Ginkgo biloba for the treatment of tinnitus

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Abstract

Introduction

Multiple interventions have been postulated for the treatment of tinnitus, but none has been established as clearly effective. Ginkgo biloba has been proposed among the alternatives.

Methods

To answer this question we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified three systematic reviews including four primary studies, all corresponding to randomized trials. We concluded the use of Ginkgo biloba probably does not decrease the severity of tinnitus. In addition, it does not reduce the intensity of tinnitus or improve the quality of life of patients.

Problem

Tinnitus is a condition that causes significant discomfort in those who suffer it. It often leads to repeated consultations at different levels of health care, and in some cases it can have a significant impact in the quality of life. The causes of this condition have not been yet fully understood, which partly explains why it has not been possible to find an effective therapy.

Among the possible treatments for its management, the use of Ginkgo biloba (mainly its extract) has been proposed. This intervention has been used by traditional Chinese medicine for thousands of years, and gradually being integrated into the Western world. Its effect would be mediated by its cerebral vasodilator and neuronal protector properties, although it is not clear if this really translates into a real clinical benefit.

Key messages

- Ginkgo biloba probably does not decrease severity of tinnitus.
- Ginkgo biloba does not reduce the intensity of tinnitus or improve quality of life.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found three systematic reviews[1-3] including four primary studies[4-7], all corresponding to randomized trials. This table and the summary in general are based on the latter.
What types of patients were included*	All trials included adults whose reason for consultation was the presence of tinnitus.
What types of interventions were included*	All trials evaluated the use of Ginkgo biloba in the management of tinnitus: two used EGb761 extract, 160 mg/day[5] or 120 mg/day[6]; one used LI1370 extract, 150 mg/day[4]; and one did not mention the use of any specific extract, but it was administered in a dose of 120 mg/day[7]. All trials compared against placebo.
What types of outcomes were measured	The different trials measured multiple outcomes, which were pooled by the systematic reviews as follow: • Severity of tinnitus, through a subjective scale. • Impact on the quality of life, through subjective scoring scales. • Intensity of tinnitus, using audiometry in decibels (dB) and through subjective scoring scales. • Presence of side effects to the use of Ginkgo biloba. The average follow-up 12.5 weeks with a range between 12 and 14 weeks.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Summary of Findings

The information on the effects of Ginkgo biloba is based on four randomized trials that included 1246 patients.

One trial reported the severity of tinnitus through an unspecified subjective scale (978 patients)[4]; three trials measured the impact on quality of life through an unspecified score form[4,5] or subjective survey ('Tinnitus Handicap Inventory' and 'Glasgow Health Status Inventory')[7] (1147 patients). Three trials measured the intensity of tinnitus[4-6], using a subjective scale[4,5] or audiometry and a subjective scale[6](1180 patients) and two trials measured adverse effects (1044 patients)[4,7]. The summary of findings is as follows:

- Ginkgo biloba probably does not decrease the severity of tinnitus. The certainty of the evidence is moderate.
- Ginkgo biloba does not improve the quality of life of patients with tinnitus. The certainty of the evidence is high.
- Ginkgo biloba does not reduce the intensity of tinnitus. The certainty of the evidence is high.
- Ginkgo biloba is not associated with adverse effects in patients with tinnitus. The certainty of the evidence is high.

Ginkgo biloba for tinnitus		
Patients	Adults consulting for tinnitus	
Intervention	Ginkgo biloba	
Comparison	Placebo	
Outcomes	Effect	Certainty of the evidence (GRADE)
Severity of tinnitus	One trial [4] noted there was no difference between the experimental and control group.	⨁⨁⨁◯[1] Moderate
Quality of life	Three trials [4],[5],[7] indicated there was no difference between the experimental group and placebo.	⨁⨁⨁⨁ High
Intensity of tinnitus	One trial [6] measured this outcome with decibel audiometry indicating there was no difference between the experimental group and the control group. Three trials [4],[5],[6] measured this outcome with a subjective scale indicating there was no difference between the experimental group and placebo.	⨁⨁⨁⨁ High
Side effects	Two trials noted [4],[7] there was no difference between the experimental and control group.	⨁⨁⨁⨁ High
GRADE: Degrees of evidence from the GRADE Working Group (see below).		
[1] A level of certainty of evidence was downgraded due to imprecision since it is based on a single study.		

Follow the link to access the interactive version of this table (Interactive Summary of Findings – iSoF)

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

These results are applicable to adults whose main symptom is tinnitus. Out of four trials, only one included patients with acute or subchronic tinnitus, with an average duration of 134 days[5], while the rest consider patients who report the symptom for a longer time: between 1-5 years of duration[4], average duration of 4.5 years[6] and an average persistence of the symptom of 4.8 years[7].

It is relevant to mention that among the trials, two used the extract EGb761 of Ginkgo biloba[5,6] and one the extract LI 1370[4], which reflects a scarce standardization of the of the intervention, which may influence the lack of effect.

These results are not applicable to patients who present another neurological comorbidity associated with tinnitus.

About the outcomes included in this summary

The selected outcomes are those critical for decision-making according to the opinion of the authors and are in agreement, in general, with the systematic reviews identified. These are the outcomes related to the reduction of tinnitus, objectively or subjectively, in addition to the impact on the quality of life of the patients and the presence of side effects.

Regarding the outcome severity of tinnitus, one trial[4] reported there was no difference between the experimental and control group, pre- and post-intervention, through a subjective scale of 0-19 points, whose name is not detailed.

Regarding intensity of tinnitus, one trial[6] measured this outcome in decibels, using audiometry, noting that there was a non-significant reduction in the intervention group from 42.3 (36.6 to 48.1) to 39.0 (31.9 to 46.1), while the control group showed a non-significant increase from 44.1 (39.0 to 49.2) to 45.1 (39.1 to 51.2). Two other trials[4,5] used unspecified subjective scales, where one[4] showed that the volume reduction was 13.6% in experimental patients versus 12.4% in the placebo group, and the other[5] noted that on a scale from 0 to 3 points, the difference between pre- and post-intervention in the experimental group was -1 point and -0.67 in the control group, both showing there was no difference between the experimental groups in terms of reducing the intensity of tinnitus.

Regarding the outcome of quality of life, one trial[4] reported there was no difference between the experimental and placebo group, based on a subjective, unspecified scale, from 0 to 5 points pre and post-intervention. Another trial[7] did not show differences between both groups based on two surveys: the Tinnitus Handicap Inventory (the score difference between pre- and post-intervention was -4.7 points in the experimental group and -2.2 in the control group), and the Glasgow Health Status Inventory (the score difference before and after intervention was 1.94 in the experimental group and 2.52 in the control group). The third tria[5] did not report differences between groups, using a subjective scale (not specified), from 0 to 3 points, where the pre and post intervention difference in the experimental group was -0.84 and in the control group was - 0.59.

Regarding adverse effects, one trial[4] showed no difference, reporting 10.6% of patients with side effects in the experimental group and 9.5% in the control group, where at least one third were gastrointestinal symptoms. The other trial[7] also showed no differences between the two groups, with 3% in the experimental group and 6% in the placebo group presenting diarrhea, and 3% in both groups had headache.

Balance between benefits and risks, and certainty of the evidence

The results of the systematic reviews were difficult to analyze, the measures of effect were not clear and there were no meta-analyses. Notwithstanding, the certainty of the evidence is moderate to high.

Even though it is a safe intervention, it has no benefit, so, the balance between benefits and harms is not favorable.

Resource considerations

The reviews did not consider the costs associated with the use of Ginkgo biloba.

Considering the absence of benefit), regardless of the cost, the balance between cost and benefits is not favorable.

What would patients and their doctors think about this intervention

Faced with the evidence presented in this summary, most patients and doctors should lean against its use, considering Ginkgo biloba would have no effect on tinnitus.

However, in the absence of alternative treatments for this condition, it is possible that some patients would choose to use treatments without adverse effects and low cost. It is particularly important to inform patients about the limitations of the evidence.

Differences between this summary and other sources

The conclusions obtained in this summary agree with one of the systematic reviews identified[2]. However, two reviews[1,3] suggest there may be a benefit, but the evidence base is limited. The discrepancy between these reviews and this summary is explained by the interpretation about the clinical relevance of the changes observed. The opinion of the authors of this summary is they are not relevant for patients.

We did not identify international clinical guidelines about the management of tinnitus.

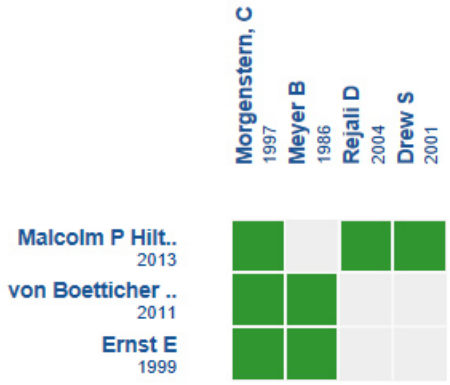
Could this evidence change in the future?

The probability that future research changes the conclusions associated with the outcomes of this summary is low, considering the certainty of the existing evidence.

We did not identify ongoing trials evaluating Ginkgo biloba for tinnitus in the International Clinical Trials Registry Platform (WHO) or ongoing systematic reviews in the Prospective Register of Systematic Reviews (PROSPERO).

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Ginkgo biloba for tinnitus.

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

www.epistemonikos.org.

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