Garlic: effects on cardiovascular risks and disease, protective effects against cancer, and clinical adverse effects

Authors' objectives
To summarise the effects of garlic on cardiovascular risk factors and disease, associations between garlic and cancer, and possible adverse effects of garlic.

Searching
Eleven electronic databases were searched to February 2000 for English and non-English citations. Citations were also sought from pertinent articles and reviews, and from manufacturers and technical experts. Full details of the search strategy were provided in the review.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) or systematic reviews of RCTs of more than 4 weeks' duration were included for questions about cardiovascular disease. Cohort or case-control studies with more than 50 participants, or RCTs were included for questions about cancer. Case reports, case series, cohort or surveillance studies, or RCTs were included for questions about adverse effects. Studies only reported in an abstract format were not included in the review.

Specific interventions included in the review
The interventions could include fresh, cooked or garlic supplements given for a minimum of 4 weeks. The actual interventions included: dehydrated garlic preparations, either standardised (allicin content of 0.52% of total tablet or minimum release of 0.3% allicin, or 2.4 mg allicin/tablet) or non-standardised; garlic ether extracts; aged-garlic extract; cold-pressed garlic oil; raw or fried garlic; garlic oil; steam-distilled, enteric-coated beta-cyclodextrin-bound garlic oil preparation; or garlic combined with other substances, such as fish oil, ginkgo, soya or hawthorn.

Participants included in the review
The participants eligible and included in the review were adults or children with or without dyslipidemia, hypertension or diabetes; those at average or high risk for cardiovascular disease; adults without cancer risk factors, precancerous conditions or malignancy; adults with cancer risk factors, but no precancerous conditions or malignancy; and adults with cancer.

Outcomes assessed in the review
For questions relating to cardiovascular disease, physiological and clinical outcomes were examined. The physiological outcomes included lipids, blood-pressure, insulin sensitivity/glucose or glycosylated haemoglobin, or antithrombotic activity. The clinical outcomes included cardiovascular morbidity or mortality (such as stroke, myocardial infarction, angina incidence or severity), peripheral vascular disease, or the numbers of cardiac procedures.

For questions relating to cancer, the outcomes were precancerous lesions, cancer, morbidity and mortality.

For questions relating to adverse effects, any reported adverse effects were assessed.

How were decisions on the relevance of primary studies made?
At least two independent reviewers scanned the titles and abstracts of all records identified from the search, using predefined selection criteria. The criteria included the types of participants, interventions, control groups, outcomes and study designs.

Assessment of study quality
Information was collated on individual studies in relation to the adequacy of randomisation (method and concealment
of assignment); whether the trial was single or double blind; whether the intervention and the control groups were adequately matched to maintain blinding; cointerventions such as diet, exercise and cardiovascular medications; and the number of study drop-outs. Two independent reviewers extracted data relating to quality.

Data extraction
Two independent physicians abstracted data from the trials that were identified in the efficacy searches. Any disagreements in extraction were less than 1% and were resolved by consensus. No formal reliability testing was done. All of the abstracted data were verified by a third person with expertise in quantitative data. One physician abstracted data about adverse effects.

Methods of synthesis
How were the studies combined?
The data were synthesised descriptively and quantitatively, where appropriate. The primary outcomes in the studies were measured with continuous rather than categorical variables. Both standardised and non-standardised (adjusted for baseline differences) mean differences between the treatment and comparison groups were used in the current report to estimate the 'effect size' for each study. Placebo-controlled RCTs with lipid outcomes were quantitatively pooled using a random-effects estimator.

The standardised mean differences were converted to clinical laboratory units to aid the interpretation of effect size standard deviation units. There was no quantitative summary of studies assessing blood-pressure, glucose or thrombotic outcomes.

Subgroup analyses were performed for: trials that used similar dried standardised preparations of garlic and enrolled participants with hypercholesterolaemia; trials with and without the combination preparations (garlic with either ginko or hawthorn). A subgroup analysis based on 'doses' of garlic supplements was not conducted because of limited variation in doses among the trials.

How were differences between studies investigated?
Differences between the studies were examined through discussion and tabulation. Furthermore, in the meta analysis of the lipid trials, outliers were identified using a standard heterogeneity chi-squared test, funnel plot and Galbraith plot.

Results of the review
A total of 131 studies were included in the review: 45 cardiovascular trials, 13 cancer survey, case-control or cohort studies, and 73 studies of adverse effects. The total number of participants included in the review was not given.

Compared with placebo, garlic preparations reduced the total cholesterol at one and 3 months: the mean reductions ranged from 1.2 to 17.3 mg/dL, and from 12.4 to 25.4 mg/dL, respectively (37 trials). No trial with 6 month outcomes (6 RCTs) found a significant reduction.

Twenty-seven small RCTs reported some beneficial effect of garlic on blood-pressure, but this was not always statistically significant. Twelve small RCTs found no clinically significant effect of garlic on blood glucose in diabetics or non-diabetics. Two further RCTs found no significant effect on insulin or C peptide levels.

Ten RCTs reported promising findings for the effects of garlic on platelet aggregation, but these were limited by their small size and short duration.

There was insufficient evidence to support or refute a beneficial effect of garlic on clinical outcomes such as myocardial infarction or claudication.

The very limited data available, mainly from case-control studies, suggested that garlic may have a beneficial effect on the odds of laryngeal, gastric, colorectal and endometrial cancer and adenomatous colorectal polyps.
The main adverse effects of garlic ingestion were smelly breath and body odour, and possibly flatulence, oesophageal and abdominal pain, small intestinal obstruction, dermatitis, rhinitis, asthma and bleeding.

**Authors' conclusions**
The available trials demonstrated promising, but modest and short-term effects of garlic supplements on lipid and antithrombotic factors. The effects of garlic on clinical outcomes were not established, and the effects on glucose tolerance and blood-pressure were none to minimal. A high dietary intake of garlic may be associated with a decreased odds of some cancers. The interpretation of the findings was hampered by the range of garlic preparations studied and the inadequate definition of the active ingredients.

**CRD commentary**
This was an excellent review that summarised the literature. It is likely to be of interest to the general public given the increased availability and use of dietary supplements. It is also of interest to clinicians given the important clinical outcomes examined in the review. The authors of the review stated clear objectives that were addressed with a series of precise questions. A comprehensive search strategy, which included English and non-English publications, was used to identify potentially eligible studies for inclusion. The review methodology was meticulous and clearly reported. The results of the review were succinctly summarised and the authors' overall conclusions are a good reflection of the evidence base. The authors also provided a good description of the limitations of the studies carried out to date, and made informed suggestions for future research.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

**Research.** The authors state that before undertaking future trials to evaluate the efficiency of garlic, the equivalency and the amount of release of the main constituents of various garlic preparations must be established. Placebos designed to stimulate garlic odour should be developed and adequacy of blinding should be assessed in trials. Well-designed randomised trials of longer than 6 months' duration, which are powered to assess morbidity and mortality outcomes as well as lipid and thrombotic outcomes, are needed. Appropriate analyses that are intention-to-treat and two-tailed should be used. The authors also indicated that further evaluations of both the associations between garlic and cancer and the adverse effects of garlic are needed.

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