kwai	900	11.7, alliin	12	123/83	118/79
Isaacsohn et al., 1998 (33)	28/22	p	GP	Kwai	900	11.7, alliin	12	119/73	123/72
Zhang et al., 2000 (34)	14/13	p	GO	Cardiomax	12.3	NR	16	114/72	109/64
Williams et al., 2005 (35)	15/15	c	AGE	Kyolic	2400	2, SAC	2	132/82	132/82
Macan et al., 2006 (36)	22/26	p	AGE	Kyolic	3050	14.7, SAC	12	122/74	127/82
Sobenin et al., 2008 (37)	23/19	p	GP	Allicor	600	7.8, alliin pt	12	143/89	140/88
Sobenin et al., 2009 (38)	G1: 30/P: 20	p	GP	G1: Allicor	G1: 600	G1: 7.8, alliin	8	G1: 156/96	150/94
	G2: 18	p	GP	G2: Allicor	G2: 2400	G2: 31.2, alliin	8	G2: 153/95	150/94
	G3: 16	P	GP	G3: Kwai	G3: 900	G3: 11.7, alliin	8	G3: 152/96	150/94
Ried et al., 2010 (39)	25/25	p	AGE	Kyolic	960	2.4, SAC	12	135/74	141/76
Ried et al., 2013 (40)	G1:18/P: 17	p	AGE	Kyolic	G1: 240	G1: 0.6, SAC	12	G1: 151/77	149/76
	G2:20	p	AGE	Kyolic	G2: 480	G2: 1.2, SAC	12	G2: 149/76	149/76
	G3: 19	p	AGE	Kyolic	G3: 960	G3: 2.4, SAC	12	G3: 149 /76	149/76
Nakasono et al., 2013 (41)	HT: 23/24	p	GP _{jpn}	Dentou-ninniku-ranwo	188	NR	12	HT: 142/91	HT: 142/92
	NT: 16/18	p	GP _{jpn}	Dentou-ninniku-ranwo	188	NR	12	NT: 134/83	NT: 134/82

¹ AGE, aged garlic extract; c, crossover trial; G1–3, garlic groups 1–3; GO, garlic oil; GP, garlic powder; GP_{jpn}, Japanese garlic powder containing egg yolk; HT, hypertensive group; NR, not reported; NT, normotensive group; p, parallel trial; P, placebo group; pt, potential; SAC, S-allylcysteine; SBP/DBP, systolic blood pressure/diastolic blood pressure.

² Manufacturers' details of brands: Allicor: INAT-Farma, Moscow, Russia; Cardiomax: Seven Seas, Hull, United Kingdom; Dentou-ninniku-ranwo: Kenkoukazou Inc, Kagoshima, Japan; Kwai: Lichtwer Pharma GmbH, Berlin, Germany; Kyolic: Wakunaga of America Co Ltd, Mission Viejo, USA & Wakunaga Pharmaceuticals Co Ltd, Hiroshima, Japan.

trial arms with different dosages of garlic in Sobenin et al. (38) and Ried et al. (38) did not change the results appreciably (Table 2).

Table 3 summarizes the results of our updated meta-analysis and earlier meta-analyses on the effect of garlic on blood pressure, illustrating blood pressure status at baseline (hypertensive or normotensive) to be a strong predictor of the magnitude of blood pressure reduction. Side effects of garlic supplements, reported by approximately one-third of participants in the trials, were generally mild and included burping, flatulence, and reflux in the first few weeks of the trial (39, 40). A small percentage of the population (4–6%) may experience more severe gastrointestinal disturbances with therapeutic dosages of garlic supplements (39, 40, 42, 43). The lower tolerance of sulfur-containing foods such as garlic and onion has been linked to genetic variation in detoxification pathways of sulfur-transferase enzymes, as well as inflammatory status, and concentrations of molybdenum and vitamin B-12 (44, 45).

Despite the general medical advice, evidence is weak for garlic supplements, including GP, GO, and AGE, to cause harmful interactions if taken in addition to blood-thinning, blood sugar-regulating, or anti-inflammatory medications (36, 46, 47). Physicians and patients need to be mindful, however, of a potentially harmful interaction of garlic with protease inhibitors in antiretroviral therapy (46).

Other cardiovascular-protective effects of garlic

Effect of garlic on cholesterol. Several meta-analyses demonstrated a cholesterol-lowering effect of garlic supplements. A

recent and most comprehensive meta-analysis including 39 trials and almost 2300 subjects suggested that garlic moderately but significantly lowers total serum cholesterol (-17 ± 6 mg/dL) and LDL cholesterol (9 ± 6 mg/dL) if taken for >2 mo by patients with slightly elevated cholesterol (>200 mg/dL, >5.5 mmol/L) (3). The 8% reduction in serum cholesterol is of clinical relevance and has been associated with a 38% risk reduction in coronary events at age 50 y (48, 49). Trials in the meta-analysis used GP ($n = 31$), GO ($n = 6$), AGE ($n = 6$), and raw garlic ($n = 3$). Nine of the trials ran between 2 and 8 wk, and 30 trials lasted >8 wk.

Side effects with garlic supplements were minimal, with one-third of participants complaining about odor and 7% experiencing mild gastrointestinal discomfort (3). In comparison, mild gastrointestinal complaints were also described by 7% in the placebo group. In contrast, current standard pharmacologic treatment for cholesterol with statins may trigger adverse effects in a considerable number of patients, including myalgia (muscle pain), muscle weakness, neuropathy, cognitive impairment, mood disorders, anxiety, and an increased risk of diabetes (50–53).

Cholesterol is essential for normal body functions that include preserving the integrity of cell membranes, facilitating cell signaling, maintaining the myelin sheath, and synthesizing steroid hormones, vitamin D, and coenzyme Q10. The inhibition of cholesterol synthesis by statin drugs may interfere with these essential pathways, resulting in detrimental effects for some patients (50–53).

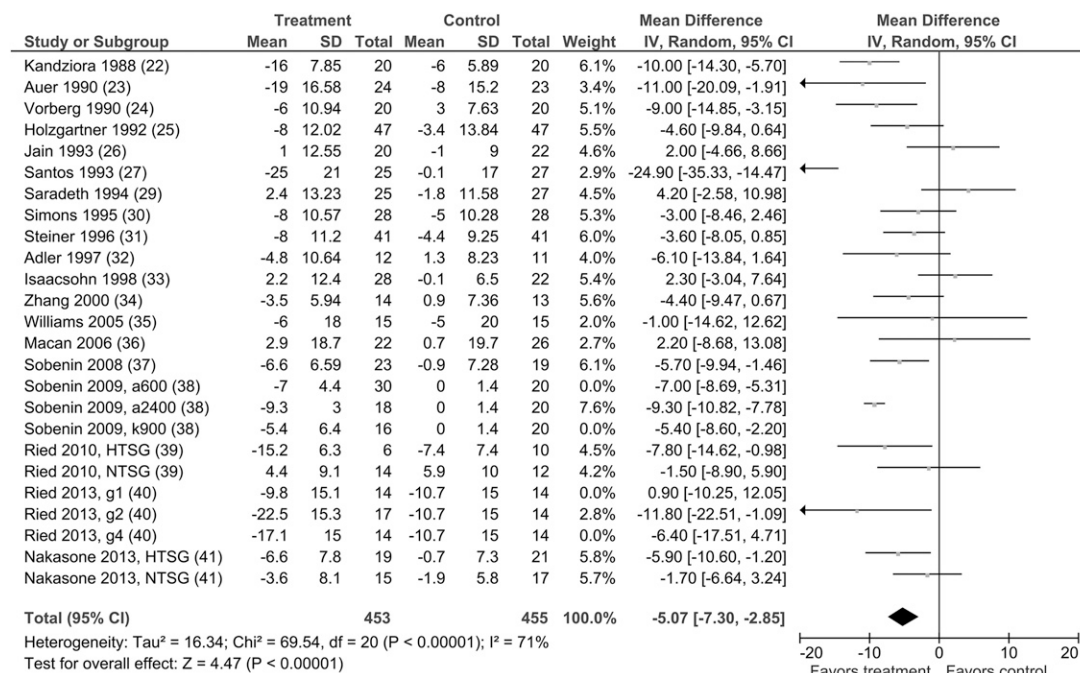


FIGURE 1 Forest plot showing the effect of garlic on systolic blood pressure; $n = 19$ trials (25 trial arms) including only 1 of 3 trial arms in 2 trials that tested different dosages of garlic compared with placebo [Sobenin 2009 (38): a2400 group; Ried 2013 (40): g2 group]. Other trial arms were tested in sensitivity analyses. Values are weighted mean differences (95% CIs) comparing changes in systolic blood pressure over time between treatment and control groups. a600, Allicor-600 mg; a2400, Allicor-2400 mg; g1, g2, g4, garlic 1-, 2-, 4-capsule group; HTSG, hypertensive subgroup; IV, inverse variance; k900, Kwai-900 mg; NTSG, normotensive subgroup.

In addition, there is cumulative evidence to suggest that lipoproteins also have a role in the immune response to infection as part of the innate immune system (54). Although HDL cholesterol plays a role in the immune response to viral and

parasitic infections, LDL cholesterol appears to be involved in the host defense to bacterial infections (54). Oxidized LDL cholesterol, on the other hand, has been associated with plaque formation and increased risk of heart attack and stroke when

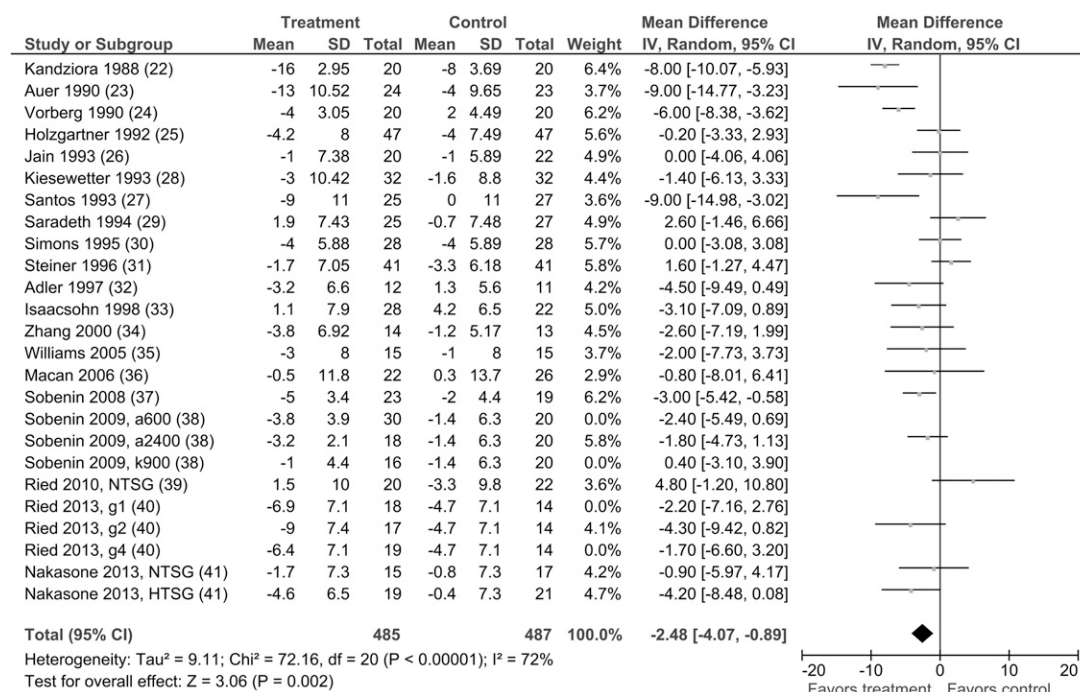


FIGURE 2 Forest plot showing the effect of garlic on diastolic blood pressure; $n = 20$ trials (25 trial arms). Values are weighted mean differences (95% CIs) comparing changes in diastolic blood pressure over time between treatment and control groups. a600, Allicor-600 mg; a2400, Allicor-2400 mg; g1, g2, g4, garlic 1-, 2-, 4-capsule group; HTSG, hypertensive subgroup; IV, inverse variance; k900, Kwai-900 mg; NTSG, normotensive subgroup.

SBP hypertensive subgroup

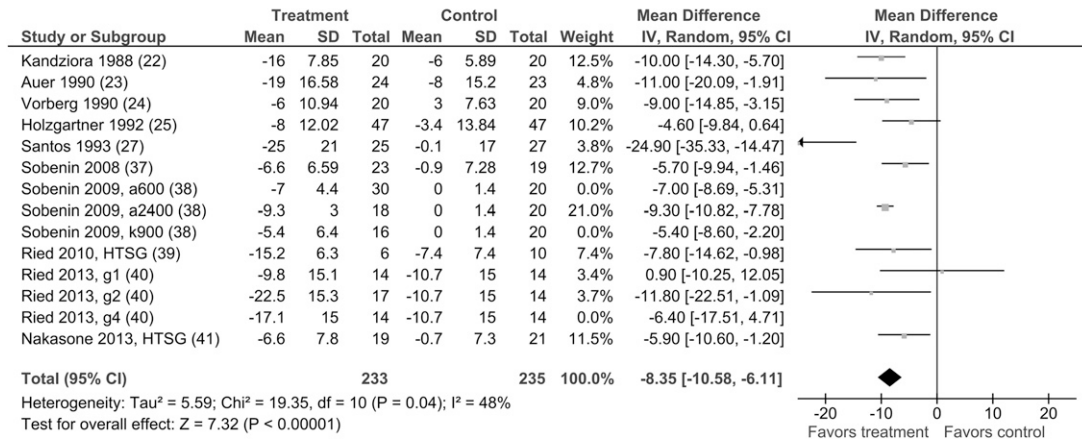


FIGURE 3 Forest plot showing the effect of garlic on systolic blood pressure in hypertensive subjects. Values are weighted mean differences (95% CIs) comparing changes in systolic blood pressure over time between treatment and control groups. a600, Allicor-600 mg; a2400, Allicor-2400 mg; g1, g2, g4, garlic 1-, 2-, 4-capsule group; HTSG, hypertensive subgroup; IV, inverse variance; k900, Kwai-900 mg; SBP, systolic blood pressure.

accumulated in the endothelium (55). The oxidation of LDL cholesterol may be generated by free radicals through dietary factors, such as consumption of *trans* fats, deep-fried foods, smoking, or the presence of high blood sugar (56). However, chemical analyses have found oxidized LDL cholesterol to consist of many heterogeneous components, suggesting multiple origins, possibly including interaction with pathogens and their toxins (57).

Because of the many purposes of cholesterol and serum lipoproteins in the human body, some of which are undoubtedly still incompletely understood, cholesterol concentrations need to be adjusted with care. Indeed, there is a growing list of clinical trials in which interference with serum cholesterol led to disappointing—and in some cases detrimental—results (58).

In contrast, garlic supplements have been linked to moderate reduction in cholesterol concentrations, therefore providing an alternative cholesterol-regulating agent with a higher safety profile than statins in patients with slightly elevated cholesterol.

Effect of garlic on immunity. Historically, garlic has been used for its anti-infective activities, immune-boosting properties, and general strengthening actions (1). In vitro and cell culture studies showed garlic to have antibacterial, antiviral, antifungal, and antiparasitic properties. Garlic was shown to stall growth of food pathogens such as *Salmonella*, *Listeria*, *Escherichia coli*, the stomach bacteria *Helicobacter pylori*, and the tuberculosis-causing pathogen *Mycobacterium tuberculosis* (59, 60). In addition, garlic inhibits biofilm formation by bacterial patho-

gens from burn wounds (61). Garlic's antiviral actions include the human rhinovirus, cytomegalovirus, herpes simplex, and influenza (62). Garlic is effective in the treatment of common yeast and fungal infections such as *Candida albicans* and *Aspergillus flavus* (63). Furthermore, garlic shows promise as an antiparasitic agent, helping in the treatment of *Cryptosporidium*, *Toxoplasma*, *Giardia*, and *Plasmodium* (64).

Garlic is a prebiotic, containing fructans and oligosaccharides, which stimulate the growth of “friendly” bacteria in the digestive tract (65, 66) that in turn make up the microbiome, which contributes to ~80% of the immune system (67). Garlic was shown to stimulate activation of the humoral and inert immune system, including the activation of macrophages by NO production and T and B cell production (68–70).

Clinical trials have shown garlic to have a beneficial effect in the prevention, duration, and severity of upper respiratory infections. A randomized, double-blind, placebo-controlled trial in 146 participants testing the effect of 180 mg GP/d over 3 mo found a 37% reduction in the number of colds (garlic compared with placebo: $n = 24$ compared with $n = 65$; $P < 0.001$) and a 30% reduction in the duration of illness (garlic compared with placebo: 1.5 compared with 5 d; $P < 0.001$) in the group taking garlic compared with the placebo group (71).

A recent trial in 120 participants that tested the effect of 2.56 g AGE/d over 3 mo found a 61% reduction in the number of days (garlic compared with placebo: 53 compared with 126 d; $P < 0.001$) and a 21% reduction in symptoms (garlic

DBP hypertensive subgroup

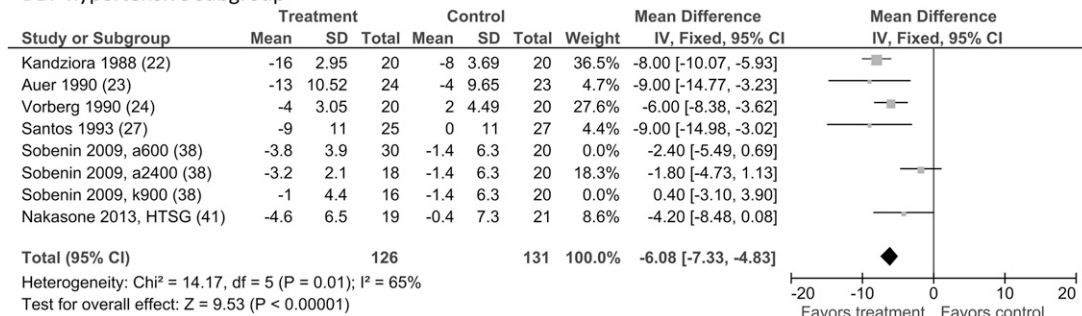


FIGURE 4 Forest plot showing the effect of garlic on diastolic blood pressure in hypertensive subjects. Values are weighted mean differences (95% CIs) comparing changes in diastolic blood pressure over time between treatment and control groups. a600, Allicor-600 mg; a2400, Allicor-2400 mg; DBP, diastolic blood pressure; HTSG, hypertensive subgroup; IV, inverse variance; k900, Kwai-900 mg.

TABLE 2 Subgroup and sensitivity analyses¹

Subgroup	Authors, year (reference)	Group	SBP/DBP		SBP	DBP
			Trials, <i>n</i>	Subjects, <i>n</i>		
By type of garlic	—	All ²	19/20	908/940	−5.1 ± 2.2	−2.6 ± 1.6
	—	GP	12/13	576/640	−5.8 ± 3.2	−3.2 ± 2.0
	—	AGE	5/5	233	−4.1 ± 3.1	0.02 ± 2.9
Sensitivity analysis						
With trial arm a600	Sobenin et al., 2009 (38)	All	19/20	920/952	−4.9 ± 2.0	−2.6 ± 1.7
With trial arm k900	Sobenin et al., 2009 (38)	All	19/20	906/938	−4.7 ± 2.0	−2.4 ± 1.7
With trial arm g1	Ried et al., 2013 (40)	All	19/20	905/941	−4.7 ± 2.2	−2.5 ± 1.7
With trial arm g4	Ried et al., 2013 (40)	All	19/20	905/942	−4.9 ± 2.2	−2.5 ± 1.8
Excluding trial	Nakasone et al., 2013 (41)	All	18/19	836/900	−5.2 ± 2.4	−2.5 ± 1.7

¹ Values are means ± SEs unless otherwise indicated. a600, Allcor-600 mg group; AGE, aged garlic extract; DBP, diastolic blood pressure; g1, garlic 1-capsule group; g4, garlic 4-capsule group; GP, garlic powder; k900, Kwai-900 mg group; SBP, systolic blood pressure.

² Includes the a2400 (Allcor-2400 mg) arm of trial in reference 38 and the g2 (garlic 2)-capsule group of trial in reference 40.

TABLE 3 Comparison of meta-analyses on the effect of garlic on blood pressure¹

Authors, year (reference)	Trials, <i>n</i>	Subjects, <i>n</i>	SBP difference (garlic vs. placebo), mm Hg			Trials, <i>n</i>	Subjects, <i>n</i>	DBP difference (garlic vs. placebo), mm Hg		
			All	Hypertensive subgroup	Normotensive subgroup			All	Hypertensive subgroup	Normotensive subgroup
Silagy and Neil, 1994 (13)	5	347	−7.7 ± 3.4	—	—	5	347	−5.0 ± 2.1	—	—
	2	87	—	−11.1 ± 6.1	—	2	87	—	−6.5 ± 3.1	—
Reinhart et al., 2008 (14)	10	444	−3.9 ± 4.4	—	—	10	444	−2.8 ± 2.4	—	—
	3	139	—	−16.3 ± 10.1	—	3	139	—	−9.3 ± 4.0	—
Ried et al., 2008 (2)	7	305	—	—	−0.5 ± 2.6	7	305	—	—	−0.9 ± 1.8
	10	503	−4.6 ± 2.8	—	—	11	567	−2.4 ± 2.5	—	—
Ried (this article)	4	221	—	−8.4 ± 2.8	—	3	127	—	−7.3 ± 1.5	—
	6	282	—	—	−2.3 ± 2.3	8	440	—	—	−0.1 ± 1.3
Ried (this article)	19	908	−5.1 ± 2.2	—	—	20	972	−2.6 ± 1.6	—	—
	10	440	—	−8.7 ± 2.2	—	8	257	—	−6.1 ± 1.3	—
	11	468	—	—	−1.5 ± 1.9	14	641	—	—	−0.4 ± 1.2

¹ Values are means ± SEs unless otherwise indicated. DBP, diastolic blood pressure; SBP, systolic blood pressure.

compared with placebo: 584 compared with 126; $P < 0.001$) (70). In this trial, a significant increase in $\gamma\delta$ -T cells ($P = 0.039$) and NK cells ($P = 0.043$) was shown in the garlic group after 45 d compared with placebo.

In addition, garlic contains the immunomodulatory proteins lectins or agglutinins [allium sativum agglutinin (ASA) I and ASA II] (66, 72). Furthermore, garlic was shown to reduce inflammatory markers, including C-reactive protein and TNF- α (73, 74). A high concentration of inflammatory C-reactive protein has been associated with greater odds of developing coronary artery disease (OR: 1.45; 95% CI: 1.25, 1.68) (75). Therefore, the beneficial effects of garlic on the immune system, including C-reactive protein and cytokines such as ILs and TNF- α , are also associated with improved cardiovascular health.

In conclusion, garlic has the potential to improve cardiovascular health on several levels. First, there is consistent evidence that garlic supplements lower blood pressure in hypertensive individuals. Second, there is strong evidence that garlic modulates cholesterol concentrations when slightly elevated. Third, garlic has several immune system-enhancing properties that directly and indirectly benefit cardiovascular health. Garlic supplements have a high safety profile and are generally well tolerated. Therefore, garlic supplements may be considered as an alternative or complementary treatment in addition to standard

medication for cardiovascular health. Further long-term trials are needed to elucidate the effect of garlic supplementation on cardiovascular morbidity and mortality.

Acknowledgments

The sole author read and approved the final version of the manuscript.

References

1. Rivlin RS. Historical perspective on the use of garlic. *J Nutr* 2001; 131(Suppl):951S–4S.
2. Ried K, Frank OR, Stocks NP, Fakler P, Sullivan T. Effect of garlic on blood pressure: a systematic review and meta-analysis. *BMC Cardio-vasc Disord* 2008;8:13.
3. Ried K, Toben C, Fakler P. Effect of garlic on serum lipids: an updated meta-analysis. *Nutr Rev* 2013;71:282–99.
4. Lawes CM, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. *Lancet* 2008;371:1513–8.
5. Martiniuk AL, Lee CM, Lawes CM, Ueshima H, Suh I, Lam TH, Gu D, Feigin V, Jamrozik K, Ohkubo T, et al. Hypertension: its prevalence and population-attributable fraction for mortality from cardiovascular disease in the Asia-Pacific region. *J Hypertens* 2007;25:73–9.
6. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–13.

7. Centers for Disease Control and Prevention. Vital signs: prevalence, treatment, and control of hypertension—United States, 1999–2002 and 2005–2008. *MMWR Morb Mortal Wkly Rep* 2011;60:103.
8. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr., Jones DW, Materson BJ, Oparil S, Wright JT Jr., et al. The 7th Report of the Joint National Committee on Prevention Detection Evaluation and Treatment of High Blood Pressure. *JAMA* 2003;289:2560–72.
9. Briganti EM, Shaw JE, Chadban SJ, Zimmet PZ, Welborn TA, McNeil JJ, Atkins RC. Untreated hypertension among Australian adults: the 1999–2000 Australian Diabetes, Obesity and Lifestyle Study. *Med J Aust* 2003;179:135–9.
10. Hobbs F, Irwin P, Rubner J. Evidence-based treatment of hypertension: what's the role of angiotensin II receptor blockers? *Br J Cardiol.* 2005;12:65–70.
11. Simons LA, Ortiz M, Calcino G. Persistence with antihypertensive medication: Australia-wide experience, 2004–2006. *Med J Aust* 2008;188:224–7.
12. Olsen H, Klemetsrud T, Stokke HP, Tretli S, Westheim A. Adverse drug reactions in current antihypertensive therapy: a general practice survey of 2586 patients in Norway. *Blood Press* 1999;8:94–101.
13. Silagy CA, Neil HA. A meta-analysis of the effect of garlic on blood pressure. *J Hypertens* 1994;12:463–8.
14. Reinhart KM, Coleman CI, Teevan C, Vachhani P, White CM. Effects of garlic on blood pressure in patients with and without systolic hypertension: a meta-analysis. *Ann Pharmacother* 2008;42:1766–71.
15. Amagase H. Clarifying the real bioactive constituents of garlic. *J Nutr* 2006;136(Suppl):716S–25S.
16. Al-Qattan KK, Thomson M, Al-Mutawa'a S, Al-Hajeri D, Drobia H, Ali M. Nitric oxide mediates the blood-pressure lowering effect of garlic in the rat two-kidney, one-clip model of hypertension. *J Nutr* 2006;136(Suppl):774S–6S.
17. Benavides GA, Squadrito GL, Mills RW, Patel HD, Isbell TS, Patel RP, Darley-Usmar VM, Doeller JE, Kraus DW. Hydrogen sulfide mediates the vasoactivity of garlic. *Proc Natl Acad Sci USA* 2007;104:17977–82.
18. Coletta C, Papapetropoulos A, Erdelyi K, Olah G, Módis K, Panopoulos P, Asimakopoulou A, Gerö D, Sharina I, Martin E. Hydrogen sulfide and nitric oxide are mutually dependent in the regulation of angiogenesis and endothelium-dependent vasorelaxation. *Proc Natl Acad Sci USA* 2012;109:9161–6.
19. Suetsuna K. Isolation and characterization of angiotensin I-converting enzyme inhibitor dipeptides derived from *Allium sativum* L (garlic). *J Nutr Biochem* 1998;9:415–9.
20. Kim-Park S, Ku DD. Garlic elicits a nitric oxide-dependent relaxation and inhibits hypoxic pulmonary vasoconstriction in rats. *Clin Exp Pharmacol Physiol* 2000;27:780–6.
21. Review Manager (RevMan) [computer program]. Version 5.2. Copenhagen (Denmark): The Nordic Cochrane Centre, The Cochrane Collaboration; 2012.
22. Kandziora J. Blutdruck- und lipidsenkende Wirkung eines Knoblauch-Präparates in Kombination mit einem Diuretikum (study 1). [Blood pressure and lipid reducing effect of a garlic supplement in combination with a diuretic (Study 1).] *Arztl Forsch* 1988;35:3–8 (in German).
23. Auer W, Eiber A, Hertkorn E, Hoehfeld E, Koehrl U, Lorenz A, Mader F, Merx W, Otto G, Schmid-Otto B, et al. Hypertension and hyperlipidaemia: garlic helps in mild cases. *Br J Clin Pract Suppl* 1990;69:3–6.
24. Vorberg G, Schneider B. Therapy with garlic: results of a placebo-controlled, double-blind study. *Br J Clin Pract Suppl* 1990;69:7–11.
25. Holzgartner H, Schmidt U, Kuhn U. Comparison of the efficacy and tolerance of a garlic preparation vs. bezafibrate. *Arzneimittelforschung* 1992;42:1473–7.
26. Jain AK, Vargas R, Gortzkowsky S, McMahon FG. Can garlic reduce levels of serum lipids? A controlled clinical study. *Am J Med* 1993;94:632–5.
27. Santos OSDeA, Gruenwald J. Effect of garlic powder tablets on blood lipids and blood pressure: a six-month placebo-controlled, double-blind study. *Br J Clin Res* 1993;4:37–44.
28. Kiesewetter H, Jung F, Jung EM, Blume J, Mrowietz C, Birk A, Koscielny J, Wenzel E. Effects of garlic coated tablets in peripheral arterial occlusive disease. *Clin Investig* 1993;71:383–6.
29. Saradeth T, Seidl S, Resch K, Ernst E. Does garlic alter the lipid pattern in normal volunteers? *Phytomedicine* 1994;1:183–5.
30. Simons LA, Balasubramaniam S, von Konigsmark M, Parfitt A, Simons J, Peters W. On the effect of garlic on plasma lipids and lipoproteins in mild hypercholesterolaemia. *Atherosclerosis* 1995;113:219–25.
31. Steiner M, Khan AH, Holbert D, Lin RI. A double-blind crossover study in moderately hypercholesterolemic men that compared the effect of aged garlic extract and placebo administration on blood lipids. *Am J Clin Nutr* 1996;64:866–70.
32. Adler AJ, Holub B. Effect of garlic and fish-oil supplementation on serum lipid and lipoprotein concentrations in hypercholesterolemic men. *Am J Clin Nutr* 1997;65:445–50.
33. Isaacsohn J, Moser M, Stein E, Dudley K, Davey J, Liskov E, Black H. Garlic powder and plasma lipids and lipoproteins: a multicenter, randomized, placebo-controlled trial. *Arch Intern Med* 1998;158:1189–94.
34. Zhang XH, Lowe D, Giles P, Fell S, Board AR, Baughan JA, Connock MJ, Maslin DJ. A randomized trial of the effects of garlic oil upon coronary heart disease risk factors in trained male runners. *Blood Coagul Fibrinolysis* 2001;12:67–74.
35. Williams MJ, Sutherland WH, McCormick MP, Yeoman DJ, de Jong SA. Aged garlic extract improves endothelial function in men with coronary artery disease. *Phytother Res* 2005;19:314–9.
36. Macan H, Uykimpang R, Alconcel M, Takasu J, Razon R, Amagase H, Niihara Y. Aged garlic extract may be safe for patients on warfarin therapy. *J Nutr* 2006;136(Suppl):793S–5S.
37. Sobenin IA, Andrianova IV, Demidova ON, Gorchakova T, Orekhov AN. Lipid-lowering effects of time-released garlic powder tablets in double-blinded placebo-controlled randomized study. *J Atheroscler Thromb* 2008;15:334–8.
38. Sobenin IA, Andrianova IV, Fomchenkov IV, Gorchakova TV, Orekhov AN. Time-released garlic powder tablets lower systolic and diastolic blood pressure in men with mild and moderate arterial hypertension. *Hypertens Res* 2009;32:433–7.
39. Ried K, Frank OR, Stocks NP. Aged garlic extract lowers blood pressure in patients with treated but uncontrolled hypertension: a randomised controlled trial. *Maturitas* 2010;67:144–50.
40. Ried K, Frank OR, Stocks NP. Aged garlic extract reduces blood pressure in hypertensives: a dose-response trial. *Eur J Clin Nutr* 2013;67:64–70.
41. Nakasone Y, Nakamura Y, Yamamoto T, Yamaguchi H. Effect of a traditional Japanese garlic preparation on blood pressure in prehypertensive and mildly hypertensive adults. *Exp Ther Med* 2013;5:399–405.
42. Beck E, Gruenwald J. *Allium sativum* in der Stufentherapie der Hyperlipidaemie. [Allium sativum for step-therapy in hyperlipidemia.] *Med Welt* 1993;44:516–20 (in German).
43. Borrelli F, Capasso R, Izzo AA. Garlic (*Allium sativum* L.): adverse effects and drug interactions in humans. *Mol Nutr Food Res* 2007;51:1386–97.
44. Waring RH, Klovra LZ, Harris RM. Diet and individuality in detoxification. *J Nutr Environ Med* 2007;16:95–105.
45. Meletis CD. Cleansing of the human body: a daily essential process. *Altern Complement Ther* 2001;7:196–202.
46. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: an updated systematic review. *Drugs* 2009;69:1777–98.
47. Harauma A, Moriguchi T. Aged garlic extract improves blood pressure in spontaneously hypertensive rats more safely than raw garlic. *J Nutr* 2006;136(Suppl):769S–73S.
48. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* 1994;308:367–72.
49. Wald NJ, Law MR. Serum cholesterol and ischaemic heart disease. *Atherosclerosis* 1995;118(Suppl):S1–5.
50. Tatley M, Savage R. Psychiatric adverse reactions with statins, fibrates and ezetimibe: implications for the use of lipid-lowering agents. *Drug Saf* 2007;30:195–201.
51. Golomb BA, Evans MA. Statin adverse effects: a review of the literature and evidence for a mitochondrial mechanism. *Am J Cardiovasc Drugs* 2008;8:373–418.
52. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, Seshasai SR, McMurray JJ, Freeman DJ, Jukema JW, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010;375:735–42.
53. Preiss D, Sattar N. Statins and the risk of new-onset diabetes: a review of recent evidence. *Curr Opin Lipidol* 2011;22:460–6.

54. Han R. Plasma lipoproteins are important components of the immune system. *Microbiol Immunol* 2010;54:246–53.
55. Willcox JK, Catignani GL, Lazarus S. Tomatoes and cardiovascular health. *Crit Rev Food Sci Nutr* 2003;43:1–18.
56. Willcox JK, Ash SL, Catignani GL. Antioxidants and prevention of chronic disease. *Crit Rev Food Sci Nutr* 2004;44:275–95.
57. Parthasarathy S, Raghavamenon A, Garelnabi MO, Santanam N. Oxidized low-density lipoprotein. *Methods Mol Biol* 2010;610:403–17.
58. Filippatos TD, Elisaf MS. High density lipoprotein and cardiovascular diseases. *World J Cardiol*. 2013;5:210.
59. Kumar M, Berwal J. Sensitivity of food pathogens to garlic (*Allium sativum*). *J Appl Microbiol* 1998;84:213–5.
60. Sivam GP. Protection against *Helicobacter pylori* and other bacterial infections by garlic. *J Nutr* 2001;131(Suppl):1106S–8S.
61. Nidadavolu P, Amor W, Tran PL, Dertien J, Colmer-Hamood JA, Hamood AN. Garlic ointment inhibits biofilm formation by bacterial pathogens from burn wounds. *J Med Microbiol* 2012;61:662–71.
62. Tsai Y, Cole LL, Davis LE, Lockwood SJ, Simmons V, Wild GC. Antiviral properties of garlic: in vitro effects on influenza B, herpes simplex and coxsackie viruses. *Planta Med* 1985;51:460–1.
63. Davis SR. An overview of the antifungal properties of allicin and its breakdown products—the possibility of a safe and effective antifungal prophylactic. *Mycoses* 2005;48:95–100.
64. Anthony J-P, Fyfe L, Smith H. Plant active components—a resource for antiparasitic agents? *Trends Parasitol* 2005;21:462–8.
65. Roberfroid MB. Prebiotics and probiotics: are they functional foods? *Am J Clin Nutr* 2000;71(Suppl):1682S–7S.
66. Chandrashekar PM, Prashanth KVH, Venkatesh YP. Isolation, structural elucidation and immunomodulatory activity of fructans from aged garlic extract. *Phytochemistry* 2011;72:255–64.
67. Furness JB, Kunze WA, Clerc N. Nutrient tasting and signalling mechanisms in the gut. II. The intestine as a sensory organ: neural, endocrine, and immune responses. *Am J Physiol* 1999;277:G922–8.
68. Abdullah T, Kirkpatrick D, Carter J. Enhancement of natural killer cell activity in AIDS patients. *DZ Onkologie* 1989;21:52–3.
69. Brosche T, Platt N. Knoblauchtherapie und zelluläre Immunabwehr im Alter. [Garlic therapy and cellular immunocompetence in the elderly.] *Z Phytother* 1994;15:23–4 (in German).
70. Nantz MP, Rowe CA, Muller CE, Creasy RA, Stanilka JM, Percival SS. Supplementation with aged garlic extract improves both NK and $\gamma\delta$ -T cell function and reduces the severity of cold and flu symptoms: a randomized, double-blind, placebo-controlled nutrition intervention. *Clin Nutr* 2012;31:337–44.
71. Josling P. Preventing the common cold with a garlic supplement: a double-blind, placebo-controlled survey. *Adv Ther* 2001;18:189–93.
72. Chandrashekar PM, Venkatesh Y. Identification of the protein components displaying immunomodulatory activity in aged garlic extract. *J Ethnopharmacol* 2009;124:384–90.
73. Zeb I, Ahmadi N, Nasir K, Kadakia J, Larijani VN, Flores F, Li D, Budoff MJ. Aged garlic extract and coenzyme Q10 have favorable effect on inflammatory markers and coronary atherosclerosis progression: a randomized clinical trial. *J Cardiovasc Dis Res* 2012;3:185–90.
74. Mozaffari-Khosravi H, Hesabgar H-a-S, Owlia M-B, Hadinedoushan H, Barzegar K, Fllahzadeh MH. The effect of garlic tablet on pro-inflammatory cytokines in postmenopausal osteoporotic women: a randomized controlled clinical trial. *J Diet Suppl* 2012;9:262–71.
75. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB, Gudnason V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004;350:1387–97.