Title
Garlic and Heart Disease 1–3

Journal
Journal of Nutrition, 146(2)

ISSN
0022-3166

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Publication Date
2016-02-01

DOI
10.3945/jn.114.202333

Peer reviewed

The Journal of Nutrition. First published ahead of print January 13, 2016 as doi: 10.3945/jn.114.202333.

The Journal of Nutrition
Supplement—2014 International Garlic Symposium: Role of Garlic in Cardiovascular Disease Prevention, Metabolic Syndrome, and Immunology

Garlic and Heart Disease[1–3]

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Abstract

Background: Thousands of studies have been published based on animal and human studies evaluating garlic's effects and safety.

Objective: We reviewed the available literature investigating the effects of garlic supplements on hypertension, hypercholesterolemia, C-reactive protein (CRP), pulse wave velocity (PWV), and coronary artery calcium (CAC), as well as available data on side effects.

Methods: We searched PubMed for all human studies using medical subject heading words through 30 May 2013 and assessed relevant review articles and original studies. Only double-blind, randomized, controlled trials and meta-analyses of double-blind, randomized, controlled trials were included. The review of articles and data extraction were performed by 2 independent authors, with any disagreements resolved by consensus.

Results: Garlic supplementation reduced blood pressure by 7–16 mm Hg (systolic) and 5–9 mm Hg (diastolic) (4 meta-analyses and 2 original studies). It reduced total cholesterol by 7.4–29.8 mg/dL (8 meta-analyses). The most consistent benefits were shown in studies that used aged garlic extract (AGE). A few small studies that used AGE also showed favorable effects on CAC, CRP, and PWV. Although garlic is generally safe, rare adverse reactions have been documented with limited causality established.

Conclusion: We conclude that garlic supplementation has the potential for cardiovascular protection based on risk factor reduction (hypertension and total cholesterol) and surrogate markers (CRP, PWV, and CAC) of atherosclerosis. Larger studies are warranted to evaluate these effects further. *J Nutr* doi: 10.3945/jn.114.202333.

Keywords: garlic, atherosclerosis, hypertension, cholesterol, heart disease, treatment

Introduction

Despite significant improvements over the last several decades in lifestyle modifications and pharmacologic management of well-established risk factors, atherosclerosis-related diseases (ARDs)[6] such as ischemic heart disease (IHD), stroke, and peripheral vascular disease remain the leading cause of mortality in developed nations (1). Thus, ongoing preventative strategies, especially for primary prevention, are an area of utmost importance (2).

Although garlic (*Allium sativum* L.) has been used for medicinal purposes for thousands of years (3) across the globe for various indications (4), speculation about the cardio-protective effects appears in ancient Indian texts (5). The earliest scientific studies exploring this possibility, to our knowledge, began in the 1950s (6). Since then, thousands of studies have been published based on animal and human studies in vitro and in vivo to isolate the active ingredients and to evaluate garlic's effects and safety. In fact, garlic is one of the most heavily researched present day herbal medicines (4) and the second most used complementary therapy (7).

There have been concerns and criticism about the use of garlic. It has been shown that the variability and the non-standardization of preparations can make comparing studies very difficult and results sometimes uninterpretable (8, 9). Even studies that have used the same preparation sometimes report different outcomes. There have also been concerns about the size and duration of many of the trials (10, 11). Lastly, many of the studies that have shown favorable effects are in vitro or animal studies, which may not translate to human benefit.

Nonetheless, as a society, we must focus on developing safe, affordable, and accessible strategies for preventing ARDs. Thus, if supported by thousands of years of clinical use and multiple small-scale studies showing favorable effects, without significant side effects or cost, it is worthwhile to pursue this therapy further.

This literature review is an effort to consolidate current knowledge in this area to better understand the effect of garlic on ARDs from a clinician's point of view. To our knowledge, there is no study investigating the effect of garlic on endpoints such as infarction, stroke, percutaneous interventions, or death (7). Thus, we summarize the evidence for the use of garlic in treating traditional clinical risk factors based on the Framingham risk score, namely, hypertension and total cholesterol (TC).

We also summarize current knowledge of the effect of garlic on emerging tools currently mentioned in guidelines for a clinician in predicting ARDs in addition to the traditional risk factors correlated to IHD, namely, coronary artery calcium (CAC), inflammatory biomarkers [C-reactive protein

Manuscript received August 21, 2014. Initial review completed September 29, 2014. Revision accepted May 13, 2015.
doi: 10.3945/jn.114.202333.

(CRP)], and tests of vascular function [pulse wave velocity (PWV)].

The safety profile will also be discussed.

Methods

Human review articles in PubMed were searched up until 31 March 2013 by using the medical subject heading word "garlic," along with one or more of the terms "hypertension," "hypercholesterolemia," "C-reactive protein," and "arterial occlusive diseases." Only double-blind, randomized, controlled trials and meta-analyses of double-blind, randomized, controlled trials were included. The review of articles and data extraction was performed by 2 independent authors, with any disagreements resolved by consensus. We prespecified the following inclusion criteria: *1*) the study had to be a cohort or double-blind design; *2*) the garlic dose had to be specified; and *3*) the study had to provide relevant data, including blood pressure, blood cholesterol, aortic stiffness, or atherosclerosis measures. The quality of the trial was analyzed by each author independently and only trials that were assessed to be appropriate by both authors were included.

Results

Hypertension. Antihypertensive therapy has been associated with a 20–25% relative risk reduction in the incidence of IHD, and a 30–40% reduction in stroke (12). It is thought that up to 50% of hypertensive patients may be using garlic as an adjunct or solely for treatment (7). Furthermore, in developing nations such as Nigeria, where complementary therapies are more affordable and accessible, garlic is heavily used for hypertension (13). The first meta-analysis of the antihypertensive effects of garlic, to our knowledge, was published in 1994 and showed favorable effects (14). However, we will focus on 4 meta-analyses and 2 original studies published since then.

Two of the 4 meta-analyses were published in 2008. In the first study, Reinhart et al. (15) found 26 randomized, controlled studies reporting blood pressure endpoints. Sixteen of these studies were excluded for poor quality (e.g., 5 were not placebo controlled, 2 were not double-blinded, and 1 had no baseline blood pressures). Of the remaining 10 studies, only 3 enrolled hypertensive patients (n = 132) at baseline, whereas the other 7 enrolled normotensive patients (n = 262). All 3 studies enrolling hypertensive patients were treated with Kwai brand garlic powder (KB GP). These patients were found to have a significant decrease in systolic blood pressure (SBP) of 16.3 mm Hg (95% CI: 6.2, 26.5) and diastolic blood pressure (DBP) of 9.3 mm Hg (95% CI: 5.3, 13.3) compared with placebo. In the remaining 7 trials enrolling normotensive patients, treatment with KB GP, Kyolic brand aged garlic extract (KB AGE), and Cardiomax brand garlic oil did not significantly lower blood pressure. Reinhart et al. concluded that garlic lowers SBP and DBP in hypertensive patients, but not in normotensive patients.

In the second study, Ried et al. (16) found 25 relevant studies and included 11 in their meta-analysis with 503 patients in an SBP arm and 565 in an DBP arm. This included 6 of the 10 studies from the meta-analysis by Reinhart et al. (15) mentioned above and only 2 of 3 studies that had hypertensive patients at baseline. In this meta-analysis, 9 studies used KB GP, 1 used KB AGE, and 1 used distilled garlic oil. Ried et al. concluded that SBP decreased by 4.6 ± 2.8 mm Hg overall. Furthermore, in patients who were hypertensive at baseline, SBP decreased by 8.4 ± 2.8 mm Hg and DBP by 7.3 ± 1.5 mm Hg. The regression analysis done by Ried et al. showed a significant association between blood pressure at the start of the intervention and the amount of blood pressure reduction as well.

In the third study, Simons et al. (11) performed a review of trials related to the effects of garlic on hypertension. They analyzed 32 trials and evaluated the quality, finding that most were of borderline quality. They scored each trial on a 9-point quality scale and awarded only 4–6 points for most individual studies. Simons et al. concluded that garlic could not be recommended for hypertension given the "low methodological quality."

Regardless, in a Cochrane Review, Stabler et al. (7) screened 72 publications and included only 2 trials in their study. They concluded that treatment with garlic decreases SBP by 10–12 mm Hg and DBP by 6–9 mm Hg.

Since the publication of the Cochrane Review by Stabler et al. (7), we identified 2 more randomized, controlled trials. First, Ried et al. (17) performed a randomized, placebo-controlled, double-blind trial meeting all quality criteria. They enrolled 84 hypertensive patients taking conventional antihypertensive medications. With the use of KB AGE at 3 different doses compared with placebo, they found a reduction in SBP of 11.8 ± 5.4 mm Hg at a dose of 2 capsules. This dose was "well tolerated and highly acceptable." Tolerability, compliance and acceptability were high (93%) in all garlic groups and highest in the groups taking 1 or 2 capsules daily.

Second, Nakasone et al. (18) evaluated prehypertensive patients (SBP: 130–139 mm Hg) to mildly hypertensive patients (SBP: 140–159 mm Hg) taking no medications and administered Dentou-ninniku-ranwo brand Japanese garlic preparation in a 12 wk randomized, placebo-controlled, double-blind trial meeting most of the quality criteria. Nakasone et al. showed a

[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-Nutraceuticos; Healthy U 2000 Ltd.; Magna; Mannavita Bvba; MaxiPharma; Medica Nord A.S.; Nature's Farm Pte. Ltd.; Nature Valley W.L.L.; Organic Health Ltd.; Oy Valioravinto Ab; Purity Life Health Products L.P.; PT Nutriprima Jayasakti; Vitaco Health Ltd.; Vitae Natural Nutrition; Sanofi Consumer Health Care; Wakunaga Pharmaceutical 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] The authors report no funding received for this study.

[3] Author disclosures: R Varshney, no conflicts of interest. MJ Budoff receives funding from Wakunaga of America Co., Ltd.

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[6] Abbreviations used: ARD, atherosclerosis-related disease; CAC, coronary artery calcium; CRP, C-reactive protein; CT, computed tomography; DBP, diastolic blood pressure; EAT, epicardial adipose tissue; IHD, ischemic heart disease; KB AGE, Kyolic brand aged garlic extract; KB GP, Kwai brand garlic powder; PWV, pulse wave velocity; SBP, systolic blood pressure; TC, total cholesterol.

reduction in SBP of 6.6–7.5 mm Hg and DBP of 4.6–5.2 mm Hg with no reported side effects.

Based on our literature review, we identified a few small studies having rigorous methodologic quality according to several authors that showed a favorable effect on blood pressure from the use of garlic preparations in the range of 7–16 mm Hg for SBP and 5–9 mm Hg for DBP compared with placebo. This effect was seen only in patients with hypertension at baseline. This effect may be in addition to other antihypertensive therapies (18), and it has been demonstrated with the use of KB GP, KB AGE, and Dentou-ninniku-ranwo preparations. Most studies have been performed with KB AGE. No studies have shown effects on endpoints such as mortality or myocardial infarction or stroke, but, of note, an amount of blood pressure reduction with other interventions has been shown to reduce IHD events by up to 40% (12).

Hypercholesterolemia. Many large-scale randomized trials have demonstrated a graded effect between degree of hypercholesterolemia and IHD (19, 20). In a meta-analysis of 61 trials with over 900,000 asymptomatic patients over 12 million patient-years and 55,000 vascular deaths, it was shown that lowering TC by 38.7 mg/dL was associated with approximately 56% [HR 0.44 (95% CI: 0.42, 0.48)], 34% [0.66 (95% CI: 0.65, 0.68)], and 17% [0.83 (95% CI: 0.81, 0.85)] lower IHD mortality in both sexes at ages 40–49, 50–69, and 70–89 y, respectively, throughout the main range of cholesterol in most developed countries, with no apparent threshold (21).

Although in vitro and animal studies have repeatedly and almost unanimously shown favorable effects from garlic consumption on hypercholesterolemia and its consequences, clinical trials have had conflicting results (3). In total, we identified 8 meta-analyses between 1993 and 2011 analyzing the effect of garlic consumption on TC. Each had different inclusion and exclusion criteria and have thus produced variable results.

The most recent meta-analysis published (22) evaluated 26 randomized, double-blind, placebo-controlled trials of 1295 subjects. It excluded 9 additional studies that met inclusion criteria but had data not amenable to pooling. In addition, 6 trials were excluded because of the inclusion of diabetic patients, 2 because they concurrently used lipid-lowering agents, 2 because they coadministered garlic with other interventions, and 1 because of a significant gender difference between the garlic and placebo groups. Only 4 of the 26 analyzed studies included normo-lipidemic patients. Garlic powder was the most used product, as were KB AGE and garlic oil. Overall, this meta-analysis concluded that garlic was superior to placebo in reducing serum TC by 10.8 mg/dL (95% CI: 17.4, 4.3, $P = 0.001$). KB AGE and KB GP were more effective in lowering TC concentrations. The authors concluded that the reduction, although significant, was unimpressive compared with reductions from the use of prescription drugs such as statins, but that it was comparable to diet modification alone.

Of the other 7 meta-analyses identified, 2 were published in 2009 and had conflicting results. Reinhart et al. (23) screened 2958 publications—until November 2007—and analyzed 29 trials. They found a similar reduction in TC of 7.35 mg/dL (95% CI: 12.8, 2.3). In contrast, in the same year, Khoo and Aziz (24) screened only 1230 studies published until March 2008, included 12 trials until March 2008 with 1056 subjects, and found no difference in TC with garlic consumption compared with placebo.

All 5 older meta-analyses published before 2008, by Alder et al. (10), Ackerman et al. (25), Stevinson et al. (26), Silagy and Neil (27), and Warshafsky et al. (28), showed favorable effects from garlic on TC of 24.7, 17.0, 15.9, 29.8, and 22.8 mg/dL, respectively. Since the publication of the most recent meta-analysis, we identified 3 randomized, controlled trials which are not applicable because they involved the coadministration of interventions besides garlic (29, 30) and open labeling (31).

Overall, various garlic preparations have shown a reduction in TC of 7.4–29.8 mg/dL. The trial showing no effect (24) was published at the same time as that by Reinhart et al. (23), but it screened and included only half as many publications. This may perhaps indicate a bias. This mild to moderate reduction in TC should be beneficial to lower cholesterol concentrations when added to statins or for patients who cannot tolerate statins.

CAC and epicardial adipose tissue. CAC is an adjusted score that is based on the amount of calcification discovered in coronary vessels by a noncontrast computed tomography (CT) scan. According to the 2010 American College of Cardiology Foundation/AHA guideline for assessment of cardiovascular disease risk in asymptomatic adults (32), not only is CAC a well-validated prognostic marker of IHD, but also, in patients who are at intermediate risk based on the Framingham risk factors (10–20% 10 y risk), CAC can additively help risk-stratify patients into low or high risk, thus influencing treatment decisions. Furthermore, serial measurements of CAC can help prognosticate patients further, and it is becoming an acceptable surrogate endpoint instead of myocardial infarction or cardiac disease mortality in studies assessing the effectiveness of interventions (33). Moreover, treatment with statins has been shown to reduce the rate of CAC progression (34, 35). It has been shown that a CAC score progression of >15% per year significantly increases mortality (36, 37).

There are 3 randomized, double-blind, placebo-controlled small studies demonstrating the favorable effects of garlic on CAC progression (38, 39, 40) as a surrogate marker for clinical endpoints. All 3 studies used the standardized KB AGE formulation at standard doses.

Budoff et al. (38) showed that in 23 patients with known coronary artery disease (CAD) or high risk patients (Framingham risk >20% over 10 y), over 1 y, KB AGE reduced the progression of CAC compared with placebo (7.5 ± 9.4% compared with 22.2 ± 18.5%, respectively). Similarly, Budoff et al. (39) showed significant results in 65 intermediate risk patients (age 60 ± 9 y) with a Framingham risk of 10–20% and baseline CAC >30. In that study, KB AGE was administered with vitamin B-12, folic acid, vitamin B-6, and L-arginine. In a 1 y follow-up, the CAC progression was significantly lower in the treatment group than in the placebo group (6.8% compared with 26.5%, $P = 0.005$). Lastly, Zeb et al. (40) enrolled 65 asymptomatic, intermediate risk (baseline CAC >10) men aged 55 ± 6 y, and treated them with KB AGE plus coenzyme Q10 compared with placebo. At 1 y, mean CAC progression was significantly lower in the treatment group than in the placebo group (32 ± 6 compared with 58 ± 8, $P = 0.01$).

Because CAC progression is associated with a greater risk of IHD and, based on these 3 small scale studies, treatment with garlic shows a decrease in the rate of progression of CAC, it can be hypothesized that garlic may decrease rates of IHD. It should be noted that, although all 3 studies used KB AGE, 2 studies used additional treatments along with KB AGE, which may have influenced the results.

In addition to CAC, CT scans can characterize the quality of the adipose tissue surrounding the coronary arteries into white or brown epicardial adipose tissue (EAT). The composition of EAT is important, because EAT is biologically active tissue that influences rates of inflammation and atherosclerosis progression and overall stability of plaque via a host of hormones and cytokines (41, 42). Although the biochemical process is complex and not fully elucidated, overall, it has been shown that a higher brown-to-white EAT ratio is favorable and is implicated with a lower risk of IHD (43, 44).

With the advent of accurate methods of measuring brown-to-white EAT ratios via CT scan technology, favorable changes in the brown-to-white EAT ratio can be demonstrated over time. KB AGE plus supplements significantly increased the brown-to-white EAT ratio compared with placebo (125 ± 38% compared with −11 ± 20%) (45).

PWV (arterial stiffness). Although not currently widely employed clinically in North America, PWV is an easy to measure noninvasive, operator independent, and highly reproducible test of aortic stiffness that is a strong predictor of IHD (46). This test, somewhat similar to the ankle-brachial index, can be useful for the clinician for risk stratification. PVW quantifies aortic stiffness by assessing the speed of blood flow in the aorta by measuring the time elapsed between the carotid and a distal pulse (e.g., radial or femoral). A meta-analysis of 17 studies in over 15,000 patients showed that a high PWV is correlated to an increased RR of an IHD event (2.26), cardiovascular disease mortality (2.02), and all-cause mortality (1.90). Thus, in the 2007 European Societies of Hypertension and Cardiology Guideline for the Management of Hypertension, PWV is incorporated as a risk assessment tool for hypertensive patients not already at high risk (47).

The Firefighter Aged Garlic Extract Investigation as a Treatment for Heart Disease (FAITH) trial evaluated the effect of garlic on PWV (48) in a randomized, double blind, placebo-controlled study of 65 intermediate-risk men. The study demonstrated that after 1 y, the mean decrease in PWV was 1.21 m/s in the intervention group (KB AGE plus coenzyme Q10) compared with placebo (P = 0.005). Although a low PWV is more favorable than a high PWV, it has yet to be shown that lowering PWV is associated with better outcomes. Nonetheless, PWV is a promising clinical tool for risk stratification for primary prevention and an easy target to follow if shown that improvement correlates to better outcomes.

Biomarkers of inflammation. Several biomarkers are showing promising results in terms of prediction of IHD events and risk stratification regardless of specified mechanisms. Of these, CRP is the most studied biomarker as a clinical predictor of IHD and it is incorporated into the 2009 Canadian Cardiovascular Society guidelines for dyslipidemia and prevention of cardiovascular disease (49). These guidelines recommend the screening of men >50 y and women >60 who are at moderate risk of IHD (determined by the Framingham risk) and whose LDL cholesterol is <3.5 mmol/L. If these patients have elevated CRP concentrations, it is recommended that statin therapy be initiated, because statins lower CRP and prevent IHD.

To our knowledge, there is no meta-analysis investigating the effects of garlic on CRP. We identified 6 studies evaluating the effects of garlic on CRP (31, 39, 40, 50–52). The only quality trial that showed a correlation between treatment with garlic and a lowered CRP concentration was by Zeb et al. (40). In that trial, KB AGE plus coenzyme Q 10 were administered to 65 intermediate-risk patients for 1 y. CRP was reduced significantly (−0.12 ± 0.24 mg/L) compared with placebo (0.91 ± 0.56 mg/L). The other 5 trials either had a poor design or showed no effect.

Adverse events and drug interactions. Garlic is very safe (53). However, there are some common side effects and rare case reports. Not all trials and meta-analyses discuss side effects, but the only statistically significant side effects of garlic treatment are body odor and halitosis (25, 26, 53). These side effects are most prominent with raw garlic and are ameliorated in some odor-free garlic preparations, such as KB AGE (53).

Some other common self-reported mild side effects are gastrointestinal intolerabilities such as abdominal pain, bloating, and flatulence (25). However, dysphagia and garlic-induced esophagitis with hematemesis or hematochezia have also been reported, along with small-bowel obstruction without causality established (53, 54).

Case reports of serious side effects include allergic reactions, including anaphylaxis. Certain patients also exhibit allergic symptoms such as dermatitis, rhinitis, asthma, urticaria, photoallergy, angioedema, and pemphigus (25, 53, 55).

There have been rare case reports of coagulation dysfunction with bleeding from excessive intake of garlic preparations (53). This includes spinal epidural hematoma, increased clotting time, postoperative bleeding, and retrobulbar hemorrhage without proven causality. There have been 2 cases of interaction with warfarin. However, Macan et al. (56) demonstrated that aged garlic extract may be safe with warfarin therapy.

Discussion

Based on the current available literature, garlic has shown favorable effects on several clinically relevant risk factors that not only help prognosticate but can alter management strategies for patients in the primary prevention of IHD. One of the challenges of studying the effects of garlic is the standardization of the preparation or active ingredient. KB AGE has shown the most consistent results, because the product is standardized to a certain level of *N*-acetylcysteine before packaging. Nonetheless, numerous trials and meta-analyses have shown favorable effects from garlic on well-accepted risk factors such as hypertension and hypercholesterolemia. SBP and DBP have been shown to be reduced by 7–16 mm Hg and 5–9 mm Hg, respectively, compared with placebo. TC has been shown to be reduced by 7.4–29.8 mg/dL. Although larger studies for clinical endpoints of morbidity and mortality have not been assessed, in a few small studies, garlic has shown favorable effects for surrogate endpoints such as CAC progression rates. Small studies have also shown garlic to improve practical clinical prognosticators such as PWV and CRP. Garlic is generally safe with mild gastrointestinal discomfort as the most common intolerability, which can be abated if an odor-free preparation such as KB AGE is used. As one of the oldest medicinal remedies ever applied, it deserves closer evaluation for its possible cardiovascular disease risk benefits.

Acknowledgments

RV and MJB are responsible for design, writing, and final content. Both authors read and approved the final manuscript.

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