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An umbrella review of garlic intake and risk of cardiovascular disease

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ABSTRACT

Purpose: To gain further insight into the strength of evidence and extent of possible biases in the scope of studies investigating the impact of garlic and garlic supplement intake on biomarkers of cardiovascular disease, we performed an umbrella review of all published meta-analyses synthesizing data from both observational studies and randomized controlled trials.

Methods: Electronic database PubMed (between 1966 and June 2015) was searched for systematic reviews and meta-analyses using following search terms: (“garlic” OR “allium sativum” OR “allicin” OR “organosulfur”) AND (“cardiovascular” OR “coronary” OR “cholesterol” OR “triglyceride” OR “atherosclerosis” OR “blood pressure” OR “hypertension” OR “blood glucose”) AND (“systematic review” OR “meta-analysis”), with no restriction to calendar data and language. Hand-search of reference lists and relevant clinical guidelines was performed as well.

Results: Nine systematic reviews investigated the effects of garlic on lipid parameters and eight systematic reviews analyzed the effects on blood pressure parameters were identified. Eight of nine meta-analyses synthesizing the effect of garlic on blood lipids reported significantly decreased total cholesterol levels. Inconsistent results could be detected for HDL-cholestrol, LDL-cholesterol, and triacylglycerols. The effect of garlic on systolic blood pressure showed consistent results across publications with 7 out of 8 meta-analyses demonstrating a substantial decrease in systolic blood pressure. Similar results could be reported regarding the effect of garlic on diastolic blood pressure, i.e. 6 out of 8 meta-analyses detected significant reductions in diastolic blood pressure levels following interventions with garlic.

Conclusion: According to the data summarized in the present umbrella review, garlic preparations as well as garlic exerted some positive effects on indicators and biomarkers of cardiovascular disease, typically without causing any serious side effects. However, with regard to the substantial heterogeneities between the different trials enrolled in the various meta-analyses of this review, a conservative interpretation of the outcome seems to be appropriate.

Introduction

Cardiovascular disease (CVD) is a major public health problem causing an estimated 32% of global deaths. Moreover, there is a significant worldwide increase in the age-standardized death rate for CVD since 1990 (Naghavi et al. 2015). The etiology of CVD is multifactorial, but these disorders are predominantely caused by modifiable risk factors such as hypercholesterolemia, hypertension and type 2 diabetes mellitus (Mendis et al. 2011; Verschuren et al. 1995).

Recently, the possible hypocholesterolemic effect of different dietary components, i.e. beta-glucan, soy protein, isoflavones, plant sterols and stanols and garlic have attracted interest, and there are efforts to apply them as strategies for the prevention of CVD (Miettinen et al. 2011; Stelmach-Mardas et al. 2014).

Garlic (Allium sativum) is among the most popular vegetables worldwide, especially used as a spice in the Mediterranean and Asian cuisine (FAO 2014), and is characterized by high contents of flavonoid and organosulfur compounds such as allicin, alliin, S-allylcysteine, or S-allyl mercaptocysteine along with a variety of other bioactive nonsulfur compunds, e.g. steroid saponins (Amagase 2006). Research in animal studies showed that garlic compounds are associated with potential anti-lipidemic, anti-thrombotic, anti-hypertensive, anti-atherogenic and anti-glycemic modes of action (Al-Qattan et al. 2006; Kim-Park and Ku 2000; Sun Jong et al. 2009). Allium sativum

Abbreviations: CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OQAQ, overview of quality assessment questionnaire; RCT, randomized controlled trials; SBP, systolic blood pressure; T2D, type 2 diabetes mellitus; TC, total-cholesterol.

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and garlic supplements have been investigated in various studies analyzing their potential preventive effect with respect to risk of CVD by improving its biochemical markers (Rahman and Lowe 2006).

However, systematic reviews and meta-analyses of randomized controlled trials investigating the effectiveness of garlic preparations on disorders of the cardiovascular system yielded conflicting results (Pittler and Ernst 2007; Zeng et al. 2013). Uncertainties regarding correlations between intake of either natural garlic or garlic supplements and CVD could be the result of confounding factors (e.g. preexisting medical conditions such as adiposity or type 2 diabetes) or due to methodological issues, e.g. reporting bias or insufficient sample size estimates of trials.

To gain further insight into the strength of evidence and extent of possible biases in the scope of studies investigating the impact of garlic and garlic supplement intake on biomarkers of CVD, we performed an umbrella review of all published meta-analyses synthesizing data from both observational studies and randomized controlled trials (RCT).

Methods

The methodological approach is based on a recently published umbrella review that focused on monounsaturated fatty acids and risk of CVD (Schwingshackl and Hoffmann 2012).

Data sources and search strategy

Electronic database PubMed (between 1966 and June 2015) was searched for systematic reviews and meta-analyses using following search terms: (“garlic” OR “allium sativum” OR “allicin” OR “organosulfur”) AND (“cardiovascular” OR “coronary” OR “cholesterol” OR “triglyceride” OR “atherosclerosis” OR “blood pressure” OR “hypertension” OR “blood glucose”) AND (“systematic review” OR “meta-analysis”), with no restriction to calendar data and language. Hand-search of reference lists and relevant clinical guidelines was performed as well.

Inclusion criteria

Studies were included in this umbrella review if they met all of the following criteria: (1) systematic review including meta-analysis (quantitative analysis) of RCTs, crossover, and observational studies; (2) garlic supplementation; garlic intake; highest vs. lowest garlic intake category; (3) Study population: >18 years, healthy, patients with type 2 diabetes mellitus (T2D), obese, overweight, hypertensive, impaired glucose metabolism and cardiovascular disease; (4) outcome parameters: blood lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, triacylglycerols), glycemic control (fasting glucose, fasting insulin, glycosylated hemoglobin), blood pressure (systolic and diastolic blood pressure), inflammation markers and cardiovascular events/mortality.

Study quality assessment

Review quality was rated using a modified version of the Overview of Quality Assessment Questionnaire (OQAQ) including a bias tool (Oxman and Guyatt, 1991) (Supplemental material, Table S1) as described recently (Greaves et al. 2011). Results of OQAQ assessments are summarized in Table 1. It should be noted that the analyses considered were in some cases based on overlapping sets of trials.

The present review included meta-analyses of intervention trials (randomized, non-randomized and crossover trials). Carry-over (a type of period-by-intervention interaction) is a common problem associated with cross-over trials, but it seems only justifiable to exclude cross-over trials from a systematic review if the design is inappropriate within the clinical context (Higgins and Green 2011). Another limitation of meta-analyses especially in nutritional intervention trials is heterogeneity of various aspects and characteristics of the study protocols. Therefore, it is not surprising that the literature chosen for the present review varies especially regarding type(s) of garlic (e.g. garlic oil, dried garlic homogenate, aged garlic extract, processed garlic capsule, time-released garlic powder, regular garlic pill, garlic powder) and study population (healthy, overweight, or obese subjects, hypercholesterolemic, normo-sensitive, or hypertensive). To address the problem of heterogeneity within the analyzed meta-analysis, we extracted information when available. A value for I^2 of >50% is considered to represent substantial heterogeneity (Higgins et al. 2003). In addition, most of the included meta-analyses did not analyze their data with respect to differential compliance (drop outs).

Evidence from meta-analyses

The detailed steps of the meta-analysis article selection process are described as a flow diagram in Fig. 1 (Moher et al. 2009). Table 2 summarizes the study characteristics of the meta-analyses included in this review.

Nine systematic reviews investigated the effects of garlic on lipid parameters (Silagy and Neil 1994a; Warshafsky et al. 1993) (Ackermann et al. 2001; Stevinson et al. 2000) (Khoo and Aziz 2009; Kwak et al. 2014; Reinhart et al. 2009; Ried et al. 2013; Zeng et al. 2012) and eight systematic reviews analyzed the effects on blood pressure parameters (Kwak et al. 2014; Reinhart et al. 2008; Ried et al. 2008; Rohner et al. 2015; Silagy and Neil 1994b; Stabler et al. 2012; Wang et al. 2015; Xiong et al. 2015). In most cases, a substantial heterogeneity within the included studies could be detected. Thus, the number of studies pooled for meta-analyses ranged from 2 to 35. Likewise, there was a wide spread in the number of included participants enrolled for each study or trial (from 87 to 2298) as well as in the duration of the intervention (7 to 84 days). In 56% of the studies, no funding sources were reported. Quality assessment (OQAQ) indicates overall moderate and good quality across all studies (Table 1).

Garlic effects on blood lipids

Eight (Silagy and Neil 1994a; Warshafsky et al. 1993) (Ackermann et al. 2001; Stevinson et al. 2000) (Kwak et al. 2014; Reinhart et al. 2009; Ried et al. 2013; Zeng et al. 2012) of nine meta-analyses synthesizing the effect of garlic on blood lipids reported significantly decreased TC levels, whereas no such changes could be found by Khoo and Aziz (2009). In the meta-analysis by Ackermann et al. (2001), the benefit of garlic on TC was only prevalent within the first 3 months post-intervention. The effect of garlic on HDL-C levels was moderate across all studies, i.e. in 6 (Silagy and Neil 1994a) (Ackermann et al. 2001) (Kwak et al. 2014; Reinhart et al. 2009; Zeng et al. 2012) out of 7 studies, garlic intake did not show significant effects on HDL-C levels at all. In one meta-analysis pooling data from 2298 participants across 30 trials, observed small increases in mean difference of HDL-C (1.49 mg/dl [95% CI: 0.19, 2.79]) (Ried et al. 2013). Subgroup analysis of trials revealed that using garlic oil (6 studies) exerted the most pronounced effect (mean difference: 5.97 mg/dl [95%CI: 1.65, 10.30]). Conflicting results are reported concerning the effects of garlic on LDL-C. In 3 out of 6 meta-analyses, LDL-C was significantly decreased following garlic administration (Ackermann et al. 2001; Kwak et al. 2014; Ried et al. 2013), while in the remaining reviews, no effect of garlic on this parameter could be observed (Khoo and Aziz 2009; Reinhart et al. 2009; Zeng et al. 2012). Three (Silagy and Neil 1994a) (Reinhart et al. 2009; Zeng et al. 2012) out of five studies reported a significant decrease in triacylglycerol levels.

The meta-analyses mentioned above included both trials enrolling healthy subjects (with respect to blood lipids) as well as individuals with hyperlipidemia or hypercholesterolemia. In some of these systematic reviews, subgroup analyses were performed to investigate