Ginkgo biloba extract for the treatment of intermittent claudication: a meta-analysis of randomized trials

Pittler M H, Ernst E

Authors' objectives
To assess the efficacy of Ginkgo biloba extract for intermittent claudication.

Searching
MEDLINE, EMBASE, BIOSIS Previews, AMED, CISCOM and the Cochrane Library were all searched from their inception to June 1998, using the search terms 'ginkgo', 'gingko' and 'maidenhair tree'. Additional material was identified by manually searching the bibliographies of retrieved studies and reviews, and by scanning the authors' personal files. The manufacturers of commercial Ginkgo biloba products were contacted for published and unpublished material. No language restrictions were applied, and articles in languages other than English or German were translated in-house.

Study selection
Study designs of evaluations included in the review
Randomised, double-blind placebo-controlled trials (RCTs) were included.

Specific interventions included in the review
Ginkgo biloba extract (120 to 160 mg/day) versus placebo. Studies that were performed using Ginkgo biloba in combination with other medications or remedies were excluded. Study duration was either 6, 12 or 24 weeks.

Participants included in the review
Patients with intermittent claudication, categorised according to the Fontaine criteria.

Outcomes assessed in the review
Pain-free walking distance, measured using devices that forced the patients to walk at a set speed. Studies that did not assess walking distance were excluded. Maximal walking distance was assessed when possible.

How were decisions on the relevance of primary studies made?
Two authors independently assessed the trials for inclusion, and any disagreements were resolved by discussion. Consensus was reached in all cases.

Assessment of study quality
The authors assessed the methodological quality of the included studies using the 5-point scoring system of Jadad et al. (see Other Publications of Related Interest). Two authors independently assessed the trials for methodological quality, and any disagreements were resolved by discussion. Consensus was reached in all cases.

Data extraction
Two authors independently performed the data extraction using standardised predefined criteria. Any disagreements were resolved by discussion and consensus was reached in all cases. The authors of original publications and of earlier reviews on the subject were contacted for additional data where required. (see Other Publications of Related Interest).

Data were extracted for the categories of: study identification, number of patients entered (analysed), study duration, daily dose of Ginkgo biloba extract, mean baseline pain-free walking distance, mean increase in pain-free walking distance, mean increase in maximal walking distance, and ergometer test speed in km/hour at the specified gradient.

Weighted means of the within-study treatment effects were calculated.
Methods of synthesis
How were the studies combined?
Weighted mean differences (WMDs) with 95% confidence intervals (CIs) were calculated using a random-effects model.

A funnel plot analysis was used to assess publication bias.

How were differences between studies investigated?
The authors do not state a method for assessing heterogeneity.

Results of the review
Eight RCTs with 415 participants were included in the review, although data were only analysed for 385 participants. Two of the studies used a crossover design.

Six trials scored at least 4 points in the 5-point quality scoring system.

Only 4 studies showed a statistically-significant difference in the increase in pain-free walking distance.

Seven of the 8 studies showed WMDs in favour of Ginkgo biloba.

The pooled WMD for all 8 trials was 34 m (95% CI: 26, 43) in favour of Ginkgo biloba.

In studies using similar methodological features (ergometer speed 3 km/hour and inclination 12%) this difference was 33 m in favour of Ginkgo biloba (95% CI: 22, 43).

Adverse events were rare, mild and transient. Five trials reported adverse effects from Ginkgo biloba, namely abdominal complaints, nausea and dyspepsia.

The funnel plot analysis showed that studies with smaller sample sizes seem evenly distributed around the WMD in pain-free walking distance, while larger studies more closely resembled the combined overall estimate. There were too few studies for a firm conclusion on whether publication bias influenced the overall result.

Cost information
The approximate daily treatment costs based on retail prices (July 1999) for a 1-month supply of medication were obtained for the American and German market. Costs for a dose of Ginkgo biloba extract (120 mg) ranged from $0.41 to $0.84 in the United States, and from $0.83 to $0.97 in Germany ($1 = DM1.84). In comparison, in the United States, costs for a daily dose of pentoxifylline (1,200 mg) ranged from $1.83 to $1.93, and for cilostazol (200 mg) from $2.90 to $4.23.

Authors' conclusions
The authors state that these results suggest that Ginkgo biloba extract is superior to placebo in the symptomatic treatment of intermittent claudication. However, the size of the overall treatment effect is modest and of uncertain clinical relevance.

CRD commentary
The authors have clearly stated the research question, and addressed study design, interventions and outcomes in their a priori inclusion and exclusion criteria. Only participant details were not stated in the inclusion and exclusion criteria.

A validated methodological quality scoring system was used.

The authors report how the study selection, quality assessment and data extraction were performed, and how many of
the authors performed these tasks.

Statistical pooling was performed using a random-effects model. Since no method for assessing heterogeneity is reported, it is unclear whether it was appropriate to pool studies.

The authors’ conclusions appear to follow from the results, but these should be viewed with caution due to the limitations of the review. This is confirmed by the authors’ statements that the processes used in the conduct of the included studies may have led to an overestimation of the treatment effects. These shortcomings included a lack of concealment of the allocation process, queries relating to the adequacy of the randomisation procedures used, and a lack of washout period in the two crossover studies.

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

**Bibliographic details**

**PubMedID**
11014719

**Other publications of related interest**


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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.