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Garlic for hypertension: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: In the past decade, *garlic* has become one of the most popular complementary therapies for blood pressure (BP) control used by hypertensive patients. Numerous clinical studies have focused on the BP-lowering effect of *garlic*, but results have been inconsistent. Overall, there is a dearth of information available to guide the clinical community on the efficacy of *garlic* in hypertensive patients.

Aim: To systematically review the medical literature to investigate the current evidence of *garlic* for the treatment of hypertension.

Methods: PubMed, the Cochrane Library and EMBASE were searched for appropriate articles from their respective inceptions until August 2014. Randomized, placebo-controlled trials comparing *garlic vs.* a placebo in patients with hypertension were considered. Papers were independently reviewed by two reviewers and were analyzed using Cochrane software Revman 5.2.

Results: A total of seven randomized, placebo-controlled trials were identified. Compared with the placebo, this meta-analysis revealed a significant lowering effect of *garlic* on both systolic BP (WMD: −6.71 mmHg; 95% CI: −12.44 to −0.99; $P = 0.02$) and diastolic BP (WMD: −4.79 mmHg; 95% CI: −6.60 to −2.99; $P < 0.00001$). No serious adverse events were reported in any of the trials.

Conclusion: The present review suggests that *garlic* is an effective and safe approach for hypertension. However, more rigorously designed randomized controlled trials focusing on primary endpoints with long-term follow-up are still warranted before *garlic* can be recommended to treat hypertensive patients.

Introduction

Hypertension affects approximately one billion people, or two-thirds of adults aged 60 years or older worldwide (Go et al. 2013; Mancia et al. 2013). A linear relationship between blood pressure (BP) and risk of cardiovascular events has been identified and, thus, hypertension is the leading risk factor for cardiovascular diseases (CVDs). Currently, the Cochrane systematic review focusing on the first-line drugs for hypertension suggested that antihypertensive agents including thiazides, angiotensin converting enzyme inhibitors, beta-blockers, and calcium channel blockers reduce the risk of mortality, stroke, coronary heart disease (CHD), and/or cardiovascular events (Wright and Musini 2009). Although effective medical treatment has been recommended by various guidelines for the management of patients with high BP, hypertension is not yet adequately controlled (Jaffe et al. 2013; James et al. 2014; Wang and Xiong 2012). In America, approximately half of the hypertensive patients have a controlled BP of ≤140/90 mmHg, and more than 13% (approximately 9 million people) had a systolic blood pressure (SBP) of ≥160 mmHg and/or diastolic blood pressure (DBP) of ≥100 mmHg (Frieden et al. 2014; Guo et al. 2012). In addition, adverse events (AEs) and the complexity of antihypertensive therapy tend to decrease treatment adherence (Bangalore et al. 2011; Wang and Manson 2013). Therefore, it is not surprising that complementary and alternative medicines (CAM) are gaining increasing popularity among patients with CVDs (Tachjian et al. 2010; Vogel et al. 2005), and there is a need to explore the integration of CAM into the treatment of hypertension (Brook et al. 2013; Xiong et al. 2013a).

Garlic, also known as *Allium sativum* L. (*Liliaceae*), is a member of the family *Alliaceae*. It has been used as an important medicinal ailment in many countries for thousands of years (Pittler and Ernst 2007). According to a survey of 10,572 patients with CVDs

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in the 2002 National Health Interview Survey, *garlic* was the second most utilized herbal products (after Echinacea) within the previous 12 months (Yeh et al. 2006). An appreciable amount of scientific reports demonstrated its therapeutic and pharmacological properties. Indeed, raw *garlic* and *garlic*-based preparations exert antihypertensive, anti-atherosclerotic, lipid-lowering, plasma fibrinogen-lowering, fibrinolytic activity-increasing, and other cardiovascular-protective effects (Campbell et al. 2001; Dhawan and Jain 2005; Durak et al. 2004; Rahman 2001; Stevinson et al. 2000; Steiner and Li 2001). It is also considered to be one of the most popular complementary therapies for BP control and is thought to be used by 53.3% of hypertensive patients (Capraz et al. 2007). Biochemically, *garlic* exerts its antihypertensive effects by inhibiting angiotensin-converting enzyme activity (Asdaqa and Inamdarb 2010; Sharifi et al. 2003), reducing the synthesis of vasoconstrictor prostanoids (Al-Qattan et al. 2001), enhancing the concentration and activity of nitric oxide and generation of hydrogen sulfide (Al-Qattan et al. 2006), and reversing arterial remodeling through upregulation of the growth suppressor p27 and the attenuation of ERK 1/2 phosphorylation (Castro et al. 2010) in *in vivo* and *in vitro* experiments. One of the active constituents believed to be responsible for its pharmacological activity is allicin, liberated from alliin (*S*-allylcysteine-*S*-oxide) and the enzyme alliinase.

Indeed, numerous clinical investigations of *garlic* have reported the possible short-term BP-lowering effects on hypertension ranging from case reports and case series to controlled observational studies and randomized controlled trials (RCTs) (Estrada and Young 1993; McMahon and Vargas 1993; Mendis 1988). However, inconsistent and sometimes controversial results have been shown in several other trials (Duda et al. 2008; Simons et al. 1995; Zimmermann and Zimmermann 1990). The possible reason for these discrepancies may be related to different preparations of *garlic* with different biological responses, deficiencies in methodology, variations in the dosage of *garlic* and different treatment durations. As shown in nine published systematic reviews and/or meta-analyses, the effects of *garlic* on BP have been summarized with inconsistent conclusions (Ackermann et al. 2001; Mahdaviroshan et al. 2014; McRae 2005; Reinhart et al. 2008; Ried et al. 2008; Simons et al. 2009; Silagy and Neil 1994; Stabler et al. 2012; Yan and Fan 2011). However, a large number of the clinical trials enrolled in these systematic reviews were conducted in healthy volunteers or patients with hyperlipidemia, or compared hypertensive patients with normal BP patients. Additionally, there was evidence that revealed that the initial BP level is an important factor affecting the BP-lowering efficacy of *garlic* (Qidwai and Ashfaq, 2013); that was, hypertensive subjects with a baseline SBP ≥140 mmHg often showed positive results (De Santos and Grunwald 1993; Holzgartner 1992; Vorberg and Schneider 1990), while normotensive subjects with SBP <140 mmHg showed null results (Al-Wafi and Al-Fartos 2010; Jain et al. 1993; Isaacsohn et al. 1998; Macan et al. 2006; Turner et al. 2004; Williams et al. 2005; Zhang et al. 2001). Although one systematic review evaluated the effect of *garlic* on cardiovascular morbidity and mortality in hypertensive patients, only two trials were included with no definite conclusions (Stabler et al. 2012). Therefore, it is still unknown whether there is robust evidence supporting the clinical effects of *garlic* for hypertensive patients, and whether *garlic* supplementation can be recommended as a routine treatment. The objective of this study was to systematically review the data from RCTs to explore whether *garlic* is an effective and safe alternative approach for the treatment of hypertension.

Methods

This meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al. 2009).

Eligibility criteria

Types of studies

Only randomized, placebo-controlled trials evaluating the effects of *garlic* or *garlic*-based preparations on hypertensive patients were considered.

Types of participants

Unlike the previously published systematic review, all the enrolled participants in this review were diagnosed with hypertension according to established definitions or guidelines. Specifically, participants were eligible if they displayed a SBP ≥140 mmHg and/or DBP ≥ 90 mmHg on at least two occasions whilst off antihypertensive treatment (after a washout period of at least 4 weeks) and/or treatment with antihypertensive medication (James et al. 2014; Mancia et al. 2013). Trials that reported the recruitment of subjects with definite hypertension but without specific diagnostic criteria were also included. If non-hypertensive patients were included in the treatment or control group, the trial was excluded. No restrictions were imposed on sex, age, or ethnic origin of the participants.

Types of interventions

RCTs comparing the efficacy of *garlic* or *garlic*-based preparations *vs.* a placebo on hypertension were identified. These studies were excluded: (a) RCTs comparing *garlic* against another non-conventional therapy, or comparing *garlic* plus other non-conventional therapies against conventional medicine; (b) RCTs comparing the effect of *garlic* on hypertensive patients *vs.* normotensive subjects; (c) studies that were not randomized, uncontrolled, and/or animal experiments; (d) studies that reported duplicated results; and (e) trials with no clinical data reported. To ensure all the relevant studies were included, we did not set any specifications for *garlic* preparations, dosage, or treatment duration. If ambiguous or missing information about the outcomes in the original studies were identified, the corresponding authors were contacted by email, fax or telephone.

Types of outcome measures

The primary outcome measures were defined as mortality and cardiovascular events including CHD, myocardial infarction, heart failure, and stroke. The secondary outcome measures were defined as SBP and DBP at the end of the treatment. BP was measured in mmHg. If BP was measured in kPa, it was multiplied by a factor of 7.5 for conversion into mmHg.

Search strategy

We searched the following three electronic databases from their inception until August 17th, 2014 for the identification of studies: PubMed (1995–2014), the Cochrane Library (1996–2014), and EMBASE (1995–2014). In order to minimize selection bias, ongoing registered clinical trials on the Chinese Clinical Trial Register (http://www.chictr.org/) and the international clinical trial registry by U.S. National Institutes of Health (http://clinicaltrials.gov/) were also searched. Keywords for databases searching were: (“*garlic* ” OR “garlicin” OR “*garlic* oil” OR “*garlic* oil macerates” OR “*garlic* extract” OR “*garlic* cloves” OR “*garlic* powder” OR “aged *garlic* extract” OR “*Allium sativum*” OR “alliinase” OR “allicin”) AND (“hypertension” OR “blood pressure” OR “high blood pressure”) AND (“clinical trial” OR “randomized trial” OR “randomized controlled trial”). There were no restrictions on language or publication in the search strategy. Citations of reviews and meta-analyses of *garlic* for the treatment of hypertension were also examined. Experts in the field were contacted to identify any other trials missed in our search.